

Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Appendix A – Appendix Tables

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Document Guide

This Document Guide is intended to orient readers to the organization of the Oxides of Nitrogen Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 14 chapters, which can all be found at <https://www.epa.gov/isa/integrated-science-assessment-isa-oxides-nitrogen-health-criteria>.

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Appendix A – Appendix Tables

A.1. Respiratory Effects – Short-term Exposure

Appendix Table 3-1 Epidemiologic studies of short-term oxides of nitrogen exposure and emergency department visits and hospital admissions for asthma

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Emergency Department Visits for Asthma						
Li et al. (2011) Medicaid n = 7,063 patients, 12,933 events Detroit, MI, U.S. 2004–2006	Pediatric Medicaid population ages 2–18 years	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2006	NO ₂ (ppb) Mean = 16.75±7.28 Median = 15.74 (IQR 9.65) Min = 2.15 Max = 55.22 P25 = 11.54 P75 = 21.19	ED visits for asthma: Medicaid beneficiary and claims data from the Michigan Data Warehouse of the Michigan Department of Community Health	Logistic Regression Adjusted for: season, day of week, relative humidity, temperature (spline), and calendar time (spline)	Lag 0–4 % Increase (95% CI) ^b 5.14% (-0.52, 11.12)
Peel et al. (2005) n = 4,407,535 visits Atlanta, GA, U.S. Individuals who have reported to one of the hospitals in the Atlanta metropolitan statistical area Time-series	Individuals who have reported to one of the hospitals in the Atlanta metropolitan statistical area	Central site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1993–2000	NO ₂ (ppb) Mean = 45.9±17.3 P10 = 25 P90 = 68	ED visits for asthma: Electronic records from individual hospitals	Poisson Adjusted for: temporal trends (cubic splines with monthly knots), season indicator variables, daily average temperature and dew point (cubic splines), and indicator variables for day of week, federal holidays, and hospital entry and exit.	Lag 0–2 % Increase (95% CI) ^b 1.75% (-0.30, 3.85)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Stieb et al. (2009)	Administrative ED visits	Central site monitor	NO ₂ (ppb)	ED visits for asthma: Electronic records from individual hospitals	Poisson	Lag 2
n = nearly 400,000 ED visits			Montreal		Adjusted for: temporal trends (natural splines), holidays, temperature and relative humidity (natural splines), and time of day	% Increase (95% CI) ^b
Canada		Averaging time: NO ₂ - 24-hour average	Mean = 19.5±7.6			0.00% (-2.63, 2.70)
1990s and early 2000s			P25 = 14.0			
Time-series		Exposure years: 1992–2003	P75 = 23.5			
			Ottawa			
			Mean = 18.8±8.8			
			P25 = 12.7			
			P75 = 24.0			
			Edmonton			
			Mean = 21.9±9.4			
			P25 = 14.7			
			P75 = 27.6			
			Saint John			
			Mean = 9.3±5.5			
			P25 = 5.1			
			P75 = 12.3			
			Halifax			
			Mean = 17.5±5.8			
			P25 = 13.6			
			P75 = 21.0			
			Toronto			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 22.7±7.6 P25 = 17.6 P75 = 27.5 Vancouver Mean = 18.7±7.4 P25 = 13.6 P75 = 19.7			
Strickland et al. (2010) n = 591,386 ED visits for asthma Atlanta, GA, U.S. Follow-up: 1993–2004 Case-crossover	Children aged 5–17 years	Central site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1993-2004	NO ₂ (ppb) Mean = 23.3±9.7 IQR = 12.9	ED visits for asthma: Electronic records from individual hospitals	Poisson Adjusted for: day-of-season (cubic polynomial), dew point temperature (cubic polynomial), minimum temperature (cubic polynomial), year, month, day of week, hospital, and maximum temperature	Lag 0–7 % Increase (95% CI) ^b 7.0% (3.0, 11.0)
Villeneuve et al. (2007) n = 57,912 E ED visits for asthma Edmonton, Canada 1992–2002 Case-crossover	Individuals two years of age and older in the census metropolitan area of Edmonton, Canada	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–2002	NO ₂ (ppb) Summer Median = 17.5 P25 = 14.0 P75 = 22.0 Winter Median = 28.5	ED visits for asthma: Electronic records from individual hospitals	Logistic Regression Adjusted for: same day temperature and relative humidity	Lag 0–4 % Increase (95% CI) ^b 4.48% (0.77, 8.32)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 22.5 P75 = 35.5			
† Alhanti et al. (2016) Atlanta n = 389,863 ED visits Dallas n = 102,155 ED visits St. Louis n = 119,952 ED visits Atlanta, GA; Dallas, TX; St. Louis, MO, U.S. 1993-2009 (Atlanta), 2006-2009 (Dallas), 2001-2007 (St. Louis) Time series	ED visits from 3 metropolitan areas: 20 counties around Atlanta, 12 counties around Dallas, and 16 counties around St. Louis.	Monitors Averaging time: NO ₂ - 1-hour max Exposure years: 1993-2009	NO ₂ (ppb) Atlanta Mean = 21.1±8.6 Dallas Mean = 23.2±10.4 St. Louis Mean = 28.1±8.6	ED visits with ICD-9 code 493 or 786.07	Poisson Adjusted for: natural cubic splines with 3 degrees of freedom (d.f.) of lag 0 minimum temperature, 2-day moving average (of the previous day and 2 days prior) minimum temperature, and 2-day moving average (of the previous day and 2 days prior) dew point temperature; temporal controls included indicator variables for day of week, federal holidays, and days commonly celebrated as holidays (e.g., the day after Thanksgiving) and a natural cubic spline of time (d.f. = 8 per year)	% increase (95% CI) ^b White: 4.21 % (0.04, 8.56) non-white: 19.67% (14.06, 25.55) Males: 15.14% (10.74, 19.71) Females: 6.35% (1.13, 11.84)
† Bi et al. (2023) Environmental Exposures and Health Across the Nation (ENVISION) Study N = 3,190,333	Included patients with a primary diagnosis of asthma. The ED visit data were checked for implausible values, facility closures, abnormal distributional	Fixed site monitor, CMAQ Method validation NR Averaging time:	NO ₂ (ppb) Overall Mean = 22.6±9.6 Min = 2.9 Max = 70.8	ED visits for asthma: Inpatient billing records from individual states	Poisson Adjusted for: maximum temperature (natural cubic spline), average dew point temperature (natural cubic spline),	NO ₂ ; Lag 0–7 % Increase (95% CI) ^b 3.32% (1.54, 5.14) NO _x ; Lag 0–7

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Georgia, California, New York, North Carolina, Utah, New Jersey, Maryland, Missouri, Arizona, Nevada, U.S. 2005–2014 Time-series	trends, and missingness. Missing values for essential variables, admission date, and patient ZIP codes were excluded from the analysis. Additionally, any visit without at least one ICD diagnosis code was excluded from the analysis. We restricted the study population to patients with a residential ZIP code within 30 mi of 53 Air Quality System PM speciation monitoring sites in the 10 states.	NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2005–2014	NO _x (ppb) Overall Mean = 48.7±38.1 Min = 3.4 Max = 323.7		day of week, holiday, hospital indicator, influenza ED visits, and calendar time (natural cubic spline with 12 knots/year)	% Increase (95% CI) ^b 2.19% (0.93, 3.47)
† Cisneros et al. (2021) n=19,735 ED visits Sacramento, San Francisco, Fresno, Los Angeles, and San Diego, CA, U.S. 2005-2015 Case-crossover	ED visit data for the cold season were obtained from California's Office of Statewide Health Planning and Development.	EPA's AQS Averaging time: NO ₂ -24-hour average Exposure years: 2005-2015	NO ₂ (ppb) Mean = 18	ED visits with ICD-9 code 493 for asthma related visits	Logistic regression Adjusted for: temperature (restricted cubic spline), relative humidity (restricted cubic spline)	Lag 1 OR (95% CI) ^b 1.40 (1.31, 1.50) Lag 0-1 1.47 (1.36, 1.59) Lag 0-14 2.07 (1.85, 2.32) Lag 0-30 5.80 (4.62, 7.29)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Krall et al. (2018)	ED visits using electronic billing data from the 20-county Atlanta, GA metropolitan area; the 7-county Birmingham, AL metropolitan area, the 12-county Dallas-Fort Worth metropolitan area, the 3-county Pittsburgh area, and the 16-county St. Louis metropolitan area.	Hybrid model Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Atlanta Mean = 21.6±7 Birmingham Mean = 13.2±4.3 Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5 Birmingham Mean = 24.5±13.8 Dallas Mean = 41.4±32.2 Pittsburgh Mean = 56±35.8 St. Louis Mean = 51.3±30.9	ED visits for asthma: electronic billing data	Bayesian Hierarchical Model Adjusted for: weekday, season, holidays, meteorology (cubic splines of lag 0–2 and lag 3–7 temperature and dew-point temperature), temporal trends (cubic splines of time with one df per month), and the hospitals reporting data for each day.	NO ₂ ; Lag 0–7 % Increase (95% CI) ^b 22.91% (15.89, 30.35) NO _x ; Lag 0–7 % Increase (95% CI) ^b 9.51% (0.18, 19.71)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†O'Lenick et al. (2017) n = 128,758 ED visits for asthma Atlanta, GA, U.S. January 1, 2002–December 31, 2008 Cohort	ED visits for asthma. We restricted our analyses to the paediatric population (5–18 years old) and to patients with a residential ZIP code (defined as US Postal Service delivery areas) located wholly or partially in 20-county Atlanta	CMAQ, Chemical transport model Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2002–2008	NR	ED visits for asthma: Georgia Hospital Association	Logistic Regression Adjusted for: season, holidays, maximum temperature (cubic polynomial), average dewpoint (cubic polynomial), and calendar time (cubic spline)	Lag 0–2 % Increase (95% CI) ^b 2.01% (-0.97, 5.08)
†Raun et al. (2019) n = 18,542 ambulance treated asthma attacks Houston, TX, U.S. 2004–2016 Case-crossover	Ambulance-treated asthma attacks from the Houston Fire Department emergency medical service call database	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2016	NO ₂ (ppb) Mean = 12.7±6 Median = 11.7 (IQR 8.4) P5 = 4.8 P25 = 8.1 P75 = 16.5 P95 = 23.9	Ambulance treated asthma attacks: Houston Fire Department emergency medical service call database	Logistic Regression Adjusted for: apparent temperature	Lag 0 % Increase (95% CI) ^b 14.88% (7.39, 22.89)
†Sharma et al. (2023) Statewide Planning and Research Cooperative System SPARCS n = 145,838 ED visits for asthma New York City, NY, U.S. Follow-up: 2005–2011	Children aged 5–17 in New York City	Spatiotemporal/geospatial model Model validated against fixed site monitors (r ² = 0.44) Averaging time: NO ₂ - 1-hour max	Mean = 27.59±10.73 Median = 25.97 (IQR 13.89) Min = 3.73 Max = 100.84	ED visits for asthma: New York Statewide Planning and Research Cooperative System (SPARCS)	Logistic Regression Adjusted for: temperature (natural cubic spline) and relative humidity	Lag 0–6 % Increase (95% CI) ^b 10.80% (9.34, 12.27)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort		Exposure years: 2005–2011				
† Szyszkowicz et al. (2018)	ED visits for respiratory diseases retrieved from the National Ambulatory Care Reporting System (NACRS)	Central site monitor	NO ₂ (ppb)	ED visits for asthma: National Ambulatory Care Reporting System (NACRS) database maintained by the Canadian Institute for Health Information (CIHI)	Logistic Regression	Lag 2
n = 223,841 ED visits for asthma		Averaging time: NO ₂ - 24-hour average	Algoma Mean = 5.1 IQR = 4 Min = 0 Max = 24		Adjusted for: temperature and relative humidity (natural splines) and an indicator for days with influenza.	% Increase (95% CI) ^b Males, Warm Season: 8.87% (3.76, 14.24)
Algoma, Halton, Hamilton, Ottawa, Peel, Toronto, York, Middlesex, Essex, Ontario, Canada.		Exposure years: 2004–2011	Essex Mean = 15.6 IQR = 8.1 Min = 2.4 Max = 55.5			Females, Warm Season: 11.45% (4.49, 18.88)
April 2004–December 2011			Halton Mean = 12.9 IQR = 7.7 Min = 1 Max = 51.2			
Case-crossover			Hamilton Mean = 13.9 IQR = 9.5 Min = 1.7 Max = 63			
			Middlesex Mean = 10.9 IQR = 7 Min = 0 Max = 51			
			Ottawa Mean = 8.7			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			IQR = 7 Min = 1 Max = 47 Peel Mean = 13.2 IQR = 9.5 Min = 2 Max = 54 Toronto Mean = 18.5 IQR = 9.4 Min = 4.5 Max = 62.1 York Mean = 8.2 IQR = 7 Min = 0 Max = 47			
†Weichenthal et al. (2016) n = 128,731 ED visits for asthma Toronto, Hamilton, Barrie, Chatham, Cornwall, Kingston, Kitchener, Oakville, Oshawa, Petawawa, Peterborough, Port Stanley, Sarnia, St. Catharines, Thunder Bay, Ontario, Canada. 2004–2011 Case-crossover	ED visits for respiratory diseases retrieved from the National Ambulatory Care Reporting System (NACRS)	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2011	NO ₂ (ppb) Mean = 12.9±7.79 Median = 11.5 (IQR 10.6) Max = 65	ED Visits for Asthma: National Ambulatory Care Reporting System (NACRS) database maintained by the Canadian Institute for Health Information (CIHI)	Logistic Regression Adjusted for: 3-day mean ambient temperature and relative humidity (cubic splines) and daily counts of emergency room visits for influenza.	Lag 0–2 % Increase (95% CI) ^b 1.03 (1.00, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Xiao et al. (2016) n = 148,256 ED visits for asthma Georgia, U.S. 2002–2008 Case-crossover	ED visits for children aged 0–18 years obtained from the Georgia Hospital Association	CMAQ Model validated against central site monitors ($r^2 = 0.69$) Averaging time: NO ₂ - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Mean = 9.22±9.62 IQR = 9.33 Min = 0.07 Max = 73.88 P25 = 2.7 P75 = 12.03	ED Visits for Asthma: Georgia Hospital Association	Logistic Regression Adjusted for: cubic polynomials for 3-day moving average temperature and 3-day moving average humidity; an indicator for warm season (May–October) vs cool season (November–April), holiday, and lag holiday (indicating whether one of the previous 2 days was a holiday); and product terms between the warm season indicator and the cubic polynomials for temperature, humidity, and day-of-season.	Lag 0–2 % Increase (95% CI) ^b 3.23% (0.45, 6.10)
†Ye et al. (2016) n = NR Atlanta, GA, U.S. August 1998–December 2008 Cohort	Daily counts of ED visits for asthma among patients living within the five-county Atlanta area	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max Exposure years: 1998–2008	NO ₂ (ppb) Overall, 1-h max Median = 39.3 P25 = 29.5 P75 = 50	ED Visits for Asthma: Individual-level billing records from metropolitan Atlanta hospitals as part of SOPHIA	Poisson Adjusted for: calendar time (spline), max temperature (cubic function), minimum temperature (cubic function), mean dew point temperature (cubic function), day of week, holiday, season, and hospital participation periods	Lag 0–2 % Increase (95% CI) ^b 3.79% (1.67, 5.96)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Hospital Admissions for Asthma						
Anderson et al. (1998) n = 35.1 HA for asthma/day London, U.K. 1987–1992 Time-series	Admissions to all National Health Service hospitals in London. All ages	Fixed site monitor Averaging time: NO ₂ - 24-hour avg Exposure years: 1987–1992	24-hr average Mean = 37.2±12.3 Median = 36 (IQR 12) Min = 14 Max = 182 P5 = 22 P10 = 25 P25 = 30 P75 = 42 P90 = 50 P95 = 58	Asthma hospital admissions: National Health Service Hospital Episode System	Poisson Adjusted for: time trends, season, day of week, public holidays, and influenza epidemics	Lag 0–3 % Increase (95% CI) ^b : 4.14% (1.93, 6.40)
Ko et al. (2007) n = 69,716 Hong Kong, China January 2000–December 2005 Time-series	Hospital admissions to 15 major hospitals in Hong Kong for asthma	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2000–2005	NO ₂ (ppb) Mean = 28.3±10.3 (53.2±19.3 µg/m ³) Median = 27 (IQR 12.5) (50.8 µg/m ³ (IQR 23.6 µg/m ³) Min = 7.07 (13.3 µg/m ³) Max = 79.45 (149.5 µg/m ³) P25 = 21 (40 µg/m ³) P75 = 33.8 (63.6 µg/m ³)	Asthma hospital admissions: Electronic records from the Hong Kong Hospital Authority Head Office	Poisson Adjusted for: calendar time, day of the week, daily mean temperature and humidity, and holidays	Lag 0–3 % Increase (95% CI) ^b : 11.0% (8.1, 13.8)
Son et al. (2013) n = 114.1 HA for asthma/day Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, Ulsan, Jeju, South Korea January 2003–December 2008	Individuals hospitalized due to allergic diseases, asthma, croup, pneumonia, bronchiolitis, respiratory infection (including bronchitis, chronic obstructive pulmonary disease, and	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years:	NO ₂ (ppb) Fall Mean = 24.1±8.8 Spring Mean = 24.6±7.7 Summer Mean = 17.9±5.7	Asthma hospital admissions: data from the National Health Insurance Corporation, Republic of Korea	Bayesian Hierarchical Model Adjusted for: city, day of the week, calendar time (natural cubic spline), temperature (natural cubic spline), humidity (natural cubic spline),	Lag 0 % Increase (95% CI) ^b : 3.63% (0.52, 6.84)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cross-Sectional	pneumonitis), or cardiovascular diseases.	January 2003–December 2008	Winter Mean = 26.8±9.4		and atmospheric pressure (natural cubic spline)	
Strickland et al. (2011) n = 41,741 Atlanta, GA, U.S. Follow-up: 1993–2004 Time-series	Hospital admissions for pediatric asthma	Central site monitor, Spatiotemporal/geospatial model Averaging time: NO ₂ - 1-hour max Exposure years: 1993–2004	NO ₂ (ppb) Mean = 42 IQR = 19.7	Asthma hospital admissions: Electronic records from individual hospitals	Poisson Adjusted for: maximum temperature, day of week, year, month, hospital; calendar time (cubic polynomial), average dew point temperature (cubic polynomial), and average minimum temperature (cubic polynomial)	Lag 0–2 % Increase (95% CI) ^b One central Site Monitor: 6.54% (3.46, 9.71) Unweighted average across monitors: 9.99% (5.51, 14.66) Population-weighted average across monitors: 13.33% (7.55, 19.42)
†Wei et al. (2022) Medicaid n = 1,627,002 Nationwide, U.S. 2000–2012 Case-crossover	Asthma inpatient claims among Medicaid fee-for-service beneficiaries <65 years of age	Ensemble machine learning model LOOCV against central site monitors (r ² = 0.79) Averaging time: NO ₂ - 1-hour max Exposure years: 2000–2012	NO ₂ (ppb) Mean = 17.1±12 Median = 13.9 (IQR 14.5) P5 = 3.9 P25 = 8.3 P75 = 22.8 P95 = 40.8	Asthma hospital admissions: Inpatient claims from the Center for Medicare and Medicaid Services	Logistic Regression Adjusted for: air temperature (penalized cubic splines), relative humidity (penalized cubic splines), and lag -1 exposure (negative exposure control)	% Increase (95% CI) ^b Lag 0: 1.00% (0.38, 1.64) Lag 1: 2.27% (1.64, 2.92) Lag 2: 2.53% (2.02, 3.04) Lag 3: 3.04% (2.40, 3.69) Lag 4: 2.79% (2.15, 3.43) Lag 5: 1.76% (1.26, 2.27) Lag 6: 1.26% (0.75, 1.76) Lag 0–6 7.24% (6.18, 8.32) <100 ppb: 7.24% (6.04, 8.45) <80 ppb: 7.51% (6.31, 8.72) <60 ppb: 8.31% (7.11, 9.54)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						<40 ppb: 13.3% (11.3, 15.3)
						<30 ppb: 14.4% (11.5, 17.4)

List of abbreviations in alphabetical order: AL = Alabama; CI = confidence interval; CMAQ = Community Multiscale Air Quality; df = degrees of freedom; ED = emergency department; ENVISION = Environmental Exposures and Health Across the Nation; GA = Georgia; HA = hospital admissions; ICD = International Classification of Diseases; IQR = interquartile range; LOOCV = leave-one-out cross-validation; MI = Michigan; MO = Missouri; NACRS = National Ambulatory Care Reporting System; NR = not reported; NY = New York; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NO = nitric oxide; P# = #th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; SOPHIA = System for Organizing and Prioritizing Health Information for Asthma; SPARCS = Statewide Planning and Research Cooperative System; TX = Texas; U.K. = United Kingdom; U.S. = United States.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-2 Epidemiologic studies of short-term oxides of nitrogen exposure and respiratory symptoms and asthma medication use

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Gent et al. (2023) n = 117 Massachusetts, CT, U.S. Recruitment: September 2015–April 2019 Intervention: Study years NR Quasi-experimental	Families of children ages 5–11 years with asthma. Eligibility included asthma symptoms and/or medication use during the previous 12 months and no other respiratory co-morbidities or use of steroid medication for conditions other than asthma.	Personal monitor or sampler Averaging time: NO ₂ - 5-week integrated average Exposure years: During treatment period	---	Asthma symptoms: self-reported asthma symptoms	---	---

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Hao et al. (2022) n = 40 Los Angeles, CA; Santa Monica, CA, U.S. February 2019–December 2019 Panel	Children aged 8–16 years with moderate-to-severe asthma from certain asthma clinics in Los Angeles and Santa Monica	Spatiotemporal/geospatial model, Dispersion model Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average, NO - 24-hour average Exposure years: NA	NO ₂ (ppb) Mean = 7.6±4.6 Min = 0.27 Max = 35.9 NO _x (ppb) Mean = 9.5±6.1 Min = 0.27 Max = 36.0 NO (ppb) Mean = 1.8±2.4 Min = 0 Max = 17.3	Rescue inhaler use (number of puffs used): Bluetooth-enabled inhaler sensor	Linear mixed effects Adjusted for: sex, race, Hispanic ethnicity, caretaker's education level, household income, personal and ambient relative humidity and temperature, subject's person-day level time–activity patterns, asthma medication use, outdoor physical activities, exposure to smoking (exposure to secondhand smoking in the home and in utero exposure to maternal smoking), home characteristics (kitchen ventilation, fuel use, presence of pets), and day of the week	NO, Lag 0 RR (95% CI) ^c 1.80 (1.37, 2.35) NO ₂ , Lag 0 RR (95% CI) ^c 1.20 (0.85, 1.68) NO _x , Lag 0 RR (95% CI) ^c 1.61 (1.23, 2.11)
† Su et al. (2022) AIR Louisville n = 1,039 Louisiana, KY, U.S. June 2012–November 2017 Cohort	Adults with a self-reported diagnosis of asthma and a current prescription for a sensor-compatible inhaled medication for asthma.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2012–2017	NO ₂ (ppb) Mean = 11.4±7	Rescue inhaler use (number of puffs used): Bluetooth-enabled inhaler sensor	Poisson Adjusted for: age, gender, self-reported race-ethnicity, asthma status, daily weather conditions, ambient pollen and mould counts, and census-tract-level socioeconomic status	Lag 0 IRR (95% CI) ^b 1.28 (1.25, 1.31)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Su et al. (2024) n = 3,386 California, U.S. 2012–2019 Cohort	Participants with a self-reported diagnosis of asthma or COPD.	Hybrid model Out-of-sample cross validation (r2 = 0.796) Averaging time: NO ₂ - 24-hour average Exposure years: 2012–2019	NO ₂ (ppb) Mean = 8.303±5.22 IQR = 7 Min = 1 Max = 52 P25 = 4.39 P75 = 11.39	Rescue inhaler use (number of puffs used): Bluetooth-enabled inhaler sensor	Poisson Adjusted for: age, gender, baseline and weekly disease status, season, and meteorologic variables	Lag 0 IRR (95% CI) ^b 1.07 (1.05, 1.09)

List of abbreviations in alphabetical order: CA = California; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CT = Connecticut; IQR = interquartile range; IRR = incidence rate ratio; KY = Kentucky; NA = not applicable; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NO = nitric oxide; NR = not reported; P# = #th percentile; ppb = parts per billion; RR = relative risk; U.S. = United States.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-3 Animal toxicological studies of airway responsiveness in models of asthma

Study Details and Population	Exposure Details	Endpoints Examined*
† Yue et al. (2017) Mouse (BALB/c) gestational exposure (GD 0 to GD 20), males and females n = 3–10/group	Whole body inhalation with room air controls 2,500 ppb (2.5ppm) NO ₂ , 5 hr/d for 20 d	10 wk after exposure (OVA-sensitized mice) • AHR (↑)
† Yue et al. (2018) Mouse (BALB/c) gestational exposure (GD 0 to GD 21), sex not reported n = 3–11/group	Whole body inhalation with room air controls 2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 21 d	9 wk after exposure (sensitized mice) • AHR (↑)

List of abbreviations in alphabetical order: AHR = airway hyperreactivity; BAL = bronchioalveolar lavage; d = day; GD = gestational day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: ↑ = at least one experimental group had a statistically significant increase.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-4 Epidemiologic studies of short-term oxides of nitrogen exposure and lung function and pulmonary inflammation in populations with asthma

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Delfino et al. (2008) n = 53 Los Angeles, CA, U.S. Enrollment: 2003–2004 Follow-up: 10 days Cohort	Schoolchildren with asthma who were aged 9–18 years. Recruited based on referral by local school district nurses	Personal monitor or sampler, Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2003–2004	NO ₂ (ppb) Central site Mean = 25±3 Median = 25.3 (IQR 6.3) Min = 19.9 Max = 29.2 Personal exposure Mean = 28.6±13.2 Median = 26.7 (IQR 16.8) Min = 2.8 Max = 105.7	Home Spirometry	Linear Mixed Model Adjusted for: previous FEV ₁ measurement, personal temperature, personal relative humidity, cumulative inhaler use on the previous day, and inhaler use during the last night	% Predicted FEV ₁ (95% CI) ^b -2.08 (-3.37, -0.80)
Greenwald et al. (2013) n = 38 El Paso, TX, U.S. Enrollment: March 2010 Follow-up: 13 weeks Panel	Elementary school students who were 6–12 years of age, in good health, and had physician-diagnosed asthma, and lived in a non-smoking household	Fixed site monitor, Central site monitor Averaging time: NO ₂ 96-hr average Exposure years: 2010	NO ₂ (ppb) School A – Indoor Mean = 6.2±2.6 Median (IQR) = 5.9 (3.1) School A – Outdoor Mean = 6.5±3.2 Median (IQR) = 6.2 (3.0)	Supervised Spirometry	Linear Mixed Model Adjusted for: school, ambient temperature and relative humidity, and indoor NO levels	% Predicted FEV ₁ (95% CI) ^c Indoor NO ₂ : -14.00 (-32.00, 7.30) Outdoor NO ₂ : -17.00 (-32.00, 0.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			School B – Indoor Mean = 16.7±3.3 Median (IQR) = 16.2 (4.8) School B – Outdoor Mean = 17.5±6.1 Median (IQR) = 16.6 (4.0)			
Holguin et al. (2007) n = 194 Juarez, Mexico Enrollment: 2001–2002 Follow-up: Over 4 months Cohort	Children ages 6–12 years with and without physician-diagnosed asthma	Fixed site monitor Averaging time: NO ₂ 2-week average Exposure years: 2001–2002	NO ₂ (ppb) Mean = 18.2±9.6	Supervised Spirometry	Linear Mixed Model Adjusted for: sex, age, body mass index, day of the week, season, total number of years of maternal education, total number of years of paternal education, and passive smoking	% Predicted FEV ₁ (95% CI) ^b -2.40 (-5.07, 0.27)
Martins et al. (2012) n = 51 Viseu, Portugal Enrollment: 2006 Follow-up: 2006–2007 Panel	Children in primary schools who had suffered from parent reported wheezing in previous 12 months	Time-weighted exposure estimates based indoor and outdoor concentrations at children's schools and homes measured via personal samplers and fixed site monitors	NO ₂ (ppb) School - Outdoor Range of means across visits = 6.4–11.2 Indoor concentrations at schools and homes	Supervised Spirometry	Generalized Estimating Equation Adjusted for: age, sex, parental smoking, parental education, atopic status, time of the visit, average temperature, relative humidity, height, weight, older siblings, mould or dampness at	% Predicted FEV ₁ : -23.75 (-44.65, -2.84) % Predicted FEF _{25-75%} : -38.39 (-70.77, -6.00) % Predicted FEV ₁ /FVC: -10.50 (-21.51, 0.51) % Predicted post-bronchodilator FEV ₁ :

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		Averaging time: weekly avg Exposure years: 2006–2007	were undetectable		home, fireplace at home, and presence of pets at home	17.76 (3.42, 32.10)
† Eckel et al. (2016)	Participants were children from a CHS cohort originally recruited in 2002–2003 from kindergarten or first-grade classrooms in southern California. Participants were aged between 12–15 years old.	Other Method validation NR Averaging time: NO - 1-hour max Exposure years: 2010	NO (ppb) 7:00-9:59 h Median = 3.3 Min = 0 Max = 58.5 P5 = 0.3 P25 = 1.4 P75 = 6.3 P95 = 14.1 10:00-11:59 h Median = 1.9 Min = 0 Max = 41.4 P5 = 0.1 P25 = 0.6 P75 = 4.4 P95 = 18.4 12:00-16:07 h Median = 1 Min = 0 Max = 15.8 P5 = 0 P25 = 0.4 P75 = 2.2 P95 = 4.5 Overall Median = 1.9	Supervised Spirometry	Linear Regression Adjusted for: age, sex, race/ethnicity, rhinitis history, ever report of doctor-diagnosed asthma, use of asthma medications in the past 12 months, secondhand tobacco smoke exposure, highest attained parental education, time of FeNO test, FeNO analyser and CHS community	Percent Difference (95% CI) ^c DawNO: 0.20 (-4.80, 4.60) FeNO ₃₀₀ : 6.50 (0.30, 13.10) FeNO ₅₀ : 2.80 (-3.30, 9.30) J'awNO: 4.00 (-2.80, 11.30) Ppb change (95% CI) ^c CANO: 0.10 (0.04, 0.16)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 0 Max = 58.5 P5 = 0.1 P25 = 0.7 P75 = 4.3 P95 = 13.4			
† Hao et al. (2022) n = 40 Los Angeles, CA; Santa Monica, CA, U.S. February 2019–December 2019 Panel	Children aged 8–16 years with moderate-to-severe asthma from certain asthma clinics in Los Angeles and Santa Monica	Spatiotemporal/geospatial model, Dispersion model Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average, NO - 24-hour average Exposure years: NA	NO ₂ (ppb) Mean = 7.6±4.6 Min = 0.27 Max = 35.9 NO _x (ppb) Mean = 9.5±6.1 Min = 0.27 Max = 36.0 NO (ppb) Mean = 1.8±2.4 Min = 0 Max = 17.3	Home Spirometry	Linear Mixed Model Adjusted for: sex, race, Hispanic ethnicity, caretaker's education level, household income, personal and ambient relative humidity and temperature, subject's person-day-level-time activity patterns, asthma medication use, outdoor physical activities, exposure to smoking (exposure to secondhand smoking in the home and in utero exposure to maternal smoking), home characteristics (kitchen ventilation, fuel use, presence of pets), and day of the week	Ambient NO ₂ % Predicted FEV ₁ : -6.61 (-29.22, 16.00) % Predicted PEF: 12.65 (-9.04, 34.35) Traffic-Related NO ₂ % Predicted FEV ₁ : -7.32 (-17.32, 2.68) % Predicted PEF: -7.18 (-16.39, 2.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Ierodiakonou et al. (2015) Childhood Asthma Management Program (CAMP) n = 1,003 Boston, MA; Albuquerque, NM; Baltimore, MD; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO, U.S., and Toronto, Ontario, Canada Enrollment: Study years NR Follow-up: 4 years Cohort	Children diagnosed with asthma 5–12 years of age	Fixed site monitor Averaging time: NO ₂ 4-month average Exposure years: 1993–1999	NO ₂ (ppb) Median = 22 (IQR 13) P10 = 11 P25 = 26 P75 = 28 P90 = 35	Supervised Spirometry	Linear Mixed Model Adjusted for: city, season (sine and cosine functions of time), gender, ethnicity, in utero smoking exposure, annual family income, and treatment group	Lag 0 % Predicted pre-bronchodilator FEV ₁ : -0.14 (-0.49, 0.21) % Predicted pre-bronchodilator FVC: -0.01 (-0.29, 0.27) Lag 0–6 % Predicted pre-bronchodilator FEV ₁ : -0.11 (-0.66, 0.43) % Predicted pre-bronchodilator FVC: 0.06 (-0.36, 0.47)

List of abbreviations in alphabetical order: CA = California; CAMP = Childhood Asthma Management Program; CANO = alveolar nitric oxide concentration; CHS = Children's Health Study; CI = confidence interval; CO = Colorado; DawNO = airway wall nitric oxide flux; FeNO = fractional exhaled nitric oxide; FEF_{25-75%} = forced expiratory flow at 25-75% of pulmonary volume; FEV₁ = forced expiratory volume in 1 second; FEV₁/FVC = ratio of FEV₁ to forced vital capacity; FVC = forced vital capacity; IQR = interquartile range; J_{aw}NO = maximum airway wall nitric oxide flux; MA = Massachusetts; MD = Maryland; MO = Missouri; NM = New Mexico; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NO = nitric oxide; NR = not reported; P# = #th percentile; PEF = peak expiratory flow; ppb = parts per billion; RR = relative risk; TX = Texas; U.S. = United States; WA = Washington.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-5 Animal toxicological studies of pulmonary inflammation and oxidative stress in models of asthma

Study Details and Population	Exposure Details	Endpoints Examined*
† Yue et al. (2017)	Whole body inhalation with room air controls	1 d–10 wk after exposure
Mouse (BALB/c)		IL-4/13 promoter methylation (↓)
gestational exposure (GD 0 to GD 20), males and females	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	10 wk after exposure
n = 3–20/group		- OVA-specific IgE (↑) - Total IgE (NS)
		10 wk after exposure (sensitized mice)
		- ELISA – IFNγ (↓) - ELISA – Th2 cytokines (↑) - FACS – inflammatory cells (↑) - IHC (More profound inflammatory cell infiltration, mucous cell metaplasia, and collagen deposition)
† Yue et al. (2018)	Whole body inhalation with room air controls	9 wk after exposure
Mouse (BALB/c)		- BAL – inflammatory cells (↑) - ELISA and Western blot – Th1 signaling (↓)
gestational exposure (GD 0 to GD 21), sex not reported	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 21 d	- ELISA and Western blot – Th2 signaling (↑) - IHC (more dramatic airway remodeling, inflammation, and mucus production)
n = 3–11/group		OVA specific IgE (↑)
† de Broucker et al. (2015)	Whole body inhalation with filtered air controls	2 hr after exposure (d 0–22)
Rat (Brown Norway)		8-Isoprostane (↑) - BAL % neutrophils (NS) - EBC volume (NS)
adult, males	2,000 ppb (2 ppm) NO ₂ , 6 hr/d for 22 d	2 hr after exposure (d 22)
n = 6/group		Total BAL cells (NS)

List of abbreviations in alphabetical order: BAL = bronchioalveolar lavage; d = day; EBC = exhaled breath condensate; ELISA = enzyme-linked immunosorbent assay; FACS = fluorescence-activated cell sorting; GD = gestational day; hr = hour; IHC = immunohistochemistry; n = sample size; NO₂ = nitrogen dioxide; OVA = ovalbumin; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-6 Epidemiologic studies of short-term oxides of nitrogen exposure and emergency department visits and hospital admissions for COPD

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Faustini et al. (2013) n = 100,690 hospitalizations Rome, Turin, Bologna, Florence, Milan, Palermo, Italy 2001–2005 Case-crossover	Emergency hospitalizations of individuals 35 years and older, who were discharged from 1 of 6 hospitals in their city	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2005	NO ₂ (ppb) Min = 24.5 (46.1 ug/m ³) Max = 35 (66 µg/m ³)	Hospital admissions for COPD	Logistic Regression Adjusted for: apparent temperature and low temperature (penalized splines), barometric pressure (penalized splines), temporary population decreases in the summer and during holidays, influenza epidemics and long-term trends and seasonality (three-way interaction of year, month, and day of the week)	Lag 0–1 OR (95% CI) ^b 1.04 (0.99, 1.08)
Peel et al. (2005) n = 4,407,535 visits Atlanta, GA, U.S. Individuals who have reported to one of the hospitals in the Atlanta metropolitan statistical area Time-series	Individuals who have reported to one of the hospitals in the Atlanta metropolitan statistical area	Central site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1993–2000	NO ₂ (ppb) Mean = 45.9±17.3 P10 = 25 P90 = 68	ED visits for COPD: electronic records from individual hospitals	Poisson Adjusted for: temporal trends (cubic splines with monthly knots), season indicator variables, daily average temperature and dew point (cubic splines), and indicator variables for day of week, federal holidays, and hospital entry and exit.	Lag 0–2 RR (95% CI) ^b 1.04 (1.01, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Stieb et al. (2009) n = nearly 400,000 ED visits Canada 1990s and early 2000s Time-series	Administrative ED visits	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–2003	NO ₂ (ppb) Montreal Mean = 19.5±7.6 P25 = 14.0 P75 = 23.5 Ottawa Mean = 18.8±8.8 P25 = 12.7 P75 = 24.0 Edmonton Mean = 21.9±9.4 P25 = 14.7 P75 = 27.6 Saint John Mean = 9.3±5.5 P25 = 5.1 P75 = 12.3 Halifax Mean = 17.5±5.8 P25 = 13.6 P75 = 21.0 Toronto	ED visits for COPD: electronic records from individual hospitals	Poisson Adjusted for: temporal trends (natural splines), holidays, temperature and relative humidity (natural splines), and time of day	Lag 0 RR (95% CI) ^b 1.00 (0.94, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 22.7±7.6 P25 = 17.6 P75 = 27.5 Vancouver Mean = 18.7±7.4 P25 = 13.6 P75 = 19.7			
† Krall et al. (2018) n = 76 cases/day Atlanta, GA; St. Louis, MO; Dallas, TX; Pittsburgh, Pennsylvania; Birmingham, AL, U.S. 2002–2008 Time-series	ED visits using electronic billing data from the 20-county Atlanta, GA metropolitan area; the 7-county Birmingham, AL metropolitan area, the 12-county Dallas-Fort Worth metropolitan area, the 3-county Pittsburgh area, and the 16-county St. Louis metropolitan area.	Hybrid model Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Atlanta Mean = 21.6±7 Birmingham Mean = 13.2±4.3 Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5 Birmingham Mean = 24.5±13.8	ED visits for COPD: electronic billing data	Bayesian Hierarchical Model Adjusted for: weekday, season, holidays, meteorology (cubic splines of lag 0–2 and lag 3–7 temperature and dew-point temperature), temporal trends (cubic splines of time with 1 df per month), and the hospitals reporting data for each day.	Lag 0–7 NO ₂ RR (95% CI) ^b 1.10 (1.01, 1.19) NO _x RR (95% CI) ^b 1.04 (0.94, 1.14)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Dallas Mean = 41.4±32.2			
			Pittsburgh Mean = 56±35.8			
			St. Louis Mean = 51.3±30.9			
† Szyszkowicz et al. (2018) n = COPD: 183,544 URI: 717,676 Algoma, Ontario, Halton, Ontario, Hamilton, Ontario, Ottawa, Ontario, Peel, Ontario, Toronto, Ontario, York, Ontario, Middlesex, Ontario, Essex, Ontario, Canada April 2004–December 2011 Case-crossover	ED visits for respiratory diseases retrieved from the National Ambulatory Care Reporting System (NACRS)	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2011	NO ₂ (ppb) Algoma Mean = 5.1 IQR = 4 Min = 0 Max = 24 Essex Mean = 15.6 IQR = 8.1 Min = 2.4 Max = 55.5 Halton Mean = 12.9 IQR = 7.7 Min = 1 Max = 51.2 Hamilton Mean = 13.9 IQR = 9.5 Min = 1.7 Max = 63 Middlesex Mean = 10.9	ED visits for COPD: National Ambulatory Care Reporting System (NACRS) database maintained by the Canadian Institute for Health Information (CIHI)	Logistic Regression Adjusted for: temperature and relative humidity (natural splines) and an indicator for days with influenza.	Lag 2 OR (95% CI) ^b Females, Warm Season: 1.00 (0.97, 1.03) Males, Warm Season: 1.03 (0.99, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			IQR = 7 Min = 0 Max = 51			
			Ottawa Mean = 8.7 IQR = 7 Min = 1 Max = 47			
			Peel Mean = 13.2 IQR = 9.5 Min = 2 Max = 54			
			Toronto Mean = 18.5 IQR = 9.4 Min = 4.5 Max = 62.1			
			York Mean = 8.2 IQR = 7 Min = 0 Max = 47			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Weichenthal et al. (2016) n = Asthma: 128,731 COPD: 298,751 Total Respiratory: 1,181,961 Toronto; Hamilton; Barrie; Chatham; Cornwall; Kingston; Kitchener; Oakville; Oshawa; Petawawa; Peterborough; Port Stanley; Sarnia; St. Catharines; Thunder Bay, Ontario, Canada. 2004–2011 Case-crossover	ED visits for respiratory diseases retrieved from the National Ambulatory Care Reporting System (NACRS)	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2011	NO ₂ (ppb) Mean = 12.9±7.79 Median = 11.5 (IQR 10.6) Max = 65	ED visits for COPD: National Ambulatory Care Reporting System (NACRS) database maintained by the Canadian Institute for Health Information (CIHI)	Logistic Regression Adjusted for: 3-day mean ambient temperature and relative humidity (cubic splines) and daily counts of emergency room visits for influenza.	Lag 0 OR (95% CI) ^b 1.01 (1.00, 1.03)

List of abbreviations in alphabetical order: AL = Alabama; CI = confidence interval; CIHI = Canadian Institute for Health Information; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; ED = emergency department; GA = Georgia; IQR = interquartile range; MO = Missouri; NACRS = National Ambulatory Care Reporting System; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NO = nitric oxide; NR = not reported; OR = odds ratio; P# = #th percentile; ppb = parts per billion; RR = relative risk; TX = Texas; U.S. = United States.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-7 Epidemiologic studies of short-term oxides of nitrogen exposure and respiratory symptoms and COPD medication use

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Aglan et al. (2023) Study of Pollution and COPD Exacerbation (SPACE) n = 30 Boston, MA, U.S. February 2017–January 2019 Panel	Former smokers with COPD. Participants with history of lung cancer or other lung diseases were not eligible for participation	Personal monitor or sampler, Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2017–2019	NO ₂ (ppb) Community-Level Median = 7.2 (IQR 4.7) Personal Median = 6.7 (IQR 5.3)	Respiratory symptoms: self-reported	Logistic Regression Adjusted for: previous-day temperature, humidity, season, age, sex, race, height, weight, total pack-year smoking history, and education	Lag 0 OR (95% CI) ^b Worsening of breathing symptoms Personal monitor: 0.47 (0.17, 1.28) Central site: 1.18 (0.52, 2.66) Worsening of bronchitic symptoms - Personal monitor: 0.64 (0.20, 2.08) Central site: 2.58 (1.00, 6.66)
†Devries et al. (2016) N = 168 Worcester County, MA, U.S. January 2011–March 2012 Case-crossover	Included COPD patients. 75 were subsequently excluded since they did not have at least one exacerbation over the course of the study period and three were excluded because they were hospitalized or in a long-term care facility within the seven days prior to completing one of their exposure questionnaires.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2011-2012	NO ₂ (ppb) Overall Mean = 11±5 Min = 2.79 Max = 40	Respiratory symptoms: self-reported	Logistic Regression Adjusted for: meteorological variables (i.e., temperature and humidity); self-reported hours spent outdoors, exercise, and respiratory and non-respiratory infections; and season	Lag 1–7 OR (95% CI) ^c Worsening of respiratory symptoms 1.06 (0.98, 1.16) +SO ₂ : 0.96 (0.88, 1.06) +PM _{2.5} : 1.17 (1.05, 1.30)
†Evangelopoulos et al. (2021) n = 115	Patients who were former smokers and diagnosed with COPD	Personal monitor or sampler	NO ₂ (ppb) Mean = 14±6	COPD exacerbation: pulmonologist-	Logistic Regression Adjusted for: age, sex,	Lag 0 OR (95% CI) ^b

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
London, U.K. Study years NR (follow-up over 128 days) Panel	were recruited through the Clinical Practice Research Datalink	Averaging time: NO ₂ - 24-hour average, NO - 24-hour average Exposure years: NA	Median = 12 (IQR 5) P25 = 10 P75 = 15 NO (ppb) Mean = 9±11 Median = 5 (IQR 7) P25 = 3 P75 = 10	reviewed self-reported symptoms diary	COPD severity, Index of Multiple Deprivation, inhaled corticosteroid medication use, time (cubic spline), and temperature (natural spline)	NO 1.41 (1.22, 1.63) +PM _{2.5} : 1.36 (1.17, 1.59) +PM ₁₀ : 1.35 (1.16, 1.57) +NO ₂ : 1.33 (1.15, 1.54) +CO: 1.34 (1.15, 1.57) +O ₃ : 1.42 (1.23, 1.64) NO ₂ 1.52 (1.26, 1.85) +PM _{2.5} : 1.50 (1.24, 1.83) +PM ₁₀ : 1.50 (1.24, 1.82) +NO: 1.39 (1.14, 1.70) +CO: 1.43 (1.18, 1.74) +O ₃ : 1.54 (1.27, 1.86)
† Magzamen et al. (2018) VA Puget Sound Health Care System N = 35 Seattle, WA; Tacoma, WA, U.S. December 2011–October 2013 Panel	Eligibility criteria included: (1) COPD diagnosis, (2) forced expiratory volume in 1 s (FEV ₁)/forced vital capacity (FVC) <0.70 with a FEV ₁ % predicted <80%, (3) use of an albuterol SABA inhaler, (4) former smoker with >10 pack year smoking history and no current exposure to secondhand smoke, (5) age >40 years, (6) a resident of King or	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2011–2013	NO ₂ (ppb) Overall Median = 12 Min = 1.3 Max = 36.3 P25 = 8.08 P75 = 16.29	Rescue inhaler use (number of puffs used): Bluetooth-enabled inhaler sensor	Poisson Adjusted for: supplemental oxygen, FEV ₁ % predicted, long-acting anticholinergic use, mMRC Dyspnea Scale score, and winter season	Lag 0 RR (95% CI) ^b 1.10 (1.01, 1.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	Pierce Counties in Washington State (regions with air pollution monitors) and (7) no exacerbations in the 4 weeks prior to enrolment. Exclusion criteria included: (1) clinical diagnosis of asthma, (2) subjects needing assistance in walking and (3) a modified Medical Research Council (mMRC) Dyspnea Scale score of 4.					
† Pfeffer et al. (2019) n = 440 London, U.K. 1996–2015 Time-series	Patients (mean age 68 years) with COPD living in London	Central site monitor Averaging time: NO _x - 24-hour average Exposure years: 1996–2015	NO _x (µg/m ³) Median = 48.5 (IQR 46.5) P25 = 31.6 P75 = 78.1	COPD exacerbation: self-reported worsening of respiratory symptoms. The presence of cold symptoms was used a marker of a “viral-type” exacerbation, and symptoms of increased sputum volume or purulence were used as markers for “bacterial-type” exacerbation	Logistic Regression Adjusted for: lagged temperature, seasonality, and longitudinal trend	Lag 2–4 OR (95% CI) ^c All COPD Exacerbation: 1.00 (0.99, 1.01) Bacterial-type COPD Exacerbation: 1.00 (0.99, 1.02) Viral-type COPD Exacerbation: 1.02 (1.01, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Ross et al. (2023) Canadian Cohort Obstructive Lung Disease (CanCOLD) N = 449 Nationwide, Canada July 1, 2012–December 31, 2019 Case-crossover	Subjects in this study were selected if they had COPD diagnosed by spirometry and if they also experienced at least one exacerbation subsequent to COPD diagnosis.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2012–2019	NO ₂ (ppb) Cool Median = 13.78 (IQR 10.27) P25 = 8.42 P75 = 18.69 Warm Median = 9.27 (IQR 7.3) P25 = 5.55 P75 = 12.84	COPD exacerbation: Telephone interview on symptom exacerbation (increased dyspnea, sputum volume, or purulence lasting 48+ hours)	Generalized Estimating Equations Adjusted for: within participant event clusters and city	Lag 0–6 OR (95% CI) ^b COPD Exacerbation - Cool Season: 1.33 (0.71, 2.49) COPD Exacerbation - Warm Season: 0.80 (0.36, 1.76)
† Su et al. (2024) n = 3,386 California, U.S. 2012–2019 Cohort	Participants with a self-reported diagnosis of asthma or COPD.	Hybrid model Out-of-sample cross validation (r ² = 0.796) Averaging time: NO ₂ - 24-hour average Exposure years: 2012–2019	NO ₂ (ppb) Mean = 8.303±5.22 IQR = 7 Min = 1 Max = 52 P25 = 4.39 P75 = 11.39	Rescue inhaler use (number of puffs used): Bluetooth-enabled inhaler sensor	Poisson Adjusted for: sex, age, controller medication use, baseline status, disease type, weekly SABA use, daily maximum temperature and maximum relative humidity	Lag 0 IRR (95% CI) ^b 1.07 (1.05, 1.09)

List of abbreviations in alphabetical order: CanCOLD = Canadian Cohort Obstructive Lung Disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; IRR = incidence rate ratio; MA = Massachusetts; mMRC = modified Medical Research Council; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NO = nitric oxide; NR = not reported; OR = odds ratio; P# = #th percentile; ppb = parts per billion; RR = relative risk; SABA = short-acting beta agonist; SPACE = Study of Pollution and COPD Exacerbation; U.K. = United Kingdom; U.S. = United States; VA = Veterans Affairs; WA = Washington.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-8 Epidemiologic studies of short-term oxides of nitrogen exposure and lung function and pulmonary inflammation in populations with COPD

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Chen et al. (2023) Study of Pollution and COPD Exacerbation (SPACE), Beth Israel Deaconess Medical Center (BIDMC) N = 30 Boston, MA, U.S. Enrollment: February 24, 2017–January 17, 2019 Follow-up: 4 non-consecutive months Cohort	To be eligible, study participants were required to be former smokers without any active smoking for at least 6 months prior to enrollment, have a ≥10 pack-year smoking history, and have a home address within 50km of the Harvard air pollution supersite in Boston, MA, and a clinical diagnosis of COPD with at least moderate airflow obstruction, defined as forced expiratory volume in 1 second (FEV ₁)/forced vital capacity (FVC) ratio of <0.70 and FEV ₁ <80% predicted, using National Health and Nutrition Examination Survey III prediction equations. Participants with a history of lung cancer, interstitial lung	Personal monitor or sampler, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2017–2019	NO ₂ (ppb) Overall Median = 6.8 (IQR 5.4)	Home Spirometry	Linear Mixed Effects Adjusted for: age, sex, body mass index, season, humidity, and temperature	ΔFEV ₁ (mL) (95% CI) ^b Physical Activity T1 (<1,988 steps): -105.56 (-152.04, -59.07) PA T2 (1,988 to 4,168 steps): -48.89 (-94.26, -3.52) PA T3 (>4,168 steps): -5.93 (-68.15, 56.30)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	diseases, or bronchiectasis were ineligible to participate.					
† Evangelopoulos et al. (2021) n = 115 London, U.K. Study years NR (follow-up over 128 days) Panel	Patients who were former smokers and diagnosed with COPD were recruited through the Clinical Practice Research Datalink	Personal monitor or sampler Averaging time: 24-hour average Exposure years: NA	NO ₂ (ppb) Mean = 14±6 Median = 12 (IQR 5) P25 = 10 P75 = 15 NO (ppb) Mean = 9±11 Median = 5 (IQR 7) P25 = 3 P75 = 10	Home Spirometry	Linear Regression Adjusted for: age, sex, COPD severity, Index of Multiple Deprivation, inhaled corticosteroid medication use, time (cubic spline), and temperature (natural spline)	ΔPEF (L/min) (95% CI) ^b NO Winter: -0.12 (-1.16, 0.92) Summer: -0.54 (-3.42, 2.34) Fall: 0.04 (-1.68, 1.76) Spring: 0.68 (-2.73, 4.09) NO ₂ Winter: 1.26 (-1.84, 4.36) Summer: 1.18 (-3.13, 5.49) Fall: -2.30 (-7.36, 2.76) Spring: -2.38 (-4.97, 0.21)
† McHugh et al. (2023) n = 144 Boston, MA, U.S. Recruitment: 2012–2017 Panel	COPD patients at the VA Boston Healthcare System who were age 40 years or older, were former smokers who had smoked at least 10 pack-years of cigarettes and had a FEV ₁ /FVC < 0.70 on screening postbronchodilator spirometry or emphysema reported on a clinical CT scan report.	Personal monitor or sampler, Central site monitor Averaging time: NO ₂ - 24-hour average, Other, NO ₂ – 1-week Exposure years: NA	NO ₂ (ppb) Indoor Mean = 9.4±8.1 Median = 6.8 (IQR 6.8) P25 = 4.4 P75 = 11.2 Outdoor Mean = 13.3±3.2 Median = 13 (IQR 4.4) P25 = 10.9 P75 = 15.3	Supervised Spirometry	Linear Mixed Effects Adjusted for: race/ethnicity, gender, history of diabetes, heart disease, statin use, age, BMI, respiratory illness in the past 2 weeks, season, average ambient temperature, and relative humidity Adjusted for: NA	β (mL) (95% CI) ^c Pre-bronchodilator ΔFEV ₁ : -3.96 (-26.31, 18.49) ΔFVC: -9.77 (-44.14, 24.56) ΔFEV ₁ /FVC: -0.21 (-4.58, 4.48) ΔFEV ₁ ; FEV ₁ < 50%: -17.36 (-58.35, 23.60) ΔFEV ₁ ; FEV ₁ ≥50%: -1.64 (-24.80, 21.57) ΔFVC; FEV ₁ < 50%: -28.22 (-91.49, 35.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Nurhussien et al. (2022) Study of Pollution and COPD	Former smokers with moderate to severe COPD. Participants had	Personal monitor or sampler, Central site	NO ₂ (ppb) Community-level	Home Spirometry	Linear Mixed Effects Adjusted for:	ΔFVC; FEV ₁ ≥50%: -6.22 (-42.16, 29.71)
						ΔFEV ₁ /FVC; FEV ₁ < 50%: 2.25 (-6.42, 10.93)
						ΔFEV ₁ /FVC; FEV ₁ ≥50%: -0.82 (-5.74, 4.07)
						Post-bronchodilator ΔFEV ₁ : 2.08 (-19.13, 23.27)
						ΔFVC: -5.19 (-37.85, 27.43) ΔFEV ₁ /FVC: 0.99 (-3.69, 5.64)
						ΔFEV ₁ ; FEV ₁ < 50%: -5.13 (-45.53, 32.24)
						ΔFEV ₁ ; FEV ₁ ≥50%: 2.41 (-18.72, 23.57)
						ΔFVC; FEV ₁ < 50%: -27.67 (-88.55, 33.30)
						ΔFVC; FEV ₁ ≥50%: -1.16 (-32.92, 31.72)
						ΔFEV ₁ /FVC; FEV ₁ < 50%: 3.53 (-5.26, 12.30)
						ΔFEV ₁ /FVC; FEV ₁ ≥50%: 0.30 (-4.51, 5.14)
						β (mL) (95% CI) ^b Personal monitor

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Exacerbation (SPACE) n = 30 Boston, MA, U.S. February 2017–January 2019 Panel	home address near air pollution monitor site	monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2017–2019	Median = 7.1 (IQR 4.6) P25 = 5.1 P75 = 9.7 Personal Median = 6.8 (IQR 5.1) P25 = 3.8 P75 = 8.9		temperature, relative humidity, age, sex, race, height, weight, total pack-year smoking history, season, income, and education	ΔFEV ₁ : -42.64 (-70.38, -14.91) ΔFVC: -67.92 (-120.38, -15.47) ΔFEV ₁ , low EOS: 16.98 (-15.47, 49.43) ΔFEV ₁ , high EOS: -35.85 (-64.53, -7.17) Fixed site monitor ΔFEV ₁ : -11.70 (-32.83, 9.43) ΔFVC: -32.45 (-72.83, 7.92)
† Sinharay et al. (2017) n = 119 London, U.K. October 2012–June 2014 Case-crossover	Participants aged 60 years and older with stable ischemic heart disease or COPD and age-matched healthy volunteers	Central site monitor Averaging time: NO ₂ 2-hour average Exposure years: 2012–2014	Concentrations presented graphically	Supervised Spirometry	Linear regression - mixed effects Adjusted for: participant group, location, ambient temperature, and relative humidity	Δ % predicted FEV ₁ : -4.85 (-9.03, -0.67) Δ % predicted FVC: -4.99 (-8.27, -1.70)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Wu et al. (2016) n = 23 Beijing, China Enrollment: September 2013– December 2013 Follow-up: ~90 days Panel	Patients (mean age 73 yrs) physician-diagnosed with COPD	Central site monitor Averaging time: NO ₂ - 24-hour average, Other, NO ₂ weekly average	NO ₂ (ppb) Min = 2.9 (5.4 µg/m ³) Max = 101.9 (191.8 µg/m ³)	Exhaled breath samples were collected by a trained technician at participants' residences according to the ATS/ERS guidelines	Linear Mixed Effects Adjusted for: age, gender, BMI, long-term temporal trend, day-of-week variable, daily timing (morning/afternoon) of the exhaled breath measurement, temperature, and relative humidity	β (% Change) (95% CI) ^b FeNO: -4.13 (-12.24, 3.98) FeNO: -1.34 (-7.54, 4.85) FeNO: 1.25 (-4.90, 7.39) FeH ₂ S: -4.90 (-12.29, 2.50) FeH ₂ S: -0.48 (-7.34, 6.38) FeNO: -6.72 (-13.92, 0.48) FeH ₂ S: -2.78 (-10.46, 4.90) FeH ₂ S: 4.13 (-2.11, 10.37)

List of abbreviations in alphabetical order: ATS = American Thoracic Society; BIDMC = Beth Israel Deaconess Medical Center; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EOS = eosinophils; ERS = European Respiratory Society; FeH₂S = fractional exhaled hydrogen sulfide; FeNO = fractional exhaled nitric oxide; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; MA = Massachusetts; NO₂ = nitrogen dioxide; NO = nitric oxide; P# = #th percentile; PA = physical activity; ppb = parts per billion; SPACE = Study of Pollution and COPD Exacerbation; U.K. = United Kingdom; U.S. = United States; VA = Veterans Affairs.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-9 Epidemiologic studies of short-term oxides of nitrogen exposure and emergency department visits and hospital admissions for respiratory infection

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Krall et al. (2018)	ED visits using electronic billing data from the 20-county Atlanta, GA metropolitan area; the 7-county Birmingham, AL metropolitan area, the 12-county Dallas-Fort Worth metropolitan area, the 3-county Pittsburgh area, and the 16-county St. Louis metropolitan area	Hybrid model Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Atlanta Mean = 21.6±7 Birmingham Mean = 13.2±4.3 Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5 Birmingham Mean = 24.5±13.8 Dallas Mean = 41.4±32.2 Pittsburgh Mean = 56±35.8 St. Louis Mean = 51.3±30.9	ED visits using electronic billing data	Bayesian Hierarchical Model Adjusted for: Weekday, season, holidays, meteorology (cubic splines of lag 0–2 and lag 3–7 temperature and dew-point temperature), temporal trends (cubic splines of time with 1 df per month), and the hospitals reporting data for each day.	Lag 0–7 RR (95% CI) ^b NO ₂ ED Visits for Pneumonia: 1.08 (1.01, 1.14) ED Visits for URI: 1.12 (1.06, 1.17) NO _x ED Visits for Pneumonia: 1.04 (0.95, 1.14) ED Visits for URI: 1.06 (0.97, 1.15)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Pirozzi et al. (2017) n = 4,336 Utah, U.S. December 2009–November 2012 Case-crossover	Patients presenting to emergency departments with pneumonia. Excluded patients with immunocompromised conditions, subsequent episodes of pneumonia for each patient in following 12-month period	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2009–2012	NO ₂ (ppb) Cold Season Median = 22.0 Warm Season Median = 11.8	ED Visits for Pneumonia: Radiographically confirmed	Logistic Regression Adjusted for: Daily average temperature, humidity, and holidays	OR (95% CI) ^b Lag 1: 0.98 (0.90, 1.06) Lag 2: 1.00 (0.94, 1.06) Lag 3: 1.02 (0.98, 1.06) Lag 5: 1.04 (0.99, 1.09) Lag 6: 1.06 (1.00, 1.12) Lag 7: 1.08 (1.00, 1.17)
†Reilly et al. (2019) N = 996 ARDS n = 243 No ARDs n = 753 Pennsylvania, U.S. 2005–2015 Cohort	Patients were included if they presented within 24-hours of injury, had an age greater than 13, and an injury severity score greater than 15. Patients were excluded if they suffered isolated severe head injury or died or were discharged within 24 hours of presentation.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - 1- and 5-year periods Exposure years: 2005–2015	NO ₂ (ppb) Overall Median = 18.1 (IQR 4) P25 = 15.9 P75 = 19.9	Acute Respiratory Distress Syndrome: Chest radiographs	Logistic Regression Adjusted for: Age, sex, self or surrogate reported race, smoking history, alcohol use, severity of illness based on the Acute Physiology and Chronic Health Evaluation (APACHE) III score, distance to the hospital, month of admission, and median household income of the patients' home addresses' 5-digit zip code	OR (95% CI) ^c 3-day Avg NO ₂ : 1.42 (0.99, 2.04)
†Reilly et al. (2023) Molecular Epidemiology of SepSis in the Intensive care unit (MESSI) n = 1,858	Patients admitted to ICU determined to be critically ill with sepsis	Central site monitor Averaging time: NO ₂ 3-day average NO ₂ 6-week average NO ₂ 5-year	NO ₂ (ppb) 3-day average Median = 12.6 (IQR 8.1) P25 = 9.2 P75 = 17.3	Acute Respiratory Distress Syndrome: Chest radiographs	Logistic Regression Adjusted for: Age, sex, self or surrogate reported race, smoking history, alcohol use, severity of illness based on the Acute Physiology	OR (95% CI) ^c 3-day Avg NO ₂ : 1.37 (1.10, 1.71)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Pennsylvania, U.S. 2008–2018 Cross-Sectional		average Exposure years: 2008–2018			and Chronic Health Evaluation (APACHE) III score, distance to the hospital, month of admission, and median household income of the patients' home addresses' 5-digit zip code	
† Shin et al. (2022) n = NR Montreal, Halton, Ontario, London, Ontario, Toronto, Ontario, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Sudbury, Halifax, Saint John, Quebec City, Ottawa, Durham, York, Peel, Niagara, Waterloo, Sarnia, Sault Sainte Marie, Regina, Saskatoon, Calgary, Canada 1984–2012 Time-series	Mortality and hospitalization daily counts (all-cause, circulatory, and respiratory) classified by ICD-9 and 10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1984–2012	NO ₂ (ppb) Population-weighted Cold season Mean = 20±4 Warm season Mean = 16±4 Year Mean = 18 Min = 8 Max = 28	Hospital admissions for influenza and pneumonia: National Ambulatory Care Reporting System (NACRS) database maintained by the Canadian Institute for Health Information (CIHI)	Bayesian Hierarchical Model Adjusted for: Day of week, temperature, and calendar time	Lag 0 % Increase (95% CI) ^b Males Year-Round: 0.60% (-1.87, 3.14) Warm Season: 4.24% (-1.32, 10.12) Cold Season: -0.60% (-3.16, 2.03) Females Year-Round: 2.41% (-0.97, 5.91) Warm Season: -1.79% (-5.68, 2.25) Cold Season: -0.40% (-4.12, 3.47)
† Szyszkowicz et al. (2018) n = COPD: 183,544 URI: 717,676 Algoma, Ontario, Halton, Ontario, Hamilton, Ontario, Ottawa, Ontario, Peel, Ontario,	ED visits for respiratory diseases retrieved from the National Ambulatory Care Reporting System (NACRS)	Central site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Algoma Mean = 5.1 IQR = 4 Min = 0 Max = 24	ED Visits: National Ambulatory Care Reporting System (NACRS) database maintained by	Logistic Regression Adjusted for: Temperature, relative humidity, and influenza cases	Lag 8 OR (95% CI) ^b ED Visits for LRTI Warm season: 1.12 (1.07, 1.18) Cold season: 1.02 (0.99, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Toronto, Ontario, York, Ontario, Middlesex, Ontario, Essex, Ontario, Canada April 2004–December 2011 Case-crossover		Exposure years: 2004–2011	Essex Mean = 15.6 IQR = 8.1 Min = 2.4 Max = 55.5 Halton Mean = 12.9 IQR = 7.7 Min = 1 Max = 51.2 Hamilton Mean = 13.9 IQR = 9.5 Min = 1.7 Max = 63 Middlesex Mean = 10.9 IQR = 7 Min = 0 Max = 51 Ottawa Mean = 8.7 IQR = 7 Min = 1 Max = 47 Peel Mean = 13.2 IQR = 9.5 Min = 2 Max = 54 Toronto	the Canadian Institute for Health Information (CIHI)		ED Visits for URI Females: 1.03 (1.00, 1.05) Males: 1.04 (1.01, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 18.5 IQR = 9.4 Min = 4.5 Max = 62.1 York Mean = 8.2 IQR = 7 Min = 0 Max = 47			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Xiao et al. (2016) n = Asthma/wheeze: 148,256 Pneumonia: 90,063 Otitis media: 422,268 URI: 744,942 Georgia, U.S. 2002–2008 Case-crossover	ED visits for children aged 0–18 years obtained from the Georgia Hospital Association	CMAQ Model validated against central site monitors ($r^2 = 0.69$) Averaging time: NO ₂ - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Mean = 9.22±9.62 IQR = 9.33 Min = 0.07 Max = 73.88 P25 = 2.7 P75 = 12.03	ED Visits: Georgia Hospital Association	Logistic Regression Adjusted for: Cubic polynomials for 3-day moving average temperature and 3-day moving average humidity; an indicator for warm season (May–October) vs cool season (November–April), holiday, and lag holiday (indicating whether one of the previous 2 days was a holiday); and product terms between the warm season indicator and the cubic polynomials for temperature, humidity, and day-of-season.	Lag 0–2 OR (95% CI) ^b ED Visits for Pneumonia: 1.02 (0.98, 1.06) ED Visits for URI: 1.06 (1.05, 1.08)

List of abbreviations in alphabetical order: AL = Alabama; ARDS = acute respiratory distress syndrome; CI = confidence interval; CIHI = Canadian Institute for Health Information; CMAQ = Community Multiscale Air Quality; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; ED = emergency department; GA = Georgia; IQR = interquartile range; LRTI = lower respiratory tract infection; MO = Missouri; NACRS = National Ambulatory Care Reporting System; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NO = nitric oxide; NR = not reported; OR = odds ratio; P# = #th percentile; PA = Pennsylvania; ppb = parts per billion; RR = relative risk; TX = Texas; URI = upper respiratory infection; U.S. = United States.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-10 Epidemiologic studies of short-term oxides of nitrogen exposure and self-reported, physician-diagnosed, and/or laboratory-confirmed respiratory infection

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Kirwa et al. (2021) multiethnic study of atherosclerosis (MESA) N = 6,536 Chicago, IL; Baltimore, MD; Winston-Salem, NC; St. Paul, MN; New York City, NY; Los Angeles County, CA, U.S. Baseline: July 2000–August 2002 Follow-up: through 2012 Cohort	At the first MESA examination in 2000–2002, participants were 44–84 years old and did not have clinical cardiovascular disease. We excluded any observations from study visits at which a participant was taking oral steroids and those who were missing one or more covariates on all follow-up examinations.	Spatiotemporal/geospatial model, Fixed site monitor $r^2 = 0.72$ Averaging time: NO₂ - 2 weeks Exposure years: 1999–2012	Concentrations presented graphically	Respiratory infection: self-reported	Poisson Regression Adjusted for: study site, race/ethnicity, sex, age, body mass index, marital status, education level, smoking status, employment status, annual income, neighborhood level socioeconomic index, home ownership, number of household members, health insurance status, medicaid status, diabetes diagnosis, and splines of calendar time, temperature, and relative humidity	RR (95% CI)^c 28-d avg NO₂: 1.21 (1.10, 1.33) 14-d avg NO₂: 1.15 (1.05, 1.25) 14-d avg NO_x: 1.12 (1.08, 1.16) 28-d avg NO_x: 1.15 (1.10, 1.20)
†Yu et al. (2023) n = 3,735,934 82 Cities, China 2015–2019 Time-series	Influenza cases reported at the city level from the Chinese Information System for Disease Control and Prevention	Central site monitor Averaging time: NO₂ - 24-hour average Exposure years: 2015–2019	NO₂ (ppb) Shanwei (lowest mean) Mean = 6.54 (12.3 µg/m³) Median = 5.8 (IQR 4) (11 µg/m³ (IQR 7 µg/m³) Min = 2 (3 µg/m³) Max = 20 (38 µg/m³)	Influenza incidence: clinical influenza cases reported through the China Information System for Disease Control and Prevention	Poisson Regression Adjusted for: average temperature, influenza cases, relative humidity, time, day of week, and holidays	Lag 1–7 RR (95% CI)^b 1.40 (1.28, 1.53)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 4 (8 µg/m ³) P75 = 8 (15 µg/m ³) Xingtai (highest mean) Mean = 28.8 (54.2 µg/m ³) Median = 27 (IQR 15) (51 µg/m ³ (IQR 28 µg/m ³) Min = 4 (8 µg/m ³) Max = 96.2 (181 µg/m ³) P25 = 20 (38 µg/m ³) P75 = 35 (66 µg/m ³)			
† Zhang et al. (2023) n = 1,042,308 Ningbo, Changsha, Wuhan, Guangzhou, Hefei, Hangzhou, Chengdu, Kunming, Nanning, Xiamen, China 2016–2019 Cross-Sectional	Clinical influenza cases reported through the China Information System for Disease Control and Prevention	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2016–2019		Influenza incidence: clinical influenza cases reported through the China Information System for Disease Control and Prevention	Poisson Regression Adjusted for: average temperature, influenza cases, relative humidity, time, day of week, and holidays	Lag 0–14 RR (95% CI) ^b 3.03 (2.22, 4.12)

List of abbreviations in alphabetical order: CA = California; CI = confidence interval; IL = Illinois; IQR = interquartile range; MD = Maryland; MESA = Multiethnic Study of Atherosclerosis; MN = Minnesota; NC = North Carolina; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NY = New York; P# = #th percentile; ppb = parts per billion; RR = relative risk; U.S. = United States.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-11 Animal toxicological studies of respiratory infection, antibody response, and ex vivo white blood cell function

Study Details and Population	Exposure Details	Endpoints Examined*
Amoruso et al. (1981)	Whole body inhalation with unclear control conditions	Timing unclear
Rat (Sprague Dawley)		Macrophage recovery (Mean macrophage recovery was 44% of control or better)
200–250 g, females	3,900 ppb-hrs (3.9 ppm-hrs) NO ₂ , continuous for 2–3 hr	Macrophage viability (No change)
n = 4/group	5,700 ppb-hrs (5.7 ppm-hrs) NO ₂ , continuous for 2–3 hr	Superoxide anion radical production (Progressive decrease in production by alveolar macrophages)
	11,700 ppb-hrs (11.7 ppm-hrs) NO ₂ , continuous for 2–3 hr	
	18,300 ppb-hrs (18.3 ppm-hrs) NO ₂ , continuous for 2–3 hr	
	24,000 ppb-hrs (24.0 ppm-hrs) NO ₂ , continuous for 2–3 hr	
	29,100 ppb-hrs (29.1 ppm-hrs) NO ₂ , continuous for 2–3 hr	
	35,000 ppb-hrs (35.0 ppm-hrs) NO ₂ , continuous for 2–3 hr	
	38,200 ppb-hrs (38.2 ppm-hrs) NO ₂ , continuous for 2–3 hr	
	51,000 ppb-hrs (51.0 ppm-hrs) NO ₂ , continuous for 2–3 hr	
Ehrlich and Henry (1968)	Whole body inhalation with clean air controls	14 d after exposure (pre-NO ₂ exposure challenge with <i>K. pneumoniae</i>)
Mouse (Swiss)		Mortality (↑)
21 g, females	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 1 mo	
n = 30/group	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 3 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 6 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 9 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 12 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 1 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 3 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 6 mo	

Study Details and Population	Exposure Details	Endpoints Examined*
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 9 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 12 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 1 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 3 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 6 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 9 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 12 mo	
Ehrlich et al. (1977)	Whole body inhalation with filtered air controls	1 hr after exposure (immediately after NO ₂ exposure challenged with <i>S. pyrogenes</i>)
Mouse (CF-1 and CD2F1)		Mortality (↑)
5–8-wk-old females	3,500 ppb (3.5 ppm) NO ₂ , 3 hr/d for 1 d	
n = 88–790/group	2,000 ppb (2 ppm) NO ₂ , 3 hr/d for 5 d/wk for 1 wk	
	2,000 ppb (2 ppm) NO ₂ , 3 hr/d for 5 d/wk for 2 wk	
	2,000 ppb (2 ppm) NO ₂ , 3 hr/d for 5 d/wk for 4 wk	
Ehrlich et al. (1979)	Whole body inhalation with filtered air controls	14 d after exposure (pre-NO ₂ exposure challenge with <i>S. pyrogenes</i>)
Mouse (CD2F1 and CD-1)		Lung clearance (↑)
6–8-wk-old, females	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3hr/d, 5 d/wk spikes for 1 mo	Mortality (↑)
n = 8–10/group	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3hr/d, 5 d/wk spikes for 2 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3hr/d, 5 d/wk spikes for 3 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3hr/d, 5 d/wk spikes for 6 mo	
Ehrlich (1980)	Whole body inhalation with clean air controls	14 d after exposure (immediately post-NO ₂ exposure challenged with <i>S. pyrogenes</i>)

Study Details and Population	Exposure Details	Endpoints Examined*
		Mortality (↑)
Mouse (Swiss)	500 ppb (0.5 ppm) NO ₂ , continuous for 7 d	
6–8-wk-old, females	500 ppb (0.5 ppm) NO ₂ , continuous for 14 d	
n = 30–280/group	500 ppb (0.5 ppm) NO ₂ , continuous for 30 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 60 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 90 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 180 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 270 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 360 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 2 hr	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 8 hr	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 1 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 7 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 14 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 30 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 60 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 90 d	
Fujimaki et al. (1982)	Whole body inhalation with room air controls	4–5 d after exposure Antibody responses (↓)
Mouse (BALB/c)		
7-wk-old, males	400 ppb (0.4 ppm) NO ₂ , continuous for 4 wk	
n = 6/group		

Study Details and Population	Exposure Details	Endpoints Examined*
	1,600 ppb (1.6 ppm) NO ₂ , continuous for 4 wk	
Graham et al. (1987)	Whole body inhalation with room air controls	Timing Unclear (18-hr post-exposure challenge with <i>S. zooepidemicus</i>)
Mouse (CD-1)		Mortality (↑)
4–6-wk-old, females	4,500 ppb (4.5 ppm) NO ₂ , continuous for 1 hr	
n = 16–41/group	4,500 ppb (4.5 ppm) NO ₂ , continuous for 3.5 hr	Timing Unclear (immediate challenge with <i>S. zooepidemicus</i>)
	4,500 ppb (4.5 ppm) NO ₂ , continuous for 7 hr	Mortality (↑)
Henry et al. (1970)	Whole body inhalation with ambient air controls	0–7 d after exposure (Post-2 mo exposure challenged with <i>K. pneumoniae</i>)
Squirrel monkey		Lung clearance (5 of 7 monkeys with bacteria in lungs)
600–800g, males	5,000 ppm (5 ppm) NO ₂ , continuous for 24 hr	Mortality (2 of 7 monkeys died)
n = 3–9/group	5,000 ppb (5 ppm) NO ₂ , 23 hr/d for 2 mo	0–7 d after exposure (Post-1 mo exposure challenged with <i>K. pneumoniae</i>)
	10,000 ppm (10 ppm) NO ₂ , continuous for 24 hr	Lung clearance (2 of 4 monkeys with bacteria in lungs)
	10,000 ppb (10 ppm) NO ₂ , 23 hr/d for 1 mo	Mortality (1 of 4 monkeys died)
		0–7 d after exposure (Pre-24 hr exposure challenged with influenza)
		Mortality (5,000 ppb = 1 of 3 monkeys died; 10,000 ppb 6 of 6 monkeys died)
Lefkowitz et al. (1986)	Whole body inhalation with room air controls	5 d after exposure
Mouse (CD-1)		Antibody responses (↓)
age not reported, females	5,000 ppb (5 ppm) NO ₂ , continuous for 24 hr	
n = 30/group		
Maigetter et al. (1978)	Whole body inhalation with filtered air controls	0 d after exposure
Mouse (CD-1)		LPS-stimulation index (generally decreased in NO₂ exposed animals, independent of time or dose)
5–6-wk-old, males	500 ppb (0.5 ppm) NO ₂ , continuous for 1 mo	
n = 9/group	500 ppb (0.5 ppm) NO ₂ , continuous for 3 mo	PHA-stimulation index (generally decreased in NO₂ exposed animals, independent of time or dose)

Study Details and Population	Exposure Details	Endpoints Examined*
	500 ppb (0.5 ppm) NO ₂ , continuous for 6 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 9 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 12 mo	
	100 ppb (0.1 ppm) + 250 ppb (0.25 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 1 mo	
	100 ppb (0.1 ppm) + 250 ppb (0.25 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 3 mo	
	100 ppb (0.1 ppm) + 250 ppb (0.25 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 6 mo	
	100 ppb (0.1 ppm) + 250 ppb (0.25 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 9 mo	
	100 ppb (0.1 ppm) + 250 ppb (0.25 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 12 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 1 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 3 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 6 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 9 mo	
	100 ppb (0.1 ppm) + 500 ppb (0.5 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 12 mo	
	100 ppb (0.1 ppm) + 1000 ppb (1.0 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 1 mo	
	100 ppb (0.1 ppm) + 1000 ppb (1.0 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 3 mo	

Study Details and Population	Exposure Details	Endpoints Examined*
	100 ppb (0.1 ppm) + 1000 ppb (1.0 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 6 mo	
	100 ppb (0.1 ppm) + 1000 ppb (1.0 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 9 mo	
	100 ppb (0.1 ppm) + 1000 ppb (1.0 ppm) spikes NO ₂ , continuous with 3 hr/d, 5 d/wk spikes for 12 mo	
Rose et al. (1988)	Whole body inhalation with filtered air controls	1–8 days after final NO ₂ exposure (challenged with murine cytomegalovirus)
Mouse (CD-1)	1,000 ppb (1 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	• Rate of infection (↑) • Viral potency (↑)
4–6-wk-old, sex not reported	2,500 ppb (2.5 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	
n = 4–24/group	5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	
	10,000 ppb (10 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	
Rose et al. (1989)	Whole body inhalation with room air controls	90 min after exposure (alveolar macrophages)
	Alveolar macrophage study	• Phagocytosis (↓)
Mouse (CD-1)	1,000 ppb (1 ppm) NO ₂ , 6 hr/d for 2 days followed by intratracheal ¹⁹⁸ Au-colloid	30–40 d after final NO ₂ exposure (murine cytomegalovirus)
4–6-wk-old, sex not reported	5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 2 days followed by intratracheal ¹⁹⁸ Au-colloid	• Viral reinfection (↑)
n = 4–22/group	15,000 ppb (15 ppm) NO ₂ , 6 hr/d for 2 days followed by intratracheal ¹⁹⁸ Au- colloid	
	Murine cytomegalovirus study	
	1,000 ppb (1 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	
	2,500 ppb (2.5 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	

Study Details and Population	Exposure Details	Endpoints Examined*
	5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 2 days followed by viral inoculation and then 6 hr/d for 4 additional days	
† Lu et al. (2023)	Whole body inhalation with clean air controls	24 hr after exposure (OVA) Lymphocyte number (blood) (↑)
Mouse (BALB/c)		
7-wk-old, males	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 30 d	- Neutrophil number (blood) (↑) - White blood cell number (blood) (↑)
n = 15/group		
† Li et al. (2022)	Whole body inhalation with clean air controls	12 hr after exposure Microbiome (intestinal) (NS)
Rat (Sprague Dawley)		
8-wk-old, males	5,000 ppb (5 ppm) NO ₂ , 5 hr/d for 14 d	
n = 8/group		
Kumae and Arakawa (2006)	Whole body inhalation with clean air controls	0 hr after exposure Alveolar macrophage ROS production (↑)
Rat (Brown Norway)	200 ppb (0.2 ppm) NO ₂ , continuous for 8 wk	
6-mo-old, females	200 ppb (0.2 ppm) NO ₂ , continuous for 12 wk	
n = 20–47/group	500 ppb (0.5 ppm) NO ₂ , continuous for 8 wk	
	500 ppb (0.5 ppm) NO ₂ , continuous for 12 wk	
	2,000 ppb (2.0 ppm) NO ₂ , continuous for 8 wk	
	2,000 ppb (2.0 ppm) NO ₂ , continuous for 12 wk	

List of abbreviations in alphabetical order: d = day; GD = gestational day; hr = hour; min = minute; mo = month; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; ROS = reactive oxygen species; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-1 Animal toxicological studies of airway responsiveness in unsensitized animals

Study Details and Population	Exposure Details	Endpoints Examined*
Kobayashi and Shinozaki (1990)	Whole body inhalation with filtered air controls	0 d after exposure Airway responsiveness (↑)
Guinea Pig (Hartley) age not reported, females n = 15/group	4,000 ppb (4 ppm) NO ₂ , continuous for 1 d 4,000 ppb (4 ppm) NO ₂ , continuous for 3 d 4,000 ppb (4 ppm) NO ₂ , continuous for 7 d	
†Lu et al. (2023)	Whole body inhalation with room air controls	7 d after exposure (no OVA) AHR (↑)
Mouse (BALB/c) 7-wk-old, males n = 7–8/group	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 30 d	
†Yue et al. (2017)	Whole body inhalation with room air controls	10 wk after exposure (unsensitized mice) AHR (NS)
Mouse (BALB/c) gestational exposure (GD 0 to GD 20), males and females n = 3–10/group	2,500 ppb (2.5ppm) NO ₂ , 5 hr/d for 20 d	
†Yue et al. (2018)	Whole body inhalation with room air controls	9 wk after exposure (unsensitized mice) AHR (NS)
Mouse (BALB/c) gestational exposure (GD 0 to GD 21), sex not reported n = 3–11/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 21 d	

List of abbreviations in alphabetical order: AHR = airway hyperresponsiveness; d = day; GD = gestational day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-13 Epidemiologic studies of short-term oxides of nitrogen exposure and lung function in the general population or populations without pre-existing respiratory diseases

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Dales et al. (2013) n = 61 Sault Ste. Marie, Ontario, Canada May 2010–August 2010 Randomized crossover	Healthy, non-smoking individuals who were primarily college students. Individuals had no second-hand smoking exposure	Fixed site monitor Averaging time: NO ₂ - daily average of 8 am–6 pm Exposure years: NA	NO ₂ (ppb) High-exposure Mean = 7.07±5.13 Low-exposure Mean = 4.52±3.79 NO ₂ (ppb) High-exposure Mean = 13.97±10.4 Low-exposure Mean = 6.01±5.4	Supervised Spirometry	Linear regression - mixed effects Adjusted for: study site, day-of-the-week, mean temperature and relative humidity	β (Volume change (% predicted)) (95% CI) ^c FVC: -0.37 (-1.25, 0.52) FEV ₁ : -0.44 (-0.84, -0.04)
Strak et al. (2012) n = 31 Utrecht, The Netherlands March 2009–October 2009 Quasi-experimental	Healthy, younger, non-smoking students from Utrecht University. Exclusion criteria included smoking or living in a household with a smoker, diagnosis of asthma or COPD, or history of cardiovascular disease, diabetes, or pregnancy	Fixed site monitor Averaging time: NO ₂ 5-hr average NO _x 5-hr average Exposure years: 2009	NO ₂ (ppb) Mean = 20 Min = 9 Max = 34 NO _x (ppb) Mean = 36 Min = 14 Max = 96	Supervised Spirometry	Linear regression - mixed effects Adjusted for: temperature, relative humidity, season, pollen counts, and respiratory infection	NO ₂ β (Volume change (%)) (95% CI) ^c FVC: -3.00 (-7.20, 1.40) FVC - 2hr: -3.50 (-6.50, -0.43) FVC - 0hr: -4.30 (-7.40, -1.00) FVC - 18hr: -4.50 (-7.40, -1.40) NO _x β (Volume change (%)) (95% CI) ^c FVC - 18hr:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-2.50 (-5.40, -0.69) FVC - 0hr: -1.60 (-2.60, -0.51) FVC: -0.11 (-2.60, 2.50) FVC - 2hr: -2.00 (-4.90, -0.16)
† Chen et al. (2021) n = 62 Research Triangle, NC, U.S. October 2016–September 2019 Panel	Healthy adults 25–55 years of age, with no history of respiratory or cardiovascular disease, non-smoker for year prior, not taking B-adrenergic receptor blockers or anti-inflammatory drugs	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2016–2019	NO ₂ (ppb) Mean = 5.3±3.8 IQR = 3.8 Min = 0.8 Max = 24.2	Supervised Spirometry	Linear regression - mixed effects Adjusted for: age, sex, race, BMI, long-term and seasonal trends, day of the week, temperature, and relative humidity	β (Volume change (%)) (95% CI) ^c FEV ₁ - low omega 3, lag 1: -0.30 (-1.80, 1.10) FEV ₁ - low omega 3, lag 2: 0.30 (-1.30, 1.80) FEV ₁ - low omega 3, 5-day moving average: 1.20 (-1.20, 3.60) FEV ₁ - high omega 3, lag 4: 0.00 (-1.40, 1.40) FEV ₁ - low omega 3, lag 4: 0.60 (-0.70, 1.90) FEV ₁ - high omega 3, lag 3: 0.90 (-0.50, 2.30) FVC - low omega 3, lag 1: 0.30 (-0.70, 1.30) FVC - low omega 3, lag 2: 0.80 (-0.30, 1.90) FEV ₁ - low omega 3, lag 3: 0.30 (-1.10, 1.80) FEV ₁ - low omega 3, lag 0: 0.80 (-0.70, 2.30) FVC - high omega 3, lag 0: 0.90 (0.00, 1.80) FEV ₁ - high omega 3, lag 0: 1.00 (-0.20, 2.30) FEV ₁ - high omega 3, lag 1: 0.90 (-0.60, 2.40) FVC - low omega 3, 5-day moving

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						average: 0.80 (-1.00, 2.60) FVC - high omega 3, lag 4: 0.50 (-0.50, 1.50) FVC - high omega 3, 5-day moving average: 2.10 (-0.60, 0.40) FEV ₁ - high omega 3, 5-day moving average: 2.60 (0.40, 4.80) FEV ₁ - high omega 3, lag 2: 1.20 (-0.10, 2.50) FVC - low omega 3, lag 0: 0.70 (-0.40, 1.80) FVC - high omega 3, lag 3: 0.50 (-0.60, 1.50) FVC - low omega 3, lag 3: -0.60 (-1.70, 0.50) FVC - low omega 3, lag 4: -0.20 (-1.10, 0.80) FVC - high omega 3, lag 1: 1.20 (0.20, 2.20) FVC - high omega 3, lag 2: 1.00 (0.00, 1.90)
†Sinharay et al. (2017) n = 119 London, U.K. October 2012–June 2014 Case-crossover	Participants aged 60 years and older with stable ischemic heart disease or COPD and age-matched healthy volunteers	Central site monitor Averaging time: NO ₂ 2-hour average Exposure years: NA	Concentrations presented graphically	Supervised Spirometry	Linear regression - mixed effects Adjusted for: temperature and relative humidity	β (Volume change (% predicted)) (95% CI) ^c FVC - Healthy: -0.36 (-3.38, 2.66) FEV ₁ - Healthy: -0.18 (-2.87, 2.50) FEV ₁ - COPD: -4.85 (-9.03, -0.67) FVC - IHD: -1.59 (-4.38, 1.19) FVC - COPD: -4.99 (-8.27, -1.70)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						FEV ₁ - IHD: -1.03 (-3.41, 1.35)
† Zhu et al. (2023) n = 56 Shanghai, China October 2019–December 2019 Randomized crossover	Non-smoking healthy college students (>18 years of age) from a medical campus. Individuals with no history of self-reported allergy or chronic cardiopulmonary disease, lived on campus for at least 1 year, no second-hand smoking exposure, and had not used medication or dietary supplements in 2 months prior	Personal monitor or sampler Averaging time: NO ₂ – 4-hour average Exposure years: 2019	NO ₂ (ppb) High-exposure Mean = 44±9 Median = 45 (IQR 10) Min = 23 Max = 59 P25 = 39 P75 = 49 Low-exposure Mean = 14±3 Median = 14 (IQR 4) Min = 8 Max = 21 P25 = 11 P75 = 15	Supervised Spirometry	Linear regression - mixed effects Adjusted for: age, sex, body mass index, and a random intercept for each participant and the previous 4-h moving average of temperature and relative humidity	β (Rate (L/s)) (95% CI) ^c MMEF: -0.20 (-0.37, -0.04) β (Ratio) (95% CI) ^c FEV ₁ /FVC: -0.88 (-1.63, -0.13) β (Volume (L)) (95% CI) ^c FEV ₁ : -0.07 (-0.14, -0.01) FVC: -0.04 (-0.11, 0.04)
List of abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV ₁ = forced expiratory volume in 1 second; FEV ₁ /FVC = ratio of forced expiratory volume in 1 second to forced vital capacity; FVC = forced vital capacity; IHD = ischemic heart disease; IQR = interquartile range; L = liter; MMEF = maximal mid-expiratory flow; NC = North Carolina; NO ₂ = nitrogen dioxide; NO _x = NO + NO ₂ ; P# = #th percentile; ppb = parts per billion; s = second; U.K. = United Kingdom; U.S. = United States. ^a For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses. ^b Effect estimates are standardized and are presented as a 20 ppb change in NO ₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO _x for 24-hour averaging time; 25 ppb change in NO ₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO _x for 1-hour maximum averaging time; 25 ppb change in NO ₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO _x for 8-hour maximum averaging time; a 10 ppb change in NO ₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO _x for annual average averaging time. ^c Estimates are not standardized. †Studies published since the 2016 Oxides of Nitrogen ISA.						

Appendix Table 3-14 Controlled human exposure studies of respiratory effects in healthy subjects

Study Details and Population	Exposure Details	Endpoints Examined*
† Brand et al. (2016)	Whole body exposure for 3 hr with 100 d after exposure	
25 young (18–33-yr-old) healthy subjects (19m/6f)	min/hr of exercise (80 W workload) to: (1) 0.0 ppb (0.0 ppm) (2) 100 ppb (0.1 ppm) (3) 500 ppb (0.5 ppm) (4) 1,500 ppb (1.5 ppm)	• Lung function – VC, FVC, FEV₁, PEF, MEF75, MEF50, MEF25, Reff, ERV, TLC, RV (NS) • Lung function – ITGV (↑) • Diffusion capacity (NS) • eNO (NS) • EBC nitrate and nitrite levels (NS) • Inflammatory mediators in nasal secretions (NS) • Sputum inflammatory cells (↓) • Sputum inflammatory cytokines (NS)

List of abbreviations in alphabetical order: d = day; EBC = exhaled breath condensate; eNO = exhaled nitric oxide; ERV = expiratory reserve volume; f = female; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; hr = hour; ITGV = intrathoracic gas volume; m = male; MEF25 = maximum expiratory flow at 25% vital capacity; MEF50 = maximum expiratory flow at 50% vital capacity; MEF75 = maximum expiratory flow at 75% vital capacity; min = minute; PEF = peak expiratory flow; ppb = parts per billion; ppm = parts per million; Reff = effective airway resistance; RV = residual volume; TLC = total lung capacity; VC = vital capacity; W = watts; yr = year.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ↑/↓ = at least one experimental group had a statistically significant increase and at least one experimental group has a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-15 Animal toxicological studies of lung function changes in unsensitized animals

Study Details and Population	Exposure Details	Endpoints Examined*
Kobayashi and Shinozaki (1990)	Whole body inhalation with filtered air controls	0 after exposure
Guinea Pig (Hartley) age not reported, females n = 15/group	4,000 ppb (4 ppm) NO ₂ , continuous for 1 d 4,000 ppb (4 ppm) NO ₂ , continuous for 3 d 4,000 ppb (4 ppm) NO ₂ , continuous for 7 d	• Specific airway resistance (NS)
† Ohyama et al. (2018)	Whole body inhalation with filtered air controls	Timing Unclear
Rat (F344)		• Baseline dynamic lung compliance (NS) • Baseline pulmonary resistance (↑)

5-wk-old, males n = 9/group	2 ppb (0.002 ppm) HONO, continuous for 42 d 4,098 ppb (4.098 ppm) HONO, continuous for 42 d 5,757 ppb (5.757 ppm) HONO, continuous for 42 d	
†Ohyama et al. (2022)	Whole body inhalation with filtered air controls	0-7 wk after exposure
Guinea Pig (Hartley) 9-wk-old, males n = 12/group	 659 ppb (0.695 ppm) HONO, continuous for 7 wk 3,425 ppb (3.425 ppm) HONO, continuous for 7 wk	• Peak expiratory flow/ tidal volume (NS) • Respiratory waveform (medium and high dose HONO had higher frequency of affected or strongly affected waveforms) • sRaw (↑)

List of abbreviations in alphabetical order: d = day; HONO = nitrous acid gas; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week.

* Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase.

† Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-16 Animal toxicological studies of pulmonary inflammation, injury, and oxidative stress in unsensitized animals

Study Details and Population	Exposure Details	Endpoints Examined*
Ayaz and Csallany (1978)	Whole body inhalation with filtered air controls	0 d after exposure (1,000 ppb NO ₂ deficient vitamin E)
Mouse (C57BL/6J) 21-day-old, females n = 5–10/group	 500 ppb (0.5 ppm) NO ₂ , continuous for 17 mo 1,000 ppb (1 ppm) NO ₂ , continuous for 17 mo	• Lung tissue GSH-P Activity (↓) 0 d after exposure (1,000 ppb NO₂ high vitamin E) • Lung tissue GSH-P Activity (NS) 0 d after exposure (1,000 ppb NO₂ normal vitamin E) • Lung tissue GSH-P Activity (NS) 0 d after exposure (500 ppb NO₂ deficient vitamin E) • Lung tissue GSH-P Activity (↓) 0 d after exposure (500 ppb NO₂ high vitamin E) • Lung tissue GSH-P Activity (NS) 0 d after exposure (500 ppb NO₂ normal vitamin E) • Lung tissue GSH-P Activity (NS)
†Duong-Quy et al. (2014)	Whole body inhalation with room air controls	0 d after exposure
		• ELISA oxidative stress and VEGF signaling (↑)

Rat (Sprague Dawley) developmental exposure (GD - 1 to PND 7), sex not reported n = 4–6/group	5,000 ppb (5 ppm) NO, continuous for 7 d	7 d after exposure - IHC – VEGF signaling (↑) - IHC – oxidative stress (↑) - Lung weight (↑) - Western blot – VEGF signaling (↑) - ELISA oxidative stress and VEGF signaling (↑) - IHC – VEGF signaling (NS) - IHC – VEGF signaling (NS) - IHC – oxidative stress (NS) - Lung weight (NS) - Western blot – VEGF signaling (NS)
Gregory et al. (1983)	Whole body inhalation with filtered air controls	1.7–2.7 wk after exposure (1,000 ppb, 5,000 ppb, 1,000 ppb with 5,000 ppb spikes) 1.7 wk after exposure (1,000 ppb and 1,000 ppb with 5,000 ppb spikes) - Lung histology (Histologically unremarkable) 1.7 wk after exposure (1,000 ppb, 5,000 ppb, and 1,000 ppb with 5,000 ppb spikes) - Lung damage (BAL ALKP, LDH and GSH-P) (NS) 1.7 wk after exposure (5,000 ppb) - Lung damage (BAL GSH-P) (NS) - Lung tissue GSH-P and G-6P-DH (NS) - Lung tissue GSH-R (↑) 2.7 wk after exposure (1,000 ppb, 5,000 ppb, and 1,000 ppb with 5,000 ppb spikes) - Lung damage (BAL ALKP, LDH, GSH-P) (↑) - Lung tissue GSH-P and G-6P-DH (NS)
†Han et al. (2017)	Whole body inhalation with filtered air controls	24 hr after exposure (28 d exposure) - ICC (Increased epithelial cell damage, inflammatory cell infiltration, and mucus production) - PCR – Th 1 response (↓) - PCR – inflammation and Th2 response (↑)
Rat (Wistar) 6-wk-old, males n = 3–10/group	1063 ppb (2 mg/m ³) NO ₂ , 5 hr/d for 28 d 2,658 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 28 d 2,658 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 42 d	

Kumae and Arakawa (2006)	Whole body inhalation with clean air controls	0 after exposure
Rat (Brown Norway)		- Alveolar macrophage IFN gamma (↑) - Alveolar macrophage IL-1 beta (↑)
6-mo-old, females	200 ppb (0.2 ppm) NO ₂ , continuous for 8 wk	Alveolar macrophage TNF alpha (↑)
n = 20–47/group	200 ppb (0.2 ppm) NO ₂ , continuous for 12 wk	
	500 ppb (0.5 ppm) NO ₂ , continuous for 8 wk	
	500 ppb (0.5 ppm) NO ₂ , continuous for 12 wk	
	2,000 ppb (2.0 ppm) NO ₂ , continuous for 8 wk	
	2,000 ppb (2.0 ppm) NO ₂ , continuous for 12 wk	
†Lu et al. (2023)	Whole body inhalation with room air controls	7 d after exposure (no OVA)
Mouse (BALB/c)		- ELISA – IFNγ (↓) - ELISA – IL-4 (NS) - ELISA – IL-4/IFNγ (↑) - IHC – inflammatory mediators (↑)
7-wk-old, males	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 30 d	
n = 7–8/group		
†Yue et al. (2017)	Whole body inhalation with room air controls	0 d after exposure (PND 1–42)
Mouse (BALB/c)		FACS – inflammatory cells (↑)
developmental exposure (GD 0 to GD 20), males and females	2,500 ppb (2.5ppm) NO ₂ , 5 hr/d for 20 d	1d–42 d after exposure (PND 1–42)
n = 3–10/group		- ELISA – IFNγ (↓) - ELISA – Th 2 cytokines (↑) - IHC (Increased cell infiltration and collagen deposition with NO₂ PND 1 and 7 but not in PND 21 or 42)
		10 wk after exposure (unsensitized mice)
		- ELISA – IFNγ (NS) - ELISA – Th2 cytokines (NS) - FACS – inflammatory cells (NS) - IHC (No reported difference from control)

List of abbreviations in alphabetical order: d = day; ELISA = enzyme-linked immunosorbent assay; FACS = fluorescence-activated cell sorting; GD = gestational day; GSH-P = glutathione peroxidase; hr = hour; IHC = immunohistochemistry; ICC = immunocytochemistry; mo = month; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; VEGF = vascular endothelial growth factor; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-17 Epidemiologic studies of short-term oxides of nitrogen exposure and hospital admissions for aggregated respiratory conditions

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Luginaah et al. (2005) n = 4,214 admissions Windsor, Ontario, Canada Follow-up: 1995–2000 Time-series and Case-crossover	Individuals admitted into one of the hospitals in Windsor with a primary diagnosis of respiratory disease. Inclusion criteria, individuals with Ontario Health Insurance Plan	Fixed site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1995–2000	NO ₂ (ppb) Mean = 38.9±12.3 IQR = 16 Min = 0 Max = 117	Hospital Admissions for Respiratory Disease: daily hospital admission records for Ontario Health Insurance Plan patients were obtained from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database	Generalized Additive Model Adjusted for: day of the week, calendar time (natural spline), humidity (natural spline), barometric pressure (natural spline), and temperature (natural spline)	Lag 1 RR (95% CI) ^b Females: 1.04 (0.96, 1.13) Males: 0.93 (0.86, 1.01)
Son et al. (2013) n = NR Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, Ulsan, Jeju, South Korea January 2003–December 2008 Cross-Sectional	Individuals hospitalized due to allergic diseases, asthma, croup, pneumonia, bronchiolitis, respiratory infection (including bronchitis, chronic obstructive pulmonary disease, and pneumonitis), or cardiovascular diseases.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: January 2003–December 2008	NO ₂ (ppb) Fall Mean = 24.1±8.8 Spring Mean = 24.6±7.7 Summer Mean = 17.9±5.7 Winter Mean = 26.8±9.4	Hospital Admissions for Respiratory Disease: data from the National Health Insurance Corporation, Republic of Korea	Bayesian Hierarchical Model Adjusted for: day of the week, calendar time (natural spline), humidity (natural spline), barometric pressure (natural spline), and temperature (natural spline)	Lag 0 RR (95% CI) ^b Year-round: 1.04 (1.01, 1.06) Summer: 1.16 (1.05, 1.28) Fall: 1.05 (1.00, 1.11) Winter: 1.00 (0.95, 1.05) Spring: 1.02 (0.97, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Huang et al. (2022) n = NR Toronto, Vancouver, Edmonton, Calgary, Canada 1996–2012 Case-crossover	All-age cause specific mortality and morbidity data	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1996–2012	NO ₂ (ppb) Calgary Mean = 21.5 Edmonton Mean = 19.5 Toronto Mean = 21.9 Vancouver Mean = 16.5	Hospital Admissions for Respiratory Disease: Hospital admissions using electronic billing data acquired by Health Canada	Bayesian Hierarchical Model Adjusted for: temperature (spline with 4 df)	Lag 0–1 RR (95% CI) ^b 1.02 (0.99, 1.05)
†Huang et al. (2023) n = NR Canada 2001–2018 (Hospitalizations) 2001–2015 (Mortality) Time-series	Daily mortality and hospitalizations (non-accidental all-cause, circulatory, and respiratory) using ICD-10 codes	Central site monitor Averaging time: 3-hour max Exposure years: 2001–2018	NO ₂ (ppb) Mean = 16.7 Median = 16.9 Min = 7.1 Max = 30 P25 = 12.9 P75 = 19.5	Hospital Admissions for Respiratory Disease: Hospital Morbidity Database and Discharge Abstract Database from the Canadian Institute for Health Information	Bayesian Hierarchical Model Adjusted for: temperature (spline with 4 df)	Lag 0–1 RR (95% CI) ^c 1.01 (1.01, 1.02)
†Shin et al. (2021) n = 94,532/year (Hospital Admissions) 8,487/year (Mortality) 24 Canadian Cities, Canada	Daily counts of respiratory hospital admissions and mortality data (ages 1+ years) from the Canadian Institute for Health Information and the national Vital	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years:	NO ₂ (ppb) Cold Season Mean = 20±3.7 Warm Season Mean = 18±3.5	Hospital Admissions for Respiratory Disease: Hospitalization data were obtained from the Canadian	Bayesian Hierarchical Model Adjusted for: day of the week, calendar time (Slepian smoother), and	Lag 0 RR (95% CI) ^b 1.01 (1.00, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
1996–2012 (Hospital admissions) 1984–2012 (Mortality) Time-series	Statistics database, respectively.	1996–2012 (Hospital admissions) 1984–2012 (Mortality)		Institute for Health Information	temperature (natural spline)	
† Shin et al. (2022) n = NR Montreal, Halton, Ontario, London, Ontario, Toronto, Ontario, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Sudbury, Halifax, Saint John, Quebec City, Ottawa, Durham, York, Peel, Niagara, Waterloo, Sarnia, Sault Sainte Marie, Regina, Saskatoon, Calgary, Canada 1984–2012 Time-series	Mortality and hospitalization daily counts (all-cause, circulatory, and respiratory) classified by ICD-9 and 10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1984–2012	NO ₂ (ppb) Population-weighted Cold season Mean = 20±4 Warm season Mean = 16±4 Year Mean = 18 Min = 8 Max = 28	Hospital Admissions for Respiratory Disease: Hospitalization data were obtained from the Canadian Institute for Health Information	Bayesian Hierarchical Model Adjusted for: day of the week, calendar time (Slepian smoother), and temperature (natural spline)	Lag 0 RR (95% CI) ^b Males Year-round: 1.01 (1.00, 1.03) Warm season: 1.02 (0.99, 1.06) Cold season: 1.00 (0.99, 1.02) Females Year-round: 1.02 (1.00, 1.04) Warm season: 1.05 (1.01, 1.09) Cold season: 1.01 (0.99, 1.03)

List of abbreviations in alphabetical order: CI = confidence interval; CIHI = Canadian Institute for Health Information; df = degrees of freedom; ICD = International Classification of Diseases; IQR = interquartile range; NO₂ = nitrogen dioxide; NR = not reported; P# = #th percentile; ppb = parts per billion; RR = relative risk; U.K. = United Kingdom; U.S. = United States.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-18 Epidemiologic studies of short-term oxides of nitrogen exposure and emergency department visits for aggregated respiratory conditions

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Tolbert et al. (2007) n = 10,206,389 visits Atlanta, GA, U.S. Follow-up: 1993–2004 Time-series	Billing records for all emergency department visits for residents of the Atlanta MSA at the time of the visit	Central site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1993–2004,	NO ₂ (ppb) Mean = 43.2 Median = 41 (IQR 23) Min = 1 Max = 191 P10 = 22 P25 = 31 P75 = 54 P90 = 66	ED Visits for Respiratory Disease: Electronic records from individual hospitals	Poisson Adjusted for: hospital, day of week, holidays, season, daily average temperature (cubic spline), dew point temperature (cubic spline), calendar time (cubic spline)	Lag 0–2 RR (95% CI) ^b 1.02 (1.00, 1.03)
† Cromar et al. (2020) California’s Office of Statewide Health Planning and Development (OSHPD) N = 1,373,165 ED visits California, U.S. 2012–2014 Time-series	All respiratory ED visits from were gathered from this population and coded according to the 9 th version of the International Classification of Diseases. Respiratory visits were defined as asthma, upper respiratory infection, pneumonia, and chronic obstructive pulmonary disease.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2012–2014	NO ₂ (ppb) March - October San Francisco Bay Area Median = 13.9 (IQR 13.3) San Joaquin Valley Median = 19 (IQR 15) Southern California Median = 23 (IQR 20.3) November - February San Francisco Bay Area Median = 28.7 (IQR 13.6) San Joaquin Valley	ED Visits for Respiratory Disease: California’s Office of Statewide Health Planning and Development	Poisson Adjusted for: day of week, long-term trends (spline), seasonality (spline), relative humidity (spline), same day temperature (spline), and lagged temperature (spline)	Quantitative results presented in figures. Forest plots depict some variation across regions and seasons, but evidence of positive associations in general.

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 28 (IQR 16) Southern California Median = 35.9 (IQR 17.1)			
† Ebelt et al. (2022) n = 230,718 Atlanta, GA, U.S. January 2009–December 2013 Time-series	Cardiorespiratory ED visits of patients living in Atlanta	Central site monitor, CMAQ, Spatiotemporal/geospatial model, LUR Averaging time: NO ₂ - 1-hour max Exposure years: 2009–2013	NO ₂ (ppb) Central monitor Median = 29.7 (IQR 17.9) Max = 82.5 CMAQ Median = 20.9 (IQR 22.8) Max = 119.9 CMAQ data fusion Median = 16.7 (IQR 15.4) Max = 117.3 CMAQ kriging Median = 12.8 (IQR 16) Max = 88.7 IDW Median = 19.5 (IQR 14.2) Max = 82.2 Kriging Median = 17.3 (IQR 13.5) Max = 79.5	ED Visits for Respiratory Disease: Georgia Hospital Association	Poisson Adjusted for: geographic area, hospital, day of week, federal holidays, calendar holidays, season, maximum temperature, minimum temperature, dew point temperature, calendar time (cubic spline with 2 knots per month)	Lag 0–7 RR (95% CI) ^b Central Monitor: 0.99 (0.97, 1.01) Site Average at Central Monitor: 0.99 (0.97, 1.01) IDW at Central Monitor: 0.99 (0.97, 1.00) CMAQ at Central Monitor: 1.03 (1.01, 1.04) CMAQ-Kriging at Central Monitor: 0.99 (0.97, 1.01) CMAQ-Fusion at Central Monitor: 1.03 (1.01, 1.05) Kriging at Central Monitor: 0.99 (0.97, 1.01) LUR at Central Monitor: 1.06 (1.03, 1.09) Site Average, Full Spatial: 0.99 (0.97, 1.01) IDW, Full Spatial: 1.05 (1.03, 1.07) CMAQ, Full Spatial: 1.03 (1.02, 1.04) CMAQ-Kriging, Full Spatial:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			LUR Median = 13.1 (IQR 14.7) Max = 75.9 Site average Median = 16.8 (IQR 14.3) Max = 70.8			1.01 (0.99, 1.02) CMAQ-Fusion, Full Spatial: 1.04 (1.02, 1.05) Kriging, Full Spatial: 1.07 (1.05, 1.09) LUR, Full Spatial: 1.06 (1.04, 1.09)
†Kral et al. (2018) n = 1,310 cases/day Atlanta, GA; St. Louis, MO; Dallas, TX; Pittsburgh, Pennsylvania; Birmingham, AL, U.S. 2002–2008 Time-series	ED visits using electronic billing data from the 20-county Atlanta, GA metropolitan area; the 7-county Birmingham, AL metropolitan area, the 12-county Dallas-Fort Worth metropolitan area, the 3-county Pittsburgh area, and the 16-county St. Louis metropolitan area.	Hybrid model Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Atlanta Mean = 21.6±7 Birmingham Mean = 13.2±4.3 Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5 Birmingham Mean = 24.5±13.8 Dallas	ED Visits for Respiratory Disease: ED visits using electronic billing data	Bayesian Hierarchical Model Adjusted for: weekday, season, holidays, meteorology (cubic splines of lag 0–2 and lag 3–7 temperature and dew-point temperature), temporal trends (cubic splines of time with 1 df per month), and the hospitals reporting data for each day.	Lag 0–7 RR (95% CI) ^b NO ₂ : 1.13 (1.07, 1.20) NO _x : 1.06 (0.95, 1.18)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 41.4±32.2			
			Pittsburgh Mean = 56±35.8			
			St. Louis Mean = 51.3±30.9			
† Perlmutter and Cromar (2019) n = 858,030 Bronx County, NY, Queens County, NY, U.S. 2005–2010 Time-series	Emergency department visits for respiratory disease from the New York Statewide Planning and Research Cooperative System (SPARCS)	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2005–2010	NO ₂ (ppb) Cold Season Mean = 40.0 Median = 39.2 P5 = 21.7 P25 = 31.8 P75 = 46.6 P95 = 62.0 Warm Season Mean = 41.1 Median = 40.8 P5 = 19.6 P25 = 31.8 P75 = 49.3 P95 = 64.4	ED Visits for Respiratory Disease: New York Statewide Planning and Research Cooperative System (SPARCS)	Poisson Adjusted for: day of week, long-term trends (spline), seasonality (spline), relative humidity (spline), same day temperature (spline), and lagged temperature (spline)	Lag 0–3 RR (95% CI) ^b 1.03 (1.01, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Weichenthal et al. (2016) n = Asthma: 128,731 COPD: 298,751 Total Respiratory: 1,181,961 Toronto, Hamilton, Barrie, Chatham, Cornwall, Kingston, Kitchener, Oakville, Oshawa, Petawawa, Peterborough, Port Stanley, Sarnia, St. Catharines, Thunder Bay, Ontario, Canada 2004–2011 Case-crossover	ED visits for respiratory diseases retrieved from the National Ambulatory Care Reporting System (NACRS)	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2011	NO ₂ (ppb) Mean = 12.9±7.79 Median = 11.5 (IQR 10.6) Max = 65	ED Visits for Respiratory Disease: National Ambulatory Care Reporting System (NACRS) database maintained by the Canadian Institute for Health Information (CIHI)	Logistic Regression Adjusted for: 3-day mean ambient temperature and relative humidity (restricted cubic splines with three knots), and daily counts of emergency room visits for influenza	Lag 0–2 OR (95% CI) ^b 0.99 (0.97, 1.01)

List of abbreviations in alphabetical order: AL = Alabama; CI = confidence interval; CIHI = Canadian Institute for Health Information; CMAQ = Community Multiscale Air Quality; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; ED = emergency department; GA = Georgia; IDW = inverse distance weighting; IQR = interquartile range; LUR = land use regression; NACRS = National Ambulatory Care Reporting System; NO₂ = nitrogen dioxide; NO_x = NO + NO₂; NY = New York; OR = odds ratio; P# = #th percentile; PA = Pennsylvania; ppb = parts per billion; RR = relative risk; SPARCS = Statewide Planning and Research Cooperative System; TX = Texas; U.S. = United States..

aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 3-19 Epidemiologic studies of short-term oxides of nitrogen exposure and respiratory mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Bellini et al. (2007) Meta-analysis of the Italian studies on short-term effects of air pollution (MISA) 15 Italian cities	Meta-analysis of data from Italian studies on short-term health effects of air pollution	Central site monitors	NR	Respiratory mortality data from local health and statistics departments	Bayesian Random Effects Adjusted for: Meta-analysis: confounders vary by study, but typically include time trends, meteorological conditions, and influenza epidemics	Lag 0–1 % Increase (95% CI) ^b 1.44% (-2.96, 6.04)
Chen et al. (2012b) China Air Pollution and Health Effects Study (CAPES) n = 107 respiratory deaths/day Shanghai, Tianjin, Beijing, Hong Kong, Wuhan, Xi'an, Guangzhou, Fuzhou, Lanzhou, Nanjing, Suzhou, Shenyang, Anshan, Taiyuan, Hangzhou, Urumqi, China 1996–2010 Time-series	Daily mortality data of urban residents from Municipal Center for Disease Control and Prevention Averaging time: NO ₂ - 24-hour average Exposure years: 1996–2010	Central site monitor	NO ₂ (ppb) Min = 2 Max = 135	Respiratory mortality data were obtained from the Municipal Center for Disease Control and Prevention in each city or from the Census and Statistic Department	Bayesian Hierarchical Model Adjusted for: calendar time (natural spline), day of the week, temperature, and relative humidity	Lag 0–1 % Increase (95% CI) ^b 9.82% (5.57, 14.24)
Chiusolo et al. (2011) n = 276,205	Individuals greater than 35 years of age, in 10 Italian cities, who deceased between	Central site monitor Averaging time:	NO ₂ (ppb) Range of means across cities =	Respiratory mortality data were obtained	Logistic Regression Adjusted for: population decrease, holidays,	Lag 1–5 % Increase (95% CI) ^b

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Rome, Turin, Bologna, Cagliari, Florence, Mestre-Venice, Milan, Palermo, Pisa, Taranto, Italy 2001–2005 Case-crossover	2001–2005 of natural causes	NO ₂ - 24-hour average Exposure years: 2001–2005	11.7 to 35.1	from the census office registry	influenza epidemics, barometric pressure, and apparent temperature	Year-round: 13.74% (2.84, 25.79) Warm Season: 41.34% (16.25, 71.84)
Faustini et al. (2013) n = 100,690 hospitalizations Rome, Turin, Bologna, Florence, Milan, Palermo, Italy 2001–2005 Case-crossover	Emergency hospitalizations of individuals 35 years and older, who were discharged from 1 of 6 hospitals in their city	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2005	NO ₂ (ppb) Min = 24.5 Max = 35	Local mortality registries	Logistic Regression Adjusted for: apparent temperature (penalized spline), low temperature (penalized spline), barometric pressure (penalized spline), population decreases in the summer, and influenza epidemics, long-term trends and seasonality (triple interaction of year, month, and day)	% Increase (95% CI) ^b Lag 0: 0.57% (-20.20, 26.73) Lag 0–1: 4.36% (-6.61, 16.62) Lag 0–3: 13.99% (-0.15, 30.13) Lag 2–5: 28.63% (13.95, 45.21) Lag 0–5: 24.47% (7.42, 44.23)
Meng et al. (2013) n = 32.2 COPD deaths/day Shanghai, Beijing, Hong Kong, Guangzhou, China 1996–2008 Time-series	Deaths obtained from the Municipal Center for Disease Control and Prevention in each city	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1996–2008	NO ₂ (ppb) Shanghai Mean = 35.4±13.3 Beijing Mean = 30.6±13.1 Hong Kong Mean = 31.2±10.7 Guangzhou	COPD mortality data were obtained from the Municipal Center for Disease Control and Prevention in each city	Generalized Additive Model Adjusted for: day of the week, calendar time (natural spline), temperature (natural spline), and relative humidity (natural spline)	Lag 0–1 % Increase (95% CI) ^b COPD Mortality: 7.14% (5.39, 8.92)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 35.1±16.8			
Wong et al. (2008) n = 45.6 respiratory deaths/day Shanghai, Hong Kong, Wuhan, Bangkok, China, Taiwan Bangkok, 1999–2003 Hong Kong, 1996–2002 Shanghai and Wuhan, both 2001–2004 Time-series	Health data of adults (all ages) from the Ministry of Public Health in Bangkok, the Census and Statistics Department in Hong Kong, the Shanghai Municipal Center of Disease Control and Prevention in Shanghai, and the Wuhan Centre for Disease Prevention and Control in Wuhan	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1999–2004	NO ₂ (ppb) Bangkok Mean = 23.8 Median = 21.1 (IQR 12.3) Min = 8.4 Max = 74.19 Hong Kong Mean = 31.2 Median = 30 (IQR 13) Min = 5.47 Max = 89.02 Shanghai Mean = 35.4 Median = 33.2 (IQR 15) Min = 7.23 Max = 134.8 Wuhan Mean = 27.5 Median = 25.1 (IQR 13) Min = 10.2 Max = 67.71	Mortality data retrieved from local health authorities, bureaus of statistics, and centers for disease control	Generalized Additive Model Adjusted for: calendar time (natural spline), temperature, and relative humidity	Lag 0–1 % Increase (95% CI) ^b 5.70% (2.64, 8.85)
†Chen et al. (2018) N = ~290,000,000	Daily cause-specific mortality counts in 272	Fixed site monitor Method validation	NO ₂ (ppb) Overall	Daily death counts from respiratory	Bayesian Hierarchical Model	% Increase (95% CI) ^b Respiratory Mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
China 2013–2015 Time-series	main Chinese cities; all ages.	NR Averaging time: NO ₂ - annual average Exposure years: 2013–2015	Mean = 16±5.8 Median = 16 Min = 5.3 Max = 35 P25 = 12 P75 = 20	disease were obtained from China's Disease Surveillance Points System	Adjusted for: calendar time (natural spline), temperature (natural spline), relative humidity (natural spline), and day of the week	Lag 0: 3.43% (2.28, 4.59) Lag 1: 3.82% (2.85, 4.79) Lag 2: 2.28% (1.14, 3.43) Lag 3: 1.51% (0.19, 2.85) Lag 0–1: 4.59% (3.43, 5.76) COPD Mortality Lag 0: 4.59% (3.24, 5.96) Lag 1: 4.20% (2.85, 5.57) Lag 2: 1.89% (0.76, 3.05) Lag 3: 0.38% (-1.12, 1.90) Lag 0–1: 6.16% (4.40, 7.94)
† Gariazzo et al. (2023) n = 1,769,660 Italy 2013–2015 Time-series	Daily mortality counts (natural, cardiovascular, cardiac, ischemic, cerebrovascular, respiratory, mental, nervous, metabolic, diabetes) classified using ICD-10 codes from the Italian National Institute of Statistics	Hybrid model Cross-validation at R ² = 0.6 Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2015	NO ₂ (ppb) Rural Mean = 6.27 Median = 5 (IQR 3.9) Min = 1.4 Max = 39.2 P25 = 3.8 P75 = 7.65 Suburban Mean = 10.5 Median = 9.35 (IQR 6.01) Min = 2.3 Max = 56.02 P25 = 6.9	Mortality data retrieved from the Italian National Institute of Statistics	Poisson Adjusted for: municipality-specific long-term seasonal time trends, day of the week, province-specific air temperature, bank holidays, summer population decreases, and influenza epidemics.	% Increase (95% CI) ^b Lag 0–1: 4.82% (-5.64, 16.45) Lag 2–5: 24.30% (3.88, 48.73) Lag 0–5: 27.55% (4.00, 56.44)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 12.9 Urban Mean = 15.8 Median = 14.7 (IQR 8.29) Min = 3.2 Max = 61.6 P25 = 11.2 P75 = 19.5 Mean = 7.81 Median = 6.32 (IQR 5.74) Min = 1.4 Max = 61.6 P25 = 4.0 P75 = 9.99			
† Huang et al. (2021) n = 716,541 Shanghai, Tianjin, Beijing, Changsha, Chongqing, Guangzhou, Jinan, Lanzhou, Nanjing, Qingdao, Suzhou, Shenyang, Dalian, Hefei, Chengdu, Dazhou, Haerbin, Hengyang, Huanggang, Kunming, Linyi, Luoyang, Nanchang, Nanning, Nantong, Shijiazhuang, Suzhou, Weifang, Xian, Xiangyang, Xinyang, Yancheng, Zhengzhou, Zhoukou, Zunyi, China	Older adults aged 65 years and older from cities with daily COPD related death counts greater than 3 in individuals 65 years and older	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2017	NO ₂ (ppb) Mean = 21.4 Min = 13.2 Max = 29.0	Daily death counts of COPD were obtained from the Chinese Centers for Disease Control and Prevention	Generalized Additive Model Adjusted for: temperature (natural spline), relative humidity (natural spline), calendar time (natural spline), and day of the week	Lag 0–2 % Increase (95% CI) ^b COPD Mortality: 3.35% (2.05, 4.67)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2013–2017						
Time-series						
† Huang et al. (2022)	All-age cause specific mortality and morbidity data	Central site monitor	NO ₂ (ppb)	Mortality data obtained from Health Canada	Bayesian Hierarchical Model	Lag 0–1
n = NR			Calgary Mean = 21.5			% Increase (95% CI) ^b
Toronto, Vancouver, Edmonton, Calgary, Canada		Averaging time: NO ₂ - 24-hour average	Edmonton Mean = 19.5		Adjusted for: temperature (spline with 4 df)	7.16% (-2.81, 18.16)
1996–2012		Exposure years: 1996–2012	Toronto Mean = 21.9			
Case-crossover			Vancouver Mean = 16.5			
† Huang et al. (2023)	Daily mortality and hospitalizations (non-accidental all-cause, circulatory, and respiratory) using ICD-10 codes	Central site monitor	NO ₂ (ppb)	Hospital Morbidity Database and Discharge Abstract Database from the Canadian Institute for Health Information	Bayesian Hierarchical Model	Lag 0–1
n = NR			Mean = 16.7			% Increase (95% CI) ^c
Canada		Averaging time: 3-hour max	Median = 16.9		Adjusted for: temperature (spline with 4 df)	Non-informative prior: 0.25% (-1.25, 1.71)
2001–2018 (Hospitalizations)		Exposure years: 2001–2018	Min = 7.1			Weakly informative prior: 1.09% (0.02, 1.29)
2001–2015 (Mortality)			Max = 30			
Time-series			P25 = 12.9			
			P75 = 19.5			
† Li et al. (2021)	Deaths recorded in the Death Register and Report Information System of Chinese Center for Disease Control and Prevention	Central site monitor	NO ₂ (ppb)	Respiratory mortality: daily death counts from respiratory disease were obtained from the Chinese Centers	Generalized Additive Model	Lag 0–1
n = 9,600,000			Mean = 21.1±5			% Increase (95% CI) ^b
Shanghai, Tianjin, Beijing, Changsha, Chongqing, Guangzhou, Changchun, Fuzhou, Hohhot, Jinan,		Averaging time: NO ₂ - 24-hour average	Median = 20 (IQR 8.72)		Adjusted for: calendar time (natural cubic spline), 4-day moving average temperature	2.77% (1.74, 3.82)
			Min = 12.1			
			Max = 32.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Lanzhou, Nanjing, Qingdao, Suzhou, Xining, Shenyang, Dalian, Hefei, Chengdu, Dazhou, Haerbin, Hengyang, Huanggang, Kunming, Linyi, Luoyang, Nanchang, Nanning, Nantong, Shijiazhuang, Suzhou, Weifang, Xian, Xiangyang, Xinyang, Yancheng, Zhengzhou, Zhoukou, Zunyi, Qiqihaer, Suihua, Tangshan, Wulumuqi, Xiamen, Yantai, Yinchuan, Yueyang, Yuncheng, China 2013–2017 Time-series		Exposure years: 2013–2017		for Disease Control and Prevention	(natural cubic spline), and day of the week	
† Liu et al. (2019) n = 4,454 Hubei province, China 2013–2018 Case-crossover	Individuals identified in the Hubei provincial cause of death surveillance system who lived in Hubei before death and died from asthma	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2018	NO ₂ (ppb) Mean = 19.7±11.1 Median = 17.4 (IQR 13.9) Min = 0.85 Max = 82.54 P25 = 11.6 P75 = 26.0	Hubei provincial cause of death surveillance system	Logistic Regression Adjusted for: daily average temperature (natural cubic spline) and daily average relative humidity (natural cubic spline)	Lag 0–3 % Increase (95% CI) ^b Asthma Mortality: 16.11% (1.43, 32.91)
† Liu et al. (2022) n = 3,063,192 Georgia, Massachusetts, Michigan, New Jersey, Indiana, Kansas, Ohio, U.S.	Daily mortality (all-cause, cardiovascular, respiratory) classified by ICD-10 codes	Hybrid model Out-of-sample predicted r ² = 0.79 Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Mean = 21.2±12.1	Respiratory mortality: Death certificate data were obtained from each state's department of health	Logistic Regression Adjusted for: temperature (lag 0 and lag 1–3), humidity (lag 0 and lag 1–3), and lag -1 exposure (negative control)	Lag 0–2 % Increase (95% CI) ^b 1.84% (0.01, 3.70)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2000–2015		Exposure years: 2000–2015				
Case-crossover						
† Meng et al. (2021)	Mortality data (total, cardiovascular, and respiratory) obtained from local authorities within each selected country/region using ICD-9 and 10 codes	Fixed site monitor	NO ₂ (ppb)	Respiratory mortality data retrieved from local health authorities and bureaus of statistics	Poisson	Lag 1
n = 62,800,000		Averaging time: NO ₂ - 24-hour average	Pooled Median = 14.3 P25 = 10.4 P75 = 19.2		Adjusted for: calendar time (natural cubic spline), temperature (natural spline), and relative humidity (natural spline)	% Increase (95% CI) ^b 1.78% (0.81, 2.76)
United States, Sweden, China, United Kingdom, Canada, Spain, Japan, South Korea, Taiwan, Brazil, Switzerland, Colombia, Thailand, Germany, Czech Republic, Greece, Australia, Finland, Chile, Estonia, Portugal, Romania		Exposure years: 1973–2018	United States Median = 15.3 P25 = 11.1 P75 = 20.5			
1973–2018						
Time-series						
† Perez et al. (2015)	ED admissions and deaths (all cause, cardiovascular, respiratory) classified using ICD-10 codes	Central site monitor	NO ₂ (ppb)	Respiratory mortality data obtained from the Federal Office of Statistics and the Statistical Offices of the cantons of Valais and Grisons	Poisson	Lag 0–3
n = 2,240,694		Averaging time: NO ₂ - 24-hour average	Region AG/BE/LU/SO Mean = 21		Adjusted for: day of the week, holiday, temperature, relative humidity, barometric pressure, daily influenza incidence, and calendar time (penalized spline)	% Increase (95% CI) ^b 10.55% (1.80, 20.04)
Switzerland						
1995–2010		Exposure years: 1995–2010	Region AG/BL/BS/SO Mean = 14.1			
Time-series			Region AI/AR/FL/SG Mean = 9.62			
			Region AI/AR/SG/TG			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 8.18			
			Region BE Mean = 14.6			
			Region BE/FR/SO Mean = 8.61			
			Region GR Mean = 16.6			
			Region LU/NW/OW/ SZ/UR Mean = 12.6			
			Region LU/ZG Mean = 14.3			
			Region SG/SH/SZ/ZH Mean = 19.1			
			Region TISoprace- neri/GR Mean = 13.0			
			Region TISottoceneri Mean = 20.4			
			Region VS Mean = 18.9			
† Schwarz et al. (2024)	Mortality data from the MCC database	Central site monitor	NO ₂ (ppb)	Respiratory mortality data retrieved from	Poisson	Lag 1
n = 29,300,000 (estimate as			Median = 13.6		Adjusted for: calendar	% Increase (95% CI) ^b

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
exact numbers are not reported)		Averaging time: NO ₂ - 24-hour average	P25 = 9.94 P75 = 18.3	local health authorities and bureaus of statistics	time (natural spline), day of the week, 4-day moving average temperature (natural spline), and 3-day moving average relative humidity (natural spline)	1995–2001: 1.48% (-0.19, 3.16) 2002–2008: 2.09% (0.91, 3.28) 2009–2016: 1.36% (0.47, 2.26)
United States, Sweden, China, France, United Kingdom, Canada, Spain, Japan, South Korea, Taiwan, Iran, South Africa, Switzerland, Norway, Colombia, Thailand, Czech Republic, Greece, Mexico, Finland, Estonia, Portugal, Cyprus, Kuwait		Exposure years: 1994–2016				
January 1, 1995–December 31, 2016						
Cross-Sectional						
† Shin et al. (2021)	Daily counts of respiratory hospital admissions and mortality data (ages 1+ years) from the Canadian Institute for Health Information and the national Vital Statistics database, respectively.	Central site monitor	NO ₂ (ppb)	Respiratory mortality data were obtained from National Vital Statistics	Bayesian Hierarchical Model	Lag 0
n = 8,487 deaths/year		Averaging time: NO ₂ - 24-hour average	Cold Season Mean = 20±3.7 Warm Season Mean = 18±3.5		Adjusted for: day of the week, calendar time (Slepian smoother), and temperature (natural spline)	% Increase (95% CI) ^b : 4.24% (1.32, 7.25)
24 Canadian Cities, Canada		Exposure years: 1996–2012 (Hospital admissions) 1984–2012 (Mortality)				
1996–2012 (Hospital admissions)						
1984–2012 (Mortality)						
Time-series						
List of abbreviations in alphabetical order: AG = Aargau; AI = Appenzell Innerrhoden; AR = Appenzell Ausserrhoden; BE = Bern; BL = Basel-Landschaft; BS = Basel-Stadt; CA = California; CAPES = China Air Pollution and Health Effects Study; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CY = Cyprus; df = degrees of freedom; FL = Fürstentum Liechtenstein; FR = Fribourg; GR = Graubünden; ICD = International Classification of Diseases; IQR = interquartile range; LU = Luzern; MCC = Multi-Country Collaborative; MISA = Meta-analysis of the Italian studies on short-term effects of air pollution; NO ₂ = nitrogen dioxide; NR = not reported; OW = Obwalden; ppb = parts per billion; P# = #th percentile; RR = relative risk; SG = St. Gallen; SO = Solothurn; SZ = Schwyz; TG = Thurgau; TI = Ticino; UR = Uri; U.S. = United States; VS = Valais; ZG = Zug; ZH = Zürich.						
^a For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.						
^b Effect estimates are standardized and are presented as a 20 ppb change in NO ₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO _x for 24-hour averaging time; 25 ppb change in NO ₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO _x for 1-hour maximum averaging time; 25 ppb change in						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
NO ₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO _x for 8-hour maximum averaging time; a 10 ppb change in NO ₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO _x for annual average averaging time.						
^a Estimates are not standardized.						
†Studies published since the 2016 Oxides of Nitrogen ISA.						

A.2. Respiratory Effects – Long-term Exposure

Appendix Table 4-1 Epidemiologic studies of long-term exposure to oxides of nitrogen and asthma incidence in children

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Carlsten et al. (2011b) n = 184 Vancouver, Canada Enrollment: 1995 Follow-up: 2003 Cohort	Birth cohort of children with a high risk of asthma: 1 parent/sibling with asthma or 2 parents/siblings with other allergic disease.	LUR Model validated against central site monitor: $R^2 = 0.69$ Model validated against mobile monitors: $R^2 = 0.44$ Averaging time: NO ₂ - annual average Exposure years: 1995 (temporally adjusted from 2003 annual estimates)	NO ₂ (ppb) Mean = 17.3±3.1	Asthma incidence: diagnosis of asthma upon evaluation by a single pediatric allergist	Logistic Regression Adjusted for: Individual level: intervention group, atopy at 12 months, ethnicity, gender, mother, father or sibling history of asthma, and maternal post-secondary education.	OR (95% CI) ^b 2.89 (0.76, 10.96)
Clark et al. (2010) n = 20,364 Southwest British Columbia, Canada Enrollment: 1999–2000 Follow-up: 2003 Case-Control	Administrative birth cohort from the BC Ministry of Health Services, the BC Vital Statistics Agency, and the BC Perinatal Database Registry. Children were excluded for low birth weight, preterm birth, or multiple births.	LUR, Central site monitor Model validated against central site monitors: $R^2 = 0.69$ Model validated against mobile monitors: $R^2 = 0.44$ Averaging time: NO ₂ - annual average	NO ₂ (ppb) IDW Asthma Cases Mean = 16.31±4.81 Median = 16.99 (IQR = 6.66) P25 = 12.90 P75 = 19.57 Controls Mean = 15.87±4.70 Median = 15.93 (IQR = 6.54) P25 = 12.60	Asthma incidence: cases were defined as children with a minimum of two primary care physician diagnoses in a rolling 12-month period or a minimum of one hospital admission for asthma	Logistic Regression Adjusted for: Individual level: parity, breast-feeding, income, maternal education status, birth weight, and gestational length.	OR (95% CI) ^b LUR: 1.26 (1.08, 1.47) IDW (central site): 1.24 (1.14, 1.34)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		Exposure years: 1999–2000	P75 = 19.14 LUR Asthma Cases Mean = 15.85±2.90 Median = 15.34 (IQR = 3.68) P25 = 13.90 P75 = 17.58 Controls Mean = 15.7±2.81 Median = 15.27 (IQR = 2.60) P25 = 13.8 P75 = 17.4			
Gehring et al. (2010) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort n = 3,863 West, North, Center, The Netherlands Enrollment: 1996–1997 Follow-up: 8 years Cohort	Birth cohort formed by recruiting women in second trimester of pregnancy	LUR R ² = 0.85 Averaging time: Not mentioned in LUR description Exposure years: NR	NO ₂ (ppb) Mean = 13.5 Median = 14 (IQR = 5.53) Min = 6.7 Max = 31 P10 = 7.81 P25 = 9.83 P75 = 15.4 P90 = 18.4	Asthma incidence: parental reported	Generalized estimating equation Adjusted for: Individual level: sex, study arm (intervention or natural history), use of mite-impermeable mattress covers, allergies of mother and father, maternal and paternal education, maternal smoking during pregnancy, breastfeeding, presence of a gas stove in the child's home, presence of older siblings, smoking, signs of dampness and pets in the child's home, day-care attendance, and Dutch nationality	OR (95% CI) ^b 1.32 (0.94, 1.86)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Gruzieva et al. (2013) Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) n = 3,633 Stockholm County, Sweden Enrollment: 1994–1996 Follow-up: First 12 years of life Cohort	Children born between 1994 and 1996 in 4 municipalities in Stockholm County, representing urban and suburban areas	Dispersion model R ² = 0.74-0.80, range Averaging time: NO _x - annual average Exposure years: 1994–2008	NO _x (µg/m ³) 2–4 years Mean = 13.4 4–8 years Mean = 10.6 8–12 years Mean = 7.8 First year of life Mean = 21.4 Second year of life Mean = 18.6	Asthma incidence: 1–2 y: asthma defined as three or more episodes of wheeze in combination with treatment with inhaled corticosteroids or signs of bronchial hyperreactivity without concomitant respiratory infection. 4, 8, and 12 y: at least four episodes of wheeze in the last 12 months, or at least one episode in combination with prescription of inhaled corticosteroids	Logistic Regression Adjusted for: Individual-level: municipality, socioeconomic status, heredity, and the year the house was built.	OR (95% CI) ^c 1.87 (1.00, 3.44)
MacIntyre et al. (2014a) Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE), Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort, German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy (GINIplus), Life Style	High-risk infants randomized prior to birth	LUR, Dispersion model Averaging time: NO ₂ - annual average Exposure years: 1999–2000, 2003, 2004–2005, 2007 (differed by cohort)	NO ₂ (ppb) Mean = 12.1±4.3 IQR = 5.47 Min = 1.2 Max = 35.5	Asthma incidence: parental-reported physician diagnosed asthma	Logistic Regression Adjusted for: Individual level: study cohort, city, intervention, infant sex, maternal age at birth, maternal smoking during pregnancy, environmental tobacco smoke in the home, birth weight, and parental atopy.	OR (95% CI) ^b 1.48 (1.06, 2.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Factors on the Development of the Immune System and Allergies in East and West Germany birth cohorts (LISA), Study on Global Aging and Adult Health (SAGE), Gene and Environment: Prospective Study on Infancy (GASPII)						
n = 5,115						
Sweden, Canada, Germany, Netherlands, Italy						
Follow-up: Until 8 years of age						
Cohort						
Oftedal et al. (2009)	Children born in Oslo 1992–1993 and resided in Oslo in the first year of life and in the last year	Dispersion model, Other R ² (in winter) = 0.37, R ² (all seasons) = 0.58 Averaging time: NO ₂ - annual average, Other, NO ₂ annual average of birth to asthma onset Exposure years: 1992–2002	NO ₂ (ppb) 1st year of life Mean = 20.9 Median = 21.5 (IQR = 14.8) Min = 0.8 Max = 45 P25 = 13.2 P75 = 28.1 2nd year of life Mean = 16.5 Median = 16.9 (IQR = 12.8) Min = 0.9 Max = 37.5	Asthma incidence: parental-reported physician diagnosed asthma	Cox PH Model Adjusted for: Individual level: sex, parental atopy, paternal education, maternal smoking in pregnancy, maternal marital status at the child's birth, and cohort.	RR (95% CI) ^b 0.87 (0.76, 1.00)
Oslo Birth Cohort						
n = 2,871						
Oslo, Norway						
Enrollment: 1992–1993 Follow-up: 2001–2002						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 9.99 P75 = 22.8 Previous year Mean = 13.4 Median = 13.4 (IQR = 9.6) Min = 0.74 Max = 34.6 P25 = 8.34 P75 = 17.9			
Ranzi et al. (2014) Gene and Environment Prospective Study on Infancy in Italy (GASPII) n = 672 Rome, Italy Enrollment: June 2003–October 2004 Follow-up: 6 months, 15 months, 4 years, 7 years Cohort	Newborns enrolled at delivery from two obstetric hospitals	LUR R ² = 0.704 Averaging time: NO ₂ - annual average, Other, NO ₂ time-weighted average of exposure from conception to 6 months before interview Exposure years: 2007	NO ₂ (ppb) Mean = 20.13 Median = 19.9 (IQR = 4.54) Min = 8.08 Max = 31.66 P10 = 15.59 P25 = 17.8 P75 = 22.34 P90 = 25.06	Asthma incidence: parental reported; Respiratory questionnaire was adapted from the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire for school children	Logistic Regression Adjusted for: Individual level: gender, age, breastfeeding at 3 months, presence of any pets in home, siblings, day-care attendance, maternal and paternal smoking, maternal smoking during pregnancy, maternal and paternal education, presence of molds or dampness at home, familial asthma or allergies	OR (95% CI) ^b 1.17 (0.62, 2.19)
†Buteau et al. (2020) n = 722,667 Quebec, Canada Enrollment: April 2002–March 2011	Children born in Quebec, Canada 2002–2011, identified with health administrative datasets	Dispersion model – NO ₂ from industrial sources Averaging time: NO ₂ - annual average	NO ₂ (µg/m ³) Dispersion models Mean = 1.26±20.28 Median = 0.91 (IQR 1.06) Min = 0 Max = 60.57	Asthma incidence: Quebec Integrated Chronic Disease Surveillance System; Two or more physician claims or at least one hospital	Cox PH Model Adjusted for: Individual level: age, sex, and calendar year. Contextual: material and social deprivation.	HR (95% CI) ^c 1.21 (1.19, 1.23)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow-up: April 2002–March 2011 Cohort		Exposure years: 2002–2011	P10 = 0.21 P25 = 0.58 P75 = 1.64 P90 = 2.51 P99 = 5.4	discharge for asthma within 2 years		
† Dearborn et al. (2023) the Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) cohort, the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) study, Environmental Influences on Child Health Outcomes ECHO-PATHWAYS, The Infant Development and the Environment Study (TIDES) n = 224 Seattle, WA; Shelby County, TN; San Francisco, CA; Minneapolis, MN; Rochester, NY, U.S. Enrollment: 2006–2016 Follow-up: when children were 4–6 years Cohort	Recruited women aged 16–40 years in their second trimester with a singleton, low-medical-risk pregnancy; children with bronchiolitis	Spatiotemporal/geospatial model Averaging time: NO ₂ 2-year average Exposure years: 2006–2019	NO ₂ (ppb) Median = 8.5 (IQR = 3.5) P25 = 6.4 P75 = 9.9	Asthma prevalence: parental reported; Respiratory questionnaire was adapted from the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire for school children	Poisson Adjusted for: Individual level: age at outcome assessment, sex, season, year of birth, site, race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, index, cotinine, and reported postnatal secondhand smoke exposure. Contextual: neighborhood deprivation.	RR (95% CI) ^b 0.34 (0.16, 0.72)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Fuertes et al. (2020)	Participants in European birth cohorts	LUR, Dispersion model	NO ₂ (ppb)	Asthma prevalence: parental reported	Logistic Regression	NO ₂
Gene and Environment Prospective Study on Infancy in Italy (GASPII), INMA, Infancia y Medio Ambiente, Etude des Determinanta pre-et postnatal du developpement et de la sante de l'Enfant (EDEN), Born In Bradford (BIB), Mother-child Greek cohort (RHEA)		Method validation NR	BIB Mean = 12.7 Median = 12.5		Adjusted for: Individual level: sex, exact age at follow-up, maternal and paternal asthma and hay fever, maternal and paternal education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home during early-life, mold or dampness at home during early-life, furry pets in the home during early-life, use of gas for cooking.	OR (95% CI) ^b Age 4 y: 0.91 (0.63, 1.31) Age 8 y: 1.18 (0.84, 1.64)
n = 6,856		Averaging time: NO ₂ - annual average, NO _x - annual average	EDEN Mean = 11.5 Median = 10.5			NO _x
Rome, Italy; Gipuzkoa, Spain; Sabadell, Spain; Valencia, Spain; Nancy, France; Poitiers, France; Bradford, U.K.; Heraklion, Greece		Exposure years: 2002–2011	GASPII Mean = 23.5 Median = 23			OR (95% CI) ^b Age 4 y: 0.98 (0.86, 1.11) Age 8 y: 1.14 (0.93, 1.14)
2003–2011			INMA - Sab Mean = 20.1 Median = 20.9			
Cohort			INMA - Val Mean = 14.5 Median = 14.6			
			INMA Gip Mean = 8.18 Median = 8.56			
			RHEA Mean = 6.54 Median = 5.95			
			NO _x (ug/m ³)			
			BIB Mean = 39.4 Median = 39.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			GASPII Mean = 69.8 Median = 65.5			
			INMA - Gip Mean = 31.5 Median = 32.9			
			INMA - Sab Mean = 65.3 Median = 65.9			
			INMA - Val Mean = 44 Median = 43.9			
			RHEA Mean = 17.6 Median = 16.3			
† Gehring et al. (2015)	Participants were from European birth cohorts with health outcomes measured during childhood and adolescence	LUR R ² = 0.82-0.89 Averaging time: NO ₂ - annual average Exposure years: 2008–2010	NO ₂ (ppb) Birth address Mean = 10.8 Min = 3.0 Max = 33.4 Latest address Mean = 9.8 Min = 1.9 Max = 32.4	Asthma incidence: parental reported	Cox PH Model Adjusted for: Individual level: sex, maternal and paternal asthma and hay fever, native nationality, parental education, breastfeeding, older siblings, day-care attendance, maternal smoking during pregnancy, parental smoking at home, mold or dampness at home, pets, use of gas for cooking, municipality (BAMSE only), and cohort.	OR (95% CI) ^b 1.26 (1.04, 1.52)
Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE), Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort, German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy (GINIplus), Lifestyle-related factors on the Immune System and the						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
development of Allergies in childhood (LISApplus) study n = 14,126 Munich, Germany; Stockholm County, Sweden; North Rhine-Westphalia, Netherlands Enrollment: 1994–1999 Follow-up: 14–16 years Cohort						
† Gehring et al. (2020) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort N = 2,135 Nationwide, Netherlands Recruitment: 1996–1997 Follow-up: 20 years Cohort	All participants with data on incident asthma and data on air pollution exposure at the birth address and/or current address for at least one of the questionnaire surveys were included (n = 3687), of which 90% (3314 out of 3687) had data for seven or more of the 12 questionnaire surveys, and only few (59 (3%) out of 3687) had data for a single questionnaire survey only.	LUR, Averaging time: NO ₂ - annual average Exposure years: 2008–2010	NO ₂ (ppb) 20-year follow-up address Mean = 13.5±3.9 Median = 13 (IQR = 4.7) Min = 5 Max = 33.7 Birth Address Mean = 12.9±3.8 Median = 12.9 (IQR = 4.9) Min = 4.8 Max = 46.6	Asthma incidence: parental reported; MeDALL guidelines	Logistic Regression Adjusted for: Individual level: sex, age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking, mold/dampness at home, pets, and use of gas for cooking.	OR (95% CI) ^b 1.33 (1.08, 1.63)
† Knibbs et al. (2018) Australian Child Health and	Children aged 7–11 years during 2007–2008. Randomly	Central site monitor, LUR, Central site monitor	NO ₂ (ppb) Recent exposure	Asthma prevalence: parental reported; Respiratory	Logistic Regression Adjusted for:	OR (95% CI) ^b Lifetime avg NO ₂ : 1.54 (1.08, 2.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Air Pollution Study (ACHAPS) n = 2,630 Western Australia, Victoria, New South Wales, Queensland, South Australia, Australian Capital Territory, Australia 2007-2008 Cross-Sectional	selected classes within 55 schools	$R^2 = 0.76$ Averaging time: NO ₂ - annual average Exposure years: 2006–2011	(average in prior year) Mean = 8.8 Median = 7.9 (IQR = 4)	questionnaire was adapted from the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire for school children	Individual level: age, sex, and parental education. Contextual: index of education and occupation and index of relative socio-economic advantage and disadvantage.	Annual avg NO ₂ : 2.92 (1.79, 4.76)
†Lavigne et al. (2018) n = 761,172 Ontario, Canada April 1, 2006-March 31, 2012 Cohort	Cohort of pregnant women who gave birth to live-born singleton infants	LUR Averaging time: NO ₂ - annual average Exposure years: 2006-2012	NO ₂ (ppb) First trimester: Mean = 13.2±7.8 Second trimester: Mean = 13.2±7.8 Third trimester: Mean = 13.1±7.8 Pregnancy average: Mean = 13.2±7.8 First year of life: Mean = 13.1±7.8 Lifetime exposure: Mean = 13.0±7.8	ICD-10 codes from the Ontario Asthma Surveillance Information System	Cox proportional hazards models Adjusted for: maternal age at delivery, infant sex, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, maternal atopy, gestational age, birthweight, residential greenness exposure during pregnancy, dissemination area median family income, dissemination area proportion of population who are visible minority and dissemination area proportion of the adult female population aged 25–64 years old who completed post-secondary education	HR (95% CI) ^b First trimester: 1.13 (1.10, 1.15) Second trimester: 1.20 (1.18, 1.22) Third trimester: 0.99 (0.97, 1.01) Entire pregnancy: 1.11 (1.08, 1.14) First year of life: 1.09 (1.07, 1.11) Lifetime exposure: 1.00 (0.98, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Oudin et al. (2017) n = 745,171 Stockholm, Västra Götaland, Skåne, Västerbotten, Sweden Enrollment: 2005 Follow-up: 2007–2010 Cohort	Individuals under 18 years of age who had a registered address in study area 2007–2010. Exclusion if had record of dispensed asthma medication 2005–2006	LUR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Cases: Mean = 5.6 Controls: Mean = 5.4	Asthma incidence: Data from the Swedish National Board of Health and Welfare on dispensed medication related to asthma	Logistic Regression Adjusted for: Individual level: age at baseline, sex, maternal and paternal education, smoking, and maternal BMI.	OR (95% CI) ^b 1.04 (1.02, 1.06)
†Pedersen et al. (2023) Danish Medical Birth Registry n = 1,060,154 Denmark Enrollment: 1998–2016 Follow-up: 1998–2017 Cohort	Singleton births born between 1998–2016	Hybrid model R ² (range, including other pollutants; NO ₂ not specified) = 0.54–0.89 Averaging time: NO ₂ - annual average Exposure years: 1997–2017	NO ₂ (ppb) Prenatal exposures Mean = 9.3±3.9 Postnatal exposures Mean = 8.93±4	Asthma incidence: first registered diagnosis from hospital admission, emergency room, and outpatient contacts	Cox PH Model Adjusted for: Individual level: age, sex, household income, maternal education, birth order, season of birth, smoking during pregnancy, and municipality.	HR (95% CI) ^b Prenatal exposure: 1.09 (1.05, 1.12) Postnatal exposure: 1.04 (1.01, 1.08) Prenatal exposure adjusted for postnatal: 1.07 (1.02, 1.11)
†Sbihi et al. (2016) n = 65,254 Vancouver metropolitan region, Canada Enrollment: 1999–2002 Follow-up: Until 10 years of age	Children born in greater Vancouver metropolitan region to mothers with universal health insurance program and who resided for complete pregnancy in Vancouver	LUR, IDW Averaging time: NO and NO ₂ - time-weighted average exposure incorporating residential mobility during pregnancy	NO ₂ (ppb) Pre-school Cases: 17.9±3.6 Controls: 17.7±3.7 School age Cases: 17.8±3.6	Asthma incidence: Billing and hospital discharge records; two primary-care physician diagnoses or one hospital admission in a rolling 12-month period	Logistic Regression Adjusted for: Individual level: breastfeeding status at the time of discharge, parity, maternal education, household income,	OR (95% CI) ^b IDW: 1.18 (1.09, 1.27) LUR: 1.02 (0.97, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort			Controls: 17.9±3.7		gestational length and birthweight.	
† Sbihi et al. (2017) n = 65,254 Vancouver, Canada Enrollment: 1999–2002 Follow-up: 10 years Cohort	Birth cohort in Vancouver	Hybrid model Averaging time: NO ₂ - Average over pregnancy period	NO ₂ (ppb) Median = 17.7	Asthma incidence: Billing and hospital discharge records; two primary-care physician diagnoses or one hospital admission in a rolling 12-month period	Multinomial logistic regression Adjusted for: Individual level: sex, parity, breastfeeding initiation, birth weight, delivery mode, maternal smoking, maternal educational attainment, and household income.	RR (95% CI) ^c relative to nonasthma trajectory Chronic asthma trajectory; early onset: 1.51 (1.22, 1.89) Chronic asthma trajectory; late onset: 1.25 (1.07, 1.46) Transient asthma trajectory: 1.08 (0.94, 1.23)
† Tétreault et al. (2016a) n = 216,746 Quebec, Canada Enrollment: April 1996–March 2011 Follow-up: April 1996–March 2011 Cohort	Children born in Quebec identified using administrative health databases	LUR Averaging time: NO ₂ - annual average Exposure years: 1996–2011	NO ₂ (ppb) Birth address Mean = 15.51 Median = 15.07 (IQR = 5.45) Min = 4.47 Max = 35.9 P25 = 12.67 P75 = 18.12 Time-varying exposures Mean = 14.8 Median = 14.35 (IQR = 5.27) Min = 4.47 Max = 39.36	Asthma incidence: Quebec Integrated Chronic Disease Surveillance System; Two or more physician claims or at least one hospital discharge for asthma within 2 years	Cox PH Model Adjusted for: Individual level: year of birth and sex. Contextual: indices of social and material deprivation.	HR (95% CI) ^b Annual average at birth: 1.07 (1.05, 1.10) 1-year moving average: 1.07 (1.05, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 12.02 P75 = 17.29			
† Yu et al. (2024) Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE) n = 2,371 Stockholm, Sweden Enrollment: 1994–1996 (at birth) Follow-up: through 24 years old Cohort	Population-based birth cohort with newborns recruited in the Stockholm region, Sweden.	Dispersion model Model validated against one traffic monitoring site and two urban background sites (R ² = 0.98) Averaging time: NOx - annual average Exposure years: 1990–2020	NOx (µg/m ³) 8-yr Follow-up Mean = 16.8±14.03 First year of life Mean = 28.9±24.1	Asthma incidence: parental- or self-reported; questionnaire for asthma incidence based on MeDALL guidelines	Cox PH Hazard Model Adjusted for: Individual level: age, sex, air pollution exposure at baseline, parental education, and parental occupation. Contextual: neighborhood median income at birth	OR (95% CI) ^b All asthma: 0.94 (0.83, 1.05) Nonallergic asthma: 0.86 (0.75, 1.00) Allergic asthma: 1.05 (0.87, 1.27)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Zanobetti et al. (2024) The Environmental Influences on Child Health Outcomes (ECHO) Children’s Respiratory and Environmental Workgroup (CREW) consortium n = 5,279 Boston, MA; Bronx, NY; Baltimore, MD; St. Louis, MO; Los Angeles, CA; New York City, NY; Detroit, MI; Manhattan, NY; Cincinnati, OH; Tucson, AZ; Madison, WI, U.S. Enrollment CAS: 1987–1989 CCAAPS: 2001–2003 CCCEH: 1998–2006 COAST: 1998–2000 EHAAS: 1994–1996 IIS: 1997–2003 URECA: 2004–2006 WHEALS: 2003–2007 Follow-up through 11 years old Cohort	8 of the 12 longitudinal birth cohorts participating in CREW, representing a diverse sample of children throughout the U.S. in urban, suburban, and rural environments.	Hybrid model Averaging time: NO₂ - annual average Exposure years: Varied by cohort. Exposure periods included first year of life, average of year 1 and 2, and average of years 1 through 3	Exposure concentrations presented graphically.	Asthma incidence: caregiver report of physician-diagnosed asthma	Cox PH Model Adjusted for: Individual level: mother’s education, child’s race and ethnicity, sex, smoking during pregnancy, parental history of asthma and an indicator variable for cohort	HR (95% CI)^b Asthma incidence - 4 y: 1.99 (1.09, 3.63) Asthma incidence - 11 y: 1.85 (1.12, 3.05)

List of abbreviations in alphabetical order: ACHAPS = Australian Child Health and Air Pollution Study; BAMSE = Children, Allergy, Milieu, Stockholm, Epidemiological Survey; BC = British Columbia; BMI = body mass index; CAS = Childhood Asthma Study; CCAAPS = Cincinnati Childhood Allergy and Air Pollution Study; CCCEH = Columbia Center for Children's Environmental Health; CI = confidence interval; CREW = Children's Respiratory and Environmental Workgroup; EHAAS = Environmental Health and Allergy Study; ECHO = Environmental Influences on Child Health Outcomes; FACES = Fresno Asthmatic Children's Environment Study; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GASPII = Gene and Environment Prospective Study on Infancy in Italy; Gip = Gipuzkoa; GINIplus = German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy; HR = hazard ratio; IDW = inverse distance weighting; IIS = Infant Immune Study; INMA; Environment and Childhood (in Spanish); ISAAC = International Study on Asthma and Allergies in Childhood; IQR = interquartile range; LISApplus = Lifestyle-related factors on the Immune System and the development of Allergies in childhood study; LUR = land use regression; MeDALL = Mechanisms of the Development of ALLergy; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OP = organophosphate; OR = odds ratio; P# = #th percentile; PIAMA = Prevention and Incidence of Asthma and Mite Allergy Birth Cohort; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than 10 µm; ppb = parts per billion; RHEA = Mother-child Greek cohort; RR = relative risk; Sab = Sabadell; SAGE = Study of African Americans, Asthma, Genes, and Environments; TIDES = The Infant Development and the Environment Study; URECA = Urban Environment and Childhood Asthma; Val = Valencia; WHEALS = Wayne County Health, Environment, Allergy and Asthma Longitudinal Study; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-2 Epidemiologic studies of long-term exposure to oxides of nitrogen and asthma incidence in adults

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Castro-Giner et al. (2009) European Community Respiratory Health Survey (ECRHS II) n = 2,577 Barcelona, Albacete, Huelva, Galdakao, Oviedo, Spain; Paris, Grenoble, France; Umeå, Uppsala, Sweden; Ipswich, Norwich, U.K.; Erfurt, Germany; Antwerp, Belgium Enrollment: 1990 Follow-up: 10 years later	Adults 20–44 years of age at recruitment to cohort. Cohort sampled randomly from multiple locations	Spatio-temporal model	NR	Asthma incidence: Self-reported	Logistic Regression Adjusted for: Individual level: center, sex, age, environmental tobacco smoke, and smoking status.	OR (95% CI) ^b Non-movers: 2.39 (1.10, 5.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort						
Jacquemin et al. (2009) European Community Respiratory Health Survey (ECRHS) n = 4,185 Barcelona, Albacete, Huelva, Galdakao, Oviedo, Spain; Paris, Bordeaux, Grenoble, Montpellier, France; Umeå, Uppsala, Goteborg, Sweden; Ipswich, Norwich, U.K.; Erfurt, Hamburg, Germany; Antwerp, South Antwerp, Belgium; Basel, Switzerland; Reykjavík, Iceland; Bergen, Norway; Tartu, Estonia; Groningen, Geleen, Bergen op Zoom, Netherlands; Verona, Pavia, Turin, Italy Enrollment: 1991–1993 Follow-up: 1999–2001	Adults aged 20–44 in 1991–1993 were randomly selected from 28 cities in 11 western European countries. Inclusion included no asthma at enrollment	LUR R ² = 0.60 Exposure years: 2001	NO ₂ (ppb) Range of medians across cities = 6.4 to 30.3	Asthma incidence: Self-reported	Logistic Regression Adjusted for: Individual level: sex, age, socioeconomic status, atopy, family history of asthma or atopy, and smoking	OR (95% CI) ^b 1.96 (1.04, 3.71)
Cohort						
Modig et al. (2009) European Community Respiratory Health Survey (ECRHS), Respiratory Health in Northern Europe (RHINE)	Adults in certain Swedish cities born between 1945 and 1973 with negative answers to questions regarding if they had an asthma attack in the year prior	Dispersion model, Other R ² (Gothenburg) = 0.79, R ² (Uppsala) = 0.71, R ² (Umea) = 0.68	NO ₂ (ppb) Mean = 9.51±3.4 (17.9±6.4 µg/m ³) Median = 9.14 (IQR 5) (17.2 µg/m ³ (IQR 9 µg/m ³)	Asthma incidence: Self-reported	Logistic Regression Adjusted for: Individual level: city, sex, body mass index, age, smoking history,	OR (95% CI) ^b 2.25 (1.00, 5.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 3,824 Gothenburg, Umeå, Uppsala, Sweden Enrollment: 1990 Follow-up: 1999 Cohort	or are taking medicine for asthma	Averaging time: NO ₂ monthly average during winter Exposure years: 1990	Min = 1.8 (3.3 µg/m ³) Max = 24.2 (45.6 µg/m ³) P25 = 6.86 (12.9 µg/m ³) P75 = 11.6 (21.9 µg/m ³)		water damage or mold in the home at any time during the last 8 yrs.	
† Gandini et al. (2018b) Italian Longitudinal Study (ILS) N = 74,989 Italy Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008 Cohort	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity. Averaging time: NO ₂ - annual average Exposure years: 1999, 2003, 2005, 2007	NO ₂ (ppb) Men <i>Metropolitan</i> Mean = 22.1±6.16 <i>Rural</i> Mean = 10.3±4 <i>Urban</i> Mean = 13.9±5.2 Women <i>Metropolitan</i> Mean = 22.1±6.16 <i>Rural</i> Mean = 10.3±4.2 <i>Urban</i> Mean = 13.9±5.1	Asthma incidence: Health records database; first hospital admission for asthma	Cox PH Model Adjusted for: Individual level: age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, and BMI. Contextual: type of municipality (rural, urban, metropolitan areas)	HR (95% CI) ^b 1.12 (0.81, 1.54)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Liu et al. (2021a) †Brunekreef et al. (2021) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), Danish Nurse Cohort (DNC), Stockholm Diabetes Prevention Program (SDPP), Stockholm Cohort of 60-year-olds (SIXTY), Stockholm Screening Across the Lifespan Twin study (SALT) N = 98,326 Stockholm, Kungsholmen, Sweden; Nationwide, Denmark Recruitment: 1992–2004 Follow-up: 2011–2015 Cohort	Excluded 821 with asthma diagnoses before the beginning of follow-up and 7580 with missing information on confounders.	LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Asthma Mean = 13.95±4.14 (26.25±7.79 µg/m ³) No Asthma Mean = 13.33±4.24 (25.08±7.97 µg/m ³) Total Mean = 13.3±4.24 (25.1±7.97 µg/m ³)	Asthma incidence: First inpatient, outpatient, or ED visit for asthma for the Danish cohorts and first inpatient visit for Swedish cohort	Cox PH Model Adjusted for: Individual level: age, sex, study, calendar year of baseline, smoking status, smoking duration, smoking intensity, BMI, marital status, employment status, and education level. Contextual: area-level mean income.	HR (95% CI) ^b <40 ug/m ³ : 1.43 (1.26, 1.62) <30 ug/m ³ : 1.61 (1.30, 2.01) <20 ug/m ³ : 1.50 (0.86, 2.63)
†Liu et al. (2021d) Danish Nurse Cohort n = 28,731 Denmark	Female nurses older than 44 years of age	Hybrid model Averaging time: NO ₂ - annual average	NO ₂ (ppb) Mean = 6.797±4.19 IQR = 4.35 Min = 1.36 Max = 41.86	Asthma incidence: Danish National Patient Register; First inpatient, outpatient, or	Cox PH Model Adjusted for: Individual level: age, year of baseline, calendar year of follow-up, smoking status,	HR (95% CI) ^b <40 ug/m ³ : 1.58 (1.25, 1.98) <30 ug/m ³ : 1.80 (1.35, 2.40) <20 ug/m ³ : 1.89 (1.27, 2.80) <15 ug/m ³ : 2.13 (1.18, 3.85)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 1993–1999 Follow-up: 1993–2015 Cohort		Exposure years: NA		ED visit for asthma	smoking duration, smoking intensity, marital status, occupational status, leisure time, physical activity status, vegetable consumption, avoids fatty meat, and alcohol consumption.	<10 ug/m ³ : 0.80 (0.20, 3.27)
†Shin et al. (2021) Ontario Population Health and Environment Cohort (ONPHEC) n = 5,064,225 Ontario, Canada Enrollment: 2001–2015 Follow-up: 2001–2015 Cohort	Participants aged 35–85 years who were eligible for a publicly funded health insurance program, no physician diagnosed COPD or asthma	LUR R ² = 0.73 Averaging time: NO ₂ - annual average Exposure years: 2005–2011	NO ₂ (ppb) Mean = 18±8	Asthma incidence: Two or more ambulatory care visits or at least one hospitalization within 2 years	Cox PH Model Adjusted for: Individual level: age and sex. Contextual: neighborhood-level SEP	HR (95% CI) ^b 1.00 (0.99, 1.01)
†Wang et al. (2023b) UK Biobank n = 265,506 England, Wales, Scotland, U.K. Enrollment: 2006–2010 Follow-up: 2015, 2019 Cohort	Individuals aged 37–73 in England, Scotland, and Wales. Participants were excluded if they had asthma/COPD/lung cancer or self-reported use of medication for chronic lung diseases at baseline or missing air pollution data.	LUR Model developed across 36 study areas in Europe. In the U.K. study areas (3), model R ² captured 83–89% of NO ₂ variation and 83–91% of NO _x variation, with root mean squared	NO ₂ (ppb) Mean = 15.48±4.87 (29.12±9.16 µg/m ³) NO ₂ (ppb) Mean = 43.79±15.52	Asthma incidence: Self-reports, primary care records, and hospital admission data	Cox PH Model Adjusted for: Individual level: age, sex, ethnicity, annual household income, education, smoking status, pack-years of smoking, BMI, and family history of chronic lung multimorbidity.	HR (95% CI) ^b Asthma incidence: 1.04 (0.98, 1.10) Asthma → chronic lung multimorbidity: 1.53 (1.25, 1.87)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		errors of 2.4–6.6 $\mu\text{g}/\text{m}^3$ for NO_2 and 4.9–16.2 $\mu\text{g}/\text{m}^3$ for NO_x. The cross-validated R^2 across the U.K. varied from 80–87% for NO_2 and 78–88% for NO_x. Averaging time: NO_2 - annual average, NO_x - annual average Exposure years: 2010 for NO_x; 2005–2007 and 2010 for NO_2				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†]Zhu et al. (2023) UK Biobank n = 298,738 U.K. Enrollment: Study years NR Follow-up: Study years NR through Dec 2020 Cohort	Individuals living in the U.K. aged 37–73 at enrollment. Participants excluded if there was a mismatch between genetic and reported sex, were nonwhite, and missing data on exposure, lifestyle factors, and genetic risk.	LUR Model developed across 36 study areas in Europe. In the three U.K. study areas (3), model captured 83–89% of NO₂ variation, with root mean squared errors of 2.4–6.6 µg/m³. The cross-validated R² across the U.K. varied from 80–87%. Averaging time: NO₂ - annual average Exposure years: 2010	NO ₂ (ppb) Mean = 13.91±3.98	Asthma incidence: Self-reports, primary care records, and hospital admission data	Cox PH Model Adjusted for: Individual level: age, sex, region, household income, education level, employment status, Townsend deprivation index, BMI, smoking status, alcohol status, diet, and physical activity	HR (95% CI)^b 1.08 (1.00, 1.16)

List of abbreviations in alphabetical order: BMI = body mass index; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; DCH = Danish Diet, Cancer and Health; DNC = Danish Nurse Cohort; ED = emergency department; ECRHS = European Community Respiratory Health Survey; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IQR = interquartile range; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; ONPHEC = Ontario Population Health and Environment Cohort; OR = odds ratio; P# = #th percentile; ppb = parts per billion; RHINE = Respiratory Health in Northern Europe; SALT = Stockholm Screening Across the Lifespan Twin study; SDPP = Stockholm Diabetes Prevention Program; SEP = socioeconomic position; SIXTY = Stockholm Cohort of 60-year-olds; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; U.K. = United Kingdom; U.S. = United States; µg/m³ = micrograms per cubic meter..

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-3 Animal toxicology studies of asthma development

Study Details & Population	Exposure Details	Endpoints Examined*
Gregory et al. (1983)	Whole body inhalation with filtered air controls	6 wk after exposure (1,000 ppb, 1,000 ppb with 5,000 ppb spikes) Lung damage (BAL ALKP, LDH, GSH-P) (NS) Lung tissue GSH-R, GSH-P, and G-6P-DH (NS)
Rat (F344)	1,000 ppb (1 ppm) NO ₂ , 7 hr/d for 75 d	6 wk after exposure (5,000 ppb) Lung damage (BAL ALKP, LDH) (NS) Lung damage (BAL GSH-P) (↑) Lung tissue GSH-P, and G-6P-DH (↑) Lung tissue GSH-R (NS)
14–16-wk-old, males and females	1,000 ppb (1 ppm) with two 1.5 hr spikes of 5,000 ppb (5 ppm) NO ₂ , 7 hr/d for 75 d	15 wk after exposure (1,000 ppb) Lung histology (Histologically unremarkable)
n = 4–6/group	5,000 ppb (5 ppm) NO ₂ , 7 hr/d for 75 d	15 wk after exposure (5,000 ppb, 1,000 ppb with 5,000 ppb spikes) Lung histology (Subpleural macrophage accumulation and focal hyperinflation)
Hayashi et al. (1987)	Whole body inhalation with room air controls	0 d after exposure Histology (Increased mast cell number and signs of degranulation in the trachea and bronchi) Morphology (Increased signs of lung damage and edema following NO ₂ exposure. Similar changes in low and high exposure concentrations. Changes seen after shorter exposure times with higher concentration.)
Rat (Wistar)	20,000 ppb (20 ppm) NO ₂ , continuous for 20 hr	1–35 d after exposure Morphology (Increased mast cells in trachea)
80–300g, males	500 ppb (0.5 ppm) NO ₂ , continuous for 7 d to 19 mo	
n = 2–11/group	10,000 ppb (10 ppm) NO ₂ , continuous for 3 d to 14 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 5 min to 6 d	

Study Details & Population	Exposure Details	Endpoints Examined*
Kobayashi and Miura (1995) Guinea Pig (Hartley) 10-wk-old, males n = 12–15/group	Whole body inhalation with filtered air controls 60 ppb (0.06 ppm) NO ₂ , continuous for 6 wk 60 ppb (0.06 ppm) NO ₂ , continuous for 12 wk 500 ppb (0.5 ppm) NO ₂ , continuous for 6 wk 500 ppb (0.5 ppm) NO ₂ , continuous for 12 wk 1,000 ppb (1 ppm) NO ₂ , continuous for 6 wk 1,000 ppb (1 ppm) NO ₂ , continuous for 12 wk 2,000 ppb (2 ppm) NO ₂ , continuous for 6 wk 2,000 ppb (2 ppm) NO ₂ , continuous for 12 wk 4,000 ppb (4 ppm) NO ₂ , continuous for 6 wk 4,000 ppb (4 ppm) NO ₂ , continuous for 12 wk	0 d after exposure Airway responsiveness to histamine (↑) Specific airway resistance (↑)
Kubota et al. (1987) Rat (JCL:Wistar) 2-mo-old, males n = 3–4/group	Whole body inhalation with filtered air controls 40 ppb (0.04 ppm) NO ₂ , continuous for 9 mo 40 ppb (0.04 ppm) NO ₂ , continuous for 18 mo 40 ppb (0.04 ppm) NO ₂ , continuous for 27 mo 400 ppb (0.4 ppm) NO ₂ , continuous for 9 mo 400 ppb (0.4 ppm) NO ₂ , continuous for 18 mo 400 ppb (0.4 ppm) NO ₂ , continuous for 27 mo 4,000 ppb (4 ppm) NO ₂ , continuous for 9 mo 4,000 ppb (4 ppm) NO ₂ , continuous for 18 mo 4,000 ppb (4 ppm) NO ₂ , continuous for 27 mo	Timing unclear Morphology (Morphologic lesions seen with NO ₂ exposure in a dose and time dependent manner)

Study Details & Population	Exposure Details	Endpoints Examined*
Sagai et al. (1984)	Whole body inhalation with filtered air controls	0 d after exposure
Rat (JCL:Wistar)	40 ppb (0.04 ppm) NO ₂ , continuous for 9 mo	Ethane evolution (in breath) (↑)
2-mo-old, males	40 ppb (0.04 ppm) NO ₂ , continuous for 18 mo	Lung 6-phosphogluconate dehydrogenase (↑)
n = 6–12/group	40 ppb (0.04 ppm) NO ₂ , continuous for 27 mo	Lung G-6P-DH (↑)
	400 ppb (0.4 ppm) NO ₂ , continuous for 9 mo	Lung GSH-P activity with H ₂ O ₂ (↓)
	400 ppb (0.4 ppm) NO ₂ , continuous for 18 mo	Lung GSH-R (↑)
	400 ppb (0.4 ppm) NO ₂ , continuous for 27 mo	Lung nonprotein sulfhydryls (↑)
	4,000 ppb (4 ppm) NO ₂ , continuous for 9 mo	Lung TBA reactant content (↑)
	4,000 ppb (4 ppm) NO ₂ , continuous for 18 mo	Pentane evolution (in breath) (NS)
	4,000 ppb (4 ppm) NO ₂ , continuous for 27 mo	
†Han et al. (2017)	Whole body inhalation with filtered air controls	24 hr after exposure (28 d exposure)
Rat (Wistar)	1,063 ppb (2 mg/m ³) NO ₂ , 5 hr/d for 28 d	ICC (Increased epithelial cell damage, inflammatory cell infiltration, and mucus production)
6-wk-old, males	2,658 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 28 d	PCR - Th 1 response (↓)
n = 3–10/group	2,658 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 42 d	PCR - inflammation and Th2 response (↑)
†Lu et al. (2023b)	Whole body inhalation with room air controls	7 d after exposure (No OVA)
Mouse (BALB/c)	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 30 d	AHR (↑)
7-wk-old, males		ICC (Increased inflammation, airway thickening and mucus production)
n = 7–8/group		OVA-specific IgE (↑)
		Oxidative stress (NS)
		Total IgE (NS)

Study Details & Population	Exposure Details	Endpoints Examined*
† Yue et al. (2018)	Whole body inhalation with room air controls	9 wk after exposure (unsensitized mice)
Mouse (BALB/c)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 21 d	AHR (NS)
gestational exposure (GD 0 to GD 21), sex not reported		
n = 3–11/group		

List of abbreviations in alphabetical order: AHR = airway hyperresponsiveness; ALKP = alkaline phosphatase; BAL = bronchioalveolar lavage; d = day; G-6P-DH = glucose-6-phosphate dehydrogenase; GD = gestational day; GSH-P = glutathione peroxidase; GSH-R = glutathione reductase; hr = hour; ICC = immunocytochemistry; LDH = lactate dehydrogenase; min = minute; mo = month; n = sample size; NO₂ = nitrogen dioxide; OVA = ovalbumin; ppb = parts per billion; ppm = parts per million; TBA = thiobarbituric acid; wk = week

*Simplified results interpreted as: NS = no experimental groups were statistically significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-4 Epidemiologic studies of long-term exposure to oxides of nitrogen and asthma severity

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Andersen et al. (2012)	Adults aged 50–65 years from two cities in Denmark	Dispersion model	NO ₂ (ppb)	Asthma hospital admissions:	Cox PH Model	HR (95% CI) ^b
Danish Diet, Cancer and Health (DCH)		Averaging time: NO ₂ - annual average, Other, NO ₂ 35-year average	Median = 8.08 (IQR 3.1) (15.2 µg/m ³ (IQR 5.8 µg/m ³)	Danish Hospital Discharge Register	Adjusted for: Individual level: smoking status, smoking duration, environmental tobacco smoke, occupational exposure, sex, BMI, and education level.	1.44 (1.13, 1.83)
n = 53,695		NO ₂ 15-year average				
Copenhagen, Aarhus, Denmark		Exposure years: 1971–2006				
Enrollment: 1993–1997 Follow-up: 1993–2006						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Belanger et al. (2013) Study of Traffic, Air quality and Respiratory health (STAR) n = 1,342 Massachusetts, Connecticut, U.S. Enrollment: 2006–2009 Follow-up: 1 year Cohort	Children recruited through flyers sent to schools with gas lines. Eligible children were ages 5–10 years, had caregiver that spoke English, and active asthma	Personal monitor or sampler Averaging time: NO ₂ -monthly average Exposure years: 2006–2010	NO ₂ (ppb) Mean = 10.6±9.4 IQR = 8 P25 = 4.5 P75 = 12.5	Asthma severity score based on the Global Initiative for Asthma guidelines Respiratory symptoms: Parental-reported	Logistic Regression Adjusted for: Individual level: age, sex, atopy, season of monitoring, sensitization and exposure to indoor allergens, and maintenance medication use.	OR (95% CI) ^c One-level increase in asthma severity score: 1.37 (1.01, 1.89) Prevalent wheeze: 1.49 (1.09, 2.03) Prevalent night-time symptoms: 1.52 (1.16, 2.00) Rescue medication use: 1.78 (1.33, 2.38)
Gehring et al. (2010) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort n = 3,863 West, North, Center, Netherlands Enrollment: 1996–1997 Follow-up: 8 years Cohort	Birth cohort formed by recruiting women in second trimester of pregnancy	LUR R ² = 0.85 Averaging time: Not mentioned in LUR description Exposure years: NR	NO ₂ (ppb) Mean = 13.5 (25.4 µg/m ³) Median = 14 (IQR 5.53) (26 µg/m ³) (IQR 10.4 µg/m ³) Min = 6.7 (12.6 µg/m ³) Max = 31 (58.4 µg/m ³) P10 = 7.81 (14.7 µg/m ³) P25 = 9.83 (18.5 µg/m ³) P75 = 15.4 (28.9 µg/m ³) P90 = 18.4 (34.7 µg/m ³)	Respiratory symptoms: Parental reported	Generalized estimating equation Adjusted for: Individual level: sex, study arm (intervention or natural history), use of mite-impermeable mattress covers, allergies of mother and father, maternal and paternal education, maternal smoking during pregnancy, breastfeeding, presence of a gas stove in the child's home, presence of older siblings, smoking, signs of dampness and pets in	OR (95% CI) ^b Asthma symptoms, children: 1.17 (0.98, 1.39) Wheeze, children: 1.27 (1.07, 1.50)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					the child's home, day-care attendance, and Dutch nationality	
Gruzieva et al. (2013)	Children born between 1994 and 1996 in 4 municipalities in Stockholm County, representing urban and suburban areas	Dispersion model	NO _x (µg/m ³)	Wheeze symptoms: Self-reported	Logistic Regression	OR (95% CI) ^b
Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE)		R ² = 0.74-0.80, range	2–4 years Mean = 13.4		Adjusted for:	1.19 (0.81, 1.77)
n = 3,633		Averaging time: NO _x - annual average, Other, NO _x multi-year average (since prior follow-up)	4–8 years Mean = 10.6		Individual level: municipality, socioeconomic status, heredity, and the year residence was built.	
Stockholm County, Sweden			8–12 years Mean = 7.8			
Enrollment: 1994–1996		Exposure years: 1994–2008	First year of life Mean = 21.4			
Follow-up: First 12 years of life			Second year of life Mean = 18.6			
Cohort						
Jacquemin et al. (2009)	Adults aged 20–44 in 1991–1993 were randomly selected from 28 cities in 11 western European countries. Inclusion included no asthma at enrollment	LUR	NO ₂ (ppb)	Respiratory symptoms: Self-reported	Logistic Regression	OR (95% CI) ^b
European Community Respiratory Health Survey (ECRHS)		R ² = 0.60	Range of medians across cities = 6.4 to 30.3		Adjusted for:	Breathlessness: 1.59 (1.01, 2.51)
n = 4,185		Exposure years: 2001			Individual level: sex, age, socioeconomic status, atopy, family history of asthma or atopy, and smoking	Wheezing: 1.59 (1.01, 2.51)
Barcelona, Albacete, Huelva, Galdakao, Oviedo, Spain; Paris, Bordeaux, Grenoble, Montpellier, France; Umeå, Uppsala, Goteborg, Sweden; Ipswich, Norwich, U.K.; Erfurt,						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Hamburg, Germany; Antwerp, South Antwerp, Belgium; Basel, Switzerland; Reykjavík, Iceland; Bergen, Norway; Tartu, Estonia; Groningen, Geleen, Bergen op Zoom, Netherlands; Verona, Pavia, Turin, Italy Enrollment: 1991–1993 Follow-up: 1999–2001 Cohort						
McConnell et al. (2003) n = 475 Southern California, U.S. Recruitment: 1993, 1996 Follow-up: 1996–1999 Cohort	Cohort of children aged 9–10 and 12–13 years with asthma in 12 Southern California communities. Children with history of asthma and completed 2 or more follow-up questionnaires included	Fixed site monitor Averaging time: NO₂ - annual average Exposure years: 1996–1999	NO₂ (ppb) Mean = 19.4±11.3 Min = 4.2 Max = 38	Asthma or bronchitic symptoms: self-reported	Logistic Regression Adjusted for: Individual level: age, maternal and child's smoking history, sex, and race	OR (95% CI)^b 1.22 (1.00, 1.49)
†Berhane et al. (2016) Children's Health Study (CHS) n = 4,602 Southern California, U.S. Enrollment: 1993–2003 Follow-up: 1993–2012	Children 5–18 years of age in Southern California communities	Fixed site monitor Averaging time: NO₂ - annual average Exposure years: 1992–2012	NO₂ (ppb) 1992–2000 Mean = 25.2 1995–2003 Mean = 24.2	Bronchitic symptoms: Parent or child report of a daily cough for 3 months in a row, congestion or phlegm other than when accompanied by	Logistic Regression Adjusted for: Individual level: age, sex, race/ethnicity, exposure to secondhand smoke, and exposure to cockroaches at home.	OR (95% CI)^b Age 10 y All: 1.62 (1.15, 2.29) Males: 1.96 (1.35, 2.82) Females: 1.36 (0.93, 1.99) Age 15 y All: 1.75 (1.25, 2.45) Males:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort			2002–2011 Mean = 18.5	a cold, or bronchitis		1.50 (1.21, 1.85) Females: 1.43 (1.16, 1.75)
†Garcia et al. (2024) Children’s Health Study (CHS) N = 1,308 Southern California, U.S. Recruitment: 1992–2003 Follow-up: 20 years Cohort	Participants from these two cohorts were not included in the follow-up study and thus this analysis because 1) they were older, and the study focus was to capture the full range of childhood, including early childhood; and 2) they had more limited residential address information. Excluded 79 participants who provided no information on bronchitic symptoms, the outcome of interest, as well as one identified duplicate record or were missing valid estimates of mean childhood exposure to all pollutants.	Fixed site monitor Method validation NR Averaging time: NO ₂ - annual average Exposure years: 1992–2012	NO ₂ (ppb) Adult Bronchitic Symptoms Mean = 26.8±11 No Adult Bronchitic Symptoms Mean = 25.9±11.1 Total Cohort Mean = 26.1±11.1	Bronchitic symptoms: Self-reported	Logistic Regression Adjusted for: Individual level: race and ethnicity, childhood household income, maternal smoking during pregnancy, presence of smoker in childhood home, presence of mold/mildew in childhood home, town at study recruitment, and Southern California Children’s Health Study cohort; and age, latest education, current smoking status, and body mass index at adult assessment.	OR (95% CI) ^b All adults: 1.60 (1.13, 2.28) Adults, no childhood asthma: 1.49 (1.05, 2.11) Adults, childhood asthma: 2.07 (1.33, 3.20)
†Keirbulck et al. (2023) CONSTANCES n = 135,165 France	French adults aged 18–69 from the database e National Pension Insurance Fund (CNAV: Caisse	LUR R ² = 0.588 Averaging time: NR	NO ₂ (ppb) Mean = 12.5 (23.5 µg/m ³) IQR = 9.19 (17.3 µg/m ³)	Asthma symptom score: Validated and standardized European Community Respiratory	Negative binomial regression Adjusted for:	RMS (95% CI) ^b 1.13 (1.11, 1.15)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2012–2017 Cross-Sectional	Nationale d'Assurance Vieillesse)	Exposure years: 2010		Health Survey (ECRHS) questionnaires	Individual level: age, sex, smoking status, and educational level. Contextual: French Deprivation Index.	
† Mendy et al. (2019) NHANES n = 6,488 U.S. 2005–2006 Cross-Sectional	Participants in 2005–2006 NHANES with data on endotoxin and could be linked spatially and temporally to air pollution data. All ages.	CMAQ Averaging time: NO ₂ - annual average Exposure years: 2004–2006	NO ₂ (ppb) Median = 7.37 (IQR 9.92) P5 = 1.96 P25 = 3.18 P75 = 13.1 P95 = 21.84	ED visits for asthma: Self-reported	Logistic Regression Adjusted for: Individual level: age, sex, race/ethnicity, presence of a smoker in the house, poverty/income ratio, and body mass index. Contextual: census region and level of urbanization.	OR (95% CI) ^c 2.85 (1.24, 6.53)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Tétreault et al. (2016b) n = 162,752 Quebec, Canada Enrollment: April 1996– March 2011 Follow-up: Diagnosis of asthma until March 2011 Cohort	Asthmatic children born 1996–2011	LUR Averaging time: NO ₂ - annual average Exposure years: NA	NO ₂ (ppb) Birth Mean = 15.51 Median = 15.12 (IQR 4.95) Min = 6.49 Max = 31.15 P25 = 12.93 P75 = 17.88 Time dependent Mean = 15.04 Median = 14.68 (IQR 4.99) Min = 6.08 Max = 31.15 P25 = 12.42 P75 = 17.42	Asthma exacerbation: hospital admission or an emergency room visit for asthma in children already diagnosed with asthma.	Cox PH Model Adjusted for: Individual level year of birth, and sex. Contextual area-level indices of social and material deprivation	HR (95% CI) ^b Annual avg at birth: 0.99 (0.97, 1.01) Time-dependent exposure: 1.21 (1.13, 1.29)

List of abbreviations in alphabetical order: Avg = average; CHS = Children's Health Study; CI = confidence interval; CMAQ = Community Multiscale Air Quality; CNAV = Caisse Nationale d'Assurance Vieillesse; CONSTANCES = Cohorte des Consultants des Centres d'Examens de Santé; DCH = Danish Diet, Cancer and Health; ECRHS = European Community Respiratory Health Survey; ED = emergency department; HR = hazard ratio; IQR = interquartile range; LUR = land use regression; NHANES = National Health and Nutrition Examination Survey; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OP = organophosphate; OR = odds ratio; P# = #th percentile; PH= proportional hazards; ppb = parts per billion; RMS = risk mean score; STAR = Study of Traffic, Air quality and Respiratory health; U.K. = United Kingdom; U.S. = United States; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-5 Animal toxicology studies of asthma severity

Study Details & Population	Exposure Details	Endpoints Examined*
† Han et al. (2017)	Whole body inhalation with filtered air controls	24 hr after exposure (42 d exposure OVA sensitization)
Rat (Wistar)	1063 ppb (2 mg/m ³) NO ₂ , 5 hr/d for 28 d	BAL - inflammatory cells (↑)
6-wk-old, males	2,658 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 28 d	ICC and TEM (More severe inflammatory cell infiltration, airway remodeling, and collagen and mucus production)
n = 3–10/group	2,658 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 42 d	OVA specific IgE (↑)
		PCR - MUC5AC (NS)
		PCR - Th1 response (↓)
		PCR - inflammation and Th2 response (NS)
		Western blot - inflammation and Th2 signaling (↑)
† Lu et al. (2023a)	Whole body inhalation with room air controls	24 hr after exposure (24°C)
Mouse (BALB/c)	5,000 ppb NO ₂ , 4 hr/d for 30 d	AHR (↑)
6–8-wk-old, males		ELISA - IFNγ (NS)
n = 7–8/group		ELISA - IL-4 (↑)
		ELISA - IL-4/IFNγ (↑)
		ELISA - oxidative stress (↑)
		ICC (More collagen deposition, mucus production, and airway wall thickening)
		IHC - TRPV1 (NS)
		IHC - inflammatory signaling (↑)
		OVA specific IgE (NS)
		Total IgE (NS)
† Lu et al. (2023b)	Whole body inhalation with room air controls	7 d after exposure (OVA)
Mouse (BALB/c)	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 30 d	AHR (↑)
7-wk-old, males		ELISA - IFNγ (NS)
n = 7–8/group		ELISA - IL-4 (NS)
		ELISA - IL-4/IFNγ (↑)
		ICC (Increased inflammation, airway thickening and mucus production)
		IHC - inflammatory mediators (↑)
		OVA-specific IgE (NS)
		Oxidative stress (NS)
		Total IgE (↑)

Study Details & Population	Exposure Details	Endpoints Examined*
† Lu et al. (2024)	Whole body inhalation with clean air controls	24 hr after exposure (OVA)
Mouse (BALB/c)	5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 38 d	Airway reactivity (↑)
7-wk-old, males		Lung histology (Greater inflammation and airway remodeling)
n = 2–6/group		Lung inflammatory protein levels (IL-1b, TNFa, IL-17,) (↑)
		Oxidative stress (MDA) (↑)
		Oxidative stress (SOD, GSH-P) (NS)
		Serum OVA-specific IgE (↑)
		Th2/Th1 balance (IL-4/IFNg) (↑)
† Yue et al. (2018)	Whole body inhalation with room air controls	9 wk after exposure
Mouse (BALB/c)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 21 d	BAL - inflammatory cells (↑)
gestational exposure (GD 0 to GD 21),		ELISA and Western blot - Th1 signaling (↓)
sex not reported		ELISA and Western blot - Th2 signaling (↑)
n = 3–11/group		IHC (More dramatic airway remodeling, inflammation, and mucus production)
		9 wk after exposure (sensitized mice)
		AHR (↑)

List of abbreviations in alphabetical order: AHR = airway hyperresponsiveness; BAL = bronchioalveolar lavage; d = day; ELISA = enzyme-linked immunosorbent assay; GD = gestational day; GSH-P = glutathione peroxidase; hr = hour; ICC = immunocytochemistry; IHC = immunohistochemistry; MDA = malonaldehyde; n = sample size; NO₂ = nitrogen dioxide; OVA = ovalbumin; ppb = parts per billion; ppm = parts per million; SOD = superoxide dismutase; TEM = transmission electron microscopy; Th = T helper; wk = week.

*Simplified results interpreted as: NS = no experimental groups were statistically significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-6 Epidemiologic studies of long-term exposure to oxides of nitrogen and development of COPD

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Andersen et al. (2011)	Adults aged 50–64 living in the area	Dispersion model	NO ₂ (ppb)	COPD	Cox PH Model	HR (95% CI) ^b
Danish Diet, Cancer and Health (DCH)	between 1993 and 1997	Averaging time: NO ₂ - annual average	15 yr-average Mean = 9.09±3.3 Median = 7.71 (IQR 3.3)	Incidence: Danish Hospital Discharge Register; First	Adjusted for: Individual level: smoking status, smoking duration, smoking	35-y avg NO ₂ : 1.28 (1.07, 1.54) 25-y avg NO ₂ : 1.22 (1.03, 1.44)
n = 52,799						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Denmark Enrollment: 1993–1997 Follow-up: 1993–2006 Cohort		Exposure years: 1971–2006	25 yr-average Mean = 9.46±3 Median = 8.24 (IQR 3.4) 35 yr-average Mean = 9±2.8 Median = 8.13 (IQR 3.1)	COPD hospital admission	intensity, environmental tobacco smoke, body mass index, educational level, occupational exposure, and fruit consumption.	15-y avg NO ₂ : 1.16 (0.99, 1.35)
Gan et al. (2013) n = 467,994 Vancouver, Canada Enrollment: 1994–1998 Follow-up: 1999–2002 Cohort	Vancouver residents registered with the provincial health insurance plan, resided in region for 5-year exposure period, aged 45–85 years, and no previous physician diagnosis of COPD	LUR Averaging time: NO ₂ 5-year average Exposure years: 1994–1998	NO ₂ (ppb) Mean = 17.1±4.3 Median = 16.3 (IQR 4.5) Min = 8.13 Max = 30.7 P25 = 14.2 P75 = 18.7	COP incidence: Provincial hospitalization database; first hospitalization record with COPD as the principal diagnosis	Cox PH Model Adjusted for: Individual level: age, sex, SES, asthma, diabetes, CHD, and HHD.	RR (95% CI) ^b 1.00 (0.90, 1.11)
†Bourbeau et al. (2022) Canadian Cohort Obstructive Lung Disease (CanCOLD) n = 1,452 Toronto, Vancouver, Montreal, Kingston, Halifax, Quebec City, Ottawa, Saskatoon, Calgary, Canada 2009–2015 Cross-Sectional	Noninstitutionalized adults aged 40 and older. Selected individuals with airflow obstruction (COPD), and sex and age matched individuals without COPD	LUR R ² = 0.73 Averaging time: NO ₂ - annual average Exposure years: 2005–2012	NO ₂ (ppb) Mean = 12.8 IQR = 9.2 Min = 0.5 Max = 33	COPD prevalence was defined using NHANES III reference values for the lower limit of normal (LLN). Individuals with an FEV1/FVC ratio below the LLN were classified as having COPD.	Logistic Regression Adjusted for: Individual level: age, sex, body mass index, educational level, tobacco status, pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, respiratory medication intake, and Canadian Cohort Obstructive Lung Disease study site.	OR (95% CI) ^b 1.21 (0.83, 1.76)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Doiron et al. (2019) UK Biobank n = 303,887 U.K. 2006–2010 Cross-Sectional	Individuals aged 40–69 years from largely urban areas of England, Wales, and Scotland, recruited from the U.K. National Health Services register	LUR R ² = 0.87 Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Mean = 13.98±3.98 (26.31±7.49 µg/m ³) IQR = 5.2 (9.7 µg/m ³) Min = 6.872 (12.93 µg/m ³) Max = 57.658 (108.49 µg/m ³)	COPD incidence using the Global Lung Function Initiative (GLI) 2012 reference values for lower limit of normal (LLN). Individuals with a FEV1/FVC ratio below the LLN were classified as having COPD	Logistic Regression Adjusted for: Individual level: age, sex, body mass index, household income, education level, smoking status, and passive smoking exposure at home.	OR (95% CI) ^b 1.24 (1.20, 1.28)
† Gandini et al. (2018b) Italian Longitudinal Study (ILS) N = 74,989 Italy Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008 Cohort	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity. Averaging time: NO ₂ - annual average	NO ₂ (ppb) Men <i>Metropolitan</i> Mean = 22.1±6.16 <i>Rural</i> Mean = 10.3±4 <i>Urban</i> Mean = 13.9±5.2 Women <i>Metropolitan</i> Mean = 22.1±6.16 <i>Rural</i> Mean = 10.3±4.2 <i>Urban</i> Mean = 13.9±5.1	COPD incidence: Health records database; first hospital admission for COPD	Cox PH Model Adjusted for: Individual level: age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, and BMI. Contextual: type of municipality (rural, urban, metropolitan areas)	HR (95% CI) ^b 0.89 (0.83, 0.96)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		Exposure years: 1999, 2003, 2005, 2007				
† Hooper et al. (2018)	Women with a sister diagnosed with breast cancer, but no person breast cancer diagnosis at the time of baseline interview	LUR	NO ₂ (ppb)	Chronic bronchitis: Self-reported questionnaire based on classical symptom-based definition of chronic cough productive of phlegm for at least 3 mo out of a year for a minimum of 2 consecutive years	Logistic Regression	OR (95% CI) ^b
NIEHS Sister Study cohort		R ² = 0.85	Median = 11.7 (IQR 7.3)		Adjusted for:	Chronic bronchitis incidence: 1.00 (0.89, 1.12)
n = 39,844		Averaging time: NO ₂ - annual average			Individual level: age, race/ethnicity, body mass index, education, household income, occupational exposure to vapors/fumes or dust, smoking status, total pack-years, and environmental tobacco smoke exposure.	Chronic bronchitis prevalence: 1.07 (0.99, 1.16)
U.S.						
Enrollment: 2003–2009		Exposure years: 2000				
Follow-up: through 2014						
Cohort						
† Kwon et al. (2020)	Individuals residing in areas near cement plants	LUR	NO ₂ (ppb)	COPD severity: CT measurements were obtained using a dual-source CT scanner at full inspiration and expiration in the supine position. Wall area percent was defined as (100 x wall area/total bronchial area). Emphysema	Linear regression	β (% change) (95% CI) ^b
COPD in Dusty Areas (CODA) cohort		R ² = 0.82	Mean = 13.6±2.1		Adjusted for:	Mean Wall Area: 1.27 (-1.47, 4.00)
n = 457		Averaging time: NO ₂ - annual average	Median = 13.5 (IQR 3)		Individual level: age, gender, education, height, weight, smoking, pack-years, medication use, job, calendar year at PFT test, asthma, and COPD.	β (NA) (95% CI) ^b
South Korea			P5 = 10.2			Emphysema Index: 1.53 (-1.60, 4.67)
2012–2017		Exposure years: 2010	P25 = 12.3			
Cross-Sectional			P75 = 15.3			
			P95 = 17.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				index was calculated as the percentage of lung area below -950 HU threshold.		
† Liu et al. (2021a)	Excluded 821 with asthma diagnoses before the beginning of follow-up and 7580 with missing information on confounders.	LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Asthma Mean = 13.95±4.14 (26.25±7.79 µg/m ³) No Asthma Mean = 13.33±4.24 (25.08±7.97 µg/m ³) Total Mean = 13.3±4.24 (25.1±7.97 µg/m ³)	COPD incidence: First inpatient, outpatient, or ED visit for COPD for the Danish cohorts and first inpatient visit for Swedish cohort	Cox PH Model Adjusted for: Individual level: age, sex, study, calendar year of baseline, smoking status, smoking duration, smoking intensity, BMI, marital status, employment status, and education level. Contextual: area-level mean income.	HR (95% CI) ^b 1.22 (1.12, 1.32) <40 ug/m ³ : 1.24 (1.14, 1.35) <30 ug/m ³ : 1.41 (1.21, 1.64) <20 ug/m ³ : 1.12 (0.73, 1.70)
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), Danish Nurse Cohort (DNC), Stockholm Diabetes Prevention Program (SDPP), Stockholm Cohort of 60-year-olds (SIXTY), Stockholm Screening Across the Lifespan Twin study (SALT)						
N = 98,326						
Stockholm, Kungsholmen, Sweden; Nationwide, Denmark						
Recruitment: 1992–2004 Follow-up: 2011–2015						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Liu et al. (2021d) Danish Nurse Cohort n = 28,731 Denmark Enrollment: 1993–1999 Follow-up: 1993–2015 Cohort	Female nurses older than 44 years of age	Hybrid model Averaging time: NO ₂ - annual average	NO ₂ (ppb) Mean = 6.797±4.19 (12.79±7.89 µg/m ³) IQR = 4.35 (8.19 µg/m ³) Min = 1.36 (2.55 µg/m ³) Max = 41.86 (78.76 µg/m ³)	COPD incidence: Danish National Patient Register; First inpatient, outpatient, or ED visit for COPD	Cox PH Model Adjusted for: Individual level: age, year of baseline, calendar year of follow-up, smoking status, smoking duration, smoking intensity, marital status, occupational status, leisure time, physical activity status, vegetable consumption, avoids fatty meat, and alcohol consumption.	HR (95% CI) ^b <40 µg/m ³ : 1.63 (1.22, 2.18) <30 µg/m ³ : 1.92 (1.33, 2.75) <20 µg/m ³ : 2.19 (1.34, 3.58) <15 µg/m ³ : 1.63 (1.06, 2.51) <10 µg/m ³ : 1.20 (0.42, 3.42)
† Liu et al. (2021b) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), Danish Nurse Cohort (DNC), Stockholm Diabetes Prevention Program (SDPP), Stockholm Cohort of 60-year-olds (SIXTY), Stockholm Screening Across the Lifespan Twin study (SALT) n = 98,508	Adults residing in Denmark and Sweden	LUR R ² = 0.59 Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) COPD Mean = 14.63±3.99 (27.53±7.51 µg/m ³) No COPD Mean = 13.28±4.24 (24.98±7.97 µg/m ³) Total Mean = 13.34±4.24 (25.11±7.97 µg/m ³)	COPD incidence: First inpatient, outpatient, or ED visit for COPD for the Danish cohorts and first inpatient visit for Swedish cohort	Cox PH model Adjusted for: Individual level: age (time axis), sex (strata), study (strata), calendar year of baseline, smoking (status, duration, intensity, and intensity), BMI (category), marital status, employment status and education levels. Contextual: area-level mean annual income	HR (95% CI) ^b 1.22 (1.12, 1.32)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Sweden, Denmark						
Enrollment: 1992–2004 Follow-up: 1999–2006						
Cohort						
† Shin et al. (2021)	Participants aged 35–85 years who were eligible for a publicly funded health insurance program, no physician diagnosed COPD or asthma	LUR R ² = 0.73 Averaging time: NO ₂ - annual average Exposure years: 2005–2011	NO ₂ (ppb) Mean = 18±8	COPD incidence: Two or more ambulatory care visits or at least one hospitalization within 2 years	Cox PH Model Adjusted for: Individual level: age and sex. Contextual: neighborhood-level SEP	HR (95% CI) ^b 1.02 (1.01, 1.03)
Ontario Population Health and Environment Cohort (ONPHEC)						
n = 5,064,225						
Ontario, Canada						
Enrollment: 2001–2015 Follow-up: 2001–2015						
Cohort						
† Wang et al. (2023b)	Individuals aged 37–73 in England, Scotland, and Wales. Participants were excluded if they had asthma/COPD/lung cancer or self-reported use of medication for chronic lung diseases at baseline or missing air pollution data.	LUR Model developed across 36 study areas in Europe. In the U.K. study areas (3), model R ² captured 83–89% of NO ₂ variation and 83–91% of NO _x variation, with root mean squared errors of 2.4–6.6 µg/m ³ for NO ₂ and	NO ₂ (ppb) Mean = 15.48±4.87 (29.12±9.16 µg/m ³) NO ₂ (ppb) Mean = 43.79±15.52	COPD incidence: Self-reports, primary care records, and hospital admission data	Cox PH Model Adjusted for: Individual level: age, sex, ethnicity, annual household income, education, smoking status, pack-years of smoking, BMI, and family history of chronic lung multimorbidity.	HR (95% CI) ^b COPD incidence: 1.12 (1.08, 1.16) COPD → chronic lung multimorbidity: 1.04 (0.80, 1.34)
UK Biobank						
n = 265,506						
England, Wales, Scotland						
Enrollment: 2006–2010 Follow-up: 2015, 2019						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		4.9–16.2 µg/m ³ for NO _x . The cross-validated R ² across the U.K. varied from 80–87% for NO ₂ and 78–88% for NO _x . Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2010 for NO _x ; 2005–2007 and 2010 for NO ₂				
† Xu et al. (2024)	Participants aged 40–65 years living near one of seven study centers in Northern Europe.	Dispersion model	NO ₂ (ppb)	COPD incidence: Self-reported COPD or chronic bronchitis	Poisson regression	IRR (95% CI) ^b
Respiratory Health in Northern Europe (RHINE) III		DEHM/UBM model validated against central site monitors (r = 0.70, 0.60, and 0.73 in Denmark, Norway, and Sweden, respectively).	1990 Mean = 8.339±4.13 (15.69±7.77 µg/m ³)		Adjusted for:	Annual avg 1990: 1.26 (0.82, 1.92)
n = 5,355		Airviro model validated against central site monitors in Tartu, Estonia.	2000 Mean = 7.451±3.82 (14.02±7.18 µg/m ³)		Individual level: sex, age, study center, education, body mass index, smoking status, smoking duration, and smoking intensity.	Annual avg 2000: 1.37 (0.93, 2.01)
Reykjavík, Iceland; Bergen, Norway; Aarhus, Denmark; Gothenburg, Umeå, Uppsala, Sweden; Tartu, Estonia			2010 Mean = 7.111±4 (13.38±7.6 µg/m ³)			Annual avg 2010: 1.28 (0.93, 1.76)
Enrollment: 2010–2012						
Follow-up: through 2021						
Cohort						
		Averaging time: NO ₂ - annual				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		average				
		Exposure years: 1990–2010				

List of abbreviations in alphabetical order: Avg = average; BMI = body mass index; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; DEHM = Danish Eulerian Hemispheric Model; DCH = Danish Diet, Cancer and Health; ED = emergency department; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = hazard ratio; IQR = interquartile range; IRR = incidence rate ratio; LUR = land use regression; NIEHS = National Institute of Environmental Health Sciences; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; P# = #th percentile; ppb = parts per billion; RHINE = Respiratory Health in Northern Europe; RMSE = root mean squared error; SALT = Stockholm Screening Across the Lifespan Twin study; SDPP = Stockholm Diabetes Prevention Program; SEP = socioeconomic position; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; U.K. = United Kingdom; U.S. = United States; UBM = Urban Background Model; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-7 Animal toxicology studies of COPD development

Study Details & Population	Exposure Details	Endpoints Examined*
Kubota et al. (1987)	Whole body inhalation with filtered air controls	Timing unclear
Rat (JCL:Wistar)	40 ppb (0.04 ppm) NO ₂ , continuous for 9 mo	Morphometry (Increased alveolar wall thickness in a dose and time dependent manner)
2-mo-old, males	40 ppb (0.04 ppm) NO ₂ , continuous for 18 mo	
n = 3–4/group	40 ppb (0.04 ppm) NO ₂ , continuous for 27 mo	
	400 ppb (0.4 ppm) NO ₂ , continuous for 9 mo	
	400 ppb (0.4 ppm) NO ₂ , continuous for 18 mo	
	400 ppb (0.4 ppm) NO ₂ , continuous for 27 mo	
	4,000 ppb (4 ppm) NO ₂ , continuous for 9 mo	
	4,000 ppb (4 ppm) NO ₂ , continuous for 18 mo	
	4,000 ppb (4 ppm) NO ₂ , continuous for 27 mo	
†Ohyama et al. (2018)	Whole body inhalation with filtered air controls	Timing unclear
Rat (F344)	2 ppb (0.002 ppm) HONO, continuous for 42 d	Lung histopathology (Bronchial smooth muscle hypertrophy, pulmonary emphysema-like alterations in the alveolar duct centriacinar regions, and increased goblet cells)
5-wk-old, males	4,098 ppb (4.098 ppm) HONO, continuous for 42 d	Lung mRNA expression (Cxcl-1 and TNF-alpha) (NS)
n = 9/group	5,757 ppb (5.757 ppm) HONO, continuous for 42 d	Lung mRNA expression (Muc5ac) (↑)
		Lung weight (NS)
†Ohyama et al. (2020)	Whole body inhalation with filtered air controls	0 d after exposure
Guinea Pig (Hartley)	100 ppb (0.1 ppm) HONO, continuous for 28 d	SEM (Dose dependent changes in alveolar duct regions)
6-wk-old, males	400 ppb (0.4 ppm) HONO, continuous for 28 d	TEM (Dose dependent changes in alveolar duct regions)
n = 2–3/group	1,700 ppb (1.7 ppm) HONO, continuous for 28 d	Alveolar mean linear intercept (Lm) (↑)
		Thickness of the bronchial smooth muscle layer (NS)

List of abbreviations in alphabetical order: Cxcl-1 = Chemokine (C-X-C motif) ligand 1; d = day; HONO = Nitrous Acid; Lm = Mean Linear Intercept; mo= month; mRNA = Messenger Ribonucleic Acid; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; SEM = Scanning Electron Microscopy; TEM = Transmission Electron Microscopy; TNF-alpha = Tumor Necrosis Factor-alpha; wk = week.

*Simplified results interpreted as: NS = no experimental groups were statistically significantly different from control; † = at least one experimental group had a statistically significant increase.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-8 Epidemiologic studies of long-term exposure to oxides of nitrogen and respiratory infection

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Aguilera et al. (2013) INMA, Infancia y Medio Ambiente n = 2,199 Gipuzkoa, Sabadell, Valencia, Asturias, Spain Enrollment: 2003–2008 Follow-up: 18 months after birth Cohort	Pregnant women enrolled during first prenatal care visit. Inclusion criteria for women included 16 years of age or older, wished to deliver in the reference hospital, singleton pregnancy, no communication problems, no assisted conception	LUR R ² (range) = 0.52–0.75 Averaging time: NO ₂ - annual average	Concentrations presented graphically	LRTI incidence: parental-reported physician-diagnosed LRTI	Logistic regression Adjusted for: Individual level: childcare attendance, siblings at birth, maternal asthma, parental allergy, maternal age at delivery, pre-pregnancy body mass index, and cotinine levels in urine at 32 weeks of gestation.	RR (95% CI) ^b 1.10 (0.97, 1.24)
MacIntyre et al. (2014b) European Study of Cohorts for Air Pollution Effects (ESCAPE) N = 16,059 Stockholm, Sweden; Rome, Italy; Wesel, Munich, Leipzig, Bad Honnef, Germany; Asturias, Gipuzkoa, Sabadell, Valencia, Spain; Manchester, England 1994–2008	Pooled analysis of 10 ESCAPE birth cohorts	LUR Averaging time: NO ₂ - annual average	NO ₂ (ppb) Ranges of means across cohorts = 6.6–23.0±4.9–5.5	Pneumonia, croup, and otitis media incidence: parental-report of physician-diagnosed pneumonia, otitis media, and croup	Logistic regression Adjusted for: Individual level: Municipality (BAMSE), sex, older siblings, breastfeeding at 6 months, atopy of either parent, any child-care reported during follow-up, maternal smoking during pregnancy, any environmental tobacco smoke in the child's home reported during	OR (95% CI) ^b Pneumonia: 1.64 (1.04, 2.58) +PM _{2.5} : 1.32 (0.73, 2.41) +PM _{2.5} Abs: 1.37 (0.56, 3.33) Otitis media: 1.18 (1.04, 1.33) +PM _{2.5} : 1.12 (0.92, 1.35) +PM _{2.5} Abs: 1.12 (0.87, 1.43)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort					follow-up, visible mold or dampness in the home, use of gas stove, birth season, parental socioeconomic status, and intervention (GINIplus, MAAS, PIAMA).	Croup: 0.93 (0.70, 1.23)
Neupane et al. (2010) n = 839 Hamilton, Ontario, Canada Enrollment: July 2003–April 2005 Case-Control	Patients aged 65 or older residing in catchment area. Cases present to emergency department with two of the following symptoms: high temperature, cough, chest pain, shortness of breath, or crackles on auscultation. Additionally, chest radiography indicating pneumonia. Controls excluded if pneumonia diagnosis in past year or active infection	Central site monitor, LUR Averaging time: NO ₂ - annual average Exposure years: 2002	NO ₂ (ppb) Bicubic splined regression Mean = 18.68 Median = 18.52 (IQR 5.46) Min = 12.47 Max = 27.44 P5 = 13.2 P25 = 15.72 P75 = 21.18 P95 = 24.79 Inverse distance weighting function Mean = 20.14 Median = 19.87 (IQR 2.14) Min = 14.93 Max = 26.87 P5 = 16.11 P25 = 19.21 P75 = 21.35 P95 = 23.27 Land use regression Mean = 15	Community acquired pneumonia: self-reported	Logistic regression Adjusted for: Individual level: Age, sex, education, smoking history, and history of exposure to gases, fumes, or chemical at work	OR (95% CI) ^b 1.93 (1.00, 3.73)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 14.98 (IQR 2.91) Min = 8.79 Max = 25.67 P5 = 10.49 P25 = 13.62 P75 = 16.53 P95 = 18.53			
Smith et al. (2016) n = 6,913 Northern California, U.S. Enrollment: January 1996– December 2010 Case-Control	Northern California members of insurance plan, newly diagnosed active pulmonary tuberculosis cases and matched controls	Central site monitor Averaging time: 24-month NO ₂ average Exposure years: 1995–2010	NO ₂ (ppb) Median = 14.4 Min = 0.3 Max = 39.0 P20 = 9.8 P40 = 13.3 P60 = 15.1 P80 = 17.7	Pulmonary TB incidence: insurance records; either: a) a new clinical diagnosis and a prescription for at least 30 days of anti-tuberculosis medication; or b) an initial positive TB culture.	Logistic regression Adjusted for: Individual level: age, sex, and race/ethnicity.	OR (95% CI) ^c Ref (1 st Quintile): --- 2 nd Quintile: 1.17 (0.93, 1.46) 3 rd Quintile: 1.17 (0.93, 1.48) 4 th Quintile: 1.27 (1.01, 1.61) 5 th Quintile: 1.42 (1.10, 1.84)
Sunyer et al. (2004) Asthma Multicentre Infants Cohort Study (AMICS) n = 1,611 Barcelona, Menorca, Spain; Ashford, U.K. Enrollment: 1995–1998 Follow-up: 1995–1999	Birth cohorts were recruited during pregnancy. Two cohorts were population based, women presenting for prenatal care. One cohort was hospital-based, mothers enrolled in last trimester at one hospital	Fixed site monitor Averaging time: Average 2-week NO ₂ Exposure years: 1995–1998	NO ₂ (ppb) Barcelona Median = 45.9 P25 = 34.5 P75 = 59.6 Ashford Median = 5.79	LRTI incidence: maternal reports and medical and prescription records	Logistic regression Adjusted for: Individual level: Sex, family size, breastfeeding, maternal smoking, social class, and season.	OR (95% CI) ^c Ref (≤ 5 ug/m ³): --- 5–10 ug/m ³ : 0.92 (0.67, 1.26) 10–30 ug/m ³ : 0.99 (0.73, 1.36) 30+ ug/m ³ : 0.69 (0.50, 0.95)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort			P25 = 3.64 P75 = 8.85 Menorca Median = 11.86 P25 = 5.99 P75 = 21.22			
†Gandini et al. (2018b) Italian Longitudinal Study (ILS) N = 74,989 Italy Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008 Cohort	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity. Averaging time: NO ₂ - annual average Exposure years: 1999, 2003, 2005, 2007	NO ₂ (ppb) Men Metropolitan Mean = 22.1±6.16 Rural Mean = 10.3±4 Urban Mean = 13.9±5.2 Women Metropolitan Mean = 22.1±6.16 Rural Mean = 10.3±4.2 Urban Mean = 13.9±5.1	LRTI incidence: Health records database; first hospital admission for LRTI	Cox PH Model Adjusted for: Individual level: Age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, and BMI. Contextual: type of municipality (rural, urban, metropolitan areas).	HR (95% CI) ^b 1.10 (1.00, 1.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Kaspersen et al. (2024) Danish national administrative cohort N = 3,653,490 Denmark 2004–2016 Nested case-control	Danish-born residents aged 18–64 years	Dispersion model DEHM/UBM model Averaging time: NO ₂ and NO _x - annual average	Results presented graphically	RTI incidence: Danish National Patient Registry; first hospital contact for ALRI	Logistic regression Adjusted for: Individual level: age, sex, ethnicity, urban or rural home area, education level, average total household income before tax, smoking status, drinking status, BMI, asthma, and COPD.	NO ₂ OR (95% CI) ^b 2.20 (2.11, 2.30) NO _x OR (95% CI) ^b 1.48 (1.45, 1.52)
†Kennedy et al. (2018) n = 22,441 Atlanta, GA, U.S. Enrollment: 2000–2010 Follow-up: 2000–2012 Cohort	Children born 2000–2010 and insured by Kaiser Permanente Georgia	Dispersion model Averaging time: NO _x - annual average Exposure years: 2010	NO _x (ppm) Median = 0.06 (IQR 0.04) Min = 0.01 Max = 0.59	Pneumonia, bronchiolitis, and otitis media incidence: insurance records; first diagnosis	Cox PH Model Adjusted for: Individual level: child race, child sex, maternal asthma, maternal education, maternal prenatal smoking, birth year, and maternal age. Contextual: neighborhood socioeconomic status and city region.	HR (95% CI) ^c Pneumonia: 1.06 (0.97, 1.20) Bronchiolitis: 1.19 (1.12, 1.27) Otitis media: 1.17 (1.11, 1.22)
†Kirwa et al. (2021) Multiethnic study of atherosclerosis (MESA) N = 6,536 Chicago, IL; Baltimore, MD;	At the first MESA examination in 2000–2002, participants were 44–84 years old and did not have clinical cardiovascular disease. We excluded any observations from	Spatiotemporal/geospatial model, Fixed site monitor R ² = 0.72 Averaging time: NO ₂ - 2 weeks	Concentrations presented graphically	Respiratory infection prevalence: self-reported; experienced or been diagnosed with a cold or influenza, febrile	Poisson regression Adjusted for: Individual level: race/ethnicity, sex, age, body mass index, marital status, education level, smoking status,	NO ₂ RR (95% CI) ^b 1.04 (0.95, 1.14) NO _x

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Winston-Salem, NC; St. Paul, MN; New York City, NY; Los Angeles County, CA, U.S. Baseline: July 2000–August 2002 Follow-up: through 2012 Cohort	study visits at which a participant was taking oral steroids and those who were missing one or more covariates on all follow-up examinations.	Exposure years: 1999–2012		illness, sinus infection, bronchitis or pneumonia in the preceding 2 weeks	employment status, annual income, home ownership, number of household members, having health insurance, whether on Medicaid, diabetes diagnosis based on ADA criteria, study site, and splines of calendar time. Contextual: neighborhood level socioeconomic index.	RR (95% CI) ^b 1.07 (0.94, 1.22)
† Madsen et al. (2017) Norwegian Mother and Child Cohort Study (MoBa) n = 17,533 Oslo, Bergen, Akershus, Hordaland, Norway Enrollment: 1999–2008 Follow-up: 8 and 18 months Cohort	Pregnant women recruited across Norway only singleton births included	LUR R ² (range) = 0.55–0.85 Averaging time: NO ₂ average, whole pregnancy Exposure years: 2010, 2011	NO ₂ (ppb) Whole pregnancy Mean = 7.23±3.7 (13.6±6.9 µg/m ³)	LRTI incidence: maternal reports. LRTIs included respiratory syncytial virus, bronchiolitis, bronchitis and pneumonia.	Generalized linear model Adjusted for: Individual level: maternal age at delivery, study area, years of birth, maternal marital status, maternal education, sex of child, maternal pre-pregnancy BMI, smoking during pregnancy, parity, and maternal atopy	RR (95% CI) ^b 0–6 months: 0.98 (0.72, 1.34) 6–18 months: 1.10 (0.90, 1.34)
† Wang et al. (2023a) UK Biobank n = 445,473 U.K.	Participants 40–69 years of age	LUR NO ₂ R ² = 0.87; NO _x R ² = 0.88 Averaging time: NO ₂ - annual	NO ₂ (ppb) Mean = 15.51±4.88 (29.18±9.18 µg/m ³) IQR = 5.788 (10.89 µg/m ³) Min = 4.71 (8.86	Pneumonia incidence: Self-reports, primary care records, and hospital admission data	Cox PH Model Adjusted for: Individual level: age, sex, ethnicity, education level, average total household income	NO ₂ HR (95% CI) ^b Full study populaiton: 1.22 (1.17, 1.26)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 2006–2010 Follow-up: 2006–2019 Cohort		average, NO _x - annual average Exposure years: NO _x (2010); NO ₂ (2005–2007 and 2010)	μg/m ³) Max = 66.496 (125.12 μg/m ³) NO _x (μg/m ³) Mean = 43.9±15.57 IQR = 16.52 Min = 19.74 Max = 265.94		before tax, drinking status, BMI, asthma, and COPD. Contextual: urban or rural home area.	Male: 1.22 (1.16, 1.27) Female: 1.22 (1.15, 1.28) Low income: 1.27 (1.22, 1.33) High income: 1.11 (1.04, 1.18) NO _x HR (95% CI) ^c Full study population: 1.06 (1.04, 1.07)
† Danesh Yazdi et al. (2021) Medicare N = 63,006,793 U.S. 2000–2016 Cohort	All fee-for-service Medicare beneficiaries who were 65 years of age or older and who lived in the contiguous United States between 2000 and 2016 as derived from the Medicare denominator file and the Medicare Provider Analysis and Review file.	Spatiotemporal/geospatial model, LUR, Chemical transport model R ² values of 0.84 for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2000–2016	NO ₂ (ppb) Exposure Across Person-Years Mean = 19.5 Median = 17.44 Min = 0.01 Max = 127.63 P10 = 8.13 P25 = 11.51 P75 = 25.88 P90 = 33.88	Pneumonia incidence: Hospital admissions from the Centers for Medicare and Medicaid Services	Doubly robust additive model Adjusted for: Individual level: age, race, sex, year, region, Medicaid eligibility, and distance to nearest hospital. Contextual: proportion of the population >65 years of age living below the poverty line, population density, median value of owner occupied properties, proportion of the population listed as Black, median	β (Risk Difference) (95% CI) ^b -0.01 (-0.02, -0.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					household income, proportion of housing units occupied by the owner, proportion of the population identified as Hispanic, proportion of the population >65 years of age who had not graduated from high school, BMI, smoking rate, lung cancer hospitalization rate, proportion of Medicare beneficiaries with at least 1 hemoglobin A1c test in a year, proportion of elderly diabetic beneficiaries who had a lipid panel test in a year, proportion of beneficiaries who had an eye examination in a year, proportion of beneficiaries with at least 1 ambulatory doctor visit in a year, and proportion of female beneficiaries who had a mammogram during a 2-year period.	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Zhang et al. (2024) Danish Nurse Cohort n = 23,912 Nationwide, Denmark Enrollment: 1993 or 1999 Follow-up: through 2018 Cohort	Female nurses who were 44 years of age or older and were members of the Danish Nurses Organization	Hybrid model Averaging time: NO ₂ - annual average Exposure years: 1979–2018	NO ₂ (ppb) 3-yr avg prior to baseline Mean = 10.7±3.6 (20.2±6.7 µg/m ³)	ALRI incidence: Danish National Patient Registry; first hospital contact for ALRI	Cox PH Model Adjusted for: Individual level:	HR (95% CI) ^b 1.45 (1.27, 1.65)

List of abbreviations in alphabetical order: ADA = American Diabetes Association; ALRI = Acute Lower Respiratory Infection; BMI = body mass index; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; DEHM = Danish Eulerian Hemispheric Model; ED = emergency department; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; ESCAPE = European Study of Cohorts for Air Pollution Effects; GINIplus = German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy; HR = hazard ratio; IQR = interquartile range; LRTI = Lower Respiratory Tract Infection; LUR = land use regression; MoBa = Norwegian Mother and Child Cohort Study; NHANES = National Health and Nutrition Examination Survey; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OR = odds ratio; P# = #th percentile; PECOS = Population, Exposure, Comparator, Outcome, Study Design; PH = proportional hazards; PIAMA = Prevention and Incidence of Asthma and Mite Allergy Birth Cohort; PM_{2.5} = particulate matter with a diameter less than 2.5 micrometers; PM_{2.5} Abs = PM_{2.5} absorbance; ppb = parts per billion; RR = relative risk; SES = socioeconomic status; TB = Tuberculosis; U.K. = United Kingdom; U.S. = United States; UBM = Urban Background Model; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-9 Animal toxicology studies of respiratory infection

Study Details & Population	Exposure Details	Endpoints Examined*
Ehrlich and Henry (1968)	Whole body inhalation with filtered air controls prior to infection with <i>K. pneumoniae</i>	0–14 d after exposure (continuous, 6 hr/d, 18 hr/d) mortality (↑)
Mouse (Swiss Albino)		0–24 hr after exposure (continuous exposure, 6 hr/d, 18 hr/d)
21g, females	500 ppb (0.5 ppm) NO ₂ , continuous for 1 mo	bacterial clearance (↓)
n = 4–110/group	500 ppb (0.5 ppm) NO ₂ , continuous for 3 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 6 mo	
	500 ppb (0.5 ppm) NO ₂ , continuous for 12 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 1 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 3 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 6 mo	
	500 ppb (0.5 ppm) NO ₂ , 18 hr/d for 12 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 1 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 3 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 6 mo	
	500 ppb (0.5 ppm) NO ₂ , 6 hr/d for 12 mo	

Study Details & Population	Exposure Details	Endpoints Examined*
Ehrlich (1980)	Whole body inhalation with clean air controls	14 d after exposure (Immediately post-NO ₂ exposure challenged with <i>K. pneumoniae</i>)
Mouse (Swiss)	500 ppb (0.5 ppm) NO ₂ , continuous for 7 d	Mortality (↑)
6–8-wk-old, sex not reported	500 ppb (0.5 ppm) NO ₂ , continuous for 14 d	
n = 30–280/group	500 ppb (0.5 ppm) NO ₂ , continuous for 30 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 60 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 90 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 180 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 270 d	
	500 ppb (0.5 ppm) NO ₂ , continuous for 360 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 2 hr	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 8 hr	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 1 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 7 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 14 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 30 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 60 d	
	1,500 ppb (1.5 ppm) NO ₂ , continuous for 90 d	

Study Details & Population	Exposure Details	Endpoints Examined*
Henry et al. (1970)	Whole body inhalation with ambient air controls	0-21 d post-exposure after exposure (10 ppm for 1mo, 5 ppm for 2mo)
Squirrel Monkey	5,000 ppb (5 ppm) NO ₂ , continuous for 2 mo	Mortality after bacterial infection (↑)
600–800g, males	10,000 ppb (10 ppm) NO ₂ , continuous for 1 mo	Weekly during exposure and then 3 d-3 wk post exposure (10 ppm for 1mo)
n = 3–9/group		Respiratory function (minute volume) (increased tidal volume)
		Weekly during exposure and then 3d-12d post-exposure (5 ppm for 2mo)
		Respiratory function (minute volume, tidal volume, respiratory rate)
		(increased respiratory rate, decreased tidal volume, mixed minute volume)
		2-10 d of exposure after exposure (5 ppm or 10 ppm 24 hr after viral infection)
		Mortality after viral infection (↑)
Miller et al. (1987)	Whole body inhalation with filtered air controls	14 d after exposure (Immediately after NO ₂ exposure challenged with <i>S. zooepidemicus</i>)
Mouse (CD-1)	200 ppb (0.2 ppm) NO ₂ , 23 hr/d for 16 wk	Mortality (↑)
6–8-wk-old, females	200 ppb (0.2 ppm) NO ₂ , 23 hr/d for 32 wk	
n = 18–21/group	200 ppb (0.2 ppm) NO ₂ , 23 hr/d for 52 wk	
	200 ppb (0.2 ppm) + 780 ppb (0.78 pm) spikes NO ₂ , 23 hr/d with two 1 hr/d spikes for 16 wk	
	200 ppb (0.2 ppm) + 780 ppb (0.78 pm) spikes NO ₂ , 23 hr/d with two 1 hr/d spikes for 32 wk	
	200 ppb (0.2 ppm) + 780 ppb (0.78 pm) spikes NO ₂ , 23 hr/d with two 1 hr/d spikes for 52 wk	

List of abbreviations in alphabetical order: d = day; hr = hour; mo = month; LDH = lactic dehydrogenase; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: NS = no experimental groups were statistically significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease.

Appendix Table 4-10 Epidemiologic studies of long-term exposure to oxides of nitrogen and lung function and development

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Ackermann-Lieblich et al. (1997) Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) n = 9,651 Basel, Geneva, Aarau, Davos, Lugano, Montana, Payerne, Wald, Switzerland 1991 Cross-Sectional	Random sample of adults aged 18–60 years living in eight areas in Switzerland drawn from registry. Subjects were residents in area for at least 3 years	Central site monitor Averaging time: NO ₂ - annual average Exposure years: 1991	NO ₂ (ppb) Mean = 18.9±8.5 (35.6±16 µg/m ³) Min = 4.9 (9.2 µg/m ³) Max = 30.7 (57.7 µg/m ³)	Supervised Spirometry	Linear regression Adjusted for: age, height, weight, the square of the natural logarithm of age, gender, and atopic status	β (Volume (L)) (95% CI) ^b FVC: -0.02 (-0.03, -0.02) FEV1: -0.01 (-0.02, -0.01)
Breton et al. (2011) Children's Health Study (CHS) n = 2,106 Southern California, U.S. Enrolled: 1993, 1996 Follow-up: 8 years Cohort	Children in the fourth grade enrolled in one of the 12 schools	Fixed site monitor Averaging time: NO ₂ - annual average Exposure years: 1994–Present		Supervised Spirometry	Linear regression - mixed effects Adjusted for: height, gender, BMI, whether the child ever had asthma, respiratory illness at time of testing, exercise, smoking, ethnicity, cohort, town, field technician, and ancestry indicators (q factors) and GSS genotype	β (Rate (mL/s)) (95% CI) ^b MMEF: -54.38 (-90.80, -17.96) β (Volume (mL)) (95% CI) ^b FEV1: -29.83 (-49.97, -9.70) FVC: -29.84 (-54.73, -4.95)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Eenhuizen et al. (2013) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort n = 765 Netherlands October 2000–November 2001 Cross-Sectional	Women recruited in second trimester	LUR R ² = 0.85 Averaging time: NO ₂ - annual average Exposure years: 1999–2000	NO ₂ (ppb) Mean = 13.53 (25.45 µg/m ³) Median = 13.84 (IQR 5.479) (26.04 µg/m ³) Min = 6.686 (12.58 µg/m ³) Max = 30.54 (57.46 µg/m ³) P25 = 9.896 (18.62 µg/m ³) P75 = 15.38 (28.93 µg/m ³)	Supervised airway resistance measurement	Linear regression Adjusted for: age, sex, height, nationality, siblings, mother smoking during pregnancy, pets, mould/damp spots, smoking inside child's home, use of gas for cooking, geyser without outlet, parental allergy and education of parents, temperature, relative humidity and season Adjusted for: age and sex	β (kPa/L/s) (95% CI) ^b Rint - full model: 0.04 (0.04, 0.05) Rint - basic model: 0.06 (0.05, 0.06)
Forbes et al. (2009) Health Survey for England n = 61,799 U.K. 1995, 1996, 1997, 2001 Cross-Sectional	Adults invited based on random sampling by postcode. Exclusions included pregnancy, recent surgery, or recent admission to hospital with heart complaint or stroke	Dispersion model Averaging time: NO ₂ - annual average Exposure years: 1994–1997, 2000–2001		Supervised Spirometry	Linear regression Adjusted for: age, sex, height and all their two-way interactions, pack-years of active smoking, passive smoking (in non-smokers), social class, region and season	β (Volume (mL)) (95% CI) ^b FEV₁ All: -41.40 (-57.39, -25.40) Men: -62.09 (-102.55, -21.64) Women: -22.58 (-50.80, 5.64) 16–44 years: -13.17 (-34.81, 8.47) 45–74 years: -58.33 (-79.03, -37.63) 75+ years: -73.38 (-119.48, -27.28)
Gauderman et al. (2004) Children's Health Study (CHS) n = 1,759	Fourth graders (average age 10 yrs) from elementary schools in	Fixed site monitor Averaging time: NO ₂ - annual average		Supervised Spirometry	Linear regression - mixed effects Adjusted for: height, BMI, race, presence or	β (Volume (mL)) (95% CI) ^b FVC: -27.46 (-54.74, -0.17) FEV ₁ : -29.31 (-47.96, -10.65)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Southern California, U.S. Enrollment: 1993 Follow-up: 1993–2001 Cohort	12 communities in Southern California	Exposure years: 1994–2000			absence of Hispanic ethnic background, doctor-diagnosed asthma, smoking, exposure to environmental tobacco smoke, and exercise or respiratory tract illness on the day of the test	MMEF: -60.98 (-109.13, -12.83)
Gehring et al. (2013) Manchester Asthma and Allergy Study (MAAS), Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE), European Study of Cohorts for Air Pollution Effects (ESCAPE), German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy (GINIplus), Lifestyle-related factors on the Immune System and the development of Allergies in childhood (LISApus) study n = 5,921 Sweden, U.K., Germany, Netherlands 2000–2007 Cross-Sectional	Children aged 6–8 years	LUR R ² (NO ₂ range) = 0.67–0.84; R ² (NO _x range) = 0.76–0.82 Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2008–2010	NO _x (µg/m ³) Min = 11.5 Max = 110 NO _x (µg/m ³) Min = 6 Max = 59.8	Supervised Spirometry	Linear regression - mixed effects Adjusted for: age, sex, height, weight, recent respiratory infections, ethnicity/nationality, parental education, allergic mother, allergic father, breastfeeding, mother smoking during pregnancy, smoking at home, mold/dampness at home, furry pets at home, and study region	β (Percent difference (%)) (95% CI) ^c FEV1: -0.82 (-1.52, -0.11) FVC: -1.93 (-3.42, -0.41) PEF: -0.82 (-1.69, 0.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Ofstedal et al. (2008)	Children from birth cohort that have lived in Oslo since birth	Dispersion model	NO ₂ (ppb)	Supervised Spirometry	Linear regression	β (mL/s) (95% CI) ^b
Oslo Birth Cohort		Averaging time: NO ₂ 3-day average	First year exposure Mean = 20.8 (39.1 $\mu\text{g}/\text{m}^3$)		Adjusted for: sex, height, age, body mass index, birth weight, temperature lags 1–3 d before the lung function test, current asthma, indicator for participation in Oslo Birth Cohort, maternal smoking in early lifetime, parental ethnicity, education, and smoking	FEF25: -58.71 (-97.65, -19.78) FEF50: -37.36 (-71.21, -3.50) PEF: -57.96 (-92.60, -23.31) PEF - Boys: -39.07 (-85.43, 7.28) FEF25 - Boys: -36.81 (-89.96, 16.34) FEF50 - Boys: -17.65 (-63.80, 28.50) PEF - Girls: -82.48 (-134.63, -30.32) FEF25 - Girls: -88.11 (-145.69, -30.52) FEF50 - Girls: -62.70 (-112.83, -12.57)
n = 2,307		NO ₂ weekly average				β (Volume (mL)) (95% CI) ^b
Oslo, Norway		Early exposure in first and second year of life	Lifetime exposure Mean = 15 (29 $\mu\text{g}/\text{m}^3$)			FVC - Girls: 6.18 (-12.70, 25.07) FEV1: -5.97 (-18.10, 6.15) FVC: -1.44 (-14.66, 11.78) FEV1 - Boys: -10.92 (-27.81, 5.97) FVC - Boys: -9.20 (-27.85, 9.44) FEV1 - Girls: -1.99 (-19.43, 15.45)
Enrollment: Study years NR		Total lifetime exposure				
Follow-up: 2001–2002		Exposure years: 1992–2002				
Cohort						
Schikowski et al. (2005)	Women aged 54–55 that resided in selected areas. Inclusion included that residence	Central site monitor, Other	NO ₂ (ppb)	Supervised Spirometry	Linear regression - mixed effects	β (Relative mean difference (L)) (95% CI) ^b
Study on the influence of Air pollution on Lung function,		Averaging time:	Mean = 21 (39 $\mu\text{g}/\text{m}^3$)		Adjusted for: age,	FEV1: 1.13 (1.10, 1.16)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Inflammation and Ageing (SALIA) n = 4,757 Dortmund, Duisburg, Essen, Gelsenkirchen, Herne, Dülmen, Borken, Germany 1985–1994 Cross-Sectional	could be merged with geographic coordinates	NO ₂ - annual average, Other, NO ₂ 5-year annual average Exposure years: 1985–1994	Median = 22 (41 µg/m ³) Min = 11 (20 µg/m ³) Max = 32 (60 µg/m ³) P25 = 15 (29 µg/m ³) P75 = 24 (45 µg/m ³)		smoking, SES, occupational exposure, BMI Adjusted for: age, smoking, SES, occupational exposure	FVC: 1.15 (1.12, 1.17) β (Relative mean difference) (95% CI) ^b FEV1/FVC: 1.16 (1.16, 1.17)
Schultz et al. (2012) Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) n = 1,924 Stockholm County, Sweden Enrollment: 1994–1996 Follow-up: 8 years after birth Cohort	New-born infants were recruited from 4 areas in Stockholm County	Dispersion model R ² range = 0.74–0.80 Averaging time: NO _x - annual average, Other, NO _x 4-year average (years 1–4) NO _x 4-year average (years 4–8) Exposure years: 1990–2004		Supervised Spirometry	Linear regression Adjusted for: municipality, sex, age, height, and heredity	β (Volume (mL)) (95% CI) ^c FEV1: -34.90 (-80.10, 10.40)
Urman et al. (2014) Children's Health Study (CHS) n = 1,811	Children enrolled in cohort when participants were 5–7 years of age (2002–2003)	LUR R ² (NO) = 0.63, R ² (NO ₂) = 0.71, R ² (NO _x) = 0.71		Supervised Spirometry	Linear regression - mixed effects Adjusted for: height, BMI, sex, age, race, Hispanic ethnicity,	NO β (Percent predicted (%)) (95% CI) ^b FEV1: -1.45 (-2.78, -0.12) FVC:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Southern California, U.S. 2007–2008 Cross-Sectional		Averaging time: NO ₂ - annual average, NO _x - annual average, NO - annual average Exposure years: 2005–2006			respiratory illness at time of test, field technician, and study community	-2.05 (-3.35, -0.74) NO _x β (Percent predicted (%)) (95% CI) ^b FVC: -1.74 (-2.93, -0.55) FEV1: -1.23 (-2.45, -0.01)
† Bourbeau et al. (2022) Canadian Cohort Obstructive Lung Disease (CanCOLD) n = 1,452 Toronto, Vancouver, Montreal, Kingston, Halifax, Quebec City, Ottawa, Saskatoon, Calgary, Canada 2009–2015 Cross-Sectional	Noninstitutionalized adults aged 40 and older. Selected individuals with airflow obstruction (COPD), and sex and age matched individuals without COPD	LUR R ² = 0.73 Averaging time: NO ₂ - annual average Exposure years: 2005–2012	NO ₂ (ppb) Mean = 12.8 IQR = 9.2 Min = 0.5 Max = 33	Supervised Spirometry	Linear regression Adjusted for: age, sex, body mass index, educational level (high school or lower vs. postsecondary education), tobacco status (never smoker, former smoker, or current smoker), pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, respiratory medication intake, and CanCOLD site	β (Ratio) (95% CI) ^b FEV1/FVC: -1.20 (-2.72, 0.33) FEV1/FVC - neighbourhood material deprivation: -1.09 (-2.66, 0.49) β (Volume (mL)) (95% CI) ^b FEV1: -125.00 (-213.64, -36.36) FEV1 - neighbourhood material deprivation: -119.67 (-211.74, -27.61) FVC: -113.37 (-231.14, 4.40)
† Cakmak et al. (2016) n = 1058 Windsor, Ontario, Canada 2005	Children with and without asthma in grades 4–6 in the Windsor public school system	LUR Averaging time: NO ₂ - annual average Exposure years: 2005	NO ₂ (ppb) Mean = 11.6±1.8	Supervised Spirometry	Linear regression - mixed effects Adjusted for: race (Caucasian versus other), smokers at home, pets at home, acute respiratory illness	β (Volume (L), % predicted) (95% CI) ^b FEV1 - Income \$35,000–80,000 CAD: 4.14 (-1.48, 9.76) FEV1 - Income <\$35,000 CAD: -8.55 (-15.75, -1.34) FEV1 - Income >\$80,000 CAD:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cross-Sectional					(cold/bronchitis/pneumonia) in the preceding two weeks, any medication for wheezing/asthma in the preceding two weeks, percent of immigrants in census subdivision, and latitude and longitude of postal code representative point	-0.84 (-3.39, 1.72) FVC - Income \$35,000–80,000 CAD: 3.22 (-1.04, 7.47) FVC - Income >\$80,000 CAD: -1.10 (-3.96, 1.76) FVC - Income <\$35,000 CAD: -4.98 (-10.07, 0.11)
†Decrue et al. (2022)	Birth cohort recruited since 1999 in Bern and since 2012 in Basel	Hybrid model	NO ₂ (µg/m ³)	Supervised Spirometry	Linear regression - mixed effects	β (mL/min) (95% CI) ^c
Bern-Basel Infant Lung Development Cohort		Averaging time:	NO ₂ second trimester	Supervised FeNO	Adjusted for: sex, weight at lung function measurement, season and postconceptional age at lung function measurement, gestational age at birth, maternal smoking during pregnancy, maternal asthma (defined as self-reported or doctor-diagnosed), days of supplementary oxygen, days of mechanical ventilation (defined as cPAP and intubation). Additionally, minute ventilation in FeNO models	Minute ventilation - Moderate to late preterm: 45.40 (-32.40, 123.20) Minute ventilation - Preterm: -12.70 (-71.50, 46.00) Minute ventilation - Term: -2.50 (-43.80, 38.90) β (ppb) (95% CI) ^c FeNO - Term: -0.60 (-1.40, 0.30) FeNO - Preterm: 1.50 (-0.20, 3.10) FeNO - Moderate to late preterm: 0.50 (-1.40, 2.50)
n = 771		Average exposure for second trimester	Mean = 17.6 Min = 5.3	measurement		β (Ratio) (95% CI) ^c tPTEF/tE - Term: 1.07 (-0.46, 2.61) tPTEF/tE - Preterm: 0.82 (-0.83, 2.47) tPTEF/tE - Moderate to late preterm: 1.25 (-1.02, 3.51)
Bern, Basel, Switzerland		Average postnatal	Max = 52.8			
Enrollment: 1999		Exposure years:	Postnatal NO ₂			
Follow-up: 44 weeks after birth		NA	Mean = 17.4 Min = 4.8 Max = 42.3			
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Doiron et al. (2019)	Individuals aged 40–69 years from largely urban areas of England, Wales, and Scotland, recruited from the UK National Health Services register	LUR R ² = 0.87 Averaging time: NO ₂ - annual average	NO ₂ (ppb) Mean = 13.98±3.98 (26.31±7.49 µg/m ³) IQR = 5.2 (9.7 µg/m ³) Min = 6.872 (12.93 µg/m ³) Max = 57.658 (108.49 µg/m ³)	Supervised Spirometry	Linear regression Adjusted for: age (continuous), age-squared, sex, height, body mass index (kg/m ²), household income (<31000 GBP/ ≥31000 GBP), education level (lower vocational or less/higher vocational or more), smoking status (never/former/current) and passive smoking exposure at home (none/any).	β (Ratio) (95% CI) ^b FEV1/FVC - Non-obese: -3.89 (-4.53, -3.26) FEV1/FVC - Obese: -4.91 (-6.10, -3.73) FEV1/FVC - Male: -4.27 (-5.15, -3.40) FEV1/FVC - Female: -4.23 (-4.98, -3.49) FEV1/FVC: -4.27 (-4.85, -3.70) FEV1/FVC - Household income (<31,000 GBP): -6.51 (-7.44, -5.58) FEV1/FVC - Age <65 years: -3.84 (-4.44, -3.24) FEV1/FVC - Age ≥ 65 years: -6.59 (-8.19, -4.99) FEV1/FVC - Household income (≥31,000 GBP): -2.65 (-3.36, -1.95) β (Volume (mL)) (95% CI) ^b FVC - Non-obese: -59.55 (-65.96, -53.15) FVC - Obese: -76.73 (-88.65, -64.81) FEV1 - Household income (<31,000 GBP): -67.29 (-74.87, -59.70) FEV1 - Household income (≥31,000 GBP): -41.04 (-47.50, -34.57) FVC - Household income (<31,000 GBP): -88.29 (-97.06, -79.51) FEV1 - Non-obese:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-59.63 (-64.93, -54.32) FEV1 - Obese: -75.94 (-85.95, -65.93) FEV1 - Female: -52.70 (-57.98, -47.43) FVC - Male: -76.86 (-86.35, -67.38) FVC - Female: -52.05 (-58.44, -45.65) FEV1 - Age <65 years: -61.25 (-66.36, -56.13) FEV1 - Age ≥65 years: -59.53 (-71.15, -47.92) FVC - Age <65 years: -65.59 (-71.77, -59.41) FVC - Age ≥65 years: -51.58 (-65.43, -37.72) FEV1: -63.69 (-68.38, -59.01) FVC: -62.98 (-68.63, -57.32) FEV1 - Male: -77.56 (-85.50, -69.62) FVC - Household income (≥31,000 GBP): -41.68 (-49.06, -34.29)
†Hüls et al. (2019) Study on the Influence of Air Pollution on Lung Function, Inflammation and Ageing (SALIA) n = 601 Ruhr, Muensterland, Germany	Women from an urban area and a rural area in Germany, mean age 54 years at baseline (1985–1994)	LUR R ² = 0.88 Averaging time: NO ₂ 2-year average NO _x 2-year average	NO ₂ (µg/m ³) Baseline Mean = 33.4 IQR = 13.8 Min = 20.3 Max = 84.1 First follow-up Mean = 23.4	Supervised Spirometry	Linear regression Adjusted for: age, level of education, smoking, and exposure to second-hand smoke Linear regression - mixed effects	NO ₂ β (Change in z-score (per decrease in NO ₂)) (95% CI) ^c FEV1 - Overweight: 0.15 (-0.01, 0.31) FEV1 - Obese: 0.14 (-0.04, 0.31) FVC - Underweight to normal: -0.07 (-0.25, 0.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 1985–1994 Follow-up: 2007–2010 and 2012–2013 Cohort and Cross-Sectional		Exposure years: 2008–2009	IQR = 7.5 Min = 18.4 Max = 68.2 Second follow-up Mean = 19.7 IQR = 6.3 Min = 16.1 Max = 46.1 NO _x (µg/m ³) Baseline Mean = 52.8 IQR = 39 Min = 26.8 Max = 184.1 First follow-up Mean = 34.1 IQR = 19.7 Min = 21.7 Max = 116.1 Second follow-up Mean = 27.7 IQR = 16.1 Min = 18.7 Max = 98.9		Adjusted for: age, BMI at baseline, change of BMI during the study period, level of education, smoking (categorized as current, former or never smoking) and exposure to second hand smoke (SHS)	FEV1 - Underweight to normal: 0.09 (-0.09, 0.28) FVC - Overweight: 0.04 (-0.11, 0.19) FEV1/FVC - Obese: 0.23 (0.04, 0.43) FVC - Obese: -0.01 (-0.17, 0.16) FEV1/FVC - Underweight to normal: 0.24 (0.04, 0.45) FEV1/FVC - Overweight: 0.14 (-0.04, 0.31) β (Change in z-score) (95% CI) ^c FEV1 - Baseline: -0.16 (-0.24, -0.09) FEV1 - 1 st follow-up: -0.05 (-0.17, 0.07) FEV1 - 2 nd follow-up: 0.10 (-0.11, 0.31) FVC - Baseline: -0.11 (-0.17, -0.04) FVC - 2 nd follow-up: 0.00 (-0.20, 0.19) FEV1/FVC - Baseline: -0.09 (-0.16, -0.03) FEV1/FVC - 1 st follow-up: -0.03 (-0.13, 0.07) FVC - 1 st follow-up: -0.03 (-0.14, 0.07) FEV1/FVC - 2 nd follow-up: 0.11 (-0.05, 0.26) NO _x β (Change in z-score (per decrease in NO _x)) (95% CI) ^c

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						FEV1/FVC - Underweight to normal: 0.09 (-0.06, 0.24) FEV1/FVC - Overweight: 0.05 (-0.07, 0.17) FEV1/FVC - Obese: 0.13 (-0.02, 0.28) FEV1 - Underweight to normal: 0.04 (-0.10, 0.18) FEV1 - Overweight: 0.10 (-0.01, 0.21) FEV1 - Obese: 0.06 (-0.08, 0.19) FVC - Underweight to normal: -0.02 (-0.15, 0.11) FVC - Overweight: 0.05 (-0.05, 0.15) FVC - Obese: -0.02 (-0.15, 0.10) β (Change in z-score) (95% CI) ^c FEV1 - Baseline: -0.09 (-0.15, -0.04) FEV1 - 1 st follow-up: -0.06 (-0.16, 0.04) FEV1 - 2 nd follow-up: 0.10 (-0.07, 0.26) FVC - Baseline: -0.06 (-0.11, -0.02) FVC - 1 st follow-up: -0.05 (-0.14, 0.03) FVC - 2 nd follow-up: 0.01 (-0.14, 0.16) FEV1/FVC - Baseline: -0.05 (-0.09, 0.00) FEV1/FVC - 1 st follow-up: -0.10 (-0.09, 0.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						FEV1/FVC - 2 nd follow-up: 0.10 (-0.02, 0.22)
† Ierodiakonou et al. (2015) Childhood Asthma Management Program (CAMP) n = 1,003 Boston, MA; Albuquerque, NM; Baltimore, MD; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; U.S., Toronto, Ontario, Canada Enrollment: Study years NR Follow-up: 4 years Cohort	Children diagnosed with asthma 5–12 years of age	Fixed site monitor Averaging time: NO ₂ 4-month average Exposure years: 1993–1999	NO ₂ (ppb) Median = 22 (IQR 13) P10 = 11 P25 = 26 P75 = 28 P90 = 35	Supervised Spirometry	Linear regression - mixed effects Adjusted for: city, season, random intercept for subject	β (% Predicted) (95% CI) ^c Post-BD FVC: -0.20 (-0.40, -0.10) Post-BD FEV1: -0.20 (-0.40, 0.01)
† Keidel et al. (2019) European Study of Cohorts for Air Pollution Effects (ESCAPE), Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), European Community Respiratory Health Survey (ECRHS), Epidemiologic Study on the Genetics and Environment of Asthma (EGEA), European Community Respiratory Health Survey (ECRHS II)	Adults aged 18–60 years, some recruited individuals were from oversampling asthmatics	LUR Averaging time: NO ₂ - annual average Exposure years: 2008–2011		Supervised Spirometry	Linear regression - mixed effects Adjusted for: sex, age, height, smoking, pack-years, BMI, and occupation (manual vs non-manual)	β (Volume (mL)) (95% CI) ^b FEV1 - occupation: -22.02 (-45.54, 1.51) FEV1 - all SES variables: -24.08 (-47.61, -0.56) FVC - education low: -10.54 (-56.26, 35.19) FVC - education medium: -36.69 (-74.79, 1.41) FEV1 - education: -23.90 (-47.32, -0.47) FVC - education high: -41.40 (-77.24, -5.55) FEV1 - education low: -0.94 (-40.45, 38.57) FEV1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 6,502						-21.26 (-44.78, 2.26) FVC: -29.73 (-57.30, -2.16) FVC - education: -32.36 (-59.93, -4.80) FVC - occupation: -29.92 (-57.48, -2.35) FVC - all SES variables: -32.18 (-59.84, -4.52) FEV1 - education medium: -27.28 (-60.12, 5.55) FEV1 - education high: -34.43 (-65.29, -3.58)
	Barcelona, Albacete, Huelva, Galdakao, Oviedo, Spain; Paris, Grenoble, Lyon, Marseille, France; Umeå, Sweden; Geneva, Basel, Lugano, Switzerland; Ipswich, Norwich, U.K.; Erfurt, Germany; Antwerp, Belgium; Verona, Pavia, Turin, Italy					
	Enrollment: 1991–1995 Follow-up: 2000–2007					
	Cross-Sectional					
† Knibbs et al. (2018)	Children aged 7–11 years during 2007–2008. Randomly selected classes within 55 schools	Central site monitor, LUR, Central site monitor R ² = 0.76 Averaging time: NO ₂ - annual average, Other, NO ₂ Lifetime exposure (average of daily levels) NO ₂ Prior exposure (average of daily levels excluding prior year) NO ₂ Average of daily levels in year prior	NO ₂ (ppb) Recent exposure (average in prior year) Mean = 8.8 Median = 7.9 (IQR 4)	Supervised Spirometry Supervised FeNO measurement	Linear regression Adjusted for: age, sex, parental education, index of education and occupation, index of relative socio-economic advantage and disadvantage, monthly (for month of testing) and annual average daily mean temperature	β (Percent increase (%)) (95% CI) ^b FeNO: 92.50 (42.50, 142.50) β (Percent predicted (%)) (95% CI) ^b FVC pre-bronchodilator: -2.78 (-4.69, -0.86) FVC post-bronchodilator: -2.98 (-5.09, -0.86) FEV1/FVC pre-bronchodilator: -0.25 (-1.45, 0.95) FEV1/FVC post-bronchodilator: -0.25 (-1.25, 0.75) FEV1 post-bronchodilator: -3.38 (-5.53, -1.23) FEV1 pre-bronchodilator: -3.08 (-5.19, -0.96)
	Australian Child Health and Air Pollution Study (ACHAPS)					
n = 2,630						
	Western Australia, Victoria, New South Wales, Queensland, South Australia, Australian Capital Territory, Australia					
	2007–2008					
	Cross-Sectional					

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		NO ₂ Monthly estimates for most recent year				
		Exposure years: 2006–2011				
† Kuang et al. (2023)	Older adults aged 45 and above	Spatiotemporal/geospatial model	NO ₂ (ppb)	Self-administered peak flow meter	Linear regression - mixed effects	β (Rate (L/min)) (95% CI) ^b
China Health and Retirement Longitudinal Study (CHARLS)		Averaging time: NO ₂ - annual average	Mean = 14.8±6.75 (27.9±12.7 µg/m ³)		Adjusted for: (demographic characteristics) age, sex, marital status, educational level, and residence; (behavioral and health factors) age, sex, marital status, educational level, residence, alcohol consumption, smoking status, intensity of physical activity, BMI, prevalence of chronic diseases, and self-rated health status; and (environmental factors) age, sex, marital status, educational level, residence, alcohol consumption, smoking status, intensity of physical activity, BMI, prevalence of chronic diseases, self-rated health status, household fuel type of	PEF: -23.14 (-26.72, -19.57)
n = 13,614						PEF - demographic characteristics: -41.96 (-45.63, -38.29)
Nationwide, China		Exposure years: 2011–2015				PEF - behavioral and health factors: -40.64 (-44.31, -36.97)
2011–2015						PEF - environmental factors: -40.83 (-44.78, -36.88)
Panel						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					cooking/heating, outdoor temperature	
† Kwon et al. (2020)	Individuals residing in areas near cement plants	LUR	NO ₂ (ppb)	Supervised Spirometry	Linear regression	β (Volume (L)) (95% CI) ^b
COPD in Dusty Areas (CODA) cohort		R ² = 0.82	Mean = 13.6±2.1 Median = 13.5 (IQR 3)		Adjusted for: age, gender, education, height, weight, smoking, pack-years, medication use, and job	FEV1 - Male: -0.03 (-0.28, 0.22) FEV1 - Female: 0.10 (-0.28, 0.48)
n = 457		Averaging time: NO ₂ - annual average	P5 = 10.2 P25 = 12.3 P75 = 15.3 P95 = 17.2			FVC - Male: -0.37 (-0.67, -0.07) FVC - Female: -0.10 (-0.60, 0.40)
South Korea		Exposure years: 2010				FEV1: 0.00 (-0.22, 0.22) FVC: -0.30 (-0.57, -0.03)
2012–2017						
Cross-Sectional						
† LISS (2020)	Children randomly selected from elementary schools and middle schools chosen from the different districts	LUR	NO ₂ (μg/m ³)	Supervised Spirometry	Linear regression	β (Rate (mL/s)) (95% CI) ^c
Seven Northeast Cities (SNEC) study		R ² (range) = 0.64–0.72	Mean = 34±4.6		Adjusted for: age, gender, smoking exposure, parental education, breastfeeding status, income, home coal use, house pet, family history of atopy, temperature during investigation, and study districts	PEF - Normal weight: -65.56 (-114.80, -16.32) MMEF - Normal weight: -40.22 (-77.27, -3.18) PEF - Overweight: 6.16 (-93.51, 105.84) MMEF - Overweight: 17.35 (-56.22, 90.91) PEF - Obese: 57.20 (-47.15, 161.54) MMEF - Obese: -1.64 (-77.90, 74.62)
n = 6,740		Averaging time: NO ₂ 4-year average				β (Volume (mL)) (95% CI) ^c
Shenyang, Dalian, Benxi, Liaoyang, Dandong, Anshan, Fushun, China		Exposure years: 2009–2012				FEV1 - Normal weight: -8.20 (-29.46, 13.06) FVC - Normal weight: 1.12 (-23.31, 25.55) FVC - Overweight: -20.65 (-69.96, 28.67)
April 2012–May 2013						
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						FEV1 - Overweight: -12.51 (-56.08, 31.07) FVC - Obese: -39.39 (-96.77, 17.99) FEV1 - Obese: -24.87 (-72.97, 23.24)
† Schultz et al. (2015)	Children born in different areas of Sweden	Dispersion model	NOx (µg/m ³)	Supervised Spirometry	Linear regression	β (Volume (mL)) (95% CI) ^c
Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE)		Averaging time: NOx - annual average, Other, NOx average of 1–8 years	Mean = 20.9		Adjusted for: age, gender, height, weight, and municipality at birth	FEV1: -12.50 (-26.40, 1.40) FEV1/FVC - Females: 0.10 (-0.20, 0.50)
n = 1,931		NOx average of 8–16 years			Linear regression - mixed effects	FEV1: -15.80 (-33.60, 2.00)
Sweden						FEV1 - Males: -23.30 (-44.80, -1.70)
Enrollment: 1994–1996 (birth)		Exposure years: 1990, 1995, 2000, 2002, 2003, 2004, 2006, 2010 and 2015			Adjusted for: time dependent covariates (height, age, weight) and fixed covariate (municipality at birth as well as gender in unstratified analyses)	FEV1 - Females: -0.30 (-17.40, 16.80) FEV1/FVC: -0.10 (-0.30, 0.20) FEV1/FVC - Males: -0.30 (-0.70, 0.10)
Follow-up: Until 16 years of age						FEV1 - Males: -30.40 (-59.10, -1.70)
Cohort						FEV1 - Females: 0.90 (-20.30, 22.10) FVC: -10.70 (-30.70, 9.40) FVC - Males: -17.60 (-49.90, 14.60) FVC - Females: 1.00 (-23.20, 25.20)
						β (Volume change (mL)) (95% CI) ^c
						FEV1 change: -0.30 (-12.40, 11.90) FEV1 change - Males: 0.60 (-19.70, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						FEV1 change - Females: 0.30 (-12.70, 13.30)
† Usemann et al. (2019) Bern-Basel Infant Lung Development Cohort n = 241 Bern, Switzerland Enrollment: 2002–2010 Follow-up: 2008–2016 Cohort	Healthy term-born infants	Spatiotemporal/geospatial model Averaging time: NO ₂ - annual average, Other, NO ₂ average from birth until 6 years of age Exposure years: 2002–2016	NO ₂ (ppb) 1st year of life Mean = 9.35±2.7 (17.6±5.1 µg/m ³) IQR = 3.8 (7.2 µg/m ³) Min = 5 (9.4 µg/m ³) Max = 18.3 (34.4 µg/m ³) Mean = 8±2.3 (15±4.3 µg/m ³) IQR = 2.8 (5.3 µg/m ³) Min = 4.5 (8.5 µg/m ³) Max = 16 (30.2 µg/m ³) 6th year of life Mean = 6.8±2 (12.8±4 µg/m ³) IQR = 2.6 (4.9 µg/m ³) Min = 4 (7 µg/m ³) Max = 14.1 (26.6 µg/m ³)	Supervised Spirometry	Linear regression Adjusted for: sex, child's age, height, child's diagnosis of asthma, maternal atopy, environmental tobacco exposure and short-term exposure to the examined air pollutant	β (Volume (mL)) (95% CI) ^b FEV1, 1st year of life exposure: -66.90 (-155.76, 21.95) FEV1, 6th year of life exposure: -155.52 (-293.19, -17.86) FEV1, exposure from birth until 6th year: -37.70 (-72.30, -3.10)
† Yu et al. (2023b) Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE)	Children a part of BAMSE cohort with spirometry data at 8 years and at a second time point	Dispersion model R ² = 0.98 Averaging time: NO _x - annual	NO _x (µg/m ³) 8yrs Median = 17 (IQR 14.1)	Supervised Spirometry	Linear regression - mixed effects Adjusted for: age, sex, height, body mass index (BMI) at age 8 years,	β (Difference (mL/yr)) (95% CI) ^c FEV1 growth: -1.70 (0.16, -3.57) FVC growth: -3.29 (-0.35, -6.23)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 1,104 Stockholm, Sweden Enrollment: 2004–2006 Follow-up: 8, 16, 24 years Cohort		average Exposure years: 1990, 1995, 2000, 2011, 2015 and 2020	16yrs Median = 10.4 (IQR 9.4) 24yrs Median = 9.93 (IQR 7.65)		municipality at birth, parental education level at birth, parental occupation at birth, maternal smoking during pregnancy, environmental tobacco smoke at 8 years, air pollution exposure during the first year of life, BMI at 16 and 24 years, active smoking at 16 and 24 years, and education level at 24 years	
† Zhang et al. (2021a) Children’s Health Study (CHS) n = 3,607 Southern California, U.S. Enrollment: 2002–2003 Follow-up: 2004–2005, 2011–2012 Cohort	Children enrolled in kindergarten and first grade, assessed when aged 6–17yrs	Central site monitor Averaging time: NO ₂ - annual average Exposure years: 2004–2012		Supervised FeNO measurement	Linear regression - mixed effects Adjusted for: sex, race, age, height and natural log-transformed FeNO at the previous visit. Model with additional adjustments also adjusts for respiratory allergy, asthma, medication use, wheeze, secondhand tobacco smoking, recent respiratory illness, room air nitric oxide, month, temperature, and prior 7-day average of the same pollutant	β (% Difference) (95% CI) ^b Percent difference in FeNO: 14.96 (6.06, 23.87) Percent difference in FeNO - additional adjustments, short-term exposure: 23.93 (15.00, 32.85)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Zhao et al. (2021) German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy (GINIplus), Life Style Factors on the Development of the Immune System and Allergies in East and West Germany birth cohorts (LISA) n = 2,224 Munich, Wesel, Germany 2010–2013 Cross-Sectional	Adolescents (15 yrs of age) from multiple cities in Germany	LUR Averaging time: NO ₂ - 24-hour average Exposure years: 2008–2009		Supervised Spirometry	Linear regression Adjusted for: age, sex, height, region, maternal smoking during pregnancy, maximal parental education, short-term air pollution and asthmatic status	β (% Change) (95% CI) ^b FEV1/FVC - Overweight/obesity: -1.90 (-7.60, 3.80) FVC - Normal weight: 1.90 (-0.95, 4.75) FEV1/FVC - Underweight: 0.00 (-6.84, 6.84) FEV1/FVC - Normal weight: 0.00 (-1.90, 1.90) FVC - Underweight: -11.02 (-20.15, -1.90) PEF - Underweight: -19.77 (-31.17, -8.36) FVC - Overweight/obesity: -13.30 (-22.43, -4.18) PEF - Overweight/obesity: -7.98 (-21.48, 5.51) FEV1 - Underweight: -11.02 (-21.29, -0.76) FEV1 - Normal weight: 1.52 (-1.33, 4.37) PEF - Normal weight: 1.90 (-1.71, 5.51) FEV1 - Overweight/obesity: -15.21 (-24.90, -5.51)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† de F C Lichtenfels et al. (2018)	Subjects enrolled in Lifelines cohort study, designed to investigate chronic diseases and healthy aging. Inclusion criteria included having complete data on lung function and environmental exposure	LUR Averaging time: NO ₂ - annual average Exposure years: 2007–2013	NO ₂ (ppb) Mean = 8.66±1.7 (16.3±3.2 µg/m ³) Min = 5 (9.4 µg/m ³) Max = 17.4 (32.8 µg/m ³)	Supervised Spirometry	Linear regression Adjusted for: (FEV1 and FVC) sex, age, height, BMI, current-smoking, and pack-years; (FEV1/FVC) sex, age, BMI, current-smoking, and pack-years; (FEF25–75) sex, age, height, BMI, current-smoking, pack-years, and FVC	β (Rate (mL/s)) (95% CI) ^b FEF25–75: 241.79 (-131.34, 614.92) β (Ratio) (95% CI) ^b FEV1/FVC: 2.82 (-0.09, 5.74) β (Volume (mL)) (95% CI) ^b FEV1: 4.52 (-178.38, 187.41) FVC: -200.02 (-412.36, 12.32)
Lifelines cohort n = 1,017 Netherlands 2007–2013 Cross-Sectional						

List of abbreviations in alphabetical order: ACHAPS = Australian Child Health and Air Pollution Study; BAMSE = Children, Allergy, Milieu, Stockholm, Epidemiological Survey; BMI = body mass index; CAMP = Childhood Asthma Management Program; CHARLS = China Health and Retirement Longitudinal Study; CHS = Children's Health Study; CI = confidence interval; CODA = COPD in Dusty Areas; COPD = Chronic Obstructive Pulmonary Disease; DEHM = Danish Eulerian Hemispheric Model; ECRHS = European Community Respiratory Health Survey; EGEA = Epidemiologic Study on the Genetics and Environment of Asthma; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; ESCAPE = European Study of Cohorts for Air Pollution Effects; FEF₂₅₋₇₅ = forced expiratory flow at 25-75% of pulmonary volume; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GINIplus = German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy; HR = hazard ratio; IQR = interquartile range; LISApplus = Lifestyle-related factors on the Immune System and the development of Allergies in childhood study; LRTI = Lower Respiratory Tract Infection; LUR = land use regression; mL/s = milliliters per second; MMEF = maximal mid-expiratory flow; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OP = organophosphate; OR = odds ratio; P# = #th percentile; PECOS = Population, Exposure, Comparator, Outcome, Study Design; PIAMA = Prevention and Incidence of Asthma and Mite Allergy Birth Cohort; PM_{2.5} = particulate matter with a diameter less than 2.5 micrometers; ppb = parts per billion; PEF = peak expiratory flow; RR = relative risk; SALIA = Study on the influence of Air pollution on Lung function, Inflammation and Ageing; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; SES = socioeconomic status; SHS = second-hand smoke; SNEC = Seven Northeast Cities; U.K. = United Kingdom; U.S. = United States; UBM = Urban Background Model; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-11 Animal toxicology studies of lung function and development

Study Details & Population	Exposure Details	Endpoints Examined*
Miller et al. (1987)	Whole body inhalation with filtered air controls	0 d and 30 d after exposure
Mouse (CD-1)	200 ppb with 2x 800 ppb spikes (0.2 ppm with 2x 0.8 ppm spikes) NO ₂ , 23 hr/d for 32 wk	End-expiratory volume (NS)
6–8-wk-old, females	200 ppb (0.2 ppm) NO ₂ , 23 hr/d for 52 wk	Multiple-breath nitrogen washout (↓)
n = 5–21/group	200 ppb with 2x 800 ppb spikes (0.2 ppm with 2x 0.8 ppm spikes) NO ₂ , 23 hr/d for 52 wk	Respiratory-system compliance (NS)
	200 ppb (0.2 ppm) NO ₂ , 23 hr/d for 16 wk	Vital capacity (NS)
	200 ppb with 2x 800 ppb spikes (0.2 ppm with 2x 0.8 ppm spikes) NO ₂ , 23 hr/d for 16 wk	
	200 ppb (0.2 ppm) NO ₂ , 23 hr/d for 32 wk	

List of abbreviations in alphabetical order: d = day; hr = hour; min = minute; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: NS = no experimental groups were statistically significantly different from control; ↓ = at least one experimental group had a statistically significant decrease

Appendix Table 4-12 Epidemiologic studies of long-term exposure to oxides of nitrogen and interstitial lung disease

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Cui et al. (2023)	UK Biobank participants aged 37–73 years without IPF or secondary pulmonary fibrosis diseases at baseline	LUR	NO ₂ (ppb)	IPF: Diagnosis and date of incidence of IPF were recorded by hospital episode databases from England, Wales and Scotland. Excluded a range of diseases	Cox PH	HR (95% CI) ^b
UK Biobank		LOOCV NO ₂ R ² = 0.87; NO _x R ² = 0.88	Mean = 14.16±4.06 Median = 13.89 (IQR = 5.25) Min = 6.87 Max = 57.66 P10 = 9.10 P25 = 11.35 P75 = 16.60 P90 = 19.16		Adjusted for: Individual level: Age, body mass index, sex, ethnicity, smoking status, alcohol intake, metabolic equivalent of task, and healthy diet score.	1.22 (1.06, 1.40)
n = 433,738 (1,380 cases)						
U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average				
Enrollment: 2006–2010						
Follow-up: Enrollment through 2020						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort		Exposure years: 2010	NO _x (μg/m ³) Mean = 43.99±15.65 Median = 42.21 (IQR 16.58) Min = 19.74 Max = 265.94 P10 = 26.46 P25 = 34.17 P75 = 50.75 P90 = 61.6	of secondary pulmonary fibrosis to improve the specificity of the IPF diagnosis.	Contextual: Townsend deprivation index,	
† Sack et al. (2017) MESA Air n = 5,495 Baltimore, MD; Chicago, IL; Los Angeles County, CA; New York City, NY; St Paul, MN; and Winston Salem, NC, U.S. Enrollment: 2000–2007 Follow-up: 2010–2012 Cohort	Adults aged 45–84 years free of known cardiovascular disease at baseline	LUR	NO ₂ (ppb) HAA cohort mean = 21.3±9.2 ILA cohort mean = 21.0±9.1 NO _x (ppb) HAA cohort mean = 50.1±27.5 ILA cohort mean = 49.1±26.9	ILAs: Board-certified radiologists reviewed full lung CT scans for ILAs, which was defined as any scan read as “definite” ILD or “suspicious” for ILAs. HAAs: measured on non-contrast cardiac CT scans and defined as the percentage NO _x 50.1±27.5 49.1±26.9 of the imaged lung volume	Linear Mixed Model (ILAs) Logistic Regression (HAA) Adjusted for: Individual level: age, sex, race/ethnicity, study site, educational attainment, job exposure matrix, height, body mass index, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of image lung, percent emphysema on CT scan, and CT scanner type.	NO ₂ OR (95% CI) ^c ILA: 1.23 (0.87, 1.76) β (% change) (95% CI) ^c HAA: 0.17 (-0.16, 0.51) NO _x OR (95% CI) ^c ILA: 1.62 (0.97, 2.71) β (% change) (95% CI) ^b HAA: 0.45 (-0.02, 0.92)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				having attenuation values between -600 and -250 Hounsfield Units (HU)		
† Tomos et al. (2021) n = 118 Greece 2013–2019 Cohort	All IPF patients referred to a local Greek hospital's pulmonary Medicine Department from October 2013 to June 2019 were included.	Dispersion model Averaging time: NO ₂ - annual average Exposure years: 2002-2019	NO ₂ (ppb) Mean = 11.8±9.9 Min = 0.3 Max = 29.7	IPF exacerbation: Worsening of dyspnea within the last 30 days, exclusion of identifiable causes, with new ground glass opacities or consolidations confirmed by chest computed tomography (CT)	Logistic Regression Adjusted for: Individual level: age, sex, smoking status, and antifibrotic therapy	OR (95% CI) ^b 2.20 (1.31, 3.70)

List of abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; CT = computed tomography; HAA = high attenuation areas; HR = hazard ratio; HU = Hounsfield Units; ILAs = interstitial lung abnormalities; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; LOOCV = leave-one-out cross-validation; LUR = land use regression; MESA = Multi-Ethnic Study of Atherosclerosis; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; OR = odds ratio; P# = #th percentile; PH = proportional hazards; ppb = parts per billion; U.K. = United Kingdom; U.S. = United States; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 4-13 Epidemiologic studies of long-term exposure to oxides of nitrogen and respiratory mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Abbey et al. (1999) Adventist Health Study (AHS) n = 6,338 San Diego, Los Angeles, San Francisco, CA, U.S. Enrollment: 1977 Follow-up: 1977–1992 Cohort	Non-Hispanic white Seventh-day Adventists residing in California areas who were ages 27–95 yrs at baseline. Participants lived 10yrs or longer within 5 miles of their residence at enrollment, residing in air basins including San Francisco, South Coast, or San Diego	Fixed site monitor Averaging time: NO ₂ cumulative monthly average (enrollment through month of death) Exposure years: 1966–1992	NO ₂ (ppb) Mean = 36.78±12.99 IQR = 19.78	Mortality records from California death certificate files, National Death Index, and alternative tracing procedures	Cox PH Model Adjusted for: Individual level: age at baseline, pack-years of past smoking, years lived with a smoker, years worked with a smoker, years of education at baseline, employment in an occupation with significant exposure to air pollutants for more than 10 yr, and body mass index.	HR (95% CI) ^b Females: 0.98 (0.87, 1.11) Males: 0.93 (0.81, 1.06)
Dimakopoulou et al. (2014) European Study of Cohorts for Air Pollution Effects (ESCAPE) n = 307,553 Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands Baseline recruitment (Range): 1985–2007 Cohort	Pooled analysis of data from 16 well-established ESCAPE cohorts	LUR Averaging time: NO ₂ – monthly Exposure years: 2008–2011	NO ₂ (ppb) Concentrations presented graphically	National Mortality Registries	Cox PH Model Adjusted for: Individual level: age, sex, calendar time, smoking status, smoking intensity, smoking duration, environmental tobacco smoke, occupation, employment status, intake of fruit, intake of vegetables, marital status, educational level, and body mass index.	HR (95% CI) ^b 0.89 (0.65, 1.22)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					Contextual: area-level socioeconomic status.	
Jerrett et al. (2013) Cancer Prevention Study II (CPS-II) N = 73,711 California, U.S. Enrollment: 1982 Follow-up: 2000 Cohort	Subjects with valid postal addresses, residents of California, and excluded those with missing data on key covariates	LUR Averaging time: NO ₂ - monthly Exposure years: 1998–2002	NO ₂ (ppb) Overall Mean = 12.27 Median = 12.12 P5 = 7.93 P10 = 8.81 P25 = 10.21 P75 = 14.33 P90 = 16.22 P95 = 17.09	Death records	Cox PH Model Adjusted for: Individual level: lifestyle, dietary, demographic, occupational, and educational factors. Contextual: unemployment, poverty, income inequality, and racial composition.	HR (95% CI) ^b 1.00 (0.83, 1.20)
Lipsett et al. (2011) California Teachers Study (CTS) n = 101,784 California, U.S. Enrollment: 1995 Follow-up: 1997, 2000 Cohort	Current and former public school professionals who were female enrollees in the State Teachers' Retirement System	Fixed site monitor Averaging time: NO ₂ - monthly average Exposure years: 1996–2005	NO ₂ (ppb) Mean = 33.59±9.63 IQR = 10.29 Min = 5.24 Max = 67.19 NOx (ppb) Mean = 95.6±34.5 IQR = 48.31 Min = 7.31 Max = 221.4	Mortality records from the California Department of Public Health, the U.S. Social Security Administration death master file, and the National Death Index	Cox PH Model Adjusted for: Individual level: age, race, smoking status, total pack-years, body mass index, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication, and aspirin use.	NO ₂ HR (95% CI) ^b 0.93 (0.76, 1.14) NOx HR (95% CI) ^b 0.94 (0.83, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					Contextual: income, income inequality, education, population size, racial composition, and unemployment.	
†Bouma et al. (2023) Statistics Netherlands (CBS) N = 10,735,734 Netherlands Enrollment: 2013 Follow-up: 2013–2019 Cohort	Adults aged 30 years and older on January 1 st , 2013	Dispersion model R ² = 0.60 Averaging time: NO ₂ - annual average Exposure years: 2016	NO ₂ (ppb) Overall Mean = 10.52±2.64 Median = 10.4 (IQR 3.47) P25 = 8.806 P75 = 12.27	Dutch digital municipal population register	Cox PH Model Adjusted for: Individual level: age, sex, standardized household income, region of origin, and marital status. Contextual: neighborhood- and regional-level mean income per income recipient, unemployment rate, social assistance, percentage non-western immigrants, and percentage of low education level.	HR (95% CI) ^b 1.18 (1.13, 1.23)
†Brunekreef et al. (2021) †Strak et al. (2021) Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) Administrative Cohorts n = 29,998,227	Pooled analysis of data from eight well-established ESCAPE cohorts and analysis of seven large administrative cohorts in Europe.	LUR, Chemical transport model, Hybrid model R ² = 58% Averaging time: NO ₂ - annual average	NO ₂ (ppb) Pooled Cohort Mean = 13±4.28 Median = 12.83 (IQR 5.394) Min = 1.42 Max = 43.06 P5 = 6.86 P25 = 10.37	National mortality databases	Cox PH Model Adjusted for: Pooled Cohort: Individual level: age, sex, study, calendar year of baseline, smoking status, smoking duration, smoking intensity, BMI, marital	HR (95% CI) ^b Pooled Cohort Respiratory Mortality 1.20 (1.07, 1.34) 40 µg/m ³ : 1.20 (1.06, 1.35) <30 µg/m ³ : 1.10 (0.92, 1.31)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Pooled Cohorts n = 393,604		Exposure years: 2010	P75 = 15.77 P95 = 21.01		status, employment status, and education level.	<20 µg/m ³ : 1.08 (0.67, 1.74)
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands			Administrative Cohorts (Ranges)		Contextual: area-level mean income.	COPD Mortality 1.28 (1.11, 1.47)
Recruitment: 1985–2011 (Range) Follow-up: 2011–2017 (Range)			Mean = 15.26–32.90±6.10–7.94 Median = 14.60–33.40		Administrative Cohorts: Individual level (vary by cohort): age, sex, years of enrollment, smoking, BMI, education, household income, employment status.	Administrative Cohort Meta-analysis Respiratory Mortality 1.11 (1.05, 1.18)
Cohort					Contextual: area-level morbidity and mortality rates, area-level smoking rates, area-level alcohol use, area-level exercise, area-level BMI.	<40 µg/m ³ : 1.13 (1.07, 1.20) <30 µg/m ³ : 1.20 (1.11, 1.30) <20 µg/m ³ : 1.18 (0.91, 1.53)
						Belgian Cohort Respiratory Mortality 1.02 (1.00, 1.05) COPD Mortality 0.99 (0.95, 1.03)
						Danish Cohort Respiratory Mortality 1.26 (1.22, 1.31) COPD Mortality 1.29 (1.23, 1.34)
						Dutch Cohort Respiratory Mortality 1.07 (1.03, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Crouse et al. (2015) Canadian Census Health and Environment Cohort (CanCHEC)	Non-institutionalized individuals 25 years of age and older and	LUR R ² = 0.43 Averaging time:	NO ₂ (ppb) Mean = 11.6 Median = 10.4 (IQR 10.5)	Canadian Mortality Database	Cox PH Model Adjusted for:	COPD Mortality
						1.11 (1.05, 1.17)
						English Cohort
						Respiratory Mortality
						1.09 (1.04, 1.14)
						COPD Mortality
						1.11 (1.04, 1.20)
						Norwegian Cohort
						Respiratory Mortality
						1.23 (1.09, 1.38)
						COPD Mortality
						1.36 (1.30, 1.43)
						Rome Cohort
						Respiratory Mortality
						1.03 (0.96, 1.10)
						COPD Mortality
						1.11 (1.07, 1.16)
						Swiss Cohort
						Respiratory Mortality
						1.10 (1.06, 1.14)
						COPD Mortality
						1.13 (1.06, 1.20)
						HR (95% CI) ^b
						Respiratory Mortality:
						1.04 (1.01, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 301,115 Nationwide, Canada Enrollment: 1991 Follow-up: 1991–2006 Cohort	residing in Canada in 1991.	NO ₂ - 7-yr MA; 1-yr lag Exposure years: 1984–2006	Min = 0 Max = 51.5 P25 = 6 P75 = 16.5		Individual level: aboriginal ancestry, visible minority status, highest level of education, employment status, occupational class, immigrant status, marital status, and income. Contextual: percent of immigrants, percent of adults without high school diploma, percent of subjects in lowest income quintile	COPD Mortality: 1.08 (1.04, 1.13)
† Eum et al. (2019) Medicare n = 14,100,000 Nationwide, U.S. Enrollment: December 2000–December 2008 Follow-up: December 2000–December 2008 Cohort	Medicare enrollees aged 65–120 years living in the conterminous U.S.	AQS Averaging time: NO ₂ - 12-month moving average Exposure years: 2000–2008	NO ₂ (ppb) Median = 14.23 P25 = 9.69 P75 = 18.63	National Death Index	Cox PH Model Adjusted for: Individual level: age, gender, and race	HR (95% CI) ^c COPD Mortality: 0.96 (0.95, 0.97) HR (95% CI) ^b Respiratory Mortality: 1.05 (1.04, 1.06) Pneumonia Mortality: 1.28 (1.26, 1.29)
† Eum et al. (2022) Medicare n = 49,712,702	Open cohort of Medicare beneficiaries aged ≥65 years residing in the contiguous U.S.	LUR 81% of the spatial (R ² = 0.81), 73% of temporal (R ² = 0.73), and 84% of	NO ₂ (ppb) Mean = 10.9±6.44 Median = 9.14 (IQR 7.85) Min = 1.03	National Death Index	Cox PH Model Adjusted for: Individual level: sex, race, age, and ZIP code.	HR (95% CI) ^c Respiratory Mortality: 1.17 (1.15, 1.19) COPD Mortality: 1.06 (1.03, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Nationwide, U.S. Enrollment: 2001–2008 Cohort	between 2001 and 2008.	the spatiotemporal variation ($R^2 = 0.84$) in monthly mean NO_2 concentrations from 2000 to 2010, with an absolute average bias of 2.4 ppb; the model performance was lower in rural ($R^2 = 0.69$) as compared to urban ($R^2 = 0.80$) areas, suggesting greater exposure error for rural ZIP codes Averaging time: NO_2 - 12-month moving average Exposure years: 2000–2008	Max = 47.04 P25 = 6.16 P75 = 13.98		Contextual: socioeconomic status.	Pneumonia Mortality: 1.33 (1.29, 1.37)
†Gariazzo et al. (2021) Rome Longitudinal Study n = 482,259 Rome, Italy Enrollment: 2001	Aged 30+ at enrollment, resided in same address for 5+ years before enrollment	Chemical transport model, Ensemble machine learning model, Dispersion model CTM: Used FARM model incorporated local emissions	NO_2 (ppb) CTM: 1km resolution Mean = 15.5 ± 2.0 Median = 15.5 (IQR 19.1) Min = 8.34 Max = 19.1 P5 = 12.0	Rome Municipal Register	Cox PH Model Adjusted for: Individual level: age, sex, marital status, place of birth, education, and occupation. Contextual: area-based socioeconomic position.	HR (95% CI) ^b Chemical Transport Model (1km): 1.05 (0.91, 1.22) Dispersion Model (200m): 1.02 (0.97, 1.07) Ensemble Model (200m): 1.00 (0.95, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow-up: 2015 Cohort		inventory and meteorological data, boundary conditions from previous nation-wide simulations ($R^2 = 0.49$) ML: Used random forest incorporating FARM, satellite, land cover, and traffic data (10-fold CV $R^2 = 0.62$) Dispersion: Used Parallel Micro-Swift-Spray and no-traffic FARM models ($R^2 = 0.44$) Averaging time: NO ₂ - annual average Exposure years: 2015	P25 = 14.2 P75 = 16.9 P95 = 19.0 Dispersion model: 200m resolution Mean = 22.7±5.58 Median = 22.7 (IQR 7.92) Min = 5.9 Max = 45 P5 = 14 P25 = 19 P75 = 26.5 P95 = 32.4 Ensemble model: 200m resolution Mean = 23.3±5.2 Median = 22.2 (IQR 7.65) Min = 10.9 Max = 35.9 P5 = 15.7 P25 = 19.5 P75 = 27.2 P95 = 32.8			
†Hvidtfeldt et al. (2019) Danish Diet, Cancer and Health (DCH) N = 49,564 Copenhagen, Aarhus, Denmark	Men and women aged 50–64 who lived in the areas of Copenhagen and Aarhus and were born in Denmark. Exclusion criteria included having cancer at or prior to baseline, having unavailable	Hybrid model Method validation NR Averaging time: NO ₂ - annual average	NO ₂ (ppb) Median = 13 (25 µg/m ³) P5 = 9.51 (17.9 µg/m ³) P95 = 20.9 (39.4 µg/m ³)	Danish Register of Cause of Death	Cox PH Model Adjusted for: Individual level: age, sex, calendar time, educational level, marital status, occupational status, smoking, alcohol	HR (95% CI) ^b Respiratory Mortality: 1.06 (0.95, 1.18)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 1993–1997 Follow-up: through 2015 Cohort	residential address history (therefore exposure history), and those who had missing confounder information.	Exposure years: 1979–2015			consumption, physical activity, BMI, waist circumference, ETS, and fruit and vegetable consumption. Contextual: neighborhood-level SES [proportion of households (PH) without a car, PH living in rented dwellings, proportion of inhabitants (PI) being unemployed, PI being single parents (sole providers), PI with a criminal record, PI with only basic education, PI with a low disposable income, PI with a manual profession, and PI being immigrants or descendants from non-Western countries].	
† Klompaker et al. (2020) Public Health Monitor full (imputed) population n = 339,633 complete case population n = 244,814 Netherlands Enrollment: September–	Dutch citizens 19 years or older	LUR Averaging time: NO ₂ - annual average Exposure years: 2013	NO ₂ (ppb) Complete case population Median = 12.27 (IQR 4.01) (23.08 µg/m ³ (IQR 7.54 µg/m ³) Full population Median = 12.23 (IQR 4.04) (23.01	Dutch longitudinal mortality database	Cox PH Model Adjusted for: Individual level: age, sex, region of origin, education, paid occupation, standardized household income, physical activity, BMI, smoking status, cigarettes	HR (95% CI) ^b Respiratory Mortality: 0.95 (0.79, 1.15)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
November 2012 Follow-up: 2013–2017 Cohort			μg/m ³ (IQR 7.61 μg/m ³)		smoked, alcohol status, and glasses alcohol. Contextual: postal code-level composite SES, neighborhood-level mean income, neighborhood-level unemployment, neighborhood-level percentage of immigrants, regional-level mean income, regional-level unemployment, and regional-level percentage of immigrants.	
† Klompaker et al. (2021b) n = 10,481,566 Netherlands Follow-up period: January 1, 2013–December 31, 2018 Cohort	Dutch populations aged 30+	Hybrid model, LUR, Dispersion model Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Median = 14 (IQR 4.4) (26.3 μg/m ³ (IQR 8.3 μg/m ³))	Dutch longitudinal mortality database	Cox PH Model Adjusted for: Individual level: age, sex, standardized household income, region of origin, and marital status. Contextual: regional-level socio-economic composite score, regional-level mean income per income recipient, regional-level unemployment rate, regional-level percentage non-western immigrants, and the	HR (95% CI) ^b Respiratory Mortality: 1.14 (1.10, 1.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					difference between neighborhood and region of mean income, unemployment rate, non-western immigrants and the composite SES score.	
† Klompaker et al. (2021a)	Full Dutch population aged 29+	LUR, Dispersion model, Hybrid model	NO ₂ (ppb) LUR Mean = 12.9±3.7	Dutch longitudinal mortality database	Cox PH Model Adjusted for: Individual level: age, sex, neighborhood, standardized household income, region of origin, and marital status. Contextual: regional-level socio-economic composite score, regional-level mean income per income recipient, regional-level unemployment rate, regional-level percentage non-western immigrants, and the difference between neighborhood and region of mean income, unemployment rate, non-western immigrants and the composite SES score.	HR (95% CI) ^b LUR: 0.99 (0.95, 1.04) Dispersion model: 1.07 (1.03, 1.11) Hybrid model: 1.07 (1.03, 1.12)
Statistics Netherlands (CBS)						
N = 10,532,360		LUR: Explained variance for 86% NO ₂				
Netherlands		Hybrid: Explained variance for 59% NO ₂	Dispersion Model Mean = 12.7±3.6			
Enrollment: January 1, 2008 Follow-up: through December 31, 2012						
Cohort		Averaging time: NO ₂ - annual average	Hybrid Model Mean = 16.5±3.8			
		Exposure years: 2007–2010				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Li et al. (2024) UK Biobank n = 366,478 (6,113 Respiratory Mortality; 1,243 COPD Mortality) U.K. Enrollment: 2006–2010 Follow-up: through 2022 Cohort	Individuals aged 40–69 from various regions across the U.K. Participants with self-reported respiratory diseases at baseline were excluded.	LUR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2005–2007 and 2010	NO ₂ (ppb) Mean = 15.57±4.92 (29.29±9.25 µg/m ³) NO _x (µg/m ³) Mean = 43.99±15.67	National Health Service	Cox PH Model Adjusted for: Individual level: age, sex, ethnicity, UK Biobank assessment center, education level, average total household income, BMI, smoking status, alcohol consumption status, fruit consumption, physical activity level, prevalent hypertension, and prevalent diabetes.	NO ₂ HR (95% CI) ^b Respiratory Mortality: 1.41 (1.31, 1.51) COPD Mortality: 1.69 (1.44, 1.97) NO _x HR (95% CI) ^b Respiratory Mortality: 1.07 (1.05, 1.08) COPD Mortality: 1.11 (1.08, 1.41)
† Lim et al. (2019) NIH-AARP Diet and Health Study N = 566,398 n = 548,780 (96.9% of cohort) California; Florida; Louisiana; New Jersey; North Carolina; Pennsylvania; Atlanta GA, Detroit MI, U.S. Enrollment: 1995–1996 Follow-up: through December 2011 Cohort	Members of AARP aged 50–71 years who responded to a mailed questionnaire.	Hybrid model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 1990–2012	NO ₂ (ppb) Mean = 11.1±5.6 Min = 1.5 Max = 31.7	U.S. Social Security Administration Death Master File and the National Death Index	Cox PH Model Adjusted for: Individual level: age, sex, race, location, body mass index, education, smoking, diet, and marital status. Contextual: median income and percentage with high school education	HR (95% CI) ^b Pneumonia and Influenza Mortality: 1.22 (1.11, 1.35) COPD Mortality: 1.03 (0.98, 1.08) Respiratory Mortality: 1.04 (1.00, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Raaschou-Nielsen et al. (2020) n = n:4,401,348 Denmark Enrollment: April 2, 1968 Follow-up: January 1, 1991–December 31, 2015 Case-Control	All persons who have lived in Denmark at one point in time since April 2, 1968, who were born between 1921 and 1985, and aged 30 to 85 years.	Chemical transport model Averaging time: NO ₂ - time-weighted average Exposure years: 1991–2015	NO ₂ (ppb) Cases Mean = 9.51 (17.9 µg/m ³) Median = 8.98 (IQR 5) (16.9 µg/m ³ (IQR 9.5 µg/m ³) Min = 2.5 (4.7 µg/m ³) Max = 38.8 (73.1 µg/m ³) P5 = 4.7 (8.9 µg/m ³) P25 = 6.86 (12.9 µg/m ³) P75 = 11.9 (22.4 µg/m ³) P95 = 15.5 (29.1 µg/m ³) P99 = 17.4 (32.7 µg/m ³) Controls Mean = 9.3 (17.5 µg/m ³) Median = 8.77 (IQR 4.9) (16.5 µg/m ³ (IQR 9.2 µg/m ³) Min = 2.5 (4.7 µg/m ³) Max = 44.8 (84.3 µg/m ³) P5 = 4.7 (8.8 µg/m ³) P25 = 6.75 (12.7 µg/m ³) P75 = 11.6 (21.9 µg/m ³)	Danish Register of Cause of Death	Logistic Regression Adjusted for: Individual level: sex, age, calendar time, match, marital status, educational level, occupational status, income, country of origin, and number of children. Contextual: neighborhood-level car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent households, immigrants, and criminal records.	MRR (95% CI) ^b 1.16 (1.10, 1.22)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			$\mu\text{g}/\text{m}^3$ P95 = 15.3 (28.7 $\mu\text{g}/\text{m}^3$ P99 = 17.2 (32.3 $\mu\text{g}/\text{m}^3$)			
[†] So et al. (2020) Danish Nurse Cohort (DNC) N = 24,541 Denmark Enrollment: 1993 and 1999 Follow-up: through December 2013 Cohort	Female nurses (aged >44 years) of the Danish Nurse Organization who could be linked to the Danish Civil Registration System.	Hybrid model Method validation NR Averaging time: NO ₂ - 3-year moving average; 1-year lag Exposure years: 1990–2012	NO ₂ (ppb) Cohort Baseline (1993 or 1999) Mean = 7.12 (13.4 $\mu\text{g}/\text{m}^3$)	Danish Register of Cause of Death	Cox PH Model Adjusted for: Individual level: age, body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, and use of hormone therapy.	HR (95% CI) ^b Respiratory Mortality: 0.97 (0.74, 1.28) <30 $\mu\text{g}/\text{m}^3$: 1.28 (0.86, 1.89) <20 $\mu\text{g}/\text{m}^3$: 1.56 (0.90, 2.72) <15 $\mu\text{g}/\text{m}^3$: 2.41 (1.09, 5.34)
[†] So et al. (2022) Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) n = 3,083,227 Nationwide, Denmark Enrollment: January 2000 Follow-up: through December 2017 Cohort	Cohort of individuals 30 years or older	LUR, Chemical transport model 0.58 Averaging time: NO ₂ - annual average Exposure years: 1999–2017	NO ₂ (ppb) Mean = 10.8±4.22 (20.3±7.94 $\mu\text{g}/\text{m}^3$) IQR = 5.47 (10.3 $\mu\text{g}/\text{m}^3$) Min = 2 (3.7 $\mu\text{g}/\text{m}^3$) Max = 38.4 (72.2 $\mu\text{g}/\text{m}^3$) P5 = 5 (9.4 $\mu\text{g}/\text{m}^3$) P25 = 7.76 (14.6 $\mu\text{g}/\text{m}^3$) P75 = 13.2 (24.9 $\mu\text{g}/\text{m}^3$) P95 = 19 (35.7 $\mu\text{g}/\text{m}^3$)	Danish Register of Cause of Death	Cox PH Model Adjusted for: Individual level: age, sex, parish level, household income, occupational status, immigrant status, marital status, and highest completed education level regional mean household income. Contextual: regional percentage of unemployment and the	HR (95% CI) ^b Respiratory Mortality: 1.16 (1.13, 1.19) COPD Mortality: 1.18 (1.13, 1.23) Asthma Mortality: 1.26 (1.07, 1.47) ALRI Mortality: 1.12 (1.06, 1.18)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					difference of mean household income and percentage of unemployment, between parish and region.	
† Tao et al. (2024)	General population in England enrolled in the UK Biobank.	LUR	NO ₂ (ppb)	National Health Service	Cox PH Model	HR (95% CI) ^b 1.08 (1.03, 1.14)
UK Biobank		Method validation NR	Advantaged neighborhood Mean = 12.3 (23.2 µg/m ³)		Adjusted for:	
n = 421,650		Averaging time: NO ₂ - annual average	Median = 12.15 (22.87 µg/m ³)		Individual level: age, gender, race, BMI, smoking status, alcohol consumption, healthy diet score, educational level, and income level.	
Nationwide, England		Exposure years: 2005, 2006, 2007, and 2010	P5 = 7.85 (14.77 µg/m ³) P25 = 10.32 (19.42 µg/m ³) P75 = 14.22 (26.76 µg/m ³) P95 = 17.13 (32.23 µg/m ³)		Contextual: neighborhood environment.	
Enrollment: 2006–2010			Disadvantaged neighborhood Mean = 20.13 (37.87 µg/m ³) Median = 19.12 (35.97 µg/m ³) P5 = 13.54 (25.48 µg/m ³) P25 = 16.83 (31.67 µg/m ³) P75 = 22.92 (43.12 µg/m ³) P95 = 29.7 (55.8 µg/m ³)			
Follow-up: through September 2021						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Intermediate neighborhood Mean = 15.13 (28.47 µg/m ³) Median = 14.89 (28.01 µg/m ³) P5 = 8.891 (16.73 µg/m ³) P25 = 12.61 (23.73 µg/m ³) P75 = 17.3 (32.6 µg/m ³) P95 = 21.83 (41.07 µg/m ³)			
† Turner et al. (2016) Cancer Prevention Study II n = 669,046 U.S. Enrollment: 1982 Follow-up: through 2004 Cohort	Participants were at least 30 years of age and had a family member aged 45 years or older with complete data on residence and covariates.	LUR R ² = 0.78 Averaging time: NO ₂ - annual average Exposure years: 2006	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 (IQR 6) Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P95 = 21.2	National Death Index	Cox PH Model Adjusted for: Individual level: age, race, sex, education, marital status, body mass index, cigarette smoking status, cigarettes smoked per day, years smoked, age started smoking younger than 18 years, passive smoking, vegetable intake, fruit intake, fiber intake, fat intake, alcohol consumption, industrial exposures, and occupational dirtiness index.	HR (95% CI) ^b COPD Mortality: 0.97 (0.91, 1.04) Respiratory Mortality: 0.99 (0.95, 1.04) Pneumonia and Influenza Mortality: 1.07 (0.99, 1.15)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					Contextual: median household income and percentage of African Americans, Hispanics, postsecondary education, unemployment, and poverty.	
† Weichenthal et al. (2017b) Canadian Census Health and Environment Cohort (CanCHEC) n = 2,448,500 Nationwide, Canada Enrollment: May 2011 Follow-up: May 2011–December 2011 Cohort	Non-institutionalized Canadian citizens linked to annual postal code histories and Social Insurance Numbers. Those without air pollution estimates, less than 25 or older than 90 years of age, or immigrants were excluded.	LUR Model validated against 2006 NAPS monitoring data (R ² = 0.73) Averaging time: NO ₂ - 3-yr MA; 1-yr lag Exposure years: 1981–2012	NO ₂ (ppb) Mean = 11.47 Median = 10.31 Max = 64.78 P5 = 3.36 P25 = 6.44 P75 = 15.1 P95 = 24.52	Canadian Mortality Database	Cox PH Model Adjusted for: Individual level: age, sex, visible minority status, Aboriginal status, marital status, educational attainment, income, and employment status. Contextual: percent unemployed, percent not graduated from high school, percent low income status within census divisions, population density, population center size, and airshed.	HR (95% CI) ^b 1.11 (1.08, 1.15)
† Zhang et al. (2021b) Ontario Health Study (OHS) N = 88,615 Ontario, Canada	Adult Ontario residents aged 30 years or older at enrollment who had valid information on vital status over follow-up and had complete data on air pollution	LUR Model was validated against NAPS ground monitor measurements in	NO ₂ (ppb) Baseline Mean = 10.9±5.3 Median = 10 (IQR 7.9)	Ontario Registrar General Death Database	Cox PH Model Adjusted for: Individual level: age, sex, ethnicity and survey year; born in Canada, educational	HR (95% CI) ^b 1.54 (1.22, 1.94)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 2009–2013 Follow-up: until December 31, 2017 Cohort	exposures and covariates.	2006 ($R^2 = 0.73$). Averaging time: NO ₂ - 3, 4, and 5-yr MA Exposure years: 2006	P25 = 6.5 P75 = 14.4		level, marital status, and household income, body mass index, fruit and vegetable intake, smoking, alcohol consumption, physical activity, environmental exposure to tobacco smoke at home and workplace. Contextual: rural/urban, north/south, and neighborhood-level socio-economic factors, including percentage of recent immigrants, percentage of population aged ≥ 15 years without employment, percentage of population aged ≥ 15 years with educational level lower than high school, and income.	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Zhu et al. (2024)	Participants aged 40–69 years recruited from 22 assessment centers.	LUR	NO ₂ (ppb)	National Health Service	Cox PH Model	NO ₂
UK Biobank		Cross-validation	Mean = 14.17±4.06		Adjusted for:	HR (95% CI) ^b
n = 461,112		R ² = 0.87 for NO ₂ ;	(26.66±7.63 µg/m ³)		Individual level: age,	1.24 (1.12, 1.37)
Nationwide, U.K.		Cross-validation	IQR = 5.23 (9.85		sex, race, education	NO _x
		R ² = 0.88 for NO _x .	µg/m ³)		level, income,	
			Min = 6.872 (12.93		Townsend deprivation	HR (95% CI) ^b
Enrollment: 2006–2010		Averaging time:	µg/m ³)		index, smoking status,	1.10 (1.06, 1.15)
Follow-up: through October 2021		NO ₂ - annual	Max = 57.658		pack-year of smoking,	
		average, NO _x -	(108.49 µg/m ³)		drinking status, drinking	
		annual average	P25 = 11.37 (21.39		consumption, physical	
			µg/m ³)		activity, MET minutes	
Cohort		Exposure years:	P75 = 16.6 (31.24		per week, dietary	
		2010	µg/m ³)		behaviors.	
			NO _x (µg/m ³)			
			Mean = 44.02±15.65			
			IQR = 16.55			
			Min = 19.74			
			Max = 265.94			
			P25 = 34.22			
			P75 = 50.77			

List of abbreviations in alphabetical order: ACS = American Cancer Society; ALRI = Acute Lower Respiratory Infection; AQS = Air Quality System; BMI = body mass index; CBS = Statistics Netherlands; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; CTS = California Teachers Study; CV = cross-validation; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ratio; IQR = interquartile range; LOOCV = leave-one-out cross-validation; LUR = land use regression; MA = moving average; MET = metabolic equivalent of task; MI = myocardial infarction; MRR = mortality rate ratio; NAPS = National Air Pollution Surveillance; NIH = National Institutes of Health; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OP = organophosphate; OR = odds ratio; P# = #th percentile; PH = proportional hazards; SES = socioeconomic status; U.K. = United Kingdom; U.S. = United States; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA

A.3. Cardiovascular Effects – Short-term Exposure

Appendix Table 5-1 Epidemiologic studies of short-term oxides of nitrogen exposure and ischemic heart disease

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Barnett et al. (2006) n = NR Perth, Sydney, Melbourne, Canberra, Brisbane, Christchurch, Auckland, Australia, New Zealand 1998–2001 Case-crossover	Residents living in study area between the ages of 15 and 64 and 65+ (older adults)	Fixed site monitor Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 1998–2001	NO ₂ (ppb) 1-hour Auckland Mean = 19.1 Min = 4.2 Max = 86.3 Brisbane Mean = 17.3 Min = 4 Max = 44.1 Canberra Mean = 17.9 Min = 0 Max = 53.7 Christchurch Mean = 15.7 Min = 1.2 Max = 54.6 Melbourne Mean = 23.2 Min = 4.4 Max = 62.5 Perth Mean = 21.3 Min = 4.4 Max = 48 Sydney Mean = 22.6 Min = 5.2 Max = 51.4	State government health departments	Time stratified case-crossover Adjusted for: seasonal changes, respiratory epidemics, temperature, relative humidity, pressure, extremes of hot and cold, day of week, public holiday, day after public holiday, rainfall in some	β (%) (95% CI) ^b IHD - Lag 0–1 / ≥ 65 : 6.27 (2.94, 9.61) MI - Lag 0–1 ≥ 65 : 17.25 (3.53, 30.98)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			24-hour Auckland Mean = 10.2 Min = 1.7 Max = 28.9 Brisbane Mean = 7.6 Min = 1.4 Max = 19.1 Canberra Mean = 7 Min = 0 Max = 22.5 Christchurch Mean = 7.1 Min = 0.2 Max = 24.5 Melbourne Mean = 11.7 Min = 2 Max = 29.5 Perth Mean = 9 Min = 2 Max = 23.3 Sydney Mean = 11.5 Min = 2.5 Max = 24.5			
Bhaskaran et al. (2011)	All STEMI, non-STEMI and troponin positive ACS events among patients discharged for these conditions.	Central site monitor	NO ₂ (ppb)	MINAP Registry	Case-crossover framework	β (%) (95% CI) ^b MI - Lag 0–2: 4.14 (1.32, 6.96)
MINAP		Averaging time:	Median = 16 (31 $\mu\text{g}/\text{m}^3$)		Adjusted for:	
n = 79,288		1–6, 7–12, 13–18, 19–24, 25–72	P25 = 10 (19 $\mu\text{g}/\text{m}^3$)		temperature, relative humidity, day of week,	
England, Wales, U.K.		hours; cumulative	P75 = 25 (47 $\mu\text{g}/\text{m}^3$)		Flu and RSV,	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
2003–2006		over 72 hours			seasonality within calendar month strata	
Case-crossover		Exposure years: 2003–2006				
Larrieu et al. (2007)	Hospitalizations for cardiovascular diseases in study area	Fixed site monitor	NO ₂ (ppb)	private hospitalization data	Poisson Regression	β (%) (95% CI) ^b
n = NR		Averaging time: NO ₂ - annual average	Bordeaux Mean = 11.9 (22.3 $\mu\text{g}/\text{m}^3$)		Adjusted for: temperature, holidays, influenza periods	IHD - Lag 0–1: 6.40 (3.20, 9.60)
Paris, Bordeaux, Le Havre, Lille, Lyon, Marseille, Rouen, Toulouse, France		Exposure years: 1998–2003	Le Havre Mean = 13.7 (25.8 $\mu\text{g}/\text{m}^3$)			
1998–2003			Lille Mean = 17.4 (32.7 $\mu\text{g}/\text{m}^3$)			
Time-series			Lyon Mean = 24.9 (46.8 $\mu\text{g}/\text{m}^3$)			
			Marseille Mean = 19.3 (36.4 $\mu\text{g}/\text{m}^3$)			
			Paris Mean = 23.6 (44.4 $\mu\text{g}/\text{m}^3$)			
			Rouen Mean = 16.2 (30.4 $\mu\text{g}/\text{m}^3$)			
			Toulouse			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 14 (26 μg/m ³)			
Linn et al. (2000)	Excluded patients younger than 30 years of age and prescheduled hospital admissions	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–1995	NO ₂ (ppb) Autum Mean = 4100±1400 (4.1±1.4 ppm) Min = 1600 (1.6 ppm) Max = 8400 (8.4 ppm) Spring Mean = 2800±900 (2.8±0.9 ppm) Min = 1100 (1.1 ppm) Max = 6100 (6.1 ppm) Summer Mean = 3400±1000 (3.4±1 ppm) Min = 700 (0.7 ppm) Max = 6700 (6.7 ppm) Winter Mean = 3400±1300 (3.4±1.3 ppm) Min = 1100 (1.1 ppm) Max = 9100 (9.1 ppm)	Hospital admissions data	Poisson Regression Adjusted for: temporal variation, weather	RR (95% CI) ^b MI - Lag 0: 1.02 (1.00, 1.04)
n = NR Los Angeles, CA, U.S. 1992–1995 Time-series						
Mann et al. (2002)	Residents who were Southern California	Fixed site monitor	NO ₂ (ppb)	Southern California	Poisson Regression	β (%) (95% CI) ^b IHD - Lag 0–1 (No secondary

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
N = 54,863 IHD admissions California, U.S. 1988–1995 Time-series	Kaiser Permanente members at any point during study period and who lived within 20 km of one of 5 particle air pollution monitors	Averaging time: NO ₂ - 24-hour average Exposure years: 1988–1995	24-hour average Mean = 37.2±15.7 Median = 34.8 (IQR 20.2) Min = 3.68 Max = 138 P25 = 25.6 P75 = 45.8	Kaiser Permanente Records	Adjusted for: day of the week, study year, day of study, temperature, relative humidity	disease): 3.36 (2.16, 4.56) MI - Lag 0: 4.08 (2.11, 6.05)
Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases Myocardial Ischaemia National Audit Project (MINAP) database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST elevation MI, non-ST elevation MI, or troponin-positive acute coronary syndrome.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	National databases with diagnosis information	Logistic Regression Adjusted for: age, sex	β (%) (95% CI) ^b IHD - Lag 0–4: 0.67 (-0.50, 1.84) MI - Lag 0–4: 2.01 (0.25, 3.76) Non-STEMI - Lag 0–4: 2.59 (0.21, 4.98) STEMI - Lag 0–4: 1.17 (-1.51, 3.85)
Peel et al. (2007) SOPHIA n = 4,407,535 ED Visits Atlanta, GA, U.S. 1993–2000	NR	Fixed site monitor Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 1993–2000	NO ₂ (ppb) Absolute differences between average level on case days and control days 1-hour Mean = 16.3±12.7 P10 = 2.8 P90 = 32.8	ED visit records	Case-crossover framework Adjusted for: time stratification, cubic splines for average daily temperature and dew point temperature	OR (95% CI) ^b IHD - Lag 0–2: 1.03 (1.00, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Case-crossover			Daily levels 1-hour Mean = 45.9±17.3 P10 = 25 P90 = 68			
Rich et al. (2010) MIDAS Total MI N = 5,864 New Jersey, U.S. January 1, 2004–December 31, 2006 Case-crossover	Participants were ≥18 years of age, residents of New Jersey at the time of their MI, and who were without a previous diagnosis of MI. Those who were not admitted into the hospital were not included in this data set.	Fixed site monitor Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2004–2006	NO ₂ (ppb) IQR = 16	Hospital Discharge	Case-crossover Adjusted for: time stratification, non-time varying confounders controlled by design	OR (95% CI) ^b Transmural MI - Lag 0: 1.13 (1.01, 1.25) Transmural MI - Lag 0 (PM _{2.5}): 1.05 (1.01, 1.25)
Simpson et al. (2005) n = NR Perth, Sydney, Melbourne, Brisbane, Australia January 1996–December 1999 Time-series	IHD Hospital Admission Events	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1996–1999	NO ₂ (ppb) Brisbane Mean = 21.4 Min = 2.1 Max = 63.3 Melbourne Mean = 23.7 Min = 4.4 Max = 66.7 Perth Mean = 16.3 Min = 1.9 Max = 41 Sydney Mean = 23.7	Hospital records	APHEA2 Adjusted for: temporal trends, seasonality, weather	RR (95% CI) ^b IHD - Lag 0–1: 1.04 (1.02, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Min = 6.5 Max = 59.4			
Stieb et al. (2009) n = nearly 400,000 ED visits Canada 1990s and early 2000s Time-series	Administrative ED visits	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–2003	NO ₂ (ppb) IQR=16 ppb	Hospital records	Poisson Regression Adjusted for: temporal cycles, weather, day of week, holidays	β (%) (95% CI) ^b MI - Lag 0: 2.83 (0.22, 5.43) MI - Lag 0 (CO): 1.28 (-2.95, 5.52)
Szyszkowicz (2007) N = 340,286 recorded and diagnosed ED visits Montreal, Canada 1997–2002 Other (Specify in notes box)	ED visits for ischemic heart disease	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1997–2002	NO ₂ (ppb) Overall Mean = 19.4±7.6 Min = 4.3 Max = 89	Hospital records	Poisson Regression Adjusted for: temperature, relative humidity	β (%) (95% CI) ^b Angina - Lag 0: 12.42 (4.21, 20.63)
Szyszkowicz (2009) N = 157,028 ED visits Toronto, Vancouver, Montreal, Edmonton, Halifax, Ottawa, Canada 1992–1999 Time-series	ED visits for chest pain	Chemical transport model Averaging time: NO ₂ - 24-hour average Exposure years: 1992–1999	NO ₂ (ppb) All Cities Mean = 20.1 Edmonton Mean = 21.9 Halifax Mean = 17.5 Montreal Mean = 18.4	ED visits records	Poisson Regression Adjusted for: temperature, relative humidity	β (%) (95% CI) ^b IHD - Lag 1: 3.98 (2.54, 5.42)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Ottawa Mean = 18.8			
			Sunnybrook Mean = 23.4			
			Toronto Mean = 22.9			
			Vancouver Mean = 16.8			
Wang et al. (2015) n = 25,894 Alberta, Canada April 1999–March 2010 Case-crossover	Using Alberta Health administrative database patients records with a primary diagnosis code of AMI. Aged 20 or over and resident of Alberta during an AMI event living 15 km or less to the closest effective air pollution monitoring station in Alberta.	Fixed site monitor Air pollution data from 65 monitor stations in Alberta during the study period. Monitor data was obtained from the Environment Canada National Ambient Pollution Surveillance database. Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, NO - 1-hour max, NO - 24-hour average Exposure years: 1999–2010	NO ₂ (ppb)	Alberta health administrative databases	Conditional Logistic Regression Adjusted for: time stratification, temperature, dew point temperature and wind speed	OR (95% CI) ^c AMI - lag 1 (6 h avg): 1.09 (1.04, 1.15) OR (95% CI) ^b NSTEMI - lag 1 ≥65 yrs (24 h avg): 1.15 (1.05, 1.27)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
von Klot et al. (2005) N = 22,006 Stockholm, Rome, Augsburg, Germany, Helsinki, Barcelona, Spain, Sweden, Spain, Italy, Germany, Finland Recruitment: 1992–2000 Follow-up: 29 th day after index event until center-specific end of the follow-up period Cohort	Incident myocardial infarction survivors: aged 35 years or more who had their first myocardial infarction during the recruitment period; excluded recurrent events	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–2000	NO ₂ (ppb) Augsburg Mean = 26.4 (49.6 µg/m ³) P5 = 16 (30 µg/m ³) P25 = 21.1 (39.7 µg/m ³) P75 = 30.4 (57.2 µg/m ³) P95 = 40 (75.3 µg/m ³) Barcelona Mean = 25.4 (47.7 µg/m ³) P5 = 9.6 (18 µg/m ³) P25 = 18 (34 µg/m ³) P75 = 32 (60 µg/m ³) P95 = 44 (83 µg/m ³) Helsinki Mean = 16 (30.1 µg/m ³) P5 = 6.9 (13 µg/m ³) P25 = 11.3 (21.2 µg/m ³) P75 = 19.5 (36.7 µg/m ³) P95 = 28.1 (52.9 µg/m ³) Rome Mean = 37 (70 µg/m ³) P5 = 24.9 (46.8 µg/m ³)	Hospital records	Poisson Regression Adjusted for: meteorology, seasonality	RR (95% CI) ^b Angina - Lag 0: 1.16 (1.03, 1.31) MI - Lag 0: 1.14 (0.99, 1.32)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P25 = 32.2 (60.5 µg/m ³) P75 = 42 (79.1 µg/m ³) P95 = 50.1 (94.3 µg/m ³) Stockholm Mean = 12.1 (22.8 µg/m ³) P5 = 5.47 (10.3 µg/m ³) P25 = 8.5 (16 µg/m ³) P75 = 15 (28 µg/m ³) P95 = 20.9 (39.4 µg/m ³)			
† Butland et al. (2016) MINAP N = 626,239 England, Wales Outcome data for study period: 2003–2010 Case-crossover	Excluded patients with missing geocodes, insufficient information on date of event, missing information on discharge diagnosis or linked to areas outside England and Wales.	Fixed site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 2001–2010	NO ₂ (ppb)	MINAP Registry	Conditional Logistic Regression Adjusted for: sex, age, smoking status, SES	β (%) (95% CI) ^b MI / Lag 0–2: 0.34 (-0.38, 1.05) NSTEMI / Lag 0–2: 1.02 (0.02, 2.01) STEMI / Lag 0–2: -0.60 (-1.86, 0.66) β (%) (95% CI) ^b MI - Lag 0–2 (O ₃): 0.26 (-0.49, 1.02) NSTEMI / Lag 0–2 (O ₃): 1.05 (-0.02, 2.13) STEMI - Lag 0–2 (O ₃): -0.87 (-2.16, 0.43) MI - Lag 0–2 (PM _{2.5}): 0.53 (-0.32, 1.37) NSTEMI / Lag 0–2 (PM _{2.5}): 1.62 (0.43, 2.80)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						STEMI - Lag 0–2 (PM _{2.5}): -0.26 (-1.73, 1.20)
† Chen et al. (2022c)	Patients with ACS from 2,239 hospitals in 318 Chinese cities.	Fixed site monitor	NO ₂ (ppb)	CCA Database	Conditional Logistic Regression	β (%) (95% CI) ^b
Chinese Chest Pain Center		Averaging time: NO ₂ - 1-hour max	Overall Mean = 17.9±13.1 (33.7±24.6 µg/m ³)		Adjusted for: sex, age, season, geographic region, time of day, proximity to major roads, history of smoking, and history of chronic cardiorespiratory diseases	ACS / non-smokers: 4.43 (2.16, 6.69) ACS / smokers: 7.16 (5.68, 8.64)
N = 1,292,880		Exposure years: 2015–2020	Median = 14 (27 µg/m ³) P25 = 8.5 (16 µg/m ³) P75 = 24 (45 µg/m ³)			β (%) (95% CI) ^b
China						ACS - Lag 0–24 hr: 5.05 (4.43, 5.67)
January 1, 2015–September 30, 2020						NSTEMI - Lag 0–24 hr: 4.63 (3.26, 6.01)
Case-crossover						STEMI - Lag 0–24 hr: 4.72 (3.68, 5.77) Unstable angina - Lag 0–24 hr: 5.67 (4.72, 6.62)
† Ha et al. (2017)	Included singleton pregnancies that were complicated by cardiovascular events at labor/delivery. Excluded women who had a repeated event in a second pregnancy.	CMAQ, Fixed site monitor	NO _x (ppb)	Labor/delivery discharge summary	Conditional Logistic Regression	OR (95% CI)
Consortium on Safe Labor (2002-2008)		Method validation	Overall Mean = 26.39 IQR = 22.24 Min = 4.66 Max = 134.76 P25 = 12.06 P75 = 34.29		Adjusted for: time stratification, meteorological factors	IHD - 7-d avg: 0.99 (0.48, 2.01)
N = 680		NR				
U.S.		Averaging time: NO _x - 24-hour average				
2002–2008		Exposure years: 2002–2008				
Case-crossover						
† Krall et al. (2018)	NR	Hybrid model	NO ₂ (ppb)	ED visits using electronic billing data	Poisson Regression	NO ₂
n = NR		Method validation	Atlanta Mean = 21.6±7		Adjusted for: weekday, season, holidays, meteorology, temporal trends, and hospital	RR (95% CI) ^b
Atlanta, GA, St. Louis, MO, Dallas, TX, Pittsburgh, Pennsylvania, Birmingham, AL,		NR	Birmingham Mean = 13.2±4.3			IHD - lag 0: 1.04 (1.02, 1.07)
		Averaging time: NO ₂ - 1-hour max,				NO _x

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
U.S. 2002–2008 Time-series		NO _x - 1-hour max Exposure years: 2002–2008	Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5 Birmingham Mean = 24.5±13.8 Dallas Mean = 41.4±32.2 Pittsburgh Mean = 56±35.8 St. Louis Mean = 51.3±30.9		reporting data for each day	RR (95% CI) ^b IHD - lag 0: 1.01 (1.00, 1.02)
† Liu et al. (2020) N = 6,142 Calgary, Canada 2004–2012 Case-crossover	Adults over the age of 18 at time of incidence of MI, living in Calgary and admitted to hospital with a diagnosis of MI during the study period. Patients who died before presentation to an emergency	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average	NO ₂ (ppb) Overall Mean = 17.9±8.95 Median = 18.33 (IQR 12.33)	APPROACH Registry	Logistic Regression Adjusted for: temperature, relative humidity	OR (95% CI) ^b MI - Lag 0–4: 0.98 (0.87, 1.09) MI - Lag 0–2: 1.06 (0.96, 1.16) MI - Lag 0: 1.00 (0.93, 1.07) MI - Lag 1: 1.04 (0.97, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	department were excluded.	Exposure years: 2004–2012				MI - lag 2: 1.03 (0.96, 1.11)
† Shin et al. (2022) n = NR Montreal, Halton, Ontario, London, Ontario, Toronto, Ontario, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Sudbury, Halifax, Saint John, Quebec City, Ottawa, Durham, York, Peel, Niagara, Waterloo, Sarnia, Sault Sainte Marie, Regina, Saskatoon, Calgary, Canada 1984–2012 Time-series	Mortality and hospitalization daily counts (all-cause, circulatory, and respiratory) classified by ICD-9 and 10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1984–2012	NO ₂ (ppb) Population-weighted Cold season Mean = 20±4 Warm season Mean = 16±4 Year Mean = 18 Min = 8 Max = 28	Hospitalization, ICD Codes I20-I25	Generalized additive quasi-Poisson with Bayesian hierarchical model Adjusted for: day of week, temperature using smoothing functions in non-linear relationship for calendar time and temperature, respectively.	β (%) (95% CI) ^b IHD / females, cold: -1.00 (-3.30, 1.30) IHD / females, warm: -0.40 (-5.80, 5.00) IHD / females: -0.60 (-3.40, 2.20) IHD / males, cold: 1.20 (-1.20, 3.60) IHD / males, warm: 5.80 (2.60, 9.00) IHD / males: 3.20 (1.40, 5.00)
† Weichenthal et al. (2016) NACRS N = 30,101 Ontario, Canada April 1, 2004–December 31, 2011 Case-crossover	All myocardial infarction cases with three digit postal codes corresponding to residences in these cities at the time of admission were eligible	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2011	NO ₂ (ppb) Overall Mean = 12.3±7.63 Median = 10.8 (IQR 10.3) Max = 65	NACRS, CIHI	Logistic Regression Adjusted for: Temperature, relative humidity	β (%) (95% CI) ^b MI - 3-d avg: 8.80 (-3.40, 21.00) MI - 3-d avg (PM _{2.5}): 7.40 (-1.70, 16.50) MI - 3-d avg (O ₃): 12.00 (2.10, 21.90) MI - 3-d avg (O ₃ , PM _{2.5} *GSH): 8.40 (-1.20, 18.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yamaji et al. (2017) n = 56,863 Japan January 2011–December 2012 Panel	Patients with consecutive ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention.	Central site monitor Selected 243 observatories where NO and NO ₂ were obtained throughout 2011–2012	NO _x (ppb) Mean = 20.7±19.1 Median = 14.9 (IQR 17) Min = 0 Max = 328 P25 = 8.71 P75 = 25.8 Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average, NO - 24-hour average Exposure years: 2011–2012	J-PCI Registry	Generalized Linear Models Adjusted for: temperature, day of the week, holidays, administrative district	OR (95% CI) ^b STEMI - Lag NR - Summer: 0.94 (0.87, 1.01) STEMI - Lag NR - Winter: 1.01 (0.98, 1.05) STEMI - Lag NR / ≤69 yrs: 1.01 (0.98, 1.04) STEMI - Lag NR / >69 yrs: 1.02 (0.99, 1.05) STEMI - Lag NR: 1.01 (0.99, 1.03)

List of abbreviations in alphabetical order: ACS = Acute Cardiac Syndrome; AMI = Acute Myocardial Infarction; APPROACH = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; BMI = body mass index; CCA = Chinese Cardiovascular Association; CI = confidence interval; ED = Emergency Department; ICD = International Classification of Disease; IHD = Ischemic Heart Disease; LUR = land use regression; Max = Maximum; MI = Myocardial Infarction; MIDAS = Myocardial Infarction Data Acquisition System; Min = Minimum; MINAP = Myocardial Ischemia National Audit Project; NACRS = National Ambulatory Care Reporting System; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; NSTEMI = Non-ST Elevation Myocardial Infarction; OR = odds ratio; P10 = 10th Percentile; P25 = 25th Percentile; P75 = 75th Percentile; P90 = 90th Percentile; ppb = parts per billion; RR = Relative Risk; SOPHIA = Study of Particles and Health in Atlanta; STEMI = ST Elevation Myocardial Infarction; µg/m³ = micrograms per cubic meter.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-2 Epidemiologic studies of short-term oxides of nitrogen exposure and arrhythmia and cardiac arrest

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Bartell et al. (2013) N = 55 Los Angeles, CA, U.S. Before 2005 (did not explicitly state) Cohort	Older adult nonsmokers with CAD who were recruited from four retirement communities in Los Angeles Air Basin	Fixed site monitor Averaging time: NO _x - 1-hour max Exposure years: NR	NO _x (ppb) Overall Mean = 46.6±31.4 IQR = 42.3 Min = 3.2 Max = 183.7	ECG	Generalized Estimating Equations Adjusted for: daily average actigraph-derived physical activity and heart rate, temperature of the same lag average, day of week, seasonal study phase (mean centered exposure), and community group (mean centered exposure)	RR (95% CI) ^b Ventricular Tachycardia: 1.52 (0.57, 4.04)
Ensor et al. (2013) n = 11,677 Houston, TX, U.S. 2004–2011 Case-crossover	All cases in which EMS performs chest compressions are considered OHCA cases. Cases included non–dead-on-arrival adults aged ≥18 years from Houston Fire Department EMS calls.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2011	NO ₂ (ppb) Mean = 9.11±4.17 Median = 8.41 (IQR 5.65) P5 = 3.51 P25 = 6.01 P75 = 11.66 P95 = 16.87	EMS data	Logistic Regression Adjusted for: apparent temperature (spline, 2 df), time stratification	β (%) (95% CI) ^b OHCA: -0.33 (-14.67, 14.00)
Link et al. (2013) N = 176 followed for at least 90 days Boston, MA, U.S. Recruitment: September 2006–March 2010 Follow-up: at least 90 days	Inclusion criteria included prior implantation of a dual chamber ICD and residential zip codes within a 50-km radius the Harvard Supersite air quality monitoring station. Exclusions included age younger	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2010	NO ₂ (ppb) Overall Mean = 16.1 Median = 15.2 P25 = 11.9 P75 = 19.2	ICD code	Conditional Logistic Regression Adjusted for: time-stratified matching on weekday and hour of the day within the same calendar month, temperature and dew point	β (%) (95% CI) ^b Arrhythmia: 21.92 (-34.25, 78.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort	than 18 years, chronic AF, lack of follow-up at Tufts medical center, terminal illness, or inability to give informed consent.					
Metzger et al. (2007) n = 884 Atlanta, GA, U.S. January 1, 1993–December 31, 2002 Cohort	Patients from 3 cardiac electrophysiology clinics in Atlanta. Detected events that were determined to be not ventricular in origin (e.g., supraventricular tachycardia, sinus tachycardia, lead fracture, electromagnetic interference, or oversensing) were excluded from the analysis.	Central site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1993–2002	NO ₂ (ppb) Mean = 44.9±17.7 Median = 43 Min = 7 Max = 181 P10 = 24 P90 = 68	ICD codes	Generalized Estimating Equations Adjusted for: day of week, holidays, long term time trends and seasonality (cubic splines), temperature (cubic lag 0), dewpoint	OR (95% CI) ^b OHCA: 1.00 (0.96, 1.04)
Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases Myocardial Ischaemia National Audit Project (MINAP) database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST elevation MI, non-ST elevation MI, or	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	National Registry	Logistic Regression Adjusted for: age, sex	β (%) (95% CI) ^b Arrhythmia - Lag 0–4: 2.43 (0.50, 4.35) Atrial Fibrillation - Lag 0–4: 2.34 (0.21, 4.47) Arrhythmia - <70 yrs: 1.51 (-1.21, 4.22) Arrhythmia - ≥70 yrs: 3.09 (0.54, 5.64) Atrial Fibrillation - <70 yrs: 1.00 (-2.13, 4.14) Atrial Fibrillation - ≥70 yrs: 3.26 (0.54, 5.98)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	troponin-positive acute coronary syndrome.					Arrhythmia - Male: 1.76 (-0.84, 4.35) Arrhythmia - Female: 3.01 (0.38, 5.64) Atrial Fibrillation - Male: 2.34 (-0.59, 5.27) Atrial Fibrillation - Female: 2.34 (-0.50, 5.18)
Tsai et al. (2009) n = 21,581 Taipei, Taiwan 2000–2006 Case-crossover	Those who used the National Health Insurance Program in Taiwan from 2000–2006.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2000–2006	NO ₂ (ppb) Mean = 28.45 Median = 27.77 (IQR 10.08) Min = 3.98 Max = 77.97 P25 = 23.18 P75 = 33.26	Taiwanese NHI Program: ICD9 427	Conditional Logistic Regression Adjusted for: time stratification with meteorologic variables	OR (95% CI) ^b arrhythmia/warm: 1.19 (1.10, 1.28) arrhythmia/cool: 1.34 (1.24, 1.45) arrhythmia/warm (PM ₁₀): 1.16 (1.06, 1.28) arrhythmia/cool (PM ₁₀): 1.32 (1.21, 1.44) arrhythmia/warm (SO ₂): 1.25 (1.16, 1.36) arrhythmia/cool (SO ₂): 1.48 (1.37, 1.61) arrhythmia/warm (CO): 1.14 (1.02, 1.28) arrhythmia/cool (CO): 1.32 (1.16, 1.50) arrhythmia/warm (O ₃): 1.10 (1.02, 1.19) arrhythmia/cool (O ₃): 1.46 (1.36, 1.57)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Wichmann et al. (2013) n = 4,657 Copenhagen, Denmark 2000–2010 Case-crossover	OHCAs were identified from the MECU in Copenhagen. Patients with obvious signs of death (i.e. trauma, rigor mortis, livores) or those where resuscitation was judged effortless (i.e. ROSC not attained) by the emergency physician at the scene were not recorded as OHCAs.	Central site monitor Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average Exposure years: 2000–2010	NO _x (ppb) Mean = 14±7.89 Median = 12.05 (IQR 8.5) P25 = 8.59 P75 = 17.09 NO _x (ppb) Mean = 11.05±4.86 Median = 10.31 (IQR 6.42) P25 = 7.45 P75 = 13.87	MECU - Utstein criteria for OHCA	Conditional Logistic Regression Adjusted for: time-stratification, holidays	β (%) (95% CI) ^b OHCA - Lag 0–5: 2.93 (-11.17, 17.02) OHCA - Lag 0: -8.51 (-19.68, 2.66) OHCA - Lag 3 / Female: 23.67 (3.72, 43.62) OHCA - Lag 3 / Male: 1.33 (-13.16, 15.82) OHCA - Lag 3: 9.04 (-2.66, 20.74)
†Dales et al. (2020) The Ontario ICD Registry N = 10,320 Ontario, Canada Enrollment: January 2007–2012 Follow-up: through May 2012 Case-crossover	Patients were eligible if they had an ICD implant for primary or secondary prevention, or if the ICD was replaced	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2007–2012	NO ₂ (ppb) Cold Mean = 13.46±7.24 Median = 12.37 (IQR 10) Overall Mean = 11.44±6.78 Median = 10.04 (IQR 9.29) Warm Mean = 9.43±5.6 Median = 8.16 (IQR 7.56)	Ontario Registry, ICD codes	Conditional Logistic Regression; Cox proportional hazard Adjusted for: 24 hour mean temperature, relative humidity, and barometric pressure	OR (95% CI) ^b ICD event, Central: 0.62 (0.36, 1.06) ICD event, Eastern: 0.65 (0.19, 2.24) ICD event, Metro Toronto: 0.92 (0.47, 1.78) ICD event, Northern: 0.49 (0.01, 16.88) ICD event, Southwestern: 1.48 (0.54, 4.09) ICD event. Lag 0-3, cold: 0.82 (0.53, 1.26) ICD event. Lag 0-3, warm: 0.65 (0.33, 1.29) ICD event. Lag 0-3: 0.78 (0.54, 1.12) ICD event. Lag 0, cold: 1.16 (0.87, 1.54) ICD event. Lag 0, warm: 0.64 (0.40, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						ICD event. Lag 0: 1.00 (0.78, 1.28)
† Ha et al. (2017) Consortium on Safe Labor (2002-2008) N = 680 U.S. 2002–2008 Case-crossover	Included singleton pregnancies that were complicated by cardiovascular events at labor/delivery. Excluded women who had a repeated event in a second pregnancy.	CMAQ, Fixed site monitor Method validation NR Averaging time: NO _x - 24-hour average Exposure years: 2002–2008	NO _x (ppb) Overall Mean = 26.39 IQR = 22.24 Min = 4.66 Max = 134.76 P25 = 12.06 P75 = 34.29	Labor and delivery discharge records	Conditional Logistic Regression Adjusted for: time stratification, meteorological factors	OR (95% CI) ^b Cardiac Arrest, lag 0–7: 1.42 (1.08, 1.86) Cardiac Arrest, lag 0: 1.44 (1.16, 1.78) Cardiac Arrest, lag 1: 1.54 (1.22, 1.94) Cardiac Arrest, lag 6: 1.47 (1.17, 1.84) Cardiac Arrest, lag 7: 0.99 (0.78, 1.26)
† Krall et al. (2018) n = NR Atlanta, GA, St. Louis, MO, Dallas, TX, Pittsburgh, Pennsylvania, Birmingham, AL, U.S. 2002–2008 Time-series	NR	Hybrid model Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Atlanta Mean = 21.6±7 Birmingham Mean = 13.2±4.3 Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5	ED visits using electronic billing data	Poisson Regression Adjusted for: weekday, season, holidays, meteorology, temporal trends, and hospital reporting data for each day	NO ₂ RR (95% CI) ^b Dysrhythmia - lag 0 MCM: 1.04 (1.01, 1.08) NO _x RR (95% CI) ^b dysrhythmia - lag 0 MCM: 1.03 (1.01, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Birmingham Mean = 24.5±13.8			
			Dallas Mean = 41.4±32.2			
			Pittsburgh Mean = 56±35.8			
			St. Louis Mean = 51.3±30.9			
† Kranc et al. (2021)	Excluded cases of traumatic event causing OHCA and OHCA cases in patients younger than 18 years	Fixed site monitor Averaging time: NO ₂ - 1-hour max, Other, NO ₂ - 2-hour moving average	NO ₂ (ppb) Overall Mean = 9.2±5.3 Median = 7.9 Min = 0.8 Max = 38.7	National Israeli EMS registry	Logistic Regression Adjusted for: temperature, relative humidity	OR (95% CI) ^b OHCA: 1.11 (0.95, 1.29) OHCA/Females: 1.00 (0.79, 1.26) OHCA/Males: 1.20 (0.98, 1.47) OHCA/ <70 yrs: 1.02 (0.77, 1.34) OHCA/ ≥70 yrs: 1.15 (0.96, 1.38)
Israeli EMS N = 12,401 Israel 2016–2017 Case-crossover		Exposure years: 2016–2017				
† Lee et al. (2019)	Patients diagnosed with Afib for the first time; patients with any previous inpatient and outpatient diagnosis of Afib before this admission were excluded	Fixed site monitor Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2006–2011	NO ₂ (ppb) Overall Mean = 15.24±6.32 Median = 14.57 (IQR 8.54) Min = 0.61 Max = 56.48 P25 = 10.51 P75 = 19.05	Taiwan NHI program	Poisson Regression Adjusted for: temperature, relative humidity	NO OR (95% CI) ^b Atrial Fibrillation, lag 1–5: 1.43 (0.65, 3.12) Atrial Fibrillation, lag 1: 0.83 (0.50, 1.38) NO ₂ OR (95% CI) ^b
Taiwan National Health Insurance Program (NHI) N = 670 Taiwan Program Implementation: March 1, 1995						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Study years: 2006–2011			NO (ppb)			Atrial Fibrillation, lag 1–5: 0.84 (0.46, 1.54)
Case-crossover			Overall Mean = 4.1±2.87 Median = 3.28 (IQR 2.2) Min = 0.65 Max = 77.01 P25 = 2.49 P75 = 4.69			Atrial Fibrillation, lag 1: 0.89 (0.61, 1.28)
			NO _x (ppb)			NO _x
			Overall Mean = 19.4±8.19 Median = 17.79 (IQR 9.56) Min = 2.3 Max = 129.92 P25 = 13.69 P75 = 23.25			OR (95% CI) ^b Atrial Fibrillation, lag 1–5: 1.00 (0.55, 1.80) Atrial Fibrillation, lag 1: 0.82 (0.57, 1.19)
† Raza et al. (2019)	Cases that were dead on the arrival, cases with missing time data, and those whom personal identification number was not available were excluded	Fixed site monitor	NO ₂ (ppb)	Swedish EMS registry	Logistic Regression	OR (95% CI) ^c OHCA, 2-hr moving avg: 0.97 (0.94, 1.00)
Swedish Register for Cardiopulmonary Resuscitation		Method validation NR	Gothenburg 2-hour Cases Mean = 12.5±9.3 (23.5±17.5 µg/m ³)		Adjusted for: temperature, relative humidity	OR (95% CI) ^b OHCA, 24-hr moving avg: 0.89 (0.79, 1.00)
N = 11,923		Averaging time: NO ₂ - 1-hour max, NO ₂ - annual average, Other, NO ₂ - 2-hour	2-hour Controls Mean = 12.5±9.46 (23.6±17.8 µg/m ³)			OHCA, 2-hr moving avg (O ₃ , ρ = -0.54): 0.97 (0.94, 1.00)
Stockholm, Gothenburg, Malmo, Sweden		Exposure years: 2006–2014	2-hour Overall Mean = 12.3±9.25 (23.1±17.4 µg/m ³) IQR = 9.99 (18.8			
2006–2014						
Case-crossover						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			µg/m³) P5 = 2.9 (5.4 µg/m³) P95 = 30.6 (57.5 µg/m³) 24-hour Cases Mean = 12.1±6.48 (22.8±12.2 µg/m³) 24-hour Controls Mean = 12.2±6.59 (22.9±12.4 µg/m³) 24-hour Overall Mean = 12.3±6.54 (23.1±12.3 µg/m³) IQR = 7.65 (14.4 µg/m³) P5 = 4.6 (8.6 µg/m³) P95 = 24.8 (46.6 µg/m³) Malmo 2-hour Cases Mean = 9.51±5.8 (17.9±11 µg/m³) 2-hour Controls Mean = 9.73±6.01 (18.3±11.3 µg/m³) 2-hour Overall Mean = 9.14±5.69 (17.2±10.7 µg/m³) IQR = 6.54 (12.3 µg/m³) P5 = 2.9 (5.5 µg/m³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P95 = 20.4 (38.3 $\mu\text{g}/\text{m}^3$) 24-hour Cases Mean = 9.14 $\pm$ 4.1 (17.2 $\pm$ 7.8 $\mu\text{g}/\text{m}^3$) 24-hour Controls Mean = 9.14 $\pm$ 4.1 (17.2 $\pm$ 7.8 $\mu\text{g}/\text{m}^3$) 24-hour Overall Mean = 9.14 $\pm$ 4 (17.2 $\pm$ 7.6 $\mu\text{g}/\text{m}^3$) IQR = 5.3 (10 $\mu\text{g}/\text{m}^3$) P5 = 4 (7.6 $\mu\text{g}/\text{m}^3$) P95 = 17.1 (32.1 $\mu\text{g}/\text{m}^3$) Stockholm 2-hour Cases Mean = 7.4 $\pm$ 6.32 (14 $\pm$ 11.9 $\mu\text{g}/\text{m}^3$) 2-hour Controls Mean = 7.49 $\pm$ 6.4 (14.1 $\pm$ 12 $\mu\text{g}/\text{m}^3$) 2-hour Overall Mean = 6.96 $\pm$ 5.8 (13.1 $\pm$ 11 $\mu\text{g}/\text{m}^3$) IQR = 6.48 (12.2 $\mu\text{g}/\text{m}^3$) P5 = 1 (2 $\mu\text{g}/\text{m}^3$) P95 = 18.8 (35.4 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			24-hour Cases Mean = 6.9±4 (13±8 µg/m ³) 24-hour Controls Mean = 6.9±4 (13±8 µg/m ³) 24-hour Overall Mean = 6.96±4 (13.1±7.6 µg/m ³) IQR = 4.8 (9.1 µg/m ³) P5 = 2 (3.8 µg/m ³) P95 = 14.7 (27.6 µg/m ³) NO ₂ (µg/m ³) Gothenburg 2-hour Cases Mean = 23.5±17.5 2-hour Controls Mean = 23.6±17.8 2-hour Overall Mean = 23.1±17.4 IQR = 18.8 P5 = 5.4 P95 = 57.5 24-hour Cases Mean = 22.8±12.2 24-hour Controls			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 22.9±12.4 24-hour Overall Mean = 23.1±12.3 IQR = 14.4 P5 = 8.6 P95 = 46.6 Malmo 2-hour Cases Mean = 17.9±11 2-hour Controls Mean = 18.3±11.3 2-hour Overall Mean = 17.2±10.7 IQR = 12.3 P5 = 5.5 P95 = 38.3 24-hour Cases Mean = 17.2±7.8 24-hour Controls Mean = 17.2±7.8 24-hour Overall Mean = 17.2±7.6 IQR = 10 P5 = 7.6 P95 = 32.1 Stockholm 2-hour Cases Mean = 14±11.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			2-hour Controls Mean = 14.1±12 2-hour Overall Mean = 13.1±11 IQR = 12.2 P5 = 2 P95 = 35.4 24-hour Cases Mean = 13±8 24-hour Controls Mean = 13±8 24-hour Overall Mean = 13.1±7.6 IQR = 9.1 P5 = 3.8 P95 = 27.6			
†Santurtún et al. (2016) n = 81,035 Barcelona, Murcia, Spain, Alicante, Cantabria, Malaga, Seville, Valladolid, Biscay, Saragossa, Spain 2005–2010 Time-series	Representing approximately 33.5% of the total Spanish population from 9 regions patient information was collected from the Spanish National Institute of Statistics.	Hybrid model Hourly data of NO ₂ concentrations were measured using chemiluminescence. One fixed measurement station was selected in each region using the following criteria: being free from the direct	NO ₂ (ppb) Autumn Mean = 16.89 (31.79 µg/m ³) Spring Mean = 13.38 (25.17 µg/m ³) Summer Mean = 11.91 (22.41 µg/m ³) Winter Mean = 17.18 (32.32	Spanish National Institute of Statistics; ICD-9 code 427	Poisson Regression Adjusted for: Regional population	β (%) (95% CI) ^b Arrhythmia - lag 0 / autumn: 31.61 (23.52, 39.70) Arrhythmia - lag 0 / spring: 18.06 (12.04, 24.08) Arrhythmia - lag 0 / summer: 21.45 (15.43, 27.47) Arrhythmia - lag 0 / winter: 35.75 (27.66, 43.84) Arrhythmia - lag 0: 26.34 (22.39, 30.29)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
		influence of local point sources and thus representative of background boundary layer air, and having an NO ₂ series containing at least 80 % of days with recorded data during the studied	µg/m ³) Year Round Mean = 14.75 (27.76 µg/m ³)			
		Averaging time: NO ₂ - 24-hour average				
		Exposure years: 2005–2010				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Zhao et al. (2020)	NR	Fixed site monitor	NO ₂ (ppb)	National Registry: Fire and Disaster Management Agency	Conditional Logistic Regression Adjusted for: Temperature, relative humidity	OR (95% CI) ^b OHCA, lag0–3: 0.97 (0.93, 1.00) OHCA, lag 0: 0.99 (0.97, 1.01) OHCA, lag 1: 0.97 (0.95, 1.00) OHCA, lag 2: 0.98 (0.96, 1.00) OHCA, lag 3: 1.00 (0.98, 1.02) OHCA, lag0–3 (PM _{2.5} , ρ = 0.43): 0.86 (0.82, 0.91)
All-Japan Utstein Registry of the FDMA		Method validation NR	Overall Mean = 9.75 IQR = 6.46			
N = 249,372		Averaging time:	Min = 0			
Japan		NO ₂ - 1-hour max,	Max = 45.02			
		NO ₂ - 24-hour average	P5 = 3.45 P25 = 5.91 P75 = 12.37 P95 = 20.19			
January 1, 2014–December 31, 2015		Exposure years: 2014-2015				
Case-crossover						

List of Abbreviations in alphabetical order: Afib = Atrial Fibrillation; AMI = Acute Myocardial Infarction; BMI = body mass index; CAD = Coronary Artery Disease; CI = confidence interval; df = degrees of freedom; ED = Emergency Department; EMS = Emergency Medical Service; FDMA = Fire and Disaster Management Agency; ICD = Implantable Cardioverter Defibrillator; LUR = land use regression; Max = Maximum; MCM = Multi-City outcome Model; MECU = Mobile Emergency Care Unit; MI = Myocardial Infarction; MIDAS = Myocardial Infarction Data Acquisition System; Min = Minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; NSTEMI = Non-ST Elevation Myocardial Infarction; OHCA = Out of hospital Cardiac Arrest; OR = odds ratio; P10 = 10th Percentile; P25 = 25th Percentile; P75 = 75th Percentile; P90 = 90th Percentile; ppb = parts per billion; ROSC = Return of Spontaneous Circulation; RR = Relative Risk; STEMI = ST Elevation Myocardial Infarction.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-3 Animal toxicology studies of arrhythmia and cardiac arrest

Study Details and Population	Exposure Details	Endpoints Examined*
†Farraj et al. (2016)	Whole body inhalation with filtered air controls	5.5 hr after exposure Cardiac arrhythmia (NS)
Rat (Spontaneously Hypertensive) 12-wk-old, males n = 6/group	300 ppb (0.3 ppm) NO ₂ , continuous for 3 hr	21 hr after exposure Aconitine sensitivity (↑)

List of abbreviations in alphabetical order: hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; † = at least one experimental group had a statistically significant increase

†Studies published since the 2016 Oxides of Nitrogen ISA

Appendix Table 5-4 Epidemiologic studies of short-term oxides of nitrogen exposures and cerebrovascular disease and stroke

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Chen et al. (2014) N = 5,257 patients Edmonton, Canada April 1, 1992–March 31, 2002 Time-series	ED visits for acute ischemic stroke between 1998 and 2002	Fixed site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1998	NO ₂ (ppb) All Year Mean = 23.68±11.83 Median = 21.33 (IQR 17.17) P5 = 8.33 P95 = 45.67 Cold Seasons Mean = 28.96±11.71 Median = 28 (IQR 17.33) P5 = 11.54 P95 = 49.33 Warm Seasons Mean = 18.32±9.26 Median = 16.17 (IQR 11.17) P5 = 7.17 P95 = 36.67	ED visit records	Logistic Regression Adjusted for: temperature, relative humidity	OR (95% CI) ^b IS, Lag 1–8 hr: 1.07 (0.97, 1.18)
Larrieu et al. (2007) n = NR Paris, Bordeaux, Le Havre, Lille, Lyon, Marseille, Rouen,	Hospitalizations for cardiovascular diseases in study area	Fixed site monitor Averaging time: NO ₂ - annual average	NO ₂ (ppb) Bordeaux Mean = 11.9 (22.3 µg/m ³)	private hospitalization data	Poisson Regression Adjusted for: temperature, holidays, influenza periods	β (%) (95% CI) ^b Stroke - Lag 0–1: -0.75 (-1.51, 0.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Toulouse, France 1998–2003 Time-series		Exposure years: 1998–2003	Le Havre Mean = 13.7 (25.8 μg/m ³) Lille Mean = 17.4 (32.7 μg/m ³) Lyon Mean = 24.9 (46.8 μg/m ³) Marseille Mean = 19.3 (36.4 μg/m ³) Paris Mean = 23.6 (44.4 μg/m ³) Rouen Mean = 16.2 (30.4 μg/m ³) Toulouse Mean = 14 (26 μg/m ³)			
Linn et al. (2000) n = NR Los Angeles, CA, U.S. 1992–1995 Time-series	Excluded patients younger than 30 years of age and prescheduled hospital admissions ⁰¹¹	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–1995	NO ₂ (ppb) Autum\ Mean = 4100±1400 (4.1±1.4 ppm) Min = 1600 (1.6 ppm) Max = 8400 (8.4 ppm)	Hospital admissions data	Poisson Regression Adjusted for: temporal variation, weather	β (%) (95% CI) ^b CBVD - Lag 0: 0.80 (-0.77, 2.38) Occlusive Stroke - Lag 0: 4.04 (2.04, 6.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Spring Mean = 2800±900 (2.8±0.9 ppm) Min = 1100 (1.1 ppm) Max = 6100 (6.1 ppm) Summer Mean = 3400±1000 (3.4±1 ppm) Min = 700 (0.7 ppm) Max = 6700 (6.7 ppm) Winter Mean = 3400±1300 (3.4±1.3 ppm) Min = 1100 (1.1 ppm) Max = 9100 (9.1 ppm)			
Peel et al. (2007)	NR	Fixed site monitor	NO ₂ (ppb)	ED visit records	Case-crossover framework	OR (95% CI) ^b CBVD - Lag 0–2: 1.03 (1.01, 1.06)
SOPHIA		Averaging time:	Absolute differences		Adjusted for: time	
ED visits n = 4,407,535		NO ₂ - 1-hour max,	between average		stratification, cubic	
Atlanta, GA, U.S.		NO ₂ - 24-hour average	level on case days and control days		splines for average daily temperature and dew point temperature	
1993–2000		Exposure years: 1993–2000	1-hour Mean = 16.3±12.7 P10 = 2.8 P90 = 32.8			
Case-crossover			Daily levels 1-hour Mean = 45.9±17.3			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P10 = 25 P90 = 68			
Villeneuve et al. (2006) N = 12,422 stroke visits Edmonton, Canada April 1, 1992–March 31, 2002 Case-crossover	Emergency department visits for stroke among older adults	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–2002	NO ₂ (ppb) All year Mean = 24±9.8 Median = 22 (IQR 13.5) P25 = 16.5 P75 = 30 Summer Mean = 18.6±6.4 Median = 17.5 (IQR 8) P25 = 14 P75 = 22 Winter Mean = 29.4±9.6 Median = 28.5 (IQR 13) P25 = 22.5 P75 = 35.5		Hospital admissions Adjusted for: temperature, relative humidity	OR (95% CI) ^b Cerebral Ischemia: 0.99 (0.90, 1.08)
Villeneuve et al. (2012) n = 5927 Edmonton, Canada 2003–2009 Case-crossover	Stroke patients admitted to ED departments	Fixed site monitor Averaging time: 3-day average Exposure years: 2003–2009	NO ₂ (ppb) All months Mean = 12.4 P25 = 6.6 P75 = 16 Cool Season Mean = 16.7±8.6 P25 = 6.6 P75 = 16	Hospital admissions data	Logistic Regression Adjusted for: temperature, relative humidity	OR (95% CI) ^b Stroke - Lag 0–1/warm: 1.32 (0.95, 1.83) Stroke, Lag 0–1/cold: 0.96 (0.85, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Warm Season Mean = 8±3.8 P25 = 6.6 P75 = 16			
Wellenius et al. (2005)	Medicare beneficiaries ≥65 years of age in the 9 US cities; those with hospital admission with a primary discharge diagnosis of ischemic stroke	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1986–1999	NO ₂ (ppb) Overall Median = 23.54 P10 = 13.71 P25 = 18.05 P75 = 29.98 P90 = 36.54	Hospital admissions data	case-crossover method Adjusted for: seasonality, time trends, chronic and slowly varying potential confounders	β (%) (95% CI) ^b HS - Lag 0, ≥65: 0.64 (-4.53, 5.81) IS - Lag 0, ≥65: 4.93 (2.97, 6.89)
Medicare N = 155,503 hospital admissions Chicago, IL, Seattle, WA, Pittsburgh, Pennsylvania, Salt Lake City, UT, Cleveland, OH, Detroit, MI, Birmingham, AL, Minneapolis, MN, New Haven, CT, U.S. 1986–1999 Case-crossover						
Wellenius et al. (2012)	Included those 21 years or older admitted to the BIDMC with neurologist-confirmed ischemic stroke; excluded those with in- hospital strokes or transient ischemic attacks	Fixed site monitor Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 1999–2008	NO ₂ (ppb) Overall Mean = 19.1±6.3 Median = 18.2 (IQR 8.1) P25 = 14.6 P75 = 22.7	Medical records	Logistic Regression Adjusted for: seasonality, time trends, chronic and slowly varying potential confounders	OR (95% CI) ^b IS - Lag 1: 1.32 (1.07, 1.63)
N = 1,763 Boston, MA, U.S. April 1, 1999–October 31, 2008 Case-crossover						
[†] Groves et al. (2020)	Patients in the Adult Patient Database	Fixed site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Mean = 8 P25 = 5 P75 = 12	The Australia and New Zealand Intensive Care	Logistic Regression Adjusted for: temperature, humidity,	RR (95% CI) ^b Stroke - lag 0–2: 1.38 (0.83, 2.31)
n = 46,96 Victoria, New South Wales, Australia						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
January 1, 2008–December 31, 2016		Exposure years: 2007–2016		Society Adult Patient Database	flu activity score, public holidays	
Time-series						
† Ha et al. (2017)	Included singleton pregnancies that were complicated by cardiovascular events at labor/delivery. Excluded women who had a repeated event in a second pregnancy.	CMAQ, Fixed site monitor	NO _x (ppb)	Hospital Discharge (ICD-9)	Conditional Logistic Regression	OR (95% CI) ^b
Consortium on Safe Labor (2002-2008)		Averaging time: NO _x - 24-hour average	Overall Mean = 26.39 IQR = 22.24 Min = 4.66 Max = 134.76		Adjusted for: time stratification, meteorological factors	stroke prior to labor/delivery - 7-d avg: 0.64 (0.32, 1.29)
N = 680						stroke prior to labor/delivery - Lag 0: 0.83 (0.41, 1.67)
U.S.		Exposure years: 2002–2008	P25 = 12.06 P75 = 34.29			stroke prior to labor/delivery - Lag 2: 0.26 (0.09, 0.80)
2002–2008						stroke prior to labor/delivery - Lag 3: 0.57 (0.27, 1.21)
Case-crossover						stroke prior to labor/delivery - Lag 4: 0.92 (0.51, 1.66)
						stroke prior to labor/delivery - Lag 5: 0.70 (0.36, 1.36)
† Hasegawa et al. (2022)	Identified individuals who were hospitalized with a primary diagnosis of ischemic stroke; included only the first admission; excluded patients with outpatient or inpatient claims with an IS disease code within 36 months before their current admission, and	Fixed site monitor	NO ₂ (ppb)	National Database of Health Insurance Claims and Specific Health Checkups of Japan	Poisson Regression	β (%) (95% CI) ^b
National Database of Health Insurance Claims and Specific Health Checkups of Japan		Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average	Overall Mean = 10.25±3.46 Median = 10.15 Min = 2.43 Max = 18.53	Adjusted for: calendar time, temperature, relative humidity, public holidays, and day of the week		Stroke - lag 0: 3.78 (2.10, 5.46)
Hospital admission N = 335,248		Exposure years: 2016–2019	P25 = 7.26 P75 = 13.08			Stroke - lag 1: 1.20 (-0.98, 3.38)
Japan						Stroke - lag 2: -3.99 (-5.89, -2.08)
April 1, 2016–March 31, 2019						Stroke - lag 0 (SO _x , O _x , PM _{2.5}): 4.23 (1.67, 6.79)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort	those without records of procedure codes for brain CT or MRI after hospital admission, and those younger than 20 years					
† Ho et al. (2022a) n = 12,636 Singapore 2009–2018 Case-crossover	Hemorrhagic stroke cases reported to the Singapore Stroke Registry (SSR) from 2009-2018	Fixed site monitor Daily pollutant levels were collected by the NEA via 22 remote stations deployed across the island Averaging time: NO ₂ - 24-hour average Exposure years: 2009–2018	NO ₂ : (ppb) Mean = 23.9±7 Median = 23.3 Min = 6.8 Max = 53.4 P25 = 18.8 P75 = 28.4 Mean = 31.8±4.7 Median = 30.4 Min = 26.4 Max = 53.4 P25 = 28.4 P75 = 33.9	Singapore Stroke Registry	Poisson Regression Adjusted for: temperature, relative humidity, and total rainfall	IRR (95% CI) ^c HS - Tertile 2 vs. Tertile 1, lag 1: 0.97 (0.92, 1.01) HS - Tertile 2 vs. Tertile 1, lag 3: 0.94 (0.90, 0.99) HS - Tertile 2 vs. Tertile 1, lag 5: 0.97 (0.93, 1.02) HS - Tertile 2 vs. Tertile 1: 0.96 (0.92, 1.01) HS - Tertile 3 vs. Tertile 1, lag 1: 0.94 (0.89, 0.98) HS - Tertile 3 vs. Tertile 1, lag 3: 0.95 (0.90, 0.99) HS - Tertile 3 vs. Tertile 1, lag 5: 0.97 (0.92, 1.01) HS - Tertile 3 vs. Tertile 1: 0.97 (0.93, 1.02)
† Ho et al. (2022b) Singapore Stroke Registry AIS episodes N = 51,675 Singapore 2009–2018 Case-crossover	All daily reported cases of AIS between 2009 and 2018	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2009–2018	NO ₂ (ppb) Overall Mean = 12.68±3.74 (23.85±7.04 µg/m ³) Median = 12.37 (IQR 5.09) (23.27 µg/m ³) Min = 3.6 (6.77 µg/m ³)	Singapore Stroke Registry	Poisson Regression Adjusted for: temperature, relative humidity, and total rainfall	IRR (95% CI) ^b IS - lag 0: 0.99 (0.96, 1.02) HS - Tertile 3 vs. Tertile 1: 0.97 (0.93, 1.02) HS - Tertile 2 vs. Tertile 1: 0.96 (0.92, 1.01) HS - Tertile 3 vs. Tertile 1, lag 1: 0.94 (0.89, 0.98) HS - Tertile 2 vs. Tertile 1, lag 1: 0.97 (0.92, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Max = 28.37 (53.38 $\mu\text{g}/\text{m}^3$)			HS - Tertile 3 vs. Tertile 1, lag 3: 0.95 (0.90, 0.99) HS - Tertile 2 vs. Tertile 1, lag 3: 0.94 (0.90, 0.99) HS - Tertile 3 vs. Tertile 1, lag 5: 0.97 (0.92, 1.01) HS - Tertile 2 vs. Tertile 1, lag 5: 0.97 (0.93, 1.02)
†Kim et al. (2022)	Cases: Participants who were diagnosed with stroke; excluded those who were diagnosed with stroke before 2004, those who did not have a BMI record.	Hybrid model	NO ₂ (ppb)	ICD-10 codes I60 and I69	Logistic Regression	OR (95% CI) ^b
Korean National Health Insurance Service-Health Screening Cohort	Control group: included participants who did not have a diagnosis of stroke from 2002 through 2015; excluded those who did not have records since 2004 and those were diagnosed with ICD codes I60 and I69	Method validation NR	7 days Control Mean = 22.7 $\pm$ 10.9 Stroke Mean = 22.1 $\pm$ 10.4		Adjusted for: age, sex, income, region of residence, obesity, smoking, alcohol consumption, and CCI score	HS - 7-d avg: 0.86 (0.83, 0.90) HS - 7-d avg: 0.89 (0.83, 0.96) HS - 30-d avg: 0.84 (0.80, 0.87) HS - 30 d avg: 0.89 (0.82, 0.97)
Stroke n = 21,240 Controls n = 84,960		Averaging time: NO ₂ - annual average, Other,	30 days Control Mean = 22.7 $\pm$ 9.9 Stroke Mean = 22.1 $\pm$ 9.7			Stroke - 7-d avg: 0.50 (0.42, 0.59) Stroke - 30-d avg: 0.44 (0.36, 0.54) Stroke - 7-d avg (SO ₂ , O ₃ , CO, PM ₁₀): 0.84 (0.80, 0.88) Stroke - 30-d avg (SO ₂ , O ₃ , CO, PM ₁₀): 0.82 (0.78, 0.86)
South Korea		NO ₂ - 7-day NO ₂ - 30 days NO ₂ - 3 months				
2002–2015		Exposure years: 2004–2015				
Cohort						
†Krall et al. (2018)	NR	Hybrid model	NO ₂ (ppb)	ED visits using electronic billing data	Poisson Regression	NO ₂
n = NR		Method validation NR	Atlanta Mean = 21.6 $\pm$ 7		Adjusted for: weekday, season, holidays, meteorology, temporal	RR (95% CI) ^c Stroke - lag 0 PCA: 1.06 (1.02, 1.09)
Atlanta, GA, St. Louis, MO,						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Dallas, TX, Pittsburgh, Pennsylvania, Birmingham, AL, U.S. 2002–2008 Time-series		Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max Exposure years: 2002–2008	Birmingham Mean = 13.2±4.3 Dallas Mean = 19.7±8.2 Pittsburgh Mean = 26.5±8.1 St. Louis Mean = 21.3±6.3 NO _x (ppb) Atlanta Mean = 45.6±30.5 Birmingham Mean = 24.5±13.8 Dallas Mean = 41.4±32.2 Pittsburgh Mean = 56±35.8 St. Louis Mean = 51.3±30.9		trends, and hospital reporting data for each day	NO _x RR (95% CI) ^b Stroke - lag 0 MCM: 1.04 (1.01, 1.06)
† Li et al. (2023) n = Hospital Admissions: 271,394 Beibu Gulf Region, China 2013–2016	Patients with a principal diagnosis of stroke were included, while those who had missing information on age, sex, and who residential location was	Hybrid model r ² = 0.84 Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) On Case Days Mean = 11.1±5.63 (20.9±10.6 µg/m ³) Median = 10.2 (IQR 5.95) (19.2 µg/m ³) (IQR 11.2 µg/m ³) P25 = 7.65 (14.4	Daily hospital admission records	Logistic Regression Adjusted for: temperature, relative humidity, holidays	OR (95% CI) ^b Stroke - 2-d avg: 1.14 (1.09, 1.19) HS - 2-d avg: 0.93 (0.85, 1.02) IS - 2 d avg: 1.19 (1.12, 1.26) IS / cool season:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Case-crossover	outside of the study area were excluded.	Exposure years: 2013–2016	$\mu\text{g}/\text{m}^3$ P75 = 13.6 (25.6 $\mu\text{g}/\text{m}^3$) On Control Days Mean = 11.1±5.58 (20.9±10.5 $\mu\text{g}/\text{m}^3$) Median = 10.2 (IQR 5.95) (19.2 $\mu\text{g}/\text{m}^3$) (IQR 11.2 $\mu\text{g}/\text{m}^3$) P25 = 7.65 (14.4 $\mu\text{g}/\text{m}^3$) P75 = 13.6 (25.6 $\mu\text{g}/\text{m}^3$)			1.26 (1.17, 1.36) IS / warm season: 0.97 (0.85, 1.09) Stroke / cool season: 1.21 (1.14, 1.28) Stroke / warm season: 0.92 (0.82, 1.04) Stroke (PM ₁₀ , $\rho = 0.72$): 1.16 (1.07, 1.26) Stroke (PM _{2.5} , $\rho = 0.80$): 1.19 (1.06, 1.35) Stroke (SO ₂ , $\rho = 0.71$): 1.12 (1.05, 1.18) Stroke (O ₃ , $\rho = 0.36$): 1.15 (1.10, 1.20) Stroke (CO, $\rho = 0.69$): 1.14 (1.08, 1.20) IS (PM ₁₀ , $\rho = 0.72$): 1.22 (1.10, 1.35) IS (PM _{2.5} , $\rho = 0.80$): 1.24 (1.08, 1.41) IS (SO ₂ , $\rho = 0.71$): 1.14 (1.08, 1.21) IS (O ₃ , $\rho = 0.36$): 1.19 (1.11, 1.28) IS (CO, $\rho = 0.69$): 1.20 (1.10, 1.31)
† Liu et al. (2023) CSCA N = 824,808	Stroke patients were recruited in the admitted hospitals using inclusion criteria: older than 18 years,	Fixed site monitor Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour	NO ₂ (ppb) Case Days Mean = 18.4±9.41 (34.7±17.7 $\mu\text{g}/\text{m}^3$)	WHO criteria, CT and MRI	Logistic Regression Adjusted for: ambient temperature, relative humidity, and holiday	β (%) (95% CI) ^b IS - lag 01: 4.33 (3.44, 5.21) IS - lag 01, cold: 4.25 (3.20, 5.31)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
China 2015–2019 Case-crossover	have a primary diagnosis of acute stroke confirmed by CT/MRI, within 7 days of symptom onset, admitted either directly to a hospital ward or through the ER department, without cerebral venous sinus thrombosis or non-cerebrovascular diseases. Patients with missing information of key variables were excluded.	average Exposure years: 2015–2019	IQR = 12.6 (23.8 µg/m ³) Control Days Mean = 18.4±8.02 (34.6±15.1 µg/m ³) IQR = 12.6 (23.7 µg/m ³)			IS - lag 01, warm: 3.99 (2.20, 5.78)
†Sun et al. (2019) Women's Health Initiative (WHI) Stroke incident N = 5,417 U.S. 1993–2012 Case-crossover	Women aged 50-79 years; restricted to participants who experiences a stroke event between enrollment and September 14, 2012, had no history of stroke upon enrollment, had a known address at the time of stroke, and for who the date of stroke hospitalization was documented	Fixed site monitor The performance of these models has been assessed using cross-validation parameters including SPE, PE, and root mean square standardized (RMSS). The PEs and SPEs of the six air pollutants in 2000, 2005, and 2010 are very close to 0 with a range from 0 to 0.27 for PE and -0.11 to 0.04 for	NO ₂ (ppb) Overall Mean = 15.4±8 IQR = 10.2 NO ₂ (ppb) Overall Mean = 27.8±24.6 IQR = 21.8	Women's Health Initiative	Logistic Regression Adjusted for: Mean ambient temperature, dew point temperature	OR (95% CI) ^b HS - 1-d moving avg: 1.47 (0.84, 2.57) HS - 2-d moving avg: 1.84 (0.94, 3.60) HS - 3-d moving avg: 2.21 (1.04, 4.70) IS - 1-d moving avg: 0.96 (0.74, 1.25) IS - 2-d moving avg: 0.96 (0.70, 1.32) IS - 3-d moving avg: 0.93 (0.64, 1.35) Stroke, 1-d moving avg: 1.00 (0.79, 1.27) Stroke, 2-d moving avg: 1.08 (0.81, 1.44) Stroke, 3-d moving avg: 1.08 (0.78, 1.49)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
		SPE, and the RMSSs are all close to 1				
		Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average				
		Exposure years: 1993–2012				
† Tian et al. (2018)	Admissions under the age of 18 were excluded; Admission without brain computed tomography or MRI were excluded	Fixed site monitor	NO ₂ (ppb)	Insurance Records	Poisson Regression	β (%) (95% CI) ^b
UEBMI		Averaging time:	Northern China		Adjusted for: poisson regression (2nd stage to pool regional/national estimates)	IS - lag0:
Admissions N = 2,032,667		NO ₂ - 24-hour average	Mean = 17.1±5.8 (32.2±11 µg/m ³)			6.91 (5.47, 8.35)
China		Exposure years:	Median = 18 (IQR 9.25) (33 µg/m ³)			IS - lag0/ warm, low-polluted:
2014–2016		2014–2016	(IQR 17.4 µg/m ³)			-3.46 (0.04, -6.96)
Time-series			Min = 6.4 (12 µg/m ³)			IS - lag0/ warm, low-polluted:
			Max = 31.7 (59.7 µg/m ³)			15.81 (9.33, 22.28)
			P25 = 12.2 (22.9 µg/m ³)			IS - lag0/ warm, highly polluted:
			P75 = 21.4 (40.3 µg/m ³)			5.19 (3.42, 6.96)
			Overall			IS - lag0/ warm, highly polluted:
			Mean = 16±5.74 (31±10.8 µg/m ³)			7.79 (5.80, 9.78)
			Median = 16.4 (IQR 8.13) (30.9 µg/m ³)			IS - lag0/ warm:
			(IQR 15.3 µg/m ³)			8.54 (6.12, 10.97)
			Min = 5.3 (10 µg/m ³)			IS - lag 0/cool:
			Max = 31.7 (59.7 µg/m ³)			9.45 (6.04, 12.85)
						IS (PM _{2.5}):
						5.56 (4.44, 6.68)
						IS (SO ₂):
						3.96 (2.74, 5.18)
						IS (CO):
						5.58 (4.29, 6.87)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			$\mu\text{g}/\text{m}^3$ P25 = 11.9 (22.4 $\mu\text{g}/\text{m}^3$) P75 = 20 (37.7 $\mu\text{g}/\text{m}^3$) Southern China Mean = 15.8±5.58 (29.7±10.5 $\mu\text{g}/\text{m}^3$) Median = 15.9 (IQR 8.34) (29.9 $\mu\text{g}/\text{m}^3$ (IQR 15.7 $\mu\text{g}/\text{m}^3$) Min = 5.3 (10 $\mu\text{g}/\text{m}^3$) Max = 27.6 (51.9 $\mu\text{g}/\text{m}^3$) P25 = 11 (21 $\mu\text{g}/\text{m}^3$) P75 = 19.5 (36.7 $\mu\text{g}/\text{m}^3$)			
† Wilker et al. (2018) n = 577 cases U.S. 2006–2011 Case-crossover	Patients (18 yrs or older) admitted to Mass General Hospital with ICH	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2006–2011	NO ₂ (ppb)	Medical Records (acute ICH patients)	Conditional Logistic Regression Adjusted for: time stratification, barometric pressure, temperature, dew point temperature	OR (95% CI) ^b NO ₂ exposure not associated with deep or lobar ICH.

List of Abbreviations in alphabetical order: CI = Confidence Interval; CBVD = cerebrovascular disease; CSCA = Chinese Stroke Center Alliance; CT = Computed Tomography; ED = Emergency Department; HS = Hemorrhagic Stroke; ICH = Intracerebral Hemorrhage; IQR = Interquartile Range; IQR = Interquartile Range; IS = Ischemic Stroke; Max = Maximum; MI = Myocardial Infarction; MRI = magnetic imaging resonance; NEA = National Environment Agency; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OR = Odds Ratio; P10 = 10th Percentile; P25 = 25th Percentile; P75 = 75th; P90 = 90th Percentile; PE = Prediction Error; ppm = part per million; RR = Relative Risk; SOPHIA = Study of Particles and Health in Atlanta; SPE = standardized prediction error; UEBMI = Urban Employee Basic Medical Insurance.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-5 Epidemiologic studies of short-term oxides of nitrogen exposure and heart failure

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases MINAP database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST elevation MI, non-ST elevation MI, or troponin-positive acute coronary syndrome.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	National databases with diagnosis information	Logistic Regression Adjusted for: age, sex	β (%) (95% CI) ^b HF, lag 0–4: 3.68 (1.67, 5.69) HF, Age <70: 3.76 (0.96, 6.56) HF, Age ≥70 3.51 (0.75, 6.27) HF, Male 4.93 (0.59, 9.28) HF, Female 3.35 (1.13, 5.56)
Stieb et al. (2009) n = nearly 400,000 ED visits Canada 1990s and early 2000s	Administrative ED visits	Central site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Montreal Mean = 19.4±7.6 Ottawa Mean = 18.8±8.8	ED visits	Poisson regression Adjusted for: seasonal trends, day of the week, holidays	β (%) (95% CI) ^b HF - Lag 0: 5.11 (1.20, 9.02) HF - Lag 1: 3.04 (-1.52, 7.61) HF - Lag 2: 2.07 (-3.48, 7.61)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Time-series		Exposure years: 1992–2003	Edmonton Mean = 21.9±9.4 Saint John Mean = 9.3±5.5 Halifax Mean = 17.5±5.8 Toronto Mean = 22.7±7.6 Vancouver Mean = 18.7±4.6			
Yang (2008) n = 24,240 Taipei, Taiwan 1996–2004 Case-crossover	Patients admitted for CHF	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1996–2004	NO ₂ (ppb) Mean = 30.59 Median = 30.03 Min = 3.84 Max = 77.97 P25 = 25.32 P75 = 35.56	Hospital Admissions	Conditional Logistic Regression Adjusted for: temperature and humidity	OR (95% CI) ^b CHF: 1.37 (1.22, 1.53)
†Ha et al. (2017) Consortium on Safe Labor (2002-2008) N = 680 U.S. 2002–2008	Included singleton pregnancies that were complicated by cardiovascular events at labor/delivery. Excluded women who had a repeated event in a second pregnancy.	CMAQ, Fixed site monitor Method validation NR Averaging time: NO _x - 24-hour average	NO _x (ppb) Overall Mean = 26.39 IQR = 22.24 Min = 4.66 Max = 134.76 P25 = 12.06 P75 = 34.29 NO _x (ppb)	Electronic medical records; labor and delivery discharge summary	Logistic Regression Adjusted for: time stratification, meteorological variables	OR (95% CI) ^b HF, lag 0–7: 2.46 (1.15, 5.28) HF, lag 0: 1.74 (0.95, 3.17) HF, lag 1: 1.68 (1.08, 2.60) HF, lag 6: 3.10 (1.26, 7.64)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Case-crossover		Exposure years: 2002–2008	Overall Mean = 26.39 IQR = 22.24 Min = 4.66 Max = 134.76 P25 = 12.06 P75 = 34.29			HF, lag 7: 0.68 (0.31, 1.48)
† Krall et al. (2018)	NR	Hybrid model	NO ₂ (ppb)	ED visits using electronic billing data	Poisson Regression	NO ₂
n = NR		Method validation NR	Atlanta Mean = 21.6±7		Adjusted for: weekday, season, holidays, meteorology, temporal trends, and hospital reporting data for each day	RR (95% CI) ^b CHF ED visits, MCM Lag 0: 1.05 (1.01, 1.08)
Atlanta, GA, St. Louis, MO, Dallas, TX, Pittsburgh, Pennsylvania, Birmingham, AL, U.S.		Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max	Birmingham Mean = 13.2±4.3			NO _x
2002–2008		Exposure years: 2002–2008	Dallas Mean = 19.7±8.2			RR (95% CI) ^b CHF ED visits, MCM Lag 0: 1.04 (1.02, 1.06)
Time-series			Pittsburgh Mean = 26.5±8.1			
			St. Louis Mean = 21.3±6.3			
			NO _x (ppb)			
			Atlanta Mean = 45.6±30.5			
			Birmingham Mean = 24.5±13.8			
			Dallas Mean = 41.4±32.2			
			Pittsburgh			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 56±35.8			
			St. Louis Mean = 51.3±30.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zhao et al. (2023)	Included cases from outside the hospital setting that were presuming to have cardiac etiology, cases with an initial diagnosis of heart failure, cases with rapid onset or acute worsening or chronic heart failure requiring urgent medical evaluation and treatment.	Fixed site monitor	NO ₂ (ppb)	Ambulance Records	Conditional Logistic Regression	NO
Gunma Prefectural Comprehensive Medical Information System		Method validation	Overall		Adjusted for: time stratification, temperature and humidity	OR (95% CI) ^b
N = 53,006		NR	Mean = 7.82			HF - Lag 0–1: 1.49 (0.52, 4.28)
		Averaging time:	Median = 6.83 (IQR 6.18)			HF - Lag 0: 0.96 (0.44, 2.12)
		NO ₂ - 1-hour max,	P5 = 1.54			HF - Lag 1: 1.64 (0.76, 3.54)
		NO ₂ - 24-hour average, NO _x - 1-hour max, NO _x - 24-hour average,	P25 = 4.17			HF - Lag 2: 1.06 (0.46, 2.45)
Gunma, Japan		NO - 1-hour max, NO - 24-hour average	P75 = 10.34			
January 1, 2015–December 31, 2015			P95 = 17.42			
Cohort			NO (ppb)			NO ₂
	Excluded arrests with an obvious preceding non-cardiac event (trauma, poisoning, drowning, overdose, asphyxia, electrocution) or primary respiratory arrests.		Overall			OR (95% CI) ^b
		Exposure years: 2015	Mean = 1.7			HF - Lag 0–1: 0.92 (0.50, 1.70)
			Median = 1.12 (IQR 1.27)			HF - Lag 0: 1.06 (0.66, 1.71)
			P5 = 0.07			HF - Lag 1: 0.87 (0.54, 1.39)
			P25 = 0.61			HF - Lag 2: 0.87 (0.53, 1.42)
			P75 = 1.88			
			P95 = 5.28			
			NO _x (ppb)			NO _x
			Overall			OR (95% CI) ^b
			Mean = 9.51			HF - Lag 0–1: 1.03 (0.54, 1.96)
			Median = 8.06 (IQR 6.99)			HF - Lag 0: 1.03 (0.64, 1.66)
			P5 = 2.04			HF - Lag 1: 1.03 (0.64, 1.66)
			P25 = 5.01			HF - Lag 2: 0.91 (0.55, 1.52)
			P75 = 12			
			P95 = 21.79			

List of Abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; CHF = Congestive Heart Failure; HF = Heart Failure; MINAP = Myocardial Ischaemia National Audit Project; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; OR = Odds Ratio; P10 = 10th Percentile; P25 = 25th Percentile; P75 = 75th Percentile; P90 = 90th Percentile; ppb = parts per billion; RR = Relative Risk.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-6 Epidemiologic studies of short-term oxides of nitrogen exposure and increased blood pressure and hypertension

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Szyszkowicz et al. (2012) N = 5,365 cases n = 2,069 male cases n = 3,296 female cases Edmonton, Canada April 1992–March 2002 Case-crossvoer	Emergency department visits with ICD-9 code 401.9	NAPS Monitors Averaging time: NO ₂ -24-hr average Exposure years: 1992–2002	NO ₂ (ppb) Mean = 21.9±9.4 Median = 19.7 (IQR: 12.8) Max = 67.6	ED Visits	Conditional Logistic Regression Adjusted for: time stratification	OR (95% CI) ^b Hypertension - Lag 0–2: 1.13 (1.02, 1.25) Hypertension - Lag 0: 1.03 (0.94, 1.13) Hypertension - Lag 1: 1.02 (0.93, 1.11) Hypertension - Lag 2: 1.06 (1.11, 1.01) Hypertension - Lag 3: 1.10 (1.00, 1.20) Hypertension - Lag 4: 1.06 (0.97, 1.16) Hypertension - Lag 5: 1.05 (1.00, 1.10) Hypertension - Lag 6: 1.03 (0.95, 1.12) Hypertension - Lag 7: 1.06 (0.97, 1.16)
[†] Adar et al. (2018) Multiethnic study of atherosclerosis (MESA)	Men and women, aged 45 to 84 years, who were free of clinical cardiovascular disease,	Spatiotemporal/ge ospatial model, Fixed site monitor	NO ₂ (ppb) 1 day Exam 1: 2000–2002	SBP	Linear mixed effects models Adjusted for: age at exam, sex, race/ethnicity,	B (mm Hg) (95% CI) ^b DBP, lag 1, 2, 7 and 30 days:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
N = 5,587	weighed <136 kg, and had no impediments to long-term participation.	$r^2 = 0.5\text{--}0.9$	Mean = 24.5±13.4		education, study site, neighborhood SES and its interaction with study site, season and its interaction with study site, BMI, waist-to-hip ratio, tobacco smoke exposure, physical activity, and calendar time (as noted), random slopes and intercepts for subject	No association after adjustment for calendar time (Figure Only)
Chicago, IL, Baltimore, MD, Los Angeles, CA, St. Paul, MN, New York City, NY, Forsyth County, NC, U.S.	Restricted to participant visits with information on air pollution, key covariates, and blood pressure. Analysis of incident hypertension further restricted to those without prevalent hypertension at baseline.	Averaging time: NO ₂ - annual average	Exam 2: 2002–2004 Mean = 23.5±12.5			SBP, lag 1, 2, 7 and 30 days: No association after adjustment for calendar time (Figure Only)
Enrollment: 2000–2002 Follow-up: 2002–2007, 2010–2012		Exposure years: 1999–2011	Exam 3: 2004–2005 Mean = 20.2±11.1			
Cohort			Exam 4: 2005–2007 Mean = 20.2±11.1			
			Exam 5: 2010–2012 Mean = 20.6±11.2			
			1 year			
			Exam 1: 2000–2002 Mean = 21.8±9.2			
			Exam 2: 2002–2004 Mean = 20.7±9.1			
			Exam 3: 2004–2005 Mean = 19.6±8.2			
			Exam 4: 2005–2007 Mean = 19.4±8.1			
			Exam 5: 2010–2012 Mean = 15.6±7.7			
			2 day			
			Exam 1: 2000–2002 Mean = 23.8±13.2			
			Exam 2: 2002–2004 Mean = 22.7±12.6			
			Exam 3: 2004–2005 Mean = 19.4±10.7			
			Exam 4: 2005–2007 Mean = 20.2±11			
			Exam 5: 2010–2012 Mean = 19.9±11			
			7 day			
			Exam 1: 2000–2002 Mean = 25.5±13.6			
			Exam 2: 2002–2004			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Biel et al. (2020) N = 46 Toronto, Canada	NR	Fixed site monitor	Mean = 24.2±12.8 Exam 3: 2004–2005 Mean = 20.9±11.1 Exam 4: 2005–2007 Mean = 21.6±11.2 Exam 5: 2010–2012 Mean = 21.2±11.1	SBP and DBP	Weighted quantile sum regression Adjusted for: physical activity, temperature, relative humidity, proportion of time	β (mm Hg) (95% CI) ^b DBP: -11.85 (-20.07, -3.63) DBP: -1.19 (-9.70, 7.33) SBP:
		Method validation	30-min Average Mean = 10.5±3.5			
		NR	Median = 10.5 (IQR 4)			
		Averaging time:	30 day Exam 1: 2000–2002 Mean = 21.5±9.6 Exam 2: 2002–2004 Mean = 20.8±9.6 Exam 3: 2004–2005 Mean = 18.5±8.5 Exam 4: 2005–2007 Mean = 19.1±8.6 Exam 5: 2010–2012 Mean = 14.8±8.5 60 day Exam 1: 2000–2002 Mean = 21.6±9.5 Exam 2: 2002–2004 Mean = 20.8±9.5 Exam 3: 2004–2005 Mean = 18.8±8.5 Exam 4: 2005–2007 Mean = 19.1±8.6 Exam 5: 2010–2012 Mean = 14.8±8.5			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
May 2016–August 2016 Cohort		NO ₂ - 24-hour average Exposure years: 2016	P5 = 5.1 P25 = 8.2 P75 = 12.3 P95 = 15.7 Daily Visit Average Mean = 11.8±3 Median = 11.3 (IQR 2.7) P5 = 7.5 P25 = 10 P75 = 12.7 P95 = 17.4		spent in different contexts, week vs. weekend, living standard of areas where the BP measurements were taken, and hourly time trend	4.30 (-6.41, 15.00) SBP: 4.67 (-7.59, 16.93)
†Mann et al. (2021) The Children’s Health and Air Pollution Study (CHAPS) N = 299 California, U.S. 2015–2017 Cross-Sectional	Children ages 6–8; residence in Fresno or Clovis for at least the past 3 months, residence within 20 km of the central air quality monitoring site, no plans to move from the Fresno/ Clovis area in the next 2 years, English- or Spanish-speaking, and no cancer, HIV, or autoimmune disease	Fixed site monitor, LUR Models for NO ₂ explain 99% of the observed temporal variance and 74% or the observed spatial variance Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages Exposure years: 2013–2017	NO ₂ (ppb) 1-Day Lag Mean = 6.98 Median = 5.07 (IQR 6.42) 1-Month Average Mean = 7.17 Median = 6.65 (IQR 6.46) 1-Week Average Mean = 7.19 Median = 6.01 (IQR 6.04) 1-Year Average Mean = 7.6 Median = 7.71 (IQR 1.74) 3-Month Average Mean = 7.3	SBP and DBP	GAM Adjusted for: race/ethnicity, age, sex SES	β (mm Hg) (95% CI) ^b DBP, 1 day lag: 1.21 (-3.84, 6.26) DBP, 1 month: 1.65 (-0.43, 3.74) DBP, 1 week: 1.00 (-0.64, 2.65) SBP, 1-mo: 5.61 (0.22, 11.20) SBP, 1 day lag: 2.88 (-5.30, 11.07) SBP, 1 week: 2.96 (-0.62, 6.54)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Median = 6.88 (IQR 6.2)			
			6-Month Average Mean = 7.48 Median = 7.38 (IQR 3.42)			
† Scheers et al. (2018)	Included 10 healthy retired male-female couples with both partners fulfilling the following: aged 60–75, never or >1-year former smokers, good general health, willing and available to travel during the study period, and fluent in Dutch. Excluded participants with mobility problems, a history of cardiovascular disease, cancer, or other disease that could interfere the measurements, or would represent a risk during travel.	Personal monitor or sampler, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2014	NO ₂ (ppb) 2013 November Mean = 10.3±2.2 (19.4±4.2 µg/m ³) October Mean = 29.2±0.85 (54.9±1.6 µg/m ³) September Mean = 13.3±3.6 (25.1±6.8 µg/m ³) 2014 January Mean = 14±2.8 (26±5.2 µg/m ³) July Mean = 8.98±2.1 (16.9±3.9 µg/m ³) June Mean = 10.2±0.5 (19.2±1 µg/m ³) March Mean = 14.6±4.4 (27.5±8.2 µg/m ³) May Mean = 8.98±3.3 (16.9±6.3 µg/m ³) September	SBP and DBP	Linear mixed models Adjusted for: age at baseline, sex, date of measurement, ambient temperature, relative humidity, heart rate, having a cold, high blood pressure medication, and smoking status	β (mm Hg) (95% CI) DBP (personal): -0.28 (-1.00, 0.43) SBP (personal): -0.14 (-1.17, 0.88) β (mm Hg) (95% CI) ^b DBP (area): -2.48 (-5.70, 0.73) PP (area): -1.32 (-3.93, 1.30) PP (personal): 0.41 (-2.31, 3.14) SBP (area): -3.69 (-8.37, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 12.1±3 (22.8±6 µg/m ³) NO ₂ (µg/m ³) 2013 November Mean = 19.4±4.2 October Mean = 54.9±1.6 September Mean = 25.1±6.8 2014 January Mean = 26±5.2 July Mean = 16.9±3.9 June Mean = 19.2±1 March Mean = 27.5±8.2 May Mean = 16.9±6.3 September Mean = 22.8±6 NO ₂ (ppb) 2013 November Mean = 19.4±4.2 October Mean = 54.9±1.6 September Mean = 25.1±6.8 2014			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			January Mean = 26±5.2 July Mean = 16.9±3.9 June Mean = 19.2±1 March Mean = 27.5±8.2 May Mean = 16.9±6.3 September Mean = 22.8±6			
† Stieb et al. (2018) n = 72 Prince George, British Columbia, Canada 2014–2015 Panel	Adults aged 55 years and older, non-smokers, not exposed at home to environmental tobacco smoke, no seasonal allergies, not having certain cardiovascular conditions	Fixed site monitor Averaging time: NO ₂ - daily 3hr max Exposure years: 2014–2015	NO ₂ (ppb) 2014 Mean = 24.6±12.3 Min = 4.2 Max = 52.5 2015 Mean = 22.2±7.9 Min = 5.1 Max = 41.2	SBP and DBP	linear mixed effects models Adjusted for: age at visit, self-reported race-ethnicity, education, treatment arms, US Census region, day of the week, season, BMI, neighborhood SEP, pack-year of smoking, diabetes, calendar time, temperature, dew point temperature, relative humidity, wind speed, and a random slope for age, barometric pressure (DBP only)	β (mm Hg) (95% CI) ^b DBP / pre-exercise intervention: -0.36 (-0.74, 0.03) DPB / pre-exercise control: -0.10 (-0.52, 0.31) SBP / pre-exercise control: -0.36 (-0.74, 0.03) SBP / pre-exercise intervention: -0.29 (-0.67, 0.09)
† Wen et al. (2023) Women's Health Initiative (WHI) n = NR United States	Postmenopausal women 50 to 79 years of age	AQS Averaging time: NO ₂ -24-hour average Exposure years:	NO ₂ (ppb) Lag 0–6 day Mean = 18.7±7.1 Lag 3–5 day Mean = 18.3±7.7	SBP and DBP	linear mixed effects models Adjusted for: age at visit, self-reported race-ethnicity, education, treatment arms, US Census region, day of the week, season, BMI, neighborhood SEP, pack-year of smoking, diabetes,	β (mm Hg) (95% CI) ^b DBP, lag 3–5 d /no adjustment for calendar time: 0.92 (0.83, 1.02) DBP, lag 3–5 d: 0.28 (0.18, 0.38) SBP, lag 3–5 d: -0.45 (-0.63, -0.27) SPB, lag 3–5 d /no adjustment

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Recruitment: 1993–1998 Follow-up: 2005 Cohort		1993–2005			calendar time, temperature, dew point temperature, relative humidity, wind speed, and a random slope for age, barometric pressure (DBP only)	for calendar time: 1.29 (1.11, 1.47)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†de Prado-Bert et al. (2022)	Children	LUR	NO ₂ (ppb)	SBP and DBP	Linear regression	β (log2 fold change of protein levels) (95% CI) ^b
Human Early-life Exposome project (HELIX)		ESCAPE-LUR	24 h avg (school/home)		Adjusted for: child's sex, cohort, self-reported maternal education, self-reported ancestry, mean temperature, child's age and height	DBP/home (1 d): 0.61 (-0.56, 1.77)
n = 1170		Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, NO ₂ Other, 1-week avg	Median = 1.8 (IQR 0.37) (3.4 µg/m ³ (IQR 0.7 µg/m ³)			DBP/home (1 week): 0.35 (-0.99, 1.69)
France, U.K., Spain, Norway, Greece, Lithuania			Annual avg (home) Median = 1.9 (IQR 0.32) (3.5 µg/m ³ (IQR 0.6 µg/m ³)			DBP/school (1 d): 0.58 (-0.57, 1.73)
Follow-up (age 7-11): 2014–2015		Exposure years: 2013–2015	Annual avg (school) Median = 1.9 (IQR 0.27) (3.5 µg/m ³ (IQR 0.5 µg/m ³)			DBP/school (1 week): 0.30 (-1.02, 1.63)
Cohort			Week avg (school/home) Median = 1.9 (IQR 0.37) (3.5 µg/m ³ (IQR 0.7 µg/m ³)			SBP/home (1 d): 0.93 (-0.29, 2.16)
						SBP/home (1 week): 1.21 (-0.19, 2.61)
						SBP/school (1 d): 1.02 (-0.19, 2.22)
						SBP/school (1 week): 1.24 (-0.15, 2.63)

List of Abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; HR = hazard ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO = nitric oxide; NO_x = nitrogen oxides; NR = not reported; ppb = parts per billion; O₃ = ozone; OR = odds ratio; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-7 Animal toxicology studies of increased blood pressure and hypertension

Study Details and Population	Exposure Details	Endpoints Examined*
Li et al. (2011)	Whole body inhalation with filtered air controls	18 hr after exposure
Rat (Wistar)	2,657 ppb (5 mg/m ³) NO ₂ , 6 hr/d for 7 d	• Cardiac apoptosis (p53, bax/bcl-2 ratio, TUNEL stain) (↑)
280–300g, males	5,313 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 7 d	
n = 6/group	10,627 ppb (20 mg/m ³) NO ₂ , 6 hr/d for 7 d	
†Farraj et al. (2016)	Whole body inhalation with filtered air controls	5.5 hr after exposure
Rat (Spontaneously Hypertensive)	300 ppb (0.3 ppm) NO ₂ , continuous for 3 hr	• SBP, DBP, pulse pressure, QA interval (NS)
12-wk-old, males		
n = 6/group		
†Ji et al. (2022)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	• HR and BP (NS)
6-wk-old, males and females		
n = 6–9/group		

List of abbreviations in alphabetical order: BP = blood pressure; d = day; DBP = diastolic blood pressure; hr = hour; HR = heart rate; min = minute; mo = month; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; SBP = systolic blood pressure; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↑/↓ = at least one experimental group had a statistically significant increase and at least one experimental group has a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-8 Epidemiologic studies of short-term oxides of nitrogen exposure and venous thromboembolism

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Dales et al. (2010)	Hospital admissions for VT	Fixed site monitor	NO ₂ (ppb)	Hospital Records	Poisson Regression	RR (95% CI) ^b
Instituto Nacional De Estadísticas		Averaging time: NO ₂ - 24-hour average	Cerrillos Mean = 44.4±33.02		Adjusted for: long-term trends, day of the week and average humidex	Pulmonary Embolism: 1.08 (1.05, 1.12) VTE: 1.10 (1.04, 1.16)
Population n = 5,400,000			Las Condes			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Santiago Province, Chile April 1998–August 2005 Time-series		Exposure years: 1998–2005	Mean = 52.77±30.21 Overall Mean = 44.73±29.25 Parque Mean = 44.72±32.7 Pudahuel Mean = 40.1±21.78			
Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases Myocardial Ischaemia National Audit Project (MINAP) database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST elevation MI, non-ST elevation MI, or troponin-positive acute coronary syndrome.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	National databases with diagnosis information	Logistic Regression Adjusted for: age, sex	β (%) (95% CI) ^b Pulmonary Embolism - lag0–4 d: -2.93 (-6.69, 0.84) Pulmonary Embolism - Male: -4.43 (-9.66, 0.79) Pulmonary Embolism - Female: -1.67 (-6.61, 3.26) Pulmonary Embolism - Age <70: -6.19 (-10.87, -1.51) Pulmonary Embolism - Age ≥70: 1.34 (-4.35, 7.02)
†Li et al. (2022a) UK Biobank N = 389,659 England, Scotland, Wales, U.K. Enrollment: 2006–2010	Excluded participants with venous thromboembolism at baseline, those with missing information on outdoor hours and residential air pollution, and those with missing	LUR Method validation NR Averaging time: NO ₂ - annual average, NO _x - annual average	NO ₂ (ppb) Daily Cumulative Exposure No Venous Thromboembolism Mean = 44.89±33.83 (84.47±63.66 µg/m ³) Venous	Hospital Records	Cox Proportional Hazards Adjusted for: age, sex, ethnicity, Townsend deprivation index, smoking status, drinking status, BMI, healthy diet score, blood pressure	NO HR (95% CI) ^b VTE, lag0: 1.02 (1.01, 1.03) NO ₂ HR (95% CI) ^b

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Follow-up: median 8.25 years Cohort	information on at least one covariate.	Exposure years: 2005–2007, 2010	Thromboembolism Mean = 50.25±35.74 (94.56±67.25 µg/m³) Overall No Venous Thromboembolism Mean = 15.43±4.88 (29.04±9.19 µg/m³) Venous Thromboembolism Mean = 15.5±4.76 (29.2±8.96 µg/m³) NO₂ (ppb) Daily Cumulative Exposure No Venous Thromboembolism Mean = 43.12±47.99 Venous Thromboembolism Mean = 49.52±51.9 Overall No Venous Thromboembolism Mean = 14.62±10.58 Venous Thromboembolism Mean = 15.18±11.16		levels, hypertension, diabetes, and dyslipidemia	VTE, lag0: 1.04 (1.02, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† de Miguel-Diez et al. (2016)	Excluded all subject that has in any diagnosis position the following: pneumonia, influenza, upper respiratory infections, urinary tract infections, myocardial infarction, and congestive heart failure	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2000–2013	NO ₂ (µg/m ³) Figure Only	Hospital Discharge	Conditional Logistic Regression Adjusted for: time stratification, meteorological factors	OR (95% CI) ^c Pulmonary Thromboembolism - 1 week avg, Lag 0: 1.02 (0.99, 1.04) Pulmonary Thromboembolism - 1.5 week avg, Lag 0: 1.00 (0.99, 1.02) Pulmonary Thromboembolism - 2 week avg, Lag 0: 0.99 (0.98, 1.01) Pulmonary Thromboembolism - 3 week avg, Lag 0: 1.02 (1.00, 1.04)
Spanish Minimum Basic Data Set (MBDS)						
Admissions N = 105,117						
Spain						
January 1, 2001–December 31, 2013						
Data collected and analyzed in 2015.						
Case-crossover						

List of Abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; HR = hazard ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO = nitric oxide; NO_x = nitrogen oxides; NR = not reported; ppb = parts per billion; O₃ = ozone; OR = odds ratio; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-9 Epidemiologic studies of short-term oxides of nitrogen exposure and aggregated cardiovascular effects

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Ballester et al. (2006)	Patients admitted to hospital with CVD	Central site monitor	NO ₂ (ppb)	Emergency hospital admissions	Poisson	β (%) (95% CI) ^b Lag 0: 1.43 (0.26, 2.60)
n = NR			Barcelona			
Valencia, Barcelona, Granada,		Averaging time: NO ₂ - 24-hour	Mean = 27.4 (51.5 µg/m ³)		Adjusted for: meteorological variables, influenza,	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Seville, Huelva, Spain		average	P10 = 15.7 (29.5 µg/m ³)		calendar variables, unusual events, seasonal trends	
1995–1999		Exposure years: 1995–1999	P90 = 39.5 (74.4 µg/m ³)			
Time-series			Bilbao Mean = 27.4 (51.6 µg/m ³) P10 = 19.6 (36.9 µg/m ³) P90 = 35.4 (66.7 µg/m ³)			
			Castellon Mean = 12.4 (23.4 µg/m ³) P10 = 6.06 (11.4 µg/m ³) P90 = 20.8 (39.2 µg/m ³)			
			Gijon Mean = 23.2 (43.7 µg/m ³) P10 = 15.5 (29.1 µg/m ³) P90 = 31.8 (59.9 µg/m ³)			
			Granada Mean = 35 (65.9 µg/m ³) P10 = 24.6 (46.3 µg/m ³) P90 = 45.8 (86.1 µg/m ³)			
			Huelva			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 16.3 (30.7 $\mu\text{g}/\text{m}^3$) P10 = 9.35 (17.6 $\mu\text{g}/\text{m}^3$) P90 = 24.5 (46.1 $\mu\text{g}/\text{m}^3$)			
			Madrid Mean = 36.4 (68.5 $\mu\text{g}/\text{m}^3$) P10 = 25.8 (48.5 $\mu\text{g}/\text{m}^3$) P90 = 49.7 (93.5 $\mu\text{g}/\text{m}^3$)			
			Oviedo Mean = 26.8 (50.5 $\mu\text{g}/\text{m}^3$) P10 = 17.7 (33.3 $\mu\text{g}/\text{m}^3$) P90 = 36.5 (68.6 $\mu\text{g}/\text{m}^3$)			
			Seville Mean = 23.2 (43.7 $\mu\text{g}/\text{m}^3$) P10 = 14.9 (28.1 $\mu\text{g}/\text{m}^3$) P90 = 32 (60 $\mu\text{g}/\text{m}^3$)			
			Valencia Mean = 40.5 (76.2 $\mu\text{g}/\text{m}^3$) P10 = 29.7 (55.9 $\mu\text{g}/\text{m}^3$) P90 = 52.9 (99.6 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Zaragoza Mean = 25.4 (47.8 µg/m ³) P10 = 13.6 (25.6 µg/m ³) P90 = 40 (75 µg/m ³)			
Fung et al. (2005) n = 11,632 Windsor, Ontario, Canada April 1, 1995–December 31, 2000 Time-series	Daily counts of hospitalization	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: April 1, 1995–December 31, 2000	NO ₂ (ppb) Mean = 38.9±12.3 Min = 0 Max = 117	Hospital admissions	APHEA2 Adjusted for: weather, seasonal trends	β (%) (95% CI) ^b Lag 0–1, 65+ yrs: 1.13 (-3.00, 5.25)
Ito et al. (2011) New York City Department of Health and Mental Hygiene (NYCDOHMH) n = NR New York City, NY, U.S. 2000–2006 Time-series	Hospitalization records who type of admission was emergency or urgent only; ≥40 years of age	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2008	NO ₂ (ppb) All Year Mean = 27.8±8.8 IQR = 11.5 Cold Season Mean = 30±8.9 Warm Season Mean = 27.5±8.6	ED visits	Poisson Adjusted for: temporal trends, day of week, same day, delayed temperature effects	β (%) (95% CI) ^b Lag 0: 4.00 (2.87, 5.13)
Larrieu et al. (2007) n = NR Paris, Bordeaux, Le Havre, Lille, Lyon, Marseille, Rouen,	Hospitalizations for cardiovascular diseases in study area	Fixed site monitor Averaging time: NO ₂ - annual average	NO ₂ (ppb) Bordeaux Mean = 11.9 (22.3 µg/m ³)	Hospitalization	Poisson Regression Adjusted for: temperature, holidays, influenza periods	ERR (95% CI) ^b Lag 0–1: 1.00 (0.13, 7.90)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Toulouse, France 1998–2003 Time-series		Exposure years: 1998–2003	Le Havre Mean = 13.7 (25.8 μg/m ³) Lille Mean = 17.4 (32.7 μg/m ³) Lyon Mean = 24.9 (46.8 μg/m ³) Marseille Mean = 19.3 (36.4 μg/m ³) Paris Mean = 23.6 (44.4 μg/m ³) Rouen Mean = 16.2 (30.4 μg/m ³) Toulouse Mean = 14 (26 μg/m ³)			
Linn et al. (2000) n = NR Los Angeles, CA, U.S. 1992–1995 Time-series	Excluded patients younger than 30 years of age and prescheduled hospital admissions.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1992–1995	NO ₂ (ppb) Autum Mean = 4100±1400 (4.1±1.4 ppm) Min = 1600 (1.6 ppm) Max = 8400 (8.4 ppm)	Hospital admissions	Poisson Regression Adjusted for: temporal variation, weather	β (%) (95% CI) ^b Lag 0: 2.82 (2.02, 3.62)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Spring Mean = 2800±900 (2.8±0.9 ppm) Min = 1100 (1.1 ppm) Max = 6100 (6.1 ppm) Summer Mean = 3400±1000 (3.4±1 ppm) Min = 700 (0.7 ppm) Max = 6700 (6.7 ppm) Winter Mean = 3400±1300 (3.4±1.3 ppm) Min = 1100 (1.1 ppm) Max = 9100 (9.1 ppm)			
Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases Myocardial Ischaemia National Audit Project (MINAP) database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST elevation MI, non-ST elevation MI, or	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	National Database	Logistic Regression Adjusted for: age, sex	β (%) (95% CI) ^b CVD HAS, lag 0–4: 1.42 (0.71, 2.13) CVD <70: 0.08 (-0.92, 1.09) CVD ≥70 2.43 (1.51, 3.35) CVD Male: 1.42 (0.46, 2.38) CVD Female: 1.42 (0.42, 2.43)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	troponin-positive acute coronary syndrome.					
Peel et al. (2007)	NR	Fixed site monitor	NO ₂ (ppb)	ED visits	Case-crossover framework	OR (95% CI) ^b Lag 0–2: 1.03 (1.01, 1.04)
Study of Particles and Health in Atlanta (SOPHIA)		Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average	Absolute differences between average level on case days and control days 1-hour Mean = 16.3±12.7 P10 = 2.8 P90 = 32.8		Adjusted for: time stratification, cubic splines for average daily temperature and dew point temperature	
Emergency department visits n = 4,407,535		Exposure years: 1993–2000	Daily levels 1-hour Mean = 45.9±17.3 P10 = 25 P90 = 68			
Atlanta, GA, U.S.						
1993–2000						
Case-crossover						
Sarnat et al. (2013)	Patients going to ED for CVD event	Fixed site monitor, Dispersion model	NO _x (ppm)	ED visits	Poisson	RR (95% CI) ^b lag 02, AERMOD: 1.01 (1.00, 1.02) Lag 02, background: 1.03 (1.01, 1.06) lag 02, central site: 1.00 (1.00, 1.01) Lag 02, Hybrid background-AERMOD: 1.01 (1.00, 1.02)
n = 101,177		Averaging time: NO ₂ - 24-hour average	Median = 30 (0.03 ppm) Min = 1.3 (0.0013 ppm) Max = 410 (0.41 ppm)		Adjusted for: temperature, relative humidity, and barometric pressure, weekly influenza	
Atlanta, GA, U.S.		Exposure years: NA	P25 = 18 (0.018 ppm) P75 = 54 (0.054 ppm)			
1999–2002						
Time-series						
Simpson et al. (2005)	IHD Hospital Admission Events	Central site monitor	NO ₂ (ppb)	Hospital records	APHEA2	RR (95% CI) ^b Lag 0–1: 1.06 (1.04, 1.08)
n = NR		Averaging time: NO ₂ - 24-hour	Brisbane Mean = 21.4 Min = 2.1		Adjusted for: temporal	
Perth, Sydney, Melbourne,						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Brisbane, Australia		average	Max = 63.3		trends, seasonality, weather	
January 1996–December 1999		Exposure years: 1996–1999	Melbourne Mean = 23.7 Min = 4.4 Max = 66.7			
Time-series			Perth Mean = 16.3 Min = 1.9 Max = 41			
			Sydney Mean = 23.7 Min = 6.5 Max = 59.4			
Son et al. (2013)	Individuals hospitalized due to allergic diseases, asthma, croup, pneumonia, bronchiolitis, respiratory infection (including bronchitis, chronic obstructive pulmonary disease, and pneumonitis), or cardiovascular diseases.	Central site monitor	NO ₂ (ppb)	Hospital admissions	Bayesian	β (%) (95% CI) ^b Lag 0:
n = NR			Busan 0 to ≥ 75 yr Mean = 23.3 $\pm$ 8.4		Adjusted for: daily mean temperature, relative humidity, barometric pressure, day of the week, time trends	3.61 (1.72, 5.49)
Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, Ulsan, Jeju, South Korea		Averaging time: NO ₂ - 24-hour average	Daegu 0 to ≥ 75 yr Mean = 24.5 $\pm$ 9.6			
January 2003–December 2008		Exposure years: January 2003–December 2008	Daejeon 0 to ≥ 75 yr Mean = 19.7 $\pm$ 7.7			
Cross-Sectional			Gwangju 0 to ≥ 75 yr Mean = 21.6 $\pm$ 8.7			
			Incheon 0 to ≥ 75 yr Mean = 28.8 $\pm$ 11.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Jeju 0 to ≥75 yr Mean = 11.5±4.5 Overall 0 to ≥75 yr Fall Mean = 24.1±8.8 0 to ≥75 yr Spring Mean = 24.6±7.7 0 to ≥75 yr Summer Mean = 17.9±5.7 0 to ≥75 yr Winter Mean = 26.8±9.4 Seoul 0 to ≥75 yr Mean = 36.9±12.6 Ulsan 0 to ≥75 yr Mean = 20.5±7.3			
Tolbert et al. (2007) n = 10,206,389 visits Atlanta, GA, U.S. Follow-up: 1993–2004 Time-series	Billing records for all emergency department visits for residents of the Atlanta MSA at the time of the visit	Central site monitor Averaging time: NO ₂ - 1-hour max Exposure years: 1993–2004,	NO ₂ (ppb) Mean = 43.2 Median = 41 (IQR 23) Min = 1 Max = 191 P10 = 22 P25 = 31	ED visit	Poisson Adjusted for: day of week, hospital entry and holidays, time, temperature, dew point temperature	RR (95% CI) ^b Lag02: 1.01 (1.00, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P75 = 54 P90 = 66			
von Klot et al. (2005)	Incident myocardial infarction survivors: aged 35 years or more who had their first myocardial infarction during the recruitment period; excluded recurrent events	Fixed site monitor $r^2 = 0.55$; correlation was 0.77 Averaging time: NO ₂ - 24-hour average Exposure years: 1992–2000	NO ₂ (ppb) Augsburg Mean = 26.4 (49.6 µg/m ³) P5 = 16 (30 µg/m ³) P25 = 21.1 (39.7 µg/m ³) P75 = 30.4 (57.2 µg/m ³) P95 = 40 (75.3 µg/m ³) Barcelona Mean = 25.4 (47.7 µg/m ³) P5 = 9.6 (18 µg/m ³) P25 = 18 (34 µg/m ³) P75 = 32 (60 µg/m ³) P95 = 44 (83 µg/m ³) Helsinki Mean = 16 (30.1 µg/m ³) P5 = 6.9 (13 µg/m ³) P25 = 11.3 (21.2 µg/m ³) P75 = 19.5 (36.7 µg/m ³) P95 = 28.1 (52.9 µg/m ³) Rome Mean = 37 (70 µg/m ³)	Hospital records	Poisson Regression Adjusted for: meteorology, seasonality	RR (95% CI) ^b Lag 0, Cardiac Readmissions: 1.16 (1.07, 1.26)
N = 22,006 Stockholm, Rome, Augsburg, Germany, Helsinki, Barcelona, Spain, Sweden, Spain, Italy, Germany, Finland Recruitment: 1992–2000 Follow-up: 29 th day after index event until center-specific end of the follow-up period Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P5 = 24.9 (46.8 $\mu\text{g}/\text{m}^3$) P25 = 32.2 (60.5 $\mu\text{g}/\text{m}^3$) P75 = 42 (79.1 $\mu\text{g}/\text{m}^3$) P95 = 50.1 (94.3 $\mu\text{g}/\text{m}^3$) Stockholm Mean = 12.1 (22.8 $\mu\text{g}/\text{m}^3$) P5 = 5.47 (10.3 $\mu\text{g}/\text{m}^3$) P25 = 8.5 (16 $\mu\text{g}/\text{m}^3$) P75 = 15 (28 $\mu\text{g}/\text{m}^3$) P95 = 20.9 (39.4 $\mu\text{g}/\text{m}^3$)			
†Chen et al. (2022b) EAC N = 1,626,017 Beijing, Guangzhou, Jinan, Luoyang, Zhengzhou, Xuchang, Zhoushan, China 2014–2019 Time-series	EAC counts due to pregnancy, traffic accidents, drowning, electric shock, and suicide events were excluded	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2014–2019	NO ₂ (ppb) Beijing Mean = 13.56±9.09 (25.51±17.1 $\mu\text{g}/\text{m}^3$) Guangzhou Mean = 24.7±10.25 (46.48±19.28 $\mu\text{g}/\text{m}^3$) Jinan Mean = 27.7±11.99 (52.1±22.57 $\mu\text{g}/\text{m}^3$) Luoyang Mean = 23.62±9.263 (44.45±17.43 $\mu\text{g}/\text{m}^3$)	Ambulance Records	Poisson Adjusted for: public holiday, day of the week, seasonal patterns, long-term trends, temperature, relative humidity	β (%) (95% CI) ^b EAC, lag01: 2.75 (0.68, 4.82) EAC, lag01, cold: -0.34 (-2.77, 2.09) EAC, lag01, warm: 1.66 (-0.38, 3.69) EAC, lag01, males: 2.15 (-0.62, 4.91) EAC, lag1, females: 3.58 (0.98, 6.17) EAC, lag01, <65 yrs: 3.65 (0.85, 6.45) EAC, lag01, ≥65 yrs: 2.60 (0.77, 4.42)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Xuchang Mean = 20.17±8.657 (37.96±16.29 µg/m ³)			EAC, lag01, PM _{2.5} : 2.52 (-0.75, 5.80)
			Zhengzhou Mean = 25.22±9.773 (47.45±18.39 µg/m ³)			EAC, lag01, O ₃ : 2.26 (-0.32, 4.84)
			Zhoushan Mean = 10.44±5.8 (19.64±11 µg/m ³)			
† Ebelt et al. (2022) n = 230,718 Atlanta, GA, U.S. January 2009–December 2013 Time-series	Cardiorespiratory ED visits of patients living in Atlanta	Central site monitor, CMAQ, Spatiotemporal/geospatial model, LUR Averaging time: NO ₂ - 1-hour max Exposure years: 2009–2013	NO ₂ (ppb) Central monitor Median = 29.7 (IQR 17.9) Max = 82.5 CMAQ Median = 20.9 (IQR 22.8) Max = 119.9 CMAQ data fusion Median = 16.7 (IQR 15.4) Max = 117.3 CMAQ kriging Median = 12.8 (IQR 16) Max = 88.7 IDW Median = 19.5 (IQR 14.2) Max = 82.2	ED visits	Poisson Adjusted for: Time, meteorology	RR (95% CI) ^b CVD ED, lag 0–7/central site: 1.02 (1.00, 1.04) CVD ED, lag 0–7/Full Spatial (Kriging): 1.04 (1.01, 1.07) CVD ED, lag 0–7/Full spatial (LUR): 0.98 (0.95, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Kriging Median = 17.3 (IQR 13.5) Max = 79.5 LUR Median = 13.1 (IQR 14.7) Max = 75.9 Site average Median = 16.8 (IQR 14.3) Max = 70.8			
† Groves et al. (2020) n = 46,96 Victoria, New South Wales, Australia January 1, 2008–December 31, 2016 Time-series	Patients in the Adult Patient Database	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2007–2016	NO ₂ (ppb) Mean = 8 P25 = 5 P75 = 12	Intensive Care Society Adult Patient Database	Logistic Regression Adjusted for: temperature, humidity, flu activity score, public holidays	RR (95% CI) ^b CVD - lag 02: 1.04 (0.09, 12.50)
† Ha et al. (2017) Consortium on Safe Labor (2002-2008) N = 680 U.S.	Included singleton pregnancies that were complicated by cardiovascular events at labor/delivery. Excluded women who had a repeated event in a second pregnancy.	CMAQ, Fixed site monitor Method validation NR Averaging time: NO _x - 24-hour average	NO _x (ppb) Overall Mean = 26.39 IQR = 22.24 Min = 4.66 Max = 134.76 P25 = 12.06 P75 = 34.29	Hospital discharge records	Logistic Regression Adjusted for: time stratification, meteorological variables	OR (95% CI) ^b CVD, lag 0–7: 1.29 (1.05, 1.59) CVD, lag 0: 1.26 (1.07, 1.49) CVD, lag 1: 1.28 (1.07, 1.53) CVD, lag 6: 1.45 (1.21, 1.73)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
2002–2008						CVD, lag 7: 1.00 (0.83, 1.20)
Case-crossover		Exposure years: 2002–2008				
[†] Krall et al. (2018)	NR	Hybrid model	NO ₂ (ppb)	ED visits	Poisson Regression	NO ₂
n = NR		Method validation NR	Atlanta Mean = 21.6±7		Adjusted for: weekday, season, holidays, meteorology, temporal trends, and hospital reporting data for each day	RR (95% CI) ^b CVD - lag 0 MCM: 1.03 (1.00, 1.05)
Atlanta, GA, St. Louis, MO, Dallas, TX, Pittsburgh, Pennsylvania, Birmingham, AL, U.S.		Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max	Birmingham Mean = 13.2±4.3			NO _x
2002–2008		Exposure years: 2002–2008	Dallas Mean = 19.7±8.2			RR (95% CI) ^b CVD - lag 0 MCM: 1.02 (1.00, 1.04)
Time-series			Pittsburgh Mean = 26.5±8.1			
			St. Louis Mean = 21.3±6.3			
			NO _x (ppb)			
			Atlanta Mean = 45.6±30.5			
			Birmingham Mean = 24.5±13.8			
			Dallas Mean = 41.4±32.2			
			Pittsburgh Mean = 56±35.8			
			St. Louis Mean = 51.3±30.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Requia et al. (2023) Respiratory n = 12,621,970 Circulatory n = 11,169,123 Brazil 2008–2018 Time-series	Hospital admissions for circulatory and respiratory diseases	Spatiotemporal/geospatial model, Ensemble machine learning model Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2008–2018	NO ₂ (ppb) Overall Mean = 1.51±1.48 Min = 0.1 Max = 10.05 P25 = 0.6 P75 = 1.88	Hospital admissions	Poisson Adjusted for: temperature, relative humidity, precipitation	RR (95% CI) ^b Cardiorespiratory, 15-d lag: 1.37 (1.24, 1.51) Circulatory 15-d lag, Ages 15–25: 0.81 (0.62, 1.05) Circulatory 15-d lag, Ages 26–35: 0.87 (0.73, 1.04) Circulatory 15-d lag, Ages 36–45: 0.95 (0.72, 1.27) Circulatory 15-d lag, Ages 46–55: 0.92 (0.84, 1.00) Circulatory 15-d lag, Ages 56–65: 0.91 (0.77, 1.08) Circulatory 15-d lag, Ages 65+: 0.94 (0.78, 1.12) Circulatory 15-d lag, females: 0.94 (0.75, 1.19) Circulatory 15-d lag, males: 0.96 (0.85, 1.09) Circulatory, 15-d lag: 0.95 (0.81, 1.11)
† Rodríguez-Villamizar et al. (2019) Individual Records on the Provision of Services (RIPS) N = 3,515,913 ED visits Bucaramanga, Bogota, Cali, Medellin, Colombia 2011–2014 Time-series	ED visits for respiratory and circulatory diseases in 4 study areas	Fixed site monitor Averaging time: NO ₂ - 24-hour average, NO ₂ - 8-hour max Exposure years: 2011–2014	NO ₂ (ppb) Bogota Mean = 17.19 (32.34 µg/m ³) Median = 16.84 (31.69 µg/m ³) Min = 6.516 (12.26 µg/m ³) Max = 33.2 (62.5 µg/m ³) P25 = 14.16 (26.65 µg/m ³) P75 = 19.94 (37.52 µg/m ³)	Medical Services	Poisson Regression Adjusted for: temperature, relative humidity, precipitation	β (%) (95% CI) ^b Circulatory ED, lag01: 11.89 (0.75, 23.02) Circulatory ED, lag01, CO: 11.89 (0.75, 23.02) Circulatory ED, lag01, O ₃ : -0.02 (-0.15, 0.12) Circulatory ED, lag01, PM _{2.5} : 13.38 (0.03, 26.72) Circulatory ED, lag01, PM ₁₀ : 9.87 (-2.27, 22.01) Circulatory ED, lag01, SO ₂ : -0.03 (-0.24, 0.18) Circulatory ED, lag01, Traffic

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Bucaramanga Mean = 12.48 (23.48 $\mu\text{g}/\text{m}^3$) Median = 11.9 (22.4 $\mu\text{g}/\text{m}^3$) Min = 2.63 (4.95 $\mu\text{g}/\text{m}^3$) Max = 30.22 (56.86 $\mu\text{g}/\text{m}^3$) P25 = 6.59 (12.4 $\mu\text{g}/\text{m}^3$) P75 = 17.1 (32.17 $\mu\text{g}/\text{m}^3$)			related PM _{2.5} : 13.38 (0.03, 26.72) Circulatory ED, lag01, Traffic related PM ₁₀ : 9.87 (-2.27, 22.01)
			Cali Mean = 7.68 (14.45 $\mu\text{g}/\text{m}^3$) Median = 7.76 (14.6 $\mu\text{g}/\text{m}^3$) Min = 1.5 (2.8 $\mu\text{g}/\text{m}^3$) Max = 19.8 (37.3 $\mu\text{g}/\text{m}^3$) P25 = 6.01 (11.3 $\mu\text{g}/\text{m}^3$) P75 = 9.19 (17.3 $\mu\text{g}/\text{m}^3$)			
			Medellin Mean = 20.1 (37.83 $\mu\text{g}/\text{m}^3$) Median = 19.6 (36.9 $\mu\text{g}/\text{m}^3$) Min = 5.772 (10.86 $\mu\text{g}/\text{m}^3$) Max = 56.97 (107.2 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P25 = 16.6 (31.3 $\mu\text{g}/\text{m}^3$) P75 = 23.19 (43.63 $\mu\text{g}/\text{m}^3$) Overall Mean = 15.3 (28.8 $\mu\text{g}/\text{m}^3$) Median = 15.56 (29.27 $\mu\text{g}/\text{m}^3$) Min = 1.5 (2.8 $\mu\text{g}/\text{m}^3$) Max = 56.97 (107.2 $\mu\text{g}/\text{m}^3$) P25 = 10.4 (19.5 $\mu\text{g}/\text{m}^3$) P75 = 19.8 (37.3 $\mu\text{g}/\text{m}^3$)			
†Seposo et al. (2020) n = 1,452,505 Japan April 2013–March 2016 Case-crossover	All-age cardiorespiratory outpatient clinic visits across 21 cities in Japan	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: April 2013–March 2016	NO ₂ (ppb) Mean = 13.23±7.13	Outpatient Records	Poisson Adjusted for: flu, temperature, region	β (%) (95% CI) ^b Outpatient CVD visits, lag 0: 5.52 (4.29, 6.75) Outpatient CVD visits, lag 0, O ₃ : 5.98 (4.73, 7.23) Outpatient CVD visits, lag 0, PM _{2.5} : 9.62 (8.22, 11.02)
†Shin et al. (2022) n = NR Montreal, Halton, Ontario, London, Ontario, Toronto, Ontario, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Sudbury, Halifax, Saint John,	Mortality and hospitalization daily counts (all-cause, circulatory, and respiratory) classified by ICD-9 and 10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Population-weighted Cold season Mean = 20±4 Warm season Mean = 16±4 Year Mean = 18	National Database	Poisson, Bayesian Adjusted for: day of week, time, temperature	β (%) (95% CI) ^b Circulatory, lag 0/females: 1.40 (0.20, 2.60) Circulatory, lag 0/males: 3.60 (2.30, 4.90) Cold, females: 2.40 (0.90, 3.90) Cold, males: 2.40 (0.30, 4.50)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Quebec City, Ottawa, Durham, York, Peel, Niagara, Waterloo, Sarnia, Sault Sainte Marie, Regina, Saskatoon, Calgary, Canada		Exposure years: 1984–2012	Min = 8 Max = 28			Warm, females: 0.40 (-3.40, 4.20) Warm, males: 5.20 (3.50, 6.90)
1984–2012						
Time-series						
†Ye et al. (2016)	NR	Fixed site monitor	NO ₂ (ppb)	ED visits	Bayesian hierarchical Poisson linear model	RR (95% CI) ^b CVD ED, lag 0: 1.00 (0.99, 1.02)
n = 3,224 days		Method validation NR	Overall, 1-h max Median = 39.3 P25 = 29.5 P75 = 50		Adjusted for: temporal trends and meteorology	
Atlanta, GA, U.S.		Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average				
August 1998–December 2008						
Cohort		Exposure years: 1998-2008				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yoo et al. (2018) Statewide Planning and Research Cooperative System SPARCS Patients n = 5,798 Population n = 1,135,474 Erie County, New York, Niagara, U.S. Records collected: January 1, 2011–December 31, 2011 Cohort	NR	CMAQ, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2011	NO ₂ (ppm) Overall Mean = 6.26±4.31 Median = 5.15 Min = 0.38 Max = 24.29 P25 = 2.87 P75 = 8.59	ED Visits	Bayesian hierarchical Poisson linear regression Adjusted for: daily meteorological data, SES, total number of health care facilities, percentage parks and grocery stores	RR (95% CI) ^c ED visits, spatial random effect: 1.14 (1.01, 1.30) ED visits, Poisson regression model: 0.93 (0.83, 1.04)

List of Abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; ED = emergency department; HR = hazard ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO = nitric oxide; NO_x = nitrogen oxides; NR = not reported; ppb = parts per billion; O₃ = ozone; OR = odds ratio; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-10 Epidemiologic studies of short-term oxides of nitrogen exposure and subclinical effects

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Baja et al. (2010) Normative Aging Study (NAS) N = 580	Community dwelling, healthy men; excluded those where the recording time of ECG was <3.5 minutes	Fixed site monitor Averaging time: NO ₂ - 1-hour max	NO ₂ (ppm) 0 HR Lag Mean = 0.021±0.008 Median = 0.02 (IQR	Supervised measurements	Mixed effect linear regression Adjusted for: age; BMI; MAP; cholesterol;	β (milliseconds) (95% CI) ^c QTc - diabetic: 7.10 (-0.12, 14.32) QTc - ever smoker: 1.97 (-2.02, 5.95)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Valid readings n = 926 Greater Boston Area, U.S. Enrollment: 1963–1968 Follow-up: 2000–2008 Cohort		Exposure years: 2000–2008	0.01) 10 HR Lag Mean = 0.019±0.009 Median = 0.018 (IQR 0.013)		diabetic status (doctor's diagnosis of disease or FBG >126 mg/dL vs. no diagnosis or FBG ≤126 mg/dL); alcohol intake (≥2 drinks/day, <2 drinks/day); cigarette smoker (never, ever); use of alpha blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonist/blockers, beta blockers, or calcium channel blockers; day of the week (Monday through Sunday); temperature; and a natural spline for long-term time trend (date)	QTc - high GSS: 3.50 (-1.86, 8.87) QTc - low GSS: 0.29 (-4.56, 5.14) QTc - never smoker: 4.18 (-2.41, 10.77) QTc - non-diabetic: 1.22 (-2.67, 5.12) QTc - nonobese: 2.28 (-1.65, 6.21) QTc - obese: 4.02 (-3.01, 11.04) QTc: 2.56 (-0.88, 6.00)
Barclay et al. (2009) n = 132 Scotland January 2003–May 2005 Panel	Non-smoking patients with chronic heart failure.	Central site monitor Averaging time: 3-day cumulative personal exposure Exposure years: January 2003–May 2005	NO ₂ (ppb) Mean = 30.1 Min = 4.626 Max = 76.42	Supervised measurements	Mixed effect linear regression Adjusted for: temperature, days since beginning of study, annual trends, and a subject indicator	NO β (Percent change (%)) (95% CI) ^b C reactive protein - NO city: 0.89 (-4.69, 6.47) d-dimer - NO city: -0.32 (-2.81, 2.18) E-selectin - NO city: 0.48 (-1.02, 1.99) Factor VII - NO city: 0.34 (-1.35, 2.02) Fibrinogen - NO city: 0.20 (-1.32, 1.71) Haematocrit - NO city: 0.10 (-0.23, 0.43) Haemoglobin - NO city:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						0.01 (-0.33, 0.31)
						IL-6 - NO city:
						2.77 (-2.81, 8.34)
						Mean corpuscular haemoglobin - NO city:
						-0.04 (-0.24, 0.17)
						Platelets - NO city:
						0.25 (-0.56, 1.05)
						vWF - NO city:
						3.52 (1.09, 5.95)
						WBC - NO city:
						-0.71 (-1.64, 0.22)
						NO ₂
						β (Percent change (%)) (95% CI) ^b
						C reactive protein - NO ₂ city:
						0.42 (-5.26, 6.11)
						C reactive protein - NO ₂ personal:
						-2.52 (-7.99, 2.95)
						d-dimer - NO ₂ city:
						-2.43 (-2.78, 2.29)
						d-dimer - NO ₂ personal:
						-0.45 (-2.99, 2.10)
						E-selectin - NO ₂ city:
						1.16 (-0.37, 2.70)
						E-selectin - NO ₂ personal:
						-0.82 (-2.34, 0.71)
						Factor VII - NO ₂ city:
						0.27 (-1.44, 1.99)
						Factor VII - NO ₂ personal:
						-0.14 (-1.90, 1.63)
						Fibrinogen - NO ₂ city:
						-0.22 (-1.76, 1.32)
						Fibrinogen - NO ₂ personal:
						-2.36 (-3.90, -0.82)
						Haematocrit - NO ₂ city:
						-0.02 (-0.35, 0.32)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						Haematocrit - NO ₂ personal: -0.42 (-0.75, -0.09) Haemoglobin - NO ₂ city: 0.04 (-0.29, 0.36) Haemoglobin - NO ₂ personal: -0.26 (-0.59, 0.06) IL-6 - NO ₂ city: 6.27 (0.59, 11.94) IL-6 - NO ₂ personal: -1.61 (-7.15, 3.94) Mean corpuscular haemoglobin - NO ₂ city: 0.05 (-0.16, 0.26) Mean corpuscular haemoglobin - NO ₂ personal: 0.03 (-0.18, 0.24) Platelets - NO ₂ city: -0.05 (-0.87, 0.77) Platelets - NO ₂ personal: 0.06 (-0.75, 0.86) vWF - NO ₂ city: 2.16 (-0.33, 4.66) vWF - NO ₂ personal: 0.76 (-1.77, 3.29) WBC - NO ₂ city: -0.72 (-1.67, 0.23) WBC - NO ₂ personal: -0.60 (-1.56, 0.36)
Delfino et al. (2010)	Older adults, 65 + years	Personal monitor or sampler	NO ₂ (ppb)	Supervised measurements	Mixed effect linear regression	NO ₂
n = 60			Cool Season			β (Percent change (%)) (95% CI) ^b
Los Angeles, CA, U.S.		Averaging time: NO _x - 24-hour average	Mean = 28.3±11.8 Median = 29.5 Min = 3.78 Max = 55.7		Adjusted for: temperature	Exhaled NO: 0.37 (-0.40, 1.15) IL-6: 0.40 (-0.06, 0.87)
2005–2006 and 2006–2007		Exposure years:	Warm Season			NO _x

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Panel		2005–2006 and 2006–2007	Mean = 26.4±12 Median = 25.7 Min = 4.52 Max = 59.8 NO _x (ppb) Cool Season Mean = 53.9±36.1 Median = 47.5 Min = 4.26 Max = 188 Warm Mean = 37.2±22.4 Median = 33.3 Min = 3.7 Max = 112			β (Percent change (%)) (95% CI) ^b Exhaled NO: 0.35 (-2.00, 2.69) IL-6: 2.35 (1.01, 3.69)
Henneberger et al. (2005) N = 56 Erfurt, Germany October 16, 2000–April 27, 2001 Panel	Subjects were required to be male, at least 50 years of age, and have doctor-diagnosed coronary artery disease. Exclusion criteria were: current smokers, patients with pacemakers, patients with recent myocardial infarction, recent bypass surgery or coronary angioplasty, bundle-branch blocks, or type 1 diabetes, and patients on anticoagulation therapy.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, NO - 24-hour average Exposure years: 2000–2001	NO ₂ (μg/m ³) Overall Mean = 34.3±11.4 Median = 34 (IQR 17.2) Min = 8 Max = 68.4 P25 = 25.3 P75 = 42.5 NO ₂ (μg/m ³) Overall Mean = 24.3±27.8 Median = 12.3 (IQR 23.5) Min = 4 Max = 137.6	Supervised measurements	Generalized additive models Adjusted for: indicator variable for each subject, long-term time trend, temperature, relative humidity, barometric pressure, and weekday of the visit	β (milliseconds) (95% CI) ^c QTc: 4.47 (1.02, 7.93)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P25 = 6.8 P75 = 30.3			
Williams et al. (2012)	Participants has to be at least 18 years of age, non-smoking, and live in a non-smoking household. The only health exclusion for the cohort was their need to be ambulatory.	Personal monitor or sampler	NO ₂ (ppb)	Supervised measurements	Mixed effect linear regression	β (millimeters) (95% CI) ^b Brachial artery diameter - lag 1: 0.08 (-0.25, 0.42) Brachial artery diameter - lag 2: -0.13 (-0.36, 0.09)
Detroit Exposure and Aerosol Research Study (DEARS)		Method validation NR	Ambient Overall Mean = 24±11.4 Median = 23 (IQR 10)		Adjusted for: age, gender, race, BMI, temperature, season, indicator for use/non-use of medication	
N = 65		Averaging time: NO ₂ - 24-hour average	Min = 0 Max = 100 P25 = 18 P75 = 28			
Detroit, MI, U.S.		Exposure years: 2005–2007	Personal Low ETS Mean = 24.8±10.6 Median = 23 Min = 5 Max = 62 Overall Mean = 27.6±19.5 Median = 24 Min = 0 Max = 191 Vest Mean = 27±18.6 Median = 24 Min = 5 Max = 191			
2005–2007						
Panel						
†Biel et al. (2020)	NR	Fixed site monitor	NO ₂ (ppb)	Supervised measurements	Mixed effect linear regression	β (Index) (95% CI) ^b RHI + noise: -0.38 (-1.34, 0.59) RHI: -0.45 (-1.45, 0.55) β (milliseconds) (95% CI) ^b rMSSD:
N = 46		Method validation NR	30-min Average Mean = 10.5±3.5 Median = 10.5 (IQR 4)		Adjusted for: temperature, alcohol intake (yes/no) and	
Toronto, Canada		Averaging time: NO ₂ - 24-hour	P5 = 5.1			
May 2016–August 2016						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort		average	P25 = 8.2 P75 = 12.3 P95 = 15.7		caffeine intake (yes/no) in the last 24 hours	17.56 (-16.59, 51.70) SDNN: 30.52 (-25.07, 86.11) β (milliseconds squared) (95% CI) ^b HF: -208.89 (-1370.37, 952.59) LF: 699.26 (-940.00, 2338.52) β (Ratio) (95% CI) ^b LF/HF: -1.48 (-5.85, 2.89)
		Exposure years: 2016	Daily Visit Average Mean = 11.8 $\pm$ 3 Median = 11.3 (IQR 2.7) P5 = 7.5 P25 = 10 P75 = 12.7 P95 = 17.4			
[†] Chen et al. (2021) n = 62 Research Triangle, NC, U.S. October 2016–September 2019 Panel	Healthy adults 25–55 years of age, with no history of respiratory or cardiovascular disease, non-smoker for year prior, not taking B-adrenergic receptor blockers or anti-inflammatory drugs	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2016–2019	NO ₂ (ppb) Mean = 5.3 $\pm$ 3.8 IQR = 3.8 Min = 0.8 Max = 24.2	Supervised measurements	Generalized mixed models Adjusted for: age, sex, race, BMI, long-term and seasonal trends, day of the week, temperature, and relative humidity Linear regression - mixed effects Adjusted for: age, sex, race, BMI, long-term and seasonal trends, day of the week, temperature, and relative humidity	β (mg/dL) (95% CI) ^b HDL - high omega 3, 5-day moving average: -16.32 (-32.37, -0.26) HDL - high omega 3, lag 0: -6.84 (-16.32, 2.63) HDL - high omega 3, lag 1: -12.63 (-23.42, -1.84) HDL - high omega 3, lag 2: -10.53 (-20.26, -0.79) HDL - high omega 3, lag 3: 2.63 (-8.68, 13.95) HDL - high omega 3, lag 4: -5.26 (-16.05, 5.53) HDL - low omega 3, 5-day moving average: -13.16 (-31.32, 5.00) HDL - low omega 3, lag 0: 2.63 (-8.95, 14.21) HDL - low omega 3, lag 1: -3.16 (-13.68, 7.37) HDL - low omega 3, lag 2: -11.58 (-23.16, 0.00) HDL - low omega 3, lag 3: -8.42 (-19.74, 2.89)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						HDL - low omega 3, lag 4: -0.53 (-10.79, 9.74) LDL - high omega 3, 5-day moving average: -8.42 (-30.00, 13.16) LDL - high omega 3, lag 0: -2.63 (-14.74, 9.47) LDL - high omega 3, lag 1: -2.63 (-17.37, 12.11) LDL - high omega 3, lag 2: -16.32 (-28.95, -3.68) LDL - high omega 3, lag 3: 5.79 (-9.21, 20.79) LDL - high omega 3, lag 4: -5.26 (-19.47, 8.95) LDL - low omega 3, 5-day moving average: -1.58 (-26.05, 22.89) LDL - low omega 3, lag 0: 5.79 (-9.21, 20.79) LDL - low omega 3, lag 1: 9.47 (-5.00, 23.95) LDL - low omega 3, lag 2: -3.16 (-18.42, 12.11) LDL - low omega 3, lag 3: -10.00 (-24.74, 4.74) LDL - low omega 3, lag 4: -3.16 (-16.32, 10.00) Total cholesterol - high omega 3, 5-day moving average: -9.47 (-25.00, 6.05) Total cholesterol - high omega 3, lag 0: -0.53 (-9.21, 8.16) Total cholesterol - high omega 3, lag 1: -2.63 (-12.89, 7.63) Total cholesterol - high omega 3, lag

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						2: -13.68 (-22.89, -4.47) Total cholesterol - high omega 3, lag 3: 0.00 (-10.26, 10.26) Total cholesterol - high omega 3, lag 4: -4.74 (-15.00, 5.53) Total cholesterol - low omega 3, 5-day moving average: -3.68 (-20.79, 13.42) Total cholesterol - low omega 3, lag 0: 4.21 (-6.32, 14.74) Total cholesterol - low omega 3, lag 1: 5.26 (-4.74, 15.26) Total cholesterol - low omega 3, lag 2: -5.79 (-16.32, 4.74) Total cholesterol - low omega 3, lag 3: -8.95 (-19.21, 1.32) Total cholesterol - low omega 3, lag 4: -1.05 (-10.53, 8.42) β (ng/mL) (95% CI) ^b D-dimer - high omega 3, 5-day moving average: 8.42 (-81.32, 98.16) D-dimer - high omega 3, lag 0: 28.95 (-18.68, 76.58) D-dimer - high omega 3, lag 1: 21.05 (-40.53, 82.63) D-dimer - high omega 3, lag 2: -4.21 (-57.11, 48.68) D-dimer - high omega 3, lag 3: -25.79 (-83.42, 31.84)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						D-dimer - high omega 3, lag 4: -30.53 (-84.47, 23.42)
						D-dimer - low omega 3, 5-day moving average: 70.53 (-40.53, 181.58)
						D-dimer - low omega 3, lag 0: 57.89 (-2.11, 117.89)
						D-dimer - low omega 3, lag 1: 55.26 (-7.89, 118.42)
						D-dimer - low omega 3, lag 2: -1.58 (-63.95, 60.79)
						D-dimer - low omega 3, lag 3: 12.63 (-49.74, 75.00)
						D-dimer - low omega 3, lag 4: 1.05 (-52.63, 54.74)
						tPA - high omega 3, 5-day moving average: -0.53 (-39.21, 38.16)
						tPA - high omega 3, lag 0: 13.16 (-9.47, 35.79)
						tPA - high omega 3, lag 1: -2.11 (-28.68, 24.47)
						tPA - high omega 3, lag 2: -8.95 (-31.84, 13.95)
						tPA - high omega 3, lag 3: -15.26 (-41.05, 10.53)
						tPA - high omega 3, lag 4: -2.63 (-28.16, 22.89)
						tPA - low omega 3, 5-day moving average: 30.53 (-15.79, 76.84)
						tPA - low omega 3, lag 0: 11.58 (-16.05, 39.21)
						tPA - low omega 3, lag 1: 2.11 (-23.68, 27.89)
						tPA - low omega 3, lag 2: 9.47 (-18.95, 37.89)
						tPA - low omega 3, lag 3:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						24.21 (-3.68, 52.11)
						tPA - low omega 3, lag 4:
						6.84 (-17.63, 31.32)
						vWF - high omega 3, 5-day moving average:
						41.58 (3.42, 79.74)
						vWF - high omega 3, lag 0:
						12.11 (-8.16, 32.37)
						vWF - high omega 3, lag 1:
						35.26 (9.74, 60.79)
						vWF - high omega 3, lag 2:
						13.68 (-8.42, 35.79)
						vWF - high omega 3, lag 3:
						24.74 (-0.53, 50.00)
						vWF - high omega 3, lag 4:
						-4.74 (-27.63, 18.16)
						vWF - low omega 3, 5-day moving average:
						26.32 (-15.26, 67.89)
						vWF - low omega 3, lag 0:
						28.42 (3.16, 53.68)
						vWF - low omega 3, lag 1:
						22.63 (-1.05, 46.32)
						vWF - low omega 3, lag 2:
						1.05 (-24.21, 26.32)
						vWF - low omega 3, lag 3:
						-10.53 (-34.47, 13.42)
						vWF - low omega 3, lag 4:
						-5.26 (-26.58, 16.05)
						β (Percent change (%)) (95% CI) ^b
						D-dimer - high omega-3 group, 5dMA:
						8.42 (-81.32, 98.16)
						D-dimer - high omega-3 group, lag 0:
						28.95 (-18.68, 76.58)
						D-dimer - high omega-3 group, lag 1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						21.05 (-40.53, 82.63)
						D-dimer - high omega-3 group, lag 2:
						-4.21 (-57.11, 48.68)
						D-dimer - high omega-3 group, lag 3:
						-25.79 (-83.42, 31.84)
						D-dimer - high omega-3 group, lag 4:
						-30.53 (-84.47, 23.42)
						D-dimer - low omega-3 group, 5dMA:
						70.53 (-40.53, 181.58)
						D-dimer - low omega-3 group, lag 0:
						57.89 (-2.11, 117.89)
						D-dimer - low omega-3 group, lag 1:
						71.05 (7.89, 134.21)
						D-dimer - low omega-3 group, lag 2:
						-1.58 (-63.95, 60.79)
						D-dimer - low omega-3 group, lag 3:
						12.63 (-49.74, 75.00)
						D-dimer - low omega-3 group, lag 4:
						1.05 (-52.63, 54.74)
						ET-1 - high omega-3 group, 5dMA:
						-226.84 (-420.26, -33.42)
						ET-1 - high omega-3 group, lag 0:
						30.00 (-71.84, 131.84)
						ET-1 - high omega-3 group, lag 1:
						-9.47 (-130.53, 111.58)
						ET-1 - high omega-3 group, lag 2:
						-54.21 (-172.63, 64.21)
						ET-1 - high omega-3 group, lag 3:
						-134.74 (-263.16, -6.32)
						ET-1 - high omega-3 group, lag 4:
						-120.53 (-241.05, 0.00)
						ET-1 - low omega-3 group, 5dMA:
						-285.26 (-490.79, -79.74)
						ET-1 - low omega-3 group, lag 0:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						-110.53 (-230.53, 9.47)
						ET-1 - low omega-3 group, lag 1:
						-73.68 (-194.47, 47.11)
						ET-1 - low omega-3 group, lag 2:
						-55.79 (-186.05, 74.47)
						ET-1 - low omega-3 group, lag 3:
						-85.26 (-213.95, 43.42)
						ET-1 - low omega-3 group, lag 4:
						-102.63 (-218.42, 13.16)
						FMD - high omega-3 group, 5dMA:
						46.84 (3.16, 90.53)
						FMD - high omega-3 group, lag 0:
						5.26 (-19.47, 30.00)
						FMD - high omega-3 group, lag 1:
						30.00 (0.79, 59.21)
						FMD - high omega-3 group, lag 2:
						30.00 (4.21, 55.79)
						FMD - high omega-3 group, lag 3:
						10.00 (-20.00, 40.00)
						FMD - high omega-3 group, lag 4:
						17.37 (-11.05, 45.79)
						FMD - low omega-3 group, 5dMA:
						0.53 (-48.42, 49.47)
						FMD - low omega-3 group, lag 0:
						-10.53 (-40.00, 18.95)
						FMD - low omega-3 group, lag 1:
						-1.58 (-29.74, 26.58)
						FMD - low omega-3 group, lag 2:
						-6.84 (-37.63, 23.95)
						FMD - low omega-3 group, lag 3:
						-13.16 (-43.68, 17.37)
						FMD - low omega-3 group, lag 4:
						11.05 (-15.79, 37.89)
						HF _n - high omega-3 group, 5dMA:
						-44.21 (-93.42, 5.00)
						HF _n - high omega-3 group, lag 0:
						-10.00 (-37.89, 17.89)
						HF _n - high omega-3 group, lag 1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						-24.74 (-58.42, 8.95)
						HFn - high omega-3 group, lag 2:
						-10.00 (-40.00, 20.00)
						HFn - high omega-3 group, lag 3:
						-37.89 (-71.58, -4.21)
						HFn - high omega-3 group, lag 4:
						-8.42 (-40.53, 23.68)
						HFn - low omega-3 group, 5dMA:
						-42.63 (-97.11, 11.84)
						HFn - low omega-3 group, lag 0:
						-11.05 (-45.26, 23.16)
						HFn - low omega-3 group, lag 1:
						-15.26 (-47.63, 17.11)
						HFn - low omega-3 group, lag 2:
						-12.63 (-48.68, 23.42)
						HFn - low omega-3 group, lag 3:
						-9.47 (-43.42, 24.47)
						HFn - low omega-3 group, lag 4:
						-20.53 (-50.79, 9.74)
						LF/HF - high omega-3 group, 5dMA:
						77.37 (-32.11, 186.84)
						LF/HF - high omega-3 group, lag 0:
						25.79 (-30.79, 82.37)
						LF/HF - high omega-3 group, lag 1:
						38.95 (-30.79, 108.68)
						LF/HF - high omega-3 group, lag 2:
						7.89 (-51.05, 66.84)
						LF/HF - high omega-3 group, lag 3:
						70.53 (-3.42, 144.47)
						LF/HF - high omega-3 group, lag 4:
						-1.58 (-63.16, 60.00)
						LF/HF - low omega-3 group, 5dMA:
						105.79 (-21.58, 233.16)
						LF/HF - low omega-3 group, lag 0:
						22.63 (-46.05, 91.32)
						LF/HF - low omega-3 group, lag 1:
						37.89 (-29.47, 105.26)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						LF/HF - low omega-3 group, lag 2: 41.05 (-33.95, 116.05)
						LF/HF - low omega-3 group, lag 3: 23.16 (-45.53, 91.84)
						LF/HF - low omega-3 group, lag 4: 39.47 (-23.16, 102.11)
						VLF - high omega-3 group, 5dMA: 23.16 (-136.84, 183.16)
						VLF - high omega-3 group, lag 0: -39.47 (-114.21, 35.26)
						VLF - high omega-3 group, lag 1: 4.21 (-94.47, 102.89)
						VLF - high omega-3 group, lag 2: -36.84 (-122.37, 48.68)
						VLF - high omega-3 group, lag 3: 102.11 (-17.11, 221.32)
						VLF - high omega-3 group, lag 4: 57.37 (-50.00, 164.74)
						VLF - low omega-3 group, 5dMA: -44.21 (-193.68, 105.26)
						VLF - low omega-3 group, lag 0: -113.16 (-190.00, -36.32)
						VLF - low omega-3 group, lag 1: -74.21 (-155.53, 7.11)
						VLF - low omega-3 group, lag 2: -56.32 (-149.21, 36.58)
						VLF - low omega-3 group, lag 3: 73.16 (-40.26, 186.58)
						VLF - low omega-3 group, lag 4: 90.53 (-16.05, 197.11)
						vWF - high omega-3 group, 5dMA: 41.58 (3.42, 79.74)
						vWF - high omega-3 group, lag 0: 12.11 (-8.16, 32.37)
						vWF - high omega-3 group, lag 1: 35.26 (9.74, 60.79)
						vWF - high omega-3 group, lag 2: 13.68 (-8.42, 35.79)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						vWF - high omega-3 group, lag 3: 24.74 (-0.53, 50.00) vWF - high omega-3 group, lag 4: -4.74 (-27.63, 18.16) vWF - low omega-3 group, 5dMA: 26.32 (-15.26, 67.89) vWF - low omega-3 group, lag 0: 28.42 (3.16, 53.68) vWF - low omega-3 group, lag 1: 22.63 (-1.05, 46.32) vWF - low omega-3 group, lag 2: 1.05 (-24.21, 26.32) vWF - low omega-3 group, lag 3: -10.53 (-34.47, 13.42) vWF - low omega-3 group, lag 4: -5.26 (-26.58, 16.05)
† Chen et al. (2022a) N = 24 Research Triangle, NC, U.S. Recruitment: December 2016– July 2019 Cohort	Eligible participants met the following criteria: 25–55 years old, BMI between 19 and 35, having no cardiovascular disease, chronic respiratory disease, cancer, uncontrolled hypertension, or diabetes; non-smokers for at least 1 year, not taking beta-adrenergic receptor blockers, statins, or anti- inflammatory drugs. These individuals were then further screened and those meeting at least one of the following criteria were	Central site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2016–2019	NO ₂ (ppb) Overall Mean = 4.8±3.4 IQR = 3.4 Min = 0.9 Max = 18	Supervised measurements	Mixed effect linear regression Adjusted for: omega-3 index age, gender, race, body mass index (BMI), long-term trend, day of week, relative humidity, and temperature	β (Percent difference) (95% CI) ^b CRP - 5-day moving average: 0.11 (-0.09, 0.31) CRP - Lag 0: 0.00 (-0.10, 0.10) CRP - Lag 1: 0.01 (-0.13, 0.15) CRP - Lag 2: 0.08 (-0.07, 0.23) CRP - Lag 3: 0.03 (-0.08, 0.14) CRP - Lag 4: 0.01 (-0.09, 0.11) IL-8 - 5-day moving average: -0.01 (-0.07, 0.05) IL-8 - Lag 0: 0.01 (-0.04, 0.06) IL-8 - Lag 1: 0.00 (-0.04, 0.04) IL-8 - Lag 2: -0.02 (-0.07, 0.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	enrolled; an in-house open-ended dietary questionnaire; Omega-3 index					IL-8 - Lag 3: 0.00 (-0.03, 0.03) IL-8 - Lag 4: 0.00 (-0.03, 0.03) TNFa - 5-day moving average: 0.00 (-0.03, 0.03) TNFa - Lag 0: 0.01 (-0.01, 0.03) TNFa - Lag 1: 0.00 (-0.02, 0.02) TNFa - Lag 2: -0.01 (-0.03, 0.01) TNFa - Lag 3: -0.01 (-0.03, 0.01) TNFa - Lag 4: 0.00 (-0.02, 0.02)
†Li et al. (2019)	Restricted to participants who lived within 50 km from the Harvard Supersite air pollution monitor in Boston; excluded those who are current smokers and those where data on BMI, alcohol intake, or pack years of smoking were missing.	Fixed site monitor Averaging time: NO _x - 24-hour average, Other, NO _x - 2-day, 3-day, 5-day, 7-day averages Exposure years: 1998–2008	NO _x (ppb) Overall Mean = 39.1±21 IQR = 19.7	Supervised measurements	Mixed effect linear regression Adjusted for: demographic variables, individual level socioeconomic position, census tract-level socioeconomic position, lifestyle factors, clinical factors, time, and meteorology	β (Percent change (%)) (95% CI) ^b Osteoprotegrin: -3.00 (-5.40, -0.60)
Framingham Heart Study Offspring and Third Generation cohort N = 3,820 Greater Boston Area, U.S. Exam 1: 1998–2001 (Framingham) Exam 2: 2005–2008 (Framingham) Exam 1: 2002–2005 (Third Generation) Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Mann et al. (2021) The Children's Health and Air Pollution Study (CHAPS) N = 299 California, U.S. 2015–2017 Cross-Sectional	Children ages 6–8; residence in Fresno or Clovis for at least the past 3 months, residence within 20 km of the central air quality monitoring site, no plans to move from the Fresno/ Clovis area in the next 2 years, English- or Spanish-speaking, and no cancer, HIV, or autoimmune disease	Fixed site monitor, LUR Models for NO ₂ explain 99% of the observed temporal variance and 74% or the observed spatial variance Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages Exposure years: 2013–2017	NO ₂ (ppb) 1-Day Lag Mean = 6.98 Median = 5.07 (IQR 6.42) 1-Month Average Mean = 7.17 Median = 6.65 (IQR 6.46) 1-Week Average Mean = 7.19 Median = 6.01 (IQR 6.04) 1-Year Average Mean = 7.6 Median = 7.71 (IQR 1.74) 3-Month Average Mean = 7.3 Median = 6.88 (IQR 6.2) 6-Month Average Mean = 7.48 Median = 7.38 (IQR 3.42)	Supervised measurements	Generalized additive models Adjusted for: Race/ethnicity, age, sex and socioeconomic status (SES)	β (Percent change (%)) (95% CI) ^c 8-Isoprostane - 1-mo avg: 25.53 (9.38, 44.06) β (Percent change (%)) (95% CI) ^b 8-Isoprostane - 1-day avg: 1.99 (-38.74, 42.72) 8-Isoprostane - 1-wk avg: 0.77 (-43.18, 44.73)
† Ni et al. (2021) Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)	Participants were randomly selected from those who submitted blood samples at Exam 2, Exam 3, and Exam 4;	Fixed site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) IQR=7.95	Supervised measurements	Generalized estimating equations Adjusted for: study site, age, sex, race/ethnicity,	β (pg/ml) (95% CI) ^b sLOX-1 - model 1: 32.61 (-3.88, 69.10) sLOX-1 - model 2: 32.42 (-4.02, 68.85)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
N = 740 Chicago, IL, Baltimore, MD, Los Angeles, CA, Winston-Salem, NC, St. Paul, MN, New York City, NY, U.S. Recruitment: 2000–2002 Follow-up: 2002–2012 Other (Specify in notes box)	those without a valid address were excluded	Exposure years: 2002–2007			household income, educational level, neighborhood SES, second-hand smoking, smoking status, use of NSAIDs or aspirin, BMI and history of diabetes and hypertension Adjusted for: study site Adjusted for: study site, age, sex and race/ethnicity Adjusted for: study site, age, sex, race/ethnicity, household income, educational level, neighborhood SES, second-hand smoking, smoking status and use of NSAIDs or aspirin	sLOX-1 - model 3: 29.47 (-6.92, 65.86) sLOX-1 - model 4: 30.28 (-6.15, 66.71) β (umol/L) (95% CI)^b Nitrate - model 1: 4.33 (-9.63, 18.29) Nitrate - model 2: 4.30 (-9.30, 17.89) Nitrate - model 3: 3.20 (-10.96, 17.36) Nitrate - model 4: 2.11 (-12.01, 16.22)
†Scheers et al. (2018) N = 20 Milan, Italy, Vindeln, Sweden, Leuven, Belgium, Sweden, Italy, Belgium Recruitment: May 2013 Assessment periods: September 2013–September 2014 Panel	Included 10 healthy retired male-female couples with both partners fulfilling the following: aged 60-75, never or >1 year former smokers, good general health, willing and available to travel during the study period, and fluent in Dutch. Excluded participants with mobility problems, a history of	Personal monitor or sampler, Fixed site monitor Method validation NR Averaging time: NO₂ - 24-hour average Exposure years: 2013–2014	NO₂ (ppb) 2013 November Mean = 10.3±2.2 (19.4±4.2 µg/m³) October Mean = 29.2±0.85 (54.9±1.6 µg/m³) September Mean = 13.3±3.6 (25.1±6.8 µg/m³) 2014	Supervised measurements	Mixed effect linear regression Adjusted for: age at baseline, sex, heart rate, smoking status, having a cold, medication use for blood pressure, date, temperature, relative humidity, and arterial pressure	β (10–3/kPa) (95% CI)^c DC - fixed site monitors: -1.58 (-3.28, 0.12) DC - personal site monitors: -1.31 (-2.69, 0.07) β (kPa) (95% CI)^c YEM - fixed site monitors: 1.56 (-0.34, 3.45) YEM - personal site monitors: 1.36 (-0.14, 2.86) β (m/s) (95% CI)^c PWV - fixed site monitors: 0.78 (-0.05, 1.61) PWV - personal site monitors:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	cardiovascular disease, cancer, or other disease that could interfere the measurements, or would represent a risk during travel.		January Mean = 14±2.8 (26±5.2 µg/m ³) July Mean = 8.98±2.1 (16.9±3.9 µg/m ³) June Mean = 10.2±0.5 (19.2±1 µg/m ³) March Mean = 14.6±4.4 (27.5±8.2 µg/m ³) May Mean = 8.98±3.3 (16.9±6.3 µg/m ³) September Mean = 12.1±3 (22.8±6 µg/m ³) NO ₂ (µg/m ³) 2013 November Mean = 19.4±4.2 October Mean = 54.9±1.6 September Mean = 25.1±6.8 2014 January Mean = 26±5.2 July Mean = 16.9±3.9 June Mean = 19.2±1 March Mean = 27.5±8.2			0.63 (-0.04, 1.30) β (mm2/kPa) (95% CI) ^c CC - fixed site monitors: -2.05 (-3.54, -0.56) CC - personal site monitors: -1.42 (-2.64, -0.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			May Mean = 16.9±6.3 September Mean = 22.8±6 NO ₂ (ppb) 2013 November Mean = 19.4±4.2 October Mean = 54.9±1.6 September Mean = 25.1±6.8 2014 January Mean = 26±5.2 July Mean = 16.9±3.9 June Mean = 19.2±1 March Mean = 27.5±8.2 May Mean = 16.9±6.3 September Mean = 22.8±6			
† Shutt et al. (2017)	Eligible participants were recruited through postings at local university and college campuses. The participants were non-smokers age 18-55 years, permanent or season residents of	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max, NO - 1-hour max	NO ₂ (ppb) Bayview Site Mean = 6.89±3.64 IQR = 4.6 College Site Mean = 4.6±2.8 IQR = 2.9	Supervised measurements	Mixed effect linear regression Adjusted for: age, sex, BMI, temperature, relative humidity, and study site	NO β (Beats per minute) (95% CI) ^b HR: 16.64 (4.16, 29.11) β (milliseconds) (95% CI) ^b rMSSD: -56.32 (-117.48, 4.84) SDNN:
N = 60						
Sault Ste. Marie, Ontario, Canada						
2010						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Case-crossover	Sault Ste. Marie Ontario, who did not work or live near the steel plant.	Exposure years: 2010	NO (ppb)			-6368.18 (-6425.80, -6310.57) β (milliseconds squared) (95% CI) ^b LF:
			Bayview Site Mean = 7.02±4.16 IQR = 4.9			-20.59 (-41.05, -0.14) β (Percent (%)) (95% CI) ^b pNN50:
			College Site Mean = 1.69±1.2 IQR = 1.3			-24.14 (-48.00, -0.27) NO ₂
			NO _x (ppb)			β (Beats per minute) (95% CI) ^b HR:
			Bayview Site Mean = 13.74±6.97 IQR = 8.7			8.14 (2.79, 13.49) β (milliseconds) (95% CI) ^b rMSSD:
			College Site Mean = 6.29±3.66 IQR = 2.95			-35.00 (-61.19, -8.81) SDNN:
						-37.27 (-61.92, -12.62) β (milliseconds squared) (95% CI) ^b LF:
						-7.73 (-16.37, 0.90) β (Percent (%)) (95% CI) ^b pNN50:
						-6.80 (-17.06, 3.46) NO _x
						β (Beats per minute) (95% CI) ^b HR:
						14.46 (5.45, 23.47) β (milliseconds) (95% CI) ^b rMSSD:
						-57.93 (-101.98, -13.88) SDNN:
						-63.61 (-105.11, -22.12) β (milliseconds squared) (95% CI) ^b LF:
						-14.07 (-28.92, 0.77)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						β (Percent (%)) (95% CI) ^b pNN50: -13.59 (-30.89, 3.71)
†Sofianopoulou et al. (2019) UK National Cohort Study of Idiopathic and Heritable PAH N = 301 England, Scotland, Wales, U.K. Enrollment: January 2014–February 2018 Follow-up: mean 3.5 years Cohort	Patients with idiopathic and heritable PAH. Eligible if they maintained the same address since diagnosis.	Fixed site monitor Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Lag 0 days Median = 15.6 (IQR 16) (29.3 $\mu\text{g}/\text{m}^3$ (IQR 30.2 $\mu\text{g}/\text{m}^3$) Lag 3 days Median = 14.5 (IQR 15) (27.3 $\mu\text{g}/\text{m}^3$ (IQR 28 $\mu\text{g}/\text{m}^3$) Lag 7 days Median = 15 (IQR 16) (28.3 $\mu\text{g}/\text{m}^3$ (IQR 30.2 $\mu\text{g}/\text{m}^3$) Lag 14 days Median = 15.5 (IQR 14.6) (29.2 $\mu\text{g}/\text{m}^3$ (IQR 27.4 $\mu\text{g}/\text{m}^3$) Overall Median = 14 (IQR 5.37) (26 $\mu\text{g}/\text{m}^3$ (IQR 10.1 $\mu\text{g}/\text{m}^3$)	Supervised measurements	Mixed effect linear regression Adjusted for: age, sex, functional class, and centre	β (Percent change (% L/min/m ²)) (95% CI) ^b CI - lag 0: 3.80 (3.74, 3.86) CI - lag 3: 3.80 (3.74, 3.86) CI - lag 7: 3.80 (3.74, 3.86) CI - lag 14: 3.80 (3.73, 3.88) β (Percent change (% mm Hg)) (95% CI) ^b PAP mean - lag 0: 3.76 (3.73, 3.80) PAP mean - lag 3: 3.76 (3.71, 3.82) PAP mean - lag 7: 3.76 (3.71, 3.82) PAP mean - lag 14: 3.76 (3.71, 3.82) β (Percent change (% Wood Units)) (95% CI) ^b PVR - lag 0: 3.73 (3.63, 3.82) PVR - lag 3: 3.73 (3.63, 3.82) PVR - lag 7: 3.73 (3.63, 3.82) PVR - lag 14: 3.76 (3.65, 3.88) β (Percent change (%mm Hg)) (95% CI) ^b RAP - lag 0: 3.84 (3.73, 3.95)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						RAP - lag 3: 3.88 (3.73, 4.03) RAP - lag 7: 3.88 (3.73, 4.03) RAP - lag 14: 3.84 (3.67, 4.01)
† Zhang et al. (2016a) n = 97 Los Angeles, CA, U.S. 2012–2014 Cross-Sectional	Older adults non-smoking adults (age Z65)	Central site monitor r ² >0.80 Averaging time: NO _x - 24-hour average Exposure years: 2012, 2014	NO _x (ppb) Ambient Mean = 35.4±27.7 IQR = 31 Min = 3.6 Max = 175.6 Personal exposure Mean = 29.3±21.8 IQR = 21.3 Min = 2.2 Max = 160.1	Supervised measurements	Mixed effect linear regression Adjusted for: days of gas stove use per week and LDL level Adjusted for: days of gas stove use per week	β (Percent change (%)) (95% CI) ^b IL-6 - Ambient exposure (1-day avg): 0.05 (0.00, 0.09) IL-6 - Ambient exposure (3-day avg): 0.02 (-0.02, 0.07) IL-6 - Ambient exposure (5-day avg): 0.01 (-0.06, 0.07) IL-6 - Ambient exposure (7-day avg): -0.02 (-0.10, 0.06) IL-6 - Personal exposure (7-day avg): -0.03 (-0.11, 0.05) oxLDL - Ambient exposure (1-day avg): 0.01 (-0.01, 0.04) oxLDL - Ambient exposure (3-day avg): 0.01 (-0.02, 0.03) oxLDL - Ambient exposure (5-day avg): 0.00 (-0.19, 0.19) oxLDL - Ambient exposure (7-day avg): -0.02 (-0.06, 0.03) oxLDL - Personal exposure (7-day

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						avg): 0.01 (-0.04, 0.05)
†Zhang et al. (2022)	Children aged 8–10 years, residence in Fresno or Clovis for at least the past three months, residence within 20 km of the central air quality monitor site, no plans to move from study area for next two years, English or Spanish speaking, no cancer, HIV, or autoimmune disease	LUR, Fixed site monitor, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, NO _x - 24-hour average, NO _x - annual average, Other, NO ₂ - weekly average NO ₂ -1-, 3-, 6-month averages NO _x - weekly average NO _x - 1-, 3-, 6-month averages Exposure years: 2019	NO ₂ (ppb) 1-day average Median = 7.31 P25 = 4.12 P75 = 13.54 1-month average Median = 8.98 P25 = 4.33 P75 = 14.05 1-week average Median = 7.92 P25 = 4.53 P75 = 14.58 1-year average Median = 8.3 P25 = 7.23 P75 = 9.4 3-month average Median = 8.48 P25 = 4.46 P75 = 13.75 6-month average Median = 8.72 P25 = 5.64 P75 = 11.65 NO _x (ppb) 1-day average	Supervised measurements	Generalized additive models Adjusted for: whether or not the child lives with a smoker, whether or not the child is Latinx, physical activity, household income, and a smoothed term for the day of study	NO ₂ β (mg/dL) (95% CI) ^b HDL - 1-day avg: -10.85 (-17.87, -3.83) HDL - 1-wk avg: -9.11 (-17.13, -1.09) β (ng/mg) (95% CI) ^b 8-Isoprostane - 1-day avg: 2.55 (2.02, 3.09) 8-Isoprostane - 1-wk avg: 2.38 (1.78, 2.97) NO _x β (mg/dL) (95% CI) ^b HDL - 1-day avg: -2.75 (-9.39, 3.89) HDL - 1-wk avg: -9.40 (-17.80, -1.01) β (ng/mg) (95% CI) ^b 8-Isoprostane - 1-day avg: 2.75 (2.18, 3.32) 8-Isoprostane - 1-wk avg: 2.46 (1.90, 3.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Median = 14.59 P25 = 10.06 P75 = 23.16 1-month average Median = 16.59 P25 = 10.79 P75 = 25.48 1-week average Median = 17.06 P25 = 10.53 P75 = 23.89 1-year average Median = 17.15 P25 = 15.36 P75 = 18.84 3-month average Median = 16 P25 = 11.47 P75 = 24.03 6-month average Median = 16.38 P25 = 13 P75 = 21.69			
† de Prado-Bert et al. (2022)	Children	LUR	NO ₂ (ppb)	Supervised measurements	Linear regression	β (95% CI) ^b
Human Early-life Exposome project (HELIX)		ESCAPE-LUR	24 h avg (school/home)		Adjusted for: child's sex, cohort, self-reported maternal education, self-reported ancestry child's age and mean temperature	Hepatocyte growth factor - home 1-day, PM _{2.5} : 1.34 (-0.60, 3.29)
n = 1170		Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, Other, 1-week avg	Median = 1.8 (IQR 0.37) (3.4 µg/m ³ (IQR 0.7 µg/m ³))			Hepatocyte growth factor - home 1-day: 1.03 (0.11, 1.94)
France, U.K., Spain, Norway, Greece, Lithuania			Annual avg (home)			Hepatocyte growth factor - home 1-wk, PM _{2.5} :

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Follow-up (age 7–11): 2014–2015		Exposure years: 2013–2015	Median = 1.9 (IQR 0.32) (3.5 µg/m ³ (IQR 0.6 µg/m ³))			1.20 (-1.73, 4.13) Hepatocyte growth factor - home 1-wk: 2.00 (0.78, 3.22)
Cohort			Annual avg (school) Median = 1.9 (IQR 0.27) (3.5 µg/m ³ (IQR 0.5 µg/m ³))			Hepatocyte growth factor - school 1-day, PM _{2.5} : 0.37 (-1.57, 2.31) Hepatocyte growth factor - school 1-day: 0.54 (-0.34, 1.43)
			Week avg (school/home) Median = 1.9 (IQR 0.37) (3.5 µg/m ³ (IQR 0.7 µg/m ³))			Hepatocyte growth factor - school 1-wk, PM _{2.5} : 0.12 (-3.48, 3.72) Hepatocyte growth factor - school 1-wk: 1.64 (0.20, 3.08)

List of abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; HR = hazard ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; O₃ = ozone; OR = odds ratio; ppb = parts per billion; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-11 Animal toxicology studies of heart rate and heart rate variability

Study Details and Population	Exposure Details	Endpoints Examined*
[†] Farraj et al. (2016)	Whole body inhalation with filtered air controls	5.5 hr after exposure
Rat (Spontaneously Hypertensive) 12-wk-old, males n = 6/group	300 ppb (0.3 ppm) NO ₂ , continuous for 3 hr	- HR (NS) - HRV (rMSSD, SDNN, HF, LF/HF) (NS)

Study Details and Population	Exposure Details	Endpoints Examined*
† Ji et al. (2022)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	HR and BP (NS)
6-wk-old, males and females		
n = 6–9/group		

List of abbreviations in alphabetical order: BP = blood pressure; d = day; HF = high-frequency; hr = hour; HR = heart rate; HRV = heart rate variability; LF = low-frequency; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; rMSSD = square root of the mean of squared differences of adjacent RR intervals; SDNN = standard deviation of RR interval; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-12 Animal toxicology studies of QT interval duration

Study Details and Population	Exposure Details	Endpoints Examined*
† Farraj et al. (2016)	Whole body inhalation with filtered air controls	5.5 hr after exposure
Rat (Spontaneously Hypertensive)	300 ppb (0.3 ppm) NO ₂ , continuous for 3 hr	Radiotelemetry (PR interval, QTc) (NS)
12-wk-old, males		
n = 6/group		

List of abbreviations in alphabetical order: d = day; hr = hour; min = minute; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control.

†Studies published since the 2016 Oxides of Nitrogen ISA

Appendix Table 5-13 Animal toxicology studies of vascular reactivity and arterial stiffness

Study Details and Population	Exposure Details	Endpoints Examined*
† Karoui et al. (2020)	Whole body inhalation with room air controls	1 hr after exposure (3 hr exposure)
Rat (Wistar)	5,000 ppb (5 ppm) NO ₂ , continuous for 3 hr	Acetylcholine-induced coronary relaxation (NS)
9–11-wk-old, males	5,000 ppb (5 ppm) NO ₂ , 3 hr/d, 5 d/wk for 3 wk	24 hr after exposure (3 hr/d, 5 d/wk for 3 wk exposure)
n = 4–6/group		Sodium nitroprusside-induced coronary relaxation (NS)

List of abbreviations in alphabetical order: d = day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-14 Controlled human exposure studies of cardiovascular effects

Study Details and Population	Exposure Details	Endpoints Examined*
† Brand et al. (2016)	Whole body exposure for 3 hr with 10 min/hr of exercise (800 d after exposure W workload) to:	
25 young (18–33-yr-old) healthy subjects (19 m/6 f)	(1) 0.0 ppb (0.0 ppm) (2) 100 ppb (0.1 ppm) (3) 500 ppb (0.5 ppm) (4) 1,500 ppb (1.5 ppm)	- Blood circulating immune cells (NS) - Blood inflammatory cytokines (NS)

List of abbreviations in alphabetical order: d = day; f = female; hr = hour; m = male; min = minute; ppb = parts per billion; ppm = parts per million; W = watts; yr = year.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ↑/↓ = at least one experimental group had a statistically significant increase and at least one experimental group has a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-15 Animal toxicology studies of blood and other markers of cardiovascular disease

Study Details and Population	Exposure Details	Endpoints Examined*
Li et al. (2011)	Whole body inhalation with filtered air controls	18 hr after exposure
Rat (Wistar) 280–300g, males n = 6/group	2,657 ppb (5 mg/m ³) NO ₂ , 6 hr/d for 7 d 5,313 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 7 d 10,627 ppb (20 mg/m ³) NO ₂ , 6 hr/d for 7 d	- Endothelial activation (ET-1, eNOS, ICAM-1) and inflammatory mediators (TNF-α, IL-1b) (↑) - Heart histology (intracellular gap increased along with increased inflammation following NO₂ exposure.) - Oxidative stress markers (Cu/Zn-SOD) (↓) - Oxidative stress markers (Mn-SOD activity, GPx activity, MDA, PCO) (↑)

Study Details and Population	Exposure Details	Endpoints Examined*
de Burbure et al. (2007)	Whole body inhalation with ambient air controls	0 d after exposure (5 ppm, Se deficient) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
Rat (Wistar)	1,000 ppb (1 ppm) NO ₂ , 6 hr/d for 4 wk	
2-mo-old, males	5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 5 d	0 d after exposure (5 ppm, Se supplement) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
n = 8/group	10,000 ppb (10 ppm) NO ₂ , 6 hr/d for 4 wk	
	50,000 ppb (50 ppm) NO ₂ , continuous for 30 min	0 d after exposure (50 ppm, Se deficient) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
		0 d after exposure (50 ppm, Se supplement) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
		2 d after exposure (5 ppm, Se deficient) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
		2 d after exposure (5 ppm, Se supplement) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
†Farraj et al. (2016)	Whole body inhalation with filtered air controls	21 hr after exposure - GSH peroxidase, total serum protein (↑) - HDL (↓) - LDL, triglycerides, SOD, GSH transferase (NS)
Rat (Spontaneously Hypertensive)	300 ppb (0.3 ppm) NO ₂ , continuous for 3 hr	
12-wk-old, males		
n = 6/group		
†Karoui et al. (2020)	Whole body inhalation with room air controls	1 hr after exposure (3 hr exposure) - Cardiac output (NS) - Interfibrillar ROS (↑) - Mitochondrial function (NS)
Rat (Wistar)	5,000 ppb (5 ppm) NO ₂ , continuous for 3 hr	
9–11-wk-old, males	5,000 ppb (5 ppm) NO ₂ , 3 hr/d, 5 d/wk for 3 wk	24 hr after exposure (3 hr exposure) Interfibrillar ROS (NS)
n = 4–6/group		

Study Details and Population	Exposure Details	Endpoints Examined*
† Li et al. (2022b)	Whole body inhalation with room air controls	12 hr after exposure
Rat (Sprague Dawley)	5,000 ppb (5 ppm) NO ₂ , 5 hr/d for 2 wk	• Cardiac Hsp70 expression (↓) • Cardiac Mfn2 expression (↓) • Cardiac proteomics (↑/↓) • ICC — heart tissue (swelled nuclei, increased intracellular gap, and increased inflammatory inflammation) • Plasma LDH (↑) • Plasma biochemical stress markers (NS) • Serum metabolomics (↑/↓) • TEM — heart tissue (increased mitochondria with reduced cristae)
8-wk-old, males		
n = 3–8/group		

List of abbreviations in alphabetical order: Cu = copper; d = day; GPx = glutathione peroxidase; GSH = glutathione; HDL = high-density lipoprotein; hr = hour; ICC = immunocytochemistry; LDL = low-density lipoprotein; MDA = malondialdehyde; min = minute; Mn = manganese; mo = month; n = sample size; NO₂ = nitrogen dioxide; PCO = protein carbonyl; ppb = parts per billion; ppm = parts per million; ROS = reactive oxygen species; Se = selenium; SOD = superoxide dismutase; TEM = transmission electron microscopy; wk = week; Zn = zinc.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ↑/↓ = at least one experimental group had a statistically significant increase and at least one experimental group has a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 5-16 Epidemiologic studies of short-term oxides of nitrogen exposure and cardiovascular mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Bellini et al. (2007)	Deaths from CVD	Fixed site monitor	NO ₂ (ppb)	Cardiovascular mortality (ICD-9 codes 390–459)	GLM for city-specific estimates, Bayesian random effects model for national estimates	% change in risk (95% CI) ^b Cardio Mortality: 1.02 (0.99, 1.04)
n = NR		Method validation NR				
Italy		Averaging time: NO ₂ - 24-hour average			Adjusted for: Age, day of the week, holidays, influenza epidemics, meteorological variables and seasonality	
1996–2002		Exposure years: 1996–2002				
Time-series						
Chen et al. (2012a)	Daily mortality data of urban residents from Municipal Center for	Central site monitor	NO ₂ (ppb) Min = 2 (4 µg/m ³)	Cardiovascular mortality (ICD-10: I00–I99)	Overdispersed Poisson GLM for city-specific estimates, Bayesian	% change in risk (95% CI) ^b Cardio Mortality - PM ₁₀ : 1.05 (1.01, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Effects Study (CAPES) n = NR Shanghai, Tianjin, Beijing, Hong Kong, Wuhan, Xi'an, Guangzhou, Fuzhou, Lanzhou, Nanjing, Suzhou, Shenyang, Anshan, Taiyuan, Hangzhou, Urumqi, China 1996–2010 Time-series	Disease Control and Prevention	Averaging time: NO ₂ - 24-hour average Exposure years: 1996–2010	Max = 135 (254 µg/m ³)		hierarchical model for national estimates Adjusted for: long-term and seasonal trends for daily mortality and weather conditions	Cardio Mortality - SO ₂ : 1.06 (1.03, 1.09) Cardio Mortality: 1.07 (1.02, 1.12)
Chen et al. (2013) China Air Pollution and Health Effects Study (CAPES) N = 48,200,000 Shanghai, Beijing, Hong Kong, Guangzhou, Fuzhou, Suzhou, Shenyang, Tangshan, China 1996–2008 Cohort	Residents in study area	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 1996–2008	NO ₂ (ppb) Beijing Mean = 31±13 (58±25 µg/m ³) Fuzhou Mean = 24±5 (45±9 µg/m ³) Guangzhou Mean = 35±17 (66±32 µg/m ³) Hong Kong Mean = 30±11 (56±20 µg/m ³) Shanghai Mean = 36±13 (67±25 µg/m ³) Shenyang	Cardiovascular mortality (ICD-10: I00–I99)	Quasi-Poisson GAM for city-specific estimates, Bayesian hierarchical model for national estimates Adjusted for: calendar time, day of week, temperature, humidity	% change in risk (95% CI) ^b Cardio Mortality - Lag 01: 1.06 (1.03, 1.08) Cardio Mortality - PM ₁₀ : 1.04 (1.02, 1.07) Cardio Mortality - SO ₂ : 1.05 (1.02, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 20±8 (37±15 µg/m ³)			
			Suzhou Mean = 24±11 (45±21 µg/m ³)			
			Tangshan Mean = 22±9.6 (41±18 µg/m ³)			
Chiusolo et al. (2011)	Individuals greater than 35 years of age, in 10 Italian cities, who deceased between 2001–2005 of natural causes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2005	NO ₂ (ppb) Bologna–Mean, Med, 90 th = 27.6, 26.6, 39.9 (52, 50, 75 µg/m ³) Cagliari - Mean, Med, 90 th = 18.1, 17.54, 28.7 (34, 33, 54 µg/m ³) Florence - Mean, Med, 90 th = 24.4, 23.4, 36.1 (46, 44, 68 µg/m ³) Mestre-Venice - Mean, Med, 90 th = 20.2, 19.1, 30.8 (38, 36, 58 µg/m ³) Milan - Mean, Med, 90 th = 31.36, 30.3, 46.8 (59, 57, 88 µg/m ³) Palermo - Mean, Med, 90 th = 27.6,	Cardiovascular mortality (ICD-9 codes 390–429)	Logistic regression Adjusted for: Population decrease, holidays, influenza epidemics, barometric pressure, apparent temperature	% change in risk (95% CI) ^b Cardio Mortality - PM ₁₀ : 1.10 (1.23, 0.98) Cardio Mortality: 1.10 (1.06, 1.15)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			27.1, 39.3 (52, 51, 74 µg/m ³) Pisa - Mean, Med, 90 th = 15.9, 15.4, 23.92 (30, 29, 45 µg/m ³) Rome - Mean, Med, 90 th = 33.0, 33.0, 43.6 (62, 62, 82 µg/m ³) Taranto - Mean, Med, 90 th = 13.8, 12.8, 21.8 (26, 24, 41 µg/m ³) Turin - Mean, Med, 90 th = 35.1, 34.01, 48.9 (66, 64, 92 µg/m ³)			
Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases Myocardial Ischaemia National Audit Project (MINAP) database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	Cardiovascular mortality (ICD-10, codes I00–I99)	Logistic regression Adjusted for: Temperature	% change in risk (95% CI) ^b AF Mortality: 0.99 (0.89, 1.10) All Cardio Mortality - 70+: 1.00 (0.98, 1.01) All Cardio Mortality - <70: 0.99 (0.96, 1.02) All Cardio Mortality - Females: 0.99 (0.97, 1.01) All Cardio Mortality - Males: 1.00 (0.98, 1.02) All Cardio Mortality: 1.00 (0.98, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	elevation MI, non-ST elevation MI, or troponin-positive acute coronary syndrome.					Arrhythmias Mortality: 0.99 (0.89, 1.11) Chronic IHD Mortality: 0.99 (0.97, 1.02) HF Mortality: 0.98 (0.92, 1.04) IHD Mortality: 0.99 (0.98, 1.01) MI Mortality: 0.99 (0.96, 1.02) Non-MI Mortality: 1.00 (0.98, 1.01) PE Mortality: 0.97 (0.87, 1.08) Stroke Mortality: 1.02 (0.99, 1.04)
Sacks et al. (2012) N = 17,968 Philadelphia, PA, U.S. May 12, 1992–September 30, 1995 Time-series	Daily cardiovascular deaths in study area	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 1992–1995	NO ₂ (ppb) Overall, 1-hour max Mean = 47.4±14.1 Median = 46.7 (IQR 16.7) Min = 15 Max = 146.7	Cardiovascular mortality (ICD-9 codes 390–429)	Generalized additive model Adjusted for: same-day temperature, Lag 1–3 day temperature, relative humidity, day-of-week Generalized linear model Adjusted for: lag 1 day temperature, lag 1 day relative humidity, day-of-week Adjusted for: same-day temperature, barometric pressure, day-of-week	% change in risk (95% CI) ^b Cardio Mortality - APHEA2 model: 1.02 (0.99, 1.05) Cardio Mortality - California model: 1.02 (0.99, 1.05) Cardio Mortality - Canada model: 1.02 (0.98, 1.05) Cardio Mortality - Harvard AT model: 1.01 (0.98, 1.04) Cardio Mortality - Harvard model: 1.02 (0.99, 1.05) Cardio Mortality - NMMAPS model: 1.01 (0.98, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					Adjusted for: same-day temperature, lag 1 day temperature, day-of-week	
					Adjusted for: same-day apparent temperature, day-of-week	
					Adjusted for: same-day temperature, lag 1–3 day temperature, same-day dew point, lag 1–3 day dew point	
Wong et al. (2008)	Health data of adults (all ages) from the Ministry of Public Health in Bangkok, the Census and Statistics Department in Hong Kong, the Shanghai Municipal Center of Disease Control and Prevention in Shanghai, and the Wuhan Centre for Disease Prevention and Control in Wuhan	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1999–2004	NO ₂ (ppb) Bangkok Mean = 23.8 (44.7 µg/m ³) Median = 21.1 (IQR 12.3) (39.7 µg/m ³) Min = 8.4 (15.8 µg/m ³) Max = 74.19 (139.6 µg/m ³) Hong Kong Mean = 31.2 (58.7 µg/m ³) Median = 30 (IQR 13) (56.4 µg/m ³) (IQR 24.4 µg/m ³) Min = 5.47 (10.3 µg/m ³) Max = 89.02 (167.5 µg/m ³)	Cardiovascular mortality (ICD-9 codes 390–459 or ICD-10 codes I00–I99)	Poisson GLM Adjusted for: seasonal patterns, long-term mortality trends, temperature, relative humidity, day-of-week, public holidays, extreme weather, influenza epidemic	% change in risk (95% CI) ^b Cardio Mortality Lag 0–1: 1.05 (1.03, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Shanghai Mean = 35.4 (66.6 $\mu\text{g}/\text{m}^3$) Median = 33.2 (IQR 15) (62.5 $\mu\text{g}/\text{m}^3$) (IQR 29 $\mu\text{g}/\text{m}^3$) Min = 7.23 (13.6 $\mu\text{g}/\text{m}^3$) Max = 134.8 (253.7 $\mu\text{g}/\text{m}^3$) Wuhan Mean = 27.5 (51.8 $\mu\text{g}/\text{m}^3$) Median = 25.1 (IQR 13) (47.2 $\mu\text{g}/\text{m}^3$) (IQR 24 $\mu\text{g}/\text{m}^3$) Min = 10.2 (19.2 $\mu\text{g}/\text{m}^3$) Max = 67.71 (127.4 $\mu\text{g}/\text{m}^3$)			
† Chen et al. (2018)	NR	Fixed site monitor	NO ₂ (ppb)	Cardiovascular mortality (ICD-10, codes I00-I99)	Over dispersed GLM for city-specific estimates, Bayesian hierarchical model for pooled estimates	% change in risk (95% CI) ^b Cardio Mortality - Age 5–64: 1.01 (1.00, 1.03) Cardio Mortality - Age 65–74: 1.03 (1.01, 1.04) Cardio Mortality - Age 75+: 1.04 (1.03, 1.05) Cardio Mortality - Females: 1.04 (1.03, 1.06) Cardio Mortality - Lag 0-1: 1.03 (1.02, 1.04) Cardio Mortality - Lag 0: 1.02 (1.02, 1.03) Cardio Mortality - Lag 1: 1.03 (1.02, 1.04)
N = ~290,000,000		Method validation NR	Overall Mean = 16±5.8 (31±11 $\mu\text{g}/\text{m}^3$)			
China		Averaging time: NO ₂ - annual average	Median = 16 (30 $\mu\text{g}/\text{m}^3$) Min = 5.3 (10 $\mu\text{g}/\text{m}^3$)		Adjusted for: calendar day to account for long-term time and seasonal trends (7 df/yr), temperature, humidity, day of week	
2013–2015		Exposure years: 2013–2015	Max = 35 (66 $\mu\text{g}/\text{m}^3$) P25 = 12 (22 $\mu\text{g}/\text{m}^3$) P75 = 20 (38 $\mu\text{g}/\text{m}^3$)			
Time-series						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						Cardio Mortality - Lag 2: 1.02 (1.01, 1.02) Cardio Mortality - Lag 3: 1.01 (1.01, 1.02) Cardio Mortality - Males: 1.03 (1.01, 1.04) CHD Mortality: 1.03 (1.02, 1.05) Hypertension: 1.05 (1.03, 1.08) Stroke Mortality: 1.03 (1.02, 1.05)
†Corso et al. (2020) n = NR Paris, Bordeaux, Clermont-Ferrand, Dijon, Grenoble, Le Havre, Lens-Douai, Lille, Lyon, Marseille, Montpellier, Nancy, Nantes, Nice, Rennes, Rouen, Strasbourg, Toulouse, France 2010–2014 Time-series	Daily mortality (total nonaccidental and cardiovascular) data classified by ICD-10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2010–2014	NO ₂ (ppb) Bordeaux Mean = 10.4 (19.6 µg/m ³) Min = 1 (2 µg/m ³) Max = 36.1 (67.9 µg/m ³) Clermont-Ferrand Mean = 13 (24 µg/m ³) Min = 1.1 (2.1 µg/m ³) Max = 55.32 (104.1 µg/m ³) Dijon Mean = 12 (22.5 µg/m ³) Min = 1.3 (2.4 µg/m ³) Max = 38.8 (73.1 µg/m ³)	Cardiovascular mortality (ICD-10, codes I00-I99)	Poisson GAM for study area-specific estimates, random-effects meta-analysis for pooled estimates Adjusted for: temperature, long-term trends, seasonality, day of week, bank holiday	% change in risk (95% CI) ^b Cardio Mortality - Cold Period (Nov–Apr) - O ₃ : 1.02 (0.98, 1.06) Cardio Mortality - Cold Period (Nov–Apr) - PM ₁₀ : 1.02 (0.97, 1.06) Cardio Mortality - Cold Period (Nov–Apr): 1.01 (0.98, 1.04) Cardio Mortality - O ₃ : 1.05 (1.02, 1.09) Cardio Mortality - PM ₁₀ : 1.04 (1.00, 1.08) Cardio Mortality - Warm Period (May–Oct) - O ₃ : 1.12 (1.05, 1.20) Cardio Mortality - Warm Period (May–Oct) - PM ₁₀ : 1.06 (1.00, 1.11) Cardio Mortality - Warm Period (May–Oct): 1.12 (1.05, 1.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Grenoble Mean = 12.6 (23.8 µg/m ³) Min = 1.4 (2.7 µg/m ³) Max = 42.9 (80.8 µg/m ³)			Cardio Mortality: 1.05 (1.02, 1.08)
			Le Havre Mean = 11.9 (22.4 µg/m ³) Min = 1 (2 µg/m ³) Max = 42 (79 µg/m ³)			
			Lens-Douai Mean = 11.5 (21.7 µg/m ³) Min = 0.5 (1 µg/m ³) Max = 43 (81 µg/m ³)			
			Lille Mean = 13.4 (25.3 µg/m ³) Min = 1.9 (3.5 µg/m ³) Max = 42.7 (80.3 µg/m ³)			
			Lyon Mean = 16.5 (31.1 µg/m ³) Min = 2.3 (4.3 µg/m ³) Max = 51.2 (96.3 µg/m ³)			
			Marseille Mean = 17.4 (32.7			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			$\mu\text{g}/\text{m}^3$ Min = 2.4 (4.5 $\mu\text{g}/\text{m}^3$) Max = 43.7 (82.3 $\mu\text{g}/\text{m}^3$)			
			Montpellier Mean = 13.8 (25.9 $\mu\text{g}/\text{m}^3$) Min = 0.58 (1.1 $\mu\text{g}/\text{m}^3$) Max = 42.3 (79.5 $\mu\text{g}/\text{m}^3$)			
			Nancy Mean = 13 (24.4 $\mu\text{g}/\text{m}^3$) Min = 2.5 (4.7 $\mu\text{g}/\text{m}^3$) Max = 35.7 (67.1 $\mu\text{g}/\text{m}^3$)			
			Nantes Mean = 9.51 (17.9 $\mu\text{g}/\text{m}^3$) Min = 0.96 (1.8 $\mu\text{g}/\text{m}^3$) Max = 39 (73.4 $\mu\text{g}/\text{m}^3$)			
			Nice Mean = 13.2 (24.9 $\mu\text{g}/\text{m}^3$) Min = 3 (5 $\mu\text{g}/\text{m}^3$) Max = 29 (55 $\mu\text{g}/\text{m}^3$)			
			Paris Mean = 19 (36			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			$\mu\text{g}/\text{m}^3$ Min = 4.4 (8.3 $\mu\text{g}/\text{m}^3$) Max = 49 (93 $\mu\text{g}/\text{m}^3$)			
			Rennes Mean = 9.94 (18.7 $\mu\text{g}/\text{m}^3$) Min = 0.37 (0.7 $\mu\text{g}/\text{m}^3$) Max = 44.88 (84.45 $\mu\text{g}/\text{m}^3$)			
			Rouen Mean = 13.7 (25.7 $\mu\text{g}/\text{m}^3$) Min = 2 (3.7 $\mu\text{g}/\text{m}^3$) Max = 40 (75 $\mu\text{g}/\text{m}^3$)			
			Strasbourg Mean = 14 (27 $\mu\text{g}/\text{m}^3$) Min = 2.5 (4.7 $\mu\text{g}/\text{m}^3$) Max = 39.1 (73.5 $\mu\text{g}/\text{m}^3$)			
			Toulouse Mean = 11.2 (21.1 $\mu\text{g}/\text{m}^3$) Min = 1.2 (2.3 $\mu\text{g}/\text{m}^3$) Max = 40.8 (76.8 $\mu\text{g}/\text{m}^3$)			
[†] Gariazzo et al. (2023) n = 1,769,660	Daily mortality counts (natural, cardiovascular, cardiac,	Hybrid model Cross-validation at	NO ₂ (ppb) Rural	Cardiovascular mortality (ICD-	Quasi-poisson GAM for province-specific estimates, random-	% change in risk (95% CI) ^b Cardio Mortality - Lag 0–5 - PM _{2.5} : 0.95 (0.90, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Italy 2013–2015 Time-series	ischemic, cerebrovascular, respiratory, mental, nervous, metabolic, diabetes) classified using ICD-10 codes from the Italian National Institute of Statistics	R ² =0.6 Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2015	Mean = 6.27 (11.8 µg/m ³) Median = 5 (IQR 3.9) (9.5 µg/m ³ (IQR 7.3 µg/m ³) Min = 1.4 (2.7 µg/m ³) Max = 39.2 (73.7 µg/m ³) P25 = 3.8 (7.1 µg/m ³) P75 = 7.65 (14.4 µg/m ³) Suburban Mean = 10.5 (19.8 µg/m ³) Median = 9.35 (IQR 6.01) (17.6 µg/m ³ (IQR 11.3 µg/m ³) Min = 2.3 (4.4 µg/m ³) Max = 56.02 (105.4 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 12.9 (24.2 µg/m ³) Urban Mean = 15.8 (29.7 µg/m ³) Median = 14.7 (IQR 8.29) (27.6 µg/m ³ (IQR 15.6 µg/m ³) Min = 3.2 (6.1 µg/m ³) Max = 61.6 (115.9 µg/m ³)	10, codes I00-I99)	effects meta-analysis for national estimates Adjusted for: long-term seasonal trends, day of week, air temperature, bank holiday, vacation period population declines, influenza epidemics	Cardio Mortality - Lag 0–5 - PM ₁₀ : 0.95 (0.90, 1.01) Cardio Mortality - Lag 0–5: 0.95 (0.89, 1.01) Cardio Mortality - Lag 0–1: 0.95 (0.91, 0.99) Cardio Mortality - Lag 2–5: 0.99 (0.92, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P25 = 11.2 (21.1 $\mu\text{g}/\text{m}^3$) P75 = 19.5 (36.7 $\mu\text{g}/\text{m}^3$) Mean = 7.81 (14.7 $\mu\text{g}/\text{m}^3$) Median = 6.32 (IQR 5.74) (11.9 $\mu\text{g}/\text{m}^3$ (IQR 10.8 $\mu\text{g}/\text{m}^3$) Min = 1.4 (2.7 $\mu\text{g}/\text{m}^3$) Max = 61.6 (115.9 $\mu\text{g}/\text{m}^3$) P25 = 4 (8 $\mu\text{g}/\text{m}^3$) P75 = 9.99 (18.8 $\mu\text{g}/\text{m}^3$)			
†Huang et al. (2023) n = NR Canada 2001–2018 (Hospitalizations) 2001–2015 (Mortality) Time-series	Daily mortality and hospitalizations (non-accidental all-cause, circulatory, and respiratory) using ICD-10 codes	Central site monitor Averaging time: 3-hour max Exposure years: 2001–2018	NO ₂ (ppb) Mean = 16.7 Median = 16.9 Min = 7.1 Max = 30 P25 = 12.9 P75 = 19.5	Cardiovascular mortality (ICD-10, codes I00–I99)	Logistic regression, hierarchical Bayesian model for pooled national estimates Adjusted for: temperature	% change in risk (95% CI) ^c Cardio Mortality - Non-informative priors - Age 65+: 1.01 (1.00, 1.02) Cardio Mortality - Non-informative priors - Age <65: 1.01 (0.99, 1.03) Cardio Mortality - Non-informative priors: 1.01 (1.00, 1.01) Cardio Mortality - Weakly informative priors: 1.01 (1.00, 1.01)
†Kim and Lee (2021) n = 689,019 Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, Ulsan, South	Cause-specific mortality (all-cause, cardiovascular, respiratory) classified by ICD-10	Central site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Busan Mean = 21.2±7.7 Daegu	Cardiovascular mortality (ICD-10, codes I00–I99)	GLM with Poisson distribution and overdispersion, random-effects meta-analysis for pooled estimates	% change in risk (95% CI) ^b Cardio Mortality - Distributed Lag 0-7: 1.01 (0.98, 1.04) Cardio Mortality - DL 0–28: 0.97 (0.91, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Korea 2006–2013 Time-series		Exposure years: 2006–2013	Mean = 23.5±10.3 Daejeon Mean = 20.8±8.9 Gwangju Mean = 20.8±8.8 Incheon Mean = 29.2±12 Seoul Mean = 34.6±12.8 Ulsan Mean = 23±8.1		Adjusted for: humidity, barometric pressure, national holidays, day of week, influenza epidemic, temperature	Cardio Mortality - DL 0–14: 1.00 (0.96, 1.04) Cardio Mortality - Lag 0–2: 1.01 (0.98, 1.03) Cardio Mortality - Lag 0–1: 1.01 (1.00, 1.03) Cardio Mortality - Lag 0: 1.00 (0.99, 1.02) Cardio Mortality - Lag 1: 1.01 (1.00, 1.03) Cardio Mortality - Lag 2: 1.00 (0.98, 1.01)
† Lanzinger et al. (2016) UFIREG n = 4,894,169 Dresden, Germany, Augsburg, Germany, Prague, Czech Republic, Ljubljana, Slovenia, Chernivtsi, Ukraine, Germany, Slovenia, Ukraine, Czech Republic Augsburg and Dresden: January 2011–December 2012; Ljubljana and Prague: January 2012–December 2013; Chernivtsi: January 2013–March 2014	Daily mortality (natural causes, cardiovascular, respiratory) of residents who died in study cities classified by ICD-10 codes. Infants aged <1 year were excluded.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2011–2013	NO ₂ (ppb) Augsburg Mean = 15±6.27 (28±11.8 µg/m ³) Median = 14.3 (IQR 8.56) (26.9 µg/m ³) (IQR 16.1 µg/m ³) Min = 2.2 (4.2 µg/m ³) Max = 39 (74 µg/m ³) Dresden Mean = 11.9±5.3 (22.3±10 µg/m ³) Median = 10.8 (IQR 6.86) (20.4 µg/m ³) (IQR 12.9 µg/m ³) Min = 2.1 (3.9 µg/m ³) Max = 35.8 (67.3	Cardiovascular mortality (ICD-10, codes I00–I99)	Quasi-poisson GAM for city-specific estimates, random-effects meta-analysis for pooled estimates Adjusted for: long-term trends, day of week, public holiday, temperature, humidity, vacation period, population declines, influenza epidemics	% change in risk (95% CI) ^b Cardio Mortality - Lag 0–5: 1.02 (0.91, 1.14) Cardio Mortality - Lag 0–1: 0.97 (0.90, 1.05) Cardio Mortality - Lag 2–5: 1.05 (0.92, 1.21)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Time-series			µg/m³) Ljubljana Mean = 13.3±7.87 (25.1±14.8 µg/m³) Median = 11.8 (IQR 8.72) (22.2 µg/m³) (IQR 16.4 µg/m³) Min = 0.96 (1.8 µg/m³) Max = 63.46 (119.4 µg/m³) Prague Mean = 11.6±6.22 (21.9±11.7 µg/m³) Median = 10.4 (IQR 8.61) (19.5 µg/m³) (IQR 16.2 µg/m³) Min = 2.4 (4.5 µg/m³) Max = 39.4 (74.2 µg/m³)			
† Li et al. (2020) n = 1,575,937 China 2013–2017 Time-series	Daily ischemic and hemorrhagic stroke mortality counts identified with ICD-10 codes from the Chinese Center for Disease Control and Prevention	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2017	NO ₂ (ppb) Mean = 21.1±5 (39.7±9.5 µg/m ³) Median = 20 (IQR 8.72) (38 µg/m ³) (IQR 16.4 µg/m ³) Min = 12.1 (22.8 µg/m ³) Max = 32.2 (60.6 µg/m ³)	Ischemic stroke (ICD-10: I63) Hemorrhagic stroke (ICD-10: I60-I61)	Gaussian GAM for city-specific estimates, random-effects meta-analysis for pooled estimates Adjusted for: calendar day to account for long-term time and seasonal trends (7 df/yr), temperature, humidity, day of week	% change in risk (95% CI) ^b Hemorrhagic Stroke Mortality - Age 65+: 1.03 (1.01, 1.04) Hemorrhagic Stroke Mortality - Age <65: 1.01 (0.99, 1.03) Hemorrhagic Stroke Mortality - CO: 1.01 (1.00, 1.02) Hemorrhagic Stroke Mortality - Female: 1.02 (1.00, 1.04) Hemorrhagic Stroke Mortality -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						Male: 1.02 (1.00, 1.04) Hemorrhagic Stroke Mortality - O ₃ : 1.02 (1.00, 1.03) Hemorrhagic Stroke Mortality - PM _{2.5} : 1.01 (1.00, 1.02) Hemorrhagic Stroke Mortality - SO ₂ : 1.02 (1.00, 1.03) Hemorrhagic Stroke Mortality: 1.02 (1.00, 1.03) Ischemic Stroke Mortality - Age 65+: 1.03 (1.02, 1.05) Ischemic Stroke Mortality - Age <65: 1.02 (0.99, 1.04) Ischemic Stroke Mortality - CO: 1.03 (1.00, 1.05) Ischemic Stroke Mortality - Female: 1.03 (1.02, 1.05) Ischemic Stroke Mortality - Male: 1.03 (1.01, 1.05) Ischemic Stroke Mortality - O ₃ : 1.03 (1.02, 1.04) Ischemic Stroke Mortality - PM _{2.5} : 1.02 (1.00, 1.04) Ischemic Stroke Mortality - SO ₂ : 1.03 (1.01, 1.05) Ischemic Stroke Mortality: 1.03 (1.00, 1.06)
[†] Li et al. (2021) n = 9,600,000 Shanghai, Tianjin, Beijing,	Deaths recorded in the Death Register and Report Information System of Chinese	Central site monitor Averaging time: NO ₂ - 24-hour	NO ₂ (ppb) Mean = 21.1±5 (39.7±9.5 µg/m ³) Median = 20 (IQR	Cardiovascular mortality (ICD-10, codes I00–I99)	Quasi-poisson GAM for city-specific estimates, random-effects meta-analysis for pooled estimates	% change in risk (95% CI) ^b Cardio Mortality - Age 0–64: 1.00 (0.99, 1.02) Cardio Mortality - Age 65–74: 1.03 (1.02, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Changsha, Chongqing, Guangzhou, Changchun, Fuzhou, Hohhot, Jinan, Lanzhou, Nanjing, Qingdao, Suzhou, Xining, Shenyang, Dalian, Hefei, Chengdu, Dazhou, Haerbin, Hengyang, Huanggang, Kunming, Linyi, Luoyang, Nanchang, Nanning, Nantong, Shijiazhuang, Suzhou, Weifang, Xian, Xiangyang, Xinyang, Yancheng, Zhengzhou, Zhoukou, Zunyi, Qiqihaer, Suihua, Tangshan, Wulumuqi, Xiamen, Yantai, Yinchuan, Yueyang, Yuncheng, China 2013–2017 Time-series	Center for Disease Control and Prevention	average Exposure years: 2013–2017	8.72) (38 µg/m ³ (IQR 16.4 µg/m ³) Min = 12.1 (22.8 µg/m ³) Max = 32.2 (60.6 µg/m ³)		Adjusted for: day of week, temperature, humidity, long-term time and seasonal trends (7 df/yr)	Cardio Mortality - Age 75+: 1.03 (1.02, 1.04) Cardio Mortality - CO: 1.01 (1.00, 1.02) Cardio Mortality - Female: 1.03 (1.02, 1.03) Cardio Mortality - Male: 1.01 (1.00, 1.02) Cardio Mortality - O ₃ : 1.02 (1.01, 1.03) Cardio Mortality - PM _{2.5} : 1.01 (1.00, 1.02) Cardio Mortality - Q1 temp: 1.01 (1.00, 1.02) Cardio Mortality - Q2 temp: 1.02 (1.01, 1.03) Cardio Mortality - Q3 temp: 1.02 (1.01, 1.04) Cardio Mortality - Q4 temp: 1.02 (1.00, 1.04) Cardio Mortality - SO ₂ : 1.02 (1.01, 1.03) Cardio Mortality: 1.02 (1.02, 1.03)
† Liu et al. (2022) n = 3,063,192 Georgia, Massachusetts, Michigan, New Jersey, Indiana, Kansas, Ohio, U.S. 2000–2015 Case-crossover	Daily mortality (all-cause, cardiovascular, respiratory) classified by ICD-10 codes	Hybrid model Out-of-sample predicted r ² = 0.79 Averaging time: NO ₂ - 24-hour average Exposure years: 2000–2015	NO ₂ (ppb) Mean = 21.2±12.1	Cardiovascular mortality (ICD-10, codes I00-I99)	Logistic regression Adjusted for: temperature, humidity, negative control outcome, negative control exposure	% change in risk (95% CI) ^b Cardio Mortality - Lag 0–2: 1.00 (0.99, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Meng et al. (2021) n = 62,800,000 U.S., Sweden, China, U.K., Canada, Spain, Japan, South Korea, Taiwan, Brazil, Switzerland, Colombia, Thailand, Germany, Czech Republic, Greece, Australia, Finland, Chile, Estonia, Portugal, Romania 1973–2018 Time-series	Mortality data (total, cardiovascular, and respiratory) obtained from local authorities within each selected country/region using ICD-9 and 10 codes	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1973–2018	NO ₂ (ppb) Pooled Median = 14.3 (26.9 µg/m ³) P25 = 10.4 (19.5 µg/m ³) P75 = 19.2 (36.2 µg/m ³) United States Median = 15.3 (28.7 µg/m ³) P25 = 11.1 (20.8 µg/m ³) P75 = 20.5 (38.6 µg/m ³)	Cardiovascular mortality (ICD-10, codes I00-I99)	Quasi-poisson GLM for city-specific estimates, random-effects meta-analysis for pooled estimates Adjusted for: long-term trends, seasonality, day of week, temperature, relative humidity	% change in risk (95% CI) ^b Cardio Mortality- Lag 1: 1.01 (1.01, 1.02) Cardio Mortality- Lag 01: 1.01 (1.01, 1.02) Cardio Mortality- Lag 2: 1.01 (1.01, 1.02) Cardio Mortality- Lag 3: 1.00 (1.00, 1.01) Cardio Mortality - United States Lag 1: 1.02 (1.01, 1.02)
†Milojevic et al. (2014) n = 452,343 England, Wales, U.K. 2003–2009 Case-crossover	Residents in England and Wales that were in one of the three databases Myocardial Ischaemia National Audit Project (MINAP) database, Hospital Episode Statistics (HES) and mortality (Office for National Statistics) and patients with a discharge diagnosis of ST elevation MI, non-ST elevation MI, or troponin-positive acute coronary syndrome.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: NR	NO ₂ (ppb) Median = 13 (24 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 20 (37 µg/m ³)	Cardiovascular mortality (ICD-10, codes I00-I99)	Logistic regression Adjusted for: temperature	% change in risk (95% CI) ^b AF Mortality: 0.99 (0.89, 1.10) All Cardio Mortality - 70+: 1.00 (0.98, 1.01) All Cardio Mortality - <70: 0.99 (0.96, 1.02) All Cardio Mortality - Females: 0.99 (0.97, 1.01) All Cardio Mortality - Males: 1.00 (0.98, 1.02) All Cardio Mortality: 1.00 (0.98, 1.01) Arrhythmias Mortality: 0.99 (0.89, 1.11) Chronic IHD Mortality: 0.99 (0.97, 1.02) HF Mortality: 0.98 (0.92, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						IHD Mortality: 0.99 (0.98, 1.01) MI Mortality: 0.99 (0.96, 1.02) Non-MI Mortality: 1.00 (0.98, 1.01) PE Mortality: 0.97 (0.87, 1.08) Stroke Mortality: 1.02 (0.99, 1.04)
† Perez et al. (2015) n = 2,240,694 Switzerland 1995–2010 Time-series	ED admissions and deaths (all cause, cardiovascular, respiratory) classified using ICD-10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1995–2010	NO ₂ (ppb) Region AG/BE/LU/SO Mean = 21 (39 µg/m ³) Region AG/BL/BS/SO Mean = 14.1 (26.6 µg/m ³) Region AI/AR/FL/SG Mean = 9.62 (18.1 µg/m ³) Region AI/AR/SG/TG Mean = 8.18 (15.4 µg/m ³) Region BE Mean = 14.6 (27.5 µg/m ³) Region BE/FR/SO	Cardiovascular mortality (ICD-10 codes I00–I99 [excluding I67.3, I68.0, I88, I97.8, I97.9, I98.0])	Poisson GAM for region-specific estimates, random-effects meta-analysis for pooled estimate Adjusted for: temperature, humidity, barometric pressure, day of week, holiday	OR (95% CI) ^b Cardio Mortality - PM ₁₀ : 1.01 (0.98, 1.04) Cardio Mortality: 1.02 (1.00, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 8.61 (16.2 µg/m ³)			
			Region GR Mean = 16.6 (31.3 µg/m ³)			
			Region LU/NW/OW/ SZ/UR Mean = 12.6 (23.7 µg/m ³)			
			Region LU/ZG Mean = 14.3 (26.9 µg/m ³)			
			Region SG/SH/SZ/ZH Mean = 19.1 (35.9 µg/m ³)			
			Region TISopraceneri/GR Mean = 13 (24 µg/m ³)			
			Region TISottoceneri Mean = 20.4 (38.4 µg/m ³)			
			Region VS Mean = 18.9 (35.6 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Schwarz et al. (2024) n = 29,300,000 (estimate as exact numbers are not reported) U.S., Sweden, China, France, U.K., Canada, Spain, Japan, South Korea, Taiwan, Iran, South Africa, Switzerland, Norway, Colombia, Thailand, Czech Republic, Greece, Mexico, Finland, Estonia, Portugal, Cyprus, Kuwait January 1, 1995, and December 31, 2016 Cross-Sectional	Mortality data from the MCC database	Central site monitor Averaging time: NO₂ - 24-hour average Exposure years: 1994–2016	NO₂ (ppb) Median = 13.6 (25.6 µg/m³) P25 = 9.94 (18.7 µg/m³) P75 = 18.3 (34.4 µg/m³)	Cardiovascular mortality (ICD-10, codes I00–I99)	Quasi-poisson GLM for city-specific estimates, random-effects meta-analysis for pooled estimates Adjusted for: long-term trends, seasonality, day of week, temperature, relative humidity	% change in risk (95% CI)^b Cardio Mortality - Lag 1 - 1995–2001: 1.01 (1.01, 1.02) Cardio Mortality - Lag 1 - 2002–2008: 1.01 (1.01, 1.02) Cardio Mortality - Lag 1 - 2009–2016: 1.01 (1.01, 1.02)
†Shin et al. (2022) n = NR Montreal, Halton, Ontario, London, Ontario, Toronto, Ontario, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Sudbury, Halifax, Saint John, Quebec City, Ottawa, Durham, York, Peel, Niagara, Waterloo, Sarnia, Sault Sainte Marie, Regina, Saskatoon, Calgary, Canada 1984–2012 Time-series	Mortality and hospitalization daily counts (all-cause, circulatory, and respiratory) classified by ICD-9 and 10 codes	Central site monitor Averaging time: NO₂ - 24-hour average Exposure years: 1984–2012	NO₂ (ppb) Population-weighted Cold season Mean = 20±4 Warm season Mean = 16±4 Year Mean = 18 Min = 8 Max = 28	Cardiovascular mortality (ICD-10, codes I00–I99)	Quasi-poisson GAM for city-specific estimates, Bayesian hierarchical model for pooled estimates Adjusted for: day of week, calendar time (Slepian smoothing to separate short- vs. long-term air pollution effects), temperature	% change in risk (95% CI)^b Cardio Mortality - Lag 0 - Cold season, female: 1.01 (0.98, 1.04) Cardio Mortality - Lag 0 - Cold season, male: 0.98 (0.96, 1.00) Cardio Mortality - Lag 0 - Warm season, female: 1.02 (0.98, 1.06) Cardio Mortality - Lag 0 - Warm season, male: 1.01 (0.98, 1.05) Cardio Mortality - Lag 0 - Year round, female: 1.05 (1.01, 1.08) Cardio Mortality - Lag 0 - Year

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						round, male: 1.05 (1.02, 1.08)
† Shin et al. (2023)	Daily circulatory hospitalizations and mortality counts across 24 census divisions in Canada assessed using ICD-9 and ICD-10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2012	NO ₂ (ppb) Cold season (Oct–Mar) Mean = 15±4.3 Warm season (Apr–Sep) Mean = 10±3.1	Cardiovascular mortality (ICD-10, codes I00-I99)	Poisson GAM for census district-specific estimates, hierarchical Bayesian model for pooled national estimates Adjusted for: calendar time, temperature	RR (95% CI) ^b Cardio Mortality - Cold season (Oct–Mar) - Lag 0: 0.99 (0.96, 1.01) Cardio Mortality - Cold season (Oct–Mar) - Lag 1: 1.01 (0.99, 1.03) Cardio Mortality - Cold season (Oct–Mar) - Lag 2: 1.01 (0.99, 1.04) Cardio Mortality - Cold season (Oct–Mar) - Lag 3: 1.02 (1.00, 1.04) Cardio Mortality - Cold season (Oct–Mar) - Lag 4: 1.02 (1.00, 1.04) Cardio Mortality - Cold season (Oct–Mar) - Lag 5: 1.01 (0.99, 1.03) Cardio Mortality - Cold season (Oct–Mar) - Lag 6: 0.99 (0.97, 1.01) Cardio Mortality - O ₃ - Year round - Lag 0: 1.00 (0.98, 1.02) Cardio Mortality - O ₃ - Year round - Lag 1: 1.02 (1.00, 1.03) Cardio Mortality - O ₃ - Year round - Lag 2: 1.01 (0.99, 1.02) Cardio Mortality - O ₃ - Year round - Lag 3: 1.00 (0.98, 1.01) Cardio Mortality - O ₃ - Year round -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						Lag 4: 1.01 (0.99, 1.02) Cardio Mortality - O ₃ - Year round - Lag 5: 1.00 (0.98, 1.02) Cardio Mortality - O ₃ - Year round - Lag 6: 0.98 (0.97, 1.00) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 0: 1.00 (0.97, 1.02) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 1: 1.01 (0.98, 1.03) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 2: 1.01 (0.99, 1.03) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 3: 1.02 (0.99, 1.04) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 4: 1.02 (1.00, 1.05) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 5: 1.01 (0.99, 1.04) Cardio Mortality - O ₃ ; Cold season (Oct–Mar) - Lag 6: 0.99 (0.97, 1.01) Cardio Mortality - O ₃ ; Warm season (Apr–Sep) - Lag 0: 1.00 (0.96, 1.03) Cardio Mortality - O ₃ ; Warm season (Apr–Sep) - Lag 1: 1.00 (0.97, 1.04) Cardio Mortality - O ₃ ; Warm season (Apr–Sep) - Lag 2: 0.99 (0.96, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						Cardio Mortality - O ₃ ; Warm season (Apr-Sep) - Lag 3: 0.96 (0.93, 1.00)
						Cardio Mortality - O ₃ ; Warm season (Apr-Sep) - Lag 4: 1.01 (0.98, 1.04)
						Cardio Mortality - O ₃ ; Warm season (Apr-Sep) - Lag 5: 0.99 (0.96, 1.03)
						Cardio Mortality - O ₃ ; Warm season (Apr-Sep) - Lag 6: 0.99 (0.95, 1.04)
						Cardio Mortality - PM _{2.5} - Year round - Lag 0: 0.99 (0.97, 1.01)
						Cardio Mortality - PM _{2.5} - Year round - Lag 1: 1.00 (0.89, 1.12)
						Cardio Mortality - PM _{2.5} - Year round - Lag 2: 1.00 (0.98, 1.02)
						Cardio Mortality - PM _{2.5} - Year round - Lag 3: 1.00 (0.98, 1.02)
						Cardio Mortality - PM _{2.5} - Year round - Lag 4: 1.01 (0.99, 1.03)
						Cardio Mortality - PM _{2.5} - Year round - Lag 5: 1.00 (0.98, 1.02)
						Cardio Mortality - PM _{2.5} -Year round - Lag 6: 0.99 (0.97, 1.00)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 0: 0.99 (0.97, 1.01)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						1.00 (0.89, 1.13)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 2:
						1.00 (0.98, 1.02)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 3:
						1.00 (0.82, 1.22)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 4:
						1.01 (0.99, 1.03)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 5:
						1.00 (0.98, 1.02)
						Cardio Mortality - PM _{2.5} +O ₃ -Year round - Lag 6:
						0.98 (0.96, 1.01)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 0:
						0.99 (0.95, 1.03)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 1:
						0.99 (0.95, 1.03)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 2:
						0.98 (0.95, 1.02)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 3:
						1.02 (0.89, 1.16)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 4:
						1.02 (0.98, 1.06)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 5:
						1.02 (0.99, 1.06)
						Cardio Mortality - PM _{2.5} +O ₃ ; Cold season (Oct–Mar) - Lag 6:
						0.81 (0.78, 0.84)
						Cardio Mortality - PM _{2.5} +O ₃ ; Warm

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						season (Apr–Sep) - Lag 0: 0.99 (0.95, 1.03) Cardio Mortality - PM _{2.5} +O ₃ ; Warm season (Apr–Sep) - Lag 1: 1.00 (0.96, 1.03) Cardio Mortality - PM _{2.5} +O ₃ ; Warm season (Apr–Sep) - Lag 2: 1.00 (0.96, 1.05) Cardio Mortality - PM _{2.5} +O ₃ ; Warm season (Apr–Sep) - Lag 3: 0.95 (0.91, 0.99) Cardio Mortality - PM _{2.5} +O ₃ ; Warm season (Apr–Sep) - Lag 4: 1.00 (0.97, 1.03) Cardio Mortality - PM _{2.5} +O ₃ ; Warm season (Apr–Sep) - Lag 5: 0.98 (0.95, 1.02) Cardio Mortality - PM _{2.5} +O ₃ ; Warm season (Apr–Sep) - Lag 6: 1.00 (0.94, 1.06) Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 0: 0.98 (0.95, 1.00) Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 1: 1.00 (0.97, 1.02) Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 2: 1.00 (0.98, 1.03) Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 3: 1.02 (0.99, 1.05) Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 4: 1.02 (0.99, 1.05) Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 5: 1.02 (0.99, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						Cardio Mortality - PM _{2.5} ; Cold season (Oct–Mar) - Lag 6: 0.98 (0.96, 1.01)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 0: 0.99 (0.96, 1.03)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 1: 1.00 (0.96, 1.03)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 2: 1.00 (0.96, 1.04)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 3: 0.96 (0.93, 1.00)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 4: 1.00 (0.97, 1.04)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 5: 0.98 (0.95, 1.02)
						Cardio Mortality - PM _{2.5} ; Warm season (Apr–Sep) - Lag 6: 0.99 (0.95, 1.04)
						Cardio Mortality - Warm season (Apr–Sep) - Lag 0: 0.99 (0.96, 1.03)
						Cardio Mortality - Warm season (Apr–Sep) - Lag 1: 1.00 (0.97, 1.03)
						Cardio Mortality - Warm season (Apr–Sep) - Lag 2: 1.00 (0.96, 1.03)
						Cardio Mortality - Warm season (Apr–Sep) - Lag 3: 0.97 (0.94, 1.00)
						Cardio Mortality - Warm season (Apr–Sep) - Lag 4: 0.97 (0.94, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						1.01 (0.98, 1.04) Cardio Mortality - Warm season (Apr–Sep) - Lag 5: 1.00 (0.96, 1.03) Cardio Mortality - Warm season (Apr–Sep) - Lag 6: 1.01 (0.98, 1.03) Cardio Mortality - Year round - Lag 0: 1.00 (0.98, 1.02) Cardio Mortality - Year round - Lag 1: 1.01 (0.99, 1.03) Cardio Mortality - Year round - Lag 2: 1.01 (0.99, 1.02) Cardio Mortality - Year round - Lag 3: 1.00 (0.99, 1.02) Cardio Mortality - Year round - Lag 4: 1.01 (0.99, 1.02) Cardio Mortality - Year round - Lag 5: 1.00 (0.89, 1.11) Cardio Mortality - Year round - Lag 6: 0.98 (0.97, 1.00)
† Stafoggia and Bellander (2020) n = 125,468 Stockholm County, Sweden 2005–2016	Individuals aged 75+ who experienced non-accidental deaths using ICD-10 codes	Spatiotemporal/geospatial model, Fixed site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) spatiotemporal model Mean = 10±5.2 (18.9±9.8 µg/m ³) Median = 8.61 (16.2 µg/m ³) Min = 0.43 (0.8	Cardiovascular mortality (ICD-10, codes I00-I99)	Logistic regression Adjusted for: temperature	% change in risk (95% CI) ^b Cardio Mortality - Cold season (Oct–Mar) - Lag 05: 0.99 (0.85, 1.16) Cardio Mortality - Cold season (Oct–Mar) - Lag 25: 1.05 (0.92, 1.19) Cardio Mortality - Lag 01: 0.99 (0.91, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Case-crossover		Exposure years: 2005–2016	$\mu\text{g}/\text{m}^3$ Max = 51.2 (96.3 $\mu\text{g}/\text{m}^3$) P25 = 6.43 (12.1 $\mu\text{g}/\text{m}^3$) P75 = 12.4 (23.4 $\mu\text{g}/\text{m}^3$) urban background monitor Mean = 7.07 ± 4 ($13.3 \pm 7.6 \mu\text{g}/\text{m}^3$) Median = 6.22 (11.7 $\mu\text{g}/\text{m}^3$) Min = 0.37 (0.7 $\mu\text{g}/\text{m}^3$) Max = 30 (56.5 $\mu\text{g}/\text{m}^3$) P25 = 4.1 (7.8 $\mu\text{g}/\text{m}^3$) P75 = 9 (17 $\mu\text{g}/\text{m}^3$)			Cardio Mortality - Lag 05: 1.07 (0.94, 1.22) Cardio Mortality - Lag 25: 1.08 (0.97, 1.21) Cardio Mortality - O ₃ - Lag 01: 1.10 (1.00, 1.21) Cardio Mortality - PM _{2.5} - Lag 01: 1.04 (0.95, 1.14) Cardio Mortality - PM ₁₀ - Lag 01: 1.06 (0.96, 1.16) Cardio Mortality - Warm season (Apr–Sep)- Lag 05: 1.22 (0.96, 1.56) Cardio Mortality - Warm season (Apr–Sep)- Lag 25: 1.12 (0.91, 1.38) Cardio Mortality - Warm season (Apr–Sep)- O ₃ - Lag 01: 1.13 (0.96, 1.33) Cardio Mortality - Warm season (Apr–Sep)- PM _{2.5} - Lag 01: 1.04 (0.87, 1.24) Cardio Mortality - Warm season (Apr–Sep)- PM ₁₀ - Lag 01: 1.00 (0.83, 1.21) Cardio Mortality - Warm season (Apr–Sep) - Lag 01: 1.17 (0.98, 1.40) Cardio Mortality - Cold season (Oct–Mar) - Lag 01: 0.94 (0.84, 1.04)
†Vanos et al. (2014) n = NR Toronto, Vancouver, Montreal, Windsor, Ontario, Edmonton,	Mortality data from 10 Canadian cities from all non-accidental, respiratory- and	Central site monitor Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) All weather types Mean = 21.1 ± 1.14 Dry moderate	Cardiovascular mortality (ICD 9)	Piece-wise Poisson GLM for city-specific estimates, random-effects meta-analysis for pooled estimates	HR (95% CI) ^b Cardio Mortality - Fall (Oct–Dec): 1.04 (1.00, 1.08) Cardio Mortality - Spring (Apr–Jun): 1.05 (1.04, 1.06) Cardio Mortality - Summer (Jul–

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Winnipeg, Saint John, Quebec City, Ottawa, Calgary, Canada 1981–1999 Time-series	cardiovascular-related causes	Exposure years: 1981–1999	Mean = 22.1±5.78 Dry polar Mean = 21.8±5.76 Dry tropical Mean = 25±6.02 Moist moderate Mean = 21.1±5.56 Moist polar Mean = 19.8±5.25 Moist tropical Mean = 22±6.42 Transition Mean = 19.5±5.12		Adjusted for: day of week	Sep): 1.04 (1.02, 1.06) Cardio Mortality - Winter (Jan–Mar): 1.03 (1.02, 1.04)
† Xu et al. (2022) n = 412,567 Jiangsu Province, China 2015–2019 Case-crossover	Daily ischemic and hemorrhagic stroke mortality from China National Mortality Surveillance System classified by ICD-10 codes	Hybrid model Model incorporated ground measurements, satellite data, atmospheric reanalysis, and model simulations with r ² = 0.84. Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Hemorrhagic stroke Mean = 18.8±7.81 (35.4±14.7 µg/m ³) Median = 17.3 (32.5 µg/m ³) Min = 2 (4 µg/m ³) Max = 68.98 (129.8 µg/m ³) P5 = 9.09 (17.1 µg/m ³) P25 = 13.2 (24.8 µg/m ³) P75 = 22.9 (43.1 µg/m ³) P95 = 33.7 (63.5 µg/m ³)	Total stroke mortality (ICD-10, I60-I64)	Logistic regression Adjusted for: temperature, humidity	% change in risk (95% CI) ^b Hemorrhagic Stroke Mortality - Lag01: 1.03 (1.01, 1.06) Hemorrhagic Stroke Mortality - Lag04 - CO: 0.99 (0.95, 1.03) Hemorrhagic Stroke Mortality - Lag04 - Cold Season: 1.07 (1.03, 1.10) Hemorrhagic Stroke Mortality - Lag04 - O ₃ : 1.04 (1.01, 1.08) Hemorrhagic Stroke Mortality - Lag04 - PM _{2.5} : 1.00 (0.95, 1.04) Hemorrhagic Stroke Mortality - Lag04 - PM ₁₀ :

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
		Exposure years: 2015–2019	Ischemic stroke Mean = 19±7.81 (35.8±14.7 µg/m ³) Median = 17.5 (32.9 µg/m ³) Min = 1.7 (3.2 µg/m ³) Max = 77.27 (145.4 µg/m ³) P5 = 9.19 (17.3 µg/m ³) P25 = 13.3 (25.1 µg/m ³) P75 = 23.3 (43.8 µg/m ³) P95 = 33.8 (63.6 µg/m ³) Total stroke Mean = 19±7.87 (35.7±14.8 µg/m ³) Median = 17.4 (32.7 µg/m ³) Min = 1.7 (3.2 µg/m ³) Max = 77.27 (145.4 µg/m ³) P5 = 9.14 (17.2 µg/m ³) P25 = 13 (25 µg/m ³) P75 = 23.1 (43.5 µg/m ³) P95 = 33.9 (63.8 µg/m ³)			1.00 (0.98, 1.02) Hemorrhagic Stroke Mortality - Lag04 - SO ₂ : 1.01 (0.97, 1.05) Hemorrhagic Stroke Mortality - Lag04 - Warm Season: 1.00 (0.94, 1.06) Hemorrhagic Stroke Mortality - Lag04: 1.06 (1.03, 1.09) Ischemic Stroke Mortality - Lag01: 1.08 (1.05, 1.10) Ischemic Stroke Mortality - Lag04 - CO: 1.06 (1.02, 1.10) Ischemic Stroke Mortality - Lag04 - Cold Season: 1.10 (1.07, 1.13) Ischemic Stroke Mortality - Lag04 - O ₃ : 1.11 (1.08, 1.14) Ischemic Stroke Mortality - Lag04 - PM _{2.5} : 1.04 (1.01, 1.07) Ischemic Stroke Mortality - Lag04 - PM ₁₀ : 1.06 (1.02, 1.10) Ischemic Stroke Mortality - Lag04 - SO ₂ : 1.08 (1.05, 1.12) Ischemic Stroke Mortality - Lag04 - Warm Season: 1.17 (1.11, 1.24) Ischemic Stroke Mortality - Lag04: 1.11 (1.09, 1.14) Total Stroke Mortality - Lag01: 1.06 (1.04, 1.07) Total Stroke Mortality - Lag04 - CO:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						1.03 (1.00, 1.06)
						Total Stroke Mortality - Lag04 - O ₃ :
						1.08 (1.06, 1.10)
						Total Stroke Mortality - Lag04 - PM _{2.5} :
						1.02 (0.99, 1.05)
						Total Stroke Mortality - Lag04 - PM ₁₀ :
						1.03 (1.01, 1.06)
						Total Stroke Mortality - Lag04 - SO ₂ :
						1.05 (1.02, 1.08)
						Total Stroke Mortality - Lag04:
						1.08 (1.07, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yap et al. (2019) n = NR Singapore 2001–2013 Time-series	General population: Mortality data from the Registry of Births & Deaths in Singapore	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2013	NO ₂ (ppb) Mean = 13±3.6 (25±6.8 µg/m ³) Min = 3.9 (7.4 µg/m ³) Max = 32.3 (60.7 µg/m ³) P10 = 8.93 (16.8 µg/m ³) P90 = 17.9 (33.7 µg/m ³)	Cardiovascular mortality (ICD-9 390–459 & ICD- 10 I00-I99)	Quasi-poisson GAM Adjusted for: day of week, long-term trends, temperature, humidity, influenza epidemic, public holidays	% change in risk (95% CI) ^b Cardio Mortality - Lag 0–30: 0.94 (0.84, 1.05) Cardio Mortality - Lag 0–15: 0.89 (0.81, 0.97) Cardio Mortality - Lag 0–5: 0.95 (0.84, 1.08) Cardio Mortality - Lag 0: 0.99 (0.94, 1.04) Cardio Mortality - Lag 1: 0.99 (0.95, 1.05) Cardio Mortality - Lag 2: 0.97 (0.92, 1.02) Cardio Mortality - Lag 3: 0.99 (0.94, 1.04)

List of Abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; CO = carbon monoxide; HR = hazard ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; O₃ = ozone; OR = odds ratio; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; RR = rate ratio; SO₂ = sulfur dioxide.

^aFor studies with standardized effect estimates, values were converted–ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

A.4. Cardiovascular Effects – Long-term Exposure

Appendix Table 6-1 Epidemiologic studies of exposure to oxides of nitrogen and myocardial infarction and coronary heart disease

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Bai et al. (2019b) ONPHEC CHF Cohort N = 1,112,060 AMI Cohort N = 1,127,209 Toronto, Canada Enrollment: April 1, 1996 Follow-up: through December 31, 2012 Cohort	Restricted to persons were aged 30-100-years, had been living in Toronto for at least 3-years prior to entry, and had no history of physician-diagnosed CHF or AMI at Enrollment	LUR The r ² value for the final regression model was 70% Averaging time: NO ₂ - 3-year moving averages Exposure years: 2002-2004	NO ₂ (ppb) Estimated Exposure Mean = 21.4 ± 3.5 Median = 21.1 (IQR 4) Min = 9.9 Max = 50.1	Hospital discharge reports and national databases	Cox proportional hazards Adjusted for: Census tract-level percentage of recent immigrants, percentage of the population aged ≥ 15-years without employment, percentage of the population aged ≥ 15-years with less than a high school education, and annual household income	HR (95% CI) ^b MI: 1.05 (1.00, 1.10)
† Bai et al. (2019a) ONPHEC AMI Cohort N = 5,141,172 Incident MI Cases N = 197,628 Enrollment: 2001 Follow-up: 2015 Cohort	Longterm residents of Ontario, Canada, Age 35-85 yrs	LUR Model explained 75% of variability in NO ₂ measurements at fixed site monitors (RMSE = 2.9 ppb) Averaging time: 3-year moving average Exposure years: 2001-2015	NO ₂ (ppb) Mean = 18.3 Median: 17.1 IQR = 13.9 Min = 2.7 Max = 71.4	Hospital Discharge Records	Cox Proportional Hazards Adjusted for: Census tract-level percentage of recent immigrants, percentage of the population aged ≥ 15-years without employment, percentage of the population aged ≥ 15-years with less than a high school education, and annual household income	HR (95% CI) ^b MI: 1.05 (1.00, 1.10)

† Brunekreef et al. (2021)	ELAPSE Project (pooled cohort): European population	LUR, Chemical transport model, Hybrid model	NO ₂ (ppb)	Registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases	Cox proportional hazards	HR (95% CI) ^b CHD: 1.08 (1.02, 1.14)
ELAPSE: CEANS,DCH,E3N cohort, ESCAPE, VHM&PP, HNR study,KORA,DNC,E PIC-MORGEN, EPIC-Prospect, EPIC-Varese		r ² = 58%	CEANS-SALT Cohort Mean = 11.31 ± 3.28 (21.29 ± 6.18 µg/m ³) Median = 11.17 (IQR 3.9) (21.02 µg/m ³ (IQR 7.33 µg/m ³)) Min = 1.58 (2.98 µg/m ³) Max = 26.85 (50.53 µg/m ³) P5 = 5.958 (11.21 µg/m ³) P25 = 9.327 (17.55 µg/m ³) P75 = 13.22 (24.88 µg/m ³) P95 = 16.94 (31.87 µg/m ³)		Adjusted for: Cohort ID, age, sex, year of Enrollment visit, smoking, BMI, marital status, employment status, 2001 neighborhood-level mean income	
n = 325,000		Averaging time: NO ₂ - annual average				
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, The Netherlands		Exposure years: 2010	CEANS-SDPP Cohort Mean = 8.259 ± 2.28 (15.54 ± 4.29 µg/m ³) Median = 8.269 (IQR 2.86) (15.56 µg/m ³ (IQR 5.38 µg/m ³)) Min = 1.57 (2.96 µg/m ³) Max = 19.71 (37.09 µg/m ³) P5 = 4.15 (7.81 µg/m ³) P25 = 6.792 (12.78 µg/m ³) P75 = 9.651 (18.16 µg/m ³) P95 = 11.94 (22.46 µg/m ³)			
Recruitment: 1992-2011 Follow-up: 2011-2017			CEANS-SIXTY Cohort Mean = 10.99 ± 3.26 (20.68 ± 6.13 µg/m ³) Median = 10.92 (IQR 4) (20.54 µg/m ³ (IQR 7 µg/m ³)) Min = 1.42 (2.68 µg/m ³) Max = 25.45 (47.88 µg/m ³) P5 = 5.69 (10.7 µg/m ³) P25 = 9.051 (17.03 µg/m ³) P75 = 12.77 (24.03 µg/m ³) P95 = 16.62 (31.28 µg/m ³)			
Cohort			CEANS-SNACK Cohort Mean = 14.56 ± 2.71			

(27.39 ± 5.09 µg/m³)
Median = 15.1 (IQR 3.92)
(28.5 µg/m³ (IQR 7.38
µg/m³))
Min = 6.176 (11.62 µg/m³)
Max = 22.65 (42.61 µg/m³)
P5 = 9.71 (18.27 µg/m³)
P25 = 12.52 (23.56 µg/m³)
P75 = 16.45 (30.95 µg/m³)
P95 = 18.04 (33.94 µg/m³)

DCH Cohort
Mean = 14.9 ± 3.64 (28.04
± 6.84 µg/m³)
Median = 15.05 (IQR 5.3)
(28.32 µg/m³ (IQR 10
µg/m³))
Min = 3.4 (6.4 µg/m³)
Max = 38.39 (72.23 µg/m³)
P5 = 8.79 (16.54 µg/m³)
P25 = 12.36 (23.26 µg/m³)
P75 = 17.68 (33.26 µg/m³)
P95 = 20.31 (38.22 µg/m³)

DNC-1999 Cohort
Mean = 13.74 ± 4.5 (25.85
± 8.47 µg/m³)
Median = 12.63 (IQR
7.345) (23.76 µg/m³ (IQR
13.82 µg/m³))
Min = 3.41 (6.42 µg/m³)
Max = 28.84 (54.26 µg/m³)
P5 = 7.286 (13.71 µg/m³)
P25 = 10.32 (19.42 µg/m³)
P75 = 17.67 (33.24 µg/m³)
P95 = 20.7 (38.95 µg/m³)

DNC-1993 Cohort
Mean = 11.6 ± 4 (21.9 ± 8
µg/m³)
Median = 10.83 (IQR
5.591) (20.37 µg/m³ (IQR
10.52 µg/m³))

Min = 2.41 (4.54 $\mu\text{g}/\text{m}^3$)
Max = 38.39 (72.23 $\mu\text{g}/\text{m}^3$)
P5 = 5.41 (10.18 $\mu\text{g}/\text{m}^3$)
P25 = 8.689 (16.35 $\mu\text{g}/\text{m}^3$)
P75 = 14.28 (26.87 $\mu\text{g}/\text{m}^3$)
P95 = 19.7 (37.07 $\mu\text{g}/\text{m}^3$)

E3N Cohort
Mean = 14.01 $\pm$ 5.18
(26.36 $\pm$ 9.75 $\mu\text{g}/\text{m}^3$)
Median = 13.06 (IQR
6.664) (24.57 $\mu\text{g}/\text{m}^3$ (IQR
12.54 $\mu\text{g}/\text{m}^3$))
Min = 1.84 (3.46 $\mu\text{g}/\text{m}^3$)
Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$)
P5 = 7.12 (13.4 $\mu\text{g}/\text{m}^3$)
P25 = 10.27 (19.32 $\mu\text{g}/\text{m}^3$)
P75 = 16.93 (31.86 $\mu\text{g}/\text{m}^3$)
P95 = 24.23 (45.59 $\mu\text{g}/\text{m}^3$)

EPIC-NL-MORGEN
Cohort
Mean = 18.36 $\pm$ 3.22
(34.55 $\pm$ 6.05 $\mu\text{g}/\text{m}^3$)
Median = 17.9 (IQR 4.77)
(33.6 $\mu\text{g}/\text{m}^3$ (IQR 8.97
 $\mu\text{g}/\text{m}^3$))
Min = 5.8 (11 $\mu\text{g}/\text{m}^3$)
Max = 36.49 (68.66 $\mu\text{g}/\text{m}^3$)
P5 = 13.91 (26.18 $\mu\text{g}/\text{m}^3$)
P25 = 15.93 (29.97 $\mu\text{g}/\text{m}^3$)
P75 = 20.69 (38.94 $\mu\text{g}/\text{m}^3$)
P95 = 23.8 (44.8 $\mu\text{g}/\text{m}^3$)

EPIC-NL-PROSPECT
Cohort
Mean = 19.11 $\pm$ 2.88
(35.96 $\pm$ 5.41 $\mu\text{g}/\text{m}^3$)
Median = 18.85 (IQR 3.86)
(35.46 $\mu\text{g}/\text{m}^3$ (IQR 7.27
 $\mu\text{g}/\text{m}^3$))
Min = 10.41 (19.58 $\mu\text{g}/\text{m}^3$)
Max = 33.03 (62.15 $\mu\text{g}/\text{m}^3$)

P5 = 14.6 (27.4 $\mu\text{g}/\text{m}^3$)
P25 = 17.28 (32.52 $\mu\text{g}/\text{m}^3$)
P75 = 21.15 (39.79 $\mu\text{g}/\text{m}^3$)
P95 = 23.72 (44.63 $\mu\text{g}/\text{m}^3$)

HNR Cohort
Mean = 20.08 ± 2.48
(37.78 ± 4.66 $\mu\text{g}/\text{m}^3$)
Median = 19.95 (IQR 2.67)
(37.54 $\mu\text{g}/\text{m}^3$ (IQR 5.03
 $\mu\text{g}/\text{m}^3$))
Min = 13.41 (25.23 $\mu\text{g}/\text{m}^3$)
Max = 39.9 (75.07 $\mu\text{g}/\text{m}^3$)
P5 = 16.61 (31.26 $\mu\text{g}/\text{m}^3$)
P25 = 18.53 (34.87 $\mu\text{g}/\text{m}^3$)
P75 = 21.2 (39.9 $\mu\text{g}/\text{m}^3$)
P95 = 24.36 (45.83 $\mu\text{g}/\text{m}^3$)

KORA-S3 Cohort
Mean = 11.23 ± 1.8 (21.13
 ± 3.3 $\mu\text{g}/\text{m}^3$)
Median = 11.14 (IQR 2.3)
(20.97 $\mu\text{g}/\text{m}^3$ (IQR 4.32
 $\mu\text{g}/\text{m}^3$))
Min = 5.538 (10.42 $\mu\text{g}/\text{m}^3$)
Max = 22.17 (41.72 $\mu\text{g}/\text{m}^3$)
P5 = 8.66 (16.3 $\mu\text{g}/\text{m}^3$)
P25 = 10.03 (18.88 $\mu\text{g}/\text{m}^3$)
P75 = 12.34 (23.21 $\mu\text{g}/\text{m}^3$)
P95 = 14.04 (26.41 $\mu\text{g}/\text{m}^3$)

KORA-S4 Cohort
Mean = 11.19 ± 1.8 (21.05
 ± 3.39 $\mu\text{g}/\text{m}^3$)
Median = 11.06 (IQR 2.39)
(20.82 $\mu\text{g}/\text{m}^3$ (IQR 4.49
 $\mu\text{g}/\text{m}^3$))
Min = 5.14 (9.68 $\mu\text{g}/\text{m}^3$)
Max = 22.17 (41.72 $\mu\text{g}/\text{m}^3$)
P5 = 9.97 (18.76 $\mu\text{g}/\text{m}^3$)
P25 = 12.35 (23.24 $\mu\text{g}/\text{m}^3$)
P75 = 14.1 (26.5 $\mu\text{g}/\text{m}^3$)
P95 = 22.17 (41.72 $\mu\text{g}/\text{m}^3$)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Pooled Cohort Mean = 13 ± 4.28 ($25 \pm 8.05 \mu\text{g}/\text{m}^3$) Median = 12.83 (IQR 5.394) ($24.14 \mu\text{g}/\text{m}^3$ (IQR $10.15 \mu\text{g}/\text{m}^3$)) Min = 1.42 ($2.68 \mu\text{g}/\text{m}^3$) Max = 43.06 ($81.02 \mu\text{g}/\text{m}^3$) P5 = 6.861 ($12.91 \mu\text{g}/\text{m}^3$) P25 = 10.37 ($19.52 \mu\text{g}/\text{m}^3$) P75 = 15.77 ($29.68 \mu\text{g}/\text{m}^3$) P95 = 21.01 ($39.53 \mu\text{g}/\text{m}^3$)			
			VHM&PP Cohort Mean = 11.67 ± 2.84 ($21.96 \pm 5.34 \mu\text{g}/\text{m}^3$) Median = 11.94 (IQR 3.71) ($22.46 \mu\text{g}/\text{m}^3$ (IQR $6.99 \mu\text{g}/\text{m}^3$)) Min = 2.05 ($3.85 \mu\text{g}/\text{m}^3$) Max = 25.66 ($48.28 \mu\text{g}/\text{m}^3$) P5 = 6.532 ($12.29 \mu\text{g}/\text{m}^3$) P25 = 9.901 ($18.63 \mu\text{g}/\text{m}^3$) P75 = 13.62 ($25.62 \mu\text{g}/\text{m}^3$) P95 = 15.8 ($29.7 \mu\text{g}/\text{m}^3$)			

†Cai et al. (2018)						
UK Biobank, EPIC-Oxford, HUNT	HUNT cohort: population-based health survey focusing on the county of Nord-Trøndelag (aged 20 or older). EPIC-Oxford cohort included individuals throughout the UK (age 20 or older).	LUR	NO ₂ (ppb)	National registries in UK and Norway	Cox proportional hazards	HR (95% CI) ^b
n = 355,732		Method validation: NR	EPIC-Oxford Cohort Mean = 15.5 ± 6.43 (29.1 ± 12.1 µg/m ³) Median = 14 (IQR 6.96) (27 µg/m ³) (IQR 13.1 µg/m ³) Min = 4 (7 µg/m ³) Max = 64.15 (120.7 µg/m ³) P5 = 7.4 (14 µg/m ³) P25 = 11.1 (20.9 µg/m ³) P75 = 18 (34 µg/m ³) P95 = 29 (55 µg/m ³)		Adjusted for: Cohort, employment, education level, smoking status	Acute coronary events: 0.91 (0.76, 1.09) IHD: 0.97 (0.87, 1.08)
Oxford, UK, England, Scotland, Wales, Nord-Trøndelag county, U.K., Norway		Averaging time: NO ₂ - annual average				
Enrollment: - UK Biobank: 2006-2010 - HUNT: 1995-1997 - EPIC-Oxford: 1993-1999	The UK Biobank cohort recruited individuals from across the UK (age 40-69).	Exposure years: 2001-2010	HUNT Cohort Mean = 6.7 ± 1.9 (12.6 ± 3.6 µg/m ³) Median = 6.22 (IQR 3) (11.7 µg/m ³) (IQR 5 µg/m ³) Min = 3.5 (6.6 µg/m ³) Max = 22 (42 µg/m ³) P5 = 4.3 (8.1 µg/m ³) P25 = 5.3 (10 µg/m ³) P75 = 8 (15 µg/m ³) P95 = 10.2 (19.2 µg/m ³)			
Follow-up: - UK Biobank: 1.3 mean years - HUNT: 14.1 mean years - EPIC-Oxford: 10.8 mean years						
Cohort			Pooled Data Mean = 14.8 ± 6.01 (27.8 ± 11.3 µg/m ³) Median = 14 (IQR 6.8) (27 µg/m ³) (IQR 12.8 µg/m ³) Min = 3.5 (6.6 µg/m ³) Max = 73.55 (138.4 µg/m ³) P5 = 5.8 (11 µg/m ³) P25 = 10.8 (20.3 µg/m ³) P75 = 17.6 (33.1 µg/m ³) P95 = 26.2 (49.3 µg/m ³)			
			UK Biobank Mean = 15.9 ± 5.47 (29.9 ± 10.3 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Median = 15.1 (IQR 5.79) (28.4 µg/m ³ (IQR 10.9 µg/m ³)) Min = 4 (7 µg/m ³) Max = 73.55 (138.4 µg/m ³) P5 = 8.77 (16.5 µg/m ³) P25 = 12.3 (23.2 µg/m ³) P75 = 18.1 (34.1 µg/m ³) P95 = 26.6 (50.1 µg/m ³)			
†Cramer et al. (2020)	Female nurses belonging to the Danish Nurse Organization (age >44- years).	Hybrid model	NO ₂ (ppb)	National patient registries	Cox proportional hazards	NO ₂
DNC		r ² values in the range of 0.7 and 0.9 depending on site, pollutant, and averaging period	Fatal Incident MI Mean = 7.55 ± 5.69 (14.2 ± 10.7 µg/m ³)		Adjusted for: Age, year of cohort entry, smoking status, pack years, consumption of fruit, avoidance of fatty meat, alcohol consumption, use of oral contraceptives, use of hormone therapy, physical activity, marital status, employment status, and level of urbanization	HR (95% CI) ^b MI, 1 yr running average: 1.10 (0.86, 1.40) MI, 3 yr running average: 1.12 (0.88, 1.43) MI, 23 yr running average: 1.25 (0.98, 1.59)
N = 22,882			MI Mean = 6.7 ± 4.3 (12.6 ± 8.1 µg/m ³)			
Denmark		Averaging time: NO ₂ - annual average, NO _x - annual average, Other, NO ₂ - 1-year running means	Overall Incident MI Mean = 7.23 ± 5.1 (13.6 ± 9.6 µg/m ³)			NO _x
Enrollment: 1993 and 1999		NO ₂ - 3-year running means	Total Mean = 6.7 ± 4.3 (12.6 ± 8.1 µg/m ³)			HR (95% CI) ^c MI, 23 yr running average: 1.04 (1.00, 1.08)
Follow-up: 2014		NO ₂ - 23-year running means	NO _x (µg/m ³)			MI, 3 yr running average: 1.02 (0.98, 1.07)
Cohort		NO _x - 1-year running means	Fatal Incident MI Mean = 24.4 ± 34.9			MI, 1 yr running average: 1.02 (0.97, 1.07)
		NO _x - 3-year running means	MI Mean = 19.1 ± 24.2			
		NO _x - 23-year running means	Overall Incident MI Mean = 22 ± 29.7			
		Exposure years: 1990-2014	Total Mean = 19.1 ± 24.4			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Gandini et al. (2018) Italian Longitudinal Study (ILS) N = 74,989 Italy Enrollment: 1999-2000 Follow-up: 1999-2002, 2003-2004, 2005-2006, 2007-2008 Cohort	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity. Averaging time: NO ₂ - annual average Exposure years: 1999, 2003, 2005, 2007	NO ₂ (ppb) Men Metropolitan Mean = 22.1 ± 6.16 (41.5 ± 11.6 µg/m ³) Rural Mean = 10.3 ± 4 (19.3 ± 8 µg/m ³) Urban Mean = 13.9 ± 5.2 (26.1 ± 9.7 µg/m ³) Women Metropolitan Mean = 22.1 ± 6.16 (41.6 ± 11.6 µg/m ³) Rural Mean = 10.3 ± 4.2 (19.3 ± 7.9 µg/m ³) Urban Mean = 13.9 ± 5.1 (26.1 ± 9.6 µg/m ³)	Hospitalization records	Cox proportional hazards Adjusted for: Age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality, and BMI	HR (95% CI) ^b Atherosclerosis disease hospitalizations: 1.20 (1.06, 1.35) Cardiac disease hospitalizations: 1.06 (1.02, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Hartiala et al. (2016) Cleveland Clinic GeneBank n = 4,600 Cleveland, OH, U.S. Enrollment: 2001-2007 Follow-up: 3-yrs Cohort	Patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography	Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 3-y average after enrollment Exposure years: 1998-2010	NO ₂ (ppb) 36 months post: Mean = 18.2 ± 2 Min = 4.9 Max = 22.1 36 months prior: Mean = 19.1 ± 1.8 Min = 7.8 Max = 23.3	Source documentation	Cox proportional hazards Adjusted for: Age, sex, education level, current smoking, and Framingham Adult Treatment Panel III risk score Logistic Regression Adjusted for: Age, sex, education level, current smoking, and Framingham Adult Treatment Panel III risk score	HR (95% CI) ^b MI: 0.82 (0.40, 1.67) OR (95% CI) ^b Atherosclerosis Severity (≥3 vessels): 0.74 (0.31, 1.77)
† Klompaker et al. (2019) Dutch Public Health Monitor 2012 (Dutch PHM 2012) n = 354,827 The Netherlands 2012 Cross-Sectional	Dutch citizens ≥ 19-years (older adults ≥ oversampled by design)	LUR leave-one-out cross-validation (LOOCV) r ² 0.81 Averaging time: NO ₂ - annual average Exposure years: 2009	NO ₂ Median = 12.4 (23.4 µg/m ³) IQR = 4.2 (7.85 µg/m ³)	Self-reported heart attack	Logistic regression Adjusted for: sex, age, marital status, region of origin, education, work, standardized household income, smoking habits, number of cigarettes/day, alcohol consumption, number of alcohol glasses/week, physical activity, body mass index, and neighborhood socioeconomic status.	OR (95% CI) ^b Heart attack: 0.95 (0.87, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Klompaker et al. (2021a) MEDPAR N = 63,009,173 U.S. Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry Cohort	Medicare beneficiaries, aged ≥ 65-years, living in the contiguous US.	Spatiotemporal/geospatial model The overall cross-validated r^2 for annual estimates was 0.84 for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) CBV Median = 16.1 (IQR 13.8) CHD Median = 16.2 (IQR 13.8) CVD Median = 16.3 (IQR 13.9) Total Cohort Median = 16.3 (IQR 13.9)	Hospital Admission	Cox proportional hazards Adjusted for: calendar year, U.S. census covariates, BRFSS covariates, region, an offset for total person-time and strata for all possible combinations of sex, race, Medicaid Eligibility, age at study entry (2-year categories), and follow-up year	HR (95% CI) ^b CHD Hospitalization: 1.03 (1.02, 1.03) CHD, < 20 ppb: 1.15 (1.13, 1.16)
†Levinsson et al. (2014) INTERGENE/ADO NIX n = 119 cases 1310 controls 1429 total Sweden April 2001 - January 2004 (case recruitment) Case-Control	CHD cases and population-based controls (25-75) in Gothenburg area, Sweden	Dispersion model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2001-2004	NO ₂ (ppb) AMI cases Mean = 7.92 ± 3.06 (14.9 ± 5.75 $\mu\text{g}/\text{m}^3$) Hypertensive controls Mean = 7.9 ± 3.2 (14.9 ± 5.93 $\mu\text{g}/\text{m}^3$) Non-hypertensive controls Mean = 8.6 ± 3.3 (16.1 ± 6.16 $\mu\text{g}/\text{m}^3$)	Hospital admission	Logistic Regression Adjusted for: Sex, age, age squared, level of education, and residential area	OR (95% CI) ^b MI: 2.96 (1.08, 8.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Olaniyan et al. (2022) CanCHEC N = 2,687,900 Canada Enrollment: 1981 Follow-up: through December 31, 2016 Cohort	Included non-institutionalized respondents who were 25-89-years of age residing in Canada. Excluded all residents of Quebec.	Chemical transport model, LUR, Fixed site monitor This model explained 75% of the variability in ground-measured NO ₂ Averaging time: NO ₂ - annual average Exposure years: 1998-2012	NO ₂ (ppb) 8.57 (range: 0.01–35.57)	Hospital Records	Cox proportional hazards Adjusted for: SES, individual-level covariates (occupational class, marital status, educational attainment, income deciles, indigenous status, visible minority status, employment status), and ecological covariates	HR (95% CI) ^b MI: 1.04 (1.00, 1.07)
†Poulsen et al. (2023c) Statistic Denmark N = 1,964,702 Denmark Enrollment: 1979 - 2005 Follow-up: 2005-2017 Cohort	All Danish citizens born after 1920, residing in Denmark on January 1, 1979, who had a continued Danish address history from January 1, 1979 until January 1, 2005, and who were 50- years or older in the study period 2005-2017. Excluded those with missing covariates	Hybrid model Method validation NR Averaging time: NO ₂ - mean monthly NO ₂ - 5-year running average Exposure years: 1995-2017	NO ₂ (ppb) Air Pollution, 5-year Median = 8.13 (15.3 µg/m ³) P5 = 4.9 (9.3 µg/m ³) P95 = 14.5 (27.3 µg/m ³)	Public registers	Cox proportional hazards Adjusted for: Age, sex, calendar year, education, occupational status, civil status, personal income, household income, country of origin, and area-level deprivation	HR (95% CI) ^b MI: 1.08 (1.05, 1.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Schwartz et al. (2023)	Medicare beneficiaries 65-years or older	Ensemble machine learning model	NO ₂ (ppb) Mean = 16.27 ± 9.11	Hospital admission	quasi-Poisson	β (per 10,000 P-Y) (95% CI) ^b
Medicare		10-fold CV r ² -0.84			Adjusted for: sex, race, age group, Medicaid eligibility, zip code-level SES and demographic data	MI / Regression w IPW: 0.93 (-0.52, 2.38)
n = 435,246		Averaging time: NO ₂ - annual average			(proportion >65-years of age living below poverty line, population density, median value of owner occupied properties, proportion of population self-reporting as Black, median household income, proportion of housing units occupied by the owner, proportion of population identified as Hispanic, proportion of the population >65-years of age who had not graduated from high school, lung cancer hospitalization rates (proxy for pack-years of smoking), mean BMI, and smoking rate)	MI / Negative Controls: 0.66 (0.79, 0.54)
U.S.		Exposure years: 2000-2016				MI / Regression adjustment: 0.13 (-0.74, 1.00)
Followup: 2000-2016						MI / DiD: -0.80 (-0.01, -1.60)
Quasi-experimental						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Danesh Yazdi et al. (2021) Medicare N = 63,006,793 U.S. 2000-2016 Cohort	All fee-for-service Medicare beneficiaries who were 65-years of age or older and who lived in the contiguous United States between 2000 and 2016 as derived from the Medicare denominator file and the Medicare Provider Analysis and Review file.	Spatiotemporal/geospatial model, LUR, Chemical transport model r ² values of 0.84 for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) Exposure Across Person-Years Mean = 19.5 Median = 17.44 Min = 0.01 Max = 127.63 P10 = 8.13 P25 = 11.51 P75 = 25.88 P90 = 33.88	Hospitalization	DRAM Adjusted for: Zip code level proportion female, race, Medicaid-eligible, age, SES, education, ever-smokers, mean BMI, access to care and other pollutants. Zip code level demographic (proportion of the study population who were female, identified as Black, identified as race other than Black or white, were Medicaid-eligible, and by age group (65-74, 75-84	β (%) (95% CI) ^b MI Hospitalization: -0.01 (-0.01, -0.01)
† Danesh Yazdi et al. (2022) MEDPAR N = 436,684 U.S. 2000-2016 Cross-Sectional	Persons aged 65-years or over in the contiguous United States who are Medicare beneficiaries and received fee for service care at a hospital.	Hybrid model Ten-fold cross validation r ² value of 0.84. Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) Exposure over two-year period Mean = 16.22 Median = 13.86 Min = 0.03 Max = 98.59 P10 = 7.15 P25 = 9.63 P75 = 20.63 P90 = 29.14	Hospitalization	DID Adjusted for: Zip code level proportion female, race, Medicaid-eligible, age, SES, education, ever-smokers, mean BMI, access to care and other pollutants. Zip code level demographic (proportion of the study population who were female, identified as Black, identified as race other than Black or white, were Medicaid-eligible, and by age group (65-74, 75-84	β (per 100,000 P-Y) (95% CI) ^b MI Hospitalization: -8.30 (-15.55, -1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Zhang et al. (2020)	Residents of the City of Toronto, aged 40- to 85-years on 1 January 2001, and had been living in Toronto for ≥ 3-years prior to cohort enrollment. Excluded immigrants and subjects living in Toronto for a short period and participants with a history of AMI/CHF at Enrollment.	LUR	NO ₂ (ppb)	Heart Disease databases	Cox proportional hazards	HR (95% CI) ^b MI: 1.07 (1.02, 1.12)
ONPHEC		r ² = 0.69	AMI Cohort Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.2 P25 = 19.1 P75 = 23.2 P95 = 28.3		Adjusted for: Income quintile, percentage of recent immigrants, percentage of population > = 15-years without employment and percentage of population aged > = 15-years with education level lower than high school	
N = 2,457,861		Averaging time: NO ₂ - annual average, Other, NO ₂ - 3-year moving average	CHF Cohort Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.1 P25 = 19 P75 = 23.2 P95 = 28.3			
Toronto, Canada		Exposure years: 2016	CVD Cohort Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.1 P25 = 19 P75 = 23.2 P95 = 28.3			
Enrollment: April 1, 1996						
Follow-up: 2016						
Cohort						

List of abbreviations in alphabetical order: µg/m³= micrograms per cubic meter; AMI=Acute Myocardial Infarction; BMI=Body Mass Index; CanCHEC= Canadian Census Health and Environment Cohort; CBV=Cerebrovascular; CEANS= Cardiovascular Effects of Air Pollution and Noise in Stockholm; CEANS-60YO= Cardiovascular Effects of Air Pollution and Noise in Stockholm-Sixty Year Old; CEANS-SALT= Cardiovascular Effects of Air Pollution and Noise in Stockholm- Stockholm Screening Across the Lifespan Twin study and TwinGene; CEANS-SDPP= Cardiovascular Effects of Air Pollution and Noise in Stockholm-Stockholm Diabetes Prevention Program; CEANS-SNAC-K= Cardiovascular Effects of Air Pollution and Noise in Stockholm-Swedish National Study on Aging and Care in Kungsholmen; CHD=Coronary Heart Disease; CHF=Congestive Heart Failure; CVD=Cardiovascular Disease; DNC=Danish Nurses' Cohort; DNC=Danish Nurses' Cohort; E3N= Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ELAPSE= Effects of Low-Level Air Pollution: A Study in Europe; EPIC-MORGEN= European Prospective Investigation into Cancer and Nutrition- Monitoring Project on Risk Factors and Chronic Diseases in Netherlands; EPIC-Oxford= European Prospective Investigation into Cancer and Nutrition- Oxford; EPIC-Oxford= European Prospective Investigation into Cancer and Nutrition- Oxford; EPIC-Prospect= European Prospective Investigation into Cancer and Nutrition-Prospect; EPIC-Varese=European Prospective Investigation into Cancer and Nutrition-Varese; ESCAPE= European Study of Cohorts for Air Pollution Effects; HNR Study= Heinz Nixdorf Recall Study; HR=Hazard Ratio; HUNT=Helseundersøkelsen i Nord-Trøndelag; IHD=Ischemic Heart Disease; ILS=Italian Longitudinal Study; INTERGENE/ADONIX= INTERplay between GENetic susceptibility and environmental factors for the risk of chronic diseases in West Sweden/ADult-Onset asthma and exhaled Nitric oxide; IQR=Interquartile Range; KORA= Cooperative Health Research in the Region of Augsburg; LUR=Land Use Regression; Max=Maximum; MEDPAR=Medicare denominator and Medicare Provider Analysis and Review; MI=Myocardial Infarction; Min=Minimum; N=sample size; NO₂=Nitrogen Dioxide; NR=Not Reported; ONPHEC=Ontario Population Health and Environment Cohort; P=Percentile; ppb=parts per billion; RSME=Root Mean Square Error; SES=socioeconomic status; VHM&PP= Vorarlberg Health Monitoring and Prevention Programme.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-2 Epidemiologic studies of exposure to oxides of nitrogen and heart failure

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Bai et al. (2019b)	Restricted to persons were aged 30-100 years, had been living in Toronto for at least 3 years prior to entry, and had no history of physician-diagnosed CHF or AMI at Enrollment	LUR	NO ₂ (ppb)	Hospital discharge records, national databases	Cox proportional hazards	HR (95% CI) ^b CHF: 1.04 (1.03, 1.04)
ONPHEC		The r ² value for the final regression model was 70%	Estimated Exposure Mean = 21.4 ± 3.5 Median = 21.1 (IQR 4) Min = 9.9 Max = 50.1		Adjusted for: Age, sex, postal code, rurality, area-level deprivation, access to healthcare	
CHF Cohort N = 1,112,060 AMI Cohort N = 1,127,209						
Toronto, Canada		Averaging time: NO ₂ - 3-year moving averages				
Enrollment: April 1, 1996 Follow-up: through December 31, 2012		Exposure years: 2002-2004				
Cohort						
[†] Bai et al. (2019a)	35-85 years of age, registered with Ontario's provincial health insurance plan, and did not have a physician-diagnosed CHF or AMI before Enrollment, live in Ontario at entry, have no missing information on exposure or covariates at Enrollment	LUR, Fixed site monitor	NO ₂ (ppb)	Hospital discharge reports and national databases	Cox Proportional Hazards	HR (95% CI) ^b CHF: 1.01 (1.00, 1.03)
ONPHEC		This model explained 73% of the variability in measurements	Mean = 18.3±8.5 Median = 17.1 (IQR 13.9) Min = 2.7 Max = 71.4 P25 = 10.9		Adjusted for: Census tract-level percentage of recent immigrants, percentage of the population aged ≥15 years without employment, percentage of the population aged ≥15 years with less than a high	
n = CHF Cohort: 5,062,146 AMI Cohort: 5,141,172						
Ontario, Canada						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: April 1, 2001 Follow-up: December 31, 2015 Cohort		Averaging time: NO ₂ - annual average Exposure years: 2005-2011	P75 = 24.8		school education, and annual household income	
† Jin et al. (2022) Medicare n = AF cohort: >30 million CHF cohort: >30 million Stroke cohort: >30 million U.S. Enrollment: 2000 Follow-up: through 2016 Cohort	Medicare enrollees with continuous enrollment in the FFS program and both Medicare part A and part B in the contiguous US.	Hybrid model r ² = 0.84 Averaging time: NO ₂ - 1-hour max Exposure years: 2000-2016	NO ₂ (ppb) AF cohort Mean = 19.8 ± 9.2 CHF cohort Mean = 19.7 ± 9.1 Stroke cohort Mean = 19.8 ± 9.2	Medicare records	Cox proportional hazards Adjusted for: age, self-reported sex, self-reported race/ethnicity, and Medicaid eligibility hyperlipidemia, hypertension, diabetes, and neighborhood-level variables (demographic, SES, healthcare-access-related and meteorological covariates for analysis)	HR (95% CI) ^b CHF, NO ₂ <18 ppb: 1.31 (1.28, 1.34) CHF: 1.12 (1.11, 1.12)
† Lim et al. (2021) DNC N = 22,189 Denmark Enrollment: 1993, 1999 Follow-up: until 2014	Female nurses who were >44 years, and who either worked or were retired in 1993 or 1999. Participants were excluded if they had missing information on vital status.	Hybrid model Method validation NR Averaging time: NO ₂ - annual average	NO ₂ (ppb) 3-Year Running Means Mean = 7.17 ± 4.3 (13.5 ± 8.1 ug/m ³) Median = 5.9 (IQR 4.6)	Danish National Patient Register, hospital records	Cox proportional hazards Adjusted for: Age, year of cohort entry, individual-level covariates, area-level covariates	HR (95% CI) ^b CHF: 1.23 (0.98, 1.55)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort		Exposure years: 1970-2014	(11.1 ug/m ³ (IQR 8.6 ug/m ³) P5 = 3 (5.6 ug/m ³) P25 = 4.4 (8.2 ug/m ³) P75 = 8.93 (16.8 ug/m ³) P95 = 15.1 (28.4 ug/m ³)			
†Wang et al. (2021)	Residents aged 40-69 years with information on lifestyle and health data, physical measurements and biological samples. Participants were excluded if they had heart failure, atrial fibrillation or coronary heart disease at Enrollment.	LUR	NO ₂ (ppb)	Self-reported information, hospital inpatient records	Cox proportional hazards	NO ₂
UK Biobank		Method validation NR	Incident Heart Failure		Adjusted for: Age, sex, race, UK biobank assessment center, Townsend Deprivation Index, alcohol consumption, smoking status, BMI, physical activity, healthy diet score, diabetes, hypertension, systolic and diastolic blood pressure	HR (95% CI) ^b CHF: 1.20 (1.09, 1.32)
N = 432,530		Averaging time: NO ₂ - annual average, NO _x - annual average	No Mean = 15.6 ± 4.9 (29.3 ± 9.3 ug/m ³) Yes Mean = 16 ± 4.8 (30 ± 9.1 ug/m ³)			NO _x
England, Scotland, Wales, U.K.						HR (95% CI) ^b CHF: 1.04 (1.02, 1.06)
Enrollment: 2006-2010 Follow-up: 2018						
Cohort		Exposure years: 2005-2010	NO _x (ug/m ³) Incident Heart Failure No Mean = 43.9 ± 15.6 Yes Mean = 46.1 ± 16.8			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Zhang et al. (2020)	Residents of the City of Toronto, aged 40 to 85 years on 1 January 2001, and had been living in Toronto for ≥ 3 years prior to cohort enrollment. Excluded immigrants and subjects living in Toronto for a short period and participants with a history of AMI/CHF at Enrollment.	LUR	NO ₂ (ppb)	Records from databases in study area	Cox proportional hazards	HR (95% CI) ^b
ONPHEC		r ² = 0.69	AMI Cohort		Adjusted for: Sex, age, Income quintile, percentage of recent immigrants, percentage of population ≥15 years without employment and percentage of population aged ≥15 years with education level lower than high school	CHF:
N = 2,457,861		Averaging time: NO ₂ - annual average, Other, NO ₂ - 3-year moving average	Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.2 P25 = 19.1 P75 = 23.2 P95 = 28.3			1.10 (1.07, 1.14)
Toronto, Canada						
Enrollment: April 1, 1996						
Follow-up: 2016						
Cohort		Exposure years: 2016	CHF Cohort Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.1 P25 = 19 P75 = 23.2 P95 = 28.3			
			CVD Cohort Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.1 P25 = 19 P75 = 23.2 P95 = 28.3			

List of abbreviations in alphabetical order: AF=Atrial Fibrillation; AMI=Acute Myocardial Infarction; CHF=Congestive Heart Failure; CI=Confidence Interval; DNC=Danish Nurse Cohort; HR=Hazard Ratio; LUR=Land Use Regression; Max=maximum; Min=minimum; NO₂=Nitrogen dioxide; NO_x=Oxides of Nitrogen; ONPHEC=Ontario Population Health and Environment Cohort; P=percentile; ppb=parts per billion; SES=socioeconomic status.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-3 Epidemiologic studies of exposure to oxides of nitrogen and atrial fibrillation

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
[†] Andersen et al. (2021)	Female nurses aged >44-years in Denmark in 1993 or in 1999	Hybrid model	NO ₂ (ppb)	Danish National Patient Register, hospital records	Cox proportional hazards	HR (95% CI) ^b AF, 23 yr avg: 0.95 (0.84, 1.09)
DNC	(Enrollment years). Women who had a hospital contact for atrial fibrillation prior to Enrollment or with missing exposure data for the cohort Enrollment years were excluded.	r ² values ranged from 0.7 to 0.9 depending on the site, pollutant, and averaging period	AF Median = 5.63 (10.6 µg/m ³) Min = 1.9 (3.6 µg/m ³) Max = 38.4 (72.3 µg/m ³) P10 = 3 (6 µg/m ³) P25 = 4.1 (7.8 µg/m ³) P75 = 8.72 (16.4 µg/m ³) P90 = 12 (22 µg/m ³)		Adjusted for: Age, year of cohort entry, smoking status, consumption of fruit, alcohol consumption, physical activity, marital status, degree of urbanization, and calendar year	
N = 23,528		Averaging time: NO ₂ - annual average, Other, NO ₂ - 3-year moving average				
Denmark		NO ₂ - 23-year moving average	No AF Median = 5.42 (10.2 µg/m ³) Min = 1.8 (3.4 µg/m ³) Max = 42.6 (80.1 µg/m ³) P10 = 3.1 (5.9 µg/m ³) P25 = 4 (7.5 µg/m ³) P75 = 8.29 (15.6 µg/m ³) P90 = 10.7 (20.2 µg/m ³)			
Enrollment: April 1993 and April 1999		Exposure years: 1970-2014	Total Median = 5.42 (10.2 µg/m ³) Min = 1.8 (3.4 µg/m ³) Max = 42.6 (80.1 µg/m ³) P10 = 3.1 (5.9 µg/m ³) P25 = 4 (7.5 µg/m ³) P75 = 8.34 (15.7 µg/m ³)			
Follow-up: July 2015						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
P90 = 10.8 (20.3 µg/m ³)						
† Hart et al. (2021)	Post-menopausal women ages 50-79 with incident atrial fibrillation. Women were excluded if they had atrial fibrillation at Enrollment, never enrolled in Medicare Parts A and B, or were missing covariates.	Hybrid model r ² = 0.85 Averaging time: NO ₂ - annual average	NO ₂ (ppb) Overall Mean = 12.3 ± 6.3 Median = 11.3 (IQR 8.5) Min = 0.5 Max = 45.6 P25 = 7.5 P75 = 16	Medicare records, ICD-9 427.31	Cox proportional hazards Adjusted for: Age, race/ethnicity, WHI study component, BMI, educational attainment, physical activity, alcohol consumption, overall diet quality, hormone replacement therapy use, smoking status and pack years, neighborhood SES	HR (95% CI) ^c AF, Q4 (16.1-45.6): 1.18 (1.13, 1.24) AF, Q3 (11.4-16 ppb): 1.06 (1.02, 1.11) AF, Q2 (7.53-11.3 ppb): 0.99 (0.94, 1.03) HR (95% CI) ^c AF, reference (<7.52 ppb): 0.00 (0.00, 0.00)
WHI N = 83,117 U.S. Enrollment: 1993-1998 Follow-up: through December 2012 Cohort		Exposure years: 1998-2012				
† Jin et al. (2022)	Medicare enrollees with continuous enrollment in the FFS program and both Medicare part A and part B in the contiguous US.	Hybrid model r ² = 0.84 Averaging time: NO ₂ - 1-hour max Exposure years: 2000-2016	NO ₂ (ppb) AF cohort Mean = 19.8 ± 9.2 CHF cohort Mean = 19.7 ± 9.1 Stroke cohort Mean = 19.8 ± 9.2	Medicare records	Cox proportional hazards Adjusted for: age, self-reported sex, self-reported race/ethnicity, and Medicaid eligibility hyperlipidemia, hypertension, diabetes, and neighborhood-level variables (demographic, SES, healthcare-access-related and meteorological covariates for analysis)	HR (95% CI) ^b AF, <18 ppb: 1.26 (1.24, 1.28) AF, <25 ppb: 1.14 (1.13, 1.14) AF: 1.06 (1.05, 1.06)
Medicare n = AF cohort: >30 million CHF cohort: >30 million Stroke cohort: >30 million U.S. Enrollment: 2000 Follow-up: through 2016 Cohort						
† Monrad et al.	Individuals between 50-	Dispersion model	NO ₂ (ppb)	Danish National	Cox proportional	NO ₂

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
(2016) DCH n = 57,053 Copenhagen, Aarhus, Denmark Enrollment: 1993-1997 Follow-up: 2011 Cohort	64-years of age, living in Copenhagen or Aarhus. Participants must have been born in Denmark and not had a history of cancer at the time of enrollment.	r ² = 0.81 Averaging time: NO ₂ – Ten-year mean exposure Exposure years: 1984-2011	Median = 8.8 (16.6 µg/m ³) Min = 4.5 (8.5 µg/m ³) Max = 34.7 (65.3 µg/m ³) NO _x (µg/m ³) Median = 20.8 µg/m ³ Min = 10.3 µg/m ³ Max = 379.6 µg/m ³	Patient Register, hospital records	hazards Adjusted for: Age, sex, BMI, waist circumference, smoking status, smoking duration, smoking intensity, intake of alcohol, sport during leisure time, length of school attendance, area-level SES position, and calendar year	IRR (95% CI) ^b AF: 1.16 (1.03, 1.30) NO _x IRR (95% CI) ^c AF Q5 (≥29.6 vs Q1 <13.8: 1.16 (1.02, 1.32) AF Q4 (20.8<29.6 µg/m ³ vs Q1 <13.8: 1.19 (1.05, 1.35) AF Q2 (13.8<16.9 µg/m ³ vs Q1 <13.8: 0.99 (0.87, 1.12) AF Q3 (16.9<20.8 µg/m ³ vs Q1 <13.8: 1.20 (1.06, 1.36)
[†] Danesh Yazdi et al. (2021) Medicare N = 63,006,793 U.S. 2000-2016 Cohort	All fee-for-service Medicare beneficiaries who were 65-years of age or older and who lived in the contiguous U.S. between 2000 and 2016 as derived from the Medicare denominator file and the Medicare Provider Analysis and Review file.	Spatiotemporal/geospatial model, LUR, Chemical transport model r ² values of 0.84 for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) Exposure Across Person-Years Mean = 19.5 Median = 17.44 Min = 0.01 Max = 127.63 P10 = 8.13 P25 = 11.51 P75 = 25.88 P90 = 33.88	Medicare records FFS hospital admissions	DRAM Adjusted for: Sex, race, age group, Medicaid eligibility, SES data	β (RD) (95% CI) ^b AF: 0.01 (0.01, 0.01)

List of abbreviations in alphabetical order: µg/m³= micrograms per cubic meter; AF=Atrial Fibrillation; CHF=Congestive Heart Failure; d=day; DCH= Danish Diet, Cancer and Health; DNC=Danish Nurses' Cohort; DRAM= Doubly Robust Additive Model; FFS=Fee for Service; HR=Hazard Ratio; IRR=Incidence Rate Ratio; LUR=Land use regression; Max=Maximum; Min=Minimum; NA=Not applicable; NO₂=Nitrogen dioxide; NO_x = nitrogen oxides; NR=Not Reported; P=Percentile; ppb=parts per billion; RR=Relative Risk; SES=socioeconomic status; WHI=Women's Health Initiative; Yr(s)=year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-4 Epidemiologic studies of exposure to oxides of nitrogen and cerebrovascular disease and stroke

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Amini et al. (2020)	Female nurses who were > 44-years of age.	Hybrid model	NO ₂ (ppb)	Patient Registry	Cox proportional hazards	HR (95% CI) ^b
DNC	Excluded those who had a stroke prior to Enrollment and those with missing exposure or covariate information	This model has been validated against all measurements in Denmark showing good performance.	All Stroke Mean = 7.49 ± 4.9 (14.1 ± 9.2 µg/m ³)		Adjusted for: Age, year of cohort entry, calendar year, income, degree of urbanicity, physical activity, alcohol drinking, smoking, marital status, fruit consumption	All Stroke, 1-year: 1.12 (0.94, 1.34)
N = 23,423						HS, 1-year: 0.93 (0.54, 1.60)
Denmark			HS Mean = 7.55 ± 5 (14.2 ± 9 µg/m ³)			IS, 1-year: 1.15 (0.96, 1.37)
Enrollment: 1993 and 1999		Averaging time:	IS			
Follow-up: December 31, 2014		NO ₂ - annual average, NO _x - annual average	Mean = 7.17 ± 4.5 (13.5 ± 8.5 µg/m ³)			
Cohort		Exposure years: 1970-2014	No Stroke Mean = 6.64 ± 4 (12.5 ± 8 µg/m ³)			
			Total Cohort Mean = 6.7 ± 4 (12.6 ± 8 µg/m ³)			
			NO _x (µg/m ³)			
			All Stroke Mean = 22.8 ± 29.2			
			Hemorrhagic Mean = 25.2 ± 29.8			
			Ischemic Mean = 22.8 ± 26.2			
			No Stroke Mean = 18.9 ± 23.9			
			Total Cohort Mean = 19.1 ± 23.9			

† Brunekreef et al. (2021)	ELAPSE Project (pooled cohort): European population	LUR, Chemical transport model, Hybrid model	NO ₂ (ppb)	Registry with Physician Adjudication	Cox proportional hazards	HR (95% CI) ^b Stroke: 1.16 (1.08, 1.24)
ELAPSE: CEANS, DCH, E3N cohort, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC-Varese		$r^2 = 58\%$	CEANS-SALT Cohort Mean = 11.31 ± 3.28 ($21.29 \pm 6.18 \mu\text{g}/\text{m}^3$) Median = 11.17 (IQR 3.9) ($21.02 \mu\text{g}/\text{m}^3$) (IQR $7.33 \mu\text{g}/\text{m}^3$) Min = 1.58 (2.98 $\mu\text{g}/\text{m}^3$) Max = 26.85 (50.53 $\mu\text{g}/\text{m}^3$) P5 = 5.958 (11.21 $\mu\text{g}/\text{m}^3$) P25 = 9.327 (17.55 $\mu\text{g}/\text{m}^3$) P75 = 13.22 (24.88 $\mu\text{g}/\text{m}^3$) P95 = 16.94 (31.87 $\mu\text{g}/\text{m}^3$)		Adjusted for: Cohort ID, age, sex, year of Enrollment visit, smoking, BMI, marital status, employment status, educational status, and 2001 neighborhood-level mean income	
n = 325,000		Averaging time: NO ₂ - annual average				
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, The Netherlands		Exposure years: 2010				
Recruitment: 1992-2011 Follow-up: 2011-2017						
Cohort			CEANS-SDPP Cohort Mean = 8.259 ± 2.28 ($15.54 \pm 4.29 \mu\text{g}/\text{m}^3$) Median = 8.269 (IQR 2.86) ($15.56 \mu\text{g}/\text{m}^3$) (IQR $5.38 \mu\text{g}/\text{m}^3$) Min = 1.57 (2.96 $\mu\text{g}/\text{m}^3$) Max = 19.71 (37.09 $\mu\text{g}/\text{m}^3$) P5 = 4.15 (7.81 $\mu\text{g}/\text{m}^3$) P25 = 6.792 (12.78 $\mu\text{g}/\text{m}^3$) P75 = 9.651 (18.16 $\mu\text{g}/\text{m}^3$) P95 = 11.94 (22.46 $\mu\text{g}/\text{m}^3$)			
			CEANS-SIXTY			

Cohort
Mean = 10.99 ± 3.26
($20.68 \pm 6.13 \mu\text{g}/\text{m}^3$)
Median = 10.92 (IQR
4) ($20.54 \mu\text{g}/\text{m}^3$ (IQR
 $7 \mu\text{g}/\text{m}^3$))
Min = 1.42 ($2.68 \mu\text{g}/\text{m}^3$)
Max = 25.45 ($47.88 \mu\text{g}/\text{m}^3$)
P5 = 5.69 ($10.7 \mu\text{g}/\text{m}^3$)
P25 = 9.051 ($17.03 \mu\text{g}/\text{m}^3$)
P75 = 12.77 ($24.03 \mu\text{g}/\text{m}^3$)
P95 = 16.62 ($31.28 \mu\text{g}/\text{m}^3$)

CEANS-SNACK
Cohort
Mean = 14.56 ± 2.71
($27.39 \pm 5.09 \mu\text{g}/\text{m}^3$)
Median = 15.1 (IQR
3.92) ($28.5 \mu\text{g}/\text{m}^3$
(IQR $7.38 \mu\text{g}/\text{m}^3$))
Min = 6.176 ($11.62 \mu\text{g}/\text{m}^3$)
Max = 22.65 ($42.61 \mu\text{g}/\text{m}^3$)
P5 = 9.71 ($18.27 \mu\text{g}/\text{m}^3$)
P25 = 12.52 ($23.56 \mu\text{g}/\text{m}^3$)
P75 = 16.45 ($30.95 \mu\text{g}/\text{m}^3$)
P95 = 18.04 ($33.94 \mu\text{g}/\text{m}^3$)

DCH Cohort
Mean = 14.9 ± 3.64
($28.04 \pm 6.84 \mu\text{g}/\text{m}^3$)
Median = 15.05 (IQR

5.3) (28.32 $\mu\text{g}/\text{m}^3$
(IQR 10 $\mu\text{g}/\text{m}^3$))
Min = 3.4 (6.4 $\mu\text{g}/\text{m}^3$)
Max = 38.39 (72.23
 $\mu\text{g}/\text{m}^3$)
P5 = 8.79 (16.54
 $\mu\text{g}/\text{m}^3$)
P25 = 12.36 (23.26
 $\mu\text{g}/\text{m}^3$)
P75 = 17.68 (33.26
 $\mu\text{g}/\text{m}^3$)
P95 = 20.31 (38.22
 $\mu\text{g}/\text{m}^3$)

DNC-1999 Cohort
Mean = 13.74 ± 4.5
($25.85 \pm 8.47 \mu\text{g}/\text{m}^3$)
Median = 12.63 (IQR
7.345) (23.76 $\mu\text{g}/\text{m}^3$
(IQR 13.82 $\mu\text{g}/\text{m}^3$))
Min = 3.41 (6.42
 $\mu\text{g}/\text{m}^3$)
Max = 28.84 (54.26
 $\mu\text{g}/\text{m}^3$)
P5 = 7.286 (13.71
 $\mu\text{g}/\text{m}^3$)
P25 = 10.32 (19.42
 $\mu\text{g}/\text{m}^3$)
P75 = 17.67 (33.24
 $\mu\text{g}/\text{m}^3$)
P95 = 20.7 (38.95
 $\mu\text{g}/\text{m}^3$)

DNC-1993 Cohort
Mean = 11.6 ± 4
($21.9 \pm 8 \mu\text{g}/\text{m}^3$)
Median = 10.83 (IQR
5.591) (20.37 $\mu\text{g}/\text{m}^3$
(IQR 10.52 $\mu\text{g}/\text{m}^3$))
Min = 2.41 (4.54
 $\mu\text{g}/\text{m}^3$)
Max = 38.39 (72.23
 $\mu\text{g}/\text{m}^3$)

P5 = 5.41 (10.18
μg/m³)
P25 = 8.689 (16.35
μg/m³)
P75 = 14.28 (26.87
μg/m³)
P95 = 19.7 (37.07
μg/m³)

E3N Cohort
Mean = 14.01 ± 5.18
(26.36 ± 9.75 μg/m³)
Median = 13.06 (IQR
6.664) (24.57 μg/m³
(IQR 12.54 μg/m³))
Min = 1.84 (3.46
μg/m³)
Max = 43.06 (81.02
μg/m³)
P5 = 7.12 (13.4
μg/m³)
P25 = 10.27 (19.32
μg/m³)
P75 = 16.93 (31.86
μg/m³)
P95 = 24.23 (45.59
μg/m³)

EPIC-NL-MORGEN
Cohort
Mean = 18.36 ± 3.22
(34.55 ± 6.05 μg/m³)
Median = 17.9 (IQR
4.77) (33.6 μg/m³
(IQR 8.97 μg/m³))
Min = 5.8 (11 μg/m³)
Max = 36.49 (68.66
μg/m³)
P5 = 13.91 (26.18
μg/m³)
P25 = 15.93 (29.97
μg/m³)
P75 = 20.69 (38.94

$\mu\text{g}/\text{m}^3$
P95 = 23.8 (44.8
 $\mu\text{g}/\text{m}^3$)

EPIC-NL-
PROSPECT Cohort
Mean = 19.11 ± 2.88
($35.96 \pm 5.41 \mu\text{g}/\text{m}^3$)
Median = 18.85 (IQR
3.86) ($35.46 \mu\text{g}/\text{m}^3$
(IQR $7.27 \mu\text{g}/\text{m}^3$))
Min = 10.41 (19.58
 $\mu\text{g}/\text{m}^3$)
Max = 33.03 (62.15
 $\mu\text{g}/\text{m}^3$)
P5 = 14.6 (27.4
 $\mu\text{g}/\text{m}^3$)
P25 = 17.28 (32.52
 $\mu\text{g}/\text{m}^3$)
P75 = 21.15 (39.79
 $\mu\text{g}/\text{m}^3$)
P95 = 23.72 (44.63
 $\mu\text{g}/\text{m}^3$)

HNR Cohort
Mean = 20.08 ± 2.48
($37.78 \pm 4.66 \mu\text{g}/\text{m}^3$)
Median = 19.95 (IQR
2.67) ($37.54 \mu\text{g}/\text{m}^3$
(IQR $5.03 \mu\text{g}/\text{m}^3$))
Min = 13.41 (25.23
 $\mu\text{g}/\text{m}^3$)
Max = 39.9 (75.07
 $\mu\text{g}/\text{m}^3$)
P5 = 16.61 (31.26
 $\mu\text{g}/\text{m}^3$)
P25 = 18.53 (34.87
 $\mu\text{g}/\text{m}^3$)
P75 = 21.2 (39.9
 $\mu\text{g}/\text{m}^3$)
P95 = 24.36 (45.83
 $\mu\text{g}/\text{m}^3$)

KORA-S3 Cohort
Mean = 11.23 ± 1.8
(21.13 ± 3.3 µg/m³)
Median = 11.14 (IQR
2.3) (20.97 µg/m³
(IQR 4.32 µg/m³))
Min = 5.538 (10.42
µg/m³)
Max = 22.17 (41.72
µg/m³)
P5 = 8.66 (16.3
µg/m³)
P25 = 10.03 (18.88
µg/m³)
P75 = 12.34 (23.21
µg/m³)
P95 = 14.04 (26.41
µg/m³)

KORA-S4 Cohort
Mean = 11.19 ± 1.8
(21.05 ± 3.39 µg/m³)
Median = 11.06 (IQR
2.39) (20.82 µg/m³
(IQR 4.49 µg/m³))
Min = 5.14 (9.68
µg/m³)
Max = 22.17 (41.72
µg/m³)
P5 = 9.97 (18.76
µg/m³)
P25 = 12.35 (23.24
µg/m³)
P75 = 14.1 (26.5
µg/m³)
P95 = 22.17 (41.72
µg/m³)

Pooled Cohort
Mean = 13 ± 4.28 (25
± 8.05 µg/m³)
Median = 12.83 (IQR
5.394) (24.14 µg/m³)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			(IQR 10.15 µg/m ³) Min = 1.42 (2.68 µg/m ³) Max = 43.06 (81.02 µg/m ³) P5 = 6.861 (12.91 µg/m ³) P25 = 10.37 (19.52 µg/m ³) P75 = 15.77 (29.68 µg/m ³) P95 = 21.01 (39.53 µg/m ³) VHM&PP Cohort Mean = 11.67 ± 2.84 (21.96 ± 5.34 µg/m ³) Median = 11.94 (IQR 3.71) (22.46 µg/m ³) (IQR 6.99 µg/m ³) Min = 2.05 (3.85 µg/m ³) Max = 25.66 (48.28 µg/m ³) P5 = 6.532 (12.29 µg/m ³) P25 = 9.901 (18.63 µg/m ³) P75 = 13.62 (25.62 µg/m ³) P95 = 15.8 (29.7 µg/m ³)			

† Cai et al. (2018)	HUNT is population-based health survey focusing on the county of Nord-Trøndelag and included those aged 20 or older. The EPIC-Oxford cohort included individuals aged at least 20-years throughout the UK. The UK Biobank cohort recruited individuals aged 40-69 from across the UK.	LUR Method validation: NR Averaging time: NO ₂ - annual average Exposure years: 2001-2010	NO ₂ (ppb) EPIC-Oxford Cohort Mean = 15.5 ± 6.43 (29.1 ± 12.1 µg/m ³) Median = 14 (IQR 6.96) (27 µg/m ³ (IQR 13.1 µg/m ³)) Min = 4 (7 µg/m ³) Max = 64.15 (120.7 µg/m ³) P5 = 7.4 (14 µg/m ³) P25 = 11.1 (20.9 µg/m ³) P75 = 18 (34 µg/m ³) P95 = 29 (55 µg/m ³) HUNT Cohort Mean = 6.7 ± 1.9 (12.6 ± 3.6 µg/m ³) Median = 6.22 (IQR 3) (11.7 µg/m ³ (IQR 5 µg/m ³)) Min = 3.5 (6.6 µg/m ³) Max = 22 (42 µg/m ³) P5 = 4.3 (8.1 µg/m ³) P25 = 5.3 (10 µg/m ³) P75 = 8 (15 µg/m ³) P95 = 10.2 (19.2 µg/m ³) Pooled Data Mean = 14.8 ± 6.01 (27.8 ± 11.3 µg/m ³) Median = 14 (IQR 6.8) (27 µg/m ³ (IQR 12.8 µg/m ³)) Min = 3.5 (6.6 µg/m ³) Max = 73.55 (138.4 µg/m ³) P5 = 5.8 (11 µg/m ³) P25 = 10.8 (20.3 µg/m ³)	Hospital Admission	Cox proportional hazards Adjusted for: Cohort, employment, education level, smoking status	HR (95% CI) ^b CBVD: 1.05 (0.89, 1.24) HS: 0.97 (0.72, 1.32) IS: 1.07 (0.83, 1.38)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 17.6 (33.1 $\mu\text{g}/\text{m}^3$) P95 = 26.2 (49.3 $\mu\text{g}/\text{m}^3$) UK Biobank Mean = 15.9 ± 5.47 ($29.9 \pm 10.3 \mu\text{g}/\text{m}^3$) Median = 15.1 (IQR 5.79) ($28.4 \mu\text{g}/\text{m}^3$ (IQR $10.9 \mu\text{g}/\text{m}^3$)) Min = 4 ($7 \mu\text{g}/\text{m}^3$) Max = 73.55 ($138.4 \mu\text{g}/\text{m}^3$) P5 = 8.77 ($16.5 \mu\text{g}/\text{m}^3$) P25 = 12.3 ($23.2 \mu\text{g}/\text{m}^3$) P75 = 18.1 ($34.1 \mu\text{g}/\text{m}^3$) P95 = 26.6 ($50.1 \mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Gandini et al. (2018)	Individuals from families residing in 1442 municipalities across Italy	Hybrid model	NO ₂ (ppb)	Hospital Records	Cox proportional hazards	HR (95% CI) ^b CBVD: 1.04 (0.97, 1.11)
ILS		Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity.	Men Metropolitan Mean = 22.1 ± 6.16 (41.5 ± 11.6 µg/m ³) Rural Mean = 10.3 ± 4 (19.3 ± 8 µg/m ³) Urban Mean = 13.9 ± 5.2 (26.1 ± 9.7 µg/m ³)		Adjusted for: Age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality, and BMI	
N = 74,989						
Italy			Women Metropolitan Mean = 22.1 ± 6.16 (41.6 ± 11.6 µg/m ³) Rural Mean = 10.3 ± 4.2 (19.3 ± 7.9 µg/m ³) Urban Mean = 13.9 ± 5.1 (26.1 ± 9.6 µg/m ³)			
Enrollment: 1999-2000 Follow-up: 1999-2002, 2003-2004, 2005-2006, 2007-2008		Averaging time: NO ₂ - annual average Exposure years: 1999, 2003, 2005, 2007				
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Hartiala et al. (2016) Cleveland Clinic GeneBank n = ~4,600 Cleveland, OH, U.S. Enrollment: 2001-2007 Follow-up: 3 yrs Cohort	Patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography	Spatiotemporal/geo spatial model Method validation NR Averaging time: NO ₂ - 3-y average after enrollment Exposure years: 1998-2010	NO ₂ 36-months post: Mean = 18.2 ± 2 Min = 4.9 Max = 22.1 36-months prior: Mean = 19.1 ± 1.8 Min = 7.8 Max = 23.3	Physician Adjudicated Self- Reports Physician Adjudicated Reports	Cox proportional hazards Adjusted for: Age, sex, education level, current smoking status, Framingham Adult Treatment Panel III risk score Cox proportional hazards Adjusted for: Age, sex, education level, current smoking, and Framingham Adult Treatment Panel III risk score	HR (95% CI) ^b Stroke: 3.11 (0.85, 11.35) Stroke: 3.11 (0.85, 11.35)
†Jin et al. (2022) Medicare n = AF cohort: >30 million CHF cohort: >30 million Stroke cohort: >30 million U.S. Enrollment: 2000 Follow-up: through 2016 Cohort	Medicare enrollees with continuous enrollment in the FFS program and both Medicare part A and part B in the contiguous US.	Hybrid model r ² = 0.84 Averaging time: NO ₂ - 1-hour max Exposure years: 2000-2016	NO ₂ (ppb) AF cohort Mean = 19.8 ± 9.2 CHF cohort Mean = 19.7 ± 9.1 Stroke cohort Mean = 19.8 ± 9.2	Medicare records Medicare claims	Cox proportional hazards Adjusted for: age, self-reported sex, self- reported race/ethnicity, and Medicaid eligibility hyperlipidemia, hypertension, diabetes, and neighborhood-level variables (demographic, SES, healthcare-access- related and meteorological covariates for analysis)	HR (95% CI) ^b Stroke: 1.10 (1.09, 1.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Kim et al. (2022) Korean NHIS-Health Screening Cohort Stroke n = 21,240 Controls n = 84,960 South Korea 2002-2015 Cohort	Cases: Participants who were diagnosed with stroke; excluded those who were diagnosed with stroke before 2004, those who did not have a BMI record. Control group: included participants who did not have a diagnosis of stroke from 2002 through 2015; excluded those who did not have records since 2004 and those were diagnosed with ICD codes I60 and I69	Hybrid model Method validation NR Averaging time: NO ₂ - annual average, Other, NO ₂ - 7-day NO ₂ - 30 days NO ₂ - 3 months Exposure years: 2004-2015	NO ₂ (ppb) 7 days Control Mean = 22.7 ± 10.9 Stroke Mean = 22.1 ± 10.4 30 days Control Mean = 22.7 ± 9.9 Stroke Mean = 22.1 ± 9.7	Medical claims	Logistic regression Adjusted for: Sex, income, region, obesity, smoking, alcohol consumption, and CCI score	OR (95% CI) ^c Stroke, 30 d exposure: 0.44 (0.36, 0.54)
† Klompaker et al. (2019) Dutch PHM 2012 n = 354,827 The Netherlands 2012 Cross-Sectional	Dutch citizens ≥19-years (older adults ≥ oversampled by design)	LUR LOOCV r ² 0.81 Averaging time: NO ₂ - annual average Exposure years: 2009	NO ₂ (ppm) Median = 23.4 (IQR 7.85)	Self-reported doctor diagnosis	Logistic regression Adjusted for: sex, age, marital status, region of origin, education, work, standardized household income, smoking habits, number of cigarettes/day, alcohol consumption, number of alcohol glasses/week, physical activity, BMI, and neighborhood SES	OR (95% CI) ^b Stroke: 1.00 (0.91, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Klompaker et al. (2021a) MEDPAR N = 63,009,173 U.S. Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry Cohort	Medicare beneficiaries, aged ≥ 65-years, living in the contiguous US from January 1, 2000 through December 31, 2016.	Spatiotemporal/geo spatial model The overall cross-validated r^2 for annual estimates was 0.84 for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) CBV Median = 16.1 (IQR 13.8) CHD Median = 16.2 (IQR 13.8) CVD Median = 16.3 (IQR 13.9) Total Cohort Median = 16.3 (IQR 13.9)	Hospital Admissions	Cox proportional Adjusted for: Calendar year, US census covariates, BRFSS covariates, US regions, an offset for total person-time and strata for all possible combinations of sex, race, Medicaid eligibility, age at study entry, and follow-up year	HR (95% CI) ^b CBVD low exposure: 1.17 (1.15, 1.18) CBVD: 1.04 (1.03, 1.04)
†Kulick et al. (2023) WHI n = 155,410 U.S. Enrollment: 1993-1998 Follow-up: through 2010 Cohort	Postmenopausal women without previous cerebrovascular disease	Spatiotemporal/geo spatial model Estimated annual average geocoded participant address-specific concentrations of NO ₂ , which were derived from similar national spatiotemporal models with the addition of station monitor data Averaging time: NO ₂ - annual average Exposure years: 1993-2010	NO ₂ (ppm) Mean = 17.2 ± 7.2 Median = 17.3 (IQR 9.5) Min = 0.9 Max = 48.4 P25 = 12.4 P75 = 21.9	Hospital Records	Cox Proportional Adjusted for: age, race, smoking, education, income, marital status, employment status, BMI, high cholesterol, family history of stroke, alcohol consumption, physical activity, WHI study component, neighborhood SES, diabetes and hypertension at enrollment, and WHI center	HR (95% CI) ^b Stroke Hospitalization: 1.06 (1.02, 1.11) CBVD event: 1.06 (1.03, 1.10) IS Hospitalization: 1.05 (1.01, 1.10) HS Hospitalization: 1.02 (0.93, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Ma et al. (2022) MEDPAR N = 17,443,900 U.S. 2000-2017 Cohort	Medicare beneficiaries aged 65 and over with continuous enrollment in Medicare FFS program; and in both Medicare Part A (hospital insurance) and Part B medical insurance). Those enrolled in only Part A or only Part B and those enrolled in Part C at any time were excluded. Those who experienced stroke one-year after enrollment were also excluded to ensure a person was stroke diagnosis free prior to the Medicare diagnosis.	Spatiotemporal/geo spatial model, Ensemble machine learning model, Fixed site monitor $r^2 = 0.84$ Averaging time: NO ₂ - annual average Exposure years: 2000-2017	NO ₂ (ppb) Full Cohort Mean = 17.5 ± 12.4	Hospitalizations	Cox proportional hazards Adjusted for: stratified by individual characteristics, adjusting for neighborhood-level socioeconomic status (SES), behavioral risk factors, health care capacity variables, land-use variables, and residual temporal and spatial trends	HR (95% CI) ^b Stroke: 1.06 (1.05, 1.06)
†Olaniyan et al. (2022) CanCHEC N = 2,687,900 Canada Enrollment: 1981 Follow-up: through December 31, 2016 Cohort	Included non-institutionalized respondents who were 25-89-years of age residing in Canada. Excluded all residents of Quebec.	Chemical transport model, LUR, Fixed site monitor This model explained 75% of the variability in ground-measured NO ₂ Averaging time: NO ₂ - annual average Exposure years: 1998-2012	NO ₂ (ppb) 8.57 (range: 0.01–35.57)	Hospitalizations	Cox proportional hazards Adjusted for: Age, SES, occupational class, marital status, educational attainment, income deciles, indigenous status, visible minority status, employment status, Canadian marginalization indices, urban form, community size, airshed	HR (95% CI) ^b Stroke: 0.99 (0.95, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Poulsen et al. (2023a)	Danish citizens born after 1920 and living in Denmark on 1 January 2005 and who were 50-years of age any time between this date and 31 December 2017. Persons diagnosed with stroke before Enrollment and had missing covariate information were excluded.	Hybrid model Method validation NR Averaging time: NO ₂ - monthly Exposure years: 1995-2017	NO ₂ (ppb) Non-Traffic Median = 5.95 (11.2 µg/m ³) P10 = 4.5 (8.5 µg/m ³) P90 = 7.12 (13.4 µg/m ³) Total Median = 8.13 (15.3 µg/m ³) P10 = 5.58 (10.5 µg/m ³) P90 = 12.6 (23.7 µg/m ³) Traffic Median = 2 (4 µg/m ³) P10 = 0.74 (1.4 µg/m ³) P90 = 5.79 (10.9 µg/m ³)	Patient Registry	Cox proportional hazards Adjusted for: Individual-level age, sex and calendar period, marital status, education, occupational status, ethnicity, personal/household income, parish-level percentage: living in social housing, being sole providers, of non-Western origin, having low income, being unemployed, having blue-collar work, having only basic education and having criminal record.	HR (95% CI) ^b Stroke, traffic: 1.00 (0.99, 1.01) Stroke, non-traffic: 1.08 (1.07, 1.09) Stroke, total NO ₂ : 1.08 (1.04, 1.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Poulsen et al. (2023b) Danish Civil Registration System N = 1,971,246 Denmark Enrollment: 1979 Follow-up 2005-2017 Cohort	All Danish citizens with a personal identification number given at birth living in Denmark on January 2005 and were >50-years.	Hybrid model $r^2 = 0.60-0.80$ Averaging time: NO ₂ - 1-hour max Exposure years: 2005-2017	NO ₂ (ppb) Non-traffic Median = 5.95 (11.2 µg/m ³) P5 = 4.1 (7.8 µg/m ³) P95 = 7.49 (14.1 µg/m ³) Total Median = 8.08 (15.2 µg/m ³) P5 = 4.9 (9.3 µg/m ³) P95 = 14.5 (27.3 µg/m ³)	Patient Registry	Cox proportional hazards Adjusted for: age, sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, with only basic education, who are unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and who live in social housing	HR (95% CI) ^b Stroke (total NO ₂): 1.08 (1.04, 1.11)
† Shin et al. (2019) ONPHEC n = 5,071,956 Ontario, Canada Enrollment: April 1, 1996 Follow-up: through March 31, 2015 Cohort	Long-term residents of Ontario, age 35-85 yrs or older, and registered with the Ontario Health Insurance Plan as of 1 April 1996, who did not have any physician-diagnosed atrial fibrillation and history of hospitalization for stroke as of 1 April 2001.	LUR, Fixed site monitor LUR model explained 73% of the variability Averaging time: NO ₂ - annual average Exposure years: 2005-2011	NO ₂ (ppb) Enrollment in 2001 Mean = 15.3 ± 8 Median = 14.1 (IQR 12.9) Min = 1.2 Max = 67 P25 = 8.4 P75 = 21.3	Administrative database	Cox proportional hazards Adjusted for: Age, sex, area-level risk factors, geographic indicator variables	HR (95% CI) ^b Stroke: 1.02 (1.00, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Stafoggia et al. (2014)	Individuals from 11 ESCAPE cohorts.	LUR	NO ₂ (ppb)	Interview, medical records, death certificates, registries	Cox proportional hazards	NO ₂
ESCAPE	Individuals were excluded if they met any of the following criteria: prevalent cases at enrollment, missing exposure data, or missing covariates.	NO ₂ and NO _x estimates based on measurements from all 11 cohorts and concentrations were assigned based on Enrollment residence of participants.	FINRISK Mean = 7.97 (15 µg/m ³) SNAC-K Mean = 9.04 (17 µg/m ³) SALT Mean = 5.85 (11 µg/m ³) 60y Mean = 5.85 (11 µg/m ³) SDDP Mean = 4.25 (8 µg/m ³) DCH Mean = 8.50 (16 µg/m ³) HNR Mean = 15.95 (30 µg/m ³) KORA Mean = 10.10 (19 µg/m ³) EPIC-Turin Mean = 28.17 (53 µg/m ³) SIDRIA-Turin Mean = 31.89 (60 µg/m ³) SIDRIA-Rome Mean = 20.73 (39 µg/m ³)		Adjusted for: Age, year of enrollment, sex, marital status, education level, occupation status, smoking status, years of smoking, cigarettes/day, mean income at municipality level and other area-level covariates	HR (95% CI) ^b Stroke: 0.98 (0.80, 1.21)
n = 99,446						
Sweden, Denmark, Italy, Germany, Finland						NO _x
Enrollment: 1992-2007						HR (95% CI) ^b Stroke: 0.98 (0.89, 1.07)
Follow-up: 2006-2010						
Cohort		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2008-2011				
			NO _x (µg/m ³) FINRISK Mean = 24 SALT Mean = 19 60y Mean = 19 SDPP Mean = 14 DCH Mean = 27 HNR Mean = 51 KORA Mean = 32 EPIC-Turin Mean = 96 SIDRIA-Turin Mean = 107 SIDRIA-Rome Mean = 82			

†Tian et al. (2022)						
UK Biobank	Participants are aged 40-69-years from the U.K.	LUR	NO ₂ (ppb)	Hospital Records	Multistate regression	NO ₂
N = 318,752	Exclusion criteria included participants who had a stroke, ischemic heart disease, or cancer at Enrollment.	Method validation NR	All Mean = 14.1 ± 4.06 (26.54 ± 7.64 µg/m ³)		Adjusted for: age, sex, ethnicity, BMI, household income, education level, smoking status, alcohol consumption status, physical activity, and family history	HR (95% CI) ^b Post-stroke CVD: 1.16 (1.08, 1.25) Incident Stroke: 1.08 (1.02, 1.14)
England, Scotland, Wales, U.K.	Participants with missing air pollution or key covariate data were also excluded.	Averaging time: NO ₂ - annual average, NO _x - annual average	Incident Stroke No Mean = 14.1 ± 4.06 (26.53 ± 7.64 µg/m ³)			NO _x
Enrollment: March 2006-October 2010		Exposure years: 2005-2007, 2010	Yes Mean = 14.2 ± 4.07 (26.71 ± 7.66 µg/m ³)			HR (95% CI) ^b Incident Stroke: 1.01 (1.00, 1.02) Post-stroke CVD: 1.02 (1.00, 1.02)
Follow-up: Enrollment to September 2021 in England, July 2021 in Scotland, and February 2018 in Wales.			Mortality No Mean = 14.09 ± 4.06 (26.51 ± 7.64 µg/m ³)			
Cohort			Yes Mean = 14.31 ± 4.07 (26.93 ± 7.66 µg/m ³)			
			Poststroke Cardiovascular Events No Mean = 14.08 ± 4.08 (26.49 ± 7.68 µg/m ³)			
			Yes Mean = 14.31 ± 4.06 (26.93 ± 7.64 µg/m ³)			
			NO _x (µg/m ³)			
			All Mean = 43.77 ± 15.54			
			Incident Stroke No Mean = 43.73 ± 15.53			
			Yes Mean = 44.33 ± 15.79			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mortality No Mean = 43.71 ± 15.52 Yes Mean = 44.82 ± 15.98 Poststroke Cardiovascular Events No Mean = 43.92 ± 15.92 Yes Mean = 44.74 ± 15.64			
† Wang et al. (2023)	Chinese adults (≥16-years) from 25 China mainland provincial regions. Participants were excluded if they were lost to follow-up, had missing chronic disease information, had a history of cardiovascular disease at enrollment, or were unable to be matched to exposure.	Spatiotemporal/geo spatial model	NO ₂ (ppb)	Self-reports	Cox proportional	HR (95% CI) ^b Stroke: 2.61 (2.10, 3.23)
CFPS		Method validation NR, but states "well-validated"	Quartile 1 (6.9-16.6) Mean = 6.59 ± 0.9 (12.4 ± 1.7 µg/m ³)	Self-reported doctor dx	Adjusted for: age, sex, BMI, educational level, marital status, employment status, health status (good, general, and poor), residence (urban, rural), and region, cigarette smoking, alcohol consumption, physical activity, household air pollution from cooking solid fuel, outdoor temperature, and RH.	
N = 36,948		Averaging time: NO ₂ - annual average	Quartile 2 (16.7-21.5) Mean = 9 ± 0.69 (17 ± 1.3 µg/m ³)			
China		Exposure years: 2010-2018	Quartile 3 (21.6-27.5) Mean = 11.4 ± 0.69 (21.5 ± 1.3 µg/m ³)			
Enrollment waves: 2010, 2014, 2016, 2018			Quartile 4 (27.6-57.4) Mean = 15.6 ± 2.2 (29.4 ± 4.2 µg/m ³)			
Follow-up: through 2018			Total Mean = 11 ± 3.6 (20 ± 6.7 µg/m ³)			
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Danesh Yazdi et al. (2021) Medicare N = 63,006,793 U.S. 2000-2016 Cohort	All fee-for-service Medicare beneficiaries who were 65-years of age or older and who lived in the contiguous United States between 2000 and 2016 as derived from the Medicare denominator file and the Medicare Provider Analysis and Review file.	Spatiotemporal/geo spatial model, LUR, Chemical transport model r ² values of 0.84 for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) Exposure Across Person-Years Mean = 19.5 Median = 17.44 Min = 0.01 Max = 127.63 P10 = 8.13 P25 = 11.51 P75 = 25.88 P90 = 33.88	Hospital Admission	DRAM Adjusted for: Sex, race, age group, Medicaid eligibility, SES data	β (%) (95% CI) ^b Stroke: 0.01 (0.00, 0.01)
† Danesh Yazdi et al. (2022) MEDPAR N = 436,684 U.S. 2000-2016 Cross-Sectional	Persons aged 65-years or over in the contiguous United States who are Medicare beneficiaries and received fee for service care at a hospital.	Hybrid model Ten-fold cross validation r ² value of 0.84. Averaging time: NO ₂ - annual average Exposure years: 2000-2016	NO ₂ (ppb) Exposure over two-year period Mean = 16.22 Median = 13.86 Min = 0.03 Max = 98.59 P10 = 7.15 P25 = 9.63 P75 = 20.63 P90 = 29.14	Hospital Discharge Rate	Adjusted for: Zip code level proportion female, race, Medicaid-eligible, age, SES, education, ever-smokers, mean BMI, access to care and other pollutants. Zip code level demographic (proportion of the study population who were female, identified as Black, identified as race other than Black or white, were Medicaid-eligible, and by age group (65-74, 75-84)	β (RD) (95% CI) ^b Stroke: 4.90 (-1.25, 11.05)

List of abbreviations in alphabetical order: $\mu\text{g}/\text{m}^3$ = micrograms per cubic meter; AF=Atrial Fibrillation; BMI=body mass index; BRFSS=Behavioral Risk Factor Surveillance System; CBV=Cerebrovascular; CBVD=cerebrovascular disease; CCI=Charleston Comorbidity Index; CEANS= Cardiovascular Effects of Air Pollution and Noise in Stockholm; CEANS-60YO= Cardiovascular Effects of Air Pollution and Noise in Stockholm-Sixty Year Old; CEANS-SALT= Cardiovascular Effects of Air Pollution and Noise in Stockholm- Stockholm Screening Across the Lifespan Twin study and TwinGene; CEANS-SDPP= Cardiovascular Effects of Air Pollution and Noise in Stockholm-Stockholm Diabetes Prevention Program; CEANS-SNAC-K= Cardiovascular Effects of Air Pollution and Noise in Stockholm-Swedish National Study on Aging and Care in Kungsholmen; CFPS= China Family Panel Studies; CHD=coronary heart disease; CHF=Congestive Heart Failure; CI=confidence interval; CVD=cardiovascular disease; d=day; DCH= Danish Diet, Cancer and Health; DNC=Danish Nurses' Cohort; E3N= Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ELAPSE= Effects of Low-Level Air Pollution: A Study in Europe; EPIC-Oxford= European Prospective Investigation into Cancer and Nutrition- Oxford; EPIC-Oxford= European Prospective Investigation into Cancer and Nutrition- Oxford; EPIC-Prospect= European Prospective Investigation into Cancer and Nutrition-Prospect; EPIC-Varese=European Prospective Investigation into Cancer and Nutrition-Varese; ESCAPE= European Study of Cohorts for Air Pollution Effects; FFS=Fee for Service; HNR Study= Heinz Nixdorf Recall Study; HS=hemorrhagic stroke; HUNT=Helseundersøkelsen i Nord-Trøndelag; IQR=interquartile range; IQR=interquartile range; IS=ischemic stroke; KORA= Cooperative Health Research in the Region of Augsburg; LOOCV= leave-one-out cross-validation; LUR=Land use regression; Max=Maximum; MEDPAR= Medicare denominator and Medicare Provider Analysis and Review; Min=Minimum; NA=Not applicable; NHIS= National Health Insurance Service; NO₂=Nitrogen dioxide; NO_x = nitrogen oxides; NR=Not Reported; ONPHEC= Ontario Population Health and Environment Cohort; OR=odds ratio; P=Percentile; PHM=Public Health Monitor; ppb=parts per billion; RR=Relative Risk; SDPP= Stockholm Diabetes Prevention Program; SES=socioeconomic status; SIDRIA= Italian Study of Respiratory Diseases in Childhood and the Environment; VHM&PP= Vorarlberg Health Monitoring and Prevention Programme; WHI=Women's Health Initiative; Yr(s)=year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-5 Epidemiologic studies of exposure to oxides of nitrogen and hypertension

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
[†] Adar et al. (2018)	Men and women, aged 45- to 84-years, who were free of clinical cardiovascular disease, weighed <136 kg, and had no impediments to long-term participation. Restricted to participant visits with information on air pollution, key covariates, and blood	Spatiotemporal/geospatial model, Fixed site monitor	NO ₂ (ppb) 1-day Exam 1: 2000-2002 Mean = 24.5 ± 13.4 Exam 2: 2002-2004 Mean = 23.5 ± 12.5 Exam 3: 2004-2005 Mean = 20.2 ± 11.1 Exam 4: 2005-2007 Mean = 20.2 ± 11.1 Exam 5: 2010-2012 Mean = 20.6 ± 11.2	Hypertension	Cox proportional hazards Adjusted for: sex, race, education, NSES, smoking exposure, physical activity, waist-to-hip ratio, BMI, study site, study site neighborhood SES, calendar time.	HR (95% CI) ^b Hypertension, no adjustment for time: 1.29 (1.11, 1.50) Hypertension, adjustment for time: 1.08 (0.92, 1.27)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Enrollment: 2000-2002	pressure. Analysis of incident		1-year Exam 1: 2000-2002 Mean = 21.8 ± 9.2			
Follow-up: 2002-2007, 2010-2012	hypertension further restricted to those without prevalent hypertension at Enrollment.		Exam 2: 2002-2004 Mean = 20.7 ± 9.1 Exam 3: 2004-2005 Mean = 19.6 ± 8.2 Exam 4: 2005-2007 Mean = 19.4 ± 8.1 Exam 5: 2010-2012 Mean = 15.6 ± 7.7			
Cohort			2-day Exam 1: 2000-2002 Mean = 23.8 ± 13.2 Exam 2: 2002-2004 Mean = 22.7 ± 12.6 Exam 3: 2004-2005 Mean = 19.4 ± 10.7 Exam 4: 2005-2007 Mean = 20.2 ± 11 Exam 5: 2010-2012 Mean = 19.9 ± 11			
			7-day Exam 1: 2000-2002 Mean = 25.5 ± 13.6 Exam 2: 2002-2004 Mean = 24.2 ± 12.8 Exam 3: 2004-2005 Mean = 20.9 ± 11.1 Exam 4: 2005-2007 Mean = 21.6 ± 11.2 Exam 5: 2010-2012 Mean = 21.2 ± 11.1			
			30-day			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Exam 1: 2000-2002 Mean = 21.5 ± 9.6 Exam 2: 2002-2004 Mean = 20.8 ± 9.6 Exam 3: 2004-2005 Mean = 18.5 ± 8.5 Exam 4: 2005-2007 Mean = 19.1 ± 8.6 Exam 5: 2010-2012 Mean = 14.8 ± 8.5 60-day Exam 1: 2000-2002 Mean = 21.6 ± 9.5 Exam 2: 2002-2004 Mean = 20.8 ± 9.5 Exam 3: 2004-2005 Mean = 18.8 ± 8.5 Exam 4: 2005-2007 Mean = 19.1 ± 8.6 Exam 5: 2010-2012 Mean = 14.8 ± 8.5			
†Bai et al. (2018) ONPHEC n = Hypertension Cohort: 893,499 Diabetes Cohort: 1,056,012 Toronto, Canada Enrollment: April 1, 1996 Follow-up: through	All Canadian-born residents, living in Toronto and were registered with Ontario's provincial health insurance plan. Restricted to ages 30-100, living in Toronto for at least three-years before cohort entry, free of hypertension or diabetes at time of Enrollment.	LUR r ² = 50% Averaging time: NO ₂ - annual average, Other, NO ₂ - 3-year moving averages Exposure years: 1996-2012	NO ₂ (ppb) Diabetes Cohort Mean = 21.4 ± 3.5 Median = 21.1 (IQR 4) Min = 9.9 Max = 50.1 Hypertension Cohort Mean = 21.5 ± 3.6 Median = 21.1 (IQR 4.1)	Hypertension	Cox proportional hazards Adjusted for: age, sex, neighborhood-level recent immigrants, unemployment rate, education, and annual household income	HR (95% CI) ^b Hypertension: 1.02 (1.00, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
December 31, 2012 Cohort			Min = 9.9 Max = 50.1			
Coogan et al. (2012) BWHS n = Hypertension cohort: 3,236 Diabetes cohort: 3,992 Los Angeles, CA, U.S. Enrollment: 1995 Follow-up: 1995-2005 Cohort	Black women, 21-69- years of age, lived in Los Angeles at Enrollment; excluded those who were free of hypertension at Enrollment and those who were free of diabetes mellitus at Enrollment	LUR, Fixed site monitor The r ² between the field measured and predicted pollutant level was 85%. Cross-validation with the 16 sites not used in model calibration indicated excellent model performance with r ² = 92%. Averaging time: NO _x - annual average Exposure years: 2006	NO _x (ppb) Overall Mean = 43.3 ± 11 Median = 41.6 P25 = 36.9 P75 = 49.2	Hypertension	Cox proportional hazards Adjusted for: age, questionnaire cycle, metropolitan area, BMI, smoking status, years of education, hours/week vigorous exercise, alcohol, vegetable/fruit diet pattern, meat/fried foods diet pattern, neighborhood SES	IRR (95% CI) ^b Hypertension: 1.31 (1.07, 1.61)
†Coogan et al. (2017) BWHS n = 33,771 56 Metropolitan Areas, U.S.	Black women 21-69 yrs at Enrollment	LUR, Unsure/Needs to be checked by EPA r ² = 0.80 Averaging time: multi-year average	NO ₂ (ppb) Mean = 18.6 Min = 1 Max = 37.7	Hypertension	Cox proportional hazards Adjusted for: age, questionnaire cycle, metropolitan area, BMI, smoking status, years of education, hours/week vigorous	HR (95% CI) ^b Hypertension: 0.92 (0.86, 0.98)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Enrollment: 1995 Follow-up: 2011 Cohort		Exposure years: 2000-2010			exercise, alcohol, vegetable/fruit diet pattern, meat/fried foods diet pattern, neighborhood SES	
Fuks et al. (2014) ESCAPE n = 113,926 Sweden, U.K., Denmark, Switzerland, Norway, Germany, Finland, The Netherlands 1992-2008 (enrollment was conducted in different years depending on the cohort in this cross-sectional analysis) Cross-Sectional	Adult men and women participating in 13 studies in Europe	LUR LUR r ² = 55% to 92% (median 82%) for NO ₂ and from 49% to 91% (median 78%) for NO _x . C-V r ² was generally less than 10% lower than the model r ² . (Beelen et al., 2013) Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 1992-2008	NO ₂ (ppb) Main Analysis Mean = 10.3 (19.3 µg/m ³) NO _x (µg/m ³) Main Analysis Mean = 32	BPLM Hypertension	logistic regression Adjusted for: age, sex, BMI, smoking status, pack-years of smoking, passive smoking, alcohol consumption, physical activity, educational level, economic activity, neighborhood SES (random intercept for neighborhood).	NO ₂ OR (95% CI) ^b BPLM: 1.02 (0.95, 1.10) Hypertension: 0.96 (0.86, 1.08) NO _x OR (95% CI) ^c BPLM: 0.98 (0.94, 1.02) Hypertension: 0.98 (0.92, 1.04)
†Fuks et al. (2017) REGICOR, DCH, SNAC-K, ESCAPE, HUBRO, HNR Study, KORA,	Excluded participants who changed their address during follow-up	Fixed site monitor, LUR, Spatiotemporal/geospatial model Method validation NR	NO ₂ (ppb) DCH Mean = 8.66 ± 4 (16.3 ± 7 µg/m ³) HNR	Incident Hypertension	Poisson regression/mixed effect models Adjusted for: age, sex, education, economic activity, BMI, smoking	NO ₂ RR (95% CI) ^b Self-reported hypertension: 1.06 (0.96, 1.16) BPLM use: 1.04 (0.92, 1.17) Measured hypertension:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
SDPP			Mean = 16.1 ± 2.6 (30.3 ± 4.9 µg/m ³)		status, pack-years of smoking, passive smoking, total alcohol consumption, wine consumption, physical activity, family history of hypertension, and area-level SES	0.94 (0.84, 1.06)
N = 74,363		Averaging time: NO ₂ - annual average, NO _x - annual average	HUBRO Mean = 11.1 ± 4.2 (20.8 ± 7.9 µg/m ³)			NO _x
Sweden, Denmark, Spain, Norway, Germany		Exposure years: 2008-2011	KORA Mean = 9.94 ± 2 (18.7 ± 3.8 µg/m ³)			RR (95% CI) ^c BPLM use: 0.99 (0.93, 1.07) Measured hypertension: 0.96 (0.91, 1.01) Self-reported hypertension: 1.03 (0.98, 1.08)
HUBRO Enrollment: 2000-2001			REGICOR Mean = 19.7 ± 7.07 (37.1 ± 13.3 µg/m ³)			
SDPP Enrollment: 1992-1994, 1996-1998			SDPP Mean = 4.5 ± 0.9 (8.4 ± 1.7 µg/m ³)			
SNAC-K Enrollment: 2001-2004			SNAC-K Mean = 9.25 ± 2.6 (17.4 ± 4.8 µg/m ³)			
DCH Enrollment: 1993-1997			NO _x (µg/m ³)			
HUBRO: Study years NR: 2000-2003			DCH Mean = 26.6 ± 18.3			
KORA: 1994-1995, 1999-2001			HNR Mean = 50.8 ± 11.9			
REGICOR: 2003-2006			HUBRO Mean = 38.1 ± 15.2			
Follow-up periods vary			KORA Mean = 32.5 ± 7.2			
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			REGICOR Mean = 66.2 ± 28.2			
			SDPP Mean = 14.4 ± 3.3			
			SNAC-K Mean = 33.5 ± 12.5			
† Hou et al. (2021) Henan Rural Cohort Study n = 38,883 Henan Province, China Study years NR Cross-Sectional	Residents of rural counties in Henan province China	Hybrid model 10-fold C-V r ² > 0.70 Averaging time: 3-year avg Exposure years: NR	NO ₂ (µg/m ³) Median = 40.29 P25 = 36.27 P75 = 42.67		Logistic regression Adjusted for: age, sex, education level, marital status and average monthly income, smoking and drinking status, physical activity, high-fat diet, fruit and vegetable intake, type 2 diabetes, family history of hypertension	OR (95% CI) ^c Hypertension: ≥ 40 µg/m ³ < 40 µg/m ³ : 1.83 (1.74, 1.93)
† Howell et al. (2019) CANHEART N = 2,469,458 Ontario, Canada Enrollment: 1991-2007 Follow-up: 2008 Cohort	Restricted to ages 40-74, residence in study area, no previous hospital admission for stroke, MI, or CHF, or no previous percutaneous coronary intervention or coronary bypass graft during enrollment period, no residence in a	LUR Model r ² of 0.73 Averaging time: NO ₂ - annual average Exposure years: 2006	NO ₂ (ppb) Least Walkable Areas Mean = 15.2 ± 4.9 Most Walkable Areas Mean = 21.4 ± 3.4	Hypertension	logistic regression Adjusted for: age, sex, ethnicity, immigration history, neighborhood median income	HR (95% CI) ^b Hypertension: 1.02 (1.01, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	long-term care facility at index or in previous 5-years, or those residing in Ontario during the preceding two-years.					
†Klompmaaker et al. (2019) Dutch PHM 2012 n = 354,827 The Netherlands 2012 Cross-Sectional	Dutch citizens ≥19-years (older adults ≥ oversampled by design)	LUR LOOCV r ² 0.81 Averaging time: NO ₂ - annual average Exposure years: 2009	NO ₂ (ppb) Median = 12.4 (IQR = 4.2) (Median = 23.4, IQR 7.85 µg/m ³)	Hypertension	Logistic regression Adjusted for: sex, age, marital status, region of origin, education, work, standardized household income, smoking habits, number of cigarettes/day, alcohol consumption, number of alcohol glasses/week, physical activity, BMI, and neighborhood SES	OR (95% CI) ^b Hypertension: 1.05 (1.01, 1.09)
†Letellier et al. (2022) Community of Mine Study N = 552 San Diego, CA, U.S. 2014-2017 Cross-Sectional	Adults, aged 35-80, living for at least 6-months in a selected census block groups. Restricted the population to participants with HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data. Participants with missing information	Fixed site monitor Correlations between predicted and actual values at the location of the omitted point were used to assess validity of modeled estimates (with a min r of 0.55). Averaging time:	NO ₂ (ppb) Dynamic Exposure Hispanic/Latino Median = 0.0425 (IQR 0.02392) (0.08 µg/m ³ (IQR 0.045 µg/m ³)) Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 µg/m ³ (IQR 0.058 µg/m ³))	Hypertension	GEE Adjusted for: age, sex, ethnicity, income, current smoking status, BMI	RR (95% CI) ^b Hypertension, dynamic: 1.10 (0.82, 1.46) Hypertension, static: 0.94 (0.68, 1.31)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	on covariates and without air pollution exposure data were excluded.	NO ₂ - annual average Exposure years: 2014-2017	Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 µg/m ³ (IQR 1.91 µg/m ³)) Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 µg/m ³ (IQR 1.17 µg/m ³))			
Levinsson et al. (2014) INTERGENE/AD ONIX n = 119 cases 1310 controls 1429 total Sweden April 2001 - January 2004 (case recruitment) Case-Control	CHD cases and population based controls (25-75) in Gothenberg area, Sweden	Dispersion model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2001-2004	NO ₂ (ppb) AMI cases Mean = 7.92 ± 3.06 (14.9 ± 5.75 µg/m ³) Hypertensive controls Mean = 7.92 ± 3.15 (14.9 ± 5.93 µg/m ³) Non-hypertensive controls Mean = 8.56 ± 3.27 (16.1 ± 6.16 µg/m ³)	Hypertension	logistic regression Adjusted for: sex, age, age squared, level of education and residential area	OR (95% CI) Hypertension: 0.69 (0.34, 1.38)
†Ni et al. (2021) CANDLE cohort N = 822 Shelby County, TN, U.S.	Women residing in Shelby County, Tennessee residents between 16-40 yrs of age, had singleton pregnancies without complications, and planned to deliver at a participating study	LUR, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR Averaging time:	NO ₂ (ppb) Postnatal Mean = 8.9 ± 1.9 Median = 8.9 (IQR 2.6) Min = 3.7 Max = 13.5 P25 = 7.6	High BP	Poisson regression Adjusted for: child age, sex, height at 4-6 yr visit, recruitment site, splines of visit date, maternal race, age at childbirth, education, log transformed	IRR (95% CI) ^b Prenatal HBP: 1.16 (0.61, 2.22) Postnatal HBP: 2.01 (0.83, 4.89) RR (95% CI) ^b 4-yr avg/High risk/postnatal: 2.01 (0.83, 4.89)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Enrollment 1: December 2006-August 2008 Enrollment 2: September 2007-July 2011 Follow-up: 8-9-years Cohort	hospital. The 1st stage of enrollment: recruited during regular obstetric appointments. The 2nd stage of enrollment: recruited from general community via media campaigns. NO	NO ₂ - annual average Exposure years: 2006-2014	P75 = 10.2 Prenatal Mean = 10 ± 2.4 Median = 10 (IQR 3.4) Min = 4 Max = 16.4 P25 = 8.3 P75 = 11.7		income adjusted by household size, breastfeeding cotinine, BMI, insurance status, maternal psychological distress, child sleep scores, child physical activity, medication, second hand smoke and Child Opportunity Index	4-yr avg/High risk/prenatal: 1.16 (0.61, 2.22)
† Ni et al. (2022) CANDLE N = 556 Mothers N = 495 Children Enrollment: NR Follow-up: NR Cohort	Pregnant women, aged 16-40 residing in Shelby County Tennessee	Spatiotemporal/geospatial model Averaging time: NO ₂ – Other: 4-yr avg Exposure years: NR	NO ₂ (ppb) 4-year avg = 9.66 ± 1.94 Prenatal: 9.05(±2.54) Postnatal: 9.67 ((±2.02)	Blood Pressure	Linear Regression Adjusted for: child age, sex, height at 4-6 yr visit, recruitment site, splines of visit date, maternal race, age at childbirth, education, log transformed income adjusted by household size, breastfeeding cotinine, BMI, insurance status, maternal psychological distress, child sleep scores, child physical activity, medication, second hand smoke and Child Opportunity Index	High Risk SPB: 9.05 (-13.20, 31.30) High Risk DPB: 9.15 (-5.58, 23.88) Low Risk SPB: -1.00 (-6.53, 4.53) Low Risk DBP: 0.90 (-4.20, 6.00)
† Shi et al. (2023) UK Biobank N = 494,750	The general population in England, Scotland, and Wales 40-69-years of age without	Dispersion model Method validation NR	NO ₂ (ppb) Mean = 9.7 ± 3.2 (18.2 ± 5.99 µg/m ³)	Registry	Cox proportional hazards Adjusted for: age, gender, ethnicity, BMI,	NO ₂ HR (95% CI) Pulmonary hypertension: 1.42 (1.37, 1.48)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
England, Scotland, Wales, U.K. Enrollment: 2006-2010 Follow-up: December 2019 Cohort	pulmonary hypertension or heart failure at Enrollment.	Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2004-2019	NO _x (µg/m ³) Mean = 27.2 ± 11		household income, education, smoking status, associated conditions, and noise	NO _x HR (95% CI) Pulmonary hypertension: 1.35 (1.31, 1.40)
† Wang et al. (2023) CFPS N = 36,948 China Enrollment waves: 2010, 2014, 2016, 2018 Follow-up: through 2018 Cohort	Chinese adults (> = 16- years) from 25 China mainland provincial regions. Participants were excluded if they were lost to follow-up, had missing chronic disease information, had a history of cardiovascular disease at enrollment, or were unable to be matched to exposure.	Spatiotemporal/geospatial model Method validation NR, but states "well-validated" Averaging time: NO ₂ - annual average Exposure years: 2010-2018	NO ₂ (ppb) Quartile 1 (6.9-16.6) Mean = 6.59 ± 0.9 (12.4 ± 1.7 µg/m ³) Quartile 2 (16.7-21.5) Mean = 9 ± 0.69 (17 ± 1.3 µg/m ³) Quartile 3 (21.6-27.5) Mean = 11.4 ± 0.69 (21.5 ± 1.3 µg/m ³) Quartile 4 (27.6-57.4) Mean = 15.6 ± 2.2 (29.4 ± 4.2 µg/m ³) Total Mean = 11 ± 3.6 (20 ± 6.7 µg/m ³)		Cox proportional Adjusted for: age, sex, BMI, educational level, marital status, employment status, health status (good, general, and poor), residence (urban, rural), and region, cigarette smoking, alcohol consumption, physical activity, household air pollution from cooking solid fuel, outdoor temperature, and RH.	HR (95% CI) ^b Hypertension: 2.20 (1.93, 2.51)
† Weng et al. (2022) UK Biobank	Participants recruited were aged 40-69-years old across the UK. Participants	LUR NO ₂ r ² = 87% NO _x r ² = 88%	NO ₂ (ppb) High Mean = 16.9 (31.8)	Hypertension	Cox proportional Adjusted for: age, sex, Townsend Deprivation	NO ₂ HR (95% CI) ^b Hypertension: 1.02 (1.00, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
N = 391,366 England, Scotland, Wales, U.K. Enrollment: 2006-2010 Follow-up: median 8.7-years Cohort	with self-reported hypertension diagnoses and medications, hospital cases, missing data at Enrollment, non-white, missing genetic data were excluded.	Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2010	µg/m ³ Median = 16.2 (30.5 µg/m ³) Min = 13.6 (25.6 µg/m ³) Max = 57.29 (107.8 µg/m ³) Low Mean = 10.8 (20.4 µg/m ³) Median = 11 (21 µg/m ³) Min = 6.86 (12.9 µg/m ³) Max = 13.6 (25.6 µg/m ³) NO _x (µg/m ³) High Mean = 53.7 Median = 49.7 Min = 41.6 Max = 265.9 Low Mean = 32.5 Median = 33.6 Min = 19.7 Max = 41.6		index, alcohol consumption, smoking status, BMI, physical activity, and diabetes	NO _x HR (95% CI) ^c Hypertension: 1.01 (1.01, 1.02)
† Yang et al. (2017) 33CCHS n = 24,845	Adults, 18-74-years old	Fixed site monitor Averaging time: Three-year average	NO ₂ (ppb) Mean = 18.75 ± 2.9 (35.28 ± 5.45 µg/m ³)	Prehypertension	Logistic regression Adjusted for: sex, BMI, nationality, education, income,	OR (95% CI) ^b Prehypertension: 1.18 (1.05, 1.32)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Northeastern China, China 2009 Cross-Sectional		Exposure years: 2009	NO ₂ (ppb)		smoking, alcohol consumption, exercise, diet, sugar intake, family history of hypertension, district and city.	
[†] Yang et al. (2018) 33CCHS n = 16,188 Northeastern China, China Study years NR Cross-Sectional	Adults 18-74-years old, no hypertension	Central site monitor Monitoring stations were measuring the background air pollution (stations were away from sources of pollution) Averaging time: 3-year average Exposure years: 2006-2008	NO ₂ (ppb) Median = 18 (IQR 5) (33 µg/m ³ (IQR 9 µg/m ³))	Prehypertension	GLM Adjusted for: age, sex, BMI, nationality, education, income, smoking, alcohol consumption, exercise, diet, sugar intake, family history of hypertension, district and city	OR (95% CI) ^b Prehypertension: 1.41 (1.11, 1.80)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zhang et al. (2023)	Middle aged and older adults	Spatiotemporal/geospatial model	NO ₂ (ppb) Mean = 16.97 ± 4.04 (31.94 ± 7.61 µg/m ³)	Hypertension	GLM Adjusted for: Temperature, relative humidity, age, sex, residence, education, marital status, smoking, drinking status, education level	OR (95% CI) ^b Hypertension: 1.32 (1.20, 1.46)
CHARLS		C-V r ² = 0.84				
n = 14,622		Averaging time: 3-yr avg				
China		Exposure years: 2013-2015				
2013-2015						
Cross-Sectional						

List of abbreviations in alphabetical order: µg/m³= micrograms per cubic meter; 33CCHS=33 Communities Chinese Health Study; BMI=Body Mass Index; BPLM=Blood Pressure Lowering Medication; BWHS=Black Women's Health Study; CANDLE= Conditions Affecting Neurocognitive development in Early Childhood; CANHEART=Cardiovascular Health in Ambulatory Care Research Team; CFPS= China Family Panel Studies; CHARLS= China Health and Retirement Longitudinal Study; C-V=Cross Validation; C-V=Cross-Validation; DCH= Danish Diet, Cancer and Health; ESCAPE= European Study of Cohorts for Air Pollution Effects; GEE=Generalized Estimating Equations; GLM=Generalized Linear Model; HBP=High Blood Pressure; HOMA-IR=Homeostatic Model Assessment for Insulin Resistance; HR=Hazard Ratio; HUBRO=OSLO Health Study; HUNT=Helseundersøkelsen i Nord-Trøndelag; INTERGENE/ADONIX= INTERplay between GENetic susceptibility and environmental factors for the risk of chronic diseases in West Sweden/ADult-Onset asthma and exhaled Nitric oxide; IQR=Interquartile Range; IRR=Incidence Rate Ratio; KORA= Cooperative Health Research in the Region of Augsburg; LOOCV= leave-one-out cross-validation; LUR=Land Use Regression; Max=Maximum; MESA=Multiethnic Study of Atherosclerosis; MetS=Metabolic Syndrome; Min=Minimum; N=sample size; NO₂=Nitrogen Dioxide; NR=Not Reported; NSES=Neighborhood Socioeconomic Status; ONPHEC=Ontario Population Health and Environment Cohort; OR=Odds Ratio; P=Percentile; PHM=Public Health Monitor; PHM=Public Health Monitor; ppb=parts per billion; REGICOR= Registre Gironí del Cor: the Girona Heart Register; RSME=Root Mean Square Error; SDPP= Stockholm Diabetes Prevention Program; SES=socioeconomic status; SNAC-K=Swedish National Study on Aging and Care in Kungsholmen.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-6 Epidemiologic studies of exposure to oxides of nitrogen and aggregated cardiovascular disease

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Alexeeff et al. (2018)	Adults who lived in the study region	Hybrid model	NO ₂ (ppb)	Medical Records	Cox proportional hazards	NO

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
KPNC N = 41,869 Oakland, California, U.S. Enrollment: 2010-2015 Follow-up: through December 31, 2015 Cohort	within Oakland, CA during January 1, 2010 to December 31, 2015. Participants were required to have a full year of prior KPNC membership, continuous KPNC membership, and continuous residency within the study region to remain in the cohort. Participants with prior cardiovascular disease were excluded.	Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2015-2016	Study Cohort Residential Addresses Mean = 9 ± 3.8		Adjusted for: Age, race, sex, BMI, NDI, smoking, Enrollment co-morbidities, medications	HR (95% CI) ^b CVD event/death: 1.09 (0.85, 1.41) NO ₂ HR (95% CI) ^b CVD event/death: 1.08 (0.86, 1.36)
† Cai et al. (2018) UK Biobank, EPIC-Oxford, HUNT n = 355,732 Oxford, UK, England, Scotland, Wales, Nord-Trondelag county, U.K., Norway Enrollment: - UK Biobank: 2006-2010 - HUNT: 1995-1997	For the HUNT cohort, respondents completed a population-based health survey focusing on the county of Nord-Trondelag and included those aged 20 or older. The EPIC-Oxford cohort included individuals aged at least 20-years throughout the United Kingdom. The UK Biobank cohort recruited individuals aged 40-69 from across the United Kingdom.	LUR Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2001-2010	NO ₂ (ppb) EPIC-Oxford Cohort Mean = 15.5 ± 6.43 (29.1 ± 12.1 µg/m ³) Median = 14 (IQR 6.96) (27 µg/m ³ (IQR 13.1 µg/m ³)) Min = 4 (7 µg/m ³) Max = 64.15 (120.7 µg/m ³) P5 = 7.4 (14 µg/m ³) P25 = 11.1 (20.9 µg/m ³) P75 = 18 (34 µg/m ³) P95 = 29 (55 µg/m ³) HUNT Cohort Mean = 6.7 ± 1.9 (12.6 ± 3.6 µg/m ³) Median = 6.22 (IQR 3)	Hospital Admission	Cox proportional hazards Adjusted for: Cohort, employment, education level, smoking status	HR (95% CI) ^b CVD: 1.05 (0.92, 1.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
- EPIC-Oxford: 1993-1999 Follow-up: 1.3 mean years - UK Biobank: 14.1 mean years - HUNT: 14.1 mean years - EPIC-Oxford: 10.8 mean years Cohort	Pooled: Excluded those with pre-existing CVD, those for whom record linkage was not possible, and those for whom information on the main adjusted variables was missing		(11.7 µg/m³ (IQR 5 µg/m³)) Min = 3.5 (6.6 µg/m³) Max = 22 (42 µg/m³) P5 = 4.3 (8.1 µg/m³) P25 = 5.3 (10 µg/m³) P75 = 8 (15 µg/m³) P95 = 10.2 (19.2 µg/m³) Pooled Data Mean = 14.8 ± 6.01 (27.8 ± 11.3 µg/m³) Median = 14 (IQR 6.8) (27 µg/m³ (IQR 12.8 µg/m³)) Min = 3.5 (6.6 µg/m³) Max = 73.55 (138.4 µg/m³) P5 = 5.8 (11 µg/m³) P25 = 10.8 (20.3 µg/m³) P75 = 17.6 (33.1 µg/m³) P95 = 26.2 (49.3 µg/m³) UK Biobank Mean = 15.9 ± 5.47 (29.9 ± 10.3 µg/m³) Median = 15.1 (IQR 5.79) (28.4 µg/m³ (IQR 10.9 µg/m³)) Min = 4 (7 µg/m³) Max = 73.55 (138.4 µg/m³) P5 = 8.77 (16.5 µg/m³) P25 = 12.3 (23.2 µg/m³) P75 = 18.1 (34.1 µg/m³) P95 = 26.6 (50.1 µg/m³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Floud et al. (2013) HYENA n = 4712 Sweden, U.K., Italy, Germany, Greece 3 yr period (2004-2006) Cross-Sectional	People who live near airports in six European countries	Dispersion model Models validated against measurements. r^2 Method validation NR Averaging time: Multi-year average Exposure years: 2004-2006	NO ₂ (ppb) Mean = 12.3 ± 0.69 ($23.2 \pm 1.3 \mu\text{g}/\text{m}^3$) Min = 0.5 ($1 \mu\text{g}/\text{m}^3$) Max = 31 ($58 \mu\text{g}/\text{m}^3$)	Self-reports	Logistic regression Adjusted for: Age, sex, education, ethnicity, BMI, physical activity, smoking, alcohol intake, night-time aircraft noise	OR (95% CI) ^b HD and Stroke/UK and Netherlands: 3.18 ($1.26, 8.02$) HD and Stroke/Sweden: 1.86 ($0.41, 8.45$)
† Gandini et al. (2018) ILS N = 74,989 Italy Enrollment: 1999-2000 Follow-up: 1999-2002, 2003-2004, 2005-2006, 2007-2008 Cohort	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to $27.95 \mu\text{g}/\text{m}^3$ by urbanicity. Averaging time: NO ₂ - annual	NO ₂ (ppb) Men Metropolitan Mean = 22.1 ± 6.16 ($41.5 \pm 11.6 \mu\text{g}/\text{m}^3$) Rural Mean = 10.3 ± 4 ($19.3 \pm 8 \mu\text{g}/\text{m}^3$) Urban Mean = 13.9 ± 5.2 ($26.1 \pm 9.7 \mu\text{g}/\text{m}^3$) Women Metropolitan Mean = 22.1 ± 6.16 ($41.6 \pm 11.6 \mu\text{g}/\text{m}^3$) Rural Mean = 10.3 ± 4.2 ($19.3 \pm 7.9 \mu\text{g}/\text{m}^3$)	Hospital Records	Cox proportional hazards Adjusted for: Age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality, and BMI	HR (95% CI) ^b Circulatory: 1.10 ($1.06, 1.14$)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
		average	Urban Mean = 13.9 ± 5.1 (26.1 ± 9.6 µg/m ³)			
		Exposure years: 1999, 2003, 2005, 2007				
†Klompemaker et al. (2021a)	Medicare beneficiaries, aged > = 65-years, living in the contiguous US from January 1, 2000 through December 31, 2016.	Spatiotemporal/geospatial model	NO ₂ (ppb)	Hospital Admission	Cox proportional hazards	HR (95% CI) ^b
MEDPAR			CBV		Adjusted for: Calendar year, US census covariates, BRFSS covariates, US regions, an offset for total person-time and strata for all possible combinations of sex, race, Medicaid eligibility, age at study entry, and follow-up year	CVD Full: 1.02 (1.01, 1.02)
N = 63,009,173		The overall cross-validated r ² for annual estimates was 0.84 for NO ₂	CHD Median = 16.2 (IQR 13.8)			CVD Low exposure: 1.11 (1.10, 1.11)
U.S.						
Enrollment: January 2000 to December 2016		Averaging time: NO ₂ - annual average	CVD Median = 16.3 (IQR 13.9)			
Follow-up: January 2000 or January of the year following entry		Exposure years: 2000-2016	Total Cohort Median = 16.3 (IQR 13.9)			
Cohort						
†Li et al. (2022)	Population based cohort of adults 40-69 at Enrollment.	LUR	NO ₂ (ppb)	self-reported physician dx	Cox proportional hazards	NO ₂
UK Biobank		C-V r ² = 0.87 (LUR-ESCAPE)	With incident microvascular disease Mean = 15.7 ± 4.9 (29.6 ± 9.2 µg/m ³)		Adjusted for: Age, sex, ethnicity, average total household income, center address, distance to the coast, smoking status, BMI, healthy diet score, alcohol consumption, sedentary time, SBP, DBP, antihypertensive	HR (95% CI) ^b
n = 396,020						Composite microvascular: 1.04 (1.03, 1.06)
U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average	Without incident microvascular disease Mean = 15.5 ± 4.9 (29.2 ± 9.3 µg/m ³)			NO _x
Enrollment: 2006-2010						HR (95% CI) ^b
Follow-up: 2020						Composite microvascular: 1.04 (1.02, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort		Exposure years: 2005-2007, 2010	NO _x (µg/m ³) With Incident microvascular disease Mean = 44.8 ± 15.8 Without incident microvascular disease Mean = 43.8 ± 15.6		medication use, diabetes, respiratory disease, and statin use	
†Luo et al. (2022)	Adults aged 40-69-years who were registered with the UK NHS and living near 1 of 22 study centers across England, Scotland, Wales, and Wales, without diabetes, stroke, IHD or cancer	LUR Median cross-validation r ² = 0.87 Averaging time: NO ₂ - annual average Exposure years: 2010-2011	NO ₂ (ppb) CMD Free Median = 14 (26 µg/m ³) P25 = 11.3 (21.2 µg/m ³) P75 = 16.5 (31.1 µg/m ³) CMM Survivor Median = 14.5 (27.3 µg/m ³) P25 = 12 (22.5 µg/m ³) P75 = 17.1 (32.1 µg/m ³) Death with CMM Median = 14.6 (27.4 µg/m ³) P25 = 12.1 (22.8 µg/m ³) P75 = 17.3 (32.5 µg/m ³) Death with FCMD Median = 14.2 (26.8 µg/m ³) P25 = 11.7 (22.1 µg/m ³) P75 = 16.9 (31.8 µg/m ³) Death without CMD	Hospital inpatient visits	Cox proportional hazards Adjusted for: Age, sex, race, education, townsend deprivation index, recruitment center	HR (95% CI) ^b FCMD to CMM: 1.12 (1.06, 1.18) Enrollment to FCMD: 1.06 (1.03, 1.09)
UK Biobank N = 410,494 England, Scotland, Wales, U.K. Enrollment: 2006-2010 Follow-up: through May 2021 Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Median = 13.9 (26.2 $\mu\text{g}/\text{m}^3$) P25 = 11.4 (21.5 $\mu\text{g}/\text{m}^3$) P75 = 16.6 (31.3 $\mu\text{g}/\text{m}^3$) FCMD Survivor Median = 14.1 (26.5 $\mu\text{g}/\text{m}^3$) P25 = 11.6 (21.8 $\mu\text{g}/\text{m}^3$) P75 = 16.7 (31.4 $\mu\text{g}/\text{m}^3$) Total Median = 13.9 (26.1 $\mu\text{g}/\text{m}^3$) P25 = 11.3 (21.3 $\mu\text{g}/\text{m}^3$) P75 = 16.6 (31.2 $\mu\text{g}/\text{m}^3$)			
†Meng et al. (2021) Medi-Cal beneficiaries N = 23,000 California, U.S. September 1, 2004, to August 31, 2010 Cohort	California's Medicaid healthcare program for low-income individuals with at least one of the following chronic conditions: asthma, chronic obstructive pulmonary disease (COPD), diabetes, and heart disease	LUR Method validation $r^2 = 0.74$ Averaging time: NO_2 -annual average Exposure year: 2004–2010	NO_2 (ppb) goods movement corridors (GMCs) Baseline year 2005 Mean = 24.0 Baseline year 2006 Mean = 23.7 Baseline year 2007 Mean = 22.8 Project year 2008 Mean = 20.7 Project year 2009 Mean = 20.4 Project year 2010 Mean = 19.3 non-goods movement corridors (NGMCs)	ED Visits/Hospitalizations	Difference in difference Adjusted for: Age, sex, race/ethnicity, language speaking, number of comorbidities in Enrollment years, county, year-specific smoking, depression, number of doctor visits, CDPS scores, percentage of unemployed, persons below poverty estimates, minority, households with no vehicle available	DiD (95% CI) ^c HD 1 yr post GMC and Controls: -0.01 (-0.11, 0.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Baseline year 2005 Mean = 22.4			
			Baseline year 2006 Mean = 22.0			
			Baseline year 2007 Mean = 21.1			
			Project year 2008 Mean = 20.0			
			Project year 2009 Mean = 19.7			
			Project year 2010 Mean = 18.7			
			Control			
			Baseline year 2005 Mean = 20.1			
			Baseline year 2006 Mean = 19.6			
			Baseline year 2007 Mean = 18.9			
			Project year 2008 Mean = 19.0			
			Project year 2009 Mean = 18.6			
			Project year 2010 Mean = 17.3			
[†] Su et al. (2020)	Patients who were diagnosed with T2D and initiated with a second-line GLA added on to metformin were included	Fixed site monitor	NO ₂ (ppb)	Health claims	Bayesian	HR (95% CI) ^b
NHIRD		Method validation	Overall		Adjusted for: Sex, age, comorbidities, medications	CVD/ Cox Proportional: 1.05 (0.88, 1.26)
N = 2,027		NR	Mean = 17.32 ± 5.628			CVD/ Weibull: 1.05 (0.87, 1.26)
Taiwan		Averaging time: NO - monthly	NO ₂ (ppb)		Cox	CVD/ Bayesian survival: 0.72 (0.48, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Enrollment: 2009-2012 Follow-up: through 2013 Cohort		NO _x - monthly NO ₂ - monthly Exposure years: 2009-2013	Overall Mean = 5.446 ± 4.026 Mean = 22.603 ± 8.993		Adjusted for: Sex, age, comorbidities, medications Weibull Adjusted for: Sex, age, comorbidities, medications	
† Wang et al. (2023) CFPS N = 36,948 China Enrollment waves: 2010, 2014, 2016, 2018 Follow-up: through 2018 Cohort	Chinese adults (> = 16- years) from 25 China mainland provincial regions. Participants were excluded if they were lost to follow-up, had missing chronic disease information, had a history of cardiovascular disease at enrollment, or were unable to be matched to exposure.	Spatiotemporal/geospatial model Method validation NR, but states "well-validated" Averaging time: NO ₂ - annual average Exposure years: 2010-2018	NO ₂ (ppb) Quartile 1 (6.9-16.6) Mean = 6.59 ± 0.9 (12.4 ± 1.7 µg/m ³) Quartile 2 (16.7-21.5) Mean = 9 ± 0.69 (17 ± 1.3 µg/m ³) Quartile 3 (21.6-27.5) Mean = 11.4 ± 0.69 (21.5 ± 1.3 µg/m ³) Quartile 4 (27.6-57.4) Mean = 15.6 ± 2.2 (29.4 ± 4.2 µg/m ³) Total Mean = 11 ± 3.6 (20 ± 6.7 µg/m ³)	Survey	Cox proportional hazards Adjusted for: Age, sex, BMI, educational level, marital status, employment status, health status, residence, region, cigarette smoking, alcohol consumption, and regular physical activity	HR (95% CI) ^b CVD: 2.30 (2.08, 2.54)
† Wu et al. (2022) Henan Rural Cohort Study N = 33,638	Ages 18-79; excluded participants with cancer, coronary heart disease, stroke, and with missing data on T2DM, hypertension, dyslipidemia, and	Hybrid (LUR and Random Forest) Averaging time: NO ₂ – 3-year averages	NO ₂ (ppb) Cardiometabolic Risk Score Mean = 21.23 ± 1.93 (39.95 ± 3.63 µg/m ³) Median = 21.41 (IQR	Clinical measurements	linear regression Adjusted for: age, sex, marital status, educational level, and personal averaged monthly income,	β (z-score) (95% CI) ^b Cardiometabolic risk score: 2.15 (1.90, 2.40)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Suiping County, Yuzhou County, Xinxiang County, Tongxu County, Yima County, China 2015-2017 Cross-Sectional	cardiometabolic risk predictors, and who were omitted information needed.	Exposure years: 2015-2017	4.12) (40.29 µg/m ³ (IQR 7.76 µg/m ³)) Min = 16 (31 µg/m ³) Max = 26.47 (49.81 µg/m ³) P25 = 19.4 (36.5 µg/m ³) P75 = 23.53 (44.27 µg/m ³)		smoking status, alcohol intake, and the diet score.	
†Wu et al. (2023)	Sample of half a million UK citizens	LUR	NO ₂ (ppb)	UK biobank data	Cox proportional hazards	NO ₂
UK Biobank n = 162,334		0.87 for NO ₂ , and 0.88 for NO _x	Mean = 14.16 ± 4.11 (26.65 ± 7.74 µg/m ³)		Adjusted for: Age, sex, ethnicity, BMI, smoking status, physical activity, household income, Townsend deprivation index, green space	HR (95% CI) ^b Healthy to multimorbidity: 1.05 (0.92, 1.20) Healthy to death: 1.06 (0.97, 1.17)
Nationwide, U.K. 2006-2010		Averaging time: NO ₂ - annual average, NO _x - annual average	NO _x (µg/m ³) Mean = 43.82 ± 15.61			Healthy to incident disease: 1.12 (1.07, 1.18)
Cohort		Exposure years: 2010-2011				NO _x HR (95% CI) ^c Healthy to incident disease: 1.05 (1.03, 1.07)

List of abbreviations in alphabetical order: µg/m³= micrograms per cubic meter; BMI=Body Mass Index; CBV=Cerebrovascular; CHD=Coronary Heart Disease; CI=Confidence Interval; CMD=Cardiometabolic Disease; CMM=Cardiometabolic Multimortality; CPFS= China Family Panel Studies; C-V=Cross Validation; CVD=Cardiovascular Disease; DBP=diastolic blood pressure; EPIC-Oxford= European Prospective Investigation into Cancer and Nutrition- Oxford; ESCAPE= European Study of Cohorts for Air Pollution Effects; FCMD=First Cardiometabolic Disease; HD=Heart Disease; HR=Hazard Ratio; HUNT=Helseundersøkelsen i Nord-Trøndelag; HYENA=Hypertension and Environmental Noise near Airports; ILS=Italian Longitudinal Study; IQR=Interquartile Range; LUR=Land Use Regression; Max=Maximum; MEDPAR=Medicare denominator and Medicare Provider Analysis and Review; Min=Minimum; N=sample size; NHIRD= Taiwan National Health Insurance Research Database; NHS=National Health Service; NO₂=Nitrogen Dioxide; NO_x=Nitrogen Oxides; NR=Not Reported; P=Percentile; ppb=parts per billion; RSME=Root Mean Square Error; SBP=systolic blood pressure; SES=socioeconomic status; T2D=Type 2 Diabetes.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-7 Epidemiologic studies of exposure to oxides of nitrogen and subclinical effects underlying cardiovascular disease

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Fuks et al. (2014)	Adult men and women participating in 13 studies in Europe n = 113,926 Sweden, U.K., Denmark, Switzerland, Norway, Germany, Finland, The Netherlands	LUR	NO ₂ (ppb)	Hypertension	Logistic regression	NO ₂
ESCAPE		LUR r ² = 55% to 92% (median 82%) for NO ₂ and from 49% to 91% (median 78%) for NO _x . C-V r ² was generally less than 10% lower than the model r ² .	Main Analysis Mean = 10.3 (19.3 µg/m ³) NO _x (µg/m ³)	BPLM	Adjusted for: age, sex, BMI, smoking status, pack-years of smoking, passive smoking, alcohol consumption, physical activity, educational level, economic activity, neighborhood SES (random intercept for neighborhood).	OR (95% CI) ^b BPLM: 1.02 (0.95, 1.10) Hypertension: 0.96 (0.86, 1.08)
1992-2008 (enrollment was conducted in different years depending on the cohort) Cross-Sectional		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 1992-2008	Main Analysis Mean = 32			NO _x OR (95% CI) ^c Hypertension: 0.98 (0.92, 1.04) BPLM: 0.98 (0.94, 1.02)
[†] Aaron et al. (2019)	Aged 45-84-years and free of clinical	Fixed site monitor, Spatiotemporal/ge	NO ₂ (ppb)	TPVV	Linear regression	NO ₂

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
MESA	cardiovascular disease at enrollment.	ospatial model	Quintile 1 Mean = 6.5 ± 2.6	Peripheral TPVV	Adjusted for: age, sex, race/ethnicity, height, weight, education, neighbourhood SES, smoking status, pack-years, second-hand smoke exposure, estimated glomerular filtration rate, scanner manufacturer and city.	β (cm ³) (95% CI) ^b TPVV: 1.08 (-1.04, 3.19) Peripheral TPVV: 1.00 (-0.19, 2.19)
N = 3,023		Method validation NR	Quintile 2 Mean = 8.4 ± 2.8			NO _x
Chicago, IL, Baltimore, MD, Los Angeles, CA, St. Paul, MN, New York City, NY, Forsyth County, NC, U.S.		Averaging time: NO ₂ - annual average, NO _x - annual average, Other, NO ₂ – 2 weeks NO _x – 2 weeks	Quintile 3 Mean = 12.7 ± 2.8 Quintile 4 Mean = 20.5 ± 4.9 Quintile 5 Mean = 25.1 ± 4.2			β (cm ³) (95% CI) ^b Peripheral TPVV: 0.68 (-0.46, 1.81) TPVV: 0.63 (-1.38, 2.63)
Enrollment: 2000-2002; 2004- 2006 Follow-up: 2010- 2012		Exposure years: 2005-2012	NO _x (ppb)			
Cohort			Quintile 1 Mean = 11 ± 4.6 Quintile 2 Mean = 14 ± 4.7 Quintile 3 Mean = 21.4 ± 4.7 Quintile 4 Mean = 35.8 ± 11.7 Quintile 5 Mean = 47.7 ± 13.2			
† Adar et al. (2018)	Men and women, aged 45- to 84-years, who were free of clinical cardiovascular disease, weighed <136 kg, and	Spatiotemporal/geospatial model, Fixed site monitor r ² = 0.5-0.9	NO ₂ (ppb) 1-day Exam 1: 2000-2002 Mean = 24.5 ± 13.4	SBP/DBP and Hypertension	Linear mixed effects (SBP/DBP) Adjusted for: sex, race/ethnicity, education,	HR (95% CI) ^b Hypertension, adjustment for time: 1.08 (0.92, 1.27) Hypertension, no
MESA						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
N = 5,587	had no impediments to long-term participation.	Averaging time: NO ₂ - annual average	Exam 2: 2002-2004 Mean = 23.5 ± 12.5 Exam 3: 2004-2005 Mean = 20.2 ± 11.1 Exam 4: 2005-2007 Mean = 20.2 ± 11.1 Exam 5: 2010-2012 Mean = 20.6 ± 11.2		study site, neighborhood SES, neighborhood SES*site, age at exam, calendar time, BMI, waist-to-hip ratio, tobacco smoke exposure, season, season*site, physical activity	adjustment for time: 1.29 (1.11, 1.50) β (mmHg) (95% CI) ^b SBP, no adjustment for time: 1.69 (0.91, 2.47) SBP: 1.69 (0.91, 2.47) DBP, no adjustment for time: 0.63 (0.22, 1.03) DPB: 0.63 (0.22, 1.03)
Chicago, IL, Baltimore, MD, Los Angeles, CA, St. Paul, MN, New York City, NY, Forsyth County, NC, U.S.		Exposure years: 1999-2011			Cox proportional hazards model	
Enrollment: 2000-2002 Follow-up: 2002- 2007, 2010-2012			1-year Exam 1: 2000-2002 Mean = 21.8 ± 9.2 Exam 2: 2002-2004 Mean = 20.7 ± 9.1 Exam 3: 2004-2005 Mean = 19.6 ± 8.2 Exam 4: 2005-2007 Mean = 19.4 ± 8.1 Exam 5: 2010-2012 Mean = 15.6 ± 7.7		Adjusted for: sex, race, education, neighborhood SES, smoking exposure, physical activity, waist-to-hip ratio, BMI, study site, study site* neighborhood SES, calendar time.	
Cohort			2-day Exam 1: 2000-2002 Mean = 23.8 ± 13.2 Exam 2: 2002-2004 Mean = 22.7 ± 12.6 Exam 3: 2004-2005 Mean = 19.4 ± 10.7 Exam 4: 2005-2007 Mean = 20.2 ± 11 Exam 5: 2010-2012 Mean = 19.9 ± 11			
			7-day Exam 1: 2000-2002 Mean = 25.5 ± 13.6 Exam 2: 2002-2004			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 24.2 ± 12.8			
			Exam 3: 2004-2005			
			Mean = 20.9 ± 11.1			
			Exam 4: 2005-2007			
			Mean = 21.6 ± 11.2			
			Exam 5: 2010-2012			
			Mean = 21.2 ± 11.1			
			30-day			
			Exam 1: 2000-2002			
			Mean = 21.5 ± 9.6			
			Exam 2: 2002-2004			
			Mean = 20.8 ± 9.6			
			Exam 3: 2004-2005			
			Mean = 18.5 ± 8.5			
			Exam 4: 2005-2007			
			Mean = 19.1 ± 8.6			
			Exam 5: 2010-2012			
			Mean = 14.8 ± 8.5			
			60-day			
			Exam 1: 2000-2002			
			Mean = 21.6 ± 9.5			
			Exam 2: 2002-2004			
			Mean = 20.8 ± 9.5			
			Exam 3: 2004-2005			
			Mean = 18.8 ± 8.5			
			Exam 4: 2005-2007			
			Mean = 19.1 ± 8.6			
			Exam 5: 2010-2012			
			Mean = 14.8 ± 8.5			
† Aung et al. (2018)	UK national residents aged between 40-69-years, who were registered with UK NHS and living <25	LUR, Spatiotemporal/geospatial model	NO ₂ (ppb)	LV EF	Multiple linear regression	NO ₂
UK Biobank		The median leave-	Overall	LV ESF	Adjusted for: age at imaging visit, sex, and ethnicity, height, BMI,	β (%) (95% CI) ^b
			Mean = 15 ± 6.06 (28.2 ±			LV EF: 0.02 (-0.26, 0.29)
			11.4 µg/m ³)	LV EDV		LV ESV: 1.45 (-0.59, 3.49)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
N = 3,920 England, Scotland, Wales, U.K. Enrollment: 2006-2010 Follow-up: 2014-2015 Cohort	miles from 1 of the 22 study assessment centers. Excluded individuals who had moved home between the Enrollment and imaging visit, and individuals who had pre-existing CVD.	one-out cross-validated variance explained by the model was 82% for NO ₂ and 78% for NO _x Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2005-2010	NO _x (µg/m ³) Overall Mean = 41.5 ± 17.1	RV ESV RV EDV RA maximal volume LA Maximal Volume LA EF RV EF LV mass RA EF	SES (average household income, employment status, Townsend deprivation index, and educational attainment, SBP, DBP, heart rate, smoking status, regular alcohol use, hypertension, diabetes mellitus, respiratory disease, antihypertensive medication, lipid-lowering medication, insulin, physical activity	LV EDV: 1.50 (0.20, 2.81) RV ESV: 1.06 (-0.97, 3.08) RV EDV: 1.40 (0.09, 2.72) RA maximal volume: -1.09 (-3.35, 1.17) LA Maximal Volume: 1.22 (-1.09, 3.53) LA EF: -0.54 (-1.28, 0.19) RV EF: 0.21 (-0.29, 0.72) LV mass: -0.58 (-1.99, 0.83) RA EF: -0.23 (-1.07, 0.61) NO _x β (%) (95% CI) ^c RV EDV: 0.58 (-0.11, 1.26) LV mass: 0.13 (-0.62, 0.89) LV EF: -0.13 (-0.40, 0.14) LA Maximal Volume: 0.48 (-0.74, 1.71) RV EF: -0.08 (-0.35, 0.18) LV ESV: 1.00 (-0.07, 2.09) RV ESV: 0.83 (-0.22, 1.89) RA EF: -0.14 (-0.59, 0.30) RA maximal volume: -0.42 (-1.61, 0.77) LA EF: -0.20 (-0.59, 0.19) β (%) (95% CI) ^b LV EDV: 0.63 (-0.05, 1.33)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Edlund et al. (2022) SCAPIS N = 6,265 Gothenburg, Sweden 2013-2017 Cohort	50-65-year old Swedish men and women in Gothenburg	Dispersion model Method validation NR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 1990, 2000, 2011, 2015	NO _x (µg/m ³) Overall Median = 32.7 (IQR 17.5) P5 = 16.7 P95 = 61.5	Any Carotid Plaque CAC score ≥100 CAC ≥10	Poisson Adjusted for: age, sex, tobacco smoking, education, waist-hip ratio, LDL, and systolic blood pressure	PR (95% CI) ^c Any Carotid Plaque: 1.00 (0.99, 1.02) CAC score ≥100: 1.05 (0.99, 1.10) CAC ≥10: 1.01 (0.98, 1.04)
† Elbarbary et al. (2021) SAGE N = 7,915 China, South Africa, Mexico, Ghana, India, Russia 2008-2010 Cross-Sectional	NR	Hybrid model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2013-2016	NO ₂ (ppb) Overall Mean = 16.22 ± 6.569 (30.52 ± 12.36 µg/m ³)	hs-CRP	Linear regression Adjusted for: age, sex, BMI, tobacco use, physical activity, education level, fruit and vegetable intake, alcohol use, type of fuel	β (%) (95% CI) ^b hs-CRP: 22.20 (16.65, 27.75)
† Endes et al. (2017) SAPALDIA N = 2,823	Randomly selected participants aged 18-60-years	Central site monitor, Dispersion model, LUR Method validation NR	NO ₂ (µg/m ³) Active Mean = 19 ± 8.3	Arterial Stiffness baPWV	Mixed effects logistic regression Adjusted for: age, sex, education, SES, smoking,	OR (95% CI) ^c baPWV (≥14.4 m/s): 0.95 (0.81, 1.12) β (m/s) (95% CI) ^c baPWV Interaction

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Switzerland Enrollment: 1991 Follow-up 1: 2001-2003 Follow-up 3: 2010-2011 Cohort		Averaging time: NO ₂ - annual average Exposure years: 2010	Inactive Mean = 20 ± 9.3		BMI, heart rate, mean arterial pressure	PA*NO ₂ : -0.11 (-0.32, 0.10)
†Farzan et al. (2021) Children and rsquo;s Health Study (CHS) N = 70 Southern California, U.S. Enrollment: 2007-2008 Follow-up: 2018-2019 Cohort	Convenience sample of the first 70 participants in CHS Cohort E with carotid ultrasounds at 10-11-years who agreed to a follow-up in adulthood 11-years later. Eligible children came from 8 selected communities, lived in non-smoking households, and had lived in the same residence from birth through ultrasound measurement (parental report).	Dispersion model, Fixed site monitor Method validation NR Averaging time: NO ₂ - monthly Exposure years: 2007-2019	NO ₂ (ppb) 24-hour average Mean = 13.7 ± 3.5 (25.7 ± 6.5 µg/m ³) Min = 5.63 (10.6 µg/m ³) Max = 18.3 (34.5 µg/m ³) NO _x (ppb) Freeway Mean = 18.9 ± 20.9 Min = 0.001 Max = 108 Non-freeway Mean = 5.9 ± 3.2 Min = 1.4 Max = 18.9 Total Mean = 24.7 ± 22.4 Min = 1.5 Max = 117.4	cIMT childhood to adulthood cIMT adult attained	Linear mixed effects Adjusted for: personal smoking, adult BMI and parental education	NO ₂ β (µm/yr) (95% CI) ^b cIMT childhood to adulthood: 1.74 (-4.54, 8.02) cIMT adult attained: 18.61 (-29.82, 67.04) NO _x β (µm/yr) (95% CI) ^b cIMT childhood to adulthood (Non-freeway): 1.06 (-7.63, 9.75) cIMT adult attained (Freeway NO _x): 20.18 (3.19, 37.18) cIMT childhood to adulthood (Freeway NO _x): 2.14 (0.81, 3.48) cIMT childhood to adulthood (Total NO _x): 1.94 (0.70, 3.18) cIMT adult attained (non-Freeway NO _x): 39.06 (-67.72, 145.84)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						cIMT adult attained (Total NO _x): 18.39 (2.55, 34.24)
† Fossati et al. (2020) INMA N = 1,724 mother-child pairs Sabadell, Valencia, Asturias, Guipuzcoa, Spain Enrollment: 2003-2008 Follow-up: 4-years Cohort	Inclusion criteria were at least 16-years, intention to give birth in the reference hospital, no problems in communication, singleton pregnancy, non-assisted conception.	LUR Method validation NR Averaging time: NO ₂ - weekly averages Exposure years: 2003-2008	NO ₂ (µg/m ³) Asturias Cohort Median = 24.45 (IQR 11) First Trimester of Pregnancy Median = 28.44 (IQR 20.19) P5 = 10.56 P95 = 61.44 Gipuzkoa Cohort Median = 16.97 (IQR 9.33) Sabadell Cohort Median = 35.4 (IQR 14.04) Valencia Cohort Median = 38.9 (IQR 25.16)	BP Lipids	Linear regression Adjusted for: sub-cohort, season of birth, and maternal age at delivery, country of origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet	β (%) (95% CI) ^c BP score: 0.07 (-0.04, 0.19) Lipid score: -0.03 (-0.15, 0.26)
† Fuks et al. (2014) ESCAPE n = 113,926 Sweden, U.K., Denmark, Switzerland, Norway, Germany, Finland, The Netherlands	Adult men and women participating in 13 studies in Europe	LUR LUR r ² = 55% to 92% (median 82%) for NO ₂ and from 49% to 91% (median 78%) for NO _x . C-V r ² was generally less than 10% lower than the model r ² . (Beelen et al., 2013)	NO ₂ (ppb) Main Analysis Mean = 10.3 (19.3 µg/m ³) NO _x (µg/m ³) Main Analysis Mean = 32	Hypertension BPLM	Logistic regression Adjusted for: age, sex, BMI, smoking status, pack-years of smoking, passive smoking, alcohol consumption, physical activity, educational level, economic activity, neighborhood SES (random intercept for neighborhood).	NO ₂ OR (95% CI) ^b BPLM: 1.02 (0.95, 1.10) Hypertension: 0.96 (0.86, 1.08) NO _x OR (95% CI) ^c Hypertension: 0.98 (0.92, 1.04) BPLM: 0.98 (0.94, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
1992-2008 (enrollment was conducted in different years depending on the cohort in this cross-sectional analysis)		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 1992-2008				
Cross-Sectional						
† Gan et al. (2014)	Healthy volunteers (35-65 yrs)	LUR	NO ₂ (ppb)	Plaque area	GLM	NO
M-CHAT n = 509 Vancouver, Canada		NO ₂ : r ² = 0.56, mean error = 0±5.2 µg/m ³ ; NO: r ² = 0.62, mean error = 2.02±15.5 µg/m ³	Mean = 9.14 ± 2.2 (17.2 ± 4.1 µg/m ³) Median = 8.77 (16.5 µg/m ³) P25 = 7.76 (14.6 µg/m ³) P75 = 9.94 (18.7 µg/m ³)	cIMT Plaque number Total Area	Adjusted for: age, sex, ethnicity, BMI, smoking status, physical activity, education, annual household income, systolic blood pressure, LDL-C, HDL-C, neighbourhood income levels, neighbourhood education levels and noise	β (mm ² /yr) (95% CI) ^b Plaque area: 0.17 (-0.26, 0.60) Total Area: 0.14 (-0.31, 0.58)
Enrollment: 2004-2005 Follow-up: 2009-2011 Cohort		Averaging time: NO ₂ - annual average, NO - annual average Exposure years: 2004-2005	NO (ppb) Mean = 22.5 ± 9.29 (27.6 ± 11.4 µg/m ³) Median = 20.3 (24.9 µg/m ³) P25 = 16.7 (20.5 µg/m ³) P75 = 25.5 (31.3 µg/m ³)			β (number/yr) (95% CI) ^b Plaque number: 0.02 (-0.02, 0.05) β (µm/yr) (95% CI) ^b cIMT: -1.82 (-4.19, 0.55)
						NO ₂ β (mm ² /yr) (95% CI) ^b Total Area: 0.37 (-0.76, 1.50) Plaque area: 0.32 (-0.79, 1.43) β (number/yr) (95% CI) ^b Plaque number: 0.05 (-0.05, 0.14)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						β ($\mu\text{m}/\text{yr}$) (95% CI) ^b cIMT: -0.28 (-6.26, 5.71)
†Hartia et al. (2016)	Patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography	Spatiotemporal/geospatial model	NO ₂ (ppm) 36-months post: Mean = 18.2 ± 2 Min = 4.9 Max = 22.1	CAD severity (1-2 vessels)	Multinomial regression	OR (95% CI) ^b CAD severity (1-2 vessels): 1.00 (0.43, 2.33)
Cleveland Clinic GeneBank		Method validation NR		CAD severity (≥ 3 vessels)	Adjusted for: age, sex, education level (college or higher, high school, less than high school), current smoking, Framingham Adult Treatment Panel III risk score	CaD severity (≥ 3 vessels): 0.74 (0.31, 1.77)
n = ~4,600		Averaging time: NO ₂ - 3-y average after enrollment	36-months prior: Mean = 19.1 ± 1.8 Min = 7.8 Max = 23.3			
Cleveland, OH, U.S.		Exposure years: 1998-2010				
Enrollment: 2001-2007						
Follow-up: 3 yrs						
Cohort						
†Hennig et al. (2020)	Participants of 45-75-years of age at Enrollment, free of CAD at Enrollment with two valid measurements for at least one marker of subclinical atherosclerosis, and with complete exposure information and nonmissing covariate data	Chemical transport model, LUR, Dispersion model	NO ₂ (ppb) CTM Mean = 21 ± 2 (39.5 ± 4 $\mu\text{g}/\text{m}^3$) LUR Mean = 16 ± 2.6 (30.2 ± 4.9 $\mu\text{g}/\text{m}^3$)	Incident CAC	Linear regression	OR (95% CI) ^b CAC, NO ₂ (LUR): 1.78 (0.99, 3.20)
HNR		Adjusted r ² within the Ruhr area: 88%		TAC, NO ₂ (CTM)	Adjusted for: age, sex, BMI, smoking, ETS, LDL-C/HDL-C, physical activity, education, traffic noise years of follow-up	TAC, NO ₂ (LUR): 1.03 (0.59, 1.79)
N = 3,480		LOOCV r ² = 82%		Incident TAC		CAC, NO ₂ (CTM): 1.39 (0.96, 2.03)
Essen, Germany, Ruhr, Bochum, Mulheim, Germany, Germany		Averaging time: NO ₂ - annual average		cIMT L, NO ₂ (CTM)	Logistic regression	TAC, NO ₂ (CTM): 1.31 (0.72, 2.37)
Enrollment: 2000-2003		Exposure years: 2000-2003, 2006-2008		cIMT R, TAC, NO ₂ (CTM)	Adjusted for: age, sex, BMI, smoking, ETS, LDL-C/HDL-C, physical activity, education, traffic noise years of follow-up	β (μm) (95% CI) ^b TAC, NO ₂ (CTM): -0.03 (-0.10, 0.03)
Follow-up: 2006-2008				TAC, NO ₂ (LUR)		cIMT L, NO ₂ (CTM): -0.14 (-6.64, 6.36)
				cIMT R, NO ₂		cIMT R, TAC, NO ₂ (CTM): -0.80 (-6.76, 5.16) TAC, NO ₂ (LUR):

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort				(LUR)		-0.03 (-0.15, 0.09)
				CAC, NO ₂ (CTM)		cIMT R, NO ₂ (LUR): -0.12 (-5.51, 5.27)
				cIMT L, NO ₂ (LUR)		CAC, NO ₂ (CTM): 0.00 (-0.03, 0.03)
				CAC, NO ₂ (LUR)		cIMT L, NO ₂ (LUR): 2.52 (-3.20, 8.24) CAC, NO ₂ (LUR): 0.00 (-0.05, 0.05)
† Honda et al. (2017)	Older adults born between 1920 and 1947 selected from eligible households identified in the Health and Retirement Study (HRS).	AQS	NO ₂ (ppb)	Hb	Poisson regression	POR (95% CI) ^b Hb: 1.45 (1.26, 1.67)
NSHAP		Averaging time: NO ₂ - 1-year moving average	Anemic Mean = 14.5 ± 6.8	Anemia	Adjusted for: age, sex, tobacco use, physical activity, education, race, region, census track median household income, percent of households living below the poverty line, urbanicity, use of: glucocorticoids, anti-neoplastics, anti-rheumatics, diuretics and recombinant erythropoietin	β (g/dL) (95% CI) ^b Hb: -0.84 (-0.84, -0.84)
N = 4,121		NO ₂ - 2-year moving average	Non-anemic Mean = 13.3 ± 6.5			
Anemic n = 1,438		NO ₂ - 3-year moving average	Total			
Non-anemic n = 2,683	U.S.	NO ₂ - 4-year moving average	Mean = 13.11 ± 7			
Enrollment period 1: 2005-2006		NO ₂ - 5-year moving average			Linear regression	
Enrollment period 2: 2010-2011		Exposure years: 1999-2007				
Cohort						
					Adjusted for: age, sex, tobacco use, physical activity, education, race, region, census track median household income, percent of households living below the poverty line, urbanicity, use of:	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					glucocorticoids, anti-neoplastics, anti-rheumatics, diuretics and recombinant erythropoietin	
† Hou et al. (2021)	Residents of rural counties in Henan province China	Unsure/Needs to checked by EPA	NO ₂ (µg/m ³)	MAP	Linear regression	β (mmHg) (95% CI) ^c
Henan Rural Cohort Study		10-fold C-V r ² > 0.70	Median = 40.29 P25 = 36.27 P75 = 42.67	MPP	Adjusted for: age, sex, education level, marital status and average monthly income, smoking and drinking status, physical activity, high-fat diet, fruit and vegetable intake, type 2 diabetes, family history of hypertension	MAP: ≥ 40 µg/m ³ < 40 µg/m ³ : 5.07 (4.79, 5.34)
n = 38,883		Averaging time: 3-year avg		DPB		PP: ≥ 40 µg/m ³ < 40 µg/m ³ : 1.56 (1.32, 1.80)
Henan Province, China		Exposure years: NR		SPB		DBP: ≥ 40 µg/m ³ < 40 µg/m ³ : 4.55 (4.31, 4.79)
Study years NR						SBP: ≥ 40 µg/m ³ < 40 µg/m ³ : 6.11 (5.72, 6.49)
Cross-Sectional						
† Johnson et al. (2020)	Patients living within the city of London for whom LUR NO ₂ were available. Analyses were limited to patients with at least 2 clinical visits to ensure inclusion of patients with detailed medical history, as well as complete residential location and demographic information including age, sex, smoking history, and SES.	LUR	NO ₂ (ppb)	Total Plaque Area	Linear regression	β (mg/dL) (95% CI) ^b
SPARC		Explained 78% of the spatial variability	Overall Mean = 5.4 ± 1.6 Median = 5.1 Min = 3 Max = 13		Adjusted for: age, sex, smoking, and SES	Total Cholesterol: 17.30 (3.55, 31.05)
N = 2,227		Averaging time: NO ₂ - 2 week				β (mm ²) (95% CI) ^b
London, Ontario, Canada		Exposure years: 2010				Total Plaque Area: 12.20 (2.90, 21.50)
1990-2013						β (mmHg) (95% CI) ^b
Cross-Sectional						SBP: 2.40 (-3.35, 8.15) DBP: 1.20 (-2.35, 4.75)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† zielska et al. (2016)	Ethnically diverse adults residing in 6 U.S. cities.	Spatiotemporal/geospatial model	NO ₂ (ppb)	CAC	mixed effects	NO ₂
MESA Air		Median (range) r ² across sites: 0.72 (0.50-0.92)	P25 = 11.8 P75 = 26.4		Adjusted for: age, sex, race/ethnicity, site, scanner type, employment outside the home, smoking status, second-hand smoke	β (Agatston units/yr) (95% CI) ^b CAC: 2.70 (-0.30, 5.70)
n = 5834			NO _x (ppb)		exposure, physical activity, adiposity, cholesterol, statin use, neighborhood SES index, income, and education	NO _x
U.S.		Averaging time: multi-year average	P25 = 21.4 P75 = 57.3			β (Agatston units/yr) (95% CI) ^b CAC/Current Smoker: 1.75 (-1.00, 4.50)
Followup: 2002-2007		Exposure years: 1999-2012				CAC: 2.40 (0.45, 4.35)
Cohort						
† Kulick et al. (2017)	Older adults (>= 50 yrs) free of clinical stroke	Other	NO ₂ (ppb)	SBI	Linear and logistic regression	NO ₂
NOMAS		Method validation NR	Mean = 29.9 IQR = 3.6	TCBV		OR (95% CI) ^b SBI: 0.97 (0.63, 1.49)
n = 1075		Averaging time: NO ₂ - annual average, NO _x - annual average	NO _x (ppb)	log-WMHV	Adjusted for: age at MRI, sex, race-ethnicity, education, insurance status, SES	β (mm ³) (95% CI) ^b TCBV: -0.01 (-0.51, 0.49) log-WMHV: -0.04 (-0.17, 0.08)
U.S.			Mean = 69.1 IQR = 14			NO _x
2003-2008		Exposure years: 2003-2008				OR (95% CI) ^b SBI: 0.99 (0.77, 1.26)
Cross-Sectional						β (mm ³) (95% CI) ^b TCBV: -0.02 (-0.31, 0.28) log-WMHV: -0.02 (-0.10, 0.05)
† Kulick et al. (2017)	Adults >= 50 yrs	Hybrid model	NO ₂ (ppb)	SBI	Linear and logistic regression	NO ₂
NOMAS MRI		Method validation NR	Mean = 29.9 IQR = 3.6	TCBV	Adjusted for: age at MRI,	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort n = 1,241 U.S. 2003-2008 Cross-Sectional		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2003-2008	NO _x (ppb) Mean = 69.1 IQR = 14	log-WMHV	sex, race-ethnicity, education, insurance status, SES	OR (95% CI) ^b SBI: 0.97 (0.63, 1.49) β (mm ³) (95% CI) ^b TCBV: -0.01 (-0.51, 0.49) log-WMHV: -0.04 (-0.17, 0.08) NO _x OR (95% CI) ^b SBI: 0.99 (0.77, 1.26) β (mm ³) (95% CI) ^b TCBV: -0.02 (-0.31, 0.28) log-WMHV: -0.02 (-0.10, 0.05)
† Laratta et al. (2020) n = 315 Greater Vancouver area, Canada 2007-2013 Cross-Sectional	Adult patients referred for attended (level I) polysomnography (PSG) for suspected OSA	LUR Road length: 0.56 Vehicle density: 0.60 Averaging time: NO ₂ - annual average Exposure years: 2007-2013	NO ₂ (ppb) Mean = 17.1 ± 4.5		Linear regression Adjusted for: sex, age, smoking and income status, and BMI	β (pg/mL) (95% CI) ^c IL10 Q4 v Q1-3: -0.90 (-34.60, 33.90)
† Letellier et al. (2022) Community of Mine Study N = 552	Adults, aged 35-80, living for at least 6-months in a selected census block groups. Restricted the population to participants with	Fixed site monitor Correlations between predicted and actual values at the location of the omitted point	NO ₂ (ppb) Dynamic Exposure Hispanic/Latino Median = 0.0425 (IQR 0.02392) (0.08 µg/m ³ (IQR 0.045 µg/m ³))	LDL, dynamic Triglycerides, static Triglycerides, dynamic	Generalized Adjusted for: sex, age, Hispanic/Latino ethnicity, income, smoking status, and BMI	RR (95% CI) ^b Dyslipidemia, static: 1.02 (0.85, 1.22) Dyslipidemia, dynamic: 1.28 (1.12, 1.46) non-hispanic, static: 0.98 (0.75, 1.28)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
San Diego, CA, U.S. 2014-2017 Cross-Sectional	HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data.	were used to assess validity of modeled estimates (with a min r of 0.55). Averaging time: NO ₂ - annual average Exposure years: 2014-2017	Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 µg/m ³ (IQR 0.058 µg/m ³) Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 µg/m ³ (IQR 1.91 µg/m ³)) Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 µg/m ³ (IQR 1.17 µg/m ³))	Dyslipidemia, static Dyslipidemia, dynamic DBP, static cholesterol, dynamic LDL, static cholesterol, static SBP, static SBP, dynamic DBP, dynamic non-hispanic, static		β (mg/dl) (95% CI) ^b LDL, dynamic: 9.03 (3.63, 14.43) Triglycerides, static: 0.09 (0.03, 0.16) Triglycerides, dynamic: 0.13 (0.05, 0.22) cholesterol, dynamic: 9.67 (3.71, 15.64) LDL, static: 2.65 (-2.71, 8.02) cholesterol, static: 2.69 (-3.12, 8.50) β (mmHg) (95% CI) ^b DBP, static: 0.28 (-1.15, 1.71) SBP, static: -0.04 (-2.64, 2.57) SBP, dynamic: 1.73 (-1.18, 4.64) DBP, dynamic: 0.53 (-0.97, 2.02)
† Luyten et al. (2020) ENVIRONAGE (Mother-child pairs n = 245 Belgium Enrollment: 2012	Excluded mother-child pairs if the child had passed away, they had moved to another country or too far from location where exam occurred, and if they were loss to follow-up	Spatiotemporal/geospatial model r ² = 78% Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - Trimester, entire pregnancy	NO ₂ (µg/m ³) Childhood Average childhood exposure Mean = 17.2 ± 3.4 IQR = 4.7 P25 = 14.6 P75 = 19.3 Day before follow-up visit Mean = 17.2 ± 9.5 IQR = 13.1	CRAE TI CRVE	Linear regression Adjusted for: sex, ethnicity, mean arterial blood pressure and BMI of the child at the moment of the follow-up visit, the season in which the follow-up examination took place, birth weight (grams), maternal age at	β (µm) (95% CI) ^c TI: 0.0027 (0.0002, 0.0005) CRAE: 2.96 (0.01, 5.87) CRVE: 4.24 (0.32, 8.16)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Follow-up: 2014-2018 Cohort		Exposure years: 2014-2018	P25 = 9.7 P75 = 22.8 Day of follow-up visit Mean = 17 ± 8.7 IQR = 10.8 P25 = 10.5 P75 = 21.3 Week before follow-up visit Mean = 17.2 ± 7.2 IQR = 10 P25 = 11.7 P75 = 21.7 Pregnancy Entire Pregnancy Mean = 19.7 ± 4.4 IQR = 6.2 P25 = 16.5 P75 = 22.7 Trimester 1 Mean = 19.9 ± 6 IQR = 9.1 P25 = 15.2 P75 = 24.3 Trimester 2 Mean = 19.8 ± 6.2 IQR = 9.1 P25 = 15 P75 = 24.1 Trimester 3 Mean = 19.6 ± 6.2 IQR = 9 P25 = 14.7 P75 = 23.7		the birth of her child and pre-pregnancy BMI, maternal education level, alcohol use of the mother during pregnancy, smoking habits of the mother before and during pregnancy, and the exposure of the child to passive smoking	
†Mann et al. (2021)	Children ages 6-8; residence in Fresno or	Fixed site monitor, LUR	NO ₂ (ppb)	8-isoprostane, 1-yr avg	GAM	β (mmHg) (95% CI) ^c DBP, 3-mo avg:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
		explained 73% of the variation observed with a rmse of 2.9 ppb				
		Averaging time: NO ₂ - annual average				
		Exposure years: 2004-2005				
†Ni et al. (2021)	Women residing in Shelby county, Tennessee residents between 16-40-yr of age, had singleton pregnancies without complications, and planned to deliver at a participating study hospital. The 1st stage of enrollment: recruited during regular obstetric appointments. The 2nd stage of enrollment: recruited from general community via media campaigns. 822 mother and child dyads who completed the age 4-to 6-year visit with blood pressure assessment and valid residential address histories.	LUR, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2006-2014	NO ₂ (ppb) Postnatal Mean = 8.9 ± 1.9 Median = 8.9 (IQR 2.6) Min = 3.7 Max = 13.5 P25 = 7.6 P75 = 10.2 Prenatal Mean = 10 ± 2.4 Median = 10 (IQR 3.4) Min = 4 Max = 16.4 P25 = 8.3 P75 = 11.7	DPB SBP	Linear regression Adjusted for: child age, sex, height at 4-6-yr visit, recruitment site, splines of visit date, maternal race, age at childbirth, education, log transformed income adjusted by household size, breastfeeding cotinine, BMI, insurance status, maternal psychological distress, child sleep scores, child physical activity, medication, secondhand smoke and Child Opportunity Index	β (percentile change) (95% CI) ^b Prenatal DBP: 2.35 (-5.15, 9.85) Postnatal SBP: 1.25 (-12.68, 15.18) Postnatal DBP: 5.00 (-5.38, 15.38) Prenatal SBP: 6.40 (-3.73, 16.53)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ni et al. (2022)	African American mothers and their children	Hybrid model	NO ₂ (ppb)	DPB	Linear regression	β (percentile change) (95% CI) ^c
CANDLE cohort		MSE r ² = 0.74–0.89	Mean = 9.66 ± 1.94	SBP	Adjusted for: child age, sex, height at 4–6 yr visit, recruitment site, splines of visit date, maternal race, age at childbirth, education, log transformed income adjusted by household size, breastfeeding cotinine, BMI, insurance status, maternal psychological distress, child sleep scores, child physical activity, medication, secondhand smoke and Child Opportunity Index	4-yr avg DPB/Low risk: 0.18 (-0.84, 1.20) 4-yr avg/High risk: 1.81 (-2.64, 6.26)
n = 556		Averaging time: 4-year avg, prenatal				4-yr avg SBP/Low risk: -0.20 (-1.30, 0.91) 4-yr avg/High risk: 1.83 (-1.11, 4.78)
Memphis, Tennessee, U.S.		Exposure years: NR				
Study years NR						
Cohort						
† Ohlwein et al. (2016)	Older adult women (69–79 yrs)	LUR	NO ₂ (ppb)	Mean Ratio LAVI	Linear regression	NO ₂
SALIA		r ² NO _x : 0.88 r ² NO ₂ : 0.89	Enrollment Median = 20.9 (39.4 µg/m ³) P25 = 18.7 (35.2 µg/m ³) P75 = 23 (44 µg/m ³)	Mean Ratio E/E'	Adjusted for: SES, smoking variables, alcohol consumption, physical activity, BMI, low density lipoprotein, high density lipoprotein and intake of statins	MR (95% CI) ^b E/E' Enrollment: 0.98 (0.88, 1.09) LAVI Enrollment: 1.11 (0.99, 1.24) E/E' Follow-up: 0.98 (0.88, 1.09) LAVI Follow-up: 1.09 (0.98, 1.21)
n = 402		Averaging time: multi-year	Follow-up Median = 13.8 (25.9 µg/m ³) P25 = 12 (23 µg/m ³) P75 = 16.9 (31.8 µg/m ³)			β (%) (95% CI) ^b LAVI Enrollment: 10.69 (-1.07, 22.45) E/E' Follow-up: -2.14 (-12.83, 8.55) E/E' Enrollment:
Ruhr, Germany		Exposure years: 2008–2009	NO _x (µg/m ³) Enrollment Median = 67 P25 = 58.8 P75 = 82.7			
2007–2010						
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Follow-up Median = 37.7 P25 = 32.7 P75 = 53.3			-2.14 (-12.83, 8.55) LAVI Follow-up: 8.55 (-2.14, 19.24) NO _x MR (95% CI) ^b LAVI Enrollment: 1.05 (1.00, 1.11) LAVI Followup: 1.04 (1.00, 1.09) E/E' Enrollment: 1.00 (0.94, 1.05) E/E' Followup: 0.99 (0.94, 1.04) β (%) (95% CI) ^b E/E' Followup: -1.00 (-6.00, 4.00) LAVI Followup: 4.00 (0.00, 9.00) LAVI Enrollment: 5.00 (0.00, 11.00) E/E' Enrollment: 0.00 (-6.00, 5.00)
†Paoin et al. (2021)	Participants were members of the EGAT1 cohort (overall EGAT study consists of three cohorts - EGAT1, 2, and 3). EGAT1 cohort participants were included if they lived in the Bangkok Metropolitan Region in 2007 and were followed up 2 or 3	Fixed site monitor Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2002-2017	NO ₂ (ppb) Overall Mean = 19.4 ± 4.5 IQR = 5 Min = 7.1 Max = 30.2	CAVI ABI	Linear mixed effects models Adjusted for: age, sex, BMI, smoking status, alcohol drinking, regular exercise, education level and income	β (%) (95% CI) ^b CAVI: 13.24 (0.71, 25.77) ABI: -0.34 (-1.22, 0.54)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Bangkok Metropolitan Region, Thailand Enrollment: 1985 Follow-up: through 2017 Cohort	times during 2007-2017. Participants were excluded if lost to follow-up or had died or moved out of the study area since 2007. Participants were also excluded from analyses of CAVI if they had ABI <0.9 or >1.3.					
†Pedersen et al. (2019) DNBC n = 1,234 Denmark Enrollment: 1996-2002 Followup: Mar 2012-Apr 2014 Cohort	Random sample of children born mothers w/ and w/o GDM	Dispersion model Method validation NR Averaging time: Prenatal, 7-yr avg (postnatal) Exposure years: 1996-2014	NO ₂ (ppb) Postnatal Median = 5.69 (10.7 µg/m ³) P5 = 4.9 (9.3 µg/m ³) P95 = 11.1 (20.9 µg/m ³) Prenatal Median = 6.11 (11.5 µg/m ³) P5 = 4 (7.5 µg/m ³) P95 = 15 (28 µg/m ³)	DBP SBP	Linear regression Adjusted for: child's age, sex, height, weight, maternal active smoking during pregnancy, maternal education, household disposable income, and area-income	β (mmHg) (95% CI) ^b Prenatal, DBP: 0.32 (-1.02, 1.66) Postnatal, DBP: 0.58 (-1.63, 2.79) Postnatal, SBP: -0.32 (-3.40, 2.76)
†Peralta et al. (2022) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort N = 363	Children born from PIAMA participants. Those who had missing information on their mother's weight during pregnancy, parental education, systolic BP, nationality were excluded from the analysis.	LUR r ² ranging between 61% and 89% Averaging time: NO ₂ - annual average	NO ₂ (ppb) Overall IQR = 2.82 (5.31 µg/m ³) P10 = 10.25 (19.28 µg/m ³) P90 = 15.78 (29.69 µg/m ³)	Change in cIMT	Quantile regression Adjusted for: age, sex, parental, exposure to indoor tobacco smoke, maternal smoking status during pregnancy, maternal BMI, breastfeeding status and Dutch nationality	β (µm) (95% CI) ^b Quantile 0.3: 15.80 (-37.38, 68.99) Quantile 0.2: 18.25 (-43.16, 79.66) Quantile 0.1: 22.57 (-53.40, 98.55) Quantile 0.4: 10.17 (-33.31, 53.65) Quantile 0.6:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
The Netherlands		Exposure years: 2009-2010				6.95 (-22.84, 36.73) Quantile 0.5: 9.21 (-30.24, 48.67) Quantile 0.8: -3.58 (-34.20, 27.04) Quantile 0.9: -24.10 (-106.75, 58.56) Quantile 0.7: 4.15 (-31.31, 39.60)
Enrollment: 1996-1997 Follow-up: 16-years Cohort						
†Pilz et al. (2018)	Excluded participants due to missing either outcome, exposure, or covariates	LUR, Spatiotemporal/geospatial model, Fixed site monitor	NO ₂ (ppb) Overall Mean = 7.4 ± 2.3 (14 ± 4.4 µg/m ³) Median = 7.17 (13.5 µg/m ³) Min = 3.7 (6.9 µg/m ³) Max = 14.6 (27.5 µg/m ³) P25 = 5.53 (10.4 µg/m ³) P75 = 9.14 (17.2 µg/m ³)	hs-CRP	Linear regression	NO ₂
KORA		Adjusted model explained variance r ² = 0.89			Adjusted for: age, sex, BMI, smoking status and month of blood draw waist-hip ratio and HDL cholesterol	β (%) (95% CI) ^b hs-CRP: 3.29 (-14.50, 21.09)
N = 2,252		Cross-validation adjusted r ² = 0.81				
Germany		Averaging time: NO ₂ - annual average, NO _x - annual average	NO _x (µg/m ³) Overall Mean = 21.7 ± 7.3 Median = 22.5 Min = 4 Max = 50.5 P25 = 17.2 P75 = 25.9			NO _x
Enrollment: 1999-2001 Follow-up: 2013-2014 Cross-Sectional		Exposure years: 2014-2015				β (%) (95% CI) ^c hs-CRP: 3.45 (-1.48, 8.61)
†Tibuakuu et al. (2017)	White, Black, Hispanic and Chinese participants aged 45–84-years and free of clinical CVD at time of enrollment were	Spatiotemporal/geospatial model	NO _x (ppb) Mean = 51.3 ± 27.8	AVC MAC	Staged linear regression Adjusted for: age, sex, race/ethnicity, metropolitan area, CT scan type, smoking status,	β (Agatston units/yr) (95% CI) ^b AVC: -0.95 (-3.10, 1.20) MAC: -1.29 (-3.17, 0.59)
MESA n = 6,253		Averaging time: NO _x - annual average				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Chicago, IL, Baltimore, MD, Los Angeles, CA, St. Paul, MN, New York City, NY, Forsyth County, NC, U.S.	recruited from six U.S. cities	Exposure years: 2000-2005			second-hand smoke exposure, physical activity, BMI, total cholesterol, HDL cholesterol, statin use, income and education	
Enrollment: 2000-2002 Follow-up: 2002-2004 and 2004-2005						
Cohort						
† Zhang et al. (2021a)	Participants who completed both questionnaires and blood tests	Hybrid model $r^2 = 0.78$	NO ₂ (ppb) Overall Mean = 13 (24 µg/m ³) IQR = 6.579 (12.38 µg/m ³)	tryglyceride HDL Cholesterol Dyslipidemia LDL	Logistic Adjusted for: age, sex, educational), BMI, smoking status, pack-years for current smokers, drinking frequency, energy types for cooking and heating Linear regression Adjusted for: age, sex, educational), BMI, smoking status, pack-years for current smokers, drinking frequency, energy types for cooking and heating	OR (95% CI) ^b Dyslipidemia: 1.22 (1.09, 1.37) β (%) (95% CI) ^b tryglyceride: 0.74 (-1.36, 2.85) HDL: -3.91 (-4.76, -3.05) Cholesterol: -2.75 (-3.69, -1.82) LDL: -2.83 (-3.99, -1.66)
China Health and Retirement Longitudinal Study (CHARLS)		Averaging time: NO ₂ - annual average				
N = 13,013		Exposure years: 2015				
China						
Enrollment: 2011-2012 Follow-up: 2015						
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zhang et al. (2022)	Children aged 8-10-years, residence in Fresno or Clovis for at least the past three-months, residence within 20 km of the central air quality monitor site, no plans to move from study area for next two-years, English or Spanish speaking, no cancer, HIV, or autoimmune disease	LUR, Fixed site monitor,	NO ₂ (ppb)	8-Isoprostane	GAM	β (ln ng/ml) (95% CI) ^c
CHAPS		Spatiotemporal/geospatial model	1-day average Median = 7.31 P25 = 4.12 P75 = 13.54	HDL	Adjusted for: living with a smoker, whether or not the child is hispanic, physical activity, household income, and a smoothed term for day of study	8-Isoprostane: 0.70 (0.50, 1.00)
N = 218		Method validation NR				8-Isoprostane: 0.80 (0.70, 1.10)
Fresno, CA, U.S.			1-month average Median = 8.98 P25 = 4.33 P75 = 14.05			8-Isoprostane: 0.80 (0.50, 1.20)
2015-2017		Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, NO _x - 24-hour average, NO _x - annual average, Other, NO ₂ - weekly average				8-Isoprostane: 0.90 (0.80, 1.10)
Cross-Sectional		NO ₂ - 1-, 3-, 6-month averages				8-Isoprostane: 0.60 (0.30, 0.90)
		NO _x - weekly average	1-week average Median = 7.92 P25 = 4.53 P75 = 14.58			8-Isoprostane: 0.70 (0.60, 0.80)
		NO ₂ - weekly average	1-year average Median = 8.3 P25 = 7.23 P75 = 9.4			β (mg/dl) (95% CI) ^c
		NO _x - 1-, 3-, 6-month averages	3-month average Median = 8.48 P25 = 4.46 P75 = 13.75			HDL: -7.90 (-15.40, -0.40)
		Exposure years: 2019	6-month average Median = 8.72 P25 = 5.64 P75 = 11.65			8-Isoprostane: -3.60 (-6.60, -0.50)
			NO ₂ (ppb)			8-Isoprostane: -2.90 (-5.40, -0.50)
			1-day average Median = 14.59			8-Isoprostane: -6.70 (-0.13, -0.30)
						HDL: -15.40 (-27.40, -3.40)
						HDL: -3.10 (-6.30, 0.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P25 = 10.06 P75 = 23.16			
			1-month average Median = 16.59 P25 = 10.79 P75 = 25.48			
			1-week average Median = 17.06 P25 = 10.53 P75 = 23.89			
			1-year average Median = 17.15 P25 = 15.36 P75 = 18.84			
			3-month average Median = 16 P25 = 11.47 P75 = 24.03			
			6-month average Median = 16.38 P25 = 13 P75 = 21.69			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zhang et al. (2023)	Middle aged and older adults	Spatiotemporal/geospatial model	NO ₂ (ppb)	MAP	Generalized linear regression	β (mmHg) (95% CI) ^b
CHARLS		C-V r ² = 0.84	Mean = 16.97 ± 4.04 (31.94 ± 7.61 μg/m ³)	SPB		MAP: 1.15 (0.58, 1.73)
n = 14,622		Averaging time: 3-yr avg		DBP	Adjusted for: Temperature, relative humidity, age, sex, residence, education, marital status, smoking, drinking status, education level	SBP: 1.70 (0.47, 2.93)
China		Exposure years: 2013-2015				DPB: 0.88 (0.39, 1.36)
2013-2015						
Cross-Sectional						
† de Prado-Bert et al. (2022)	Children	LUR	NO ₂ (μg/m ³)	SPB	Linear regression	β (mmHg) (95% CI) ^c
HELIX		ESCAPE-LUR	24-h avg (school/home) Median = 3.4 (IQR 0.7)	DPB	Adjusted for: child's sex, cohort, self-reported maternal education, self-reported ancestry, mean temperature, child's age, height, parental smoking during childhood and child BMI z-score.	Home-SBP: 2.03 (-0.36, 4.23)
n = 1170		Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, Other, 1-week avg	Annual avg (home) Median = 3.5 (IQR 0.6)			School-SPB: 2.44 (0.20, 4.68)
France, U.K., Spain, Norway, Greece, Lithuania		Exposure years: 2013-2015	Annual avg (school) Median = 3.5 (IQR 0.5)			Home-SBP: 1.50 (-0.39, 3.39)
Follow-up (age 7-11): 2014–2015			Week avg (school/home) Median = 3.5 (IQR 0.7)			School-SPB: 1.80 (-0.09, 3.69)
Cohort						

List of abbreviations in alphabetical order: $\mu\text{g}/\text{m}^3$ = micrograms per cubic meter; ABI = Ankle Brachial Index; AVC = aortic valve calcium; baPWV = brachial-ankle pulse wave; velocity; BLPM = Blood Pressure Lowering Medications; BMI = body mass index; BP = Blood Pressure; CAC = Coronary Artery; Calcification; CAD = Coronary Artery Disease; CANDLE = Conditions Affecting Neurocognitive Development in Early Childhood; CAVI = cardio-ankle vascular index; CHAPS = Childrens Health and Air Pollution Study; CI = Confidence Interval; cIMT = carotid Intima Media Thickness; cm^3 = cubic centimeters; CRAE = central retinal arteriolar equivalent; CRVE = central retinal venular equivalent; C-V = Cross Validation; DNBC = Danish National Birth Cohort; DPB = Diastolic Blood Pressure; E/E' = peak early diastolic mitral annulus velocity; EGAT = Electricity Generating Authority of Thailand; ENVIRONAGE = ENVIRONmental influence ON AGEing; ESCAPE = European Study of Cohorts for Air Pollution Effects; ETS = environmental tobacco smoke; GDM = Gestational Diabetes Mellitus; GEE = Generalized estimating equation; Hb = Hemoglobin; HDL = High Density Lipoprotein; HELIX = Human Early-life Exposome project; HNR = Heinz Nixdorf Recall study; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; hs-CRP = high-sensitivity C-reactive protein; IQR = Interquartile Range; KORA = Cooperative Health Research in the Region of Augsburg; LA EF = Left Atrial Ejection Fraction; LA = Left Atrial; LAVI = left atrial volume index; LDL = Low Density Lipoprotein; LOOCV = Leave One Out Cross-Validation; LUR = Land Use Regression; LV mass = Left Ventricular mass; LVEDV = Left Ventricular end-diastolic volume; LVEF = Left Ventricular Ejection Fraction; LVESV = Left Ventricular end-systolic volume; LVMVR = Left Ventricular mass to end-diastolic volume ratio; m/s = meter per second; MAC = mitral annular calcium; MAP = Mean Arterial Pressure; M-CHAT = the Multicultural Community Health Assessment Trial; MetS = Metabolic Syndrome; mg/dL = milligrams per deciliter; mmHg = millimeters of mercury; MPP = Mean Pulse Pressure; MR = Mean Ratio; MRI = Magnetic Resonance Imaging; NDIT = Nicotine Dependence in Teens Study; NOMAS = Northern Manhattan Study; NR = Not Reported; NSES=Neighborhood Socioeconomic Status; NSHAP = National Social Life, Health, and Aging Project; P = Percentile; POR = Prevalence Odds Ratio; Ppb = parts per billion; PWV = pulse wave velocity; RA EF = Right Atrial Ejection Fraction; RA = Right Atrial; RV EF = Right Ventricular Ejection Fraction; RVEDV = Right Ventricular end-diastolic volume; RVESV = Right Ventricular end-systolic volume; SAGE = Study on Global Aging and Adult Health; SALIA = Study on the influence of Air pollution on Lung function, Inflammation and Ageing; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; SBI = subclinical brain infarcts; SCAPIS = Swedish Cardio Pulmonary bioImage Study; SES = Socioeconomic Status; SPARC = Stroke Prevention and Atherosclerosis Research Centre; SPB = Systolic Blood Pressure; TAC = Thoracic Aortic Calcification; TCBV = total cerebral brain volume; TI = tortuosity index; TPVV = Total Pulmonary Vascular Volume; WHI = Women's Health Initiative; WMHV = White matter hyperintensity volume.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO_2 for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO_2 for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO_2 for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO_2 for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 6-8 Animal toxicology studies of subclinical effects underlying cardiovascular disease

Study Details and Population	Exposure Details	Endpoints Examined*
Takano et al. (2004)	Whole body inhalation with filtered air controls	0-d after exposure (LETO)
Rat (Long-Evans Tokushima and Otsuka Long-Evans Tokushima Fatty)	160 ppb (0.16 ppm) NO_2 , continuous for 32-wk	Body weight, total cholesterol, blood sugar, HDL/total cholesterol, triglycerides (NS)
4-wk-old, males	800 ppb (0.8 ppm) NO_2 , continuous for 32-wk	HDL ($\downarrow$)
n = 9–14/group	4,000 ppb (4.0 ppm) NO_2 , continuous for 32-wk	0-d after exposure (OLETF)
		- Body weight, total cholesterol, blood sugar (NS) - HDL, HDL/total cholesterol ($\downarrow$) - Triglycerides ($\uparrow$)

Study Details and Population	Exposure Details	Endpoints Examined*
de Burbure et al. (2007)	Whole body inhalation with ambient air controls	0-d after exposure (1 ppm/10 ppm, Se deficient) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
Rat (Wistar)	1,000 ppb (1 ppm) NO ₂ , 6-hr/d for 4-wk	0-d after exposure (1 ppm/10 ppm, Se supplement)
2-mo-old, males	5,000 ppb (5 ppm) NO ₂ , 6-hr/d for 5-d	Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
n = 8/group	10,000 ppb (10 ppm) NO ₂ , 6-hr/d for 4-wk	2-d after exposure (1 ppm/10 ppm, Se deficient) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
	50,000 ppb (50 ppm) NO ₂ , continuous for 30-min	2-d after exposure (1 ppm/10 ppm, Se supplement) Blood cell counts, serum and plasma antioxidant enzymes and oxidants (↑/↓)
†Ji et al. (2022)	Whole body inhalation with room air controls	Timing unclear - Eccentricity index, LVAWd and LVAWs (♂↓) - Histopathology - heart (cardiac hypertrophy with enlarged cardiomyocytes and intracellular spacing in male mice only) - LV dilation (LVEDD, LVESD, LVEDV, LVESV) (♂↑) - LV mass (♂↑) - LV ular short axis shortening rate, LV ejection fraction (♂↓) - LVPWd and LVPWs (NS) - PCR - cardiac damage genes (♂↑) - TUNEL staining (♂↑) - Cardiac transcriptomics (↑/↓) - Heart to body ratio (NS)
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5-hr/d for 28-d	
6-wk-old, males and females		
n = 6–9/group		

Study Details and Population	Exposure Details	Endpoints Examined*
† Karoui et al. (2020)	Whole body inhalation with room air controls	1-hr after exposure (3-hr exposure) • LV fractional shortening (↓) • LVEDD, LVESD (↑)
Rat (Wistar)	5,000 ppb (5 ppm) NO ₂ , continuous for 3-hr	24-hr after exposure (3-hr exposure) • Cardiac output (NS) • LV fractional shortening (NS) • LVEDD, LVESD (NS)
9-11-wk-old, males	5,000 ppb (5 ppm) NO ₂ , 3-hr/d, 5-d/wk for 3-wk	24-hr after exposure (3-hr/d, 5-d/wk for 3-wk exposure) • ATP production (↓) • Acceptor control ratio (↓) • Acetylcholine-induced coronary relaxation (↓) • Interfibrillar ROS (↑) • LVEDD, LVESD (↑) • OXPHOS (↓) • Sodium nitroprusside-induced coronary relaxation (NS) • fractional shortening, cardiac output (↓)
n = 4–6/group		

List of abbreviations in alphabetical order: ATP = adenosine triphosphate; d = day; HDL = high-density lipoprotein; hr = hour; min = minute; LETO = Long-Evans Tokushima; LV = left ventricle; LVAWd = left ventricular end-diastolic anterior wall thickness; LVAWs = left ventricular end-systolic anterior wall thickness; LVEDD = left ventricle end-diastolic; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume; LVESD = left ventricle end-systolic diameter; LVPWd = left ventricular end-diastolic posterior wall thickness; LVPWs = left ventricular end-systolic posterior wall thickness; mo = month; n = sample size; NO₂ = nitrogen dioxide; OLETf = Otsuka Long-Evans Tokushima fatty; OXPHOS = mitochondrial oxidative phosphorylation capacity; ppb = parts per billion; ppm = parts per million; ROS = reactive oxygen species; Se = selenium; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ↑/↓ = at least one experimental group had a statistically significant increase and at least one experimental group has a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females; ♂↓ = results were analyzed by sex and there was a statistically significant decrease in at least one male experimental group and a non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA

Appendix Table 6-9 Epidemiologic studies of exposure to oxides of nitrogen exposure and cardiovascular mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Beelen et al. (2008)	Adults aged 55–69- yrs living in	Hybrid model	NO ₂ (ppb)	Cancer registries	Cox proportional hazards	RR (95% CI) ^b
Brunekreef et al. (2009)	204	Averaging time:	Background NO ₂			CVD Mortality: 1.04 (0.96, 1.13)

NLCS	municipalities throughout the Netherlands	NO ₂ - annual average	Mean = 18.3 ± 3.9 (34.5 ± 7.3 µg/m ³) Min = 7.76 (14.6 µg/m ³) Max = 28.1 (52.8 µg/m ³)	Adjusted for: Age, sex, smoking status, area level indicators of SES		
N = 117,528		Exposure years: 1987-1996				
Netherlands			Overall NO ₂ Mean = 19.6 ± 4.4 (36.9 ± 8.2 µg/m ³) Min = 7.76 (14.6 µg/m ³) Max = 35.4 (66.7 µg/m ³)			
Recruitment: September 1986						
Follow-up: 1987–1996						
Cohort						
Beelen et al. (2014)	General population	LUR	NO ₂ (ppb)	Mortality registries	Cox proportional hazards	NO ₂
SALIA, DCH, SNAC-K, VHM&PP, HUBRO, E3N, SAPALDIA, EPIC-Oxford, EPIC-Umea, SALT/TwinGene, 60-y/IMPROVE, SDPP, EPIC-MORGEN, EPIC-Prospect, EPIC-Varese, EPIC-Turin, EPIC-San Sebastian, SIDRIA-Rome, EPIC-Athens, KORA, SIDRIA-Turin, FINRISK	adults from 22 ESCAPE cohorts in 13 countries across Europe	CV-r ² for NO ₂ ranged 0.50-0.88 CV-r ² for NO _x ranged 0.39-0.88 Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2008–2011	EPIC-Umeå Mean = 2.8 (5.2 µg/m ³) SIDRIA-Turin Mean = 31.8 (59.8 µg/m ³)		Adjusted for: Sex, calendar time, smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetable intake, alcohol consumption, BMI, educational level, occupational class, employment status, marital status, area-level socioeconomic status	HR (95% CI) ^b CVD Mortality: 1.02 (0.94, 1.11) MI Mortality: 0.96 (0.79, 1.18) CBVD Mortality: 1.02 (0.87, 1.19) IHD Mortality: 1.00 (0.84, 1.19) NO _x HR (95% CI) ^c IHD Mortality: 1.02 (0.95, 1.09) MI Mortality: 0.99 (0.90, 1.07) CVD Mortality: 1.02 (0.99, 1.06) CBVD Mortality: 1.00 (0.93, 1.08)
N = 367,383						
Sweden, France, U.K., Denmark, Spain, Italy, Switzerland, Norway, Germany, Greece, Austria, Finland, The Netherlands						

Enrollment: ranged 1985–2007 Follow-up: mean 13.9- yrs Cohort						
Carey et al. (2013) Clinical Practice Research Datalink N = 835,607 England, Scotland, Wales, U.K. Enrollment: January 1, 2003 Follow-up: 2003–2007 Cohort	Adults aged 40– 89- yrs registered with the U.K. NHS for at least one- year	Dispersion model, Fixed site monitor $r^2 = 0.57\text{--}0.80$ Averaging time: NO₂ - annual average Exposure years: 2002	NO₂ (ppb) London Region Mean = 17.7 ± 2.4 (33.3 ± 4.5 $\mu\text{g}/\text{m}^3$) North Region Mean = 12.4 ± 3.3 (23.4 ± 6.3 $\mu\text{g}/\text{m}^3$) Overall Mean = 12 ± 3.9 (22.5 ± 7.4 $\mu\text{g}/\text{m}^3$) IQR = 5.69 ($10.7 \mu\text{g}/\text{m}^3$) Min = 2.4 ($4.5 \mu\text{g}/\text{m}^3$) Max = 32.3 ($60.8 \mu\text{g}/\text{m}^3$) South Region Mean = 10.3 ± 3.2 (19.4 ± 6.1 $\mu\text{g}/\text{m}^3$)	Mortality registration records	Cox proportional hazards Adjusted for: Age, sex, smoking, BMI, education	HR (95% CI)^b Circulatory Disease Mortality: 1.05 (0.99, 1.12)
Cesaroni et al. (2013) N = 1,265,058 Rome, Italy Enrollment: 2001 Follow-up: 2001–2010 Cohort	All non- institutionalized adults aged ≥ 30- yrs residing in Rome for ≥ 5-yrs	LUR, Fixed site monitor $r^2 = 0.704$ Averaging time: NO₂ - annual average Exposure years: 2010	NO₂ (ppb) Overall Mean = 23.8 ± 7.65 ($44.8 \pm$ $14.4 \mu\text{g}/\text{m}^3$)	Rome Municipal Register	Cox proportional hazards Adjusted for: Sex, marital status, place of birth, education, occupation, area-based socioeconomic position	HR (95% CI)^b IHD Mortality: 1.10 (1.07, 1.13) CVD Mortality: 1.06 (1.04, 1.08)

Chen et al. (2013)	Canadian citizens or landed immigrants aged 35–85-yrs who filed a tax return between 1982 and 1986 when they resided in any of 10 urban centers in Ontario	LUR $r^2 = 0.70, 0.76, \text{ and } 0.77$ for Toronto, Hamilton, and Windsor, respectively. Averaging time: NO ₂ - annual average Exposure years: 2002–2004	NO ₂ (ppb) Toronto Mean = 21.7 (IQR 4.1) Hamilton Mean = 15.5 (IQR 2.9) Windsor Mean = 12.1 (2.5)	Canadian Mortality Database	Cox proportional hazards Adjusted for: Age, sex, marital status, annual household income, percent of immigrants, percent of population with less than high school education, unemployment rate, average household income	RR (95% CI) ^b IHD Mortality: 1.19 (1.08, 1.30) CBVD Mortality: 0.92 (0.79, 1.08) CVD Mortality: 1.17 (1.10, 1.23)
Gan et al. (2011)	All metropolitan Vancouver residents who registered with the provincial health insurance plan, resided in the study region during the 5-yr exposure period, aged 45–85-yrs, and without a previous diagnosis or CHD	LUR, Fixed site monitor $r^2 = 0.56$ Averaging time: NO ₂ - annual average, NO - annual average Exposure years: 1994–1998	NO ₂ (ppb) Overall Mean = 17.1 ± 4 ($32.1 \pm 8 \mu\text{g}/\text{m}^3$) Median = 16.3 (IQR 4.5) ($30.6 \mu\text{g}/\text{m}^3$ (IQR $8.4 \mu\text{g}/\text{m}^3$)) Min = 8.13 ($15.3 \mu\text{g}/\text{m}^3$) Max = 30.7 ($57.7 \mu\text{g}/\text{m}^3$) NO (ppb) Overall Mean = 26 ± 9.7 ($32 \pm 11.9 \mu\text{g}/\text{m}^3$) Median = 23.9 (IQR 10.8) ($29.3 \mu\text{g}/\text{m}^3$ (IQR $13.2 \mu\text{g}/\text{m}^3$)) Min = 7.17 ($8.8 \mu\text{g}/\text{m}^3$) Max = 103 ($126 \mu\text{g}/\text{m}^3$)	Mortality registration records	Cox proportional hazards Adjusted for: Sex, age, comorbidity, SES	NO RR (95% CI) ^b CHD Mortality: 1.08 (1.03, 1.14) NO ₂ RR (95% CI) ^b CHD Mortality: 1.09 (1.01, 1.18)
Hoek et al. (2002)	Participants aged 55–69-yrs at enrollment	Spatiotemporal/geospatial model	NO ₂ (ppb) Background (regional and	National mortality registries	Cox proportional hazards	RR (95% CI) ^b CPD Mortality - Background:

n = 4,492	from 204 (29%) of 714 municipalities with computerized registries and were covered by cancer registries in 1986.	CV RMSE ranged 0.15 for the regional background model to 0.25 for the urban background model. Averaging time: NO ₂ - 4-year Exposure years: 1987-1990	urban background only) Mean = 19.2 ± 4.2 (36.1 ± 7.9 µg/m ³) Median = 19.3 (36.4 µg/m ³) Min = 7.81 (14.7 µg/m ³) Max = 31.6 (59.5 µg/m ³) P5 = 10.8 (20.3 µg/m ³) P25 = 17.2 (32.4 µg/m ³) P75 = 21.7 (40.8 µg/m ³) P95 = 25.6 (48.2 µg/m ³) Background and Local (including distance to major roadways) Mean = 19.5 ± 4.4 (36.6 ± 8.3 µg/m ³) Median = 19.5 (36.6 µg/m ³) Min = 7.81 (14.7 µg/m ³) Max = 35.7 (67.2 µg/m ³) P5 = 10.8 (20.3 µg/m ³) P25 = 17.3 (32.6 µg/m ³) P75 = 22.1 (41.5 µg/m ³) P95 = 26.9 (50.7 µg/m ³)		Adjusted for: Age, sex, education, Quetelet-index, occupation, active and passive cigarette smoking, neighborhood socioeconomic score	1.31 (0.88, 1.96) CPD Mortality - Background and Local: 1.45 (0.99, 2.13)
Jerrett et al. (2009)	Residents of Ontario with health insurance program number who attended a respiratory disease clinic	LUR r ² = 0.7 Averaging time: NO ₂ - annual average Exposure years: 2002, 2004	NO ₂ (ppb) Overall Median = 22.9 P25 = 20.8 P75 = 24.8	National mortality registries	Cox proportional hazards Adjusted for: Sex, age, smoking status, BMI, BMI-squared, FVC (% predicted), neighborhood deprivation index, clustering on census tract	RR (95% CI) ^b Circulatory Disease Mortality: 2.53 (1.26, 5.08)
Toronto Western Hospital						
N = 2,360						
Toronto, Canada						
Enrollment: 1992–1999						

Follow-up: 1992–2002						
Cohort						
Jerrett et al. (2013)	Subjects with valid postal addresses, residents of California, and excluded those with missing data on key covariates	LUR	NO ₂ (ppb)	Medical records	Cox proportional hazards	RR (95% CI) ^b
CPS-II		Averaging time:	Overall			CVD Mortality:
N = 73,711		NO ₂ – monthly	Mean = 12.27		Adjusted for:	1.12 (1.02, 1.23)
California, U.S.		Exposure years:	Median = 12.12		Individual-level	Stroke Mortality:
Enrollment: 1982		1988–2002	P5 = 7.93		covariates, consolidated	1.20 (1.04, 1.39)
Follow-up: 1982–2000			P10 = 8.81		metropolitan statistical	IHD Mortality:
			P25 = 10.21		area city indicators,	1.17 (1.04, 1.31)
			P75 = 14.33		1990 ecologic	
			P90 = 16.22		covariates stratifying	
			P95 = 17.09		the Enrollment hazard	
Cohort					function by age, gender,	
					and race	
Krewski et al. (2000)	HSC: White adults aged 25–7--yrs residing in 1 of 6 U.S. cities. ACS	Central site monitor	NO ₂ (ppb)	Death certificates	Cox proportional hazards	RR (95% CI) ^b
HSC, CPS-II		Averaging time:	All cities			CPD Mortality:
n = 8,111		NO ₂ - annual average	IQR = 15.8		Adjusted for: Age (5-yr groupings), sex,	1.17 (1.02, 1.34)
St. Louis, MO,		Exposure years:	CPS-II		current-smokers, pack-	CPD Mortality -
Nationwide,		1977–1985	April-September		years for current	October-March: 0.98
Steubenville, OH,			Mean = 23.65		smokers, former-	(0.96, 1.00)
Portage, WI, Topeka,			October-March		smokers, pack-years for	CPD Mortality - April-
KS, Watertown, MA,			Mean = 27.2		former-smokers, high	September: 0.98 (0.95,
Kingston-Harriman,					school education, BMI,	1.02)
TN, U.S.			Harriman		and occupational	
			Mean = 14.1		exposure to dust or	
					fumes	
Enrollment: 1974–			Portage		Adjusted for: Tobacco	
1977 (HSC), 1982			Mean = 6.1		consumption, education	
(CPS-II)					level, occupational	
Follow-up: 1974–1989			St. Louis		exposure, BMI, marital	
(HSC), 1982–1989			Mean = 19.7		status, alcohol	
(CPS-II)					consumption,	
Cohort			Steubenville		interaction with gender	
			Mean = 21.9			

			Topeka Mean = 10.6			
			Watertown Mean = 18.1			
Lipsett et al. (2011)	Female current and former public school workers enrolled in the State Teachers' Retirement System	Fixed site monitor Averaging time: NO ₂ - monthly average Exposure years: 1996–2005	NO ₂ (ppb) Mean = 33.59 ± 9.63 IQR = 10.29 Min = 5.24 Max = 67.19 NO _x (ppb) Mean = 95.6 ± 34.5 IQR = 48.31 Min = 7.31 Max = 221.4	Mortality registries	Cox proportional hazards Adjusted for: Age, race, smoking status, total pack-years, BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication, and aspirin use, and for contextual variables (income, income inequality, education, population size, racial composition, and unemployment)	NO ₂ HR (95% CI) ^b CBVD Mortality: 0.86 (0.71, 1.06) CVD Mortality: 0.98 (0.88, 1.09) IHD Mortality: 1.07 (0.92, 1.24) NO _x HR (95% CI) ^b CVD Mortality: 1.05 (0.99, 1.11) IHD Mortality: 1.09 (1.00, 1.20) CBVD Mortality: 1.01 (0.90, 1.14)
CTS n = 101,784 California, U.S. Enrollment: 1995 Follow-up: 1997, 2000 Cohort						
Rosenlund et al. (2008)	Residents of Rome aged 35–84-years who experienced first coronary event during 1998–2000	LUR r ² = 0.69 Averaging time: NO ₂ - annual average	NO ₂ (ppb) Median = 21.3 – 26.0 (40–49 µg/m ³)	Mortality registry	Cox proportional hazards Adjusted for: Age, sex, SES	RR (95% CI) ^b Mortality within 28 days of First Coronary Event: 1.14 (1.04, 1.24) Mortality after Nonfatal Coronary Event: 0.91 (0.80, 1.03)
n = 11,167 incident coronary events Rome, Italy						

Enrollment: 1998 Follow-up: 2000		Exposure years: 1995-1996		Cohort		
Yorifuji et al. (2010)	Random selection of residents in all 74 municipalities in Shizuoka by stratifying sex and age groups (65-74; 75-84), excluding those with no residential information or who moved during the study period	LUR $r^2 = 0.54$ Averaging time: NO ₂ - annual average Exposure years: 2000-2006	NO ₂ (ppb) Deaths Mean = 13 ± 6.4 (25 ± 12 $\mu\text{g}/\text{m}^3$) Overall Mean = 13 ± 6.4 (25 ± 12 $\mu\text{g}/\text{m}^3$) Survivors Mean = 13 ± 6.4 (25 ± 12 $\mu\text{g}/\text{m}^3$)	Ministry of Health, Labour, and Welfare of Japan vital statistics	Cox proportional hazards Adjusted for: Age, sex, smoking category, BMI category, hypertension, diabetes, financial capability	HR (95% CI) ^b CPD Mortality: 1.32 (1.12, 1.56)
†Bouma et al. (2023)	Adults aged ≥ 30 -yrs	Dispersion model $r^2 = 0.60$ Averaging time: NO ₂ - annual average Exposure years: 2016	NO ₂ (ppb) Overall Mean = 10.52 ± 2.64 (19.79 ± 4.97 $\mu\text{g}/\text{m}^3$) Median = 10.4 (IQR 3.47) (19.5 $\mu\text{g}/\text{m}^3$ (IQR 6.52 $\mu\text{g}/\text{m}^3$)) P25 = 8.806 (16.57 $\mu\text{g}/\text{m}^3$) P75 = 12.27 (23.09 $\mu\text{g}/\text{m}^3$)	Dutch digital municipal population register	Cox proportional hazards Adjusted for: Stratified by sex and adjusted for individual-level covariates (standardized household income, region of origin, marital status), and area-level covariates (mean income per income recipient, unemployment rate, social assistance, percentage non-western immigrants, and percentage of low	HR (95% CI) ^b CVD Mortality: 1.003 (0.977, 1.029)

					education level) on the neighborhood and regional level	
† Brunekreef et al. (2021)	General population adults aged ≥30- yrs	LUR, CTM, Europe-wide LUR	NO ₂ (ppb)	National mortality databases	Cox proportional hazards	HR (95% CI) ^b CVD Mortality
† Stafoggia et al. (2022)		r ² = 0.58	8 Pooled ESCAPE Cohorts Mean = 13±4.28 (25±8.05 µg/m ³) Median = 12.83 (IQR 5.394) (24.14 µg/m ³ (IQR 10.15 µg/m ³)) Min = 1.42 (2.68 µg/m ³) Max = 43.06 (81.02 µg/m ³) P5 = 6.861 (12.91 µg/m ³) P25 = 10.37 (19.52 µg/m ³) P75 = 15.77 (29.68 µg/m ³) P95 = 21.01 (39.53 µg/m ³)		Adjusted for: Cohort ID, age, sex, yr of baseline visit, smoking (status, duration, intensity, intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income	8 pooled ESCAPE cohorts: 1.174 (1.115, 1.236) 7 administrative cohorts: Unrestricted: 1.048 (1.012, 1.085) <40 µg/m ³ : 1.057 (1.020, 1.096) <30 µg/m ³ : 1.065 (1.019, 1.113) <20 µg/m ³ : 1.075 (0.961, 1.201)
† Strak et al. (2021)		Averaging time: NO ₂ - annual average Exposure years: 2010				
8 ESCAPE cohorts: CEANS, DCH, E3N, VHM&PP, HNR, KORA, 0 DNC, EPIC-MORGEN, EPIC-Prospect			CEANS-SALT Cohort Mean = 11.31±3.28 (21.29±6.18 µg/m ³) Median = 11.17 (IQR 3.9) (21.02 µg/m ³ (IQR 7.33 µg/m ³)) Min = 1.58 (2.98 µg/m ³) Max = 26.85 (50.53 µg/m ³) P5 = 5.958 (11.21 µg/m ³) P25 = 9.327 (17.55 µg/m ³) P75 = 13.22 (24.88 µg/m ³) P95 = 16.94 (31.87 µg/m ³)			Belgian Administrative Cohort: 0.979 (0.963, 0.996) Danish Administrative Cohort: 1.132 (1.105, 1.159) Dutch Administrative Cohort: 1.032 (1.006, 1.059) English Administrative Cohort: 1.030 (0.994, 1.068) Norwegian Administrative Cohort: 1.036 (1.016, 1.056)
N = 325,367						
Copenhagen, Aarhus, Vorarlberg, Ruhr, Augsburg, Stockholm County, Sweden, France, Denmark, Germany, Austria, Netherlands						
Enrollment: 1985–205			CEANS-SDPP Cohort Mean = 8.259±2.28 (15.54±4.29 µg/m ³) Median = 8.269 (IQR 2.86) (15.56 µg/m ³ (IQR 5.38 µg/m ³)) Min = 1.57 (2.96 µg/m ³)			
Follow-up: 2015						
7 administrative cohorts:						

N = 29,912,322	Max = 19.71 (37.09 µg/m ³)	Roman Administrative Cohort: 1.084 (1.052, 1.118)
Belgian n = 6,491,801	P5 = 4.15 (7.81 µg/m ³)	
Danish n = 3,323,612	P25 = 6.792 (12.78 µg/m ³)	Swiss Administrative Cohort: 1.049 (1.026, 1.074)
Dutch n = 10,532,360	P75 = 9.651 (18.16 µg/m ³)	
English n = 1,491,124	P95 = 11.94 (22.46 µg/m ³)	
Norwegian n = 2,516,192	CEANS-SIXTY Cohort	CBVD Mortality
Italian n = 1,263,712	Mean = 10.99±3.26	8 pooled ESCAPE cohorts: 1.132 (1.020, 1.256)
Swiss n = 4,293,521	(20.68±6.13 µg/m ³)	
	Median = 10.92 (IQR 4)	
	(20.54 µg/m ³ (IQR 7 µg/m ³)	
	Min = 1.42 (2.68 µg/m ³)	
	Max = 25.45 (47.88 µg/m ³)	
	P5 = 5.69 (10.7 µg/m ³)	
	P25 = 9.051 (17.03 µg/m ³)	
	P75 = 12.77 (24.03 µg/m ³)	
	P95 = 16.62 (31.28 µg/m ³)	CMD Mortality
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands	CEANS-SNACK Cohort	8 pooled ESCAPE cohorts: 1.192 (1.134, 1.254)
	Mean = 14.56±2.71	
	(27.39±5.09 µg/m ³)	
	Median = 15.1 (IQR 3.92)	
	(28.5 µg/m ³ (IQR 7.38 µg/m ³))	IHD Mortality
	Min = 6.176 (11.62 µg/m ³)	8 pooled ESCAPE cohorts: 1.192 (1.102, 1.290)
Enrollment: 1992–2011	Max = 22.65 (42.61 µg/m ³)	
Follow-up: 2011–2017	P5 = 9.71 (18.27 µg/m ³)	
	P25 = 12.52 (23.56 µg/m ³)	
	P75 = 16.45 (30.95 µg/m ³)	
	P95 = 18.04 (33.94 µg/m ³)	
Cohort	DCH Cohort	
	Mean = 14.9±3.64	
	(28.04±6.84 µg/m ³)	
	Median = 15.05 (IQR 5.3)	
	(28.32 µg/m ³ (IQR 10 µg/m ³))	
	Min = 3.4 (6.4 µg/m ³)	
	Max = 38.39 (72.23 µg/m ³)	
	P5 = 8.79 (16.54 µg/m ³)	
	P25 = 12.36 (23.26 µg/m ³)	

P75 = 17.68 (33.26 $\mu\text{g}/\text{m}^3$)
P95 = 20.31 (38.22 $\mu\text{g}/\text{m}^3$)

DNC-1999 Cohort
Mean = 13.74 $\pm$ 4.5
(25.85 $\pm$ 8.47 $\mu\text{g}/\text{m}^3$)
Median = 12.63 (IQR 7.345)
(23.76 $\mu\text{g}/\text{m}^3$ (IQR 13.82
 $\mu\text{g}/\text{m}^3$))
Min = 3.41 (6.42 $\mu\text{g}/\text{m}^3$)
Max = 28.84 (54.26 $\mu\text{g}/\text{m}^3$)
P5 = 7.286 (13.71 $\mu\text{g}/\text{m}^3$)
P25 = 10.32 (19.42 $\mu\text{g}/\text{m}^3$)
P75 = 17.67 (33.24 $\mu\text{g}/\text{m}^3$)
P95 = 20.7 (38.95 $\mu\text{g}/\text{m}^3$)

DNC-1993 Cohort
Mean = 11.6 $\pm$ 4 (21.9 $\pm$ 8
 $\mu\text{g}/\text{m}^3$)
Median = 10.83 (IQR 5.591)
(20.37 $\mu\text{g}/\text{m}^3$ (IQR 10.52
 $\mu\text{g}/\text{m}^3$))
Min = 2.41 (4.54 $\mu\text{g}/\text{m}^3$)
Max = 38.39 (72.23 $\mu\text{g}/\text{m}^3$)
P5 = 5.41 (10.18 $\mu\text{g}/\text{m}^3$)
P25 = 8.689 (16.35 $\mu\text{g}/\text{m}^3$)
P75 = 14.28 (26.87 $\mu\text{g}/\text{m}^3$)
P95 = 19.7 (37.07 $\mu\text{g}/\text{m}^3$)

E3N Cohort
Mean = 14.01 $\pm$ 5.18
(26.36 $\pm$ 9.75 $\mu\text{g}/\text{m}^3$)
Median = 13.06 (IQR 6.664)
(24.57 $\mu\text{g}/\text{m}^3$ (IQR 12.54
 $\mu\text{g}/\text{m}^3$))
Min = 1.84 (3.46 $\mu\text{g}/\text{m}^3$)
Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$)
P5 = 7.12 (13.4 $\mu\text{g}/\text{m}^3$)
P25 = 10.27 (19.32 $\mu\text{g}/\text{m}^3$)
P75 = 16.93 (31.86 $\mu\text{g}/\text{m}^3$)

P95 = 24.23 (45.59 $\mu\text{g}/\text{m}^3$)

EPIC-NL-MORGEN Cohort

Mean = 18.36 $\pm$ 3.22

(34.55 $\pm$ 6.05 $\mu\text{g}/\text{m}^3$)

Median = 17.9 (IQR 4.77)

(33.6 $\mu\text{g}/\text{m}^3$ (IQR 8.97

$\mu\text{g}/\text{m}^3$))

Min = 5.8 (11 $\mu\text{g}/\text{m}^3$)

Max = 36.49 (68.66 $\mu\text{g}/\text{m}^3$)

P5 = 13.91 (26.18 $\mu\text{g}/\text{m}^3$)

P25 = 15.93 (29.97 $\mu\text{g}/\text{m}^3$)

P75 = 20.69 (38.94 $\mu\text{g}/\text{m}^3$)

P95 = 23.8 (44.8 $\mu\text{g}/\text{m}^3$)

EPIC-NL-PROSPECT Cohort

Mean = 19.11 $\pm$ 2.88

(35.96 $\pm$ 5.41 $\mu\text{g}/\text{m}^3$)

Median = 18.85 (IQR 3.86)

(35.46 $\mu\text{g}/\text{m}^3$ (IQR 7.27

$\mu\text{g}/\text{m}^3$))

Min = 10.41 (19.58 $\mu\text{g}/\text{m}^3$)

Max = 33.03 (62.15 $\mu\text{g}/\text{m}^3$)

P5 = 14.6 (27.4 $\mu\text{g}/\text{m}^3$)

P25 = 17.28 (32.52 $\mu\text{g}/\text{m}^3$)

P75 = 21.15 (39.79 $\mu\text{g}/\text{m}^3$)

P95 = 23.72 (44.63 $\mu\text{g}/\text{m}^3$)

HNR Cohort

Mean = 20.08 $\pm$ 2.48

(37.78 $\pm$ 4.66 $\mu\text{g}/\text{m}^3$)

Median = 19.95 (IQR 2.67)

(37.54 $\mu\text{g}/\text{m}^3$ (IQR 5.03

$\mu\text{g}/\text{m}^3$))

Min = 13.41 (25.23 $\mu\text{g}/\text{m}^3$)

Max = 39.9 (75.07 $\mu\text{g}/\text{m}^3$)

P5 = 16.61 (31.26 $\mu\text{g}/\text{m}^3$)

P25 = 18.53 (34.87 $\mu\text{g}/\text{m}^3$)

P75 = 21.2 (39.9 $\mu\text{g}/\text{m}^3$)

P95 = 24.36 (45.83 $\mu\text{g}/\text{m}^3$)

KORA-S3 Cohort
Mean = 11.23±1.8 (21.13±3.3
µg/m³)
Median = 11.14 (IQR 2.3)
(20.97 µg/m³ (IQR 4.32
µg/m³))
Min = 5.538 (10.42 µg/m³)
Max = 22.17 (41.72 µg/m³)
P5 = 8.66 (16.3 µg/m³)
P25 = 10.03 (18.88 µg/m³)
P75 = 12.34 (23.21 µg/m³)
P95 = 14.04 (26.41 µg/m³)

KORA-S4 Cohort
Mean = 11.19±1.8
(21.05±3.39 µg/m³)
Median = 11.06 (IQR 2.39)
(20.82 µg/m³ (IQR 4.49
µg/m³))
Min = 5.14 (9.68 µg/m³)
Max = 22.17 (41.72 µg/m³)
P5 = 9.97 (18.76 µg/m³)
P25 = 12.35 (23.24 µg/m³)
P75 = 14.1 (26.5 µg/m³)
P95 = 22.17 (41.72 µg/m³)

VHM&PP Cohort
Mean = 11.67±2.84
(21.96±5.34 µg/m³)
Median = 11.94 (IQR 3.71)
(22.46 µg/m³ (IQR 6.99
µg/m³))
Min = 2.05 (3.85 µg/m³)
Max = 25.66 (48.28 µg/m³)
P5 = 6.532 (12.29 µg/m³)
P25 = 9.901 (18.63 µg/m³)
P75 = 13.62 (25.62 µg/m³)
P95 = 15.8 (29.7 µg/m³)

Belgium
Mean = 16.2±3.9 (30.4±7.3
µg/m³)

Denmark
Mean = 10.8±4.2 (20.3±7.9
µg/m³)

Rome
Mean = 17.5±3.2 (32.9±6.1
µg/m³)

Norway
Mean = 8.13±4.1 (15.3±7.8
µg/m³)

Switzerland
Mean = 12.6±3.9 (23.7±7.4
µg/m³)

The Netherlands
Mean = 16.7±3.8 (31.4±7.1
µg/m³)

†Chen et al. (2023)	Adults aged 40–69- yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales, with IBD and excluding those who died within 1-yr of follow-	LUR	NO ₂ (ppb)	Self-reports, primary care, hospital inpatient data	Cox proportional hazards	NO ₂
UK Biobank		CV-r ² = 0.87 for NO ₂ ; CV-r ² = 0.88 for NO _x	NO ₂ Mean = 15 ± 4.7 (29 ± 8.9 µg/m ³) Median = 14.8 (IQR 5.53) (27.9 µg/m ³ (IQR 10.4 µg/m ³)) Min = 5.3 (10 µg/m ³) Max = 46 (86.6 µg/m ³)		Adjusted for: Age, sex, ethnicity, assessment centers, household income, smoking status, education, BMI, physical activity, healthy diet, alcohol consumption, baseline related surgery history, medication	HR (95% CI) ^b CVD Mortality - IBD: 1.15 (0.92, 1.44) CVD Mortality - CD: 0.98 (0.71, 1.35) CVD Mortality - UC: 1.17 (0.79, 1.72)
England, Scotland, Wales, U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average				NO _x
Enrollment: 2006–2010		Exposure years: 2005–2007, 2010	NO _x (µg/m ³)			HR (95% CI) ^c CVD Mortality - IBD:
Follow-up: mean 12- yrs			NO _x			

Cohort	up, those with cancer at baseline or 1-yr of follow-up, and those who moved to another address at repeat assessments		Mean = 43.9 ± 15.2 Median = 42 (IQR 15.6) Min = 19.7 Max = 247.5			1.22 (1.02, 1.47) CVD Mortality - CD: 1.03 (0.74, 1.43) CVD Mortality - UC: 1.31 (1.04, 1.64)
†Cramer et al. (2020)	Female nurses belonging to the Danish Nurse Organization aged >44-years	Hybrid model	NO ₂ (ppb)	Danish Register of Causes of Death	Cox proportional hazards	NO ₂
DNC		r ² = 0.7–0.9 depending on site, pollutant, and averaging period	Fatal Incident MI Mean = 7.55 ± 5.69 (14.2 ± 10.7 µg/m ³)		Adjusted for: Age (underlying time), yr of cohort entry, smoking status, pack-years, consumption of fruit, avoidance of fatty meat, alcohol consumption, use of oral contraceptives, use of hormone therapy, physical activity, marital status, employment status, and level of urbanization.	HR (95% CI) ^b MI Mortality - 1-yr: 1.12 (0.66, 1.90) MI Mortality - 3-yr: 1.02 (0.59, 1.77) MI Mortality - 23-yr: 1.20 (0.70, 2.04)
N = 22,882			MI Mean = 6.7 ± 4.3 (12.6 ± 8.1 µg/m ³)			
Denmark		Averaging time: NO ₂ - annual average, NO _x - annual average, Other, NO ₂ - 1-yr MA NO ₂ - 3-yr MA NO ₂ - 23-yr MA NO _x - 1-yr MA NO _x - 3-yr MA NO _x - 23-yr MA	Overall Incident MI Mean = 7.23 ± 5.1 (13.6 ± 9.6 µg/m ³)			NO _x
Enrollment: 1993 and 1999 Follow-up: 2014			Total Mean = 6.7 ± 4.3 (12.6 ± 8.1 µg/m ³)			HR (95% CI) ^c MI Mortality - 1-yr: 1.02 (0.92, 1.13) MI Mortality - 3-yr: 1.01 (0.90, 1.12) MI Mortality - 23-yr: 1.03 (0.94, 1.12)
Cohort		Exposure years: 1990-2014	NO _x (µg/m ³) Fatal Incident MI Mean = 24.4 ± 34.9 MI Mean = 19.1 ± 24.2 Overall Incident MI Mean = 22 ± 29.7			

			Total Mean = 19.1 ± 24.4			
† Crouse et al. (2015)	Non-institutionalized individuals 25-years of age and older and residing in Canada in 1991.	LUR	NO ₂ (ppb)	National mortality databases	Cox proportional hazards	HR (95% CI) ^b
CanCHEC		r ² = 0.43	Mean = 11.6			CVD Mortality: 1.051 (1.035, 1.067)
n = 301,115		Averaging time: NO ₂ - 7-yr MA; 1-yr lag	Median = 10.4 (IQR 10.5)		Adjusted for: Aboriginal ancestry, visible minority status, highest level of education, employment status, occupational class, immigrant status, marital status, income quintile, census division and census tract–census division percent of immigrants, percent of adults without high school diploma, percent of subjects in lowest income quintile	CBVD Mortality: 1.005 (0.984, 1.026)
Nationwide, Canada			Min = 0			CMD Mortality: 1.050 (1.036, 1.063)
Enrollment: 1991		Exposure years: 1984-2006	Max = 51.5			IHD Mortality: 1.078 (1.058, 1.099)
Follow-up: 1991-2006			P25 = 6			
Cohort			P75 = 16.5			
† Dalecká et al. (2021)	Women aged 51-56-years with baseline lung function measurements	LUR, Fixed site monitor	NO ₂ (ppb)	Death certificates. Includes deaths from cardiovascular disease (ICD-9 codes 400–440 or ICD-10 codes I10 –I70), lung cancer (ICD-9162/ICD-10 C33, C34), and respiratory diseases (ICD-9460–519/ICD-10 J00 – J99).	Cox proportional hazards	NO ₂
SALIA		r ² = 0.88	Overall		Adjusted for: Age, socioeconomic status, BMI, current smoking, former smoking and second-hand smoking	HR (95% CI) ^b
N = 2,527		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 20.7 (38.9 µg/m ³)			CPD Mortality - Direct Effect, FEV ₁ as Mediator: 1.333 (1.011, 1.759)
Ruhr, Germany			Median = 18.8 (IQR 8.88) (35.4 µg/m ³ (IQR 16.7 µg/m ³))			CPD Mortality - Indirect Effect, FEV ₁ as Mediator: 1.040 (1.002, 1.079)
Enrollment: 1985-1994		Exposure years: 2003-2009	P25 = 15.8 (29.8 µg/m ³)			CPD Mortality - Total Effect, FEV ₁ as Mediator: 1.386 (1.051, 1.828)
Follow-up: 2008			P75 = 24.7 (46.5 µg/m ³)			NO _x
Cohort			Overall			
			Mean = 71			
			Median = 57.3 (IQR 46)			
			P25 = 46			
			P75 = 92			

						HR (95% CI) ^c CPD Mortality - Direct Effect, FEV ₁ as Mediator: 1.306 (0.977, 1.589) CPD Mortality - Indirect Effect, FEV ₁ as Mediator: 1.027 (1.006, 1.055) CPD Mortality - Total Effect, FEV ₁ as Mediator: 1.340 (1.017, 1.636)
† Eum et al. (2019)	Medicare enrollees aged 65–120-yr living in the conterminous U.S.	AQS Averaging time: NO ₂ - 12-month MA Exposure years: 2000–2008	NO ₂ (ppb) Median = 14.23 P25 = 9.69 P75 = 18.63	National Death Index	Poisson Adjusted for: Age, gender, race, and state of residence	RR (95% CI) ^b CVD Mortality: 1.133 (1.130, 1.137) CVD Mortality - 1-yr MA: 1.138 (1.135, 1.142) CVD Mortality - 2-yr MA: 1.135 (1.132, 1.139) CVD Mortality - 3-yr MA: 1.131 (1.128, 1.135) CVD Mortality - 4-yr MA: 1.125 (1.122, 1.129) CVD Mortality - 5-yr MA: 1.119 (1.121, 1.117) CBVD Mortality: 1.092 (1.085, 1.100) IHD Mortality: 1.221 (1.217, 1.226) CHF Mortality: 0.903 (0.893, 0.914)
Medicare n = 14,100,000 Nationwide, U.S. Enrollment: December 2000–December 2008 Follow-up: December 2000–December 2008 Cohort						

† Eum et al. (2022)	Open cohort of Medicare beneficiaries aged ≥65-yrs residing in the conterminous U.S. between 2001 and 2008.	LUR Model performance was lower in rural ($r^2 = 0.69$) as compared to urban ($r^2 = 0.80$) areas, suggesting greater exposure error for rural ZIP codes Averaging time: NO ₂ - 12-mo MA Exposure years: 2000–2008	NO ₂ (ppb) Mean = 10.9 ± 6.44 Median = 9.14 (IQR 7.85) Min = 1.03 Max = 47.04 P25 = 6.16 P75 = 13.98	National Death Index	Poisson Adjusted for: Age, gender, race, and state of residence	RR (95% CI) ^b CVD Mortality: 1.23 (1.22, 1.24) CBVD Mortality: 1.25 (1.22, 1.28) IHD Mortality: 1.26 (1.23, 1.29) CHF Mortality: 1.16 (1.12, 1.21)
Medicare n = 49,712,702 Nationwide, U.S. Enrollment: 2001–2008 Follow-up: 2001–2008 Cohort						
† Gariazzo et al. (2021)	Aged ≥30-yrs and resided in same address for ≥5-yrs before enrollment	CTM, Ensemble machine learning model, Dispersion model CTM $r^2 = 0.49$ Ensemble machine learning 10-fold CV- $r^2 = 0.62$ Dispersion $r^2 = 0.44$ Averaging time: NO ₂ - annual average	NO ₂ (ppb) CTM: 1 km resolution Mean = 15.5 ± 2 (29.2 ± 3.7 $\mu\text{g}/\text{m}^3$) Median = 15.5 (IQR 19.1) (29.2 $\mu\text{g}/\text{m}^3$ (IQR 35.9 $\mu\text{g}/\text{m}^3$)) Min = 8.34 (15.7 $\mu\text{g}/\text{m}^3$) Max = 19.1 (35.9 $\mu\text{g}/\text{m}^3$) P5 = 12 (22 $\mu\text{g}/\text{m}^3$) P25 = 14.2 (26.7 $\mu\text{g}/\text{m}^3$) P75 = 16.9 (31.8 $\mu\text{g}/\text{m}^3$) P95 = 19 (35.7 $\mu\text{g}/\text{m}^3$) Dispersion: 4 m resolution Mean = 23.2 ± 7.17 (43.6 ± 13.5)	Rome Municipal Register	Cox proportional hazards Adjusted for: Sex, marital status, place of birth, education, occupation, area-based socioeconomic position	HR (95% CI) ^b CVD Mortality CTM 1 km: 1.084 (1.051, 1.118) Dispersion 200 m: 1.025 (1.013, 1.036) Ensemble 200 m: 1.015 (1.004, 1.027)
Rome Longitudinal Study n = 482,259 Rome, Italy Enrollment: 2001 Follow-up: 2015 Cohort						

	Exposure years: 2015	$\mu\text{g}/\text{m}^3$ Median = 22.3 (IQR 8.88) (41.9 $\mu\text{g}/\text{m}^3$ (IQR 16.7 $\mu\text{g}/\text{m}^3$)) Min = 5.2 (9.8 $\mu\text{g}/\text{m}^3$) Max = 108.7 (204.5 $\mu\text{g}/\text{m}^3$) P5 = 13.6 (25.5 $\mu\text{g}/\text{m}^3$) P25 = 18.1 (34.1 $\mu\text{g}/\text{m}^3$) P75 = 27.1 (50.9 $\mu\text{g}/\text{m}^3$) P95 = 35.7 (67.2 $\mu\text{g}/\text{m}^3$) 200m resolution Mean = 22.7$\pm$5.58 (42.8$\pm$10.5 $\mu\text{g}/\text{m}^3$) Median = 22.7 (IQR 7.92) (42.8 $\mu\text{g}/\text{m}^3$ (IQR 14.9 $\mu\text{g}/\text{m}^3$)) Min = 5.9 (11.1 $\mu\text{g}/\text{m}^3$) Max = 45 (84.6 $\mu\text{g}/\text{m}^3$) P5 = 14 (26.3 $\mu\text{g}/\text{m}^3$) P25 = 19 (35 $\mu\text{g}/\text{m}^3$) P75 = 26.5 (49.9 $\mu\text{g}/\text{m}^3$) P95 = 32.4 (60.9 $\mu\text{g}/\text{m}^3$) Ensemble: 200 m resolution Mean = 23.3$\pm$5.2 (43.8$\pm$9.7 $\mu\text{g}/\text{m}^3$) Median = 22.2 (IQR 7.65) (41.7 $\mu\text{g}/\text{m}^3$ (IQR 14.4 $\mu\text{g}/\text{m}^3$)) Min = 10.9 (20.5 $\mu\text{g}/\text{m}^3$) Max = 35.9 (67.6 $\mu\text{g}/\text{m}^3$) P5 = 15.7 (29.6 $\mu\text{g}/\text{m}^3$) P25 = 19.5 (36.6 $\mu\text{g}/\text{m}^3$) P75 = 27.2 (51.1 $\mu\text{g}/\text{m}^3$) P95 = 32.8 (61.7 $\mu\text{g}/\text{m}^3$)				
[†] Hamroun et al. (2024)	Individuals aged $\geq$ 18-yrs with end-stage kidney disease	Spatiotemporal/geospatial model	NO ₂ (ppb)	REIN	Cox proportional hazards	HR (95% CI) ^b CVD Mortality - 1-yr
REIN		Cross-validated	Mean = 7.116 $\pm$ 1.41 (13.39 $\pm$ 2.65 $\mu\text{g}/\text{m}^3$)		Adjusted for: Age, sex,	

n = 90,373	who began maintenance dialysis in France between January 1, 2012–December 31, 2020	against central site monitors in rural, suburban, and urban areas (Pearson r: 0.55–0.70; RMSE: <25% of the annual mean concentration).	Median = 6.893 (12.97 µg/m ³) Min = 4.57 (8.59 µg/m ³) Max = 19.1 (35.93 µg/m ³) P25 = 6.064 (11.41 µg/m ³) P75 = 7.81 (14.7 µg/m ³)		BMI, smoking status, comorbidities, mobility, dialysis care model (including peritoneal dialysis, in-center hemodialysis, self-care/home hemodialysis, and training center), conditions of dialysis initiation (functional dialysis access and emergency start), hemoglobin level (g/dL) and albumin level (g/L), the distance to the nearest dialysis center (km), the municipality population density (inhabitants/km ²), and the social deprivation index (FDep). Stratified by yr (2012–2020) and dialysis center.	lag: 1.1025 (0.9835, 1.2359)
Nationwide, France						
Enrollment: January 2012–December 2020						
Follow-up: December 2022						
Cohort		Averaging time: NO ₂ - annual average Exposure years: 2009–2020				
†Huang et al. (2023)	Participants were randomly selected from small neighborhoods, born prior to January 1, 1975 and lived in the defined area since January 1, 1998	Ensemble machine learning model Averaging time: NO ₂ - annual average Exposure years: 2013–2019	NO ₂ (ppb) 1998 Mean = 20.8 ± 8.56 (39.2 ± 16.1 µg/m ³) 2019 Mean = 23.56 ± 2.7 (44.34 ± 5.1 µg/m ³)	Family report on questionnaire or CDC (ICD-10: A00–R99)	Cox proportional hazards Adjusted for: Age, sex, BMI, level of education, income, occupational exposure, physical exercise and status of marital, smoking, and drinking	HR (95% CI) ^b CVD Mortality: 1.54 (1.44, 1.65)
n = 37,442						
Tianjin, Shenyang, Taiyuan, Rizhao, China						
January 1998–December 2019						
Cohort						

† Hvidtfeldt et al. (2019)	Adults aged 50–64- yrs who lived in the areas of Copenhagen and Aarhus and were born in Denmark, without cancer	Hybrid model Averaging time: NO ₂ - annual average Exposure years: 1979–2015	NO ₂ (ppb) Median = 13 (25 µg/m ³) P5 = 9.51 (17.9 µg/m ³) P95 = 20.9 (39.4 µg/m ³)	Danish Register of Causes of Death	Cox proportional hazards Adjusted for: Age, sex, calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, fruit and vegetable consumption, neighborhood level SES	HR (95% CI) ^b CVD Mortality: 1.22 (1.09, 1.36)
Danish DCH N = 49,564 Copenhagen, Aarhus, Denmark Enrollment: 1993–1997 Follow-up: through 2015 Cohort						
† Kang et al. (2023)	Adults aged ≥40-yrs with a health screening exam and diagnosed with COPD during January 1, 2009–December 31, 2009, who did not die in 2009	Spatiotemporal/geospatial model 10-fold cross-validation (r ² of NO ₂ in 2009 was 0.50). Averaging time: NO ₂ - annual average Exposure years: January 1, 2009 - December 31, 2013	NO ₂ (ppb) 1-year Median = 19.6 (36.9 µg/m ³) P25 = 16 (30 µg/m ³) P75 = 25.6 (48.2 µg/m ³) 3-year Median = 19.9 (37.5 µg/m ³) P25 = 16.2 (30.4 µg/m ³) P75 = 26.5 (49.8 µg/m ³) 5-year Median = 20.5 (38.5 µg/m ³) P25 = 16.2 (30.5 µg/m ³) P75 = 27.7 (52.1 µg/m ³)	NHIS-NHID	Cox proportional hazards Adjusted for: Age, sex, income percentile, BMI, smoking status, CCI, presence of exacerbation	HR (95% CI) ^b CVD Mortality, 1-yr: 0.953 (0.900, 1.010) CVD Mortality, 3-yr: 0.950 (0.893, 1.010) CVD Mortality, 5-yr: 0.968 (0.900, 1.041) CBVD Mortality, 1-yr: 0.981 (0.910, 1.058) CBVD Mortality, 3-yr: 0.913 (0.838, 0.995) CBVD Mortality, 5-yr: 0.883 (0.793, 0.983) Hypertension Mortality, 1-yr: 0.978 (0.845, 1.131) Hypertension Mortality, 3-yr: 0.983 (0.837, 1.155) Hypertension Mortality, 5-yr: 1.046 (0.862, 1.269)
Korean NHID n = 121,423 South Korea Enrollment: January 2009–December 2009 Follow-up: January 2010–December 2018 Cohort						

† Klompemaker et al. (2020)	Dutch citizens aged ≥19-years	LUR	NO ₂ (ppb)	Dutch longitudinal mortality database	Cox proportional hazards	HR (95% CI) ^b Circulatory Disease Mortality: 0.93 (0.84, 1.03)
PHM		Averaging time: NO ₂ - annual average	Complete case population Median = 12.27 (IQR 4.01) (23.08 µg/m ³ (IQR 7.54 µg/m ³))		Adjusted for: Sex, marital status, region of origin, education, paid occupation, household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses alcohol, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region, percentage of immigrants region	
full (imputed) population n = 339,633		Exposure years: 2013	Full population Median = 12.23 (IQR 4.04) (23.01 µg/m ³ (IQR 7.61 µg/m ³))			
complete case population n = 244,814						
Netherlands						
Enrollment: September–November 2012						
Follow-up: 2013–2017						
Cohort						
† Klompemaker et al. (2021c)	Dutch citizens aged ≥30-yrs	Avg of Europe-wide LUR, LUR, and Dispersion model	NO ₂ (ppb)	Dutch longitudinal mortality database	Cox proportional hazards	HR (95% CI) ^b Circulatory Disease Mortality: 1.030 (1.008, 1.052)
Dutch national administrative cohort		Averaging time: NO ₂ - annual average	Median = 14 (IQR 4.4) (26.3 µg/m ³ (IQR 8.3 µg/m ³))		Adjusted for: Sex, marital status, region of origin, education, paid occupation, household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses alcohol, PC4	
n = 10,481,566		Exposure years: 2010				
Netherlands						

Enrollment: 2009–2011					composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region, percentage of immigrants region	
Follow-up: January 2013–December 2018						
Cohort						
†Klompaker et al. (2021b)	Dutch citizens aged ≥29-yrs	Europe-wide LUR, LUR, and Dispersion model	NO ₂ (ppb)	Dutch longitudinal mortality database	Cox proportional hazards	HR (95% CI) ^b CVD Mortality
Dutch administrative cohort		LUR: Explained variance for 86% NO ₂	LUR Median = 14.8 (IQR 4.8) (23 µg/m ³ (IQR 9 µg/m ³))		Adjusted for: Age, strata (sex), random (neighborhood), standardized household income, region of origin, marital status, socio-economic composite score region, mean income per income recipient region, unemployment rate region, percentage non-western immigrants region, and the difference between neighborhood and region of mean income, unemployment rate, non-western immigrants and the composite SES score	Europe-Wide LUR: 1.032 (1.006, 1.059) LUR: 0.970 (0.944, 0.997) Dispersion: 1.000 (0.977, 1.024)
N = 10,532,360		Hybrid: Explained variance for 59% NO ₂	Dispersion Median = 14.8 (IQR 4.3) (23 µg/m ³ (IQR 8 µg/m ³))			
The Netherlands		Averaging time: NO ₂ - annual average	Hybrid Median = 16.7 (IQR 4.8) (31.5 µg/m ³ (IQR 9 µg/m ³))			
Enrollment: January 2008		Exposure years: 2007–2010	Concentrations were estimated from figure			
Follow-up: through December 2012						
Cohort						
†Lefler et al. (2019)	Adults aged 18–84- yrs	LUR	NO ₂ (ppb)	NHIS	Cox proportional hazards	HR (95% CI) ^b CPD Mortality: 1.062 (1.038, 1.086)
NHIS		Averaging time:	17-yr average (1999–2015)			

N = 635,539		NO ₂ - annual average	Mean = 10.69 ± 5.73 IQR = 6.72		Adjusted for: Age, sex, and race-ethnicity by allowing each combination of age (in one-yr increments), sex, and race-ethnicity (Hispanic, non-Hispanic Black, non-Hispanic white, other or unknown)	
Nationwide, U.S.		Exposure years: 1979–2015				
Enrollment: 1987–2014						
Follow-up: through 2015						
Cohort						
†Li et al. (2023)	Adults aged 40–69- yrs who were registered with the UK NHS and living near 1 of 22 study centers across England, Scotland, and Wales, without CVD or cancer	LUR	NO ₂ (ppb)	UK NHS	Cox proportional hazards	NO ₂
UK Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Decedents Mean = 15.77 ± 4.8 (29.67 ± 9.04 µg/m ³)		Adjusted for: Sex, ethnicity, assessment center, education, alcohol consumption status, smoking status, BMI, average total household income, physical activity, prevalent diabetes, prevalent hypertension	HR (95% CI) ^b CVD Mortality: 1.28 (1.20, 1.37)
N = 400,259		Exposure years: 2005–2007, 2010	Survivors Mean = 15.56 ± 4.92 (29.28 ± 9.26 µg/m ³)			NO _x
England, Scotland, Wales, U.K.			Total Mean = 15.6 ± 4.92 (29.3 ± 9.25 µg/m ³)			HR (95% CI) ^c CVD Mortality: 1.05 (1.04, 1.07)
Enrollment: 2006–2010						
Follow-up: through February 2020						
Cohort			NO _x (µg/m ³)			
			Decedents Mean = 45.18 ± 16.22			
			Survivors Mean = 43.94 ± 15.58			
			Total Mean = 44.01 ± 15.62			
†Lim et al. (2019)	Members of AARP aged 50–71-yrs who	Hybrid model	NO ₂ (ppb)	Death records	Cox proportional hazards	HR (95% CI) ^b IHD Mortality: 1.09 (1.06, 1.13)
NIH-AARP Diet and		Method validation	Mean = 11.1 ± 5.6			

Health Study	responded to a mailed questionnaire	NR	Min = 1.5 Max = 31.7		Adjusted for: Age, sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at individual level; and for median income and percentage with high school education at census-tract level	Cardiac Arrest, HF: 1.02 (0.97, 1.08) CVD Mortality: 1.07 (1.05, 1.10) CBVD Mortality: 1.02 (0.96, 1.08)
N = 566,398 n = 548,780 (96.9% of cohort)		Averaging time: NO ₂ - annual average				
California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Atlanta, GA; Detroit, MI, U.S.		Exposure years: 1990–2012				
Enrollment: 1995–1996						
Follow-up: through December 2011						
Cohort						
†Paul et al. (2020)	Ontario residents who were Canadian born, had lived in Ontario at least 5-yr before cohort inception, were between 35–85- yrs of age, had record of birth date and sex, and were registered with provincial health insurance at enrollment. For mortality	LUR	NO ₂ (ppb)	ONPHEC	Cox proportional hazards	HR (95% CI) ^b CVD Mortality: 1.038 (1.015, 1.062)
ONPHEC		Model was validated against NAPS ground monitor measurements in 2006 ($r^2 = 0.73$)	Cardiovascular Deaths IQR = 13.4 Min = 2.3 Max = 54.3		Adjusted for: Age, sex, region classification, area-level SES, and healthcare access. Stratified by Greater Toronto Area residence.	
N = 4,774,984						
Ontario, Canada			Cohort with Prevalent Diabetes IQR = 14.2 Min = 2.3 Max = 58.3			
Enrollment: January 2001		Averaging time: NO ₂ - 3-yr MA				
Follow-up: through December 2015		Exposure years: 2006				
Cohort			Cohort without Diabetes IQR = 13.8 Min = 2.7 Max = 71.4			

	analyses, the cohort was restricted to those with diabetes diagnoses before January 1, 2001.		Diabetes Deaths IQR = 13.2 Min = 2.3 Max = 52.4 Incident Diabetes Cases IQR = 14.2 Min = 2.7 Max = 71.4			
† Raaschou-Nielsen et al. (2020) n = 4,401,348 Denmark Enrollment: April 1968 Follow-up: January 1991–December 2015 Case-Control	All persons who have lived in Denmark at one point in time since April 2, 1968, who were born between 1921 and 1985, and aged 30–85-yrs.	CTM Averaging time: NO ₂ - time-weighted average Exposure years: 1991-2015	NO ₂ (ppb) Cases Mean = 9.51 (17.9 µg/m ³) Median = 8.98 (IQR 5) (16.9 µg/m ³ (IQR 9.5 µg/m ³)) Min = 2.5 (4.7 µg/m ³) Max = 38.8 (73.1 µg/m ³) P5 = 4.7 (8.9 µg/m ³) P25 = 6.86 (12.9 µg/m ³) P75 = 11.9 (22.4 µg/m ³) P95 = 15.5 (29.1 µg/m ³) P99 = 17.4 (32.7 µg/m ³) Controls Mean = 9.3 (17.5 µg/m ³) Median = 8.77 (IQR 4.9) (16.5 µg/m ³ (IQR 9.2 µg/m ³)) Min = 2.5 (4.7 µg/m ³) Max = 44.8 (84.3 µg/m ³) P5 = 4.7 (8.8 µg/m ³) P25 = 6.75 (12.7 µg/m ³) P75 = 11.6 (21.9 µg/m ³) P95 = 15.3 (28.7 µg/m ³) P99 = 17.2 (32.3 µg/m ³)	Danish Civil Registration system	Logistic Adjusted for: Age, sex, calendar time, marital status, educational level, occupational status, income, country of origin, number of children, car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent households, immigrants, and criminal records	IRR (95% CI) ^b CVD Mortality: 1.00 (0.97, 1.03)
† So et al. (2020) DNC	Female nurses (aged >44-yrs) of the Danish Nurse	Hybrid model Averaging time: NO ₂ - 3-yr MA; 1-yr	NO ₂ (ppb) Cohort Baseline (1993 or 1999)	Danish Register of Causes of Death	Cox proportional hazards Adjusted for: Age,	HR (95% CI) ^b CVD Mortality: 0.95 (0.81, 1.11) CVD Mortality, <20

N = 24,541	Organization who could be linked to the Danish Civil Registration System	lag	Mean = 7.12 (13.4 µg/m ³)		BMI, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy	µg/m ³ : 1.11 (0.78, 1.56) Hypertension Mortality: 1.05 (0.67, 1.65) IHD Mortality: 0.81 (0.60, 1.08) Stroke Mortality: 0.95 (0.70, 1.28) Other CVD Mortality: 1.13 (0.84, 1.54)
Denmark		Exposure years: 1990-2012				
Enrollment: 1993 and 1999						
Follow-up: through December 2013						
Cohort						
†So et al. (2022)	General population adults ≥30-yrs	LUR, CTM	NO ₂ (ppb)	Danish Register of Causes of Death	Cox proportional hazards	HR (95% CI) ^b CVD Mortality: 1.08 (1.06, 1.10) CVD Mortality, TVE: 1.02 (1.00, 1.04) CVD Mortality, <20 µg/m ³ : 1.34 (1.29, 1.40) IHD Mortality: 1.08 (1.05, 1.11) IHD Mortality, TVE: 0.98 (0.96, 1.00) IHD Mortality, <20 µg/m ³ : 1.43 (1.35, 1.52) Stroke Mortality: 1.04 (1.00, 1.08) Stroke Mortality, TVE: 0.98 (0.96, 1.00) Stroke Mortality, <20 µg/m ³ : 1.39 (1.30, 1.48)
Danish Administrative Cohort		r ² = 0.58	Mean = 10.8 ± 4.22 (20.3 ± 7.94 µg/m ³) IQR = 5.47 (10.3 µg/m ³) Min = 2 (3.7 µg/m ³) Max = 38.4 (72.2 µg/m ³) P5 = 5 (9.4 µg/m ³) P25 = 7.76 (14.6 µg/m ³) P75 = 13.2 (24.9 µg/m ³) P95 = 19 (35.7 µg/m ³)		Adjusted for: Age, sex, parish level, household income, occupational status, immigrant status, marital status, highest completed education level, regional mean household income, regional percentage of unemployment, difference of mean household income and percentage of unemployment, between parish and region	
n = 3,083,227		Averaging time: NO ₂ - annual average				
Nationwide, Denmark		Exposure years: 1999–2017				
Enrollment: January 2000						
Follow-up: through December 2017						
Cohort						
†Tao et al. (2024)	Adults aged 40–69- yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England,	LUR	NO ₂ (µg/m ³)	NHS	Cox proportional hazards	HR (95% CI) ^c CVD Mortality: 1.026 (0.994, 1.059)
UK Biobank		Averaging time: NO ₂ - annual average	Advantaged neighborhood Mean = 23.2 Median = 22.87 P5 = 14.77 P25 = 19.42 P75 = 26.76 P95 = 32.23		Adjusted for: age, gender, race, BMI, smoking status, alcohol consumption, healthy diet score, educational level, income level,	
n = 421,650		Exposure years: 2005–2007, 2010				

Nationwide, England	Scotland, and Wales		Disadvantaged neighborhood Mean = 37.87 Median = 35.97 P5 = 25.48 P25 = 31.67 P75 = 43.12 P95 = 55.8		neighborhood environment	
Enrollment: 2006–2010						
Follow-up: through September 2021						
Cohort			Intermediate neighborhood Mean = 28.47 Median = 28.01 P5 = 16.73 P25 = 23.73 P75 = 32.6 P95 = 41.07			
†Turner et al. (2016)	Adults aged ≥30-yrs with a family member aged ≥45- yrs	LUR	NO ₂ (ppb)	ICD 9 code 390-459, 250; ICD 10 code I00-I99, E10-E14	Cox proportional hazards	HR (95% CI) ^b
CPS-II		r ² = 0.78	Mean = 11.6 ± 5.1 Median = 10.8 (IQR 6)			Circulatory Disease Mortality:
n = 669,046		Averaging time: NO ₂ - annual average	Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P95 = 21.2		Adjusted for: Age, race, sex stratified and adjusted for education; marital status; BMI; BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking <18-years; passive smoking; vegetable, fruit, fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index, 1990 ecological covariates: median	1.08 (1.07, 1.10)
U.S.				ICD 9 code 420-429; ICD 10 code I30-I51		Dysrhythmias, HF, Cardiac Arrest: 1.02 (0.98, 1.06)
Enrollment: 1982		Exposure years: 2006		ICD 9 code 430-438; ICD 10 code I60-I69		CBVD Mortality: 0.99 (0.96, 1.03)
Follow-up: through 2004				ICD 9 code 410-440; ICD 10 code I20-I25, I30-I51, I60-I69, I70		CVD Mortality: 1.08 (1.06, 1.10)
Cohort				ICD 9 code 410-414; ICD 10 code I20-I25		IHD Mortality: 1.14 (1.11, 1.17)

					household income, and percent African American, Hispanic, post-secondary education, unemployment, and poverty	
†Wang et al. (2022)	Adults aged 40–69- yrs who were registered with the UK NHS and living near 1 of 22 study centers across England, Scotland, and Wales, without cancer or CVD	LUR	NO ₂ (ppb)	NHS	Cox proportional hazards	NO ₂
UK Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Overall Mean = 15.5 ± 4.9 (29.2 ± 9.2 µg/m ³)		Adjusted for: Age, sex, race, assessment center, TDI, alcohol consumption status, smoking status, BMI, physical activity, healthy diet score, diabetes, hypertension	HR (95% CI) ^b CVD Mortality: 1.08 (0.95, 1.22) CHD Mortality: 1.16 (0.97, 1.37) Stroke Mortality: 0.94 (0.71, 1.25)
N = 386,937		Exposure years: 2005–2007, 2010	NO _x (µg/m ³)			NO _x
England, Scotland, Wales, U.K.			Overall Mean = 43.8 ± 15.5			
Enrollment: 2006–2010						
Follow-up: through 2018						
Cohort						HR (95% CI) ^c CVD Mortality: 1.03 (1.00, 1.05) CHD Mortality: 1.04 (1.00, 1.08) Stroke Mortality: 0.96 (0.89, 1.03)
†Weichenthal et al. (2017)	Non-institutionalized, non-immigrant Canadian citizens aged 25-90-yrs linked to annual postal code histories and Social Insurance Numbers	LUR	NO ₂ (ppb)	Canadian Mortality Database	Cox proportional hazards	HR (95% CI) ^b CVD Mortality: 1.056 (1.037, 1.075)
CanCHEC		Model validated against 2006 NAPS monitoring data (r ² = 0.73)	Mean = 11.47 Median = 10.31 Max = 64.78 P5 = 3.36 P25 = 6.44 P75 = 15.1 P95 = 24.52		Adjusted for: stratified by age (5-yr categories), sex, airshed, and population center size, adjusted for individual-level covariates (visible minority status, aboriginal status, marital status,	
n = 2,448,500		Averaging time: NO ₂ - 3-yr MA; 1-yr lag				
Nationwide, Canada						
Enrollment: May 2011						
Follow-up: May 2011–December 2011						

Cohort		Exposure years: 1981–2012			educational attainment, income quintile, and labour force status) and neighbourhood-level covariates (percent unemployed (aged ≥25-yrs), percent not graduated from high school (aged ≥25- yrs), percent low-income status within census divisions, and population density (per km ²) within dissemination areas)	
†Yu et al. (2024)	General population in 108 municipalities across the continental U.S.	Fixed site monitor	NO ₂ (ppb)	US National Center for Health Statistics	Poisson	RR (95% CI) ^b
NMMAPS		Averaging time: NO ₂ - annual average	Mean = 30.88 ± 6.65 Median = 20.35 (IQR 7.98) Min = 3.98 Max = 45.4		Adjusted for: City-level population variation, calendar year, spatial unit, and mean summer and winter temperatures	CVD Mortality: 1.074 (1.052, 1.097)
N = 10,794,553						CVD Mortality - 1-yr lag: 1.058 (1.035, 1.082)
Nationwide, U.S.		Exposure years: 1987–2000	P25 = 16.86 P75 = 24.84			CVD Mortality - 2-yr lag: 1.066 (1.042, 1.090)
1987–2000						CVD Mortality - 3-yr lag: 1.021 (0.997, 1.046)
Time-series						
†Zhang et al. (2020)	Non-immigrant residents of Toronto, aged 40–85-yrs on 1 January 2001, living in Toronto for ≥3-yrs without a history of AMI/CHF	LUR	NO ₂ (ppb)	Ontario Registrar General Death Database	Cox proportional hazards	HR (95% CI) ^b
ONPHEC		r ² = 0.69	AMI Cohort			CVD Mortality: 1.153 (1.110, 1.197)
N = 2,457,861		Averaging time: NO ₂ - annual average, Other, NO ₂ - 3-yr MA	Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.2 P25 = 19.1 P75 = 23.2 P95 = 28.3		Adjusted for: Area-level covariates, including income quintile, percentage of recent immigrants, employment, education. Stratified by age and sex.	
Toronto, Canada		Exposure years: 2016	CHF Cohort			
Enrollment: April 1, 1996			Mean = 21.4 ± 3.7			
Follow-up: 2016						

Cohort			Median = 21 (IQR 4.1) P5 = 16.1 P25 = 19 P75 = 23.2 P95 = 28.3 CVD Cohort Mean = 21.4 ± 3.7 Median = 21 (IQR 4.1) P5 = 16.1 P25 = 19 P75 = 23.2 P95 = 28.3			
†Zhang et al. (2021b)	Ontario residents aged ≥30-yrs	LUR	NO ₂ (ppb)	Ontario Registrar General Death Database	Cox proportional hazards	HR (95% CI) ^b
OHS		Model validated against NAPS ground monitor measurements in 2006 ($r^2 = 0.73$)	Baseline Mean = 10.9 ± 5.3 Median = 10 (IQR 7.9) P25 = 6.5 P75 = 14.4		Adjusted for: whether born in Canada, educational level, marital status, household income, BMI, fruit and vegetable intake, smoking, alcohol drinking, physical activity, environmental exposure to tobacco smoke at home and working place, rural/urban, north/south and neighborhood-level socio-economic factors, including percentage of recent immigrants, percentage of population aged ≥15-yrs without employment and percentage of population aged ≥15-	CVD Mortality: 1.370 (1.202, 1.562) CVD Mortality - <17.0 ppb: 1.305 (1.106, 1.540) CVD Mortality - 4-yr MA: 1.424 (1.238, 1.638) CVD Mortality - 3-yr MA: 1.495 (1.288, 1.734) CVD Mortality - <19.5 ppb: 1.357 (1.173, 1.570)
N = 88,615						
Ontario, Canada						
Enrollment: 2009–2013		Averaging time: NO ₂ – 3-, 4-, and 5-yr MA				
Follow-up: through December 31, 2017						
Cohort		Exposure years: 2006				

					yrs with educational level lower than high school, and income quintile	
†Zhu et al. (2024)	Adults aged 40–69- yrs who were registered with the UK NHS and living near 1 of 22 study centers across England, Scotland, and Wales	LUR CV-r ² = 0.87 for NO ₂ ; CV-r ² = 0.88 for NO _x Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2010	NO ₂ (ppb) Mean = 14.17 ± 4.06 (26.66 ± 7.63 µg/m ³) IQR = 5.23 (9.85 µg/m ³) Min = 6.872 (12.93 µg/m ³) Max = 57.658 (108.49 µg/m ³) P25 = 11.37 (21.39 µg/m ³) P75 = 16.6 (31.24 µg/m ³) NO _x (µg/m ³) Mean = 44.02 ± 15.65 IQR = 16.55 Min = 19.74 Max = 265.94 P25 = 34.22 P75 = 50.77	NHS	Cox proportional hazards Adjusted for: Age, sex, race, education level, income, TDI, smoking status, pack-year of smoking, drinking status, drinking consumption, physical activity, MET minutes per week, dietary behaviors	NO ₂ HR (95% CI) ^b CVD Mortality: 1.12 (1.05, 1.19) NO _x HR (95% CI) ^c CVD Mortality: 1.06 (1.03, 1.08)
UK Biobank n = 461,112 England, Scotland, Wales, U.K. Enrollment: 2006–2010 Follow-up: through October 2021 Cohort						

List of abbreviations in alphabetical order: 60YO/IMPROVE = Stockholm 60 y old/IMPROVE Study; AIRCODEN = Danish population-based nationwide cohort; AMI = acute myocardial infarction; AQS = Air Quality System; BMI = body mass index; CanCHEC = Canadian Census Health and Environment Cohort; CBVD = cerebrovascular disease; CHF = congestive heart failure; CCHS = Canadian Community Health Survey; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CFPS = China Family Panel Studies; CHARLS = China Health and Retirement Longitudinal Study; CI = confidence interval; CLHLS = Chinese Longitudinal Healthy Longevity Survey; CMD = cardiometabolic disease; COPD = chronic obstructive pulmonary disease; CPD = cardiopulmonary disease; CPS-II = American Cancer Society Cancer Prevention Study-II; CTM = chemical transport model; CTS = California Teachers Study; CV = cross-validation; CVD = cardiovascular disease; DCH = Danish Diet, Cancer, and Health; DNC = Danish Nurse Cohort; E3N = Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale; EE = effect estimate; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; EPIC-MORGEN = EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands; EPIC-NL = European Prospective Investigation into Cancer and Nutrition in the Netherlands; ESCAPE = European Study of Cohorts for Air Pollution Effects; GRAD = Greek administrative cohort; HF = heart failure; HNR = Heinz Nixdorf Recall study; HR = hazard ratio; hrs = hours; HSC = Harvard Six Cities study; HUBRO = Oslo Health Study; ICD = International Classification of Diseases; IHD = ischemic heart disease; IPW = inverse probability weighting; IQR = interquartile range; IRR = incidence rate ratio; km = kilometer; KORA = Cooperative Health Research in the Region of Augsburg; LUR = land use regression; m = meter; MA = moving average; max = maximum; MET=Metabolic Equivalent Task; MI = myocardial infarction; min = minimum; mo = month; NAPS = National Air Pollution Surveillance program; NHID = National Health Information Database; NHIS = National Health Interview Survey; NHS = National Health Service; NIH-AARP = National Institutes of Health American Association of Retired Persons; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; NLCS = Netherlands Cohort Study on Diet and Cancer; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; NR = not reported; OHS = Ontario Health Study; ONPHEC = Ontario Population Health and Environment Cohort; OR = odds ratio; P = percentile; PHM = Public Health Monitor; ppb = parts per billion; r = correlation coefficient; REIN = Renal Epidemiology and Information Network; RHINE = Respiratory Health in Northern Europe; RMSE = root mean square error; SALIA = Study on the influence of Air pollution on Lung function, Inflammation and Ageing; SALT/TwinGene = Stockholm Screening Across the Lifespan Twin study and TwinGene; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; SDPP = Stockholm Diabetes Prevention Program; SES = socioeconomic status; SIDRIA = Italian Studies of Respiratory Disorders in Childhood and Environment; SIMSAM = Swedish administrative cohort; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; SNC = Swiss National Cohort; TDI = Townsend Deprivation Index; VCMS = Veterans' Cohort Mortality Study; VHM&PP = Austrian Vorarlberg Health Monitoring and Prevention Programme; yr = year.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA

A.5. Reproductive and Developmental Effects

Appendix Table 7-1 Epidemiologic studies of oxides of nitrogen and male reproductive function

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Sperm and Semen Production, Quality, and Function						
† Cai et al. (2023) n = 78,952 semen samples from 33,234 sperm donors China 2014–2020 Cohort	Volunteer semen donors, aged 19–45, who adhered to the 2–7 days criteria of abstinence and had a residential address within the study area to minimize exposure measurement error.	Ensemble machine learning model Averaging time: NO ₂ - annual average Exposure years: 2014–2020	NO ₂ (ppb) Mean = 23.69±0.888 (44.57±1.67 µg/m ³) Median = 23.6 (IQR 8.77) (44.41 µg/m ³) (IQR 16.5 µg/m ³) P25 = 19.2 (36.12 µg/m ³) P75 = 27.97 (52.62 µg/m ³)	The testing of semen parameters adhered to the WHO recommendation s for the examination and processing of human semen	Linear mixed models Adjusted for: age, ethnicity, abstinence period, season, year, and a natural cubic spline function of temperature during exposure period (df = 3)	β (%) (95% CI) ^b Sperm and Semen Production, Quality, and Function - Sperm concentration: -0.0073 (-0.0441, 0.0295) Sperm and Semen Production, Quality, and Function - Sperm concentration: -0.0153 (-0.0568, 0.0262) β (× 106 /mL) (95% CI) ^b Sperm and Semen Production, Quality, and Function - Sperm concentration: -0.0369 (-0.0729, -0.0010) β (× 106) (95% CI) ^b Sperm and Semen Production, Quality, and Function - Sperm count: -0.0043 (-0.0398, 0.0311)
† Nobles et al. (2018) Longitudinal Investigation of Fertility and the Environment (LIFE) Study n = 501 Michigan n = 104 Texas n = 397	Eligibility criteria include being married or in a committed relationship, being age 18 years or older, being able to communicate in English or Spanish and not having physician-	CMAQ Averaging time: NO ₂ - daily concentrations were averaged across a 72-day window and lag days 0–14, 15–29,	NO ₂ (ppb) Median = 7.3 (IQR 4.6) Min = 0.87 Max = 24.7 P25 = 5.3 P75 = 9.9	Thirty-five semen quality parameters were assessed: six general semen quality parameters; seven motility measures; six	GEE Adjusted for: age (continuous), BMI (<25, 25 to <30 and ≥30 kg/m ²), smoking (blood cotinine ≥40.35 vs. <40.35 ng/mL) and season (cold [Oct. 1st–	NO ₂ β (95% CI) ^c Sperm and Semen Production, Quality, and Function - Immature (#): -0.61 (-1.09, -0.14) Sperm and Semen Production, Quality, and Function - Total count

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Texas, Michigan, U.S. 2005–2009 Cohort	diagnosed infertility.	30–44, 45–59, and 60–72 NOx - daily concentrations were averaged across a 72-day window and lag days 0–14, 15–29, 30–44, 45–59, and 60–72 Exposure years: 2005–2009	NOx (ppb) Median = 11.2 (IQR 8.3) Min = 0.96 Max = 49.9 P25 = 7.7 P75 = 16	sperm head measures; 14 morphology measures; two sperm chromatin stability assay measures	March 31st] vs. hot [April 1st–September 30th]).	(millions): -20.64 (-38.76, -2.53) Sperm and Semen Production, Quality, and Function - Sperm head length (μm): 0.03 (0.01, 0.06) NOx β (95% CI) ^c Sperm and Semen Production, Quality, and Function - Immature (#): 0.08 (-0.28, 0.44) Sperm and Semen Production, Quality, and Function - Decreased micro head size (%): -0.09 (-0.20, 0.02) Sperm and Semen Production, Quality, and Function - Immature (#) with SO ₂ , O ₃ , CO, PM ₁₀ , and PM _{2.5} : -0.66 (-1.22, -0.09) Sperm and Semen Production, Quality, and Function - Decreased micro head size (%) with SO ₂ , O ₃ , CO, PM ₁₀ , and PM _{2.5} : -0.24 (-0.41, -0.07)
Other Male Reproductive Function Outcomes						
[†] Barrett et al. (2023) The Infant Development and the Environment Study (TIDES) N = 794 n = 687	Eligibility criteria included being >18 years of age, able to read and write in English, and at <13 wk gestation, as well as planning to deliver in a	Spatiotemporal/geospatial model Averaging time: NO ₂ - two-week Exposure years:	NO ₂ (ppb) Mini-puberty (postnatal months 1–3) Mother of males only	AGD metrics were measured a) ano-penile distance (AGD-AP), the distance from the center of the anus to the	GAM model Adjusted for: Adjusted for center, parity, race/ethnicity, education, maternal age, post-conception age at	β (mm) (95% CI) ^c Other Male Reproductive Outcomes - Male Programming Window: AGD-AP at birth: 0.00 (-0.14, 0.13) Other Male Reproductive Outcomes - Male Programming Window:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
U.S. 2010–2012 Cohort	participating study hospital.	2010–2012	Mean = 10.32±4.9 Median = 9.67 (IQR 6.2) Min = 2.19 Max = 30.42 P25 = 6.82 P75 = 13.02 MPW (gestational weeks 8–14) Mothers of males and females Mean = 9.56±4.43 Median = 8.98 (IQR 6.3) Min = 1.8 Max = 31.37 P25 = 6.06 P75 = 12.36 Mothers of males only Mean = 9.39±4.24 Median = 8.71 (IQR 6.22) Min = 2.41 Max = 24.37 P25 = 5.94 P75 = 12.16	anterior base of the penis; and b) ano-scrotal distance (AGD-AS), the distance from the center of the anus to the base of the scrotum.	AGD exam, weight-for-length/height z-score at AGD exam.	AGD-AS at birth: 0.04 (-0.07, 0.15) Other Male Reproductive Outcomes - Male Programming Window: PW at birth: 0.02 (-0.02, 0.05) Other Male Reproductive Outcomes - Male Programming Window: AGD-AP at age 1: -0.12 (-0.31, 0.07) Other Male Reproductive Outcomes - Male Programming Window: AGD-AS at age 1: 0.03 (-0.13, 0.70) Other Male Reproductive Outcomes - Male Programming Window: PW at age 1: -0.07 (-0.12, -0.02) Other Male Reproductive Outcomes - Mini-Puberty: AGD-AP at age 1: -0.06 (-0.23, 0.12) Other Male Reproductive Outcomes - Mini-Puberty: AGD-AS at age 1: -0.05 (-0.20, 0.11) Other Male Reproductive Outcomes - Mini-Puberty: PW at age 1: -0.04 (-0.08, 0.01)
† Tallon et al. (2017) National Social Life, Health, and Aging Project (NSHAP) n = 412 men with erectile dysfunction (ED) n = 132	A nationally representative probability sample of household-resident older adults ages 57–85 yrs.	AQS Method validation NR Averaging time: NO ₂ - 1–7 year moving averages	NO ₂ (ppb) 1 year IQR = 7.49 2 year IQR = 7.35	ED status was obtained through self-report to the question asking men if “during the last 12 months has there ever been a	Logistic regression Adjusted for: age, geographic region, ethnic group, education, current smoking status, obesity, diabetes, depression, season, and	OR (95% CI) ^b Other male reproductive function - Erectile dysfunction 1-year moving average: 1.14 (0.63, 2.06) Other male reproductive function - Erectile dysfunction 2-year moving average:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
men without ED n = 280			3 year	period of several	median household	1.01 (0.55, 1.87)
U.S.		Exposure years: 2005–2011	IQR = 7.18	months or more	income	Other male reproductive function -
			4 year	when you had		Erectile dysfunction 3-year moving
First wave: July 2005–March 2006			IQR = 7.82	trouble getting		average:
Second wave: August 2010–May 2011			5 year	or maintaining		1.10 (0.61, 1.98)
			IQR = 7.57	an erection?"		Other male reproductive function -
Cohort			6 year			Erectile dysfunction 4-year moving
			IQR = 7.8			average:
			7 year			1.14 (0.63, 2.06)
			IQR = 7.81			Other male reproductive function -
						Erectile dysfunction 5-year moving
						average:
						1.13 (0.63, 2.03)
						Other male reproductive function -
						Erectile dysfunction 6-year moving
						average:
						1.16 (0.65, 2.07)
						Other male reproductive function -
						Erectile dysfunction 7-year moving
						average:
						1.03 (0.58, 1.80)

List of abbreviations in alphabetical order: AGD = anogenital distance; AGD-AP = anogenital distance ano-penile distance; AGD-AS = anogenital distance ano-scrotal distance; AQS = air quality system; BMI = body mass index; CI = confidence interval; CMAQ = Community Multiscale Air Quality; CO = carbon monoxide; df = degrees of freedom; ED = erectile dysfunction; GAM = generalized additive model; GEE = generalized estimating equation; IQR = interquartile range; Max = maximum; Min = minimum; MPW = male programming window; NO₂ = nitrogen dioxide; NOx = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; P25 = 25th percentile; P75 = 75th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; PW = penile width; SO₂ = sulfur dioxide.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 30 ppb change in NOx for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NOx for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NOx for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NOx for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-2 Animal toxicological studies of oxides of nitrogen exposure and reproductive and developmental effects

Study Details and Population	Exposure Details	Endpoints Examined*
Di Giovanni et al. (1994)	Whole body inhalation with room air controls	0 d after exposure (dams)
Rat (Wistar)	1,500 ppb (1.5 ppm) NO ₂ , continuous for 20 d	- Maternal weight gain (NS) - Pregnancy length (NS) - Litter size at birth (NS) - Number of dams giving birth (NS)
developmental exposure (GD 0 to GD 20), males (pups); 240–280 g, females (dams)	3,000 ppb (3.0 ppm) NO ₂ , continuous for 20 d	PND 1, 11, and 21 after exposure (male pups)
n = 6–7/group		Weight gain (NS)
		PND 21 after exposure (male pups)
		Postnatal mortality (NS)
Gooch et al. (1977)	Unspecified inhalation conditions with filtered air controls	56 d after exposure
Mouse (C3H)		Spermatocyte chromosomal damage (NS)
males (weight/age not reported)	100 ppb (0.1 ppm) NO ₂ for 6 hr	
number of animals not reported	1,000 ppb (1 ppm) NO ₂ for 6 hr	
	5,000 ppb (5 ppm) NO ₂ for 6 hr	
Kripke and Sherwin (1984)	Whole body inhalation with filtered air controls	0 d after exposure
Rat (LEW/f mai)		Testicular histology (NS)
157.3g, males	1,000 ppb (1 ppm) NO ₂ , 7 hr/d for 5/d wk for 21 d	
n = 6/group		
Shalamberidze and Tsereteli (1971)	Unspecified inhalation conditions with unspecified controls	0 d after exposure (dams)
Rat (albino)		- Ovarian histopathology (decreased primordial follicles; sporadic mild cellular degenerative phenomena) - Uterine histopathology (depleted glandular epithelium;

Study Details and Population	Exposure Details	Endpoints Examined*
pregestational exposure (GD -90 to GD 0), males and females (pups); 165–185 g, females (dams) n = 7–10/group	67 ppb (0.067 ppm) NO ₂ , 12 hr/d for 3 mo 1,250 ppb (1.25 ppm) NO ₂ , 12 hr/d for 3 mo	sporadic mild cellular degenerative phenomena) 21 d after exposure (dams) - Litter size (↓) - Pregnancy rate (NS) 21 d after exposure (pups) - Birth weight (↓) 25 d, 29 d, 33 d after exposure (pups) - Offspring body weight (↓) During exposure (1 mo, 2 mo); 0 d, 3 mo, 7 mo after exposure (Dams) - Duration of estrus (↑) - Estrous cycle duration (↑) - Number of cycles per month (↓) - Number of normal cycles (↓)
Tabacova et al. (1985) Rat (Wistar) developmental exposure (GD 0 to GD 21), males and females n = 20/group	Whole body inhalation with filtered air controls 26.6 ppb (0.05 mg/m ³) NO ₂ , 6 hr/d for 21 d 53.2 ppb (0.1 mg/m ³) NO ₂ , 6 hr/d for 21 d 532 ppb (1 mg/m ³) NO ₂ , 6 hr/d for 21 d 5320 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 21 d	PND 1, 4, 7, 21, 30, and 60 after exposure - Offspring body weight (↓) PND 1, 4, 7, and 21 after exposure - Offspring viability (↓) PND 10, 11, 12, 13, and 14 after exposure - Incisor eruption (↓) PND 14, 15, 16, and 17 after exposure - Eye opening (↓)
†Li et al. (2022) Mouse (C57BL/6J) developmental exposure (GD 0 to PND 0), males and females (pups); 9–12 wk, females (dams) n = 30–32/group	Whole body inhalation with room air controls 2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	PND 0 after exposure - Gestation duration (NS) - Litter size (NS) - Sex ratio (NS)
†Yan et al. (2020)	Whole body inhalation with room air controls	PND 0 after exposure (dams) Pregnancy rate (NS)

Study Details and Population	Exposure Details	Endpoints Examined*
Mouse (C57BL/6) developmental exposure (GD 0 to PND 0), males and females (pups); 9–10 wk, females (dams) n = 34–54/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	- Gestation length (NS) - Litter size (NS) PND 0 after exposure (pups) - Sex ratio (NS) PND 1 after exposure (pups) - Offspring body weight (↓) Timing Unclear (pups) - Offspring mortality (NS)
† Yue et al. (2017)	Whole body inhalation with room air controls	PND 0 after exposure (dams) - Delivery rate (NS) - Litter size (NS) Timing Unclear (pups) - Offspring mortality (NS)
Mouse (BALB/c) developmental exposure (GD 0 to PND 0), males and females (pups); 9–10 wk, females (dams) n = 39–51/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	- Litter size (NS) - Pregnancy rate (NS) Timing Unclear (pups) - Offspring mortality (NS)
† Yue et al. (2018)	Whole body inhalation with room air controls	PND 0 after exposure (dams) - Litter size (NS) - Pregnancy rate (NS) Timing Unclear (pups) - Offspring mortality (NS)
Mouse (BALB/c) developmental exposure (GD 0 to PND 0), male and female pups n = 10–11/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 21 d	- Litter size (NS) - Pregnancy rate (NS) Timing Unclear (pups) - Offspring mortality (NS)
† Zhu et al. (2022)	Whole body inhalation with filtered air controls	0 d after exposure - Placenta fibrosis percentage (↑) - Placental calcification (↑) - Placental telomere length (↓)
Mouse (C57BL/6) developmental exposure (GD 0 to GD 13.5; GD 0 to GD 15.5; GD 0 to GD 18.5), females n = 3/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 13.5 d 2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 15.5 d 2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 18.5 d	- Placenta fibrosis percentage (↑) - Placental calcification (↑) - Placental telomere length (↓)

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease

List of abbreviations in alphabetical order: d = day; GD = gestational day; hr = hour; mo = month; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week

†Studies published since the 2016 Oxides of Nitrogen ISA

Appendix Table 7-3 Epidemiologic studies of oxides of nitrogen and female reproductive function

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Female Fertility						
Legro et al. (2010)	Female patients undergoing IVF from three centers: Penn State College of Medicine in Hershey, PA; Shady Grove Fertility in Rockville, MD, and Columbia University College of Physicians and Surgeons in New York, NY	AQS Averaging time: NO ₂ - 24-hour average Exposure years: 2000–2007	NO ₂ (ppb) Average daily concentration from embryo transfer to pregnancy outcome date Mean = 19±6 (0.019±0.006 ppm) Average daily concentration from embryo transfer to pregnancy test (14 days) (patient home) Mean = 19±7 (0.019±0.007 ppm) Average daily concentration from medication start to oocyte retrieval (patient home) Mean = 19±5.8 (0.019±0.0058 ppm)	Live birth	Logistic regression Adjusted for: patient's age, IVF center and the year and season of oocyte retrieval	OR (95% CI) ^b Female Reproductive Function - Fertility and Reproduction - Live birth based on oocyte retrieval to embryo transfer: 0.76 (0.62, 0.92) Female Reproductive Function - Fertility and Reproduction - Live birth based on embryo transfer to pregnancy test (14 days): 0.58 (0.44, 0.75) Female Reproductive Function - Fertility and Reproduction - Live birth based on medication start to oocyte retrieval: 0.64 (0.50, 0.82) Female Reproductive Function - Fertility and Reproduction - Intrauterine pregnancy: 0.71 (0.58, 0.86) Female Reproductive Function - Fertility and Reproduction - Live birth: 0.74 (0.60, 0.91) Female Reproductive Function - Fertility and Reproduction - Live birth based on embryo transfer to date of live birth: 0.58 (0.32, 1.05) Female Reproductive Function - Fertility and Reproduction - Pregnancy:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Average daily concentration from oocyte retrieval (patient home) Mean = 19±7 (0.019±0.007 ppm) Average daily concentration from oocyte retrieval to embryo transfer (IVF clinic) Mean = 18±4 (0.018±0.004 ppm) Daily concentration on the date of retrieval (IVF clinic) Mean = 19±8 (0.019±0.008 ppm)			0.74 (0.61, 0.90)
Slama et al. (2013) n = 1,916 Teplice District, Czech Republic Enrollment: April 2, 1994–March 31, 1999	Mothers in the Teplice District	Central site monitor Averaging time: NO ₂ - Month Exposure years: January 1994 – Onwards	NO ₂ (µg/m ³) Median = 35.9 (IQR 9.4) P25 = 31 P75 = 40.4	Pregnancy eventually ending in a live birth	Binomial regression model Adjusted for: maternal smoking, body mass index, maternal age at the start of the period of unprotected intercourse, education, marital status, parity (primiparous, yes/no), and	Fecundability ratio (FR) (95% CI) ^c Female Reproductive Function - Live birth, lag 1: 0.80 (0.71, 0.92) Female Reproductive Function - Live birth, lag 2: 0.90 (0.77, 1.04) Female Reproductive Function -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort					respiratory epidemic in previous month, year of the start of the period of unprotected intercourse (three categories)	Live birth, months1–2: 0.81 (0.69, 0.94) Female Reproductive Function - Live birth, month post outcome: 0.99 (0.84, 1.14)
† Ha et al. (2017) Longitudinal Investigation of Fertility and the Environment (LIFE) Study n = 343 Texas, Michigan, U.S. 2005–2009 Cohort	Eligible to participate if they met the following criteria: [1] they were married or in a committed relationship, [2] the female partner was aged 18–40 years and the male partner was ≥18 years, [3] they were able to communicate in English or Spanish, [4] they were off contraception for not more than two menstrual cycles before enrollment, [5] neither partner had clinically diagnosed infertility, and [6] the female partner had menstrual cycles between 21 and 42 days and they had received no contraceptive hormonal injections within the previous 12 months.	CMAQ Averaging time: NO ₂ and NO _x - Hourly concentrations were averaged for 2 weeks before ovulation in the pregnancy cycle, the last 2 weeks of pregnancy, and whole pregnancy (estimated from the date of ovulation, as determined by the fertility monitor through loss or birth). Exposure years: 2005–2009	NO ₂ (ppb) Median = 6.2 (IQR 4.8) Min = 1.1 Max = 24.7 P25 = 4.6 P75 = 9.4 NO _x (ppb) Median = 10.8 (IQR 7.5) Min = 1.8 Max = 46 P25 = 8 P75 = 15.6	A pregnancy loss was defined as a subsequent negative urine pregnancy test after a positive test, a clinically confirmed pregnancy loss, or onset of menstruation depending on gestational age.	Cox proportional hazard model Adjusted for: season, study site, maternal age, maternal race, parity condition on gravidity, maternal education, income, early pregnancy caffeine intake, maternal BMI, early pregnancy adherence to multivitamin intake, maternal blood cotinine level, and paternal blood cotinine level	NO ₂ HR (95% CI) ^c Female Reproductive Function - Fertility and Reproduction - Pregnancy Loss: 1.03 (0.98, 1.08) NO _x HR (95% CI) ^c Female Reproductive Function - Fertility and Reproduction - Pregnancy Loss: 0.98 (0.95, 1.02)
† Kioumourtzoglou et al. (2019) Boston n = 68,969 Tel Aviv n = 95,053	Live births; for Boston, pregnancies of women who lived in zip codes whose centroids were within 60 km the	AQS, Dispersion model Averaging time: NO ₂ - weekly averages	NO ₂ (ppb) Boston Mean = 17.9±4.3	Live births based on clinical and administrative databases	Poisson regression with a quasi-likelihood, and fitted distributed lag models Adjusted for: temperature	RR (95% CI) ^c Female Reproductive Function - Fertility and Reproduction - Live births in Boston: 0.87 (0.78, 0.97)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Boston, MA, U.S. and Tel Aviv District, Israel Boston: January 1, 2000–December 31, 2013 Tel Aviv: April 11, 2010–December 22, 2013 Cohort	hospital; for Tel Aviv, live births of women whose home address at the date of birth was in one of the cities that belong to the District of Tel Aviv (as defined by The Israeli Ministry of Health)	Exposure years: Boston: 1999–2013; Tel Aviv: 2009–2013	Median = 17.4 (IQR 6.2) Min = 9 Max = 33.2 P25 = 14.6 P75 = 20.8 Tel Aviv Mean = 16.8±5.8 Median = 16.3 (IQR 9.3) Min = 7.5 Max = 38.1 P25 = 11.6 P75 = 20.9			Female Reproductive Function - Fertility and Reproduction - Live births in Tel Aviv: 0.82 (0.76, 0.90)
†Quraishi et al. (2019) n = 7,463 San Francisco Bay Area, CA, Baltimore, MD, Seattle, WA, Rockville, MD, Chesterbrook, PA, U.S. January 1, 2013 and December 31, 2013 Cohort	Clinics that are a part of Integrated, a network of private fertility clinics across the United States, were recruited.	Hybrid model 0.79–0.89 Averaging time: NO ₂ - annual average Exposure years: 2012–2013	NO ₂ (ppb) Median = 9 (IQR 4.7)	Positive human chorionic gonadotropin (hCG) test (yes/no); hCG test occurs 2 weeks after embryo transfer; high hCG (>25 mIU/mL) indicates pregnancy An ultrasound occurs 5–6 weeks after embryo transfer to confirm a visible gestational sac in the uterus.	Linear regression Adjusted for: age, BMI, race, NSES, clinic location Modified Poisson regression Adjusted for: age, BMI, race, NSES, clinic location	RR (95% CI) ^c Female Reproductive Function - Fertility and Reproduction - IVF Marker: Positive hCG test: 0.99 (0.95, 1.02) Female Reproductive Function - Fertility and Reproduction - IVF Marker: Positive ultrasound: 0.98 (0.93, 1.02) Female Reproductive Function - Fertility and Reproduction - IVF Marker: Live birth: 0.96 (0.91, 1.00) Female Reproductive Function - Fertility and Reproduction - IVF Marker: Negative hCG test: 1.01 (0.96, 1.06) Female Reproductive Function - Fertility and Reproduction - IVF Marker: Negative ultrasound:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				Birth as reported to the National Artificial Reproductive Technology (ART) Surveillance System (NASS)		1.05 (0.92, 1.20) Female Reproductive Function - Fertility and Reproduction - IVF Marker: Pregnancy loss: 1.10 (0.97, 1.23) Female Reproductive Function - Fertility and Reproduction - IVF Marker: Embryo grade good: 0.99 (0.97, 1.01) β (Change in % (percent oocytes fertilized)) (95% CI) ^c Female Reproductive Function - Fertility and Reproduction - IVF Marker: Percent Oocytes Fertilized: -0.04 (-0.074, -0.00)
				Negative hCG test among those who had an embryo transfer		
				Ultrasound confirmed pregnancy not resulting in live birth		
				percent oocytes fertilized was defined as (number fertilized/number inseminated)		
				Embryos were graded as poor, fair, and good according to uniform Society for Assisted Reproductive Technology (SART) guidelines.		
Menstrual and Estrous Cycle						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Giorgis-Allemand et al. (2020) Obseff (the Observatory of fecundity in France) study n = 184 France Recruitment: 2007 Cohort	Women aged 18–44 years who had regular sexual intercourse and did not use any method to avoid pregnancy. Women must have returned the collecting kit, booklet, and provide urinary samples.	Spatiotemporal/geospatial model Averaging time: NO ₂ - 30 days before start of each menstrual cycle, 90 days before the end of the cycle, 1–10 days before the start of the index cycle (approximately corresponding to the luteal phase of the previous menstrual cycle) and in days 11–30 before the start of the index cycle (approximately corresponding to the follicular phase of the previous menstrual cycle). Exposure years: 2007	NO ₂ (µg/m ³) 30-day window Mean = 25.1 Median = 24 P5 = 9 P95 = 44.5	Women received by post a collection kit including paper pH strips that they were requested to impregnate with their first morning urine every other day during a whole menstrual cycle.	Linear regression Adjusted for: adjusted for woman age (<30; 30–34; 35–39; 40–45 years), body mass index (<25, ≥25 kg/m ² , 3 missing values imputed in the lowest category), age at menarche (8–12; 12–18 years, 3 missing values imputed in the higher category), parity (nulliparous/parous), alcohol consumption in the week before inclusion (yes/no), caffeine consumption in the week before inclusion (yes/no), active smoking at inclusion (yes/no), passive smoking at inclusion (yes/no), education level (3 categories) and professional activity (yes/no) Linear regression, mutually adjusted for PM ₁₀ Adjusted for: adjusted for woman age (<30; 30–34; 35–39; 40–45 years), body mass index (<25, ≥25 kg/m ² , 3 missing values imputed in the lowest category), age at menarche (8–12; 12–18 years, 3	β (Changes in mean duration (day)) (95% CI) ^c Female Reproductive Function - Menstrual and Estrous Cycle - Follicular phase length, 1–30 days before cycle start: 0.74 (0.15, 1.33) Female Reproductive Function - Menstrual and Estrous Cycle - Follicular phase length, 1–10 days before cycle start: 0.81 (0.37, 1.25) Female Reproductive Function - Menstrual and Estrous Cycle - Luteal phase length, 1–10 days before cycle start: 0.16 (-0.22, 0.54) Female Reproductive Function - Menstrual and Estrous Cycle - Luteal phase length, 11–30 days before cycle start: 0.3 (-0.16, 0.76) Female Reproductive Function - Menstrual and Estrous Cycle - Follicular phase length, 11–30 days before cycle start: 0.35 (-0.19, 0.89) Female Reproductive Function - Menstrual and Estrous Cycle - Luteal phase length, 1–30 days before cycle start: 0.28 (-0.19, 0.75) Female Reproductive Function - Menstrual and Estrous Cycle - Total cycle length, 11–30 days before cycle start:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					missing values imputed in the higher category), parity (nulliparous/parous), alcohol consumption in the week before inclusion (yes/no), caffeine consumption in the week before inclusion (yes/no), active smoking at inclusion (yes/no), passive smoking at inclusion (yes/no), education level (3 categories) and professional activity (yes/no)	0.22 (-0.75, 1.19) Female Reproductive Function - Menstrual and Estrous Cycle - Follicular phase length, 1-30 days before cycle start; two-pollutant model with PM ₁₀ : 0.52 (-0.12, 1.16) Female Reproductive Function - Menstrual and Estrous Cycle - Luteal phase length, 1-30 days before cycle start; two-pollutant model with PM ₁₀ : 0.41 (-0.11, 0.93) Female Reproductive Function - Menstrual and Estrous Cycle - Total cycle length, 1-30 days before cycle start; two-pollutant model with PM ₁₀ : 0.52 (-0.62, 1.62) Female Reproductive Function - Menstrual and Estrous Cycle - Total cycle length, 1–10 days before cycle start: 0.71 (-0.05, 1.47) Female Reproductive Function - Menstrual and Estrous Cycle - Total cycle length, 1-30 days before cycle start: 0.53 (-0.48, 1.54)
[†] Lin et al. (2021) Longitudinal Health Insurance Database 2000 (LHID2000) n = 296,078	Participants were selected from Taiwan National Health Insurance Research Database. Exclusion criteria included patients whose residential code was	Spatiotemporal/geospatial model Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average, NO - 24-hour average	NO ₂ (ppb) Mean = 19.3±5.49 Median = 18.9 Min = 2.71 Max = 41.6	ICD-9-CM code 625.3	Cox proportional hazard model Adjusted for: age, monthly income, urbanization level, occupation class, and comorbidities (hypertension,	NO HR (95% CI) ^c Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q2: 1.58 (1.45, 2.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Taiwan 2000–2012 Cohort	missing; patients age missing; patient suffered from dysmenorrhea or withdrew from insurance program before the index date; male patients; and patients <16 or >55.	Exposure years: January 2000–December 2012	NO (ppb) Mean = 8.91±7.93 Median = 5.53 Min = 0.46 Max = 85.3 NO _x (ppb) Mean = 28.2±12.6 Median = 24.8 Min = 4.18 Max = 127		diabetes mellitus, hyperlipidemia, heart disease, COPD, chronic kidney disease, stroke, chronic liver disease and cirrhosis, endometriosis, depression, pelvic inflammatory disease, ovarian cancer, inflammatory bowel disease, intramural fibroids or intracavity fibroids, and pregnancy before index date)	Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q4: 7.13 (6.54, 8.81) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q2: 1.00 (1.00, 1.00) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q1 (Reference): 16.70 (15.40, 18.40) NO ₂ HR (95% CI) ^c Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q2: 1.57 (1.46, 2.17) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q4: 5.33 (4.19, 6.58) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q1 (Reference): 33.1 (30.9, 37.4) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q2: 1.00 (1.00, 1.00) NO _x HR (95% CI) ^c Female Reproductive Function -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Menstrual and Estrous Cycle - Dysmenorrhea - Q2: 2.45 (2.23, 2.89) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q4: 7.53 (7.13, 8.67) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q2: 1.00 (1.00, 1.00) Female Reproductive Function - Menstrual and Estrous Cycle - Dysmenorrhea - Q1 (Reference): 27.90 (21.60, 31.30)
Morphology and Histology of Female Sex Organs						
† Feng et al. (2021) n = 600 Shanxi Province, China January 2013–December 2019 Cohort	Cases with complete medical records of basal demographic characteristics and clinically relevant diagnostic information were selected for consultation, who were aged 21–48 years old. Women with the following conditions were excluded before ovarian reserve assessment: (1) controlled ovarian stimulation (COS) for IVF treatment in this menstrual cycle before ovarian reserve	Central site monitor Averaging time: NO ₂ - monthly concentrations Exposure years: January 2013–December 2019	NO ₂ (µg/m ³) Mean = 37±9 Median = 36 (IQR 13) Min = 23 Max = 64 P25 = 30 P75 = 43	AFC is the sum of antral follicles in the left and right ovaries, which includes all follicles with diameters of 2–9 mm in both ovaries and was evaluated using transvaginal ultrasonography on the second to fourth days during the early follicular phase of spontaneous menstrual bleeding cycle with no COS.	Generalized linear model Adjusted for: age (<30, ≥30 years), BMI (<24, ≥24 kg/m ²), university degree (yes, no), employment (yes, no), parity (yes, no), infertility diagnosis factors (female factor, male factor and unexplained factor)	β (Changes in AFC) (95% CI) ^c Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 1: -0.013 (-0.036, 0.01) Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 2: -0.011 (-0.031, 0.009) Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 3: -0.018 (-0.038, 0.002) Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 1; Co-adjusted for SO ₂ : -0.007 (-0.03, 0.016)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	assessment, (2) women who did not reside in registered residential address affiliated to Shanxi, (3) polycystic ovary syndrome (PCOS), (4) One or both ovaries were difficult to visualize by using transvaginal ultrasonography scanning, (5) hyperprolactinemia, hypothyroidism or immunologic diseases, (6) Ovaries surgical treatment, chemotherapy or radiotherapy, and (7) recurrent pregnancy losses (RPL) at least three times. Women with spontaneous menstrual cycle, normal chromosomal karyotype and no relevant problems as above mentioned were included as the participants.					Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 1; Co-adjusted for CO: -0.013 (-0.036, 0.01) Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 1; Co-adjusted for O ₃ (8-hr): -0.013 (-0.036, 0.01) Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 1; Co-adjusted for PM ₁₀ : -0.008 (-0.037, 0.022) Female Reproductive Function - Morphology and Histology of Female Sex Organs - AFC, Period 1; Co-adjusted for PM _{2.5} : -0.012 (-0.038, 0.014)
Other Female Reproduction Function Outcomes						
[†] Barrett et al. (2023) The Infant Development and the Environment Study (TIDES) N = 794	Eligibility criteria included being >18 years of age, able to read and write in English, and at <13 wk gestation, as well as planning to deliver in a participating study	Spatiotemporal/geospatial model Averaging time: NO ₂ - two-week Exposure years: 2010–	NO ₂ (ppb) Mini-puberty (postnatal months 1–3) Mother of males only	A trained examiner used dial calipers to assess two AGD measures on each child. In females, we measured a) ano-fourchette	GAM model Adjusted for: Adjusted for center, parity, race/ethnicity, education, maternal age, post-conception age at AGD exam, weight-for-	β (mm) (95% CI) ^c Other Female Reproductive Outcomes - Male Programming Window: AGD-AC at birth: 0.05 (-0.05, 0.15) Other Female Reproductive Outcomes - Male Programming

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 687 U.S. 2010–2012 Cohort	hospital.	2012	Mean = 10.32±4.9 Median = 9.67 (IQR 6.2) Min = 2.19 Max = 30.42 P25 = 6.82 P75 = 13.02 MPW (gestational weeks 8–14) Mothers of males and females Mean = 9.56±4.43 Median = 8.98 (IQR 6.3) Min = 1.8 Max = 31.37 P25 = 6.06 P75 = 12.36 Mothers of males only Mean = 9.39±4.24 Median = 8.71 (IQR 6.22) Min = 2.41 Max = 24.37 P25 = 5.94 P75 = 12.16	distance (AGD-AF), the distance from the center of the anus to the posterior fourchette; and b) ano-clitoral distance (AGD-AC), the distance from the center of the anus to the anterior clitoral hood.	length/height z-score at AGD exam.	Window: AGD-AF at birth: 0.03 (-0.05, 0.11)

List of abbreviations in alphabetical order: AFC = antral follicle count; AQS = air quality system; ART = artificial reproductive technology; BMI = body mass index; CI = confidence interval; CMAQ = Community Multiscale Air Quality; CO = carbon monoxide; COS = controlled ovarian stimulation; df = degrees of freedom; FR = fecundability ratio; GAM = generalized additive model; HR = hazard ratio; hCG = human chorionic gonadotropin; ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification; IQR = interquartile range; IVF = *in vitro* fertilization; LUR = land use regression; Max = maximum; Min = minimum; MPW = male programming window; NASS = National Artificial Reproductive Technology Surveillance System (NASS); NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; NSES = neighborhood socioeconomic status; O₃ = ozone; OR = odds ratio; P25 = 25th percentile; P75 = 75th percentile; PCOS = polycystic ovarian syndrome; ppb = parts per billion; ppm = parts per million; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; RPL = recurrent pregnancy losses; RR = rate ratio; SART = Society for Assisted Reproductive Technology; SO₂ = sulfur dioxide.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-4 Epidemiologic studies of oxides of nitrogen and pregnancy outcomes of gestational diabetes mellitus

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Malmqvist et al. (2013)	Women who had singleton deliveries in the county of Scandia from 1999–2005.	Dispersion model	NO _x (µg/m ³)	Diagnosis from EHR	Logistic regression	OR (95% CI) ^b
Swedish Medical Birth Registry	Inclusion was automatic unless otherwise requested, and the study reports that no one requested to be excluded.	Method validation NR	Entire Study Period Mean = 16.4		Adjusted for: gestational diabetes, Type 1 diabetes, smoking, parity, BMI, country of origin, calendar year, and maternal age	GDM: Q1 vs Q1 (ref): 1.00 (1.00, 1.00)
N = 81,110						GDM: Q2 vs Q1: 1.19 (0.99, 1.44)
Scania County, Sweden		Averaging time: NO _x - 1-hour max, Other, NO _x -	Quartile 1 (during first trimester) Mean = 6.8			GDM: Q3 vs Q1: 1.52 (1.28, 1.82)
Singleton Deliveries between 1999–2005		Monthly means NO _x - Trimester means	Quartile 2 (during first trimester) Mean = 11.4			GDM: Q4 vs Q1: 1.69 (1.41, 2.03)
Cohort		Exposure years: 1999–2005	Quartile 3 (during first trimester) Mean = 18.2			
			Quartile 4 (during first trimester) Mean = 29.6			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Hao et al. (2023) Bureau of Epidemiology and Public Health Informatics, Kansas Preterm Birth Cohort n = 596,926 Birthweight Cohort n = 554,787 Gestational Diabetes Cohort n = 449,871 Gestational Hypertension Cohort n = 590,574 Kansas, U.S. Enrollment: 1999–2016 Follow-up: through pregnancy and birth Cohort	Only singleton pregnancies with a gestational age of 27–42 weeks with an estimated date of conception between January 1st, 2000, and December 31st, 2015, were included. We excluded births with (a) missing census tract information; (b) maternal age <10 years or >55 years; (c) birth weight <250 g or >7500 g. For the outcomes of GDM and GH, we also excluded mothers with pre-existing diabetes or pre-existing hypertension.	Spatiotemporal/geospatial model, Ensemble machine learning model Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2000–2016	NO ₂ (ppb) 1 st Trimester Mean = 10.9 2 nd Trimester Mean = 10.88 3 rd Trimester Mean = 11.01 2000–2004 Mean = 12.12 2010–2015 Mean = 10.23 Total Pregnancy Mean = 10.16	GDM: self-reported from birth certificate (excluding mothers with pre-existing diabetes or pre-existing hypertension)	Logistic regression Adjusted for: maternal education level, race, ethnicity, age, marital status, smoking, infant parity, zip code level percent below poverty, census tract level greenness, season of conception, and long-term trend using a natural cubic spline on conception date	OR (95% CI) ^b GDM (First 4 weeks of pregnancy): 1.04 (0.99, 1.10) GDM (First 6 weeks of pregnancy): 1.04 (0.99, 1.10) GDM (1st Trimester): 1.06 (1.00, 1.12) GDM (2nd Trimester): 1.01 (0.96, 1.07) GDM (1st Trimester): Race: white: 1.02 (0.96, 1.09) GDM (1st Trimester): Race: Black: 1.27 (1.03, 1.57) GDM (1st Trimester): Race: Asian: 1.16 (0.90, 1.48) GDM (1 st Trimester): Race: other: 1.13 (0.95, 1.35) GDM (1 st Trimester): Ethnicity: Hispanic: 1.16 (1.05, 1.27) GDM (1 st Trimester): Ethnicity: non-Hispanic: 1.00 (0.94, 1.07) GDM (2 nd Trimester): Race: white: 0.98 (0.92, 1.04) GDM (2 nd Trimester): Race: Black: 1.11 (0.89, 1.40) GDM (2 nd Trimester): Race: Asian: 1.06 (0.81, 1.38) GDM (2 nd Trimester): Race: other: 1.20 (1.00, 1.44) GDM (2 nd Trimester): Ethnicity: Hispanic: 1.09 (0.99, 1.21) GDM (2 nd Trimester): Ethnicity: non-Hispanic:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.98 (0.91, 1.04) GDM (1 st Trimester): Age: ≤27 years: 1.09 (0.98, 1.21) GDM (1 st Trimester): Age: >27 years: 1.05 (0.98, 1.12) GDM (2 nd Trimester): Age: ≤27 years: 0.97 (0.87, 1.08) GDM (2 nd Trimester): Age: >27 years: 1.03 (0.97, 1.10) GDM (1 st Trimester): Zip Code Level Poverty: ≤12%: 1.03 (0.95, 1.12) GDM (1 st Trimester): Zip Code Level Poverty: ≤12%: 1.04 (0.96, 1.12) GDM (2 nd Trimester): Zip Code Level Poverty: >12%: 0.99 (0.91, 1.07) GDM (2 nd Trimester): Zip Code Level Poverty: >12%: 1.00 (0.92, 1.08) GDM (1 st Trimester) co-adjusted for PM _{2.5} and O ₃ : 1.07 (1.01, 1.13) GDM (2 nd Trimester) co-adjusted for PM _{2.5} and O ₃ : 1.02 (0.97, 1.08)
†Miron-Celis et al. (2023) Better Outcomes Registry & Network (BORN) Ontario	Included singleton live births and births with estimated conception dates ranging from 20 weeks (i.e. shortest	Fixed site monitor, Spatiotemporal/geospatial model, LUR	NO ₂ (ppb) Absence of Gestational Diabetes Mean = 11.36±5.4	GDM: cases obtained from the BORN registry. From 2006–2013,	Cox proportional hazards Adjusted for: maternal age, parity, maternal	HR (95% CI) ^b GDM (preconception period): 1.07 (0.88, 1.23) GDM (pregnancy period): 1.00 (0.85, 1.16)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = 1,310,807 Ontario, Canada Births between April 1, 2006–March 31, 2018 Cohort	pregnancy) before the study started to 44 weeks (i.e. longest pregnancy). Pregnancies with postal codes of residence outside Ontario were excluded from the analysis. Subjects with pre-gestational diabetes (Type 1 or Type 2), without a valid health card number, missing date of birth, missing information on the sex of the new-born, postal code value, or mothers who did not have continuous residence in Ontario, Canada for their respective gestational period were excluded.	Method validation NR Averaging time: NO₂ - weekly Exposure years: 2006–2018	Presence of Gestational Diabetes Mean = 13.23±5.59	GDM was diagnosed in Ontario using the 2003 and 2008 Canadian Diabetes Association’s guidelines, while the updated 2013 guidelines were used from 2013 to 2018. The 2003 and 2008 guidelines recommend universal screening for GDM using a 50 g glucose challenge test (GCT) at 24–28 weeks gestation, and when positive (i.e., >7.8 mmol/L), a subsequent 75 g oral glucose tolerance test (OGTT) was needed to confirm the presence of gestational diabetes (positive thresholds: fasting, ≥5.3	smoking status, pre-pregnancy body mass index, weekly ambient temperatures, month of birth, year of birth, residing in the Greater Toronto Area, community size, deprivation quintiles, instability quintiles, dependency quintiles and ethnic quintiles	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				mmol/L; 1 h, ≥ 10.6 mmol/L; 2h, ≥ 8.9 mmol/L). GDM was diagnosed when the results showed ≥ 2 positive OGTT results or a GCT result ≥ 10.3 mmol/L. The updated 2013 guidelines proposed two diagnostic methods to ascertain gestational diabetes. The first method was nearly identical to the 2003/2008 guidelines with only a slight increase in some of the positive threshold values (i.e., 50 g GCT ≥ 11.1 mmol/L and 2 h OGTT ≥ 9.0 mmol/L). The second method was a one-step approach involving only the 75 g OGTT		

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				with the updated positive threshold values.		
† Niu et al. (2023)	Recruited participants from clinical sites that serve low-income populations in Los Angeles, California, if they met the following eligibility criteria: 18 years or older, within 30 weeks of gestation, singleton pregnancy, and speaking English or Spanish fluently. Participants with human immunodeficiency virus, having physical, mental, or cognitive disabilities that would prevent participation, or current incarceration were excluded. Also excluded those with Type 1 or 2 diabetes diagnosed before pregnancy, those reported smoking during pregnancy, and those with missing information on key covariates.	Fixed site monitor Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly NO ₂ - pregnancy Exposure years: 2015–2021	NO ₂ (ppb) Pregnancy Mean = 16.69±2.94	GDM: physician diagnosis abstracted from maternal EMR; identified by reviewing EMR results from glucose challenge test (GCT) and oral glucose tolerance test (OGTT), following the American College of Obstetricians and Gynecologists guidelines 2 [if the GCT glucose level was ≥200 mg/dL 1 h after drinking a 50 g glucose solution, or if the GCT was 140–200 mg/dL but the following OGTT had two or more high glucose levels, defined as ≥95 mg/dL at	DLM w/ robust Poisson regression Adjusted for: year and season of conception, weekly temperature, household income, maternal age, pre-pregnancy body mass index, ethnicity and nativity, parity, and enrollment timepoint robust Poisson regression Adjusted for: maternal age, maternal pre-pregnancy body mass index, maternal ethnicity and nativity, parity, family income, enrollment timepoint, history of GDM, average temperature	RR (95% CI) ^b GDM (-5 wks preconception to 5 wks post-conception): 1.15 (1.14, 1.16) GDM (1-year pre-conception): 0.98 (0.88, 1.10) GDM (-2 wks preconception to 13 wks post-conception): With maternal depression: 1.31 (1.29, 1.33) GDM (1 to 5 wks post-conception): Without maternal depression: 1.14 (1.12, 1.17) GDM (17 wks post-conception): Without maternal depression: 0.91 (0.82, 1.00) GDM (-3 wks preconception to 10 wks post-conception): Maternal age: ≥28: 1.12 (1.11, 1.13) GDM (16 to 24 wks post-conception): Maternal age: ≥28: 0.80 (0.79, 0.82) GDM (-5 wks preconception to 7 wks post-conception): Maternal age: <28: 1.82 (1.77, 1.86) GDM (24 wks post-conception): Maternal age: <28: 2.21 (2.06, 2.36) GDM (-2 wks preconception to 11 wks post-conception): pre-pregnancy BMI: ≥27.5:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				baseline, ≥ 180 mg/dL at 1 h, ≥ 155 mg/dL at 2 h, or ≥ 140 mg/dL at 3 h after drinking a standard 100g glucose solution]; single case self-reported		1.24 (1.22, 1.25) GDM (24 wks post-conception): pre-pregnancy BMI: <27.5 : 0.78 (0.60, 1.00)
†Pedersen et al. (2017c)	Women were only ineligible if they spoke sufficient Danish and intended to carry their pregnancy to term. Excluded women from the original cohort due to multiple pregnancies, abortions, molar or extra-uterine pregnancies, emigration, death or withdrawals of participation in the study and stillborn birth. Women who either reported pre-existing hypertension in the pregnancy interview or had a diagnosis of pre-existing chronic hypertension and/or diabetes before pregnancy were excluded.	Dispersion model Method validation NR Averaging time: NO ₂ - Trimester specific NO ₂ - full pregnancy period Exposure years: 1997–2002	NO ₂ ($\mu\text{g}/\text{m}^3$) Overall Median = 11.5 P5 = 5.8 P95 = 27.4	GDM: WHO criterion GDM: Danish criterion	Logistic regression Adjusted for: maternal age, parity, pre-pregnancy BMI, height, disposable income, education and season of conception	OR (95% CI) ^b GDM, WHO, 1st trimester exposure: 1.24 (1.03, 1.49) GDM, Common Danish, 1st trimester exposure: 0.89 (0.76, 1.03) GDM, WHO: Parity (nulliparous): 1.15 (0.90, 1.47) GDM, WHO: Parity (multiparous): 1.41 (1.08, 1.84) GDM, WHO: Education (low): 0.98 (0.55, 1.74) GDM, WHO: Education (middle): 1.34 (1.05, 1.70) GDM, WHO: Education (high): 1.23 (0.82, 1.52) GDM, Common Danish, 1 st trimester exposure + noise: 0.89 (0.75, 1.06) GDM, WHO, 1 st trimester exposure + noise: 1.22 (0.98, 1.53)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						GDM, WHO: Pre-pregnancy BMI (≥ 18.5 – 25 kg/m^2): 0.96 (0.69, 1.34) GDM, WHO: Pre-pregnancy BMI ($\geq 25 \text{ kg/m}^2$): 1.42 (1.15, 1.76) GDM, WHO, highest quartile vs lowest quartile: 2.07 (1.34, 3.19) GDM, WHO: Road traffic noise low ($< 57.5 \text{ dB}$): 1.10 (0.59, 2.02) GDM, WHO: Road traffic noise high ($\geq 57.5 \text{ dB}$): 1.22 (0.99, 1.50) GDM, WHO: Physical activity (some): 1.22 (0.98, 1.51) GDM, WHO: Physical activity (none): 1.28 (1.05, 1.55)
† Robledo et al. (2015) Consortium of Safe Labor (CSL) singleton pregnancies (n = 219,952) among 201,015 women Los Angeles, CA, Salt Lake City, UT, Indianapolis, IN, Cleveland, OH, Akron, OH, Springfield, MA, Brooklyn, NY,	Electronic Medical records of mothers and infants were obtained for deliveries among women and linked to hospital discharge records. Singleton pregnancies without pregestational diabetes.	CMAQ, Spatiotemporal/geospatial model Averaging time: NO _x hourly averaged across pregnancy exposure windows	NO _x (ppb) 3 months prior to conception Median = 24.27 (IQR 28.55) P25 = 14.5 P75 = 43.05 first trimester Median = 25.18	GDM as reported recorded in the medical record or in discharge records (code 648.8) using ICD-9	Binary regression models with the log link function Adjusted for: maternal age, race, and study site	Relative Risk (95% CI) ^b GDM: Preconception: 1.09 (1.04, 1.13) GDM: 1st trimester: 1.06 (1.01, 1.10) GDM: Normal weight (preconception): 1.02 (1.00, 1.03) GDM: Overweight/obese (preconception): 1.04 (0.97, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Newark, DE, Washington, DC, U.S. 2002–2008 Cohort		Exposure years: 2002–2008	(IQR 30.21) P25 = 14.97 P75 = 45.18			GDM: Normal weight (1st trimester): 1.01 (0.99, 1.10) GDM: Overweight/obese (1st trimester): 1.10 (1.03, 1.18)
† Shen et al. (2017) n = 13,434 (6,717 case and 6,717 controls) Taiwan 2006–2013 Case-Control	All singleton, first-time deliveries for each mother who had more than 1 during the time period. Exclusions for mothers who had a history of diabetes (ICD-9-CM code: 250.xx) or GDM. Controls were randomly selected for each case, by matching case on year and age at diagnosis and free from inpatient or outpatient diagnosis of diabetes.	Fixed site monitor Hourly data from fixed-site air quality monitoring stations (n = 66) between 2005–2013 were averaged to daily mean concentrations. Averaging time: NO ₂ - 24-hour average Exposure years: 2005–2013	NO ₂ (ppb) Exposure distribution concentrations are depicted graphically only (no quantitative estimates available)	GDM: Mother's GDM diagnosis in EHR at discharge	Logistic regression Adjusted for: age at delivery, primipara, monthly income, urbanization, family income, diagnosed comorbidity, Charlson Comorbidity Index, and season of delivery	OR (95% CI) ^b GDM, 12 week period prior to pregnancy: 0.96 (0.90, 1.02) GDM, 1st trimester: 0.93 (0.88, 1.00) GDM, 2nd trimester: 0.97 (0.93, 1.02)
† Sun et al. (2022) Kaiser Permanente Southern California (KPSC) N = 395,927 pregnancies Southern California, U.S. Births between January 1, 2008–December 31, 2018	Included women who gave birth to singleton children. Excluded women who were not KPSC members or with gestational age <20 or >47 weeks, without address data, or with multiple birth. We also excluded pregnancies with preexisting	Fixed site monitor r ² = 0.65–0.75 Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, Other, NO ₂ - monthly	NO ₂ (ppb) GDM Mean = 16.1±4 Non-GDM Mean = 15.6±4.1 Total Births Mean = 15.6±4.1	GDM: routinely screened between 24 and 28 weeks of gestation, with the exception of women at higher risk for GDM who are screened earlier in gestation.	Logistic regression Adjusted for: maternal age, race/ethnicity, education, block group household income, pre-pregnancy BMI, smoking during pregnancy, insurance type, season of conception and year of	OR (95% CI) ^b GDM: Entire pregnancy: 1.18 (1.15, 1.21) GDM: Preconception: 1.12 (1.10, 1.14) GDM: 1st trimester: 1.06 (1.05, 1.08) GDM: 2nd trimester: 1.08 (1.06, 1.10) GDM: Both 1 st and 2 nd trimesters: 1.11 (1.09, 1.13)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort	diabetes, or missing GDM status due to missing lab test results	Exposure years: 2007–2018		Two criteria for GDM testing were used: the Carpenter-Coustan criteria [a 1-hr 50-g glucose challenge test (GCT) >200 mg/dL or two abnormal values for 3-hour 100-g oral glucose tolerance test (OGTT), the cutoff values were fasting ≥95, 1hr ≥180, 2hr ≥155, 3hr ≥140 mg/dl; or the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [one abnormal value for 2-hour 75-g OGTT, the cutoff values were fasting ≥92, 1hr ≥180, 2hr ≥153 mg/dl]	birth; county was fitted as a random effect. Adjusted for: maternal age, race/ethnicity, education, block group household income, pre-pregnancy BMI, smoking during pregnancy, insurance type, season of conception and year of birth; county was fitted as a random effect G-computation Adjusted for: maternal age, race/ethnicity, education, block group household income, pre-pregnancy BMI, smoking during pregnancy, insurance type, season of conception, year of birth and county	GDM (overall mixture effect): 1.10 (1.08, 1.11) GDM: Maternal race/ethnicity: African American (Entire pregnancy): 1.21 (1.09, 1.35) GDM: Maternal race/ethnicity: Asian (Entire pregnancy): 1.02 (0.98, 1.07) GDM: Maternal race/ethnicity: Hispanic (Entire pregnancy): 1.24 (1.20, 1.28) GDM: Maternal race/ethnicity: non-Hispanic white (Entire pregnancy): 1.11 (1.05, 1.17) GDM: Pre-pregnancy BMI: underweight (Entire pregnancy): 0.95 (0.79, 1.15) GDM: Pre-pregnancy BMI: normal (Entire pregnancy): 1.10 (1.05, 1.15) GDM: Pre-pregnancy BMI: overweight (Entire pregnancy): 1.16 (1.11, 1.21) GDM: Pre-pregnancy BMI: obese (Entire pregnancy): 1.24 (1.20, 1.29) GDM: Chronic hypertension: yes (Entire pregnancy): 1.21 (1.10, 1.33) GDM: Chronic hypertension: no (Entire pregnancy): 1.19 (1.16, 1.22)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Wu et al. (2016) California Department of Public Health (CDPH) birth registry N = 4,370,371 pregnancies California, U.S. Births occurring from January 1, 2001–December 31, 2008 Cohort	Excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing	Chemical transport model, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2000–2008	NO ₂ (ppb) Overall Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6	GDM: diagnosed from birth certificates	Logistic regression Adjusted for: race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines	NO ₂ OR (95% CI) ^b GDM, spatial regression models in LA county, 1 st trimester: 1.05 (1.02, 1.09) GDM, exposure empirical Bayesian kriging, 2 nd trimester: 0.94 (0.89, 1.00) GDM, exposure empirical Bayesian kriging, 3 rd trimester: 0.96 (0.92, 1.01) GDM, spatial regression models in LA county, 2 nd trimester: 1.05 (1.00, 1.09) GDM, spatial regression models in LA county, 3 rd trimester: 1.02 (1.00, 1.04) GDM, exposure empirical Bayesian kriging, 1 st trimester: 0.92 (0.88, 0.97) NO _x OR (95% CI) ^b GDM, 1 st trimester: 0.98 (0.97, 1.00) GDM, 2 nd trimester: 0.99 (0.97, 1.00) GDM, 3 rd trimester: 0.99 (0.97, 1.00)
† Yan et al. (2022) Chinese Pregnant Women Cohort Study-Peking Union	Included pregnant women who were (1) at the 5–12 gestational weeks; (2) able to	Chemical transport model r ² = 0.67	NO ₂ (µg/m ³) Entire Pregnancy Gestational Diabetes	GDM: diagnosed according to the WHO 2013	Logistic regression Adjusted for: maternal age, maternal BMI	OR (95% CI) ^b GDM (Entire pregnancy): 1.04 (0.91, 1.20) GDM (Trimester 1):

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Medical College (CPWCS-PUMC)	complete the online questionnaires; (3) permanent residents of the study site; and (4) willing to sign the consent form were eligible to participate. Excluded subjects without information for the gestational outcome, birth outcome, and those delivered after December 31, 2018.	Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - weekly NO ₂ - trimester NO ₂ - entire pregnancy	Mellitus Mean = 37.8±8.1 Gestational Hypertension Mean = 37.5±8.3 No Gestational Diabetes Mellitus Mean = 36.6±7.6 No Gestational Hypertension Mean = 36.7±7.7 No Preeclampsia Mean = 36.7±7.7 Preeclampsia Mean = 37.2±10.1 Total Mean = 36.7±7.7 Trimester 1 Gestational Diabetes Mellitus Mean = 45.2±11.2 Gestational Hypertension Mean = 43.9±11.4 No Gestational Diabetes Mellitus Mean = 43.2±10.9 No Gestational Hypertension Mean = 43.4±11 No Preeclampsia Mean = 43.4±11 Preeclampsia Mean = 41.9±11.7 Total Mean = 43.4±11	criteria. Specifically, a pregnant woman had GDM if she had one or more conditions: the fasting plasma glucose >5.1 mmol/L, one-hour plasma glucose levels >10.0 mmol/L, two-hour glucose level >8.5 mmol/L after overnight fasting with a 75 g glucose load.	before pregnancy, pre-pregnancy hypertension, pre-pregnancy DM, weight gains, newborn's sex, residential region, and season of conception	1.11 (1.01, 1.23) GDM (Trimester 2): 1.02 (0.89, 1.17)
N = 3,754						
Nationwide, China						
Baseline: July 25, 2017						
Follow-up: 2 nd trimester, 3 rd trimester, 6 weeks postpartum		Exposure years: 2013–2018				
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Trimester 2 Gestational Diabetes Mellitus Mean = 35.8±10.7 Gestational Hypertension Mean = 37±11.7 No Gestational Diabetes Mellitus Mean = 34.1±10.1 No Gestational Hypertension Mean = 34.2±10.2 No Preeclampsia Mean = 34.3±10.2 Preeclampsia Mean = 38.5±13.7 Total Mean = 34.3±10.2			
			Trimester 3 Gestational Diabetes Mellitus Mean = 33.4±9.4 Gestational Hypertension Mean = 32.3±9.5 No Gestational Diabetes Mellitus Mean = 33.3±8.9 No Gestational Hypertension Mean = 33.3±9 No Preeclampsia Mean = 33.3±8.9 Preeclampsia			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 31.6±10.7 Total Mean = 33.3±9			

† Zhu et al. (2024)	Singleton births between 20 to 42 gestational weeks with birthweight ≥ 400 g from mothers without pre-pregnancy diabetes as well as residential zip code inside Western New York and estimates on air pollution levels.	Ensemble machine learning model overall cross-validated r^2 for $\text{NO}_2 = 0.788$ Averaging time: NO_2 - monthly Exposure years: 2004–2016	NO_2 (ppb) 1–6m pregnancy Mean = 20.18 ± 7.36 Median = 19.71 (IQR 10.55) Min = 1.13 Max = 43.35 1–3m pregnancy Mean = 20.17 ± 7.84 Median = 19.6 (IQR 11.2) Min = 1.09 Max = 49.33 3m preconception Mean = 20.23 ± 8.03 Median = 19.6 (IQR 11.42) Min = 1.16 Max = 49.33 3m preconception to 6m pregnancy Mean = 20.2 ± 7.13 Median = 19.79 (IQR 10.28) Min = 1.82 Max = 40.55 4–6m pregnancy Mean = 20.2 ± 7.82 Median = 19.62 (IQR 11.08) Min = 1.05 Max = 49.33	GDM: maternal diagnosis from the birth records; routine clinical screening for GDM is recommended for pregnant women at the end of the second trimester (24–28 weeks)	Logistic regression Adjusted for: year of birth, maternal age, race and ethnicity, education, pre-pregnancy body mass index, trimester when prenatal care started, parity, hypertensive disorders of pregnancy, smoking status, Area Deprivation Index 2013, and season of conception	OR (95% CI) ^b GDM (3m preconception): 1.10 (1.06, 1.14) GDM (preconception to 6m of pregnancy): 1.12 (1.08, 1.16) GDM (1–3m of pregnancy): 1.12 (1.08, 1.16) GDM (1–6m of pregnancy): 1.12 (1.08, 1.16) GDM (4–6m of pregnancy): 1.10 (1.06, 1.14) GDM (preconception to 6m of pregnancy): Q1 vs Q1 (ref): 1.00 (1.00, 1.00) GDM (preconception to 6m of pregnancy): Q2 vs Q1: 1.14 (1.07, 1.22) GDM (preconception to 6m of pregnancy): Q3 vs Q1: 1.22 (1.14, 1.30) GDM (preconception to 6m of pregnancy): Q4 vs Q1: 1.22 (1.13, 1.32) GDM (3m preconception): Q1 vs Q1 (ref): 1.00 (1.00, 1.00) GDM (3m preconception): Q2 vs Q1: 1.15 (1.08, 1.22) GDM (3m preconception): Q3 vs Q1: 1.22 (1.14, 1.30) GDM (3m preconception): Q4 vs Q1: 1.21 (1.12, 1.30)

GDM (1–3m of pregnancy): Q1 vs
 Q1 (ref):
 1.00 (1.00, 1.00)
 GDM (1–3m of pregnancy): Q2 vs
 Q1:
 1.07 (1.00, 1.14)
 GDM (1–3m of pregnancy): Q3 vs
 Q1:
 1.18 (1.10, 1.26)
 GDM (1–3m of pregnancy): Q4 vs
 Q1:
 1.22 (1.13, 1.31)

GDM (1–6m of pregnancy): Q1 vs
 Q1 (ref):
 1.00 (1.00, 1.00)
 GDM (1–6m of pregnancy): Q2 vs
 Q1:
 1.10 (1.03, 1.17)
 GDM (1–6m of pregnancy): Q3 vs
 Q1:
 1.19 (1.11, 1.27)
 GDM (1–6m of pregnancy): Q4 vs
 Q1:
 1.24 (1.16, 1.34)

GDM (4–6m of pregnancy): Q1 vs
 Q1 (ref):
 1.00 (1.00, 1.00)
 GDM (4–6m of pregnancy): Q2 vs
 Q1:
 1.05 (0.99, 1.12)
 GDM (4–6m of pregnancy): Q3 vs
 Q1:
 1.21 (1.13, 1.29)
 GDM (4–6m of pregnancy): Q4 vs
 Q1:
 1.20 (1.12, 1.29)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Copollutant: PM _{2.5} GDM (1–6m of pregnancy): 1.12 (1.07, 1.16) GDM (preconception to 6m of pregnancy): 1.12 (1.07, 1.17) GDM (1–3m of pregnancy): 1.12 (1.08, 1.16) GDM (4–6m of pregnancy): 1.09 (1.05, 1.13)

List of Abbreviations: BMI = body mass index; CI = confidence interval; CMAQ = Community Multiscale Air Quality; IQR = interquartile range; LUR = land use regression; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile; P90 = 90th percentile; P95 = 95th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; ppb = parts per billion; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-5 Epidemiologic studies of oxides of nitrogen and pregnancy outcomes of hypertensive disorders of pregnancy

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Dadvand et al. (2013) n = 8,398 preeclampsia n = 103 without preeclampsia n = 8,295 Barcelona, Spain March 2000–June 2005 Cohort	All pregnancies from the obstetrics department of the Hospital Clinic de Barcelona	LUR NO ₂ r ² = 0.68 NO _x r ² = 0.65 Averaging time: NO ₂ - entire pregnancy NO ₂ - trimester 1 NO ₂ - trimester 2 NO ₂ - trimester 3 NO _x - entire	NO ₂ (µg/m ³) Entire pregnancy Median = 55.7 (IQR 19.7) First trimester Median = 56.8 (IQR 28.1) Second trimester Median = 58 (IQR	Blood pressure reading in reference to International Society for the Study of Hypertension in Pregnancy	Logistic regression Adjusted for: neighborhood socioeconomic status, ethnic origin, education level, marital status, age, smoking, alcohol consumption, body mass index, diabetes, parity, multiple pregnancy,	NO ₂ OR (95% CI) ^b Preeclampsia, 1st trimester: 1.11 (0.91, 1.35) Preeclampsia, 2nd trimester: 1.05 (0.85, 1.30) Preeclampsia, entire pregnancy: 1.09 (0.94, 1.27) Preeclampsia, 3rd trimester: 1.17 (0.99, 1.37)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		pregnancy NO _x - trimester 1 NO _x - trimester 2 NO _x - trimester 3 Exposure years: 2000–2005	27.8) Third trimester Median = 57.7 (IQR 27.7) NO _x (µg/m ³) Entire pregnancy Median = 107.5 (IQR 43.7) First trimester Median = 105.3 (IQR 73.4) Second trimester Median = 107.8 (IQR 73.6) Third trimester Median = 106.5 (IQR 73.8)		season of conception, and year of conception	NO _x OR (95% CI) ^b Preeclampsia, 2nd trimester: 1.06 (0.90, 1.26) Preeclampsia, 1st trimester: 1.09 (0.94, 1.26) Preeclampsia, entire pregnancy: 1.07 (0.97, 1.18) Preeclampsia, 3rd trimester: 1.14 (0.99, 1.29)
Malmqvist et al. (2013)	Women who had singleton deliveries in the county of Scania from 1999–2005. Inclusion was automatic unless otherwise requested, and the study reports that no one requested to be excluded.	Dispersion model Method validation NR Averaging time: NO _x - 1-hour max, Other, NO _x - Monthly means NO _x - Trimester means	NO _x (µg/m ³) Entire Study Period Mean = 16.4 Quartile 1 (during first trimester) Mean = 6.8 Quartile 2 (during first trimester) Mean = 11.4	Diagnosis from EHR	Logistic regression Adjusted for: gestational diabetes, Type 1 diabetes, smoking, parity, BMI, country of origin, calendar year, and maternal age	NO _x OR (95% CI) ^b Preeclampsia severe, NO _x 3 rd quartile (14.2–22.6 µg/m ³): 0.99 (0.74, 1.32) Preeclampsia, NO _x 2 nd quartile (9.0–14.1 µg/m ³): 1.28 (1.13, 1.46) Preeclampsia severe, NO _x 4 th quartile (>22.7 µg/m ³): 1.48 (1.12, 1.95) Preeclampsia mild, NO _x 1 st quartile

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		Exposure years: 1999–2005	Quartile 3 (during first trimester) Mean = 18.2			(2.5–8.9 µg/m ³): 1.00 (0.00, 0.00) Preeclampsia mild, NO _x 4 th quartile (>22.7 µg/m ³): 1.51 (1.29, 1.77) Preeclampsia mild, NO _x 3 rd quartile (14.2–22.6 µg/m ³): 1.42 (1.23, 1.65) Preeclampsia, NO _x 1 st quartile (2.5–8.9 µg/m ³): 1.00 (0.00, 0.00) Preeclampsia severe, NO _x 2 nd quartile (9.0–14.1 µg/m ³): 0.96 (0.72, 1.28) Preeclampsia mild, NO _x 2 nd quartile (9.0–14.1 µg/m ³): 1.38 (1.19, 1.60) Preeclampsia, NO _x 3 rd quartile (14.2–22.6 µg/m ³): 1.33 (1.17, 1.52) Preeclampsia, NO _x 4 th quartile (>22.7 µg/m ³): 1.51 (1.32, 1.73) Preeclampsia severe, NO _x 1 st quartile (2.5–8.9 µg/m ³): 1.00 (0.00, 0.00)
Wu et al. (2009) n = 81,186 California, U.S. 1997–2006 Cohort	Residents in two areas of the South Coast Air Basin of California, who were geocoded to residential address and were singleton births.	Dispersion model Averaging time: NO _x - Entire pregnancy NO _x - First trimester NO _x - Second trimester NO _x - Third	NO _x (ppb) Entire pregnancy Mean = 7.23±5.22 IQR = 5.65 First trimester Mean = 7.45±5.68 IQR = 6.17	Diagnosis from EHR	Logistic regression Adjusted for: maternal age, maternal race/ethnicity, parity, prenatal care insurance type, poverty, season of conception, and diabetes	OR (95% CI) ^b Preeclampsia: 1.15 (1.10, 1.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		trimester	Second trimester Mean = 7.29±5.57 IQR = 6.02			
		Exposure years: 1997–2006	Third trimester Mean = 7.14±5.54 IQR = 5.88			
Wu et al. (2011) n = 81,186 California, U.S. 1997–2006 Cohort	Participants who resided in southern Los Angeles County and Orange County in the South Coast Air Basin of California. Neonatal records for singleton births, with complete full residential address or non-missing covariate information, who had successful geocoded residential addresses.	LUR, Dispersion model, Other NO r ² = 81% NO ₂ r ² = 86% NO _x r ² = 85% Averaging time: NO, NO ₂ , and NO _x from monitored data - specific exposure periods (1 st trimester, 2 nd trimester, last month before delivery, and entire pregnancy period) NO ₂ , NO _x , and NO from LUR - specific exposure periods (1 st trimester, 2 nd trimester, last month before delivery, and entire pregnancy period)	NO ₂ (ppb) LUR (adjusted) Mean = 28±7 IQR = 5.1 Monitor Mean = 24.9±7.4 IQR = 11.7 NO (ppb) LUR (adjusted) Mean = 30.9±18.1 IQR = 11.6 Monitor Mean = 30.9±15.7 IQR = 18.3 NO _x (ppb) CALINE4 Mean = 7.2±5.2 IQR = 5.6 LUR (adjusted) Mean = 59.9±20.3 IQR = 15.6	Diagnosis from EHR	Logistic regression Adjusted for: maternal age, maternal race/ethnicity, parity, diabetes, prenatal care insurance type, poverty, and season of conception	NO OR (95% CI) ^b Preeclampsia, entire pregnancy, Orange County: 0.97 (0.84, 1.11) Preeclampsia, 1 st trimester, Orange County: 1.02 (0.92, 1.14) Preeclampsia, entire pregnancy, Los Angeles: 1.09 (1.02, 1.17) Preeclampsia, 2 nd trimester, Los Angeles: 1.05 (0.94, 1.17) Preeclampsia, 1 st trimester, Los Angeles: 1.01 (0.91, 1.13) Preeclampsia, 2 nd trimester, Orange County: 1.05 (0.94, 1.17) NO ₂ OR (95% CI) ^b Preeclampsia, 1 st trimester, Los Angeles: 1.01 (0.95, 1.07) Preeclampsia, entire pregnancy, Los

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		NO _x from CALINE4 Dispersion Model - specific exposure periods (1 st trimester, 2 nd trimester, last month before delivery, and entire pregnancy period)	Monitor Mean = 55.8±22.2 IQR = 28.2			Angeles: 1.16 (0.99, 1.29) Preeclampsia, 2nd trimester, Orange County: 1.00 (0.92, 1.10) Preeclampsia, entire pregnancy, Orange County: 1.08 (0.95, 1.23) Preeclampsia, 1st trimester, Orange County: 0.98 (0.90, 1.07) Preeclampsia, 2nd trimester, Los Angeles: 1.06 (0.99, 1.13) NO_x OR (95% CI)^b Preeclampsia, 1st trimester, Los Angeles: 1.01 (0.96, 1.06) Preeclampsia, 1st trimester, Orange County: 0.97 (0.89, 1.05) Preeclampsia, entire pregnancy, Los Angeles: 1.11 (1.02, 1.20) Preeclampsia, entire pregnancy, Orange County: 1.01 (0.88, 1.16) Preeclampsia, 2nd trimester, Los Angeles: 1.05 (1.00, 1.10) Preeclampsia, 2nd trimester, Orange County: 0.99 (0.91, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Wu et al. (2016) California Department of Public Health (CDPH) birth registry N = 4,370,371 pregnancies California, U.S. Births occurring from January 1, 2001–December 31, 2008 Cohort	Excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing	Chemical transport model, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2000–2008	NO ₂ (ppb) Overall Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6	Birth certificate records	Logistic regression Adjusted for: race/ethnicity and educational level as categorical variables, and for maternal age and median household income (at census block-group level)	NO ₂ OR (95% CI) ^b Preeclampsia, 1 st trimester: 0.92 (0.85, 0.99) Preeclampsia, 2 nd trimester: 1.03 (0.96, 1.10) Preeclampsia, 3 rd trimester: 1.03 (0.96, 1.10) Preeclampsia, entire pregnancy: 0.94 (0.82, 1.08) Preeclampsia, 1 st trimester, LA County only: 0.89 (0.84, 0.94) Preeclampsia, 2 nd trimester, LA County only: 0.92 (0.87, 0.98) Preeclampsia, 3 rd trimester, LA County only: 0.92 (0.87, 0.98) Preeclampsia, entire pregnancy, LA County only: 0.90 (0.85, 0.96) NO _x OR (95% CI) ^b Preeclampsia, 1 st trimester: 0.98 (0.95, 1.00) Preeclampsia, 2 nd trimester: 0.99 (0.97, 1.02) Preeclampsia, 3 rd trimester: 0.99 (0.97, 1.02) Preeclampsia, entire pregnancy: 0.98 (0.96, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Preeclampsia, household income (1st quartile): 0.82 (0.70, 0.96) Preeclampsia, household income (2nd quartile): 0.89 (0.78, 1.02) Preeclampsia, household income (3rd quartile): 0.95 (0.83, 1.09) Preeclampsia, household income (4th quartile): 0.95 (0.83, 1.09) Preeclampsia, maternal education (<8th grade): 0.94 (0.79, 1.11) Preeclampsia, maternal education (9th grade to HS): 0.88 (0.76, 1.01) Preeclampsia, maternal education (some college): 0.93 (0.82, 1.06) Preeclampsia, race/ethnicity (African American): 0.88 (0.74, 1.05) Preeclampsia, race/ethnicity (Asian): 0.94 (0.81, 1.09) Preeclampsia, race/ethnicity (Hispanic): 0.91 (0.79, 1.05) Preeclampsia, race/ethnicity (White non-Hispanic): 0.89 (0.78, 1.02) Preeclampsia, BMI (20–24.9): Referent

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Preeclampsia, BMI (≤ 19.9): 0.77 (0.62, 0.94) Preeclampsia, BMI (25–29.9): 0.86 (0.74, 1.00) Preeclampsia, BMI (30–34.9): 0.73 (0.61, 0.86) Preeclampsia, BMI (≥ 35): 0.82 (0.69, 0.97)
† Goin et al. (2021) California Department of Public Health (CDPH) birth registry n = N births: 1,095 Oakland, California, U.S. Births between 2014–2016 Cohort	Mothers who lived in West or Downtown Oakland at the time of delivery and had a singleton live birth in a Sutter Hospital between 2014 and 2016 were eligible for inclusion.	Personal monitor or sampler, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2015–2017	NO ₂ (ppb) Overall Mean = 11.5 Median = 10.8 Min = 6.7 Max = 24 P25 = 9 P75 = 13	Diagnosis from EHR	G-computation with log-binomial regression Adjusted for: maternal race/ethnicity, health insurance type, maternal age at delivery, maternal age squared, smoking history, parity, season of conception, the block group percent with less than high school education, and the block group percent below the federal poverty level	NO ₂ RD (95% CI) ^b GH and/or preeclampsia: -1.50 (-2.50, -0.50) GH and/or preeclampsia: -0.30 (-1.90, 1.20) NO _x RD (95% CI) ^b Preeclampsia, copollutant: 1.60 (-0.20, 3.40) Preeclampsia: -1.80 (-2.90, -0.70) Preeclampsia, Black mothers: -2.80 (-5.20, -0.30)
† Hao et al. (2023) Bureau of Epidemiology and Public Health Informatics, Kansas Preterm Birth Cohort n = 596,926 Birthweight Cohort n = 554,787	Only singleton pregnancies with a gestational age of 27–42 weeks with an estimated date of conception between January 1st, 2000, and December 31st, 2015, were included. We	Spatiotemporal/geospatial model, Ensemble machine learning model Method validation NR Averaging time:	NO ₂ (ppb) 1 st Trimester Mean = 10.9 2 nd Trimester Mean = 10.88 3 rd Trimester	GH: self-reported from birth certificate (excluding mothers with pre-existing diabetes or pre-existing hypertension)	Logistic regression Adjusted for: maternal education level, race, ethnicity, age, marital status, smoking, infant parity, zip code level percent below poverty, census tract level	OR (95% CI) ^b GH (First 4 weeks of pregnancy): 0.97 (0.93, 1.01) GH (First 6 weeks of pregnancy): 0.97 (0.93, 1.01) GH (1 st Trimester): 0.97 (0.92, 1.01) GH (2 nd Trimester): 0.99 (0.94, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Gestational Diabetes Cohort n = 449,871	excluded births with (a) missing census tract information; (b) maternal age <10 years or >55 years; (c) birth weight <250 g or >7500 g. For the outcomes of GDM and GH, we also excluded mothers with pre-existing diabetes or pre-existing hypertension.	NO ₂ - 1-hour max, NO ₂ - 24-hour average	Mean = 11.01		greenness, season of conception, and long-term trend using a natural cubic spline on conception date	GH (3 rd Trimester): 1.00 (0.95, 1.05)
Gestational Hypertension Cohort n = 590,574			2000–2004 Mean = 12.12			GH (Entire pregnancy): 1.00 (0.96, 1.03)
Kansas, U.S.		Exposure years: 2000–2016	2010–2015 Mean = 10.23			GH (1 st Trimester): Race: white: 0.97 (0.93, 1.02)
Enrollment: 1999–2016						GH (1 st Trimester): Race: Black: 0.82 (0.70, 0.97)
Follow-up: through pregnancy and birth			Total Pregnancy Mean = 10.16			GH (1 st Trimester): Race: Asian: 0.98 (0.59, 1.65)
Cohort						GH (1 st Trimester): Race: other: 1.17 (0.93, 1.47)
						GH (2 nd Trimester): Race: white: 0.99 (0.94, 1.04)
						GH (2 nd Trimester): Race: Black: 0.90 (0.77, 1.05)
						GH (2 nd Trimester): Race: Asian: 1.27 (0.77, 2.10)
						GH (2 nd Trimester): Race: other: 1.02 (0.79, 1.30)
						GH (1 st Trimester): Ethnicity: Hispanic: 1.03 (0.94, 1.12)
						GH (1 st Trimester): Ethnicity: non-Hispanic: 0.95 (0.90, 1.00)
						GH (2 nd Trimester): Ethnicity: Hispanic: 1.01 (0.92, 1.10)
						GH (2 nd Trimester): Ethnicity: non-Hispanic: 0.98 (0.93, 1.03)
						GH (1 st Trimester): Age: ≤27 years: 0.96 (0.89, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						GH (1 st Trimester): Age: >27 years: 0.98 (0.92, 1.03) GH (2 nd Trimester): Age: ≤27 years: 0.99 (0.92, 1.07) GH (2 nd Trimester): Age: >27 years: 0.98 (0.93, 1.04) GH (1 st Trimester): Zip Code Level Poverty: ≤12%: 0.91 (0.85, 0.97) GH (1 st Trimester): Zip Code Level Poverty: ≤12%: 1.03 (0.96, 1.10) GH (2 nd Trimester): Zip Code Level Poverty: >12%: 0.94 (0.88, 1.01) GH (2 nd Trimester): Zip Code Level Poverty: >12%: 1.03 (0.97, 1.10) GH (1 st Trimester) co-adjusted for PM _{2.5} and O ₃ : 0.98 (0.93, 1.03) GH (2 nd Trimester) co-adjusted for PM _{2.5} and O ₃ : 0.99 (0.95, 1.04) GH (3 rd Trimester) co-adjusted for PM _{2.5} and O ₃ : 1.01 (0.96, 1.06)
†Jiang et al. (2023) China Labor and Delivery Survey (CLDS) N = 67,512	Subjects with the following conditions were excluded: missing data on HDP, chronic hypertension or hypertension with	Ensemble machine learning model, Fixed site monitor Method validation NR	NO ₂ (µg/m ³) 1 st and 2 nd Trimester Median = 37.6 (IQR 18.7)	Diagnosis and Treatment Guidelines of Hypertensive Disorders in	Generalized linear mixed model Adjusted for: ethnicity, BMI, insurance status, resident status,	OR (95% CI) ^b Overall HDP, 1 st trimester: 1.00 (0.89, 1.12) Overall HDP, 2 nd trimester: 1.13 (1.01, 1.27) Overall HDP, 1 st +2 nd trimester:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Nationwide, China March 1, 2015–December 31, 2016 Cross-Sectional	unknown cause, multiple pregnancies, stillbirths, gestational age ≤28 weeks or >44 weeks, pre-pregnancy diabetes, pre-pregnancy heart diseases, and pre-pregnancy renal diseases. We further excluded records with missing data on essential maternal and child characteristics.	Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, Other, NO ₂ - trimester Exposure years: 2013–2018	1 st Trimester Median = 36.3 (IQR 20.1) 2 nd Trimester Median = 38 (IQR 20.2)	Pregnancy and blood pressure	education, parity, mode of conception, the season of conception, fetal gender, region, GDP, apparent temperature, and random contribution of the province Adjusted for: maternal age, ethnicity, BMI, insurance status, resident status, education, parity, mode of conception, the season of conception, fetal gender, region, GDP, apparent temperature, and random contribution of the province Adjusted for: maternal age, ethnicity, BMI, insurance status, resident status, education, parity, mode of conception, the season of conception, fetal gender, GDP, region, and apparent temperature	1.06 (0.94, 1.19) GH, 1 st trimester: 0.99 (0.84, 1.17) GH, 2 nd trimester: 1.12 (0.95, 1.32) GH, 1 st +2 nd trimester: 1.03 (0.88, 1.22) PE, 1 st trimester: 1.04 (0.89, 1.22) PE, 2 nd trimester: 1.15 (0.98, 1.34) PE, 1 st +2 nd trimester: 1.10 (0.94, 1.28) Overall HDP, 1 st trimester, maternal age ≤35 yrs: 1.01 (0.89, 1.14) Overall HDP, 1 st trimester, maternal age >35 yrs: 0.90 (0.72, 1.11) Overall HDP, 2 nd trimester, maternal age ≤35 yrs: 1.18 (1.04, 1.33) Overall HDP, 2 nd trimester, maternal age >35 yrs: 0.88 (0.70, 1.09) Overall HDP, 1 st +2 nd trimester, maternal age ≤35 yrs: 1.09 (0.96, 1.23) Overall HDP, 1 st +2 nd trimester, maternal age >35 yrs: 0.88 (0.72, 1.09) GH, 1 st trimester, mixture: 1.07 (0.98, 1.17)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						GH, 2 nd trimester, mixture: 1.08 (0.98, 1.19) GH, 1 st +2 nd trimester, mixture: 1.11 (1.01, 1.22) PE, 1 st +2 nd trimester, mixture: 1.14 (1.05, 1.24) PE, 2 nd trimester, mixture: 1.25 (1.11, 1.41) PE, 1 st trimester, mixture: 1.15 (1.03, 1.28) PE, 1 st +2 nd trimester, mixture: 1.14 (1.05, 1.24)
†Niu et al. (2024) Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) N = 619 Los Angeles, CA, U.S. Baseline: 2015 Follow-up: through pregnancy and birth Cohort	Participants were recruited from clinical sites that serve low-income populations. The inclusion criteria were being 18 years of age or older, with a gestational age of ≤30 weeks, carrying a singleton pregnancy, and having fluency in English or Spanish. The exclusion criteria included HIV infection, having a physical, mental, or cognitive disability that would prevent participation, or current incarceration.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - weekly Exposure years: 2015	NO ₂ (ppb) 1 st Trimester GH Mean = 17.4±6.9 Non-GH Mean = 16.9±6 PE Mean = 16.3±5.8 2 nd Trimester GH Mean = 15.8±5.7 Non-GH Mean = 16.6±5.7 PE Mean = 16.3±5.2 3 rd Trimester GH Mean = 16.4±3.3 Non-GH	GH: physician diagnosis and BP data from EHR	Poisson regression with DLM Adjusted for: year and season of conception, weekly temperature, household income, maternal age, pre-pregnancy body mass index, ethnicity and nativity, parity, and enrollment timepoint	RR (95% CI) ^b GH, with prenatal depression, window 2 (8 to 17wk after conception): 1.58 (1.14, 2.18) GH, with prenatal depression, window 1 (9wk before conception to 3wk after conception): 1.65 (1.17, 2.34)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 16.7±2.9 PE Mean = 16.5±2.7 12 Weeks Preconception GH Mean = 17.8±5.8 Non-GH Mean = 17.2±5.8 PE Mean = 17±6			
†Nobles et al. (2019b)	All mothers with 2 or more singleton deliveries at ≥20 weeks gestation between 2002 and 2010 at one of 20 hospitals within the Intermountain Health Care system	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max, Other, NO _x - 3-months preconception, first trimester, second trimester, first 20 weeks gestation, whole pregnancy NO ₂ - 3-months preconception, first trimester, second trimester, first 20 weeks gestation, whole pregnancy	NO ₂ (ppb) Pregnancy Median = 17.4 (IQR 4.4) P25 = 15.1 P75 = 19.5 NO _x (ppb) Pregnancy Median = 35.1 (IQR 11.4) P25 = 28.9 P75 = 40.3	Diagnosis from EHR	Poisson binomial regression Adjusted for: maternal age, race/ethnicity, pre-pregnancy BMI, smoking, alcohol use, parity, insurance type, marital status, history of asthma and temperature	NO ₂ RR (95% CI) ^b Gestational hypertension, first 20wks of gestation: 1.11 (1.03, 1.20) Gestational hypertension, 3 months preconception: 1.05 (0.98, 1.12) Gestational hypertension, trimester 1: 1.08 (1.01, 1.16) Gestational hypertension, trimester 2: 1.14 (1.06, 1.22) Gestational hypertension, whole pregnancy: 1.10 (1.04, 1.15) Preeclampsia, first 20wks of gestation: 0.92 (0.84, 1.00) Preeclampsia, 3 months preconception: 0.91 (0.84, 0.99)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		Exposure years: 2002–2010				Preeclampsia, trimester 1: 0.92 (0.85, 1.01) Preeclampsia, trimester 2: 0.96 (0.89, 1.04) Preeclampsia, whole pregnancy: 0.96 (0.91, 1.02) NO_x RR (95% CI)^b Gestational hypertension, 3 months preconception: 1.01 (0.93, 1.10) Gestational hypertension, first 20wks of gestation: 1.10 (1.01, 1.21) Gestational hypertension, trimester 1: 1.07 (0.98, 1.16) Gestational hypertension, trimester 2: 1.17 (1.08, 1.27) Gestational hypertension, whole pregnancy: 1.10 (1.40, 1.16) Preeclampsia, first 20wks of gestation: 0.91 (0.82, 1.01) Preeclampsia, 3 months preconception: 0.85 (0.77, 0.93) Preeclampsia, trimester 1: 0.90 (0.82, 1.00) Preeclampsia, trimester 2: 0.99 (0.90, 1.09) Preeclampsia, whole pregnancy:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.96 (0.90, 1.02)
† Pedersen et al. (2017b)	Women were ineligible if they did not speak sufficient Danish or intended not to carry their pregnancy to term. We excluded women from the original cohort due to multiple pregnancies, abortions, molar or extrauterine pregnancies, unknown, emigration or death, stillborn birth, and withdrawals of participation in the study. Women who reported pre-existing hypertension from the pregnancy interview or those who had a diagnosis of pre-existing chronic hypertension and/or diabetes before pregnancy were excluded.	Dispersion model Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - full pregnancy period Exposure years: 1994–2006	NO ₂ (µg/m ³) 1st Trimester Mean = 13.3±7.3 Median = 11.5 P5 = 5.8 P25 = 8.7 P75 = 15.4 P95 = 27.7 2nd Trimester Mean = 13.1±7 Median = 11.3 P5 = 6 P25 = 8.8 P75 = 14.7 P95 = 27.2 3rd Trimester Mean = 12.7±6.9 Median = 11 P5 = 5.5 P25 = 8.4 P75 = 14.4 P95 = 26.4 Pregnancy Mean = 13±6.6 Median = 11 P5 = 7.1 P25 = 9.2 P75 = 14 P95 = 26.6	Diagnosis from EHR	Logistic regression Adjusted for: maternal age, parity, pre-pregnancy BMI, height, disposable income, education, and season of conception Adjusted for: maternal age, parity, pre-pregnancy BMI, height, disposable income, education, season of conception, and road traffic noise	OR (95% CI) ^b Pre-eclampsia (all subtypes), 1 st trimester: 1.07 (1.01, 1.14) Pre-eclampsia (all subtypes), 2 nd trimester: 1.07 (1.00, 1.14) Pre-eclampsia (all subtypes), 3 rd trimester: 1.07 (1.00, 1.14) Pre-eclampsia (all subtypes), full pregnancy: 1.08 (1.01, 1.15) Pre-eclampsia subtype, mild, 1 st trimester: 1.12 (1.05, 1.20) Pre-eclampsia subtype, mild, 2 nd trimester: 1.12 (1.04, 1.20) Pre-eclampsia subtype, mild, 3 rd trimester: 1.13 (1.05, 1.22) Pre-eclampsia subtype, mild, full pregnancy: 1.14 (1.06, 1.23) Pre-eclampsia subtype, severe, 1 st trimester: 0.92 (0.81, 1.05) Pre-eclampsia subtype, severe, 2 nd trimester: 0.90 (0.78, 1.04) Pre-eclampsia subtype, severe, 3 rd trimester:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						<trimester: </trimester: 0.88 (0.76, 1.02) Pre-eclampsia subtype, severe, full pregnancy: 0.90 (0.78, 1.04) Pre-eclampsia onset, early, 1 st trimester: 1.16 (1.05, 1.27) Pre-eclampsia onset, early, 2 nd trimester: 1.16 (1.05, 1.28) Pre-eclampsia onset, early, 3 rd trimester: 1.19 (1.08, 1.31) Pre-eclampsia onset, early, full pregnancy: 1.19 (1.07, 1.32) Pre-eclampsia onset, late, 1 st trimester: 1.02 (0.94, 1.10) Pre-eclampsia onset, late, 2 nd trimester: 1.01 (0.93, 1.10) Pre-eclampsia onset, late, 3 rd trimester: 0.99 (0.91, 1.08) Pre-eclampsia onset, late, full pregnancy: 1.01 (0.93, 1.10) Pre-eclampsia (all subtypes) + noise: 1.03 (0.96, 1.11) Pre-eclampsia subtype, mild + noise: 1.09 (1.00, 1.18) Pre-eclampsia subtype, severe +

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						noise: 0.88 (0.75, 1.03) Pre-eclampsia onset, early + noise: 1.10 (0.97, 1.24) Pre-eclampsia onset, late + noise: 0.99 (0.90, 1.09) Pre-eclampsia subtype, mild, 1st trimester, low road noise <57.5 dB: 0.93 (0.73, 1.16) Pre-eclampsia subtype, mild, 1st trimester, high road noise ≥ 57.5 dB: 1.11 (1.03, 1.20) Gestational hypertension, 1 st trimester: 1.03 (0.93, 1.14) Gestational hypertension, 2 nd trimester: 1.00 (0.90, 1.11) Gestational hypertension, 3 rd trimester: 1.01 (0.91, 1.13) Gestational hypertension, full pregnancy: 1.01 (0.91, 1.13) Gestational hypertension + noise: 1.01 (0.90, 1.14) Hypertensive disorders in pregnancy (all subtypes), 1 st trimester: 1.07 (1.01, 1.13) Hypertensive disorders in pregnancy (all subtypes), 2 nd trimester: 1.06 (1.00, 1.12) Hypertensive disorders in pregnancy (all subtypes), 3 rd trimester: 1.06 (1.00, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Hypertensive disorders in pregnancy (all subtypes), full pregnancy: 1.07 (1.01, 1.14) Hypertensive disorders in pregnancy (all subtypes) + noise: 1.04 (0.97, 1.11)
† Savitz et al. (2015) N = 262,946 Births New York City, NY, U.S. Birth certificates from 2008–2010 Cohort	Restricted to singleton births to nonsmoking mothers. Further excluded mothers diagnosed with pre-pregnancy hypertension, births with an estimated date of conception before July 31, 2007, or after March 12, 2010, and those missing residential address information.	Fixed site monitor, Spatiotemporal/geospatial model $r^2 = 0.79$ Averaging time: NO ₂ - annual average, Other, NO ₂ - 2-weeks Exposure years: 2008–2010	NO ₂ (ppb) Total First Trimester Mean = 27.8±6.2 Second Trimester Mean = 27±6.2	Diagnosis from EHR	Logistic regression Adjusted for: maternal age, maternal ethnicity, maternal education, Medicaid status, parity, conception year, deprivation index, BMI, BMI2, hospital Adjusted for: maternal age, maternal ethnicity, maternal education, Medicaid status, parity, conception year, deprivation index, BMI, BMI2 Adjusted for: maternal age, maternal ethnicity, maternal education, Medicaid status, parity, conception year, deprivation index, BMI, BMI2, Hospital	OR (95% CI) ^b Total hypertensive disorders, 1 st trimester: 1.00 (1.00, 1.10) Total hypertensive disorders, 2 nd trimester: 1.10 (1.00, 1.10) Total hypertensive disorders, 1 st trimester, 1 st quartile: 1.00 (0.00, 0.00) Total hypertensive disorders, 1 st trimester, 2 nd quartile: 1.03 (0.98, 1.08) Total hypertensive disorders, 1 st trimester, 3 rd quartile: 1.02 (0.98, 1.07) Total hypertensive disorders, 1 st trimester, 4 th quartile: 1.05 (1.00, 1.10) Gestational hypertension, 1 st trimester: 1.20 (1.20, 1.30) Gestational hypertension, 2 nd trimester: 1.30 (1.20, 1.40) Gestational hypertension, 1 st

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						trimester, 1st quartile: 1.00 (0.00, 0.00) Gestational hypertension, 1st trimester, 2nd quartile: 1.11 (1.02, 1.20) Gestational hypertension, 1st trimester, 3rd quartile: 1.15 (1.06, 1.25) Gestational hypertension, 1st trimester, 4th quartile: 1.31 (1.21, 1.41) Mild preeclampsia, 1st trimester: 0.89 (0.85, 0.93) Mild preeclampsia, 2nd trimester: 0.93 (0.89, 0.98) Mild preeclampsia, 1st trimester, 1st quartile: 1.00 (0.00, 0.00) Mild preeclampsia, 1st trimester, 2nd quartile: 0.99 (0.92, 1.06) Mild preeclampsia, 1st trimester, 3rd quartile: 0.93 (0.87, 1.00) Mild preeclampsia, 1st trimester, 4th quartile: 0.87 (0.81, 0.94) Severe preeclampsia/eclampsia, 1st trimester: 1.00 (0.98, 1.10) Severe preeclampsia/eclampsia, 2nd trimester: 1.00 (0.97, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Adjustment for hospital
						Total hypertensive disorders, 1 st trimester:
						0.93 (0.90, 0.96)
						Total hypertensive disorders, 2 nd trimester:
						0.96 (0.93, 0.99)
						Gestational hypertension, 1 st trimester:
						0.95 (0.90, 1.00)
						Gestational hypertension, 2 nd trimester:
						1.00 (0.95, 1.10)
						Severe preeclampsia/eclampsia, 1 st trimester:
						0.96 (0.90, 1.00)
						Severe preeclampsia/eclampsia, 2 nd trimester:
						0.93 (0.87, 0.99)
						Severe preeclampsia/eclampsia, 1 st trimester, 1 st quartile:
						1.00 (0.00, 0.00)
						Severe preeclampsia/eclampsia, 1 st trimester, 2 nd quartile:
						1.00 (0.92, 1.10)
						Severe preeclampsia/eclampsia, 1 st trimester, 3 rd quartile:
						1.02 (0.93, 1.12)
						Severe preeclampsia/eclampsia, 1 st trimester, 4 th quartile:
						1.05 (0.96, 1.15)
						Mild preeclampsia, 1 st trimester:
						0.89 (0.84, 0.93)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Mild preeclampsia, 2 nd trimester: 0.94 (0.89, 0.99)
						Copollutant Total hypertensive disorders, 1 st trimester, PM _{2.5} : 1.00 (0.99, 1.10) Total hypertensive disorders, 2 nd trimester, PM _{2.5} : 1.10 (1.00, 1.10)
						Gestational hypertension, 1 st trimester, PM _{2.5} : 1.10 (1.10, 1.20) Gestational hypertension, 2 nd trimester, PM _{2.5} : 1.30 (1.20, 1.30)
						Mild preeclampsia, 1 st trimester, PM _{2.5} : 0.90 (0.86, 0.95) Mild preeclampsia, 2 nd trimester, PM _{2.5} : 0.96 (0.90, 1.00)
						Severe preeclampsia/eclampsia, 1 st trimester, PM _{2.5} : 1.00 (0.97, 1.10) Severe preeclampsia/eclampsia, 2 nd trimester, PM _{2.5} : 1.00 (0.94, 1.10)
						Adjustment for hospital Total hypertensive disorders, 1 st trimester, PM _{2.5} : 0.92 (0.89, 0.96) Total hypertensive disorders, 2 nd

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						trimester, PM _{2.5} : 0.97 (0.93, 1.01) Gestational hypertension, 1 st trimester, PM _{2.5} : 0.94 (0.88, 1.00) Gestational hypertension, 2 nd trimester, PM _{2.5} : 1.03 (0.97, 1.09) Mild preeclampsia, 1 st trimester, PM _{2.5} : 0.88 (0.83, 0.93) Mild preeclampsia, 2 nd trimester, PM _{2.5} : 0.95 (0.89, 1.01) Severe preeclampsia/eclampsia, 1 st trimester, PM _{2.5} : 0.95 (0.89, 1.03) Severe preeclampsia/eclampsia, 2 nd trimester, PM _{2.5} : 0.92 (0.85, 0.99)
†Savitz et al. (2019) N = 257,956 births New York City, NY, U.S. Births between 2008–2010 Cohort	Excluded patients with missing or implausible gestational age (<22 or >42 weeks), multiple gestations, congenital abnormalities, known smokers, missing or implausible birth weight (<500 or >5,000g), missing covariates (e.g., education, parity),	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - 2 weeks during pregnancy Exposure years: 2008–2010	NO ₂ Exposure distribution concentrations not reported	Diagnosis from EHR	Logistic regression Adjusted for: maternal age, ethnicity, education, Medicaid status, parity, SES score, pre-pregnancy BMI, conception year, and hospital Adjusted for: maternal age, ethnicity,	OR (95% CI) ^b Gestational hypertension: 1.21 (1.15, 1.27) Gestational hypertension, with adjustment for hospital: 0.96 (0.91, 1.01) Preeclampsia, total: 0.94 (0.91, 0.98) Preeclampsia, total, with adjustment for hospital: 0.92 (0.87, 0.96)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	missing delivery hospital, or born in a hospital with fewer than 10 births over the course of the study period and restricted conception dates to avoid fixed-cohort bias.				education, Medicaid status, parity, SES score, pre-pregnancy BMI, and conception year	Preeclampsia, mild: 0.89 (0.85, 0.93) Preeclampsia, mild, with adjustment for hospital: 0.89 (0.85, 0.94) Preeclampsia, severe, with adjustment for hospital: 0.98 (0.92, 1.05) Preeclampsia, severe: 1.05 (0.99, 1.11)
†Weber et al. (2019) California Department of Public Health (CDPH) birth registry N = 252,205 births California, San Joaquin Valley, U.S. Data pulled between 2000–2006 Cohort	Eligible births were singletons, had a gestational age within 20–42 weeks, a birth weight within 500–5,000 grams and were not missing state file numbers. Subjects missing data on eligibility criteria, last menstrual period (used to determine gestational age at birth), or covariates used for adjustment (maternal age, race/ethnicity, education, prenatal care, and insurance type) were excluded.	Fixed site monitor Method validation NR Averaging time: NO₂ - 24-hour average, Other, NO₂ - trimester NO₂ - entire pregnancy NO₂ - last 6 weeks of pregnancy Exposure years: 2000–2006	NO₂ (ppb) Entire Pregnancy Median = 17.26 (IQR 4.14) Min = 6.83 Max = 32.25	Diagnosis from EHR	Logistic regression Adjusted for: maternal race/ethnicity, age, education, payment of birth expenses/insurance type, and prenatal care	OR (95% CI)^b Pregnancy-induced hypertension, 1st trimester (4th tertile vs 1,2,3 tertiles): 0.97 (0.94, 1.01) Pregnancy-induced hypertension, 2nd trimester (4th tertile vs 1,2,3 tertiles): 1.02 (0.98, 1.06) Pregnancy-induced hypertension, entire pregnancy (4th tertile vs 1,2,3 tertiles): 0.99 (0.95, 1.03)
†Weber et al. (2021) California Department of Public	Included live births delivered in California between 2000–2006.	Fixed site monitor Method validation	NO₂ Exposure distribution	Diagnosis from EHR	Logistic regression Adjusted for: maternal	OR (95% CI)^b Severe preeclampsia (>75th vs ≤75th pct):

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Health (CDPH) birth registry Preterm births n = 78,421 Term births n = 235,263 California, San Joaquin Valley, U.S. 2000–2006 Case-Control	To be included, births had to be singleton, have a weight within 500–5000 g, and be 20–41 weeks gestational age. Women diagnosed with preeclampsia who delivered at term were excluded.	NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - entire pregnancy Exposure years: 2000–2006	concentrations not reported		age (years), race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, non-Hispanic Black, Other), season of conception (winter, spring, summer, and fall), parity (1, ≥2)	1.11 (0.96, 1.29) Mild preeclampsia (>75 th vs ≤ 75 th pct): 1.13 (0.97, 1.31) Superimposed preeclampsia (>75 th vs ≤ 75 th pct): 0.99 (0.74, 1.34)
† Williams et al. (2021) Consortium on Safe Labor (2002–2008) With T1D n = 507 Without T1D n = 204,384 Nationwide, U.S. 2002–2008 Case-Control	Included deliveries at 23 weeks or later. Excluded multifetal pregnancies, mothers with thyroid disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Crohn's disease, as well as those with other autoimmune disease. Participants from one site for which ICD-9 codes were not reported and no cases of Type 1 diabetes were identified were also excluded.	CMAQ Method validation NR Averaging time: NO _x - 1-hour max, Other, NO _x - 3-month preconception period NO _x - trimester NO _x - whole pregnancy Exposure years: 2002–2008	NO _x (ppb) 1st trimester Mean = 30.26 IQR = 29.06 Min = 5.51 Max = 89.62 2nd trimester Mean = 30.13 IQR = 28.98 Min = 5.76 Max = 90.65 3 months preconception Mean = 29.02 IQR = 27 Min = 5.09 Max = 92.97 Whole pregnancy Mean = 29.8 IQR = 22.47	Diagnosis from EHR	Poisson regression Adjusted for: maternal characteristics including age (continuous), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), preconception, Body Mass Index (BMI, <18.5, 18.5–<24.9, 25–<29.9, ≥30 kg/m ²), health insurance (public, private, other), marital status (married, divorced/widowed, single, unknown), smoking during pregnancy (yes/no), alcohol use during pregnancy (yes/no), any other chronic diseases (yes/no: asthma, depression, heart disease, hypertension,	RR (95% CI) ^b Preeclampsia, whole pregnancy, Type I diabetes: 1.00 (0.99, 1.00) Preeclampsia, whole pregnancy, no autoimmune: 1.00 (1.00, 1.00) Preeclampsia, preconception, Type I diabetes: 1.00 (0.99, 1.00) Preeclampsia, preconception, no autoimmune: 1.00 (1.00, 1.00) Preeclampsia, 1st trimester, Type I diabetes: 1.00 (0.99, 1.00) Preeclampsia, 2 nd trimester, type I diabetes: 1.00 (0.99, 1.00) Preeclampsia, 1 st trimester, no autoimmune: 1.00 (1.00, 1.00) Preeclampsia, 2 nd trimester, no autoimmune: 1.00 (1.00, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 6.38 Max = 81.64		renal disease) and area-level factors including hospital type (University Teaching Hospital, Community Teaching Hospital, Non-teaching Community Hospital) and census region (Northeast, West, South, Midwest)	
† Wu et al. (2016)	Excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing	Chemical transport model, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR	NO ₂ (ppb) Overall Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6	Birth certificate records	Logistic regression Adjusted for: race/ethnicity and educational level as categorical variables, and for maternal age and median household income (at census block-group level)	NO ₂ OR (95% CI) ^b Preeclampsia, 1 st trimester, LA County only: 0.89 (0.84, 0.94) Preeclampsia, 2 nd trimester, LA County only: 0.92 (0.87, 0.98) Preeclampsia, 3 rd trimester, LA County only: 0.92 (0.87, 0.98) Preeclampsia, entire pregnancy, LA County only: 0.90 (0.85, 0.96) Preeclampsia, 1 st trimester: 0.92 (0.85, 0.99) Preeclampsia, 2 nd trimester: 1.03 (0.96, 1.10) Preeclampsia, 3 rd trimester: 1.03 (0.96, 1.10) Preeclampsia, entire pregnancy: 0.94 (0.82, 1.08) NO _x
California Department of Public Health (CDPH) birth registry						
N = 4,370,371 pregnancies						
California, U.S.						
Births occurring from January 1, 2001–December 31, 2008		Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly				
Cohort		Exposure years: 2000–2008				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						OR (95% CI) ^b
						Preeclampsia, 1 st trimester: 0.98 (0.95, 1.00)
						Preeclampsia, 2 nd trimester: 0.99 (0.97, 1.02)
						Preeclampsia, 3 rd trimester: 0.99 (0.97, 1.02)
						Preeclampsia, entire pregnancy: 0.98 (0.96, 1.01)
						Preeclampsia, household income (1 st quartile): 0.82 (0.70, 0.96)
						Preeclampsia, household income (2 nd quartile): 0.89 (0.78, 1.02)
						Preeclampsia, household income (3 rd quartile): 0.95 (0.83, 1.09)
						Preeclampsia, household income (4 th quartile): 0.95 (0.83, 1.09)
						Preeclampsia, maternal education (<8 th grade): 0.94 (0.79, 1.11)
						Preeclampsia, maternal education (9 th grade to HS): 0.88 (0.76, 1.01)
						Preeclampsia, maternal education (some college): 0.93 (0.82, 1.06)
						Preeclampsia, race/ethnicity (White non-Hispanic): 0.89 (0.78, 1.02)
						Preeclampsia, race/ethnicity

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						(African American): 0.88 (0.74, 1.05) Preeclampsia, race/ethnicity (Asian): 0.94 (0.81, 1.09) Preeclampsia, race/ethnicity (Hispanic): 0.91 (0.79, 1.05) Preeclampsia, BMI (≤19.9): 0.77 (0.62, 0.94) Preeclampsia, BMI (20–24.9): Referent Preeclampsia, BMI (25–29.9): 0.86 (0.74, 1.00) Preeclampsia, BMI (30–34.9): 0.73 (0.61, 0.86) Preeclampsia, BMI (≥35): 0.82 (0.69, 0.97)
† Yan et al. (2022) Chinese Pregnant Women Cohort Study-Peking Union Medical College (CPWCS-PUMC) N = 3,754 Nationwide, China Baseline: July 25, 2017 Follow-up: 2 nd trimester, 3 rd trimester, 6 weeks postpartum Cohort	Included pregnant women who were (1) at the 5–12 gestational weeks; (2) able to complete the online questionnaires; (3) permanent residents of the study site; and (4) willing to sign the consent form were eligible to participate. Excluded subjects without information for the gestational outcome, birth outcome, and	Chemical transport model r ² = 0.67 Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - weekly NO ₂ - trimester NO ₂ - entire pregnancy Exposure years: 2013–2018	NO ₂ (µg/m ³) Entire Pregnancy Gestational Diabetes Mellitus Mean = 37.8±8.1 Gestational Hypertension Mean = 37.5±8.3 No Gestational Diabetes Mellitus Mean = 36.6±7.6 No Gestational Hypertension Mean = 36.7±7.7 No Preeclampsia Mean = 36.7±7.7	Physician questionnaire, blood pressure	Logistic regression Adjusted for: maternal age (years), maternal body mass index before pregnancy, pre-pregnancy hypertension (yes/no), pre-pregnancy diabetes mellitus (yes/no), weight gains (kg), newborn's sex (male/female), residential region (mid-west, north, or southeast), and season of conception (spring,	NO ₂ OR (95% CI) ^b GH, 1 st trimester: 1.03 (0.84, 1.27) GH, 2 nd trimester: 1.11 (0.84, 1.45) GH, 3 rd trimester: 1.02 (0.77, 1.34) GH, entire pregnancy: 1.09 (0.82, 1.46) PE, 1 st trimester: 0.87 (0.60, 1.28) PE, 2 nd trimester: 1.06 (0.65, 1.75) PE, 3 rd trimester:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	those delivered after December 31, 2018.		Preeclampsia Mean = 37.2±10.1 Total Mean = 36.7±7.7 Trimester 1 Gestational Diabetes Mellitus Mean = 45.2±11.2 Gestational Hypertension Mean = 43.9±11.4 No Gestational Diabetes Mellitus Mean = 43.2±10.9 No Gestational Hypertension Mean = 43.4±11 No Preeclampsia Mean = 43.4±11 Preeclampsia Mean = 41.9±11.7 Total Mean = 43.4±11 Trimester 2 Gestational Diabetes Mellitus Mean = 35.8±10.7 Gestational Hypertension Mean = 37±11.7 No Gestational Diabetes Mellitus Mean = 34.1±10.1 No Gestational Hypertension		summer, autumn, and winter)	0.83 (0.49, 1.42) PE, entire pregnancy: 0.93 (0.55, 1.57)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 34.2±10.2 No Preeclampsia Mean = 34.3±10.2 Preeclampsia Mean = 38.5±13.7 Total Mean = 34.3±10.2			
			Trimester 3 Gestational Diabetes Mellitus Mean = 33.4±9.4 Gestational Hypertension Mean = 32.3±9.5 No Gestational Diabetes Mellitus Mean = 33.3±8.9 No Gestational Hypertension Mean = 33.3±9 No Preeclampsia Mean = 33.3±8.9 Preeclampsia Mean = 31.6±10.7 Total Mean = 33.3±9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Zhu et al. (2017) Consortium on Safe Labor (CSL) N = 206,054 pregnancies Nationwide, U.S. Births between 2002–2008 Cohort	Included births at ≥23 weeks of gestation and singleton pregnancies. Excluded pregnancies with multiple gestation and missing air quality data or maternal age as well as those in which the women had chronic hypertension or superimposed preeclampsia and thus were not at risk for new-onset hypertension during pregnancy. Excluded women with other hypertensive disorders during pregnancy (i.e., preeclampsia and eclampsia) to allow comparison of women with GH to a normotensive reference group	CMAQ Method validation NR Averaging time: NO _x - 1-hour max, Other, NO _x - 3 months preconception NO _x - first 20 weeks NO _x - trimester Exposure years: 2013	NO _x (ppb) 3 Months Preconception Median = 24.5 P25 = 14.8 P75 = 43.2 Gestational Weeks 1–20 Median = 26.8 P25 = 16 P75 = 45 Trimester 1 Median = 25.5 P25 = 15.2 P75 = 45.3	Diagnosis from EHR and/or the maternal discharge summary	Generalized estimating equation Adjusted for: study site, race/ethnicity, marital status, insurance, parity, pre-pregnancy body mass index, chronic disease before pregnancy (diabetes mellitus, asthma, thyroid disease, HIV), smoking during pregnancy, alcohol consumption during pregnancy, and season of conception	RR (95% CI) ^b Gestational hypertension, 3 months preconception: 1.07 (0.98, 1.17) Gestational hypertension, gestational weeks 1–20: 1.17 (1.06, 1.29) Gestational hypertension, trimester 1: 1.11 (1.01, 1.21)

List of Abbreviations: BMI = body mass index; CI = confidence interval; CMAQ = Community Multiscale Air Quality; IQR = interquartile range; LUR = land use regression; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile P95 = 95th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; ppb = parts per billion; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-6 Epidemiologic studies of oxides of nitrogen and pregnancy outcomes of placental growth and function

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
van den Hooven et al. (2012b)	Singleton, live births, without missing data for angiogenic factors, placental vascular resistance, or placenta weight, who resided and were delivered inside the study area.	Hybrid model	NO ₂ (µg/m ³)	Unilateral or bilateral uterine artery notching was assessed in the third trimester	Logistic regression	OR (95% CI) ^b
Generation R		Averaging time:	Delivery		Adjusted for: gestational age at measurement, fetal sex, maternal age, BMI, parity, ethnicity, educational level, smoking, alcohol consumption, and folic acid supplementation use	Uterine artery notching in T3:
n = 7,801		NO ₂ - 2 weeks before outcome measurement	Prior day 1–60 Mean = 39.9			Bilateral (Entire Pregnancy): 1.18 (0.79, 1.76)
Rotterdam, Netherlands		NO ₂ - 2 months before outcome measurement	Median = 40.3 (IQR 8.5)			Uterine artery notching in T3: Unilateral (Prior 2 weeks): 0.99 (0.85, 1.16)
		NO ₂ - averaged pregnancy exposure from conception until outcome measurement	Min = 18.5 Max = 65.3 P25 = 35.1 P75 = 43.6			Uterine artery notching in T3: Unilateral (Entire Pregnancy): 1.12 (0.85, 1.48)
2001–2005		Exposure years: 2001–2005	Prior day 1–14 Mean = 39.5 Median = 39.9 (IQR 10.6)			Uterine artery notching in T3: Bilateral (Prior 2 months): 1.33 (0.99, 1.78)
Cohort			Min = 15.3 Max = 67.2 P25 = 34.1 P75 = 44.7			Uterine artery notching in T3: Unilateral (Prior 2 months): 0.96 (0.79, 1.16)
			Total pregnancy period Mean = 39.9 Median = 39.6 (IQR 5)			Uterine artery notching in T3: Bilateral (Prior 2 weeks): 1.22 (0.97, 1.53)
			Min = 26.5 Max = 59.3 P25 = 37.2 P75 = 42.2			
			First trimester Prior day 1–60 Mean = 40.4 Median = 41 (IQR 7.4)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 20.2 Max = 59.3 P25 = 36.7 P75 = 44.1 Prior day 1–4 Mean = 40.4 Median = 40.5 (IQR 10) Min = 16.9 Max = 70.5 P25 = 35.2 P75 = 45.2 Total pregnancy period Mean = 40.5 Median = 41 (IQR 6.8) Min = 21 Max = 59.8 P25 = 37.2 P75 = 44 Second trimester Prior day 1–60 Mean = 40 Median = 40.8 (IQR 8) Min = 20.3 Max = 59.6 P25 = 36 P75 = 44 Prior day 1–14 Mean = 40.2 Median = 40.2 (IQR 10.4) Min = 15.1 Max = 66.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 34.6 P75 = 45 Total pregnancy period Mean = 40.2 Median = 40.4 (IQR 6.5) Min = 22.7 Max = 59.3 P25 = 37 P75 = 43.5 Third trimester Prior day 1-60 Mean = 40.4 Median = 40.8 (IQR 8.7) Min = 19.8 Max = 65.5 P25 = 35.8 P75 = 44.5 Prior day 1–14 Mean = 40.4 Median = 40.5 (IQR 10.1) Min = 16.9 Max = 67.4 P25 = 35.2 P75 = 45.3 Total pregnancy period Mean = 39.8 Median = 39.6 (IQR 5.7) Min = 25.6 Max = 58.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 36.8 P75 = 42.5			
† Ananth et al. (2018) N = 1,190 pregnancies New York City, NY, U.S. December 2008–December 2014 Case-crossover	Excluded the following: multiple births (n = 22,379), non-abruption pregnancies (n = 692,394), abruption cases with missing data on air pollution exposures (n = 3), and abruption cases with either a hospital discharge or birth records diagnosis but not both (n = 4,776).	Spatiotemporal/geospatial model, Fixed site monitor For NO ₂ , the cross-validation R ² was 78% Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - 2 weeks Exposure years: 2008–2014	NO ₂ (ppb) Abrupt Case Days Mean = 21.5±5.9 Median = 22 P5 = 11.8 P10 = 13.8 P25 = 17.2 P75 = 25.4 P90 = 29 P95 = 31.2 Control Days Mean = 21.5±5.9 Median = 21.8 P5 = 11.8 P10 = 13.7 P25 = 17.2 P75 = 25.4 P90 = 28.8 P95 = 31.1	Placental abruption: 1) based on a diagnosis of the complication by the attendant at delivery and 2) hospital delivery and discharge records using ICD-9 code 641.2	distributed lag nonlinear model Adjusted for: temperature and relative humidity; PM _{2.12} Adjusted for: temperature and relative humidity Adjusted for: temperature and relative humidity; PM _{2.11} Adjusted for: temperature and relative humidity; PM _{2.9} Adjusted for: temperature and relative humidity; PM _{2.10} Adjusted for: temperature and relative humidity; PM _{2.6} Adjusted for: temperature and relative humidity; PM _{2.7} Adjusted for: temperature and relative humidity; PM _{2.8}	OR (95% CI) ^b Cumulative Lag 0 days: 0.75 (0.58, 0.98) Cumulative Lag 0–1 days: 0.68 (0.48, 0.97) Cumulative Lag 0–1–2 days: 0.71 (0.50, 1.01) Cumulative Lag 0–1–2–3 days: 0.83 (0.60, 1.15) Cumulative Lag 0–1–2–3–4 days: 0.98 (0.69, 4.40) Cumulative Lag 0–1–2–3–4–5 days: 1.14 (0.79, 1.65) Cumulative Lag 0–1–2–3–4–5–6 days: 1.23 (0.90, 1.69) Cumulative Lag 0–1–2–3–4–5–6–7 days: 1.22 (0.91, 1.62) Lag day 3: 1.16 (0.98, 1.37) Lag day 4: 1.19 (1.02, 1.39) Lag day 5: 1.16 (1.05, 1.27) Copolutant: PM _{2.5} Lag 0 days: 0.92 (0.70, 1.19) Lag 1 days: 0.94 (0.72, 1.22) Lag 2 days: 1.11 (0.86, 1.42)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					Adjusted for: temperature and relative humidity; PM _{2.5}	Lag 3 days: 1.06 (0.83, 1.36) Lag 4 days: 1.30 (1.01, 1.67) Lag 5 days: 1.19 (0.93, 1.54) Lag 6 days: 1.32 (1.03, 1.70) Lag 7 days: 1.28 (1.00, 1.65) Warm Season: Cumulative Lag 0 days: 0.83 (0.51, 1.34) Warm Season: Cumulative Lag 0–1 days: 0.77 (0.39, 1.52) Warm Season: Cumulative Lag 0–1– 2 days: 0.79 (0.39, 1.56) Warm Season: Cumulative Lag 0–1– 2–3 days: 0.85 (0.43, 1.69) Warm Season: Cumulative Lag 0–1– 2–3–4 days: 0.94 (0.46, 1.94) Warm Season: Cumulative Lag 0–1– 2–3–4–5 days: 1.01 (0.49, 2.12) Warm Season: Cumulative Lag 0–1– 2–3–4–5–6 days: 1.04 (0.54, 2.00) Warm Season: Cumulative Lag 0–1– 2–3–4–5–6–7 days: 1.01 (0.55, 1.86) Cold Season: Cumulative Lag 0

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						days: 0.74 (0.54, 1.02) Cold Season: Cumulative Lag 0–1 days: 0.67 (0.43, 1.03) Cold Season: Cumulative Lag 0–1–2 days: 0.70 (0.46, 1.06) Cold Season: Cumulative Lag 0–1–2–3 days: 0.83 (0.57, 1.21) Cold Season: Cumulative Lag 0–1–2–3–4 days: 1.01 (0.67, 1.52) Cold Season: Cumulative Lag 0–1–2–3–4–5 days: 1.19 (0.77, 1.84) Cold Season: Cumulative Lag 0–1–2–3–4–5–6 days: 1.32 (0.91, 1.91) Cold Season: Cumulative Lag 0–1–2–3–4–5–6–7 days: 1.33 (0.95, 1.86)

† Michikawa et al. (2017)	All the live births and stillbirths after 22 weeks of gestation at cooperating hospitals throughout Japan. All women (n = 47,835), who delivered singleton births in 28 hospitals in the western part of Japan. Among 834 women, we included 821 women with abruption, who had either pollution exposure data in this study.	Fixed site monitor	NO ₂ (ppb)	placental abruption abstracted from the Japan Perinatal Registry Network database; outcome is related to obstetric complications, and routinely registered by attending physicians according to uniform coding specifications	Conditional logistic regression	OR (95% CI) ^b
Japan Perinatal Registry Network database		Averaging time: NO ₂ - 24-hour average	Case Days Mean = 10.3±7.3 Median = 9 P10 = 1.4 P25 = 4.8 P75 = 15 P90 = 20.3		Adjusted for: lag1, lag2, lag3, lag4, and lag5 simultaneously, and ambient temperature (lag1–3)	Lag 1 days: 1.00 (0.80, 1.20) Lag 2 days: 1.40 (1.10, 1.80) Lag 3 days: 0.90 (0.70, 1.10) Lag 4 days: 1.10 (0.90, 1.50) Lag 5 days: 0.90 (0.70, 1.10)
N = 821		Exposure years: 2005–2010	Controls Days Mean = 9.9±7.2 Median = 8.6 P10 = 1.3 P25 = 4.5 P75 = 14.4 P90 = 20		Adjusted for: lag2, lag3, lag4, lag5 and ambient temperature (lag1–3)	Cumulative Lag 1–2 days: 1.20 (1.00, 1.50)
Kyushu-Okinawa District, Japan					Adjusted for: lag1, lag2, lag4, lag5 and ambient temperature (lag1–3)	Cumulative Lag 1–3 days: 1.20 (0.90, 1.60)
Enrollment: 2005–2010					Adjusted for: lag1, lag2, lag3, lag5 and ambient temperature (lag1–3)	Cumulative Lag 1–4 days: 1.30 (0.90, 1.70)
Case-crossover					Adjusted for: lag1, lag2, lag3, lag5 and ambient temperature (lag1–3), ozone	Cumulative Lag 1–5 days: 1.20 (0.90, 1.80)
					Adjusted for: lag1, lag3, lag4, lag5 and ambient temperature (lag1–3)	Lag 2 days coadjusted for O ₃ : 1.40 (1.10, 1.90)
					Adjusted for: lag1, lag3, lag4, lag5 and ambient temperature (lag1–3), SO ₂	Lag 2 days coadjusted for SO ₂ : 1.40 (1.00, 1.80)
					Adjusted for: lag1, lag3, lag4, lag5 and ambient temperature (lag1–3), SPM	Lag 2 days coadjusted for SPM: 1.40 (1.10, 1.80)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					Adjusted for: lag1, lag2, lag3, lag4 and ambient temperature (lag1–3)	

List of Abbreviations: BMI = body mass index; CI = confidence interval; IQR = interquartile range; LUR = land use regression; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; SO₂ = sulfur dioxide; OR = odds ratio; P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile; P90 = 90th percentile; P95 = 95th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; ppb = parts per billion; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-7 Epidemiologic studies of oxides of nitrogen and pregnancy outcomes of pregnancy-related mental health

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Bastain et al. (2021)	Included predominantly low-income Hispanic/Latina women at community health prenatal care providers in Los Angeles, CA. Study inclusion criteria for the MADRES cohort included <30weeks gestation, ≥18years old, and English or Spanish speaking. Study exclusions included current incarceration, HIV positive status and any cognitive or	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, pregnancy Exposure years: 2015–2020	NO ₂ (ppb) Trimester 1 Mean = 16.2±5.9 Trimester 2 Mean = 17.4±5.2 Trimester 3 Mean = 17.4±5.7 Entire Pregnancy Mean = 17±2.7	Center for epidemiological studies-depression (CES-D) scale: validated 20-item instrument that was developed for use in epidemiological studies for assessing depressive symptoms experienced within the past week. Participant classified as depressed using the recommended cutoff of 16 or above, which is suggestive of clinical depression.	Multivariable logistic regression Adjusted for: recruitment site, maternal age, ethnicity by nativity, household income, education, air conditioning use during pregnancy, previous history of depression, and average temperature over the exposure averaging period	OR (95% CI) ^c Trimester 1: 1.29 (0.70, 2.40) Trimester 2: 2.63 (1.41, 4.89) Trimester 3: 0.91 (0.55, 1.49) Entire Pregnancy: 2.04 (1.13, 3.69)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	physical disability that would prevent participation in study procedures or providing informed consent.					
† Shih et al. (2021) Taiwan Birth Cohort Study (TBCS) N = 21,188 Nationwide, Taiwan Those enrolled in 2005 Cohort	Those who were unable to complete the questionnaire were excluded from the cohort. Mothers with missing or unsure answers to the question regarding PPD were excluded.	Hybrid model, LUR $r^2 = 0.9$ Averaging time: NO ₂ - trimester NO ₂ - 3 months postpartum Exposure years: 2005	NO ₂ (ppb) Trimester 1 Mean = 19.67±7.34 Median = 18.82 (IQR 10.67) Min = 3.41 Max = 40.71 P25 = 14 P75 = 24.66 Trimester 2 Mean = 19.29±7.52 Median = 18.63 (IQR 10.67) Min = 2.39 Max = 40.19 P25 = 13.67 P75 = 24.35 Trimester 3 Mean = 18.57±7.7 Median = 17.89 (IQR 10.64) Min = 2.16 Max = 41.29 P25 = 12.72 P75 = 23.35 Postpartum 3 Months	Self-report Y/N: At 6 months postpartum, mothers were asked by a survey interviewer if they had experienced Postpartum depression (PPD)	Multivariable logistic regression Adjusted for: birth order of infant, tocolysis during pregnancy, delivery method, delivery season, premature and low-birthweight infant, breastfeeding, children general health status, mother's age at childbirth, mother's education level, maternal perinatal smoking, passive smoking and alcohol consumption, annual household income, marital relationship, urban living, family supports, and ambient temperature in the same exposure period Adjusted for: birth order of infant, tocolysis during pregnancy, delivery method, delivery season, premature and low-birthweight infant, breastfeeding, children	OR (95% CI) ^c First Trimester: 1.01 (1.00, 1.01) Second Trimester: 1.00 (1.00, 1.01) Third Trimester: 1.00 (1.00, 1.01) Postpartum (3 months): 1.01 (1.00, 1.01) Additionally adjusted for PM _{2.5} First Trimester: 1.01 (1.00, 1.01) Second Trimester: 1.01 (1.00, 1.01) Third Trimester: 1.01 (1.00, 1.01) Postpartum (3 months): 1.01 (1.00, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 18.54±7.67 Median = 17.58 (IQR 10.48) Min = 2.35 Max = 40.93 P25 = 12.86 P75 = 23.34		general health status, mother's age at childbirth, mother's education level, maternal perinatal smoking, passive smoking and alcohol consumption, annual household income, marital relationship, urban living, family supports, ambient temperature in the same exposure period, and PM _{2.5} in the same exposure period	

† Sun et al. (2023)	Women who were a KPSC member, who gave birth at ≥ 20 weeks or ≤ 47 weeks gestation, who had a residential address, and who had a singleton, live birth.	Spatiotemporal/geospatial model	NO ₂ (ppb)	Postpartum depression (PPD) was first assessed using the EPDS for participants during their postpartum visits. Participants with positive screening results based on the EPDS (score ≥10) during postpartum visits were referred to a clinical interview for further assessment and follow-up care, including diagnosis and treatment. PPD diagnosis was defined by using a combination of ICD-9 and ICD-10 codes for depression and prescription medication records from the date of delivery to the first 6 months after delivery in KPSC EHRs.	Pooled logistic regression	OR (95% CI) ^c
Kaiser Permanente Southern California (KPSC)		Averaging time: NO ₂ - monthly	during pregnancy and the postpartum period Mean = 15.86±3.82 Median = 16.25 (IQR 5.38)		Adjusted for: maternal age, race and ethnicity, education, median neighborhood household income, smoking during pregnancy, season of conception, and year of infant birth. County was fitted as a random effect	First Trimester: 1.00 (0.98, 1.02) Second Trimester: 1.00 (0.98, 1.03) Third Trimester: 0.98 (0.96, 1.00) Third Trimester + after delivery: 0.97 (0.95, 1.00) Entire Pregnancy: 0.98 (0.95, 1.00) During Pregnancy + after delivery: 0.97 (0.94, 1.00)
n = 340,679		Exposure years: 2007–2017				Pre-pregnancy BMI: Normal: 0.97 (0.93, 1.01) Pre-pregnancy BMI: Underweight: 0.90 (0.77, 1.04) Pre-pregnancy BMI: Overweight: 0.97 (0.92, 1.02) Pre-pregnancy BMI: Obese: 0.97 (0.93, 1.02)
Southern California, U.S.						Maternal age: < 25: 0.91 (0.85, 0.97) Maternal age: 25-34: 0.99 (0.96, 1.02) Maternal age: ≥ 35: 0.97 (0.92, 1.03)
January 1, 2008–December 31, 2016						Maternal race/ethnicity: non-Hispanic white: 0.96 (0.92, 1.00) Maternal race/ethnicity: African American:
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.93 (0.84, 1.02) Maternal race/ethnicity: multiple/other (Pacific Islanders, Native American/Alaska Native and mothers with multiple race/ethnicities specified): 0.95 (0.85, 1.07) Maternal race/ethnicity: Hispanic: 0.99 (0.95, 1.03) Maternal race/ethnicity: Asian: 0.98 (0.90, 1.06)
						Household income: low (Q1-Q2): 0.97 (0.93, 1.01) Household income: high (Q3-Q4): 0.97 (0.94, 1.01)
						Maternal education: <college: 0.96 (0.93, 1.00) Maternal education: ≥college: 0.99 (0.95, 1.03)

List of abbreviations in alphabetical order: NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; ppb = parts per billion; LUR = land use regression; BMI = body mass index; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 μm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 μm; O₃ = ozone; CI = confidence interval; OR = odds ratio; RR = rate ratio; HR = hazard ratio

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time

^cEstimates are not standardized

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-8 Epidemiologic studies of oxides of nitrogen and pregnancy outcomes of pregnancy loss and stillbirth

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Faiz et al. (2012) n = 343, 077 NO ₂ stillbirths n = 926 New Jersey, U.S. 1998–2004 Cohort	All singleton births in New Jersey that occurred between 20 and 42 completed weeks of gestation (140–294 days of pregnancy) with birth weight of 500g or more.	Central site monitor Averaging time: NO ₂ - trimester specific mean Exposure years: 1998–2004	NO ₂ (ppb) Mean = 2.6±3.7	Stillbirths: death of fetus at 20 or more completed weeks of gestation	Generalized estimating equation Adjusted for: maternal age, race/ethnicity, educational level, prenatal care, and smoking, as well as neighborhood socioeconomic status and calendar year and month of conception and mean temperature	OR (95% CI) ^c Trimester 1: 1.16 (1.03, 1.31) Trimester 2: 1.13 (0.96, 1.32) Trimester 3: 1.05 (0.90, 1.23) Entire Pregnancy: 1.27 (1.04, 1.55)
Faiz et al. (2013) n = 1,719 NO ₂ stillbirths = 1,178 New Jersey, U.S. 1998–2004 Cohort	Singleton fetal deaths to mothers residing in New Jersey at the time of stillbirths between 20 and 42 completed weeks of gestation (140–294 days of pregnancy) and weighing at least 500 g.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1998–2004	NO ₂ (ppb) Cases Mean = 26.1±11.8 Median = 25.1 (IQR 16.5) P10 = 11.6 P25 = 17.3 P75 = 33.8 P90 = 41.8 Controls Mean = 25.4±11.9 Median = 24 (IQR 16.4) P10 = 11.3 P25 = 16.3 P75 = 32.7 P90 = 41.6	Stillbirths: fetal deaths between 20 and 42 completed weeks of gestation and weighing at least 500 g	Conditional logistic regression models Adjusted for: corresponding same lag day(s) mean apparent temperature	OR (95% CI) ^b Lag 2 days: 1.14 (0.97, 1.33) Lag 2,3 days: 1.11 (0.91, 1.36) Lag 2,3,4 days: 1.12 (0.89, 1.42) Lag 2,3,4,5 days: 1.05 (0.83, 1.33) Lag 2,3,4,5,6 days: 0.98 (0.75, 1.30)
[†] Leiser et al. (2019) N = 1,398	Cases of spontaneous pregnancy loss diagnosed in the	Fixed site monitor Averaging time:	NO ₂ (ppb) Average 3 day	Spontaneous pregnancy loss diagnosed	Conditional logistic regression	OR (95% CI) ^b 7-day average: 1.35 (1.02, 1.77)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Utah, U.S. 2007–2015 Case-crossover	UUED. Excluded 73 events that occurred to women residing outside the state of Utah at the time of spontaneous pregnancy loss. Included only the first event if the two events occurred within 14 weeks; we excluded 106 events that occurred within 14 weeks of a previous event.	NO ₂ - 24-hour average, Other, NO ₂ - 3-day, 7-day Exposure years: 2010	Mean = 18±1.1 Min = 0.8 Max = 67 Average 7 day Mean = 18±1 Min = 0.5 Max = 65 Maximum value 3 day Mean = 23±1.3 Min = 0.8 Max = 74 Maximum value 7 day Mean = 27±1.3 Min = 3 Max = 76	in the ED using diagnosis codes: ICD-9-CM: 634.xx, 632.xx, 637.9; ICD-10: O03.4, O03.6, O03.12 Spontaneous pregnancy loss diagnosed in the ED using diagnosis codes: ICD-9-CM: 634.xx, 632.xx, 637.9; ICD-10: O03.4, O03.6, O03.10 Spontaneous pregnancy loss diagnosed in the ED using diagnosis codes: ICD-9-CM: 634.xx, 632.xx, 637.9; ICD-10: O03.4, O03.6, O03.11 Spontaneous pregnancy loss diagnosed in the ED using diagnosis codes: ICD-9-CM: 634.xx, 632.xx,	Adjusted for: average daily temperature	Hispanic participants (7-day maximum): 0.99 (0.77, 1.28) Hispanic participants (7-day average): 1.26 (0.89, 1.80) Hispanic participants (3-day average): 1.11 (0.85, 1.47) Hispanic participants (3-day maximum): 1.05 (0.83, 1.34)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				637.9; ICD-10: O03.4, O03.6, O03.9		

† Sarovar et al. (2020)	Stillbirths that occurred in California. Included only singleton births. Limited our study population to include stillbirths with conception dates, estimated as two weeks after the reported last menstrual period, between 20 weeks prior to January 1, 1999, and 44 weeks prior to December 31, 2009.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 1999–2009	NO ₂ (ppb) Overall Mean = 36.8 Median = 35 P5 = 10 P95 = 72	Stillbirths identified by the Fetal Death Statistical data (defined as death of a fetus with at least 20 weeks of gestation prior to complete expulsion or extraction from mother)	Time-stratified case-crossover Adjusted for: apparent temperature (lag 2-6)	OR (calculated from percent change in odds provided by authors) (95% CI) ^b Lag 4: 1.00 (0.96, 1.05) (Lag 4) Fetal sex: male: 1.02 (0.97, 1.08) (Lag 4) Fetal sex: female: 0.99 (0.93, 1.05) (Lag 4) Maternal race/ethnicity: non-Hispanic Black: 1.10 (0.92, 1.30) (Lag 4) Maternal race/ethnicity: non-Hispanic Asian: 0.96 (0.82, 1.13) (Lag 4) Maternal race/ethnicity: Hispanic: 1.00 (0.92, 1.07) (Lag 4) Maternal race/ethnicity: non-Hispanic white: 1.03 (0.88, 1.20) (Lag 4) Gestational Length: Preterm (20-36 weeks): 1.00 (0.95, 1.05) (Lag 4) Gestational Length: 20–25 weeks: 1.02 (0.93, 1.13) (Lag 4) Gestational Length: 26-30 weeks: 0.98 (0.85, 1.12) (Lag 4) Gestational

Length: 31-33 weeks:
 0.97 (0.86, 1.10)
 (Lag 4) Gestational
 Length: 34-36 weeks:
 1.07 (0.91, 1.24)
 (Lag 4) Gestational
 Length: Term (37-44
 weeks):
 1.02 (0.93, 1.11)

(Lag 4) Maternal age: $\leq$
 24:
 1.01 (0.90, 1.13)
 (Lag 4) Maternal age: 25–
 34:
 1.08 (0.99, 1.17)
 (Lag 4) Maternal age: ≥ 35 :
 0.96 (0.87, 1.05)

(Lag 4) Cause of death:
 congenital malformations:
 1.12 (0.92, 1.37)
 (Lag 4) Cause of death:
 obstetric complications:
 0.98 (0.82, 1.17)
 (Lag 4) Cause of death:
 fetal growth:
 1.12 (0.98, 1.28)
 (Lag 4) Cause of death:
 disorders of fetus:
 1.16 (0.84, 1.60)
 (Lag 4) Cause of death:
 maternal complications:
 1.05 (0.92, 1.19)

(Lag 4) Maternal
 education: $\leq$ high school:
 1.02 (0.93, 1.12)
 (Lag 4) Maternal
 education: Some college:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						1.01 (0.94, 1.09)
† Williams et al. (2021)	Included deliveries at 23 weeks or later.	CMAQ	NO _x (ppb)	Perinatal mortality (pregnancy loss	Binary Poisson regression	NO _x
Consortium on Safe Labor (2002–2008)	Excluded multifetal pregnancies, mothers with thyroid disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Crohn's disease, as well as those with other autoimmune disease. Participants from one site for which ICD-9 codes were not reported and no cases of Type 1 diabetes were identified were also excluded.	Averaging time: NO _x - 1-hour max, Other, NO _x - 3-month preconception period	Trimester 1 Mean = 30.26 IQR = 29.06 Min = 5.51 Max = 89.62	≥23 weeks of gestation through neonatal mortality ≤7 days) as identified from medical records and ICD-9 codes	Adjusted for: maternal age, maternal race/ethnicity, preconception BMI, health insurance, marital status, smoking in pregnancy, alcohol use in pregnancy, other chronic diseases, and census region	RR (relative risk) (95% CI) ^c 3-m preconception: No Autoimmune: 0.99 (0.99, 0.99) 3-m preconception: T1D: 1.00 (0.95, 1.05) Trimester 1: T1D: 1.00 (0.95, 1.05) Trimester 1: No Autoimmune: 0.99 (0.99, 0.99) Trimester 2: T1D: 0.99 (0.95, 1.04) Trimester 2: No Autoimmune: 0.99 (0.99, 0.99) Entire Pregnancy: T1D: 0.92 (0.86, 0.98) Entire Pregnancy: No Autoimmune: 0.99 (0.98, 1.00)
With T1D n = 507 Without T1D n = 204,384		NO _x - trimester NO _x - whole pregnancy	Trimester 2 Mean = 30.13 IQR = 28.98 Min = 5.76 Max = 90.65			
Nationwide, U.S.		Exposure years: 2002–2008	3 months preconception Mean = 29.02 IQR = 27 Min = 5.09 Max = 92.97			
2002–2008			Entire pregnancy Mean = 29.8 IQR = 22.47 Min = 6.38 Max = 81.64			
Case-Control						

List of abbreviations in alphabetical order: NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; ppb = parts per billion; LUR = land use regression; BMI = body mass index; CI = confidence interval; OR = odds ratio; RR = rate ratio; IQR = interquartile range

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time

^cEstimates are not standardized

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-9 Epidemiologic studies of oxides of nitrogen and pregnancy outcomes of other pregnancy outcomes

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Ghassabian et al. (2019)	All cohorts included pregnant women who had data on first-trimester air pollution exposure and gestational thyroid function. Study excluded women with twin pregnancies, women with a history of thyroid disease, and women who reported taking medication affecting thyroid function.	LUR, Fixed site monitor	NO ₂ (µg/m ³)	Followed the recommendations of the American Thyroid Association guideline (i.e., free T4 concentrations in the lower 2.5th to 5th percentile of the population, despite a normal TSH level)	Random-effects meta-analysis of logistic regression models	NO ₂
Generation R, INMA, INfancia y Medio Ambiente, Amsterdam Born Children and Their Development Study (ABCD), Project Viva		Averaging time: ABCD, Generation R, INMA - 3 two-week air pollution monitoring campaigns were performed within 1 year (January 2009 to April 2011). NO ₂ and NO _x at the participants' home addresses were estimated on a daily basis for the whole period of pregnancy using LUR following a standardized procedure. Project Viva - calculated hourly ambient concentrations of NO ₂ by averaging data from the Massachusetts Department of Environmental Protection's greater Boston	ABCD Cohort Median = 41.6 (IQR 14.7)	Thyroid followed American Thyroid Association guideline (i.e., free T4 concentrations in the lower 2.5th to 5th percentile of the population, despite a normal TSH level)	Adjusted for: maternal age at enrollment; education; country of birth; smoking and alcohol intake during pregnancy; parity; pre-pregnancy body mass index; gestational age at thyroid measurement; socioeconomic status, defined marital status. The INMA sub-cohort was additionally adjusted for the 4 regions.	OR (95% CI) ^c Hypothyroxinemia: 0.96 (0.82, 1.12) High TSH: 1.02 (0.94, 1.12)
ABCD: n = 3,867 Generation R: n = 2,605 INMA: n = 2239 Project Viva: n = 737			Generation R Cohort Median = 40.7 (IQR 15.5)	Serum concentrations of TSH were measured at the median gestational age of 10–13 weeks depending on the cohort. Cohorts used different assays for measurements of thyroid hormones		NO _x
U.S., Spain, The Netherlands			INMA Cohort Median = 27.2 (IQR 22.2)			OR (95% CI) ^c Hypothyroxinemia: 0.95 (0.87, 1.03) High TSH: 0.99 (0.93, 1.06)
ABCD: January 2003–March 2004; Generation R: April 2002–January 2006; INMA: November 2003–January 2008; Project Viva: April 1999–November 2002			Project Viva Cohort Median = 21.6 (IQR 2.6)			
Cohort			NO _x (µg/m ³)			
			ABCD Cohort Median = 68.7 (IQR 38.8)			
			Generation R Cohort Median = 60.7 (IQR 34.8)			
			INMA Cohort Median = 51.3 (IQR 45.2)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		monitoring sites, then calculated daily and first-trimester NO ₂ exposure.				
		Exposure years: 1999–2011				

† Männistö et al. (2015)	Singleton pregnancies that resulted in deliveries at ≥ 23 weeks gestation from 12 centres across the US	Hybrid model	NO _x (ppb)	Cases were obtained from hospital discharge records. was ‘any cardiovascular event’ consisting of diagnoses of ischemic heart disease, stroke, heart failure, cardiac arrest/failure and other/ unspecified cardiovascular events	Logistic regression with GEE Adjusted for: site, maternal age, race/ethnicity, insurance status, smoking during pregnancy and pre-pregnancy body mass index Multipollutant models Adjusted for: site, maternal age, race/ethnicity, insurance status, smoking during pregnancy and pre-pregnancy body mass index, PM ₁₀ , O ₃ , CO, SO ₂	OR (95% CI) ^b No quantitative values reported in original manuscript. EEs are represented graphically in Figures 1 and 2 in the original manuscript.
Consortium on Safe Labor (2002–2008)		Averaging time: NO _x - 24-hour average	0 day lag Median = 19.6 (IQR 27.8) Min = 1.8 Max = 255.7			
n = 229,502		Exposure years: NR	1 day lag Median = 19.3 (IQR 27.9) Min = 1.8 Max = 255.7			
U.S.			2 day lag Median = 19 (IQR 27.3) Min = 1.8 Max = 255.7			
2002–2008			3 day lag Median = 18.8 (IQR 27) Min = 1.8 Max = 255.7			
Cohort			4 day lag Median = 18.9 (IQR 27.1) Min = 1.8 Max = 255.7			
			5 day lag Median = 19 (IQR 27.2) Min = 1.8 Max = 255.7			
			6 day lag			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 19.3 (IQR 27.8) Min = 1.8 Max = 255.7			
			7 day lag Median = 19.6 (IQR 27.8) Min = 1.8 Max = 255.8			

List of abbreviations in alphabetical order: NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; ppb = parts per billion; LUR = land use regression; BMI = body mass index; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; O₃ = ozone; CI = confidence interval; OR = odds ratio; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-10 Epidemiologic studies of oxides of nitrogen and birth outcomes of prenatal growth

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Prenatal Growth BW (Continuous)						
Aguilera et al. (2010)	Pregnant women who were recruited at their first routine prenatal care visit in the primary care center. Participants were excluded if < 16 years of age, having a nonsingleton	LUR r ² = 0.75 Averaging time: NO ₂ - weeks 1–12 NO ₂ - weeks 12–20	NO ₂ (µg/m ³) Weeks 1–12 Mean = 32.45±10.51 IQR = 12.19 Min = 8.91 Max = 76.16	Estimated fetal weight (EFW) was calculated using the Hadlock algorithm	Linear regression Adjusted for: season of conception, parity, maternal educational level, and maternal smoking	β (mean percent change in SD score) (95% CI) ^c Birth outcomes - Prenatal Growth - Estimated fetal weight measured at weeks 20–32 for exposure week 1–12: -1.60 (-4.63, 1.45) Birth outcomes - Prenatal Growth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: June 2004–July 2006 Cohort	pregnancy, not planning to deliver at the Sabadell hospital, and participating in an assisted reproduction program.	NO ₂ - weeks 20–32 Exposure years: 2004–2006	Weeks 12–20 Mean = 31.65±10.81 IQR = 11.47 Min = 6.65 Max = 75.14 Weeks 20–32 Mean = 32.13±10.84 IQR = 13.23 Min = 9.83 Max = 73.01			Estimated fetal weight measured at weeks 12–20 for exposure week 1–12: 1.16 (-2.83, 5.13) Birth outcomes - Prenatal Growth - Estimated fetal weight measured at weeks 12–20 for exposure week 12–20: 0.06 (-3.07, 4.27) Birth outcomes - Prenatal Growth - Estimated fetal weight measured at weeks 20–32 for exposure week 12–20: 0.52 (-2.22, 3.25) Birth outcomes - Prenatal Growth - Estimated fetal weight measured at weeks 20–32 for exposure week 20–32: 1.28 (-1.93, 4.47)
Ballester et al. (2010) INMA, Infancia y Medio Ambiente n = 785 Valencia, Spain Enrollment: November 2003–June 2005 Cohort	Pregnant women in the Valencia	LUR Averaging time: NO ₂ - Entire pregnancy NO ₂ - Trimester 1 NO ₂ - Trimester 2 NO ₂ - Trimester 3 Exposure years: 2003–2005	NO ₂ (µg/m ³) Entire pregnancy Mean = 36.9 Median = 37.9 (IQR 16.2) P25 = 29.4 P75 = 45.6 Trimester 1 Mean = 37.9 Median = 38.1 (IQR 20.3) P25 = 28.2 P75 = 48.5 Trimester 2	Birth weight was measured by the midwife that attended the birth	Linear regression Adjusted for: maternal age, maternal pre-pregnancy weight, maternal height, paternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, country of origin, sex of the infant, and season of last menstrual period	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight, Trimester 1: -12.78 (-34.54, 8.97) Birth outcomes - Prenatal Growth - Birth weight, Trimester 2: -9.96 (-32.59, 12.67) Birth outcomes - Prenatal Growth - Birth weight, Trimester 3: -4.29 (-25.92, 17.34) Birth outcomes - Prenatal Growth - Birth weight, Entire pregnancy exposure: -9.73 (-33.22, 13.76)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 35.9 Median = 35.2 (IQR 17.7) P25 = 26.5 P75 = 44.2 Trimester 3 Mean = 37 Median = 37 (IQR 18.8) P25 = 27.3 P75 = 46.1			
Estarlich et al. (2011) INMA, Infancia y Medio Ambiente n = 2,644 Spain November 2003-February 2008 Cohort	Inclusion criteria were age ≥ 16 years, singleton pregnancy, enrollment at 10–13 weeks of gestation, no assisted conception, delivery scheduled at the reference hospital, and no communication handicap.	LUR r ² = 0.521-0.750 (depending on region) Averaging time: NO ₂ - Trimester 1 NO ₂ - Trimester 2 NO ₂ - Trimester 3 Exposure years: 2003–2008	NO ₂ (ug/m ³) All Mean = 29.2±11.1 Rural Mean = 16.4±4.9 Urban Mean = 29.8±11	Birth weight was measured by the midwife attending the birth	GAM Adjusted for: maternal age, maternal pre-pregnancy weight, maternal height, paternal height, gestational weight gain, parity, cohabitation with the baby's father, maternal working status, smoking during pregnancy, country of origin, sex of the infant, rural, and season of last menstrual period, type of cooker	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Weight: -10.80 (-31.20, 9.80)
Iñiguez et al. (2012) INMA, Infancia y Medio Ambiente n = 785	Inclusion criteria: Age ≥16 years, singleton pregnancy, unassisted conception and no communication problems.	LUR r ² = 0.81 Averaging time: NO ₂ - Week 12	NO ₂ (ppb) Median = 220.2	Birth weight was measured by the midwife attending the birth	GAM Adjusted for: maternal gestational weight gain, socio-occupational status, education,	β (mean percent change in SD score) (95% CI) ^c Birth outcomes - Prenatal Growth - Estimated Fetal Weight for 0–12 week exposure period: -1.20 (-3.70, 1.30)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Spain November 2003–June 2005 Cohort		NO ₂ - Week 20 NO ₂ - Week 32 Exposure years: 2003–2005			employment, country of origin, zone of residence, parity, tobacco, alcohol and caffeine consumption and vegetable, fruit and energy intake, season of conception and the newborn's sex	Birth outcomes - Prenatal Growth - Estimated Fetal Weight for 12–20 week exposure period: -1.30 (-3.80, 1.20) Birth outcomes - Prenatal Growth - Estimated Fetal Weight for 20–32 week exposure period: -0.70 (-3.30, 1.90) Birth outcomes - Prenatal Growth - Estimated Fetal Weight for 32–birth week exposure period: -0.20 (-2.50, 2.20) Birth outcomes - Prenatal Growth - Estimated Fetal Weight for Entire pregnancy exposure period: -1.00 (-1.60, 1.60)
Pedersen et al. (2013) Gene and Environment Prospective Study on Infancy in Italy (GASPII), Generation R, INMA, Infancia y Medio Ambiente, Norwegian Mother and Child Cohort Study (MoBa), Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort, Danish National Birth Cohort (DNBC), European Study of Cohorts for Air Pollution Effects (ESCAPE), Amsterdam Born Children and Their Development Study (ABCD), Etude des Determinants Pre et Postnataux du Developpement et de la Sante	In study area, had a singleton delivery in time frame, had information about home addresses during pregnancy, infant birthweight, gestational age, and sex	LUR The LUR models explained 58-90% of the variability in the annual average concentrations of NO ₂ , and 63-88% for NO _x Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2008–2011	NO ₂ (ppb) Overall Mean = 13.9 (26.2 µg/m ³) P5 = 6.22 (11.7 µg/m ³) P95 = 24.3 (45.8 µg/m ³) NO _x (µg/m ³) Overall Mean = 45.5 P5 = 15.4 P95 = 91.1	Low birth weight at term was defined as weight <2500 g at birth after 37 weeks of gestation	Linear regression with random effect Adjusted for: gestational age (weeks and [weeks] ²), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June,	NO ₂ β (Change in birth weight (g)) (95% CI) ^b Birth outcomes - Prenatal Growth - Term birth weight for NO ₂ Exposure: -1.88 (-11.29, 7.53) NO _x β (Change in birth weight (g)) (95% CI) ^c Birth outcomes - Prenatal Growth - Term birth weight for NO _x Exposure: -1.00 (-4.00, 3.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
de l'Enfant (EDEN), Children, Allergy, Environment, Stockholm, Epidemiology (BAMSE), Born In Bradford (BIB), Mother-child Greek cohort (RHEA), KANC, DUISBURG					July–September, October–December)	
N = 74,178 births						
Sweden, France, England, Spain, Italy, Norway, Germany, Greece, Hungary, Lithuania, Netherlands						
Singleton deliveries between: February 11, 1994–June 2, 2011						
Cohort						
†Bravo et al. (2024)	All births that meet the following criteria: (1) geocoded, (2) singleton births with no known congenital anomalies that were born to mothers between ages 15-44 years old who were non-Hispanic Black or non-Hispanic white, (3) resided in the Lower Peninsula of Michigan, (4) had non-missing air pollution and temperature data for the duration of gestation, and (5) births	Ensemble machine learning model Method validation NR Averaging time: NO ₂ - 24-hour average Exposure years: 2007–2012	NO ₂ (ppb) Overall Mean = 21.4±8.28 Median = 22 (IQR 11) Min = 0.128 Max = 61.7 P25 = 16.1 P75 = 27.1	Birth weight obtained from birth records	Distributed lag nonlinear models Adjusted for: infant sex (male/female), birth order (1, 2, 3, ≥4), and maternal race (NHB, NHW); age group (15–19, 20–24, 25–29, 30–34, 35–39, 40–44 years); educational attainment (not a high school graduate, high school graduate, college graduate); marital status (married/unmarried) smoking during	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Cumulative change in birth weight for preterm births (gestational age 32-36 weeks): -4.21 (-13.18, 4.76) Birth outcomes - Prenatal Growth - Cumulative change in birth weight for early term births (gestational age 37-38 weeks): -3.06 (-7.91, 1.79) Birth outcomes - Prenatal Growth - Cumulative change in birth weight for full term births (gestational age 39-42 weeks): -11.69 (-14.46, -8.92)
N = 701,201 n = 497,897						
Michigan, U.S.						
2007–2012						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	that had non-missing infant characteristics.				pregnancy (yes/no); gestational diabetes (yes/no); hypertension (yes/no); prenatal care (yes/no); median household income in the Census block group of maternal residence; temperature; season; and year of birth	Birth outcomes - Prenatal Growth - Cumulative change in birth weight for preterm births (gestational age 32-36 weeks) - co-adjusted for PM _{2.5} : -0.25 (-9.78, 9.28) Birth outcomes - Prenatal Growth - Cumulative change in birth weight for early term births (gestational age 37-38 weeks) - co-adjusted for PM _{2.5} : -2.10 (-7.10, 2.90) Birth outcomes - Prenatal Growth - Cumulative change in birth weight for full term births (gestational age 39-42 weeks) - co-adjusted for PM _{2.5} : -11.80 (-14.66, -8.94)
† Clemente et al. (2015) INMA, Infancia y Medio Ambiente, ENVIRONAGE (ENVIRONmental influence ON AGEing) n = 926 INMA n = 376 ENVIRONAGE n = 550 Gipuzkoa, Sabadell, Valencia, Asturias, Genk, Spain, Belgium INMA Enrollment: 2004–2008; Follow-up: through 2009 (birth) ENVIRONAGE Enrollment:	INMA Cohort included pregnant women ≥ 16 years of age, a singleton pregnancy, intention to deliver at the reference hospital, no problems of communication, and no assisted conception. ENVIRONAGE Cohort included pregnant women ≥ 18 years of age, singleton pregnancy, and ability to fill out questionnaires in	LUR, Spatiotemporal/geospatial model The validation statistics gave a spatial explained variance for annual mean NO ₂ r ² = 0.52 to 0.75 Averaging time: NO ₂ - trimester 1 NO ₂ - trimester 2 NO ₂ - trimester 3 NO ₂ - entire pregnancy	NO ₂ (µg/m ³) ENVIRONAGE Cohort Entire Pregnancy Mean = 21.1±4.2 Median = 20.8 P5 = 12.6 P25 = 18.2 P75 = 23.7 P95 = 40.3 Trimester 1 Mean = 20.7±6.1 Median = 20.2 P5 = 7.3 P25 = 16.3 P75 = 24.9	Birth weight was collected by birth records.	GAM Adjusted for: newborn's sex, season of birth, maternal age, maternal smoking status, parity, ethnicity, education, gestational age (linear and quadratic), and pre-pregnancy BMI	β (differences in birth weight (g)) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight from INMA Cohort, Trimester 1: -58.20 (-94.50, -17.80) Birth outcomes - Prenatal Growth - Birth weight from INMA Cohort, Trimester 2: -56.30 (-96.20, -16.40) Birth outcomes - Prenatal Growth - Birth weight from INMA Cohort, Trimester 3: -52.10 (-93.80, -12.50) Birth outcomes - Prenatal Growth - Birth weight from ENVIRONAGE Cohort, Trimester 1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2010–2013; Follow-up: through 2014 (birth) Cohort	Dutch.	Exposure years: 2004–2014	P95 = 39.2 Trimester 2 Mean = 20.8±6 Median = 20.5 P5 = 8.6 P25 = 16.2 P75 = 25.1 P95 = 46 Trimester 3 Mean = 21.4±6.1 Median = 20.8 P5 = 9.2 P25 = 16.9 P75 = 25.6 P95 = 40.3 INMA and ENVIRONAGE Entire Pregnancy Mean = 22.7±8.3 Median = 21.2 P5 = 5.7 P25 = 17.6 P75 = 25.6 P95 = 66.7 Trimester 1 Mean = 22.7±9.8 Median = 21.2 P5 = 5.6 P25 = 16.1 P75 = 26.8 P95 = 74.2 Trimester 2 Mean = 22.6±9.1 Median = 21.3 P5 = 5.7 P25 = 15.9			-20.00 (-91.30, 51.30) Birth outcomes - Prenatal Growth - Birth weight from ENVIRONAGE Cohort, Trimester 2: -3.40 (-76.40, 69.50) Birth outcomes - Prenatal Growth - Birth weight from ENVIRONAGE Cohort, Trimester 3: -29.90 (-98.20, 38.30) Birth outcomes - Prenatal Growth - Birth weight from INMA Cohort, Entire Pregnancy: -66.40 (-110.00, -22.70) Birth outcomes - Prenatal Growth - Birth weight from INMA and ENVIRONAGE Cohorts, Trimester 1: -44.10 (-77.40, -10.80) Birth outcomes - Prenatal Growth - Birth weight from INMA and ENVIRONAGE Cohorts, Trimester 2: -36.20 (-70.90, -1.60) Birth outcomes - Prenatal Growth - Birth weight from INMA and ENVIRONAGE Cohorts, Trimester 3: -37.50 (-71.40, -3.60) Birth outcomes - Prenatal Growth - Birth weight from INMA and ENVIRONAGE Cohorts, Entire pregnancy: -47.50 (-86.60, -8.50) Birth outcomes - Prenatal Growth - Birth weight from ENVIRONAGE Cohort, Entire pregnancy:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 27.3 P95 = 74.7 Trimester 3 Mean = 23±9.3 Median = 21.5 P5 = 5.7 P25 = 16.7 P75 = 27.3 P95 = 74.4 INMA Cohort Entire Pregnancy Mean = 25.5±11.4 Median = 24 P5 = 5.7 P25 = 17.2 P75 = 32.3 P95 = 66.7 Trimester 1 Mean = 26.1±12.9 Median = 23.1 P5 = 5.6 P25 = 16.4 P75 = 33.7 P95 = 74.2 Trimester 2 Mean = 25.6±11.6 Median = 24.8 P5 = 5.7 P25 = 16.4 P75 = 31.2 P95 = 74.7 Trimester 3 Mean = 25.7±12.1 Median = 23.8 P5 = 5.7 P25 = 16.9			-19.80 (-101.10, 61.70)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 32.3 P95 = 74.4			
† Dong et al. (2022)	Excluded births without linked NO ₂ exposure data and restricted the data set to singleton full-term (between 37 and 42 weeks) live births with a minimum birth weight of 500 g and a maximum of 6,000 g. Excluded births because of their missing covariate data, mostly due to missing mother's weight gain during the pregnancy, percentage below poverty line, and the Kotelchuck's Adequacy of Prenatal Care Utilization index.	Ensemble machine learning model, Fixed site monitor, Hybrid model r ² = 0.79 Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2015	NO ₂ (ppb) 0–30 Days before delivery Mean = 22.6 IQR = 12.8 31–280 days before delivery Mean = 22.9 IQR = 10.1	Massachusetts Birth Registry records with LBW defined as birth weight less than 2,500 g	Marginal structural model using stabilized inverse-probability weights	β (differences in birth weight (g)) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight - 31–280 days NO ₂ exposure: -14.00 (-16.10, -11.80) Birth outcomes - Prenatal Growth - Birth weight - 0–30 days NO ₂ exposure: -8.20 (-10.40, -6.10)
† Guo et al. (2020)	Births among mothers were permanent residents living in Guangdong province and recorded in the China's Household Registration System. Exclusions included, stillbirths, birth between 22 and 42 completed weeks of gestation and in which the last menstrual	Central site monitor Averaging time: NO ₂ - first trimester NO ₂ - second trimester NO ₂ - third trimester NO ₂ - entire pregnancy	NO ₂ (μg/m ³) Entire pregnancy Mean = 26.28±10.97 Median = 23.87 (IQR 14.56) Min = 7.21 Max = 71.37 P25 = 17.97 P75 = 32.36 First trimester Mean = 26.56±12.27	Term low birth weight (LBW) was defined as birth weight less than 2500 g and gestational age greater than 37 weeks	GEE linear regression Adjusted for: maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, neonate's sex, gestational age as linear and quadratic terms, meteorological factors and an	β (Change in term birth weight (g)) (95% CI) ^c Birth outcomes - Prenatal Growth - Term low birth weight for exposure during trimester 1: -1.89 (-4.14, 0.36) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during trimester 2: -2.90 (-5.57, -0.23) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during trimester 3:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	period was recorded, maternal age outliers (<16 or >50 years) were then identified and excluded according to the average age of menarche and natural menopausal age in Chinese population, and missing or implausible combinations of birth weight and gestational age	Exposure years: 2014–2017	Median = 24.53 (IQR 15.47) Min = 4.56 Max = 84.7 P25 = 16.93 P75 = 32.66 Second trimester Mean = 26.12±12.35 Median = 24.27 (IQR 15.94) Min = 4.6 Max = 86.61 P25 = 16.44 P75 = 32.14 Third trimester Mean = 26.17±12.17 Median = 24.1 (IQR 15.73) Min = 4.51 Max = 87.12 P25 = 16.6 P75 = 32.62		interaction term (pollutant exposures × month of conception)	-1.44 (-4.33, 1.46) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during entire pregnancy, adjusted for CO: -0.84 (-3.73, 2.05) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during entire pregnancy, adjusted for O₃: -4.39 (-7.52, -1.26) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during entire pregnancy, adjusted for PM₁₀: 2.01 (-1.24, 5.26) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during entire pregnancy, adjusted for PM_{2.5}: 0.45 (-2.68, 3.58) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during entire pregnancy, adjusted for SO₂: -2.71 (-5.60, 0.17) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during first trimester, adjusted for CO: -0.49 (-2.81, 1.84) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during first trimester, adjusted for O₃: -3.61 (-6.43, -0.79) Birth outcomes - Prenatal Growth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Term low birth weight for exposure during first trimester, adjusted for PM₁₀: 2.78 (0.27, 5.29) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during first trimester, adjusted for PM_{2.5}: 1.47 (-0.96, 3.89) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during first trimester, adjusted for SO₂: -0.98 (-3.33, 1.37) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during second trimester, adjusted for CO: -1.22 (-3.96, 1.52) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during second trimester, adjusted for O₃: -3.75 (-6.58, -0.92) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during second trimester, adjusted for PM₁₀: -0.82 (-4.20, 2.57) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during second trimester, adjusted for PM_{2.5}: -1.27 (-4.23, 1.68) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during second trimester, adjusted for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						SO ₂ : -1.40 (-4.40, 1.60) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during third trimester, adjusted for CO: -1.27 (-4.23, 1.68) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during third trimester, adjusted for O ₃ : -1.40 (-4.40, 1.60) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during third trimester, adjusted for PM ₁₀ : -1.14 (-4.48, 2.20) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during third trimester, adjusted for PM _{2.5} : -1.33 (-4.61, 1.95) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during third trimester, adjusted for SO ₂ : -2.57 (-5.52, 0.39) Birth outcomes - Prenatal Growth - Term low birth weight for exposure during entire pregnancy: -2.71 (-5.53, 0.11)
† Hao et al. (2023) Bureau of Epidemiology and Public Health Informatics, Kansas	Only singleton pregnancies with a gestational age of 27–42 weeks with an estimated date of	Spatiotemporal/geospatial model, Ensemble machine learning model	NO ₂ (ppb) 1st Trimester Mean = 10.9	Term birth weight for births gestational age ≥37 weeks	Linear regression Adjusted for: maternal education level, race, ethnicity, age, marital	NO ₂ β (Mean difference, in grams) (95% CI) ^c Birth outcomes - Prenatal Growth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Preterm Birth Cohort n = 596,926 Birthweight Cohort n = 554,787 Gestational Diabetes Cohort n = 449,871 Gestational Hypertension Cohort n = 590,574 Kansas, U.S. Enrollment: 1999–2016 Follow-up: through pregnancy and birth Cohort	conception between January 1st, 2000, and December 31st, 2015, were included. We excluded births with (a) missing census tract information; (b) maternal age <10 years or >55 years; (c) birth weight <250 g or >7500 g. For the outcomes of GDM and GH, we also excluded mothers with pre-existing diabetes or pre-existing hypertension.	Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2000–2016	2nd Trimester Mean = 10.88 3rd Trimester Mean = 11.01 2000–2004 Mean = 12.12 2010–2015 Mean = 10.23 Total Pregnancy Mean = 10.16		status, smoking, infant parity, zip code level percent below poverty, census tract level greenness, season of conception, and long-term trend using a natural cubic spline on conception date with 5 degrees of freedom	Term birth weight - First 6 weeks: 1.58 (-1.67, 4.84) Birth outcomes - Prenatal Growth - Term birth weight - First 4 weeks: 0.99 (-2.19, 4.17) Birth outcomes - Prenatal Growth - Term birth weight - Trimester 1: 2.88 (-0.48, 6.24) Birth outcomes - Prenatal Growth - Term birth weight - Trimester 2: 3.37 (0.02, 6.73) Birth outcomes - Prenatal Growth - Term birth weight - Trimester 3: 1.39 (-2.05, 4.83) Birth outcomes - Prenatal Growth - Term birth weight - Entire pregnancy: -2.12 (-4.46, 0.22)
† Hjortebjerg et al. (2016) Danish National Birth Cohort (DNBC) N = 75,166 Nationwide, Denmark Enrollment: 1996–2002 Follow-up: during and after pregnancy Cohort	We included first enrolled pregnancy, for whom information on home addresses of the mother during pregnancy and her child's size at birth were available. Also included live-born singletons, we excluded 443 mother and child pairs with incomplete information on exposure data from conception until birth, 439 with missing or implausible birth weight and gestational	Dispersion model Method validation NR Averaging time: NO ₂ - monthly NO ₂ - trimester NO _x - monthly NO _x - trimester NO _x - pregnancy Exposure years: 1996–2002	NO ₂ (ug/m ³) All Median = 11 P5 = 7.1 P95 = 26.3 Living outside a major city Median = 10.5 P5 = 7 P95 = 19.6 Living within a major city Median = 17.1 P5 = 8.9 P95 = 39.8	Birth weight was measured by a calibrated digital baby weight or by using a steelyard, according to standard methods at each place of birth.	Linear regression Adjusted for: estational age, sex, maternal age at conception, pre-pregnancy BMI, maternal height, parity, season of conception, educational level, disposable income, smoking and alcohol consumption during pregnancy and living within one of the 3 largest cities in Denmark (Copenhagen, Aarhus or Odense) at time of birth	NO ₂ β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight: 0.21 (-5.20, 5.62) Birth outcomes - Prenatal Growth - Birth weight - Co-adjustment for traffic noise: 3.26 (-3.19, 9.71) Birth outcomes - Prenatal Growth - Birth weight: 0.21 (-5.20, 5.62) NO _x β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	age combinations, 3820 with missing information on placental weight, 1191 with missing information on head circumference, 1410 with missing information on abdominal circumference, and 5905 not being the first enrolled child within the DNBC.					Birth weight: -0.62 (-4.08, 2.85) Birth outcomes - Prenatal Growth - Birth weight - Co-adjustment for traffic noise: 1.15 (-3.07, 5.37)
[†] Johnson et al. (2022) Maternal-Infant Research on Environmental Chemicals (MIREC) Study N = 1,305 Nationwide, Canada 2008–2011 Cohort	Analyses were restricted to live, singleton, full-term births. Participants with >25% of their daily concentrations missing during the study period were excluded from PM _{2.5} and NO ₂ analyses. We also excluded participants with missing residential, BMI, income, education, infant sex, and alcohol consumption during pregnancy data. Excluded participants living in large (>20 × 20 km) forward sortation areas.	Fixed site monitor, LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2008–2011	NO ₂ (ppb) All Daily Values Mean = 16.4±13.7 Median = 12.6 Min = 0.001 Max = 119.4 Unimputed Only Mean = 18.5±13.7 Median = 15.9 Min = 0.001 Max = 118.1	Full-term births from Maternal–Infant Research on Environmental Chemicals (MIREC)	Bayesian Metropolis–Hastings algorithm and empirical density threshold Adjusted for: alcohol consumption during pregnancy, birth season, education, ethnicity, household income, marital status, maternal age at delivery, maternal smoking during pregnancy, parity, and pre-pregnancy BM	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure pre-pregnancy (days -90–0): -2.00 (-4.00, 0.00) Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure during mid-pregnancy (days 55–145): -3.00 (-5.00, -1.00) Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure Entire Pregnancy and Pre-pregnancy (days -90–272): -3.00 (-5.00, 1.00) Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure Entire Pregnancy (days 1–272): -3.00 (-5.00, 1.00) Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure Trimester 1 (days 1–91): -2.00 (-4.00, -0.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure Trimester 2 (days 92–182): -3.00 (-5.00, 1.00) Birth outcomes - Prenatal Growth - Birth weight - NO ₂ exposure Trimester 3 (days 183–272): -3.00 (-5.00, 1.00)
† Li et al. (2016a) n = 1,164,818 Los Angeles County, CA, U.S. January 1, 2001–December 31, 2008 Cohort	Births in Los Angeles County, CA, with exclusions for multiple births, recorded birth defects, and unknown birth defects status	Spatiotemporal/geospatial model Averaging time: NO ₂ - trimester 1 NO ₂ - trimester 2 NO ₂ - trimester 3 NO ₂ - entire pregnancy NO _x - trimester 1 NO _x - trimester 2 NO _x - trimester 3 NO _x - entire pregnancy Exposure years: 2001–2008	NO ₂ (ppb) Mean = 25 Median = 24.14 (IQR 11.43) P25 = 18.74 P75 = 30.17 NO _x (ppb) Mean = 17.32 Median = 26.14 (IQR 31.32) P25 = 15.48 P75 = 46.8	Birth weight was obtained from birth certificate records	Two-stage Bayesian hierarchical non-linear models	NO ₂ β (Change in term birth weight (g)) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight - Trimester 1: -0.99 (-1.39, -0.59) Birth outcomes - Prenatal Growth - Birth weight - Trimester 2: -0.79 (-1.26, -0.32) Birth outcomes - Prenatal Growth - Birth weight - Trimester 3: -1.27 (-1.72, -0.82) Birth outcomes - Prenatal Growth - Birth weight - Entire pregnancy: -1.89 (-2.23, -1.55) NO _x β (Change in term birth weight (g)) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight - Trimester 1: -0.54 (-0.80, -0.28) Birth outcomes - Prenatal Growth - Birth weight - Trimester 2: -0.52 (-0.78, -0.26) Birth outcomes - Prenatal Growth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth weight - Trimester 3: -0.61 (-0.90, -0.32) Birth outcomes - Prenatal Growth - Birth weight - Entire pregnancy: -0.87 (-1.09, -0.65)
† Mendoza-Ramirez et al. (2018)	Pregnant women (n = 1094) were randomized to receive a daily supplement of 400 mg of DHA or placebo from 18–22 weeks of pregnancy until delivery. eligible women were 18–35 years of age, at 18–22 weeks of gestation, planned to deliver at the Mexican Institute of Social Security General Hospital in Morelos, Mexico and planned to live in the area for 2 years after delivery.	LUR, Fixed site monitor Method validation NR Averaging time: NO ₂ - 2 weeks NO _x - 2 weeks NO - 2 weeks Exposure years: 2009	NO ₂ (ppb) Overall Mean = 19.9±23.8 Median = 16.5 P25 = 10.7 P75 = 20.8 NO (ppb) Overall Mean = 2.7±2.04 Median = 2.01 P25 = 1.2 P75 = 4.1 NO _x (ppb) Overall Mean = 19.6±5.6 Median = 21.04 P25 = 16.2 P75 = 23.5	Birth weight was obtained according to the technique proposed by Lohman et al., using a TANITA “mommy and baby” scale with a precision of ±20 grams.	Linear regression Adjusted for: mother’s age and height, gestational age, sex, and passive smoking	NO β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight: -42.46 (-82.73, -2.18) NO ₂ β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight: 8.06 (-4.07, 20.20) NO _x β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Birth weight: -39.61 (-77.00, -2.21)
† Ouidir et al. (2021a)	Mothers older than 18 years, delivered after 33 weeks of gestation, with single births or multiple of two.	Chemical transport model Averaging time: NO ₂ - entire pregnancy	NO ₂ (μg/m ³) 30 days before delivery Mean = 19.8±10.93 Median = 17.95	Birth weight of term births	GAM with inverse probability weighting and doubly robust methods Adjusted for: using the	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Term birth weight for Entire pregnancy: 8.97 (-4.73, 22.67) Birth outcomes - Prenatal Growth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
France		NO ₂ - trimester 1	(IQR 15.95)		stabilized inverse	Term birth weight for Trimester 1: 20.93 (9.90, 31.95)
		NO ₂ - trimester 2	P5 = 5.45		probability to be	
		NO ₂ - trimester 3	P25 = 11.04		exposed to air pollutants	Birth outcomes - Prenatal Growth -
2011		NO ₂ - 30 days	P75 = 26.99		calculated using	Term birth weight for Trimester 2: -8.93 (-21.29, 3.43)
		before delivery	P95 = 40.68		maternal education, in	
Cohort		NO ₂ - 60 days			relationship status,	Birth outcomes - Prenatal Growth -
		before delivery	60 days before		parity, sex of the child,	Birth outcomes - Prenatal Growth -
		NO ₂ - 90 days	delivery		maternal active smoking	Term birth weight for Trimester 3: -10.21 (-22.20, 1.79)
		before delivery	Mean = 18.74±10.17		during pregnancy, social	
			Median = 16.92		deprivation, maternal	Birth outcomes - Prenatal Growth -
		Exposure years: 2011	(IQR 14.31)		French citizenship,	Term birth weight for 30 days before delivery: 6.21 (-3.93, 16.35)
			P5 = 5.54		maternal age, weight	
			P25 = 10.76		before pregnancy,	Birth outcomes - Prenatal Growth -
			P75 = 25.07		maternal height and	Term birth weight for 60 days before delivery: 1.15 (-9.79, 12.10)
			P95 = 38.42		further adjusted for	
					urbanization level and	Term birth weight for 90 days before delivery: -0.78 (-12.23, 10.67)
			90 days before		season of conception	
			delivery			
			Mean = 18.61±9.82			
			Median = 16.82			
			(IQR 14)			
			P5 = 5.83			
			P25 = 10.91			
			P75 = 24.91			
			P95 = 38.05			
			Entire pregnancy			
			Mean = 20.01±8.89			
			Median = 18.85			
			(IQR 13.4)			
			P5 = 7.71			
			P25 = 12.82			
			P75 = 26.22			
			P95 = 36.15			
			Trimester 1			
			Mean = 22.08±10.34			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 20.7 (IQR 14.83) P5 = 7.44 P25 = 14.05 P75 = 28.88 P95 = 41.17 Trimester 2 Mean = 19.06±10.57 Median = 16.97 (IQR 14.63) P5 = 5.57 P25 = 10.76 P75 = 25.39 P95 = 39.98 Trimester 3 Mean = 18.8±10.06 Median = 16.95 (IQR 14.02) P5 = 5.81 P25 = 10.98 P75 = 25 P95 = 38.86			
†Peterson et al. (2022) Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) N = 281 California, U.S. Baseline: 2015 Follow-up: through pregnancy,	Eligibility criteria for cohort entry included: (1) <30 weeks pregnant, (2) ≥ 18 years of age, and (3) fluent in English or Spanish. Exclusion criteria for the study included: (1) multiple gestation; (2) having a physical, mental, or cognitive	Fixed site monitor Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - weekly NO ₂ - pregnancy Exposure years: 2015	NO ₂ (ppb) Pregnancy Average Median = 15.5 (IQR 5.6) Weekly Average Median = 15.3 (IQR 5.6)	Fetal weight was estimated from the formula from Hadcock et al. which takes into account head circumference, biparietal diameter, femur length, and abdominal circumference	Distributed lag models Adjusted for: maternal age at time of study recruitment, maternal race and ethnicity, maternal education level, household income, parity, pre-pregnancy body mass index (BMI), sex of the fetus, gestational age at	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Fetal weight: -35.60 (-98.70, 27.50)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
at birth, and during first year of life Cohort	disability that would inhibit participation or the ability to provide consent; (3) current incarceration; or (4) HIV positive status.				time of ultrasound scan, lag specific average temperature, season of ultrasound, ultrasound technician, and recruitment site	
† Savitz et al. (2019) N = 257,956 births New York City, NY, U.S. Births between 2008–2010 Cohort	Excluded patients with missing or implausible gestational age (<22 or >42 weeks), multiple gestations, congenital abnormalities, known smokers, missing or implausible birth weight (<500 or >5,000g), missing covariates (e.g., education, parity), missing delivery hospital, or born in a hospital with fewer than 10 births over the course of the study period and restricted conception dates to avoid fixed-cohort bias.	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - 2 weeks during pregnancy Exposure years: 2008–2010	NO ₂ (ppb) Exposure distribution concentrations were not reported	Birth weight was obtained from birth records and hospital discharge data	Linear regression Adjusted for: maternal age, ethnicity, education, Medicaid status, parity, SES score, pre-pregnancy BMI, conception year, hospital as fixed effect, gestation age at delivery	NO ₂ β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Change in birth weight: -5.80 (-8.70, -2.90)
† Stieb et al. (2016) Canadian Birth Database N = 2,928,515 Nationwide, Canada Live births from 1999–2008	Included singleton live births	LUR, Hybrid model This model explained 73% of the variation Averaging time: NO ₂ - annual	NO ₂ (ppb) All Mean = 13.4±7.8 Median = 11.9 (IQR 11.5) P5 = 3.7 P95 = 27.8	Term birth weight was obtained from births with gestational age >37 weeks	GEE linear regression Adjusted for: maternal age and marital status, parity, urban/rural place of residence, airshed of maternal place of residence, place of birth of mother	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Term birth weight: -9.30 (-10.80, -7.80)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort		average Exposure years: 2005–2011			(within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority, infant sex, and gestational age, Socioeconomic status; proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education	
†Villeneuve et al. (2022) Canadian Birth Database N = ~2.2 million Nationwide, Canada Births between 1999–2008 Cohort	Analyses were restricted to all singleton live births that were accessed from the Canadian Birth Database through Statistics Canada (approximately 3.2 million births). We further restricted the study population to highly urbanized areas.	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - annual average, Other, NO ₂ - pregnancy Exposure years: 1999–2008	NO ₂ (ppb) All Singleton Births Mean = 16.7	Term birth weight was obtained from births with gestational age >37 weeks	Linear regression Adjusted for: neighbourhood SES, individual covariates and visible minority	β (grams) (95% CI) ^c Birth outcomes - Prenatal Growth - Term birth weight: -15.60 (-16.70, -14.50)
Prenatal Growth BW (Binary)						
Pedersen et al. (2013) Gene and Environment Prospective Study on Infancy in Italy (GASPII), Generation	In study area, had a singleton delivery in time frame, had information about home addresses during	LUR The LUR models explained 58-90% of the variability	NO ₂ (ppb) Overall Mean = 13.9 (26.2 µg/m ³)	Low birth weight at term was defined as weight <2500 g at birth after 37	Logistic regression with random effect Adjusted for: gestational age (weeks and	NO ₂ OR (95% CI) ^b Birth outcomes - Term birth weight for NO ₂ Exposure:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
R,INMA, Infancia y Medio Ambiente, Norwegian Mother and Child Cohort Study (MoBa), Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort, Danish National Birth Cohort (DNBC), European Study of Cohorts for Air Pollution Effects (ESCAPE), Amsterdam Born Children and Their Development Study (ABCD), Etude des Determinants Pre et Postnataux du Developpement et de la Sante de l'Enfant (EDEN), Children, Allergy, Environment, Stockholm, Epidemiology (BAMSE), Born In Bradford (BIB), Mother-child Greek cohort (RHEA), KANC, DUISBURG N = 74,178 births Sweden, France, England, Spain, Italy, Norway, Germany, Greece, Hungary, Lithuania, The Netherlands Singleton deliveries between: February 11, 1994–June 2, 2011 Cohort	pregnancy, infant birthweight, gestational age, and sex	in the annual average concentrations of NO₂, and 63-88% for NO_x Averaging time: NO₂ - annual average, NO_x - annual average Exposure years: 2008–2011	P5 = 6.22 (11.7 µg/m³) P95 = 24.3 (45.8 µg/m³) NO_x (µg/m³) Overall Mean = 45.5 P5 = 15.4 P95 = 91.1	weeks of gestation	[weeks]2), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December)	1.18 (1.00, 1.39) NO_x OR (95% CI)^c Birth outcomes - Term birth weight for NO_x Exposure: 1.04 (0.97, 1.11)
Wu et al. (2016) California Department of Public Health	Excluding infants who were born to women residing outside	Chemical transport model, Spatiotemporal/ge	NO₂ (ppb) Overall	Term low birth weight was <2500 g at birth	Generalized additive mixed models with random effects	NO₂ OR (95% CI)^c

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Health (CDPH) birth registry N = 4,370,371 pregnancies California, U.S. Births occurring from January 1, 2001–December 31, 2008 Cohort	California and whose addresses could not be geocoded or who had critical identifying information missing	ospatial model, Fixed site monitor Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2000–2008	Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6		Adjusted for: race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines	Birth outcomes - Term low birth weight (EBK NO ₂ exposure): 0.99 (0.96, 1.02) NO _x OR (95% CI) ^c Birth outcomes - Term low birth weight (CALINE NO _x exposure): 1.00 (0.99, 1.02)
† Dong et al. (2022) Massachusetts Birth Registry N = 844,554 Massachusetts, U.S. Births between January 1, 2001–December 31, 2015 Cohort	Excluded births without linked BC and NO ₂ exposure data and restricted the data set to singleton full-term (between 37 and 42 weeks) live births with a minimum birth weight of 500 g and a maximum of 6,000 g. Excluded births because of their missing covariate data, mostly due to missing mother's weight gain during the pregnancy, percentage below poverty line, and the Kotelchuck's Adequacy of Prenatal Care Utilization index.	Ensemble machine learning model, Fixed site monitor, Hybrid model r ² = 0.79 Averaging time: NO ₂ - 24-hour average Exposure years: 2001–2015	NO ₂ (ppb) 0-30 Days before delivery Mean = 22.6 IQR = 12.8 31–280 days before delivery Mean = 22.9 IQR = 10.1	Massachusetts Birth Registry records with LBW defined as birth weight less than 2,500 g	Marginal structural model using stabilized inverse-probability weights	OR (95% CI) ^c Birth outcomes - Low birth weight for NO ₂ exposure for 0-30 days: 1.05 (1.02, 1.08) Birth outcomes - Low birth weight for NO ₂ exposure for 31–280 days: 1.05 (1.02, 1.08)
† Fu et al. (2022) UK Biobank	Participants were excluded for the following reasons: (1) missing BW data; (2)	LUR, Spatiotemporal/geospatial model	NO ₂ (ppb) Overall Mean = 13.8 (25.9)	Low birth weight was defined as birth weight below	Binary logistic regression Adjusted for: adjusted	NO ₂ OR (95% CI) ^b Birth outcomes - Low birth weight:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = 214,129 England, Scotland, Wales, U.K. Enrollment: 2006–2010 Cohort	non-first-born BW data; and (3) missing air pollution data.	NO ₂ r ² = 87% NO _x r ² = 88% Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2005–2007, 2010	µg/m ³) IQR = 5 (9.4 µg/m ³) Min = 6.86 (12.9 µg/m ³) Max = 57.56 (108.3 µg/m ³) P25 = 11.3 (21.3 µg/m ³) P75 = 16.3 (30.7 µg/m ³) NO _x (µg/m ³) Overall Mean = 41.9 IQR = 15.8 Min = 19.7 Max = 265.9 P25 = 34.1 P75 = 49.9	2500 g	for age, race, Townsend Deprivation index, alcohol consumption (never, previous, current, missing), smoking status (never, previous, current, missing), body mass index (<25 kg/m ² , 25– 29.9 kg/m ² , ≥30 kg/m ² , missing), physical activity (MET- min/week), diabetes at baseline (yes/no), and gestational hypertension (yes/no)	1.02 (0.97, 1.07) NO _x OR (95% CI) ^c Birth outcomes - Low birth weight: 1.01 (0.99, 1.02)
† Guo et al. (2020) n = 2,868,870 Guangdong Province, China January 1, 2014–December 31, 2017 Cohort	Births among mothers were permanent residents living in Guangdong province and recorded in the China's Household Registration System. Exclusions included, stillbirths, birth between 22 and 42 completed weeks of gestation and in which the last menstrual period was recorded, maternal age outliers (<16 or >50 years) were	Central site monitor Averaging time: NO ₂ - first trimester NO ₂ - second trimester NO ₂ - third trimester NO ₂ - entire pregnancy Exposure years: 2014–2017	NO ₂ (ug/m ³) Entire pregnancy Mean = 26.28±10.97 Median = 23.87 (IQR 14.56) Min = 7.21 Max = 71.37 P25 = 17.97 P75 = 32.36 First trimester Mean = 26.56±12.27 Median = 24.53 (IQR 15.47) Min = 4.56	Term LBW was defined as birth weight less than 2500 g and gestational age greater than 37 weeks	GEE logistic regression Adjusted for: maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, neonate's sex, gestational age as linear and quadratic terms, meteorological factors and an interaction term (pollutant exposures × month of conception)	OR (95% CI) ^c Birth outcomes - Term low birth weight for exposure during entire pregnancy: 0.97 (0.92, 1.03) Birth outcomes - Term low birth weight for exposure during trimester 1: 0.98 (0.94, 1.02) Birth outcomes - Term low birth weight for exposure during trimester 2: 0.98 (0.93, 1.03) Birth outcomes - Term low birth weight for exposure during trimester 3:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	then identified and excluded according to the average age of menarche and natural menopausal age in Chinese population, and missing or implausible combinations of birth weight and gestational age		Max = 84.7 P25 = 16.93 P75 = 32.66 Second trimester Mean = 26.12±12.35 Median = 24.27 (IQR 15.94) Min = 4.6 Max = 86.61 P25 = 16.44 P75 = 32.14 Third trimester Mean = 26.17±12.17 Median = 24.1 (IQR 15.73) Min = 4.51 Max = 87.12 P25 = 16.6 P75 = 32.62			0.97 (0.92, 1.03) Birth outcomes - Term low birth weight for exposure during entire pregnancy, adjusted for CO: 0.96 (0.90, 1.01) Birth outcomes - Term low birth weight for exposure during entire pregnancy, adjusted for O ₃ : 0.97 (0.91, 1.03) Birth outcomes - Term low birth weight for exposure during entire pregnancy, adjusted for SO ₂ : 0.98 (0.93, 1.04) Birth outcomes - Term low birth weight for exposure during entire pregnancy, adjusted for PM ₁₀ : 0.96 (0.90, 1.02) Birth outcomes - Term low birth weight for exposure during entire pregnancy, adjusted for PM _{2.5} : 0.97 (0.91, 1.03)
†Lavigne et al. (2016b) Better Outcomes Registry & Network (BORN) Ontario N = 818,400 Ontario, Canada Recruitment: January 2005–March 2012 Cohort	Pregnant women giving birth in hospitals to live born, non-planned C-sections, singleton infants in Ontario, Canada were recruited in the first trimester of pregnancy. Women with postal codes of residence outside Ontario were excluded	LUR This model explained 73% of the variations in annual 2006 NO ₂ measurements Averaging time: NO ₂ - annual average Exposure years: 2005–2011	NO ₂ (ppb) Entire Pregnancy, Overall Mean = 15.89±6.38 Median = 16 (IQR 9) P5 = 6 P95 = 26 Trimester 1, Overall Mean = 16.2±6.87 Median = 16 (IQR 10)	Term low birth weight was defined as birth weight <2500 g	Mixed effect logistic regression models Adjusted for: maternal age at delivery, maternal cigarette smoking during pregnancy, infant sex, parity, previous caesarean section delivery, urban/rural place of residence, month of birth, year of birth, census dissemination area	OR (95% CI) ^c Birth outcomes - Term low birth weight - Overall: 0.99 (0.99, 0.99) Birth outcomes - Term low birth weight for maternal comorbidity of gestational diabetes: 1.002 (0.958, 1.047) Birth outcomes - Term low birth weight for maternal comorbidity of no gestational diabetes: 0.994 (0.982, 1.004)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 6 P95 = 28 Trimester 2, Overall Mean = 16.15±6.88 Median = 16 (IQR 10) P5 = 6 P95 = 28 Trimester 3, Overall Mean = 15.93±6.87 Median = 16 (IQR 9) P5 = 5 P95 = 28		median family income, census dissemination area proportion of population who are visible minority and census dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education	Birth outcomes - Term low birth weight for maternal comorbidity of preeclampsia: 0.974 (0.931, 1.022) Birth outcomes - Term low birth weight for maternal comorbidity of no preeclampsia: 0.996 (0.986, 1.006) Birth outcomes - Term low birth weight for maternal comorbidity of asthma: 0.99 (0.94, 1.05) Birth outcomes - Term low birth weight for maternal comorbidity of no asthma: 0.988 (0.978, 0.996) Birth outcomes - Term low birth weight for maternal comorbidity of heart disease: 0.998 (0.872, 1.143) Birth outcomes - Term low birth weight for maternal comorbidity of no heart disease: 0.992 (0.980, 1.002) Birth outcomes - Term low birth weight for maternal comorbidity of diabetes: 0.992 (0.914, 1.075) Birth outcomes - Term low birth weight for maternal comorbidity of no diabetes: 0.992 (0.980, 1.002) Birth outcomes - Term low birth

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						weight for maternal comorbidity of hypertension: 0.978 (0.903, 1.059) Birth outcomes - Term low birth weight for maternal comorbidity of no hypertension: 0.992 (0.980, 1.002)
† Stieb et al. (2016)	Included singleton live births	LUR, Hybrid model	NO ₂ (ppb)	Term low birthweight (LBW, <2500g)	GEE logistic regression	OR (95% CI) ^c
Canadian Birth Database			All		Adjusted for: maternal age and marital status, parity, urban/rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority, infant sex, and gestational age, Socioeconomic status; proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education	Birth outcomes - Term LBW: 1.01 (0.99, 1.04)
N = 2,928,515		This model explained 73% of the variation	Mean = 13.4±7.8 Median = 11.9 (IQR 11.5) P5 = 3.7 P95 = 27.8			
Nationwide, Canada		Averaging time: NO ₂ - annual average				
Live births from 1999–2008		Exposure years: 2005–2011				
Cohort						
† Villeneuve et al. (2022)	Analyses were restricted to all singleton live births	Fixed site monitor, LUR	NO ₂ (ppb)	Term birth weight was obtained from	Logistic regression	OR (95% CI) ^c
Canadian Birth Database			All Singleton Births		Adjusted for:	Birth outcomes - Term low birth weight:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = ~2.2 million Nationwide, Canada Births between 1999–2008 Cohort	that were accessed from the Canadian Birth Database through Statistics Canada (approximately 3.2 million births). We further restricted the study population to highly urbanized areas.	Method validation NR Averaging time: NO ₂ - annual average, Other, NO ₂ - pregnancy Exposure years: 1999–2008	Mean = 16.7	births with gestational age >37 weeks	neighbourhood SES, individual covariates and visible minority	1.06 (1.04, 1.08)
† Wu et al. (2016) California Department of Public Health (CDPH) birth registry N = 4,370,371 pregnancies California, U.S. Births occurring from January 1, 2001–December 31, 2008 Cohort	Excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing	Chemical transport model, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2000–2008	NO ₂ (ppb) Overall Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6	Term low birth weight was <2500 g at birth	Generalized additive mixed models with random effects Adjusted for: race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines	NO ₂ OR (95% CI) ^c Birth outcomes - Term low birth weight (EBK NO ₂ exposure): 0.99 (0.96, 1.02) NO _x OR (95% CI) ^c Birth outcomes - Term low birth weight (CALINE NO _x exposure): 1.00 (0.99, 1.02)
Other Prenatal Growth						
Aguilera et al. (2010) INMA, Infancia y Medio Ambiente n = 562	Pregnant women who were recruited at their first routine prenatal care visit in the primary care center. Participants were excluded if < 16 years of age, having a	LUR r ² = 0.75 Averaging time: NO ₂ - weeks 1–12 NO ₂ - weeks 12–	NO ₂ (ug/m ³) Weeks 1–12 Mean = 32.45±10.51 IQR = 12.19 Min = 8.91 Max = 76.16	Fetal parameters recorded (in millimeters) were femur length (FL), HC, abdominal circumference	Linear regression Adjusted for: season of conception, parity, maternal educational level, and maternal pre-smoking, maternal pre-	β (mean percent change in SD score) (95% CI) ^c Birth outcomes - Other Prenatal Growth - Biparietal diameter measured at weeks 12–20 for exposure week 1–12: 1.99 (-1.60, 5.57)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Catalonia, Spain	nonsingleton pregnancy, not planning to deliver at the Sabadell hospital, and participating in an assisted reproduction program.	20 NO ₂ - weeks 20-32 Exposure years: 2004–2006	Weeks 12–20 Mean = 31.65±10.81 IQR = 11.47 Min = 6.65 Max = 75.14 Weeks 20-32 Mean = 32.13±10.84 IQR = 13.23 Min = 9.83 Max = 73.01	(AC), and biparietal diameter (BPD).	pregnancy weight Adjusted for: season of conception, parity, maternal educational level, and maternal smoking, maternal pre-pregnancy weight, and infant sex Adjusted for: season of conception, parity, maternal educational level, and maternal smoking	Birth outcomes - Other Prenatal Growth - Biparietal diameter measured at weeks 12–20 for exposure week 12–20: 2.79 (-0.49, 6.05) Birth outcomes - Other Prenatal Growth - Biparietal diameter measured at weeks 20–32 for exposure week 1–12: -2.75 (-6.01, 0.53) Birth outcomes - Other Prenatal Growth - Biparietal diameter measured at weeks 20–32 for exposure week 12–20: -1.04 (-4.00, 1.93) Birth outcomes - Other Prenatal Growth - Biparietal diameter measured at weeks 20–32 for exposure week 20–32: 0.60 (-2.84, 4.03) Growth - Abdominal circumference measured at weeks 12–20 for exposure week 1–12: 0.44 (-3.31, 4.18) Birth outcomes - Other Prenatal Growth - Abdominal circumference measured at weeks 12–20 for exposure week 12–20: 0.84 (-2.52, 4.19) Birth outcomes - Other Prenatal Growth - Abdominal circumference measured at weeks 20–32 for exposure week 1–12: -1.24 (-4.36, 1.89) Birth outcomes - Other Prenatal Growth - Abdominal circumference

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						measured at weeks 20–32 for exposure week 12–20: -0.04 (-2.85, 2.77) Birth outcomes - Other Prenatal Growth - Abdominal circumference measured at weeks 20–32 for exposure week 20–32: 0.84 (-2.44, 4.11)
						Birth outcomes - Other Prenatal Growth - Femur length measured at weeks 12–20 for exposure week 1–12: -0.23 (-3.79, 3.34) Birth outcomes - Other Prenatal Growth - Femur length measured at weeks 12–20 for exposure week 12–20: -1.27 (-4.50, 1.97) Birth outcomes - Other Prenatal Growth - Femur length measured at weeks 20–32 for exposure week 1–12: -0.12 (-3.04, 2.79) Birth outcomes - Other Prenatal Growth - Femur length measured at weeks 20–32 for exposure week 12–20: 1.81 (-0.84, 4.44) Birth outcomes - Other Prenatal Growth - Femur length measured at weeks 20–32 for exposure week 20–32: 0.84 (-2.25, 3.91)
						Birth outcomes - Other Prenatal Growth - Head circumference

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						measured at weeks 12–20 for exposure week 1–12: -1.68 (-5.26, 1.92) Birth outcomes - Other Prenatal Birth outcomes - Other Prenatal Growth - Head circumference measured at weeks 12–20 for exposure week 12–20: 1.12 (-2.17, 4.39) Birth outcomes - Other Prenatal Growth - Head circumference measured at weeks 20–32 for exposure week 1–12: -0.52 (-3.56, 2.53) Birth outcomes - Other Prenatal Growth - Head circumference measured at weeks 20–32 for exposure week 12–20: 0.48 (-2.33, 3.29) Birth outcomes - Other Prenatal Growth - Head circumference measured at weeks 20–32 for exposure week 20–32: -0.04 (-3.32, 3.24)
Ballester et al. (2010)	Pregnant women in the Valencia	LUR	NO ₂ (ug/m ³)	Birth length and head circumference were measured by a nurse when the newborn arrived in the hospital ward within the first twelve hours of life. The three	Linear regression Adjusted for: maternal age, maternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, working status in the first trimester, country of origin, and sex of the	β (cm) (95% CI) ^c Birth outcomes - Other Prenatal Growth - Birth length for Trimester 1: -0.07 (-0.15, 0.02) Birth outcomes - Other Prenatal Growth - Birth length for Trimester 2: -0.04 (-0.13, 0.04) Birth outcomes - Other Prenatal Growth - Birth length for Trimester
INMA, INfancia y Medio Ambiente n = 785 Valencia, Spain Enrollment: November 2003–June 2005		Averaging time: NO ₂ - Entire pregnancy NO ₂ - Trimester 1 NO ₂ - Trimester 2 NO ₂ - Trimester 3 Exposure years:	Entire pregnancy Mean = 36.9 Median = 37.9 (IQR 16.2) P25 = 29.4 P75 = 45.6 Trimester 1 Mean = 37.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort		2003–2005	Median = 38.1 (IQR 20.3) P25 = 28.2 P75 = 48.5 Trimester 2 Mean = 35.9 Median = 35.2 (IQR 17.7) P25 = 26.5 P75 = 44.2 Trimester 3 Mean = 37 Median = 37 (IQR 18.8) P25 = 27.3 P75 = 46.1	measures were standardized for gestational age and sex using the residuals method.	infant	3: -0.01 (-0.09, 0.08) Birth outcomes - Other Prenatal Growth - Birth length for Entire pregnancy: -0.05 (-0.15, 0.05) Birth outcomes - Other Prenatal Growth - Head circumference for Trimester 1: -0.06 (-0.14, 0.01) Birth outcomes - Other Prenatal Growth - Head circumference for Trimester 2: -0.06 (-0.13, 0.01) Birth outcomes - Other Prenatal Growth - Head circumference for Trimester 3: -0.03 (-0.10, 0.04) Birth outcomes - Other Prenatal Growth - Head circumference for Entire pregnancy: -0.06 (-0.13, 0.02)
Estarlich et al. (2011)	Inclusion criteria were age ≥ 16 years, singleton pregnancy, enrollment at 10–13 weeks of gestation, no assisted conception, delivery scheduled at the reference hospital, and no communication handicap.	LUR	NO ₂ (ug/m ³)	Birth length and HC were measured by a nurse when the newborn arrived at the hospital ward within the first 12 hr of life	GAM	β (cm) (95% CI) ^c
INMA, INfancia y Medio Ambiente		r ² = 0.521–0.750 (depending on region)	All		Adjusted for: maternal age, maternal pre-pregnancy weight, maternal height, paternal height, gestational weight gain, parity, cohabitation with the baby's father, maternal working status, smoking during	Birth outcomes - Other Prenatal Growth - Head circumference:
n = 2,644			Mean = 29.2±11.1			0.00 (-0.07, 0.06)
Spain		Averaging time:	Rural			Birth outcomes - Other Prenatal Growth - Birth length:
November 2003–February 2008		NO ₂ - Trimester 1	Mean = 16.4±4.9			-0.09 (-0.18, -0.01)
		NO ₂ - Trimester 2	Urban			
Cohort		NO ₂ - Trimester 3	Mean = 29.8±11			
		Exposure years:				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		2003–2008			pregnancy, country of origin, sex of the infant, rural, and season of last menstrual period, type of cooker, maternal education Adjusted for: maternal age, maternal pre-pregnancy weight, maternal height, paternal height, gestational weight gain, parity, cohabitation with the baby's father, maternal working status, smoking during pregnancy, country of origin, sex of the infant, rural, and season of last menstrual period, type of cooker, maternal social clas	
Iñiguez et al. (2012) INMA, INfancia y Medio Ambiente n = 785 Spain November 2003–June 2005 Cohort	Inclusion criteria: Age ≥16 years, singleton pregnancy, unassisted conception and no communication problems.	LUR $r^2 = 0.81$ Averaging time: NO ₂ - Week 12 NO ₂ - Week 20 NO ₂ - Week 32 Exposure years: 2003–2005	NO ₂ (ppb) Median = 220.2	Birth weight was measured by the midwife attending the birth	GAM Adjusted for: maternal gestational weight gain, socio-occupational status, education, employment, country of origin, zone of residence, parity, tobacco, alcohol and caffeine consumption and vegetable, fruit and energy intake, season of	β (mean percent change in SD score) (95% CI) ^c Birth outcomes - Other Prenatal Growth - Head circumference for 0–12 week exposure period: -2.10 (-4.50, 0.20) Birth outcomes - Other Prenatal Growth - Head circumference for 12–20 week exposure period: -1.80 (-4.20, 0.60) Birth outcomes - Other Prenatal Growth - Head circumference for 20–32 week exposure period:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					conception and the newborn's sex	-1.70 (-4.10, 0.70) Birth outcomes - Other Prenatal Growth - Head circumference for 32-birth week exposure period: -0.40 (-2.60, 1.70) Birth outcomes - Other Prenatal Growth - Head circumference for Entire pregnancy exposure period: -1.90 (-4.50, 0.70) Birth outcomes - Other Prenatal Growth - Length for 0–12 week exposure period: -2.90 (-5.50, -0.20) Birth outcomes - Other Prenatal Growth - Length for 12–20 week exposure period: -3.40 (-6.10, -0.80) Birth outcomes - Other Prenatal Growth - Length for 20–32 week exposure period: -2.30 (-5.00, 0.50) Birth outcomes - Other Prenatal Growth - Length for 32–birth week exposure period: -0.40 (-2.80, 2.10) Birth outcomes - Other Prenatal Growth - Length for Entire pregnancy exposure period: -2.90 (-5.80, 0.10)
Pedersen et al. (2013)	In study area, had a singleton delivery in time frame, had information about home addresses during	LUR	NO ₂ (ppb)	Head circumference was obtained from birth records and	Linear regression with random effect	NO ₂
Gene and Environment Prospective Study on Infancy in Italy (GASPII), Generation		The LUR models explained 58-90% of the variability	Overall Mean = 13.9 (26.2 µg/m ³)		Adjusted for: gestational age (weeks and	β (Change in head circumference at birth (cm)) (95% CI) ^b Birth outcomes - Other Prenatal

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
R,INMA, INfancia y Medio Ambiente, Norwegian Mother and Child Cohort Study (MoBa), Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort, Danish National Birth Cohort (DNBC), European Study of Cohorts for Air Pollution Effects (ESCAPE), Amsterdam Born Children and Their Development Study (ABCD), Etude des Determinants Pre et Postnataux du Developpement et de la Sante de l'Enfant (EDEN), Children, Allergy, Environment, Stockholm, Epidemiology (BAMSE), Born In Bradford (BIB), Mother-child Greek cohort (RHEA), KANC, DUISBURG N = 74,178 births Sweden, France, England, Spain, Italy, Norway, Germany, Greece, Hungary, Lithuania, The Netherlands Singleton deliveries between: February 11, 1994–June 2, 2011 Cohort	pregnancy, infant birthweight, gestational age, and sex	in the annual average concentrations of NO₂, and 63-88% for NO_x Averaging time: NO₂ - annual average, NO_x - annual average Exposure years: 2008–2011	P5 = 6.22 (11.7 µg/m³) P95 = 24.3 (45.8 µg/m³) NO_x (µg/m³) Overall Mean = 45.5 P5 = 15.4 P95 = 91.1	questionnaires	[weeks]2), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December)	Growth - Head circumference at birth for NO₂ Exposure: -0.15 (-0.18, -0.12) NO_x β (Change in head circumference at birth (cm)) (95% CI)^c Birth outcomes - Other Prenatal Growth - Head circumference at birth for NO_x Exposure: -0.06 (-0.07, -0.05)
Ritz et al. (2014) Behavior in Pregnancy Study	Eligible pregnant women were those aged 18 years or older,	AQS, Dispersion model, LUR	NO₂ (ppb) Entire pregnancy	Measurements of the following parameters were	Linear mixed effects model	NO β (mm) (95% CI)^c

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = 688 n = 566 California, U.S. 1993–1996 Cohort	English- or Spanish-speaking, and less than 20 weeks pregnant with a single gestation. We also excluded women whose pregnancy ended in stillbirths (n = 2), or infants with birth weights <500 g (n = 5) or gestational age 4308 days (n = 1), leaving 566 women and 17 women reporting illegal drug use during pregnancy (marijuana, cocaine, heroin or speed). Of those remaining, 478 (84%) completed three ultrasound visits, 66 (12%) two and 22 (4%) one visit.	Averaging time: NO ₂ - estimated date of conception to first ultrasound date, approximately 0–19 weeks gestation (period 1) NO ₂ - first to second ultrasound date, 19–29 weeks gestation (period 2) NO ₂ - second to third ultrasound date, 29–37 weeks gestation (period 3) NO _x -estimated date of conception to first ultrasound date, approximately 0–19 weeks gestation (period 1) NO _x - first to second ultrasound date, 19–29 weeks gestation (period 2) NO _x - second to third ultrasound date, 29–37 weeks gestation (period 3) NO ₂ - Entire pregnancy	LUR Mean = 22.7±3.9 Min = 6.1 Max = 38.2 Pregnancy period 1 Central site monitor Mean = 37.3±8 Min = 10.8 Max = 59 Pregnancy period 2 Central site monitor Mean = 37.6±9.1 Min = 10 Max = 59.1 Pregnancy period 3 Central site monitor Mean = 39.3±9.4 Min = 9 Max = 63.4 NO (ppb) Entire pregnancy LUR Mean = 21.8±6.6 Min = 5 Max = 47.8 NO _x (ppb) Entire pregnancy LUR Mean = 43.7±10.4 Min = 12.1	obtained by 5 sonographers trained and supervised by an author	Adjusted for: pregnancy period and (mean time at measurement x pregnancy period), maternal age, race/ethnicity (Hispanic, Asian and other races combined), education level, parity, prenatal care payment, marital status, maternal smoking before each ultrasound visit (yes/no), maternal infections before each ultrasound visit (yes/no), maternal height, maternal pre-pregnancy weight, weight gain in each pregnancy period, presentation (breech versus vertex/transverse), and sonographer	Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO exposure for gestational weeks 18–20: -0.21 (-0.50, 0.07) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO exposure for gestational weeks 28–30: 0.16 (-0.12, 0.43) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO exposure for gestational weeks 35–37: -0.27 (-0.58, 0.04) NO ₂ β (mm) (95% CI) ^c Birth outcomes - Other Prenatal Growth - Biparietal diameter for monitor-based NO ₂ exposure for gestational weeks 18–20: -0.49 (-1.16, 0.17) Birth outcomes - Other Prenatal Growth - Biparietal diameter for monitor-based NO ₂ exposure for gestational weeks 28–30: 0.59 (0.00, 1.18) Birth outcomes - Other Prenatal Growth - Biparietal diameter for monitor-based NO ₂ exposure for gestational weeks 35–37: -1.00 (-1.66, -0.34) Birth outcomes - Other Prenatal Growth - Biparietal diameter for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		NO - Entire pregnancy NO _x - Entire pregnancy Exposure years: 1993–1996	Max = 82.6 Pregnancy period 1 CALINE Mean = 62.9±34.9 Min = 8.2 Max = 328.1 Pregnancy period 2 CALINE Mean = 58.3±33.7 Min = 5.5 Max = 286.6 Pregnancy period 3 CALINE Mean = 57.2±32.7 Min = 4.4 Max = 288.7			LUR NO ₂ exposure for gestational weeks 18–20: -0.18 (-0.47, 0.10) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO ₂ exposure for gestational weeks 28–30: 0.17 (-0.11, 0.45) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO ₂ exposure for gestational weeks 35–37: -0.22 (-0.54, 0.10) NO _x β (mm) (95% CI) ^c Birth outcomes - Other Prenatal Growth - Biparietal diameter for CALINE4 NO _x freeways exposure for gestational weeks 18–20: 0.03 (-0.18, 0.25) Birth outcomes - Other Prenatal Growth - Biparietal diameter for CALINE4 NO _x freeways exposure for gestational weeks 28–30: 0.07 (-0.16, 0.29) Birth outcomes - Other Prenatal Growth - Biparietal diameter for CALINE4 NO _x freeways exposure for gestational weeks 35–37: -0.22 (-0.47, 0.04) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO _x exposure for gestational weeks 18–20:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-0.23 (-0.54, 0.08) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO _x exposure for gestational weeks 28–30: 0.16 (-0.14, 0.46) Birth outcomes - Other Prenatal Growth - Biparietal diameter for LUR NO _x exposure for gestational weeks 35–37: -0.31 (-0.65, 0.00)
†Hjortebjerg et al. (2016)	We included first enrolled pregnancy, for whom information on home addresses of the mother during pregnancy and her child's size at birth were available. Also included live-born singletons. we excluded 443 mother and child pairs with incomplete information on exposure data from conception until birth, 439 with missing or implausible birth weight and gestational age combinations, 3820 with missing information on placental weight, 1191 with missing information on head	Dispersion model Method validation NR Averaging time: NO ₂ - monthly NO ₂ - trimester NO _x - monthly NO _x - trimester NO _x - pregnancy Exposure years: 1996–2002	NO ₂ (µg/m ³) All Median = 11 P5 = 7.1 P95 = 26.3 Living outside a major city Median = 10.5 P5 = 7 P95 = 19.6 Living within a major city Median = 17.1 P5 = 8.9 P95 = 39.8 NO _x (µg/m ³) NR	Placental weight was measured with a digital weight without trimming the placental disk of membranes or the umbilical cord Head and abdominal circumference were measured using standard measuring tape	Linear regression Adjusted for: gestational age, sex, maternal age at conception, pre-pregnancy BMI, maternal height, parity, season of conception, educational level, disposable income, smoking and alcohol consumption during pregnancy and living within one of the 3 largest cities in Denmark (Copenhagen, Aarhus or Odense) at time of birth	NO ₂ β (g) (95% CI) ^c Birth Outcomes - Other Prenatal Growth - Placental weight: 3.92 (2.17, 5.68) Birth Outcomes - Other Prenatal Growth - Placental weight - co-adjusted for traffic noise: 5.02 (2.93, 7.11) β (mm) (95% CI) ^c Birth Outcomes - Other Prenatal Growth - Head circumference: -0.42 (-0.61, -0.23) Birth Outcomes - Other Prenatal Growth - Head circumference - co-adjusted for traffic noise: -0.35 (-0.57, -0.12) Birth Outcomes - Other Prenatal Growth - Abdominal circumference: -0.43 (-0.68, -0.17) Birth Outcomes - Other Prenatal Growth - Abdominal circumference - co-adjusted for traffic noise:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	circumference, 1410 with missing information on abdominal circumference, and 5905 not being the first enrolled child within the DNBC.					-0.50 (-0.80, -0.20) NO _x β (g) (95% CI) ^c Birth Outcomes - Other Prenatal Growth - Placental weight: -0.62 (-4.08, 2.85) Birth Outcomes - Other Prenatal Growth - Placental weight - co-adjusted for traffic noise: 1.15 (-3.07, 5.37) β (mm) (95% CI) ^c Birth Outcomes - Other Prenatal Growth - Head circumference - co-adjusted for traffic noise: -0.11 (-0.26, 0.04) Birth Outcomes - Other Prenatal Growth - Abdominal circumference: -0.15 (-0.31, 0.02) Birth Outcomes - Other Prenatal Growth - Head circumference: -0.19 (-0.31, -0.07) Birth Outcomes - Other Prenatal Growth - Abdominal circumference - co-adjusted for traffic noise: -0.14 (-0.34, 0.06)
†Ji et al. (2023)	Inclusion criteria: (1) less than 30 weeks gestation at the time of recruitment, (2) over 18 years of age, and (3) fluent English or Spanish speaker. Exclusion criteria were (1) HIV-positive status,	Spatiotemporal/geospatial model Averaging time: NO ₂ - Pregnancy average Exposure years: 2015–2021	NO ₂ (ppb) Mean = 16.4±2.9 Median = 16.5 (IQR 3.7) Min = 8.2 Max = 24.5 P10 = 12.9 P90 = 20.4	Weight measures after birth were obtained using a combination of medical record abstractions from delivery and pediatric	Linear mixed effects model Adjusted for: infant age, two spline terms, and interactions between air pollutants and age and spline terms, maternal education level,	β (Percent difference in weight) (95% CI) ^c Birth outcomes - Other Prenatal Growth - Infant attained weight at birth: -6.45 (-10.47, -2.24) Birth outcomes - Other Prenatal Growth - Infant attained weight at third trimester:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: November 2015–September 2021 Cohort	(2) physical, mental, or cognitive disability that prevents participation or providing informed consent, (3) current incarceration, and (4) multiple gestations.			healthcare visits and study-staff measurements during in person follow-up visits at target ages (birth) <i>In utero</i> estimates of fetal weight during the 3rd trimester were evaluated using head circumference (HC), abdominal circumference (AC), and femur length using the Hadlock A formula.	maternal race, pre-pregnancy BMI, hypertensive disorders, diabetic disorders, recruitment site, maternal age, parity, breastfeeding duration, postnatal air pollutant (same as the exposure), and ambient temperature	-10.94 (-16.44, -5.07)
† Leung et al. (2023) Beth Israel Deaconess Medical Center (BIDMC) N = 9,446 pregnancies Massachusetts, U.S. Deliveries between 2011–2016 Cohort	Excluded pregnant individuals who lived outside of Massachusetts and those who had their first and only prenatal visit after the 23 rd week of gestation. Further excluded those with any missing covariate or outcome data.	Ensemble machine learning model $r^2 = 0.79$ Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - weekly Exposure years: 2011–2016	NO ₂ (ppb) Overall Mean = 23	The fetal ultrasound parameters examined included biparietal diameter (BPD), head circumference (HC), femur length (FL), and abdominal circumference (AC), all of which were	Distributed lag models Adjusted for: maternal age, race, education, insurance type, parity, fetal sex, smoking, conception year, day of the year of conceptions, area deprivation index, and temperature	β (NA) (95% CI) ^c Birth Outcomes - Other Prenatal Growth - Head circumference for 16–23 weeks: -0.03 (-0.08, 0.02) Birth Outcomes - Other Prenatal Growth - Head circumference for 24–31 weeks: -0.08 (-0.16, 0.00) Birth Outcomes - Other Prenatal Growth - Head circumference for 32–40 weeks: -0.05 (-0.11, 0.01) Birth Outcomes - Other Prenatal

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				reported in millimeters.		Growth - Femur length for 16–23 weeks: -0.02 (-0.07, 0.03) Birth Outcomes - Other Prenatal Growth - Femur length for 24–31 weeks: -0.03 (-0.11, 0.05) Birth Outcomes - Other Prenatal Growth - Femur length for 32–40 weeks: -0.02 (-0.08, 0.04) Birth Outcomes - Other Prenatal Growth - Biparietal diameter for 16–23 weeks: -0.05 (-0.10, 0.00) Birth Outcomes - Other Prenatal Growth - Biparietal diameter for 24–31 weeks: -0.08 (-0.16, -0.01) Birth Outcomes - Other Prenatal Growth - Biparietal diameter for 32–40 weeks: -0.11 (-0.17, -0.05) Birth Outcomes - Other Prenatal Growth - Abdominal circumference for 16–23 weeks: -0.03 (-0.08, 0.02) Birth Outcomes - Other Prenatal Growth - Abdominal circumference for 24–31 weeks: -0.10 (-0.17, -0.02) Birth Outcomes - Other Prenatal Growth - Abdominal circumference for 32–40 weeks:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-0.05 (-0.11, 0.00)
† Peterson et al. (2022)	Eligibility criteria for cohort entry included: (1) <30 weeks pregnant, (2) ≥18 years of age, and (3) fluent in English or Spanish. Exclusion criteria for the study included: (1) multiple gestation; (2) having a physical, mental, or cognitive disability that would inhibit participation or the ability to provide consent; (3) current incarceration; or (4) HIV positive status.	Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - weekly NO ₂ - pregnancy Exposure years: 2015	NO ₂ (ppb) Pregnancy Average Median = 15.5 (IQR 5.6) Weekly Average Median = 15.3 (IQR 5.6)	Femur length (mm) defined as the length of the thigh bone Abdominal circumference (mm) which is measured at the widest part across the fetal liver Head circumference in millimeters (mm) defined as the length along the skull bone, Biparietal diameter (mm) defined as the maximum diameter of a transverse section the fetal skull from the proximal parietal bone to the inner edge of the distal parietal bone	Distributed lag models Adjusted for: maternal age at time of study recruitment, maternal race and ethnicity, maternal education level, household income, parity, pre-pregnancy body mass index (BMI), sex of the fetus, gestational age at time of ultrasound scan, lag specific average temperature, season of ultrasound, ultrasound technician, and recruitment site	β (mm) (95% CI) ^c Birth Outcomes - Other Prenatal Growth - Femur length: 0.10 (-0.60, 0.90) Birth Outcomes - Other Prenatal Growth - Abdominal circumference: -2.60 (-6.30, 1.20) Birth Outcomes - Other Prenatal Growth - Head circumference: -1.20 (-4.00, 1.60) Birth Outcomes - Other Prenatal Growth - Biparietal diameter: 0.001 (-0.90, 0.90)
Other Prenatal Growth Small-for-gestational-age (SGA)						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Ballester et al. (2010)	Pregnant women in the Valencia	LUR	NO ₂ (µg/m ³)	SGA was defined as a birth weight or length below the 10th percentile according to standard percentile charts for sex and gestational age in the Spanish population	Logistic regression	OR (95% CI) ^c
INMA, Infancia y Medio Ambiente		Averaging time: NO ₂ - Entire pregnancy	Entire pregnancy Mean = 36.9 Median = 37.9 (IQR 16.2)		Adjusted for: maternal age, maternal pre-pregnancy weight, maternal education, parity, smoking during pregnancy, gestational weight gain, country of origin, alcohol consumption during pregnancy, and season of last menstrual period	Birth outcomes - Other Prenatal Growth - SGA for length for Trimester 1: 1.14 (0.74, 1.74)
n = 785		NO ₂ - Trimester 1	P25 = 29.4			Birth outcomes - Other Prenatal Growth - SGA for length for Trimester 2: 1.42 (0.89, 2.25)
Valencia, Spain		NO ₂ - Trimester 2	P75 = 45.6			Birth outcomes - Other Prenatal Growth - SGA for length for Trimester 3: 1.10 (0.75, 1.62)
Enrollment: November 2003–June 2005		Exposure years: 2003–2005	Trimester 1 Mean = 37.9 Median = 38.1 (IQR 20.3) P25 = 28.2 P75 = 48.5		Adjusted for: maternal age, maternal pre-pregnancy weight, paternal height, gestational weight gain, parity, maternal education, country of origin, smoking during pregnancy, and season of last menstrual period	Birth outcomes - Other Prenatal Growth - SGA for length for Entire pregnancy: 1.23 (0.78, 1.95)
Cohort			Trimester 2 Mean = 35.9 Median = 35.2 (IQR 17.7) P25 = 26.5 P75 = 44.2			Birth outcomes - Other Prenatal Growth - SGA for weight for Trimester 1: 1.18 (0.89, 1.56)
			Trimester 3 Mean = 37 Median = 37 (IQR 18.8) P25 = 27.3 P75 = 46.1			Birth outcomes - Other Prenatal Growth - SGA for weight for Trimester 2: 1.37 (1.01, 1.85)
						Birth outcomes - Other Prenatal Growth - SGA for weight for Trimester 3: 1.19 (0.91, 1.55)
						Birth outcomes - Other Prenatal Growth - SGA for weight for Entire pregnancy: 1.28 (0.94, 1.74)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Guo et al. (2020) n = 2,868,870 Guangdong Province, China January 1, 2014–December 31, 2017 Cohort	Births among mothers were permanent residents living in Guangdong province and recorded in the China's Household Registration System. Exclusions included, stillbirths, birth between 22 and 42 completed weeks of gestation and in which the last menstrual period was recorded, maternal age outliers (<16 or >50 years) were then identified and excluded according to the average age of menarche and natural menopausal age in Chinese population, and missing or implausible combinations of birth weight and gestational age	Central site monitor Averaging time: NO ₂ - first trimester NO ₂ - second trimester NO ₂ - third trimester NO ₂ - entire pregnancy Exposure years: 2014–2017	NO ₂ (µg/m ³) Entire pregnancy Mean = 26.28±10.97 Median = 23.87 (IQR 14.56) Min = 7.21 Max = 71.37 P25 = 17.97 P75 = 32.36 First trimester Mean = 26.56±12.27 Median = 24.53 (IQR 15.47) Min = 4.56 Max = 84.7 P25 = 16.93 P75 = 32.66 Second trimester Mean = 26.12±12.35 Median = 24.27 (IQR 15.94) Min = 4.6 Max = 86.61 P25 = 16.44 P75 = 32.14 Third trimester Mean = 26.17±12.17 Median = 24.1 (IQR 15.73) Min = 4.51 Max = 87.12 P25 = 16.6	SGA means that an infant is smaller or less developed than normal for the baby's sex and gestational age	GEE logistic regression Adjusted for: maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, neonate's sex, gestational age as linear and quadratic terms, meteorological factors and an interaction term (pollutant exposures × month of conception)	OR (95% CI) ^c Birth outcomes - Other prenatal growth - SGA for exposure during trimester 1: 1.00 (0.98, 1.02) Birth outcomes - Other prenatal growth - SGA for exposure during trimester 2: 1.00 (0.98, 1.02) Birth outcomes - Other prenatal growth - SGA for exposure during trimester 3: 1.00 (0.98, 1.03) Birth outcomes - Other prenatal growth - SGA for exposure during entire pregnancy: 1.00 (0.97, 1.02) Birth outcomes - Other prenatal growth - SGA for exposure during entire pregnancy, adjusted for CO: 0.98 (0.96, 1.01) Birth outcomes - Other prenatal growth - SGA for exposure during entire pregnancy, adjusted for SO ₂ : 1.00 (0.98, 1.03) Birth outcomes - Other prenatal growth - SGA for exposure during entire pregnancy, adjusted for PM _{2.5} : 0.98 (0.95, 1.01) Birth outcomes - Other prenatal growth - SGA for exposure during entire pregnancy, adjusted for O ₃ : 1.01 (0.98, 1.04) Birth outcomes - Other prenatal growth - SGA for exposure during

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 32.62			entire pregnancy, adjusted for PM ₁₀ : 0.97 (0.94, 1.00)
† Lavigne et al. (2016b)	Pregnant women giving birth in hospitals to live born, non-planned C-sections, singleton infants in Ontario, Canada were recruited in the first trimester of pregnancy. Women with postal codes of residence outside Ontario were excluded	LUR	NO ₂ (ppb)	SGA was defined as <10th percentile of birth weight for gestational age)	Mixed effect logistic regression models	OR (95% CI) ^c
Better Outcomes Registry Network (BORN) Ontario		This model explained 73% of the variations in annual 2006 NO ₂ measurements	Entire Pregnancy, Overall Mean = 15.89±6.38 Median = 16 (IQR 9)		Adjusted for: maternal age at delivery, maternal cigarette smoking during pregnancy, infant sex, parity, previous caesarean section	Birth outcomes - Other prenatal growth - SGA - Overall: 0.982 (0.980, 0.985)
N = 818,400		Averaging time: NO ₂ - annual average	P5 = 6 P95 = 26		delivery, urban/rural place of residence, month of birth, year of birth, census dissemination area	Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of asthma: 0.980 (0.967, 0.993)
Ontario, Canada		Exposure years: 2005–2011	Trimester 1, Overall Mean = 16.2±6.87 Median = 16 (IQR 10) P5 = 6 P95 = 28		median family income, census dissemination area proportion of population who are visible minority and census dissemination area proportion of the adult female population aged 25–64 years old who completed postsecondary education	Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of no asthma: 0.985 (0.983, 0.987)
Recruitment: January 2005–March 2012			Trimester 2, Overall Mean = 16.15±6.88 Median = 16 (IQR 10) P5 = 6 P95 = 28			Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of heart disease: 0.979 (0.976, 1.014)
Cohort			Trimester 3, Overall Mean = 15.93±6.87 Median = 16 (IQR 9) P5 = 5 P95 = 28			Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of no heart disease: 0.985 (0.983, 0.987)
						Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of gestational diabetes: 0.994 (0.983, 1.005)
						Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of no gestational diabetes: 0.984 (0.982, 0.986)
						Birth outcomes - Other prenatal

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						growth - SGA for maternal comorbidity of preeclampsia: 0.994 (0.981, 1.007) Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of no preeclampsia: 0.985 (0.982, 0.987) Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of diabetes: 0.997 (0.975, 1.020) Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of no diabetes: 0.985 (0.982, 0.987) Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of hypertension: 0.982 (0.960, 1.005) Birth outcomes - Other prenatal growth - SGA for maternal comorbidity of no hypertension: 0.985 (0.983, 0.987)
†Nobles et al. (2019a) Longitudinal Investigation of Fertility and the Environment (LIFE) n = 501 Texas, Michigan, U.S.	Couple who were either married or in a committed relationship, 18 years or older, communicate in English and Spanish, no physician diagnosed infertility and attempting pregnancy in Michigan and Texas.	CMAQ Averaging time: NO₂ - 24-hour average, NO_x - 24-hour average Exposure years: 2005–2009	NO₂ (ppb) Median = 7.3 (IQR 4.6) Min = 0.87 Max = 24.7 P25 = 5.3 P75 = 9.9 NO_x (ppb)	The definition of fetal growth restriction was based on physician diagnosis as derived from medical record abstraction and ICD-9 codes	Generalized estimating equations with robust standard errors Adjusted for: maternal age, race/ethnicity, pre-pregnancy body mass index, smoking, alcohol, parity, insurance, marital status, asthma	NO₂ RR (95% CI)^c Birth outcomes - Other prenatal growth - Fetal growth restriction - Trimester 1: 1.15 (1.04, 1.27) Birth outcomes - Other prenatal growth - Fetal growth restriction - Trimester 2:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2005–2009				(656.5 “Poor fetal growth”)	and temperature	1.21 (1.09, 1.34)
Cohort			Median = 11.2 (IQR 8.3) Min = 0.96 Max = 49.9 P25 = 7.7 P75 = 16	Delivery records for birthweight and gestational age were used to calculate birthweight z-scores, based on United States population standards for infant sex. Infants were classified as meeting criteria for SGA <10th birth weight percentile.		Birth outcomes - Other prenatal growth - Fetal growth restriction - Trimester 3: 1.21 (1.11, 1.33) Birth outcomes - Other prenatal growth - Fetal growth restriction - Entire pregnancy: 1.17 (1.09, 1.26) Birth outcomes - Other prenatal growth - SGA - 3 months preconception: 1.02 (0.98, 1.07) Birth outcomes - Other prenatal growth - SGA - Trimester 1: 1.00 (0.95, 1.04) Birth outcomes - Other prenatal growth - SGA - Trimester 2: 1.01 (0.96, 1.06) Birth outcomes - Other prenatal growth - SGA - Trimester 3: 1.05 (1.01, 1.10) Birth outcomes - Other prenatal growth - SGA - Entire pregnancy: 1.01 (0.97, 1.04) NO _x RR (95% CI) ^c Birth outcomes - Other prenatal growth - SGA - 3 months preconception: 1.02 (0.96, 1.08) Birth outcomes - Other prenatal growth - SGA - Trimester 1: 0.97 (0.92, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - Other prenatal growth - SGA - Trimester 2: 1.00 (0.94, 1.06) Birth outcomes - Other prenatal growth - SGA - Trimester 3: 1.08 (1.03, 1.14) Birth outcomes - Other prenatal growth - SGA - Entire pregnancy: 1.00 (0.97, 1.04) Birth outcomes - Other prenatal growth - Fetal growth restriction - 3 months preconception: 1.23 (1.10, 1.38) Birth outcomes - Other prenatal growth - Fetal growth restriction - Trimester 1: 1.09 (0.97, 1.23) Birth outcomes - Other prenatal growth - Fetal growth restriction - Trimester 2: 1.14 (1.01, 1.28) Birth outcomes - Other prenatal growth - Fetal growth restriction - Trimester 3: 1.20 (1.07, 1.34) Birth outcomes - Other prenatal growth - Fetal growth restriction - Entire pregnancy: 1.12 (1.04, 1.21)
†Savitz et al. (2019) N = 257,956 births New York City, NY, U.S.	Excluded patients with missing or implausible gestational age (<22 or >42 weeks), multiple gestations, congenital abnormalities, known	Fixed site monitor, LUR Method validation NR	NO ₂ (ppb) Exposure distribution concentrations were not reported	SGA was defined as <10 th percentile of weight for gestational age	Logistic regression Adjusted for: maternal age, ethnicity, education, Medicaid status, parity, SES	NO ₂ OR (95% CI) ^c Birth outcomes - Other prenatal growth - SGA: 1.03 (1.01, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Births between 2008–2010 Cohort	smokers, missing or implausible birth weight (<500 or >5,000g), missing covariates (e.g., education, parity), missing delivery hospital, or born in a hospital with fewer than 10 births over the course of the study period and restricted conception dates to avoid fixed-cohort bias.	Averaging time: NO ₂ - 2 weeks during pregnancy Exposure years: 2008–2010			score, pre-pregnancy BMI, and conception year	
† Stieb et al. (2016) Canadian Birth Database N = 2,928,515 Nationwide, Canada Live births from 1999–2008 Cohort	Included singleton live births	LUR, Hybrid model This model explained 73% of the variation Averaging time: NO ₂ - annual average Exposure years: 2005–2011	NO ₂ (ppb) All Mean = 13.4±7.8 Median = 11.9 (IQR 11.5) P5 = 3.7 P95 = 27.8	SGA (<10 percentile of birth weight for gestational age)	GEE logistic regression Adjusted for: maternal age and marital status, parity, urban/rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority, infant sex, and gestational age, Socioeconomic status; proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over	OR (95% CI) ^c Birth outcomes - Other prenatal growth - SGA: 1.02 (1.01, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					with post-secondary education	
† Villeneuve et al. (2022)	Analyses were restricted to all singleton live births that were accessed from the Canadian Birth Database through Statistics Canada (approximately 3.2 million births). We further restricted the study population to highly urbanized areas.	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - annual average, Other, NO ₂ - pregnancy Exposure years: 1999–2008	NO ₂ (ppb) All Singleton Births Mean = 16.7	SGA was defined as <10 th percentile of birth weight for gestational age)	Logistic regression Adjusted for: neighbourhood SES, individual covariates and visible minority	OR (95% CI) ^c Birth outcomes - Other prenatal growth - SGA: 1.09 (1.08, 1.10)
Canadian Birth Database N = ~2.2 million Nationwide, Canada Births between 1999–2008 Cohort						
† Williams et al. (2021)	Included deliveries at 23 weeks or later. Excluded multifetal pregnancies, mothers with thyroid disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Crohn's disease, as well as those with other autoimmune disease. Participants from one site for which ICD-9 codes were not reported and no cases of Type 1 diabetes were identified were also excluded.	CMAQ Averaging time: NO _x - 1-hour max, Other, NO _x - 3-month preconception period NO _x - trimester NO _x - whole pregnancy Exposure years: 2002–2008	NO _x (ppb) 1 st trimester Mean = 30.26 IQR = 29.06 Min = 5.51 Max = 89.62 2 nd trimester Mean = 30.13 IQR = 28.98 Min = 5.76 Max = 90.65 3 months preconception Mean = 29.02 IQR = 27 Min = 5.09 Max = 92.97	SGA was identified from medical records and ICD-9 codes	Binary Poisson regression models with the log link function and robust standard errors Adjusted for: maternal age, maternal race/ethnicity, preconception body mass index, health insurance, marital status, smoking in pregnancy, alcohol use in pregnancy, other chronic diseases, and census region	NO _x RR (95% CI) ^c Birth outcomes - Other prenatal growth - SGA - 3 months preconception for Type 1 Diabetes: 1.01 (0.98, 1.03) Birth outcomes - Other prenatal growth - SGA - 3 months preconception for no autoimmune: 1.00 (1.00, 1.00) Birth outcomes - Other prenatal growth - SGA - Trimester 1 for Type 1 Diabetes: 0.99 (0.97, 1.01) Birth outcomes - Other prenatal growth - SGA - Trimester 1 for no autoimmune: 1.00 (1.00, 1.00) Birth outcomes - Other prenatal
Consortium on Safe Labor (2002–2008) With T1D n = 507 Without T1D n = 204,384 Nationwide, U.S. 2002–2008 Case-Control						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Whole pregnancy Mean = 29.8 IQR = 22.47 Min = 6.38 Max = 81.64			growth - SGA - Trimester 2 for Type 1 Diabetes: 1.00 (0.97, 1.02) Birth outcomes - Other prenatal growth - SGA - Trimester 2 for no autoimmune: 1.00 (1.00, 1.00) Birth outcomes - Other prenatal growth - SGA - Entire pregnancy for Type 1 Diabetes: 1.00 (0.97, 1.02) Birth outcomes - Other prenatal growth - SGA - Entire pregnancy for no autoimmune: 1.00 (1.00, 1.00)

List of Abbreviations: AC = abdominal circumference; BMI = body mass index; BPD = biparietal diameter; CI = confidence interval; FL = femur length; GAM = generalized additive model; HC = head circumference; IQR = interquartile range; LBW = low birthweight; LUR = land use regression; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; P5 = 5th percentile; P10 = 10th percentile; P25 = 25th percentile; P75 = 75th percentile; P90 = 90th percentile; P95 = 95th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; RR = rate ratio; SGA = small for gestational age.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-11 Epidemiologic studies of oxides of nitrogen and birth outcomes of preterm birth

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Wu et al. (2016) California Department of Public Health (CDPH) birth registry N = 4,370,371 pregnancies California, U.S. Births occurring from January 1, 2001–December 31, 2008 Cohort	Excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing	Chemical transport model, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR	NO ₂ (ppb) Overall Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6	Preterm birth (gestational age <37 weeks)	Generalized additive mixed models with random effects Adjusted for: race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines	NO ₂ OR (95% CI) ^c Birth outcomes - Preterm birth (EBK for NO ₂ exposure): 1.11 (1.09, 1.12) Birth outcomes - Preterm birth (Spatiotemporal for NO ₂ exposure): 0.57 (0.54, 0.60) NO _x OR (95% CI) ^c Birth outcomes - Preterm birth (CALINE NO _x exposure): 1.01 (1.00, 1.01)
† Cassidy-Bushrow et al. (2020) N = 7,961 Detroit, MI, U.S. June 8, 2008–May 9, 2010 Cohort	Women with a singleton delivery at Henry Ford Hospital and Detroit Medical Center and residing in Detroit. Excluded 1 woman with an infant of undetermined sex as we could not include her in sex-specific analysis; 4 with gestational age at delivery ≤23 weeks as this was before the time of viability; 1 woman who was 62 years old at delivery, as this was outside the expected	Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - monthly Exposure years: 2008–2009	NO ₂ (ppb) 1st Trimester Mean = 18.6±3.2 Median = 18.3 Min = 9.8 Max = 26.9 2nd Trimester Mean = 18.7±3.1 Median = 18.6 Min = 9.5 Max = 26.5 3rd Trimester Mean = 18.5±3 Median = 18.4 Min = 9.6	PTB was defined as birth occurring <37 weeks gestation. Gestational age was abstracted from the infant's medical record at delivery.	Logistic regression Adjusted for: maternal age, parity, marital status, race, clinical site, pregnancy-induced hypertension, gestational diabetes mellitus, and poverty quartiles	OR (95% CI) ^c Birth outcomes - PTB: 0.94 (0.76, 1.17)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	window of reproductive age; and 5 with gestational age at delivery ≥ 42.9 weeks. Also excluded 7 women who were of race American Indian, Native Hawaiian, or Pacific Islander, as this sub-group was too small for statistical inferences. Three women who had addresses in regions not covered by the pollutant location data were also excluded.		Max = 28 Total Mean = 18.5 $\pm$ 2.1 Median = 18.6 Min = 11.6 Max = 25.7			
†Cowan et al. (2024) NC Department of Health and Human Services & Division of Public Health N = 566,799 North Carolina, U.S. Births between January 1, 2011–December 31, 2015 Cohort	All live, singleton births with gestational age between 20 and 44 weeks with residence at delivery in NC. Excluded multiple births, deliveries outside of 20–44 weeks gestational age, and missing residential address at time of delivery that precluded geocoding.	Ensemble machine learning model, Hybrid model Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - 8-hour max, Other, NO ₂ - trimester Exposure years: 2011–2015	NO ₂ (ppb) Overall Entire Pregnancy Median = 13.14 Min = 1 Max = 33.42 P25 = 9.84 P75 = 17.24 Trimester 1 Median = 13.17 Min = 0.36 Max = 37.08 P25 = 9.53 P75 = 17.42 Trimester 2 Median = 12.92 Min = 0.78 Max = 39.89	Preterm births were defined as birth at less than 37 weeks gestation	Modified Poisson regression models Adjusted for: birthing parent race/ethnicity (white, non-Hispanic as reference), birthing parent age at delivery (centered at age 26 with a quadratic term), marital status (married as reference), Medicaid status (no as reference), education (>HS as reference), and month of conception (index variable as referent)	RD (95% CI) ^c Birth outcomes - PTB for exposure during entire pregnancy for all areas: -39.53 (-50.77, -28.28) Birth outcomes - PTB for exposure during trimester 1 for all area: -42.44 (-53.10, -31.77) Birth outcomes - PTB for exposure during trimester 2 for all areas: -45.30 (-56.14, -34.46) Birth outcomes - PTB for exposure during entire pregnancy for low NDI: -42.78 (-60.80, -24.76) Birth outcomes - PTB for exposure during trimester 1 for low NDI: -46.84 (-63.88, -29.80) Birth outcomes - PTB for exposure

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 9.44 P75 = 17.24			during trimester 2 for low NDI: -47.40 (-64.69, -30.10) Birth outcomes - PTB for exposure during entire pregnancy for medium NDI: -44.24 (-61.79, -26.68) Birth outcomes - PTB for exposure during trimester 1 for medium NDI: -46.83 (-63.45, -30.21) Birth outcomes - PTB for exposure during trimester 2 for medium NDI: -49.01 (-65.93, -32.09) Birth outcomes - PTB for exposure during entire pregnancy for high NDI: 34.70 (4.84, 64.56) Birth outcomes - PTB for exposure during trimester 1 for high NDI: 29.00 (0.52, 57.47) Birth outcomes - PTB for exposure during trimester 2 for high NDI: 17.87 (-11.17, 46.92)
†Escoto et al. (2022)	Included all live singleton births at the Hospital of the University of Pennsylvania and Pennsylvania Hospital in Philadelphia, PA from 23 April 2013 to 4 March 2017. Infant records with unrealistic birth weights (<200 g	LUR, Fixed site monitor, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 24-hour average, Other,	NO ₂ (ppb) mPTB Mean = 17±2.6 Overall Mean = 17.2±2.3 PTB Mean = 17.1±2.6	PTB was defined as birth before 37 weeks of gestation and with further distinction between spontaneous versus medically indicated PTB. sPTB was	Logistic mixed-effects model Adjusted for: age, race, BMI, nulliparity, insurance status and census tract-level percentage below poverty. Hospital and census tracts were	OR (95% CI) ^c Birth outcomes - PTB overall: 0.98 (0.92, 1.03) Birth outcomes - mPTB: 0.97 (0.89, 1.06) Birth outcomes - sPTB: 0.97 (0.90, 1.05) Birth outcomes - PTB overall - Maternal race/ethnicity: Asian NH: 1.12 (0.86, 1.46)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort	or >7000 g) or who were at <20 weeks' or >45 weeks' gestation at birth were excluded from the analysis. Additionally, patients (n = 513) missing covariate information were excluded, except for body mass index (BMI).	NO ₂ - entire pregnancy NO ₂ – trimester 1 Exposure years: 2013–2017	sPTB Mean = 17.2±2.6 Term Mean = 17.2±2.3	defined as birth following preterm labor or the spontaneous rupture of membranes. mPTB was defined as birth after labor induction or cesarian birth performed due to concern for maternal or fetal wellbeing.	included as random intercepts.	Birth outcomes - mPTB - Maternal race/ethnicity: Asian NH: 0.83 (0.47, 1.47) Birth outcomes - sPTB - Maternal race/ethnicity: Asian NH: 1.20 (0.89, 1.62) Birth outcomes - PTB overall - Maternal race/ethnicity: Black NH: 0.99 (0.92, 1.07) Birth outcomes - sPTB - Maternal race/ethnicity: Black NH: 0.99 (0.90, 1.10) Birth outcomes - mPTB - Maternal race/ethnicity: Black NH: 1.00 (0.89, 1.12) Birth outcomes - PTB overall - Maternal race/ethnicity: Hispanic: 0.91 (0.72, 1.15) Birth outcomes - sPTB - Maternal race/ethnicity: Hispanic: 0.86 (0.63, 1.17) Birth outcomes - mPTB - Maternal race/ethnicity: Hispanic: 0.97 (0.68, 1.38) Birth outcomes - PTB overall - Maternal race/ethnicity: White NH: 0.95 (0.85, 1.05) Birth outcomes - sPTB - Maternal race/ethnicity: White NH: 0.98 (0.86, 1.13) Birth outcomes - mPTB - Maternal race/ethnicity: White NH: 0.88 (0.74, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - PTB overall - Maternal race/ethnicity: Other: 1.11 (0.85, 1.45) Birth outcomes - sPTB - Maternal race/ethnicity: Other: 0.96 (0.70, 1.33) Birth outcomes - mPTB - Maternal race/ethnicity: Other: 1.58 (0.96, 2.58)
† Estarlich et al. (2016) INMA, INfancia y Medio Ambiente N = 2,409 Gipuzkoa, Sabadell, Valencia, Asturias, Spain May 2004–August 2008 Cohort	Pregnant women met the following inclusion criteria were included: >18 years, intention to deliver at the reference hospital, no problems of communication, singleton pregnancy, and no assisted conception. Women who underwent induced or spontaneous abortions or fetal deaths were excluded.	LUR, Personal monitor or sampler The R2 for these LUR models ranged between 0.51 and 0.75 for NO ₂ Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - Pregnancy Trimester Exposure years: 2004–2008	NO ₂ (ppb) Median = 15.31 (IQR = 9.62) (28.8 µg/m ³ (IQR = 18.1))	Preterm birth was considered as occurring when delivery was before completed 37 th week of gestation.	GAM Adjusted for: maternal age, smoking during pregnancy, socioeconomic status, newborn's sex, rural residence, and season of delivery	OR (95% CI) ^c Birth outcomes - Preterm birth - Exposure for entire pregnancy: 1.11 (0.86, 1.45) Birth outcomes - Preterm birth - Exposure for trimester 1: 1.02 (0.61, 1.71) Birth outcomes - Preterm birth - Exposure for trimester 2: 1.06 (0.86, 1.32) Birth outcomes - Preterm birth - Exposure for trimester 3: 1.02 (0.81, 1.27) Birth outcomes - Preterm birth - Exposure for entire pregnancy - Adjusted for benzene: 1.23 (0.84, 1.80) Birth outcomes - Preterm birth - Exposure for trimester 1 - Adjusted for benzene: 1.15 (0.80, 1.66) Birth outcomes - Preterm birth - Exposure for trimester 2 - Adjusted for benzene: 1.29 (0.92, 1.80) Birth outcomes - Preterm birth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Exposure for trimester 3 - Adjusted for benzene: 1.13 (0.79, 1.62)
† Garshol et al. (2020) Norwegian Mother and Child Cohort Study (MoBa) N = 16,262 mothers Oslo, Bergen, Akershus, Hordaland, Norway Recruitment: 1999–2008 Follow-up: through 2013 Cohort	Mothers with IBD; Based on available air pollution data (NO ₂), only participants living in Oslo, Akershus, Bergen, and Hordaland were eligible for this study	LUR, Fixed site monitor Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010–2011	NO ₂ (µg/m ³) All Women Mean = 13.6±4.2 IBD mothers Mean = 13.7±6.9 Non-IBD mothers Mean = 13.6±4.2	Preterm birth was defined as birth before 37 weeks of gestation	Logistic regression Adjusted for: maternal age, BMI, maternal education level, and maternal smoking status	OR (95% CI) ^c Birth outcomes - PTB for mean pregnancy: 1.00 (0.99, 1.01) Birth outcomes - PTB for Trimester 1: 1.00 (0.99, 1.01) Birth outcomes - PTB for Trimester 2: 1.00 (0.99, 1.01) Birth outcomes - PTB for Trimester 3: 1.00 (0.99, 1.01)
† Genin et al. (2022) N = 5,076,657 n = 5,070,262 PTB n = 278,817 France January 1, 2012–December 31, 2018 Cohort	All hospital discharge records in France with singleton, live pregnancy deliveries	Hybrid model Averaging time: NO ₂ - annual average Exposure years: 2014–2018	NO ₂ (µg/m ³) Median = 8.1 (IQR 5.75) Min = 1.39 Max = 44.46 P25 = 6.04 P75 = 11.79	PTB was defined as delivery before a gestational age of 37 weeks. The PTBs were then divided into the following gestational age classes: extremely early PTB (gestational age <28 weeks), very early PTB (a gestational age of at least 28 weeks but less than 32 weeks),	Bayesian hierarchical Poisson log-linear regression model Adjusted for: maternal age and social deprivation	RR (95% CI) ^c Birth outcomes - Overall PTB: 1.02 (1.01, 1.02) Birth outcomes - Extremely early PTB: 1.11 (1.09, 1.14) Birth outcomes - Very early PTB: 1.05 (1.03, 1.06) Birth outcomes - Moderate-to-late PTB: 1.01 (1.01, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				and moderate-to-late PTB (a gestational age of at least 32 weeks but less than 37 weeks).		
†Giorgis-Allemand et al. (2017) Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE), Gene and Environment Prospective Study on Infancy in Italy (GASPII), Generation R, INMA, Infancia y Medio Ambiente, Norwegian Mother and Child Cohort Study (MoBa), Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort, Danish National Birth Cohort (DNBC), European Study of Cohorts for Air Pollution Effects (ESCAPE), Amsterdam Born Children and Their Development Study (ABCD), Étude des Déterminants Prénataux du Développement et de la Santé de l'Enfant (EDEN), Born In Bradford (BIB), Mother-child Greek cohort (RHEA), KANC, Air Pollution and Pregnancy Outcomes (APREG) N = 71,493 births	To be included, women had to have delivered a live infant and to have resided during pregnancy in an area where air pollution models had been developed as part of the ESCAPE project. We included only singleton newborns. When women had several pregnancies during the study period, we included only the first.	LUR, Fixed site monitor Method validation NR Averaging time: NO₂ - annual average, NO_x - annual average Exposure years: 1994–2010	NR	Preterm births (births occurring before 37 weeks of gestation) were identified by the gestational duration, based whenever possible on date of conception as estimated from the last menstrual period	Logistic regression Adjusted for: infant sex, maternal educational level, parity (0, 1, or ≥2), season of conception, maternal smoking during second trimester of pregnancy, maternal weight (broken-stick model with a knot at 60 kg), maternal height (continuous coding), and age; study center was controlled for using a random-effect variable; temperature (restricted cubic-spline coding) and atmospheric pressure (continuous coding) first-trimester levels	NO₂ OR (95% CI)^c Birth outcomes - PTB for exposure during entire pregnancy: 0.96 (0.91, 1.01) Birth outcomes - PTB for exposure during previous month: 0.96 (0.92, 1.00) Birth outcomes - PTB for exposure during trimester 1: 0.97 (0.92, 1.02) Birth outcomes - PTB for exposure during trimester 2: 0.96 (0.92, 1.01) Birth outcomes - PTB for exposure during previous week: 0.98 (0.94, 1.01) NO_x OR (95% CI)^c Birth outcomes - PTB for exposure during previous month: 0.96 (0.93, 1.00) Birth outcomes - PTB for exposure during entire pregnancy: 0.96 (0.92, 1.00) Birth outcomes - PTB for exposure during trimester 1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Stockholm, Rome, Rotterdam, Oslo, Copenhagen, Amsterdam, Nancy, Poitiers, Bradford, UK, Heraklion, Greece, Gyor, Hungary, Kaunas, Lithuania, Sweden, France, England, Denmark, Spain, Italy, Norway, Greece, Hungary, Lithuania, Netherlands						0.94 (0.93, 1.01) Birth outcomes - PTB for exposure during trimester 2: 0.97 (0.93, 1.00) Birth outcomes - PTB for exposure during previous week: 0.98 (0.95, 1.01)
Recruitment: 1994–2010 Follow-up: Study years NR						
Cohort						
† Hao et al. (2016)	Singleton birth mothers and their child (27–42 weeks of gestation). Births were excluded if the maternal residential address at delivery could not be geocoded to the 2000 census block group, birth weight was <400 grams, the mother's age was <15 years or >44 years, at least one congenital anomaly was identified, or induction of labor had a procedure code (for preterm births).	CMAQ 1-hr max NO ₂ R CMAQ = 0.76 24-hr ave NO ₃ - CMAQ = 0.55 Averaging time: NO ₂ - 1-hour max, NO _x - 24-hour average Exposure years: 2002–2008	NO ₂ (ppb) 1-hr max, overall Median = 3.51 Max = 32.72 P5 = 1.16 P25 = 2.13 P75 = 6.64 NO ₂ (ppb) 24-hr ave, overall Median = 0.29 Max = 2.26 P5 = 0.07 P25 = 0.15 P75 = 0.62	Preterm birth was defined as a birth < 37 weeks of gestation.	Logistic regression with county-level fixed effects Adjusted for: maternal education, race, smoking, and long-term trend using a natural cubic spline on conception date with 5 degrees of freedom (one per year)	OR (95% CI) ^c Birth outcomes - Preterm birth for Trimester 1 Exposure: 1.009 (1.005, 1.013) Birth outcomes - Preterm birth for Trimester 2 Exposure: 1.008 (1.004, 1.012) Birth outcomes - Preterm birth for Trimester 3 Exposure: 1.010 (1.007, 1.014) Birth outcomes - Preterm birth for Entire Pregnancy Exposure: 1.012 (1.007, 1.017) Birth outcomes - Preterm birth for Trimester 1 Exposure - Maternal education ≤High school: 1.01 (1.01, 1.02) Birth outcomes - Preterm birth for Trimester 2 Exposure - Maternal education ≤High school: 1.02 (1.01, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - Preterm birth for Trimester 3 Exposure - Maternal education ≤High school: 1.02 (1.01, 1.02) Birth outcomes - Preterm birth for Entire Pregnancy Exposure - Maternal education ≤High school: 1.02 (1.02, 1.03) Birth outcomes - Preterm birth for Trimester 1 Exposure - Maternal education >High school: 1.00 (0.99, 1.00) Birth outcomes - Preterm birth for Trimester 2 Exposure - Maternal education >High school: 0.99 (0.99, 1.00) Birth outcomes - Preterm birth for Trimester 3 Exposure - Maternal education >High school: 1.00 (0.99, 1.00) Birth outcomes - Preterm birth for Entire Pregnancy Exposure - Maternal education >High school: 0.99 (0.99, 1.00) Birth outcomes - Preterm birth for Trimester 1 Exposure - Maternal race Black (author reported as African American): 1.01 (1.01, 1.02) Birth outcomes - Preterm birth for Trimester 2 Exposure - Maternal race Black (author reported as African American): 1.02 (1.01, 1.02) Birth outcomes - Preterm birth for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Trimester 3 Exposure - Maternal race Black (author reported as African American): 1.01 (1.01, 1.02) Birth outcomes - Preterm birth for Entire Pregnancy Exposure - Maternal race Black (author reported as African American): 1.02 (1.01, 1.03) Birth outcomes - Preterm birth for Trimester 1 Exposure - Maternal race Other: 1.00 (1.00, 1.01) Birth outcomes - Preterm birth for Trimester 2 Exposure - Maternal race Other: 1.00 (0.99, 1.00) Birth outcomes - Preterm birth for Trimester 3 Exposure - Maternal race Other: 1.00 (1.00, 1.01) Birth outcomes - Preterm birth for Entire Pregnancy Exposure - Maternal race Other: 1.00 (0.99, 1.01)
† Hao et al. (2023)	Only singleton pregnancies with a gestational age of 27–42 weeks with an estimated date of conception between January 1st, 2000 and December 31st, 2015, were included. We	Spatiotemporal/geospatial model, Ensemble machine learning model Method validation NR Averaging time:	NO ₂ (ppb) 1st Trimester Mean = 10.9 2nd Trimester Mean = 10.88 3rd Trimester	Gestational age < 37 weeks	Linear regression Adjusted for: maternal education level, race, ethnicity, age, marital status, smoking, infant parity, zip code level percent below poverty, census tract level	OR (95% CI) ^c Birth outcomes - Preterm birth - First 4 weeks: 1.01 (0.98, 1.04) Birth outcomes - Preterm birth - First 6 weeks: 1.01 (0.98, 1.04) Birth outcomes - Preterm birth - Trimester 1:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Gestational Diabetes Cohort n = 449,871 Gestational Hypertension Cohort n = 590,574 Kansas, U.S. Enrollment: 1999–2016 Follow-up: through pregnancy and birth Cohort	excluded births with (a) missing census tract information; (b) maternal age < 10 years or > 55 years; (c) birth weight < 250 g or > 7500 g. For the outcomes of GDM and GH, we also excluded mothers with pre-existing diabetes or pre-existing hypertension.	NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2000–2016	Mean = 11.01 2000–2004 Mean = 12.12 2010–2015 Mean = 10.23 Total Pregnancy Mean = 10.16		greenness, season of conception, and long-term trend using a natural cubic spline on conception date with 5 degrees of freedom	1.01 (0.98, 1.04) Birth outcomes - Preterm birth - Trimester 2: 1.00 (0.97, 1.03) Birth outcomes - Preterm birth - Trimester 3: 1.00 (0.97, 1.03) Birth outcomes - Preterm birth - Entire pregnancy: 1.00 (0.97, 1.03)
† Jiao et al. (2023) Kaiser Permanente Southern California (KPSC) N = 429,839 Southern California, U.S. 2008–2018 Cohort	Mothers who were members of Kaiser Permanente Southern California (KPSC), a large integrated healthcare system, with gestational ages from 20 to 47 weeks and singleton pregnancies were included. Excluded multiple births and stillbirths.	Fixed site monitor Range r ² = 0.65–0.75 Averaging time: NO ₂ - monthly NO ₂ - trimester Exposure years: 2007–2018	NO ₂ (ppb) Non-SPROMS Mean = 15.46±4.23 SPROMS Mean = 15.46±4.06 Total Pregnancies Mean = 15.62±4.21	SPROM is defined as the spontaneous ROM without the onset of labor regardless of gestational age	Logistic regression Adjusted for: maternal age, race/ethnicity, education level, income level, pre-pregnancy body mass index, smoking status, parity, year of infant birth, and season of conception	OR (95% CI) ^c Birth outcomes - Spontaneous premature rupture of membranes for exposure for trimester 1: 1.05 (1.03, 1.08) Birth outcomes - Spontaneous premature rupture of membranes for exposure for trimester 2: 0.98 (0.95, 1.01) Birth outcomes - Spontaneous premature rupture of membranes for exposure for trimester 3: 1.07 (1.05, 1.09) Birth outcomes - Spontaneous premature rupture of membranes for exposure for entire pregnancy: 1.06 (1.03, 1.09)
† Johnson et al. (2016) New York City Department of Health and Mental Hygiene (NYCDOHMH)	Included live births to residents of NYC and was limited to singleton births with 22–42 completed weeks	LUR, Spatiotemporal/geospatial model r ² = 0.79 for NO ₂	NO ₂ (ppb) 1st Trimester Overall Median = 27.3	Preterm birth was defined as births with clinical estimate of gestation < 37	Logistic mixed models Adjusted for: maternal age, race/ethnicity stratified by birthplace	OR (95% CI) ^c Birth outcomes - Medically indicated PTB for Trimester 1: 0.90 (0.81, 0.99) Birth outcomes - Medically

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = 258,294	gestation free of congenital malformations to nonsmoking mothers. We excluded births with an estimated date of conception before 31 July 2007 or after 12 March 2010, births with missing residence information for assigning exposure, covariate information, hospital of birth, and those with implausible birth weights.	Averaging time: NO ₂ - annual average	P5 = 18.8 P25 = 23.5 P75 = 31.5 P95 = 38.9	completed weeks based on ultrasound; early preterm was defined as < 32 weeks.	(non-Hispanic white, U.S./foreign-born non-Hispanic black, U.S./foreign-born Hispanic, U.S./foreign-born Asian, other, and unknown), education (< 9, 9–11, 12, 13–15, 16, or > 16 years), parity (0, 1, 2, ≥ 3), Medicaid status (yes/no), pre-pregnancy BMI, BMI2, and sex of infant; year of conception	indicated PTB for Trimester 2: 0.89 (0.80, 0.99) Birth outcomes - sPTB for Trimester 1: 0.94 (0.87, 1.02) Birth outcomes - sPTB for Trimester 2: 0.90 (0.83, 0.97) Birth outcomes - All PTB for Trimester 1: 0.92 (0.87, 0.98) Birth outcomes - All PTB for Trimester 2: 0.89 (0.83, 0.95)
New York City, NY, U.S.		Exposure years: 2008–2010	1st Trimester Temporal Median = 22.4 P5 = 17.6 P25 = 20.4 P75 = 24.6 P95 = 27.1	completed weeks. Medically indicated births were identified using either birth or hospital records. ICD-9 codes for pre-labor artificial rupture of the membrane (73.0, 73.01, 73.09, 73.1, 73.4) or cesarean section performed (74.x) in the absence of a diagnosis of early or threatened labor (644.0x, 644.1x, 644.2x) were considered “medically indicated” as were births recorded in the birth records as having labor induction or cesarean section		
Live births occurring between January 1, 2008–December 31, 2010			2nd Trimester Overall Median = 26.4 P5 = 18.1 P25 = 22.7 P75 = 30.6 P95 = 38.2			
Cohort			2nd Trimester Temporal Median = 21.8 P5 = 17.2 P25 = 19.3 P75 = 23.8 P95 = 26.9			
			Spatial Median = 26.5 P5 = 19.3 P25 = 23.5 P75 = 28.8 P95 = 35.5			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				without trial of labor.		
† Krajewski et al. (2023)	All live, singleton births without any birth defects with gestational age between 20 and 44 weeks with residence at delivery in North Carolina.	Ensemble machine learning model	NO ₂ (ppb)	Gestational age < 37 weeks	Modified Poisson regression models with robust errors	RD (95% CI) ^c
N = 1,600,409 n = 1,367,517		Method validation NR	Entire pregnancy Median = 14.97 (IQR 10.09) Min = 0.52 Max = 42.21			Birth outcomes - Preterm birth; NO ₂ for Gestational Week 1: -7.00 (-13.00, 0.00)
North Carolina, U.S.		Averaging time: NO ₂ - 8-hour max	Trimester 1 Median = 15.23 (IQR 11.14) Min = 0.27 Max = 46.49		Adjusted for: maternal marital status (married as reference), race/ethnicity (White, non-Hispanic as reference), age at delivery (continuous quadratic), Medicaid status (no as reference), and month of conception (index variable as referent)	Birth outcomes - Preterm birth; NO ₂ for Gestational Week 12: -6.00 (-12.00, 1.00)
January 1, 2003–December 31, 2015		Exposure years: 2003–2015	Trimester 2 Median = 14.84 (IQR 10.95) Min = 0.31 Max = 46.44			Birth outcomes - Preterm birth; NO ₂ for Gestational Week 24: -1.00 (-7.00, 6.00)
Cohort			Trimester 3 Median = 14.45 (IQR 10.71) Min = 0.29 Max = 50.26			Birth outcomes - Preterm birth; NO ₂ for Gestational Week 36: 0.00 (-5.00, 4.00)
			Week 1 Median = 14.84 (IQR 11.65) Min = 0.18 Max = 57.14			Birth outcomes - Preterm birth; NO ₂ for Trimester 1: -1.00 (-1.00, 0.00)
			Week 12 Median = 14.74			Birth outcomes - Preterm birth; NO ₂ for Trimester 2: -1.00 (-1.00, 0.00)
						Birth outcomes - Preterm birth; NO ₂ for Trimester 3: 0.00 (-1.00, -1.00)
						Birth outcomes - Preterm birth; NO ₂ for Entire Pregnancy: 0.00 (0.00, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			(IQR 11.51) Min = 0.18 Max = 58.12 Week 24 Median = 14.3 (IQR 11.24) Min = 0.18 Max = 59.44 Week 36 Median = 14.03 (IQR 10.99) Min = 0.23 Max = 61.6			
† Laurent et al. (2016) California Department of Public Health (CDPH) birth registry n = N birth: 3,870,696 California, U.S. Preterm births occurring between 2001–2008 Cohort	Infants with recorded birth defects or unknown birth defects status (n = 18,811 and n = 675, respectively) were excluded. We excluded birth with missing information for gestational age (n = 196,247), estimated gestational age < 121 or > 319 days (n = 2,051 and n = 41,017, respectively), implausible combinations of birth weight and gestational age (n = 17,026), or infants born to mothers > 60 years of age (n = 43). Infants conceived	Fixed site monitor, Dispersion model, Chemical transport model r ² = 0.74 Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2000–2008	NO ₂ (ppb) EBK Mean = 19.15±6.75 NO _x (ppb) CALINE Mean = 6.1±5.48	Infants born < 37 gestational weeks	Logistic regression Adjusted for: race/ethnicity and educational level using categorical variables and for maternal age and median household income at census block–group level using polynomial functions	NO ₂ OR (95% CI) ^c Birth outcomes - Preterm birth - EBK NO ₂ Exposure: 1.08 (1.07, 1.09) Birth outcomes - Preterm birth - EBK NO ₂ Exposure - Co-adjusted for O ₃ : 1.08 (1.07, 1.10) Birth outcomes - Preterm birth - EBK NO ₂ Exposure - Co-adjusted for PM _{2.5} : 0.99 (0.97, 1.00) NO _x OR (95% CI) ^c Birth outcomes - Preterm birth for CALINE4 NO _x modeled

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	> 19 weeks before the start (1 January 2001), or < 43 weeks before the end (31 December 2008) of the study (n = 389,611 and n = 38,598, respectively) were further excluded to avoid fixed cohort bias					concentrations: 1.01 (1.00, 1.01)
† Lavigne et al. (2016b) Better Outcomes Registry & Network (BORN) Ontario N = 818,400 Ontario, Canada Recruitment: January 2005–March 2012 Cohort	Pregnant women giving birth in hospitals to live born, non-planned C-sections, singleton infants in Ontario, Canada were recruited in the first trimester of pregnancy. Women with postal codes of residence outside Ontario were excluded	LUR This model explained 73% of the variations in annual 2006 NO ₂ measurements Averaging time: NO ₂ - annual average Exposure years: 2005–2011	NO ₂ (ppb) Entire Pregnancy, Overall Mean = 15.89±6.38 Median = 16 (IQR 9) P5 = 6 P95 = 26 Trimester 1, Overall Mean = 16.2±6.87 Median = 16 (IQR 10) P5 = 6 P95 = 28 Trimester 2, Overall Mean = 16.15±6.88 Median = 16 (IQR 10) P5 = 6 P95 = 28 Trimester 3, Overall Mean = 15.93±6.87	Gestational age < 37 weeks	Mixed effect logistic regression models Adjusted for: maternal age at delivery, maternal cigarette smoking during pregnancy, infant sex, parity, previous caesarean section delivery, urban/rural place of residence, month of birth, year of birth, census dissemination area median family income, census dissemination area proportion of population who are visible minority and census dissemination area proportion of the adult female population aged 25–64 years old who completed postsecondary education	OR (95% CI) ^c Birth outcomes - Preterm birth - Overall: 1.084 (1.055, 1.103) Birth outcomes - Preterm birth for maternal comorbidity of no asthma: 1.074 (1.046, 1.103) Birth outcomes - Preterm birth for maternal comorbidity of asthma: 1.065 (0.930, 1.206) Birth outcomes - Preterm birth for maternal comorbidity of no hypertension: 1.065 (1.037, 1.094) Birth outcomes - Preterm birth for maternal comorbidity of hypertension: 1.027 (0.857, 1.227) Birth outcomes - Preterm birth for maternal comorbidity of no heart disease: 1.065 (1.037, 1.084) Birth outcomes - Preterm birth for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 16 (IQR 9) P5 = 5 P95 = 28			maternal comorbidity of heart disease: 1.473 (1.065, 2.067) Birth outcomes - Preterm birth for maternal comorbidity of no diabetes: 1.065 (1.037, 1.084) Birth outcomes - Preterm birth for maternal comorbidity of diabetes: 1.238 (1.055, 1.448) Birth outcomes - Preterm birth for maternal comorbidity of no gestational diabetes: 1.055 (1.037, 1.084) Birth outcomes - Preterm birth for maternal comorbidity of gestational diabetes: 1.123 (1.018, 1.238) Birth outcomes - Preterm birth for maternal comorbidity of no preeclampsia: 1.055 (1.037, 1.084) Birth outcomes - Preterm birth for maternal comorbidity of preeclampsia: 1.185 (1.065, 1.305)
[†] Li et al. (2016b) n = 6,949 Brisbane, Australia January 1, 2009–December 31,	Births from all public and private hospitals and voluntarily reported homebirths in Brisbane.	Monitoring sites Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Mean = 6.52±3.5 Median = 5.58 (IQR 4.25) P5 = 2.47 P25 = 4	All live births occurring < 37 weeks of gestation	Logistic regression with natural cubic splines Adjusted for: Study design controls for time-invariant individual level confounders (e.g.,	OR (95% CI) ^c Birth outcomes - Preterm birth - 95th (11.3 ppb) vs. threshold (7.6 ppb): 1.17 (1.08, 1.27) Birth outcomes - Preterm birth - 75th (8.3 ppb) vs. threshold (7.6 ppb): 1.01 (0.99, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2013 Case-crossover		Exposure years: 2009–2013	P75 = 8.25 P95 = 13.63		infant sex and maternal age)	Birth outcomes - Preterm birth - 95th (11.3 ppb) vs. threshold (7.6 ppb) - Co-adjusted for CO: 1.13 (1.01, 1.26) Birth outcomes - Preterm birth - 95th (11.3 ppb) vs. threshold (7.6 ppb) - Co-adjusted for SO₂: 1.17 (1.08, 1.27) Birth outcomes - Preterm birth - 75th (8.3 ppb) vs. threshold (7.6 ppb) - Co-adjusted for CO: 1.00 (0.98, 1.02) Birth outcomes - Preterm birth - 95th (11.3 ppb) vs. threshold (7.6 ppb) - Prepregnancy medical conditions: 1.90 (1.18, 3.04) Birth outcomes - Preterm birth - 95th (11.3 ppb) vs. threshold (7.6 ppb) - No Prepregnancy medical conditions: 1.18 (1.07, 1.30) Birth outcomes - Preterm birth - 75th (8.3 ppb) vs. threshold (7.6 ppb) - Prepregnancy medical conditions: 1.67 (1.07, 2.61) Birth outcomes - Preterm birth - 75th (8.3 ppb) vs. threshold (7.6 ppb) - No Prepregnancy medical conditions: 1.01 (0.99, 1.02) Birth outcomes - Preterm birth - 75th (8.3 ppb) vs. threshold (7.6 ppb) - Co-adjusted for SO₂: 1.01 (0.99, 1.03) Birth outcomes - Preterm birth - 95th (11.3 ppb) vs. threshold (7.6 ppb) - Co-adjusted for SO₂ and CO:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						1.13 (1.01, 1.26) Birth outcomes - Preterm birth - 75th (8.3 ppb) vs. threshold (7.6 ppb) - Co-adjusted for SO ₂ and CO: 1.00 (0.98, 1.03)
† Mendola et al. (2016) Consortium of Safe Labor (2002–2008) N= 228,562 n=223,502 Los Angeles, CA, Ogden, UT, Salt Lake City, UT, Murray, UT, Sandy, UT, Provo, UT, Chicago, IL, Houston, TX, Cleveland, OH, Akron, OH, Indianapolis, IN, Miami, FL, Springfield, MA, Brooklyn, NY, Newark, DE, Baltimore, MD, Washington, DC, U.S. 2002–2008 Cohort	Births at 23 weeks' gestation or more was assembled using electronic medical records from 12 centers (19 hospitals) across the United States. Excluded were multifetal pregnancies (n = 55,050) and pregnancies missing air quality data (n = 510)	CMAQ Averaging time: Other, NO _x – weekly and entire pregnancy Exposure years: 2001–2009	NO _x (ppb) Mean = 6.52±3.5 Median = 5.58 (IQR 4.25) P5 = 2.47 P25 = 4 P75 = 8.25 P95 = 13.63	Preterm birth was defined using the best clinical gestational age recorded in the medical record	Logistic regression Adjusted for: maternal age, race, pre-pregnancy BMI, smoking and alcohol use, study site, parity, insurance status, marital status, and comorbidities	OR (95% CI) ^c Birth outcomes - Early PTB (<34 weeks) for weeks 1-7 for mothers without asthma: 1.01 (0.96, 1.07) Birth outcomes - Total PTB (<37 weeks) for weeks 1-7 for mothers with asthma: 1.13 (1.05, 1.22) Birth outcomes - Early PTB (<34 weeks) for weeks 1-7 for mothers with asthma: 1.22 (1.08, 1.37) Birth outcomes - Early PTB (<34 weeks) for 3-mo preconception period for mothers with asthma: 1.29 (1.06, 1.57) Birth outcomes - Early PTB (<34 weeks) for 3-mo preconception period for mothers without asthma: 1.09 (0.99, 1.20) Birth outcomes - Total PTB (<37 weeks) for 3-mo preconception period for mothers with asthma: 1.28 (1.13, 1.45) Birth outcomes - Total PTB (<37 weeks) for 3-mo preconception period for mothers without asthma: 1.08 (1.02, 1.14) Birth outcomes - Early PTB (<34 weeks) for weeks 22–28 for mothers

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						without asthma: 0.80 (0.75, 0.85) Birth outcomes - Total PTB (<37 weeks) for weeks 22–28 for mothers with asthma: 0.99 (0.92, 1.07) Birth outcomes - Total PTB (<37 weeks) for weeks 22–28 for mothers without asthma: 0.93 (0.90, 0.96) Birth outcomes - Total PTB (<37 weeks) for weeks 1-7 for mothers without asthma: 1.03 (1.00, 1.06) Birth outcomes - Early PTB (<34 weeks) for weeks 8-14 for mothers with asthma: 1.11 (0.98, 1.25) Birth outcomes - Early PTB (<34 weeks) for weeks 8-14 for mothers without asthma: 0.91 (0.86, 0.96) Birth outcomes - Total PTB (<37 weeks) for weeks 8-14 for mothers with asthma: 1.03 (0.95, 1.11) Birth outcomes - Total PTB (<37 weeks) for weeks 8-14 for mothers without asthma: 0.96 (0.93, 0.99) Birth outcomes - Early PTB (<34 weeks) for weeks 15–21 for mothers with asthma: 1.05 (0.93, 1.20) Birth outcomes - Early PTB (<34 weeks) for weeks 15–21 for mothers without asthma:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.85 (0.81, 0.90)
						Birth outcomes - Total PTB (<37 weeks) for weeks 15–21 for mothers with asthma: 1.00 (0.92, 1.08)
						Birth outcomes - Total PTB (<37 weeks) for weeks 15–21 for mothers without asthma: 0.94 (0.91, 0.97)
						Birth outcomes - Early PTB (<34 weeks) for weeks 22–28 for mothers with asthma: 0.92 (0.81, 1.06)
						Birth outcomes - Early PTB (<34 weeks) for last 6 weeks of pregnancy for mothers with asthma: 1.02 (0.91, 1.15)
						Birth outcomes - Early PTB (<34 weeks) for last 6 weeks of pregnancy for mothers without asthma: 0.81 (0.78, 0.84)
						Birth outcomes - Total PTB (<37 weeks) for last 6 weeks of pregnancy for mothers with asthma: 1.02 (0.95, 1.10)
						Birth outcomes - Total PTB (<37 weeks) for last 6 weeks of pregnancy for mothers without asthma: 0.85 (0.83, 0.87)
						Birth outcomes - Early PTB (<34 weeks) for entire pregnancy for mothers with asthma: 1.02 (0.90, 1.15)
						Birth outcomes - Early PTB (<34 weeks) for entire pregnancy for mothers without asthma: 0.84 (0.79, 0.90)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - Total PTB (<37 weeks) for entire pregnancy for mothers with asthma: 1.06 (0.99, 1.14) Birth outcomes - Total PTB (<37 weeks) for entire pregnancy for mothers without asthma: 0.98 (0.94, 1.01)
† Riddell et al. (2022) California Department of Public Health (CDPH) birth registry Oakland N = 16,660 San Jose N = 38,942 Oakland, California, San Jose, California, U.S. 2013–2015 Cohort	Only singleton births and preterm births were included	Personal monitor or sampler Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average Exposure years: 2015–2017	NO ₂ (ppb) Latina Median = 9 (IQR 3.8) P25 = 7.6 P75 = 11.4 Non-Latina Asian Median = 10.7 (IQR 4.6) P25 = 8.5 P75 = 13.1 Non-Latina Black Median = 8.8 (IQR 3.9) P25 = 7.3 P75 = 11.2 Non-Latina White Median = 9.9 (IQR 4.2) P25 = 8.2 P75 = 12.4	Preterm birth was defined as all births with gestational age <37 completed weeks.	Logistic regression and marginal standardization Adjusted for: season of conception, median household income of census group, percentage of the county below poverty, maternal education, type of insurance, maternal age, nulliparity and fixed effect for city	RD (95% CI) ^c Birth outcomes - PTB for non-Latina Black: 0.60 (-3.80, 5.00) Birth outcomes - PTB for Latina: 3.30 (-0.10, 6.60) Birth outcomes - PTB for non-Latina White: 0.80 (-4.00, 5.70) Birth outcomes - PTB for non-Latina Asian: -1.00 (-5.40, 3.40) Birth outcomes - PTB for non-Latina Black adjusted for BC and UFPs: 1.20 (-4.70, 7.10) Birth outcomes - PTB for Latina adjusted for BC and UFPs: 1.30 (-2.50, 5.00) Birth outcomes - PTB for non-Latina White adjusted for BC and UFPs: 4.00 (-2.60, 10.60) Birth outcomes - PTB for non-Latina Asian adjusted for BC and UFPs: 1.10 (-4.70, 6.80)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Savitz et al. (2019) N = 257,956 births New York City, NY, U.S. Births between 2008–2010 Cohort	Excluded patients with missing or implausible gestational age (<22 or >42 weeks), multiple gestations, congenital abnormalities, known smokers, missing or implausible birth weight (<500 or >5,000g), missing covariates (e.g., education, parity), missing delivery hospital, or born in a hospital with fewer than 10 births over the course of the study period and restricted conception dates to avoid fixed-cohort bias.	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - 2 weeks during pregnancy Exposure years: 2008–2010		Gestational age < 37 weeks	Logistic regression Adjusted for: maternal age, ethnicity, education, Medicaid status, parity, SES score, pre-pregnancy BMI, and conception year	OR (95% CI) ^c Birth outcomes - Preterm birth, Overall: 0.92 (0.89, 0.95) Birth outcomes - Preterm birth, Spontaneous: 0.93 (0.90, 0.96) Birth outcomes - Preterm birth, Medically indicated: 0.91 (0.87, 0.96)
†Stieb et al. (2016) Canadian Birth Database N = 2,928,515 Nationwide, Canada Live births from 1999–2008 Cohort	Included singleton live births	LUR, Hybrid model This model explained 73% of the variation Averaging time: NO ₂ - annual average Exposure years: 2005–2011	NO ₂ (ppb) All Mean = 13.4±7.8 Median = 11.9 (IQR 11.5) P5 = 3.7 P95 = 27.8	Preterm birth (gestational age <37 weeks)	GEE logstic regression Adjusted for: Maternal age and marital status, parity, urban/rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority, infant sex, and gestational age,	OR (95% CI) ^c Birth outcomes - Preterm birth: 0.98 (0.97, 0.99)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					Socioeconomic status; proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education, census dissemination are a proportion of individuals 15 and over who were unemployed	
†Stieb et al. (2019)	Included singleton live births with daily air pollution data available	Fixed site monitor	NO ₂ (ppb)	Preterm births were defined as birth at less than 37 weeks gestation	Cox proportional hazards model	HR (95% CI) ^b
Canadian Birth Database		Method validation NR	Brampton Mean = 16.2 Min = 1.8 Max = 58.1		Adjusted for: infant sex, maternal age (19 years or less, 20–39, 30–39, 40+ years), maternal marital status (single, married, separated, divorced, widowed), maternal country of birth (Canada, elsewhere), tertile of neighbourhood percent unemployed, low income, visible minority, and with post-secondary education, indicator variables for year and season of birth and a natural spline function of day of year with 3 degrees of freedom	Birth outcomes - PTB for lag 0: 0.92 (0.87, 0.97)
N = 1,248,240 singleton births		Averaging time: NO ₂ - 24-hour average	Calgary Mean = 21.3 Min = 4.9 Max = 63.7			Birth outcomes - PTB for lag 1: 0.96 (0.94, 0.97)
Toronto, Quebec, Vancouver, Montreal, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Saint John, Ottawa, Calgary, Kitchener, Ontario, Oshawa, Ontario, St. Catharines, Ontario, Victoria, St. John's, Fredericton, Trois Rivières, Mississauga, Brampton, Richmond, Nanaimo, Kamloops, Kelowna, Canada		Exposure years: 2000–2008	Edmonton Mean = 20.8 Min = 3.2 Max = 62.9			Birth outcomes - PTB for lag 2: 0.99 (0.98, 1.00)
Births between 1999–2008			Fredericton Mean = 4.9 Min = 0 Max = 34.8			Birth outcomes - PTB for lag 3: 1.01 (0.99, 1.02)
Time-series			Hamilton Mean = 17.7			Birth outcomes - PTB for lag 4: 1.00 (0.99, 1.02)
						Birth outcomes - PTB for lag 5: 0.99 (0.97, 1.00)
						Birth outcomes - PTB for lag 6: 0.97 (0.94, 0.99)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 1 Max = 62.6			
			Kamloops Mean = 10.6 Min = 0.1 Max = 38.2			
			Kelowna Mean = 9 Min = 0.2 Max = 35.3			
			Kitchener Mean = 12.2 Min = 0.8 Max = 53.2			
			Mississauga Mean = 19.8 Min = 3.2 Max = 58.9			
			Montreal Mean = 18.3 Min = 3.8 Max = 57.9			
			Nanaimo Mean = 8.4 Min = 1.1 Max = 20.1			
			Oshawa Mean = 15.3 Min = 0.3 Max = 52.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Ottawa Mean = 14.7 Min = 0 Max = 57			
			Quebec Mean = 12.8 Min = 0.4 Max = 56.9			
			Richmond Mean = 16.7 Min = 3.6 Max = 40.5			
			Saint John Mean = 7.4 Min = 0 Max = 59.4			
			St. Catharines Mean = 13.9 Min = 2.1 Max = 77.6			
			St. John's Mean = 7.8 Min = 0.1 Max = 57.8			
			Toronto Mean = 21.9 Min = 4.8 Max = 62.3			
			Vancouver			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 22.5 Min = 4.7 Max = 43.2 Victoria Mean = 11.1 Min = 0.5 Max = 30.9 Windsor Mean = 18.4 Min = 2.9 Max = 55.7 Winnipeg Mean = 11.8 Min = 1.1 Max = 39.3			
† Villeneuve et al. (2022) Canadian Birth Database N = ~2.2 million Nationwide, Canada Births between 1999–2008 Cohort	Analyses were restricted to all singleton live births that were accessed from the Canadian Birth Database through Statistics Canada (approximately 3.2 million births). We further restricted the study population to highly urbanized areas.	Fixed site monitor, LUR Method validation NR Averaging time: NO ₂ - annual average, Other, NO ₂ - pregnancy Exposure years: 1999–2008	NO ₂ (ppb) All Singleton Births Mean = 16.7	Gestational age < 37 weeks	Logistic regression Adjusted for: neighbourhood SES, individual covariates and visible minority	OR (95% CI) ^c Birth outcomes - Preterm birth: 0.98 (0.97, 0.99)
† Weber et al. (2019) California Department of Public Health (CDPH) birth registry	Eligible births were singletons, had a gestational age within 20–42 weeks, a birth	Fixed site monitor Method validation NR	NO ₂ (ppb) Entire Pregnancy Median = 17.26	Preterm birth was defined as gestational age <37 weeks and	Logistic regression Adjusted for: maternal race/ethnicity, age,	OR (95% CI) ^c Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for entire pregnancy and

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = 252,205 births California, San Joaquin Valley, U.S. Data pulled between 2000 - 2006 Cohort	weight within 500–5,000 grams and were not missing state file numbers. Subjects missing data on eligibility criteria, last menstrual period (used to determine gestational age at birth), or covariates used for adjustment (maternal age, race/ethnicity, education, prenatal care, and insurance type) were excluded.	Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - trimester pregnancy NO ₂ - last 6 weeks of pregnancy Exposure years: 2000–2006	(IQR 4.14) Min = 6.83 Max = 32.25	was further divided into categories (20–27, 28–31, 32–33, 34–36 weeks)	education, payment of birth expenses/insurance type, and prenatal care	without the presence of maternal hypertension: 1.07 (1.04, 1.11) Birth outcomes - Preterm birth at gestational age 34–36 weeks for exposure for entire pregnancy and presence of maternal hypertension: 1.04 (0.94, 1.16) Birth outcomes - Preterm birth at gestational age 32–33 weeks for exposure for entire pregnancy and presence of maternal hypertension: 1.16 (0.96, 1.41) Birth outcomes - Preterm birth at gestational age 32–33 weeks for exposure for entire pregnancy and without the presence of maternal hypertension: 1.11 (1.02, 1.20) Birth outcomes - Preterm birth at gestational age 28–31 weeks for exposure for entire pregnancy and presence of maternal hypertension: 0.99 (0.78, 1.26) Birth outcomes - Preterm birth at gestational age 28–31 weeks for exposure for entire pregnancy and without the presence of maternal hypertension: 1.13 (1.03, 1.24) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for entire pregnancy and presence of maternal hypertension: 1.49 (1.00, 2.21) Birth outcomes - Preterm birth at gestational age 20–27 weeks for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						exposure for entire pregnancy and without the presence of maternal hypertension: 1.21 (1.06, 1.37) Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for trimester 1 and presence of maternal hypertension: 1.06 (0.96, 1.17) Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for trimester 1 and without the presence of maternal hypertension: 1.02 (0.99, 1.06) Birth outcomes - Preterm birth at gestational age 32-33 weeks for exposure for trimester 1 and presence of maternal hypertension: 1.22 (1.02, 1.46) Birth outcomes - Preterm birth at gestational age 32-33 weeks for exposure for trimester 1 and without the presence of maternal hypertension: 0.98 (0.91, 1.06) Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for trimester 1 and presence of maternal hypertension: 0.98 (0.78, 1.22) Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for trimester 1 and without the presence of maternal hypertension:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						1.14 (1.05, 1.25) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for trimester 1 and presence of maternal hypertension: 1.30 (0.89, 1.91) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for trimester 1 and without the presence of maternal hypertension: 1.04 (0.92, 1.17) Birth outcomes - Preterm birth at gestational age 34–36 weeks for exposure for trimester 2 and presence of maternal hypertension: 0.96 (0.87, 1.06) Birth outcomes - Preterm birth at gestational age 34–36 weeks for exposure for trimester 2 and without the presence of maternal hypertension: 1.03 (1.00, 1.06) Birth outcomes - Preterm birth at gestational age 32–33 weeks for exposure for trimester 2 and presence of maternal hypertension: 1.00 (0.83, 1.20) Birth outcomes - Preterm birth at gestational age 32–33 weeks for exposure for trimester 2 and without the presence of maternal hypertension: 1.04 (0.96, 1.12) Birth outcomes - Preterm birth at gestational age 28–31 weeks for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						exposure for trimester 2 and presence of maternal hypertension: 0.85 (0.67, 1.07) Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for trimester 2 and without the presence of maternal hypertension: 1.01 (0.92, 1.11) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for trimester 2 and presence of maternal hypertension: 0.74 (0.49, 1.13) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for trimester 2 and without the presence of maternal hypertension: 1.04 (0.92, 1.17) Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for trimester 3 and presence of maternal hypertension: 0.95 (0.86, 1.05) Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for trimester 3 and without the presence of maternal hypertension: 0.99 (0.96, 1.02) Birth outcomes - Preterm birth at gestational age 32-33 weeks for exposure for trimester 3 and presence of maternal hypertension: 0.90 (0.74, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - Preterm birth at gestational age 32-33 weeks for exposure for trimester 3 and without the presence of maternal hypertension: 1.05 (0.97, 1.13)
						Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for trimester 3 and presence of maternal hypertension: 0.90 (0.71, 1.14)
						Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for trimester 3 and without the presence of maternal hypertension: 0.94 (0.85, 1.03)
						Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for last 6 weeks and presence of maternal hypertension: 0.92 (0.83, 1.02)
						Birth outcomes - Preterm birth at gestational age 34-36 weeks for exposure for last 6 weeks and without the presence of maternal hypertension: 0.99 (0.96, 1.02)
						Birth outcomes - Preterm birth at gestational age 32-33 weeks for exposure for last 6 weeks and presence of maternal hypertension: 0.88 (0.72, 1.06)
						Birth outcomes - Preterm birth at gestational age 32-33 weeks for exposure for last 6 weeks and

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						without the presence of maternal hypertension: 1.01 (0.94, 1.09) Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for last 6 weeks and presence of maternal hypertension: 0.87 (0.69, 1.09) Birth outcomes - Preterm birth at gestational age 28-31 weeks for exposure for last 6 weeks and without the presence of maternal hypertension: 0.97 (0.89, 1.07) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for last 6 weeks and presence of maternal hypertension: 0.87 (0.58, 1.32) Birth outcomes - Preterm birth at gestational age 20–27 weeks for exposure for last 6 weeks and without the presence of maternal hypertension: 1.05 (0.93, 1.19)
†Williams et al. (2021) Consortium on Safe Labor (2002–2008) With T1D n = 507 Without T1D n = 204,384 Nationwide, U.S.	Included deliveries at 23 weeks or later. Excluded multifetal pregnancies, mothers with thyroid disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Crohn's disease, as well as those	CMAQ Method validation NR Averaging time: NO_x - 1-hour max, Other, NO_x - 3-month preconception	NO_x (ppb) 1st trimester Mean = 30.26 IQR = 29.06 Min = 5.51 Max = 89.62 2nd trimester Mean = 30.13	Preterm birth was < 37 weeks of gestation and categorized into overall, spontaneous preterm delivery, indicated preterm delivery based on ICD-9	Binary Poisson regression models with the log link function and robust standard errors Adjusted for: maternal age, maternal race/ethnicity, preconception body mass index, health	RR (95% CI)^c Birth outcomes - Preterm birth - 3 months preconception for Type 1 Diabetes: 0.99 (0.99, 1.00) Birth outcomes - Preterm birth - 3 months preconception for no autoimmune: 0.99 (0.99, 0.99)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
2002–2008 Case-Control	with other autoimmune disease. Participants from one site for which ICD-9 codes were not reported and no cases of Type 1 diabetes were identified were also excluded.	period NO _x - trimester NO _x - whole pregnancy Exposure years: 2002–2008	IQR = 28.98 Min = 5.76 Max = 90.65 3 months preconception Mean = 29.02 IQR = 27 Min = 5.09 Max = 92.97 Whole pregnancy Mean = 29.8 IQR = 22.47 Min = 6.38 Max = 81.64	codes and medical records	insurance, marital status, smoking in pregnancy, alcohol use in pregnancy, other chronic diseases, and census region	Birth outcomes - Preterm birth - Indicated - 3 months preconception for Type 1 Diabetes: 1.00 (0.99, 1.02) Birth outcomes - Preterm birth - Indicated - 3 months preconception for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Spontaneous - 3 months preconception for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Spontaneous - 3 months preconception for Type 1 Diabetes: 0.99 (0.99, 1.00) Birth outcomes - Preterm birth - Entire pregnancy for no autoimmune: 0.99 (0.98, 0.99) Birth outcomes - Preterm birth - Entire pregnancy for Type 1 Diabetes: 0.99 (0.98, 1.00) Birth outcomes - Preterm birth - Indicated - Entire pregnancy for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Indicated - Entire pregnancy for Type 1 Diabetes: 1.00 (0.99, 1.02) Birth outcomes - Preterm birth - Spontaneous - Entire pregnancy for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Type 1 Diabetes: 0.98 (0.97, 0.99) Birth outcomes - Preterm birth - Spontaneous - Entire pregnancy for no autoimmune: 0.98 (0.98, 0.99) Birth outcomes - Preterm birth - Trimester 1 for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Trimester 1 for Type 1 Diabetes: 0.99 (0.98, 1.00) Birth outcomes - Preterm birth - Indicated - Trimester 1 for no autoimmune: 0.99 (0.98, 1.00) Birth outcomes - Preterm birth - Indicated - Trimester 1 for Type 1 Diabetes: 0.99 (0.98, 1.01) Birth outcomes - Preterm birth - Spontaneous - Trimester 1 for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Spontaneous - Trimester 1 for Type 1 Diabetes: 0.99 (0.98, 1.00) Birth outcomes - Preterm birth - Trimester 2 for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Trimester 2 for Type 1 Diabetes: 0.99 (0.99, 1.00) Birth outcomes - Preterm birth -

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Indicated - Trimester 2 for no autoimmune: 1.00 (0.99, 1.02) Birth outcomes - Preterm birth - Indicated - Trimester 2 for Type 1 Diabetes: 0.99 (0.98, 1.01) Birth outcomes - Preterm birth - Spontaneous - Trimester 2 for no autoimmune: 0.99 (0.99, 0.99) Birth outcomes - Preterm birth - Spontaneous - Trimester 2 for Type 1 Diabetes: 1.00 (0.99, 1.01)
† Wu et al. (2016) California Department of Public Health (CDPH) birth registry N = 4,370,371 pregnancies California, U.S. Births occurring from January 1, 2001-December 31, 2008 Cohort	Excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing	Chemical transport model, Spatiotemporal/geospatial model, Fixed site monitor Method validation NR Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2000–2008	NO ₂ (ppb) Overall Mean = 15.4 Median = 13.6 (IQR 11.7) P5 = 2.9 P95 = 33.6	Preterm birth (gestational age <37 weeks)	Generalized additive mixed models with random effects Adjusted for: race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines	NO ₂ OR (95% CI) ^c Birth outcomes - Preterm birth (EBK for NO ₂ exposure): 1.11 (1.09, 1.12) Birth outcomes - Preterm birth (Spatiotemporal for NO ₂ exposure): 0.57 (0.54, 0.60) NO _x OR (95% CI) ^c Birth outcomes - Preterm birth (CALINE NO _x exposure): 1.01 (1.00, 1.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Xiao et al. (2023) China Birth Cohort Study N = 108,418 n = 103,040 China September 17, 2018 - December 31, 2020 Cohort	To be eligible for participation, pregnant women had to meet the following criteria: (1) Chinese nationality; (2) gestational age between 6 and 13 complete weeks at recruitment, including both naturally conceived pregnancies and those conceived using assisted reproductive technologies; (3) intention to attend routine antenatal examinations and deliver at the study site, with plans to continue residing locally for at least one year; (4) absence of notifiable infectious diseases such as hepatitis B, syphilis, and HIV; and (5) ability to comprehend the study and provide informed, written consent.	China National Environmental Monitoring Center (CNEMC) network Averaging time: Other: NO ₂ – trimester-specific average	NO ₂ (ppb) Overall Mean = 16.80±3.27 (31.6±11.8 µg/m ³)	Gestational age was measured in days, based on the date of the last menstrual period in combination with confirmatory ultrasound examinations. PTB was defined as delivery prior to 37 completed weeks of gestation.	GAM Adjusted for: sex of newborn, maternal age, ethnicity, education, income, environmental tobacco exposure, use of air purifier, proximity to main roads and noise disturbance	RR (95% CI) ^c Birth outcomes - PTB at 75th vs. threshold: 1.00 (1.00, 1.00) Birth outcomes - PTB at 80th vs. threshold: 1.03 (1.02, 1.05) Birth outcomes - PTB at 90th vs. threshold: 1.21 (1.16, 1.27) Birth outcomes - PTB at 95th vs. threshold: 1.44 (1.33, 1.56) Birth outcomes - PTB at 85th vs. threshold: 1.10 (1.07, 1.13)

List of abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; GAM: generalized additive model; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; NO = nitric oxide; ppb = parts per billion; LUR = land use regression; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; O₃ = ozone; OR = odds ratio; PTB = preterm birth; RR = rate ratio.

aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-12 Epidemiologic studies of oxides of nitrogen and birth outcomes of birth defects

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Any Birth Defects						
†Al Noaimi et al. (2021) National Birth Defect Registry (NBDR), National Collaborative Perinatal Neonatal Network (NCPNN), Lebanese Ministry of Public Health (MoPH) Controls n = 8,321 Cases n = 315 Lebanon June 2014-June 2017 Case-Control	Cases included live births, stillbirths, and terminated pregnancies. Controls included all infants born without a congenital illness during the same period.	Fixed site monitor Averaging time: NO₂ - weekly Exposure years: 2013–2015	NO₂ (ppb) Concentrations only reported graphically	Registered cases were obtained from the National Birth Defect Registry (NBDR), a database maintained by the Lebanese Ministry of Public Health (MoPH). Controls included all infants born without a congenital illness during the same period in a member hospital of the National Collaborative	Logistic regression Adjusted for: active tobacco smoking during pregnancy, parental consanguinity, folic acid intake, mother's educational level, maternal obesity, residential distance to station, and combined criteria air pollutants' exposure	OR (95% CI)^b Birth outcomes - Overall birth defects: 1.01 (0.98, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				Perinatal Neonatal Network (NCPNN) records.		
† Cowan et al. (2024) NC Department of Health and Human Services Division of Public Health N = 566,799 North Carolina, U.S. Births between January 1, 2011-December 31, 2015 Cohort	All live, singleton births with gestational age between 20 and 44 weeks with residence at delivery in NC. Excluded multiple births, deliveries outside of 20-44 weeks gestational age, and missing residential address at time of delivery that precluded geocoding.	Ensemble machine learning model, Hybrid model Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - 8-hour max, Other, NO ₂ - trimester Exposure years: 2011–2015	NO ₂ (ppb) Overall Entire Pregnancy Median = 13.14 Min = 1 Max = 33.42 P25 = 9.84 P75 = 17.24 Trimester 1 Median = 13.17 Min = 0.36 Max = 37.08 P25 = 9.53 P75 = 17.42 Trimester 2 Median = 12.92 Min = 0.78 Max = 39.89 P25 = 9.44 P75 = 17.24	Birth defects were identified from the North Carolina birth defect monitoring program (NCBDMP)	Linear binomial regression models Adjusted for: birthing parent age at delivery (centered at age 26 with a quadratic term), race/ethnicity (white, non-Hispanic as reference), and education (>HS as reference)	PD (95% CI) ^b Birth outcomes - Overall birth defects: -45.09 (-51.88, -38.30) Birth outcomes - Overall birth defects for high NDI: -32.31 (-46.10, -18.53) Birth outcomes - Overall birth defects for medium NDI: -22.70 (-31.94, -13.47) Birth outcomes - Overall birth defects for low NDI: -37.65 (-47.34, -27.96)
Congenital Heart Defects						
Stingone et al. (2014) National Birth Defects Prevention Study (NBDPS) n = 3,328 cases n = 4,632 controls	All controls and eligible cases with a simple, isolated CHD (i.e., a single CHD with no extra-cardiac birth defects present) and an estimated date of	AQS Averaging time: NO ₂ - 1-hour max Exposure years: 1997 - 2006	NO ₂ (ppb) Median = 33.3 P10 = 18.9 P90 = 45.5	Cases with a simple, isolated CHD (i.e., a single CHD with no extra-cardiac birth defects present) were	Logistic regression Adjusted for: maternal race, age, educational attainment, household income, maternal smoking status and	OR (95% CI) ^b Birth Defects: Conotruncal (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Tetralogy of Fallot (≥90th percentile, or ≥45.5 ppb): 1.51 (0.89, 2.57)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
U.S. October 1, 1997 - December 31, 2006 Cohort	delivery (i.e., due date) from 1 October 1997 through 31 December 2006.			reviewed by clinical geneticists using standardized study protocols to determine study eligibility and classification, and cases with chromosomal/microdeletion disorders and disorders of known single-gene deletion causation are excluded.	alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio	Birth Defects: Transposition of the great arteries ($\geq$90th percentile, or $\geq$45.5 ppb): 1.29 (0.69, 2.38) Birth Defects: Transposition of the great arteries (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Transposition of the great arteries (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.18 (0.71, 1.95) Birth Defects: Transposition of the great arteries (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.24 (0.75, 2.04) Birth Defects: Left ventricular outflow tract obstructions (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Left ventricular outflow tract obstructions (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.44 (1.00, 2.08) Birth Defects: Left ventricular outflow tract obstructions (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.49 (1.03, 2.15) Birth Defects: Conotruncal (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.36 (0.99, 1.88) Birth Defects: Conotruncal (50th

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.32 (0.96, 1.82) Birth Defects: Conotruncal (≥90th percentile, or ≥45.5 ppb): 1.42 (0.96, 2.11) Birth Defects: Anomalous pulmonary venous return (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 0.54 (0.28, 1.03) Birth Defects: Anomalous pulmonary venous return (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 0.57 (0.30, 1.09) Birth Defects: Anomalous pulmonary venous return (≥90th percentile, or ≥45.5 ppb): 0.89 (0.41, 1.94) Birth Defects: Total anomalous pulmonary venous return (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Tetralogy of Fallot (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Tetralogy of Fallot (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.51 (0.98, 2.34) Birth Defects: Tetralogy of Fallot (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.27 (0.82, 1.97) Birth Defects: Hypoplastic left heart

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						syndrome (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.07 (0.65, 1.78) Birth Defects: Hypoplastic left heart syndrome (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.04 (0.62, 1.72) Birth Defects: Hypoplastic left heart syndrome (≥90th percentile, or ≥45.5 ppb): 0.85 (0.43, 1.68) Birth Defects: Septal, including cases of muscular ventricular septal defects (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Septal, including cases of muscular ventricular septal defects (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.24 (0.94, 1.64) Birth Defects: Septal, including cases of muscular ventricular septal defects (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.23 (0.94, 1.63) Birth Defects: Septal, including cases of muscular ventricular septal defects (≥90th percentile, or ≥45.5 ppb): 1.44 (1.02, 2.03) Birth Defects: Perimembranous ventricular septal defects (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Perimembranous ventricular septal defects (10th

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						percentile to <50th percentile or 18.9 to <33.33 ppb): 1.13 (0.78, 1.64) Birth Defects: Perimembranous ventricular septal defects (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.18 (0.82, 1.71) Birth Defects: Perimembranous ventricular septal defects (≥90th percentile, or ≥45.5 ppb): 1.47 (0.94, 2.30) Birth Defects: Atrial septal defect (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Atrial septal defect (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.29 (0.87, 1.91) Birth Defects: Atrial septal defect (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.25 (0.84, 1.86) Birth Defects: Atrial septal defect (≥90th percentile, or ≥45.5 ppb): 1.23 (0.74, 2.04) Birth Defects: Other conotruncals (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Other conotruncals (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 1.33 (0.55, 3.22) Birth Defects: Other conotruncals (50th percentile to <90th percentile,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						or 33.33 to <45.5 ppb): 1.81 (0.76, 4.31) Birth Defects: Other conotruncals (≥90th percentile, or ≥45.5 ppb): 1.49 (0.52, 4.24) Birth Defects: Anomalous pulmonary venous return (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Right ventricular outflow tract obstructions (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 1.50 (1.01, 2.24) Birth Defects: Right ventricular outflow tract obstructions (≥90th percentile, or ≥45.5 ppb): 2.22 (1.40, 3.52) Birth Defects: Pulmonary/tricuspid atresia (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Pulmonary/tricuspid atresia (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 2.45 (0.86, 6.95) Birth Defects: Total anomalous pulmonary venous return (10th percentile to <50th percentile or 18.9 to <33.33 ppb): 0.51 (0.28, 1.03) Birth Defects: Total anomalous pulmonary venous return (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 0.57 (0.30, 1.09) Birth Defects: Total anomalous

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						pulmonary venous return (≥ 90th percentile, or ≥ 45.5 ppb): 0.89 (0.41, 1.94) Birth Defects: Atrioventricular septal defect (referent, or < 10th percentile or < 18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Atrioventricular septal defect (10th percentile to < 50th percentile or 18.9 to < 33.33 ppb): 0.63 (0.27, 1.47) Birth Defects: Atrioventricular septal defect (50th percentile to < 90th percentile, or 33.33 to < 45.5 ppb): 0.66 (0.29, 1.54) Birth Defects: Atrioventricular septal defect (≥ 90th percentile, or ≥ 45.5 ppb): 0.64 (0.20, 1.98) Birth Defects: Right ventricular outflow tract obstructions (referent, or < 10th percentile or < 18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Right ventricular outflow tract obstructions (10th percentile to < 50th percentile or 18.9 to < 33.33 ppb): 1.32 (0.88, 1.97) Birth Defects: Aortic stenosis (referent, or < 10th percentile or < 18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Aortic stenosis (10th percentile to < 50th percentile or 18.9 to < 33.33 ppb):

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						2.22 (0.94, 5.26)
						Birth Defects: Aortic stenosis (50th percentile to <90th percentile, or 33.33 to <45.5 ppb):
						1.66 (0.69, 3.99)
						Birth Defects: Aortic stenosis (≥90th percentile, or ≥45.5 ppb):
						2.22 (0.83, 5.97)
						Birth Defects: Pulmonary/tricuspid atresia (50th percentile to <90th percentile, or 33.33 to <45.5 ppb):
						2.02 (0.71, 5.79)
						Birth Defects: Pulmonary/tricuspid atresia (≥90th percentile, or ≥45.5 ppb):
						2.33 (0.71, 7.68)
						Birth Defects: Pulmonary valve stenosis (referent, or <10th percentile or <18.9 ppb):
						1.00 (1.00, 1.00)
						Birth Defects: Pulmonary valve stenosis (10th percentile to <50th percentile or 18.9 to <33.33 ppb):
						1.02 (0.66, 1.59)
						Birth Defects: Pulmonary valve stenosis (50th percentile to <90th percentile, or 33.33 to <45.5 ppb):
						1.30 (0.85, 2.00)
						Birth Defects: Pulmonary valve stenosis (≥90th percentile, or ≥45.5 ppb):
						2.03 (1.23, 3.33)
						Birth Defects: Coarctation of the aorta (10th percentile to <50th percentile or 18.9 to <33.33 ppb):
						1.74 (0.91, 3.32)
						Birth Defects: Coarctation of the

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						aorta (50th percentile to <90th percentile, or 33.33 to <45.5 ppb): 2.34 (1.24, 4.42) Birth Defects: Left ventricular outflow tract obstructions (≥90th percentile, or ≥45.5 ppb): 1.53 (0.98, 2.39) Birth Defects: Coarctation of the aorta (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00) Birth Defects: Coarctation of the aorta (≥90th percentile, or ≥45.5 ppb): 2.50 (1.21, 5.18) Birth Defects: Hypoplastic left heart syndrome (referent, or <10th percentile or <18.9 ppb): 1.00 (1.00, 1.00)
† Al Noaimi et al. (2021) National Birth Defect Registry (NBDR), National Collaborative Perinatal Neonatal Network (NCPNN), Lebanese Ministry of Public Health (MoPH) Controls n = 8,321 Cases n = 315 Nationwide, Lebanon June 2014-June 2017 Case-Control	Cases included live births, stillbirths, and terminated pregnancies. Controls included all infants born without a congenital illness during the same period.	Fixed site monitor Averaging time: NO ₂ - weekly Exposure years: 2013–2015	NO ₂ (ppb) Concentrations only reported graphically	Registered cases were obtained from the National Birth Defect Registry (NBDR), a database maintained by the Lebanese Ministry of Public Health (MoPH). Controls included all infants born without a congenital	Logistic regression Adjusted for: active tobacco smoking during pregnancy, parental consanguinity, folic acid intake, mother's educational level, maternal obesity, residential distance to station, and combined criteria air pollutants' exposure	OR (95% CI) ^b Birth Defects: CHD: 1.02 (0.95, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				illness during the same period in a member hospital of the National Collaborative Perinatal Neonatal Network (NCPNN) records.		
† Buteau et al. (2023) N = 1,342,198 Quebec, Canada 2000–2016 Cohort	We restricted the cohort to newborns conceived between 2000 and 2016. We excluded stillbirths because information on heart defects was not available.	LUR, Fixed site monitor r ² = 73% Averaging time: NO ₂ - trimester NO ₂ - monthly Exposure years: 2006	NO ₂ (ppb) 1st Trimester Mean = 11.3±8.6 Median = 8.74 (IQR 11.4) P5 = 2.3 P25 = 4.6 P75 = 16 P95 = 28.8 Month of Conception Mean = 11.3±8.8 Median = 8.6 (IQR 11.2) P5 = 2.2 P25 = 4.6 P75 = 15.8 P95 = 29.3	Heart defects were identified during ultrasound screening in the second or third trimester or during clinical examination upon delivery. Heart defects were documented on physician discharge summaries and coded using ICD-9 or ICD-10 codes	Logistic regression Adjusted for: maternal age, parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, maternal comorbidity, and season of conception	OR (95% CI) ^b Birth Defects: Any critical heart defect: 0.97 (0.89, 1.06) Birth Defects: Critical coarctation of the aorta: 1.10 (0.92, 1.31) Birth Defects: Critical Tetralogy of Fallot: 0.93 (0.77, 1.11) Birth Defects: Any noncritical heart defect: 1.11 (1.08, 1.14) Birth Defects: Noncritical ventricular septal defect: 1.00 (0.95, 1.05) Birth Defects: Noncritical atrial septal defect: 1.18 (1.12, 1.25)
† Cowan et al. (2024) NC Department of Health and Human Services Division of Public Health	All live, singleton births with gestational age between 20 and 44 weeks with residence at delivery in NC.	Ensemble machine learning model, Hybrid model Method validation	NO ₂ (ppb) Overall Entire Pregnancy Median = 13.14	Birth defects were identified from the North Carolina birth defect	Linear binomial regression models Adjusted for: birthing parent age at delivery	PD (95% CI) ^b

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
N = 566,799 North Carolina, U.S. Births between January 1, 2011-December 31, 2015 Cohort	Excluded multiple births, deliveries outside of 20-44 weeks gestational age, and missing residential address at time of delivery that precluded geocoding.	NR Averaging time: NO ₂ - 24-hour average, NO ₂ - 8-hour max, Other, NO ₂ - trimester Exposure years: 2011–2015	Min = 1 Max = 33.42 P25 = 9.84 P75 = 17.24 Trimester 1 Median = 13.17 Min = 0.36 Max = 37.08 P25 = 9.53 P75 = 17.42 Trimester 2 Median = 12.92 Min = 0.78 Max = 39.89 P25 = 9.44 P75 = 17.24	monitoring program (NCBDMP)	(centered at age 26 with a quadratic term), race/ethnicity (white, non-Hispanic as reference), and education (>HS as reference)	Birth Defects: Atrioventricular septal defects for high NDI: -9.26 (-55.98, 37.75) Birth Defects: Pulmonary valve atresia/stenosis: -15.58 (-28.08, -3.08) Birth Defects: Pulmonary valve atresia/stenosis for low NDI: -0.90 (-2.42, 0.62) Birth Defects: Pulmonary valve atresia/stenosis for medium NDI: -1.47 (-2.73, -0.22) Birth Defects: Pulmonary valve atresia/stenosis for high NDI: -5.20 (-41.33, 30.93) Birth Defects: Tetralogy of Fallot (TOF): -11.72 (-33.80, 10.36) Birth Defects: Tetralogy of Fallot (TOF) for low NDI: -16.46 (-51.16, 18.25) Birth Defects: Tetralogy of Fallot (TOF) for medium NDI: -11.10 (-41.87, 19.67) Birth Defects: Tetralogy of Fallot (TOF) for high NDI: -5.22 (-47.44, 37.00) Birth Defects: Atrioventricular septal defects for medium NDI: -11.07 (-22.49, 0.34) Birth Defects: Atrioventricular septal defects: -12.31 (-23.93, -0.70) Birth Defects: Atrioventricular

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						septal defects for low NDI: -10.33 (-44.66, 23.99)
† Huang et al. (2019)	Included live births, stillbirths with ≥ 500 g of birth weight or ≥ 20 weeks of gestational age. Birth records with incomplete residential information, records of multiparous births, and records of births in families residing in mountainous areas or at locations beyond 20 km from the nearest air monitoring station were excluded.	Fixed site monitor, Spatiotemporal/geospatial model r ² = 0.90 Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average Exposure years: 2006–2014	NO ₂ (ppb) Overall Mean = 17.5±4.3 Median = 17.8 (IQR 5.8) P25 = 14.7 P75 = 20.4	Cases were identified by ICD-10 codes: VSD (Q210), ASD (Q211), ToF (Q213), endocardial cushion defect (ECD; Q212), transposition of the great arteries (TGA; Q203), and pulmonary artery and valve stenosis (PVAS; Q221) and confirmed by autopsy, echocardiogram, or cardiac catheterization	Logistic regression Adjusted for: infant sex, maternal age, season of conception, maternal diabetes and hypertension, maternal smoking during pregnancy, socioeconomic status of the residential township, and birth year	OR (95% CI) ^b Birth Defects: Overall CHDs: 0.97 (0.82, 1.15) Birth Defects: Endocardial cushion defect: 1.07 (0.43, 2.66) Birth Defects: Pulmonary artery and valve stenosis: 1.20 (0.71, 2.04) Birth Defects: Atrial septal defect: 0.70 (0.47, 1.05) Birth Defects: Tetralogy of Fallot: 0.97 (0.65, 1.45) Birth Defects: Ventricular septal defect: 0.95 (0.71, 1.28) Birth Defects: Transposition of the great arteries: 0.96 (0.58, 1.58)
† Lavigne et al. (2019)	Pregnant women giving birth to live born singleton infants in Toronto. Subjects were excluded if they had a residential postal code outside Toronto, a missing postal code, a missing health card number, a missing date of birth and/or missing information on sex.	LUR, Fixed site monitor The final model explained 67% of the variation in mean UFPs. Averaging time: NO ₂ - weekly	NO ₂ (ppb) Overall Mean = 16.1±5.7 Median = 15.3 (IQR 4.7)	Cases with any major CHDs (International Classification of Diseases [ICD]-10: Q20–Q26) as well as seven major subtypes: transposition of great vessels (ICD-10 code: Q203),	Logistic regression Adjusted for: maternal age at delivery, infant sex, parity, maternal smoking status during pregnancy, gestational age, birth weight, maternal diabetes, maternal preeclampsia, three neighbourhood-level socioeconomic	OR (95% CI) ^b Birth Defects: Overall congenital heart defects: 1.02 (0.94, 1.10) Birth Defects: Atrial septal defect: 1.05 (0.93, 1.19) Birth Defects: Ventricular septal defect: 1.01 (0.85, 1.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort		Exposure years: 2002–2009		ventricular septal defect (ICD-10 code: Q210), atrial septal defect (ICD-10 code: Q211), atrioventricular defect (ICD-10 code: Q212), tetralogy of Fallot (ICD-10 code: Q213), tricuspid atresia and stenosis (ICD-10 code Q224), pulmonary valve stenosis (ICD-10 code Q221) and coarctation of aorta (ICD-10 code: Q251)	status (SES) variables, random-effects for neighbourhood in the city of Toronto, and random effects for clustering within families	
†Pedersen et al. (2017a)	Women were ineligible if they did not speak sufficient Danish to participate in the interviews or not intended to carry their pregnancy to term. We excluded individuals due to missing information on exposure, multiple pregnancies, abortions, mola or ectopic	Dispersion model This method has been successfully validated. Averaging time: NO ₂ - 1st trimester NO ₂ - 3 months prior to LMP NO ₂ - full pregnancy	NO ₂ (µg/m ³) 1st trimester Median = 11.3 (IQR 6.6)	Congenital anomalies were classified according to the recommendation s from EUROCAT for congenital heart defects (CHD) (Q20-Q26), severe cardio-heart defects (CHD, Q200,	Logistic regression Adjusted for: parental age, maternal smoking, maternal alcohol consumption, maternal education and disposable income	OR (95% CI) ^b Birth Defects: Severe CHD: 0.98 (0.80, 1.22) Birth Defects: Tetralogy of Fallot: 1.08 (0.61, 1.93) Birth Defects: CHDs: 0.93 (0.83, 1.04) Birth Defects: Ventricular septal defect: 0.94 (0.78, 1.12) Birth Defects: Atrial septal defect: 0.85 (0.68, 1.04) Birth Defects: Coarctation of aorta:
Danish National Birth Cohort (DNBC)						
N = 84,218 children						
Nationwide, Denmark						
Enrollment: 1996–2002						
Follow-up started at 12th week of gestation						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Case-Control	pregnancies, emigration or infant death, if the pregnancy outcome was a stillbirth or withdrawals of participation in the study. Furthermore, participants with missing information on maternal smoking, alcohol, parity and/or paternal age were excluded.	Exposure years: 1996–2002		Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262)		0.89 (0.57, 1.38) Birth Defects: Pulmonary valve stenosis: 0.90 (0.56, 1.44)
†Yan et al. (2021)	Live births and stillbirths of at least 28 gestational weeks born to women living in the defined surveillance areas are recruited and followed for 42 days after birth. Excluded records with non-Chinese nationality of mothers. In addition, birth records missing important variables (i.e. date of birth, gestational age, etc.), or maternal age greater than 60 years old were also excluded from the analysis.	Ensemble machine learning model, Spatiotemporal/geospatial model, Fixed site monitor	NO ₂ (ug/m ³) Overall Mean = 33.9±13.1 Median = 33.8 (IQR 20.5) Min = 6.2 Max = 77.8	China National Population-based Birth Defects Surveillance System (CNPBDS) with ICD 10 diagnosis code, Q21.1	Mixed effects logistic regression Adjusted for: newborns sex, gestational age, birth weight, and birth season; the maternal age, gravidity, ethnicity, and number of births the mother has had; the residential status, urban/rural classification, regional economic development level, and local health investment; as well as the atmospheric pressure, evaporation, precipitation, sunshine duration, and wind speed	OR (95% CI) ^b Birth Defects: Isolated atrial septal defect during entire pregnancy: 1.33 (1.22, 1.45) Birth Defects: Isolated atrial septal defect during entire pregnancy for females: 1.30 (1.15, 1.47) Birth Defects: Isolated atrial septal defect during entire pregnancy for males: 1.32 (1.18, 1.48)
CNPBDS		Method validation NR				
n = All Births: 1,253,633 ASD Cases: 2,930		Averaging time: NO ₂ - trimester				
Nationwide, China		Exposure years: 2013–2016				
October 1, 2013 - December 31, 2016						
Case-Control						
Neural Tube Defects						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Al Noaimi et al. (2021) National Birth Defect Registry (NBDR), National Collaborative Perinatal Neonatal Network (NCPNN), Lebanese Ministry of Public Health (MoPH) Controls n = 8,321 Cases n = 315 Nationwide, Lebanon June 2014-June 2017 Case-Control	Cases included live births, stillbirths, and terminated pregnancies. Controls included all infants born without a congenital illness during the same period.	Fixed site monitor Method validation NR Averaging time: NO₂ - weekly Exposure years: 2013–2015	NO₂ (ppb) Concentrations only reported graphically	Registered cases were obtained from the National Birth Defect Registry (NBDR), a database maintained by the Lebanese Ministry of Public Health (MoPH). Controls included all infants born without a congenital illness during the same period in a member hospital of the National Collaborative Perinatal Neonatal Network (NCPNN) records.	Logistic regression Adjusted for: active tobacco smoking during pregnancy, parental consanguinity, folic acid intake, mother's educational level, maternal obesity, residential distance to station, and combined criteria air pollutants' exposure	OR (95% CI)^b Birth Defects: NTDs: 0.94 (0.90, 0.99)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Pedersen et al. (2017a) Danish National Birth Cohort (DNBC) N = 84,218 children Nationwide, Denmark Enrollment: 1996–2002 Follow-up started at 12th week of gestation Case-Control	Women were ineligible if they did not speak sufficient Danish to participate in the interviews or not intended to carry their pregnancy to term. We excluded individuals due to missing information on exposure, multiple pregnancies, abortions, mola or ectopic pregnancies, emigration or infant death, if the pregnancy outcome was a stillbirth or withdrawals of participation in the study. Furthermore, participants with missing information on maternal smoking, alcohol, parity and/or paternal age were excluded.	Dispersion model Averaging time: NO ₂ - 1st trimester NO ₂ - 3 months prior to LMP NO ₂ - full pregnancy Exposure years: 1996–2002	NO ₂ (ug/m ³) 1st trimester Median = 11.3 (IQR 6.6)	Congenital anomalies were classified according to the recommendations from EUROCAT for nervous system including neural tube defects (Q00-Q07)	Logistic regression Adjusted for: parental age, maternal smoking, maternal alcohol consumption, maternal education and disposable income	OR (95% CI) ^b Birth Defects: NTDs: 0.77 (0.55, 1.06)
Orofacial Defects						
† Pedersen et al. (2017a) Danish National Birth Cohort (DNBC) N = 84,218 children Nationwide, Denmark	Women were ineligible if they did not speak sufficient Danish to participate in the interviews or not intended to carry their pregnancy to term. We excluded	Dispersion model Averaging time: NO ₂ - 1st trimester NO ₂ - 3 months prior to LMP NO ₂ - full pregnancy	NO ₂ (ug/m ³) 1st trimester Median = 11.3 (IQR 6.6)	Congenital anomalies were classified according to the recommendations from EUROCAT for	Logistic regression Adjusted for: parental age, maternal smoking, maternal alcohol consumption, maternal	OR (95% CI) ^b Birth Defects: Cleft lip with or without cleft palate: 0.98 (0.77, 1.26) Birth Defects: Orofacial clefts: 0.95 (0.77, 1.18)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 1996–2002 Follow-up started at 12th week of gestation Case-Control	individuals due to missing information on exposure, multiple pregnancies, abortions, mola or ectopic pregnancies, emigration or infant death, if the pregnancy outcome was a stillbirth or withdrawals of participation in the study. Furthermore, participants with missing information on maternal smoking, alcohol, parity and/or paternal age were excluded.	Exposure years: 1996–2002		orofacial clefts (Q35-Q37)	education and disposable income	Birth Defects: Cleft palate: 0.89 (0.56, 1.35)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Zhu et al. (2015) Consortium on Safe Labor (2002–2008) n = 188,102 U.S. 2002–2008 Case-Control	Participants of the Consortium on Safe Labor who had maternal demographic characteristics, medical history, labor, delivery, and obstetric and neonatal outcomes for deliveries between January 1, 2002 to January 31, 2008. Infants with missing discharge summaries and no ICD-9 code data chromosomal anomalies, and congenital anomalies other than orofacial defects were excluded.	CMAQ CMAQ was used to estimate criteria air pollutant levels in the 15 non-overlapping hospital referral regions involved in the CSL with a 36-km horizontal resolution domain. Inverse distance weighting based method was used to adjust the raw CMAQ estimations. Averaging time: NO _x - three month average, 6-week average for during organogenesis at weeks 3-8 of gestation, and weekly averages for weeks 1–10 of gestation. Exposure years: 2002–2008	NO _x (ppb) Controls Median = 24.8 (IQR 29.92) P25 = 15.54 P75 = 45.46 Median = 24.42 (IQR 26.23) P25 = 15.88 P75 = 42.12 Isolated cleft lip with or without cleft palate Median = 23.5 (IQR 16.84) P25 = 15.45 P75 = 32.29 Median = 22.99 (IQR 29.25) P25 = 15.58 P75 = 44.84 Isolated cleft palate Median = 25.56 (IQR 36.97) P25 = 18.92 P75 = 55.89 Median = 24.79 (IQR 22.97) P25 = 15.97 P75 = 38.94	ICD-9 codes of 749, 749.01, 749.02, 749.03, 749.04 for cleft palate and 749.1, 749.11, 749.12, 749.14, 749.2, 749.21, 749.22, 749.23, 749.24, 749.25 for cleft lip with or without cleft palate	Logistic regression Adjusted for: site/region, maternal age (<20, 20–24, 25–29, 30–34, ≥35years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other/unknown), marital status (married/living with a partner or not), insurance (private or other/none), pre-pregnancy BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m ² or missing), nulliparity (yes or no), season of conception (spring, summer, fall, winter), smoking and/or alcohol consumption during pregnancy (yes or no), multiple birth (yes or no), preexisting or gestational diabetes mellitus (yes or no)	OR (95% CI) ^b Birth Defects: Cleft palate for weeks 3-8 of gestation: 3.64 (1.73, 7.66) Birth Defects: Cleft lip with or without cleft palate for 3 months preconception: 0.89 (0.53, 1.50) Birth Defects: Cleft lip with or without cleft palate for weeks 3-8 of gestation: 1.37 (0.88, 2.13) Birth Defects: Cleft palate for 3 months preconception: 1.58 (0.70, 3.55)
Other Birth Defects						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Lin et al. (2014) N = 1,510,064 n = 18,557 cases n = 1,687 controls n = 16,870 Taiwan January 1, 2001 - December 31, 2007 Matched pairs case-control	Live, singleton births from the Taiwanese Birth Registry	Central site monitor Averaging time: Other: NO ₂ - weekly average for gestational weeks 1-4, weeks 5-8, and weeks 9-12	NO ₂ (ppb) Mean = Cases: 0.75±1.25 Mean = Controls: 0.79±1.39	The definition of limb defects included polydactyl (ICD-9-CM:755.00), syndactyly (ICD-9-CM:755.10), and reduction deformities of limbs (ICD-9-CM:755.20,755.30).	Logistic regression Adjusted for: maternal age, socio-economic status	OR (95% CI) ^b Birth Defects: Syndactyly for Weeks 9-12: 0.97 (0.83, 1.14) Birth Defects: Reduction deformities of limbs for Trimester 1 exposure: 0.99 (0.74, 1.33) Birth Defects: Reduction deformities of limbs for Weeks 1-4: 0.95 (0.73, 1.23) Birth Defects: Polydactyly for Weeks 1-4: 0.97 (0.88, 1.08) Birth Defects: Polydactyly for Weeks 5-8: 1.01 (0.91, 1.12) Birth Defects: Polydactyly for Weeks 9-12: 1.00 (0.91, 1.11) Birth Defects: Syndactyly for Trimester 1 exposure: 1.03 (0.87, 1.23) Birth Defects: Syndactyly for Weeks 1-4: 1.06 (0.90, 1.24) Birth Defects: Syndactyly for Weeks 5-8: 1.05 (0.90, 1.23) Birth Defects: Limb defects for Weeks 1-4: 0.96 (0.88, 1.03) Birth Defects: Limb defects for Weeks 5-8: 0.98 (0.90, 1.06) Birth Defects: Limb defects for Weeks 9-12:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.97 (0.89, 1.05) Birth Defects: Limb defects for Trimester 1 exposure: 0.96 (0.88, 1.05) Birth Defects: Reduction deformities of limbs for Weeks 5-8: 1.06 (0.82, 1.37) Birth Defects: Reduction deformities of limbs for Weeks 9-12: 0.98 (0.76, 1.27) Birth Defects: Polydactyly for Trimester 1 exposure: 0.99 (0.89, 1.11)
† Al Noaimi et al. (2021) National Birth Defect Registry (NBDR), National Collaborative Perinatal Neonatal Network (NCPNN), Lebanese Ministry of Public Health (MoPH) Controls n = 8,321 Cases n = 315 Lebanon June 2014-June 2017 Case-Control	Cases included live births, stillbirths, and terminated pregnancies. Controls included all infants born without a congenital illness during the same period.	Fixed site monitor Method validation NR Averaging time: NO ₂ - weekly Exposure years: 2013–2015	NO ₂ (ppb) Concentrations only reported graphically	Registered cases were obtained from the National Birth Defect Registry (NBDR), a database maintained by the Lebanese Ministry of Public Health (MoPH). Controls included all infants born without a congenital illness during the same period in a member hospital of the National Collaborative Perinatal	Logistic regression Adjusted for: active tobacco smoking during pregnancy, parental consanguinity, folic acid intake, mother's educational level, maternal obesity, residential distance to station, and combined criteria air pollutants' exposure	OR (95% CI) ^b Birth outcomes - Musculoskeletal defects: 1.04 (0.98, 1.09) Birth outcomes - Genitourinary defects: 1.01 (0.96, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				Neonatal Network (NCPNN) records.		
†Choi et al. (2019) National Birth Defects Prevention Study (NBDPS) n = Cases: 615 Controls: 5,701 Georgia, Arkansas, Iowa, California, New York, North Carolina, Texas, Utah, Massachusetts, U.S. 1997–2006 Case-Control	Excluding 1) infants with absent, partially absent, or missing bony elements of the extremities; 2) cases of CLDs with a known chromosomal anomaly; and 3) infants whose mothers said they had diabetes before they were pregnant.	Fixed site monitor Method validation NR Averaging time: NO₂ - 1-hour max, NO₂ - 24-hour average Exposure years: 1997–2006	NO₂ (ppb) Cases Mean = 18.3 Min = 2.7 Max = 49.7 Controls Mean = 17.7 Min = 0.9 Max = 47.5	Eligible cases of CLDs were determined by a clinical geneticist, excluding 1) infants with absent, partially absent, or missing bony elements of the extremities; 2) cases of CLDs with a known chromosomal anomaly; and 3) infants whose mothers said they had diabetes before they were pregnant. The clinical geneticist classified CLDs into isolated (i.e., CLD was the only major structural birth defect) or non-isolated (additional co-	Logistic regression Adjusted for: study center, maternal age, race/ethnicity, and education	OR (95% CI)^b Birth Defects: Congenital limb deficiencies for NO₂ exposure: 1.10 (0.96, 1.26) Birth Defects: Congenital limb deficiencies for NO₂ max exposure: 1.04 (0.90, 1.21)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				occurring major birth defect(s)) cases, and further categorized CLDs into subtypes including longitudinal and transverse. Cases of transverse (ICD-9 codes: 755.20, 755.24, 755.30, 755.34), longitudinal (755.25–755.27, 755.35–37), and preaxial limb deficiencies (755.26, 755.36; a subtype of longitudinal) were used in the current study for additional analyses by subtypes.		
† Cowan et al. (2024) NC Department of Health and Human Services Division of Public Health N = 566,799 North Carolina, U.S.	All live, singleton births with gestational age between 20 and 44 weeks with residence at delivery in NC. Excluded multiple births, deliveries outside of 20-44 weeks gestational age, and	Ensemble machine learning model, Hybrid model Method validation NR Averaging time: NO ₂ - 24-hour	NO ₂ (ppb) Overall Entire Pregnancy Median = 13.14 Min = 1 Max = 33.42 P25 = 9.84 P75 = 17.24	Birth defects were identified from the North Carolina birth defect monitoring program (NCBDMP)	Linear binomial regression models Adjusted for: birthing parent age at delivery (centered at age 26 with a quadratic term), race/ethnicity (white, non-Hispanic as	PD (95% CI) ^b Birth outcomes - Limb reduction defects for low NDI: -5.69 (-47.47, 36.08) Birth outcomes - Limb reduction defects for high NDI: -19.71 (-80.55, 41.13) Birth outcomes - Limb reduction defects:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Births between January 1, 2011-December 31, 2015 Cohort	missing residential address at time of delivery that precluded geocoding.	average, NO ₂ - 8-hour max, Other, NO ₂ - trimester Exposure years: 2011–2015	Trimester 1 Median = 13.17 Min = 0.36 Max = 37.08 P25 = 9.53 P75 = 17.42 Trimester 2 Median = 12.92 Min = 0.78 Max = 39.89 P25 = 9.44 P75 = 17.24		reference), and education (>HS as reference)	-10.02 (-62.42, 42.38) Birth outcomes - Gastroschisis: -7.10 (-35.50, 21.30) Birth outcomes - Limb reduction defects for medium NDI: -10.49 (-46.27, 25.30) Birth outcomes - Gastroschisis for medium NDI: -9.51 (-40.37, 21.35) Birth outcomes - Gastroschisis for high NDI: 2.87 (-42.12, 47.87) Birth outcomes - Gastroschisis for low NDI: -13.77 (-51.02, 23.48)
†Harari-Kremer et al. (2021) Israeli Ministry of Health N = 696,461 Nationwide, Israel Births between 2009–2015 Cohort	Included all term newborns who were born in Israel, resided in localities within the exposure models' boundaries, and were not hospitalized in a neonatal intensive care unit. (NICU) (n = 1,016,261). Of this cohort we excluded neonates with addresses that could not be geocoded (n = 126,527) and further excluded those born after March 28, 2015, and those with missing data on gestational age.	Hybrid model, Spatiotemporal/geospatial model NO _x r ² = 0.67 NO ₂ r ² = 0.75 Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average, Other, NO ₂ - weekly NO _x - weekly Exposure years: 2008–2015	NO ₂ (ppb) Overall Mean = 13.3±3.6 NO _x (ppb) Overall Mean = 20.9±7.2	Heel-stick blood spots are sent to the national neonatal screening laboratory. Non-NICU newborns are screened for CHT by measuring TT4 blood concentrations, with a subsequent measurement of thyroid stimulating hormone for newborns in the lowest daily TT4 decile. Final	Logistic regression Adjusted for: ethnicity, socioeconomic status, geographical area, conception season, conception year, gestational age, birth weight, and child's sex	NO ₂ OR (95% CI) ^b Birth Defects: Congenital hypothyroidism with NO ₂ exposure in trimester 1: 0.91 (0.76, 1.08) Birth Defects: Congenital hypothyroidism with NO ₂ exposure in postnatal period (negative exposure control for trimester 1): 0.99 (0.91, 1.07) Birth Defects: Congenital hypothyroidism with NO ₂ exposure in trimester 1 mutually adjusted for trimester 2 and trimester 3 and postnatal period: 0.87 (0.73, 1.05) Birth Defects: Congenital hypothyroidism with NO ₂ exposure in postnatal period (negative

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				CHT diagnoses are reported back to the national lab. In newborns initially diagnosed with permanent CHT, the diagnosis might be changed to transient CHT if the newborn is taken off treatment, up to age 3 years. Such changes are diagnosed at pediatric endocrinology units and are also reported to the national lab.		exposure control for trimester 1) mutually adjusted for trimester 2 and trimester 3 and postnatal period: 1.05 (0.96, 1.15) Birth Defects: Congenital hypothyroidism with NO₂ exposure in trimester 2 mutually adjusted for trimester 2 and trimester 3 and postnatal period: 1.03 (0.86, 1.22) Birth Defects: Congenital hypothyroidism with NO₂ exposure in trimester 2: 1.02 (0.86, 1.21) Birth Defects: Congenital hypothyroidism with NO₂ exposure in postnatal period (negative exposure control for trimester 2): 0.94 (0.86, 1.03) Birth Defects: Congenital hypothyroidism with NO₂ exposure in trimester 3: 1.25 (1.06, 1.47) Birth Defects: Congenital hypothyroidism with NO₂ exposure in postnatal period (negative exposure control for trimester 3): 1.02 (0.94, 1.11) Birth Defects: Congenital hypothyroidism with NO₂ exposure in postnatal period (negative exposure control for trimester 2) mutually adjusted for trimester 2 and trimester 3 and postnatal period: 0.99 (0.91, 1.07) Birth Defects: Congenital hypothyroidism with NO₂ exposure

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						in trimester 3 mutually adjusted for trimester 2 and trimester 3 and postnatal period: 1.28 (1.09, 1.51) Birth Defects: Congenital hypothyroidism with NO₂ exposure in postnatal period (negative exposure control for trimester 3) mutually adjusted for trimester 2 and trimester 3 and postnatal period: 0.92 (0.84, 1.01) NO_x OR (95% CI)^b Birth Defects: Congenital hypothyroidism with NO_x exposure in trimester 1: 0.91 (0.78, 1.06) Birth Defects: Congenital hypothyroidism with NO_x exposure in trimester 3: 1.22 (1.07, 1.39) Birth Defects: Congenital hypothyroidism with NO_x exposure in postnatal period (negative exposure control for trimester 1): 0.98 (0.84, 1.14) Birth Defects: Congenital hypothyroidism with NO_x exposure in trimester 2: 1.05 (0.91, 1.22) Birth Defects: Congenital hypothyroidism with NO_x exposure in postnatal period (negative exposure control for trimester 2): 0.89 (0.75, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in trimester 1 mutually adjusted for trimester 2 and trimester 3 and postnatal period: 0.88 (0.74, 1.04)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in postnatal period (negative exposure control for trimester 3): 1.04 (0.89, 1.22)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in trimester 2 mutually adjusted for trimester 2 and trimester 3 and postnatal period: 1.05 (0.91, 1.22)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in postnatal period (negative exposure control for trimester 2) mutually adjusted for trimester 2 and trimester 3 and postnatal period: 0.97 (0.83, 1.14)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in trimester 3 mutually adjusted for trimester 2 and trimester 3 and postnatal period: 1.23 (1.08, 1.41)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in postnatal period (negative exposure control for trimester 1) mutually adjusted for trimester 2 and trimester 3 and postnatal period: 1.10 (0.93, 1.30)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth Defects: Congenital hypothyroidism with NO _x exposure in postnatal period (negative exposure control for trimester 3) mutually adjusted for trimester 2 and trimester 3 and postnatal period: 0.86 (0.73, 1.02)
† Huang et al. (2020)	Included live births or stillbirths with gestational age ≥20 weeks or birth weight ≥500 g. Excluded multiparous births and those without complete residential information. To ensure sufficient monitoring stations for further spatial interpolation, we also excluded births in mountainous or eastern coastal areas of Taiwan or births that occurred beyond 20 km of the nearest air quality monitoring station. Because hypospadias is rare in female infants, we further excluded births with female or undetermined sex.	Fixed site monitor NO ₂ r ² = 0.93 NO _x r ² = 0.67 Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, NO _x - 1-hour max, NO _x - 24-hour average Exposure years: 2006–2014	NO ₂ (ppb) Overall Mean = 18.3±5.6 Median = 18 (IQR 8) P25 = 14 P75 = 22 NO _x (ppb) Overall Mean = 24.2±8.3 Median = 22.9 (IQR 11.6) P25 = 17.8 P75 = 29.3	The cases of the study were defined as full-term infants reported to have hypospadias with ICD-10-CM code Q54 and those without any chromosomal abnormality with ICD-10-CM codes, Q90–Q99	Logistic regression Adjusted for: maternal age, birth weight, season of conception, annual household income and population density of residential township, maternal diabetes and hypertension, maternal smoking, and birth year	NO ₂ OR (95% CI) ^b Birth Defects: Hypospadias for NO ₂ exposure for the 1–2 month preconception period: 0.76 (0.55, 1.07) Birth Defects: Hypospadias for NO ₂ exposure for the 2–3 month preconception period: 0.89 (0.65, 1.21) Birth Defects: Hypospadias for NO ₂ exposure for the 0–3 month preconception period: 0.85 (0.59, 1.21) Birth Defects: Hypospadias for NO ₂ exposure for the 0–1 month preconception period: 0.97 (0.69, 1.36) Birth Defects: Hypospadias for NO ₂ exposure for the 0–3 month postconception period: 1.07 (0.75, 1.52) Birth Defects: Hypospadias for NO ₂ exposure for the 0–1 month postconception period: 0.94 (0.68, 1.30) Birth Defects: Hypospadias for NO ₂ exposure for the 1–2 month

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						postconception period: 1.13 (0.80, 1.59) Birth Defects: Hypospadias for NO ₂ exposure for the 2-3 month postconception period: 1.14 (0.82, 1.59) Birth Defects: Hypospadias for NO ₂ exposure for the 3-6 month postconception period: 1.02 (0.71, 1.46) Birth Defects: Hypospadias for NO ₂ exposure for the 3-4 month postconception period: 1.01 (0.73, 1.41) Birth Defects: Hypospadias for NO ₂ exposure for the 4-5 month postconception period: 1.03 (0.74, 1.44) Birth Defects: Hypospadias for NO ₂ exposure for the 5-6 month postconception period: 1.00 (0.71, 1.42) NO _x OR (95% CI) ^b Birth Defects: Hypospadias for NO _x exposure for the 2-3 month preconception period: 0.87 (0.63, 1.18) Birth Defects: Hypospadias for NO _x exposure for the 0-3 month preconception period: 0.84 (0.59, 1.20) Birth Defects: Hypospadias for NO _x exposure for the 0–1 month postconception period:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.88 (0.64, 1.21)
						Birth Defects: Hypospadias for NO _x exposure for the 1–2 month postconception period: 1.08 (0.77, 1.51)
						Birth Defects: Hypospadias for NO _x exposure for the 2-3 month postconception period: 1.05 (0.76, 1.45)
						Birth Defects: Hypospadias for NO _x exposure for the 0–1 month preconception period: 0.99 (0.70, 1.39)
						Birth Defects: Hypospadias for NO _x exposure for the 1–2 month preconception period: 0.75 (0.54, 1.05)
						Birth Defects: Hypospadias for NO _x exposure for the 3-4 month postconception period: 0.95 (0.68, 1.33)
						Birth Defects: Hypospadias for NO _x exposure for the 4-5 month postconception period: 0.91 (0.66, 1.26)
						Birth Defects: Hypospadias for NO _x exposure for the 5-6 month postconception period: 0.92 (0.66, 1.29)
						Birth Defects: Hypospadias for NO _x exposure for the 0-3 month postconception period: 0.99 (0.69, 1.40)
						Birth Defects: Hypospadias for NO _x exposure for the 3-6 month

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						postconception period: 0.92 (0.65, 1.30)
† Kotecha et al. (2020) n = 7,984,366 England, U.K., Wales January 1, 2001–December 31, 2012 Cohort	Live births in England and Wales with complete covariate data.	Spatiotemporal/geospatial model Averaging time: NO ₂ - annual average Exposure years: 2001–2012	NO ₂ (ug/m ³) Quintile 1 Mean = 10.76 Min = 2.81 Max = 13.91 Quintile 2 Mean = 16.19 Min = 13.91 Max = 18.18 Quintile 3 Mean = 20.13 Min = 18.18 Max = 22.15 Quintile 4 Mean = 24.78 Min = 22.15 Max = 27.83 Quintile 5 Mean = 33.76 Min = 27.83 Max = 66.04	Infant deaths (death occurring in the first year of life) were classified as neonatal deaths (death occurring within the first 28 days of life, i.e., at age 0–27 days) or post-neonatal deaths (death occurring from 28 days to 1 year of age) and cause of death using ICD-10 codes.	Logistic regression Adjusted for: Index of Multiple Deprivation (IMD), birthweight, maternal age, sex, and multiple birth	OR (95% CI) ^b Birth Defects: Infant death from congenital malformations (Quintile 4): 1.11 (1.02, 1.22) Birth Defects: Infant death from congenital malformations (Quintile 5): 1.16 (1.06, 1.26) Birth Defects: Infant death from congenital malformations (Quintile 1, referent): 1.00 (1.00, 1.00) Birth Defects: Infant death from congenital malformations (Quintile 2): 1.00 (0.91, 1.09) Birth Defects: Infant death from congenital malformations (Quintile 3): 0.99 (0.91, 1.09)

†Pedersen et al. (2017a)	Women were ineligible if they did not speak sufficient Danish to participate in the interviews or not intended to carry their pregnancy to term. We excluded individuals due to missing information on exposure, multiple pregnancies, abortions, mola or ectopic pregnancies, emigration or infant death, if the pregnancy outcome was a stillbirth or withdrawals of participation in the study. Furthermore, participants with missing information on maternal smoking, alcohol, parity and/or paternal age were excluded.	Dispersion model This method has been successfully validated. Averaging time: NO ₂ - 1st trimester NO ₂ - 3 months prior to LMP NO ₂ - full pregnancy Exposure years: 1996–2002	NO ₂ (ug/m ³) 1st trimester Median = 11.3 (IQR 6.6)	Congenital anomalies were classified according to the recommendations from EUROCAT for limb (Q69-Q74) Congenital anomalies were classified according to the recommendations from EUROCAT for multiple congenital anomalies (major congenital anomalies in more than one organ system) and chromosomal abnormalities (Q90- Q92, Q93, Q96-Q99) Congenital anomalies were classified according to the recommendations from EUROCAT for eye (Q10-Q15)	Logistic regression Adjusted for: parental age, maternal smoking, maternal alcohol consumption, maternal education and disposable income	OR (95% CI) ^b Birth Defects: Limb anomalies: 1.01 (0.95, 1.08) Birth Defects: Multiple congenital anomalies: 0.99 (0.82, 1.20) Birth Defects: Eye anomalies: 0.87 (0.66, 1.15) Birth Defects: Ear, face, and neck anomalies: 1.22 (0.98, 1.52) Birth Defects: Respiratory system anomalies: 0.95 (0.67, 1.36) Birth Defects: Digestive system anomalies: 0.99 (0.82, 1.18) Birth Defects: Urinary anomalies: 1.14 (0.98, 1.33) Birth Defects: Genital anomalies: 1.06 (0.90, 1.25) Birth Defects: Chromosomal anomalies: 0.93 (0.73, 1.19)

Congenital
anomalies were
classified
according to the
recommendation
s from
EUROCAT for
ear, face and
neck (Q16-Q18)

Congenital
anomalies were
classified
according to the
recommendation
s from
EUROCAT for
respiratory
system (Q30,
Q32-Q34)

Congenital
anomalies were
classified
according to the
recommendation
s from
EUROCAT for
digestive system
(Q38-Q45,
Q790)

Congenital
anomalies were
classified
according to the
recommendation
s from
EUROCAT for
urinary (Q60-

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				Q64, Q794)		
				Congenital anomalies were classified according to the recommendations from EUROCAT for genital (Q50-Q52, Q54-Q56)		

List of Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; NR = not reported; OR = odds ratio; ppb = parts per billion; RR = rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-13 Epidemiologic studies of oxides of nitrogen and birth outcomes of infant mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Chen et al. (2021)	Cases were singleton post-neonatal infant deaths. Controls were randomly selected 20 sex-matched controls who were born on the same day and were still alive on the date of death of the specified infant in the case group.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: January 1997 to December 2002	NO ₂ (ppb)	Cases selected from birth registration data. Cases selected from death registration data. Post-neonatal mortality defined as the death of an infant between 28 days and 1 year of age.	Conditional logistic regression Adjusted for: birth weight, parity, marital status, maternal age, paternal education, temperature, and humidity	OR (95% CI) ^b SIDS: 1 day lag: 1.30 (1.00, 1.69) SIDS: 2 day lag: 1.28 (0.98, 1.66) SIDS: 5 day lag: 1.35 (1.04, 1.74) SIDS: 8 day lag: 1.28 (0.97, 1.68) SIDS: 11 day lag: 1.17 (0.90, 1.51) SIDS: 14 day lag:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				ICD-9 used to identify cause of death. SIDS (ICD-9 codes 798.0, E911, E912, and E913) and respiratory deaths (ICD-9 codes 010e012, 460e514, 516e519, 769, and 770)		1.35 (1.05, 1.73) SIDS: 1 day lag (O ₃ + PM ₁₀): 1.49 (1.08, 2.05) SIDS: 2 day lag (O ₃ + PM ₁₀): 1.49 (1.07, 2.06) SIDS: 5 day lag (O ₃ + PM ₁₀): 1.56 (1.15, 2.13) SIDS: 8 day lag (O ₃ + PM ₁₀): 1.82 (1.31, 2.54) SIDS: 11 day lag (O ₃ + PM ₁₀): 1.44 (1.04, 1.99) SIDS: 14 day lag (O ₃ + PM ₁₀): 1.54 (1.12, 2.10) Respiratory deaths: 1 day lag: 0.94 (0.59, 1.50) Respiratory deaths: 2 day lag: 0.96 (0.59, 1.56) Respiratory deaths: 5 day lag: 0.94 (0.58, 1.52) Respiratory deaths: 8 day lag: 1.12 (0.68, 1.86) Respiratory deaths: 11 day lag: 0.59 (0.36, 0.99) Respiratory deaths: 14 day lag: 0.90 (0.56, 1.46) Respiratory deaths: 1 day lag (O ₃ + PM ₁₀): 1.06 (0.58, 1.93) Respiratory deaths: 2 day lag (O ₃ + PM ₁₀): 1.06 (0.58, 1.95) Respiratory deaths: 5 day lag (O ₃ + PM ₁₀): 0.92 (0.52, 1.64)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Respiratory deaths: 8 day lag (O ₃ + PM ₁₀): 1.08 (0.58, 2.01) Respiratory deaths: 11 day lag (O ₃ + PM ₁₀): 0.46 (0.24, 0.90) Respiratory deaths: 14 day lag (O ₃ + PM ₁₀): 0.72 (0.39, 1.33)

† Kotecha et al. (2020)	Live births in England and Wales with complete covariate data.	Spatiotemporal/geospatial model	NO ₂ (µg/m ³)	Infant deaths (death occurring in the first year of life) obtained from UK's Office for National Statistics	Logistic regression	OR (95% CI) ^c
n = 7,984,366		Averaging time: NO ₂ - annual average	Quintile 1 Mean = 10.76 Min = 2.81 Max = 13.91		Adjusted for: Index of Multiple Deprivation (IMD), birthweight, maternal age, sex, and multiple birth	Infant mortality - Quintile 1: 1.00 (1.00, 1.00)
England, U.K., Wales						Infant mortality - Quintile 2: 1.01 (0.97, 1.05)
January 1, 2001-December 31, 2012		Exposure years: 2001–2012	Quintile 2 Mean = 16.19 Min = 13.91 Max = 18.18	Perinatal cause-specific Infant deaths (death occurring in the first year of life) obtained from UK's Office for National Statistics		Infant mortality - Quintile 3: 0.98 (0.95, 1.02)
Cohort			Quintile 3 Mean = 20.13 Min = 18.18 Max = 22.15			Infant mortality - Quintile 4: 1.04 (1.01, 1.08)
			Quintile 4 Mean = 24.78 Min = 22.15 Max = 27.83	Congenital malformations cause-specific Infant deaths (death occurring in the first year of life) obtained from UK's Office for National Statistics		Infant mortality - Quintile 5: 1.07 (1.03, 1.11)
			Quintile 5 Mean = 33.76 Min = 27.83 Max = 66.04			Infant mortality - Perinatal - Quintile 1: 1.00 (1.00, 1.00)
						Infant mortality - Perinatal - Quintile 2: 1.02 (0.97, 1.07)
						Infant mortality - Perinatal - Quintile 3: 0.98 (0.93, 1.03)
						Infant mortality - Perinatal - Quintile 4: 1.03 (0.98, 1.08)
						Infant mortality - Perinatal - Quintile 5: 1.06 (1.01, 1.11)
				Respiratory cause-specific Infant deaths (death occurring in the first year of life) obtained from UK's Office for		Infant mortality - Congenital malformations - Quintile 1: 1.00 (1.00, 1.00)
						Infant mortality - Congenital malformations - Quintile 2: 1.00 (0.91, 1.09)
						Infant mortality - Congenital malformations - Quintile 3: 0.99 (0.91, 1.09)
						Infant mortality - Congenital

National Statistics	malformations - Quintile 4: 1.11 (1.02, 1.22)
Endocrine cause-specific Infant deaths (death occurring in the first year of life) obtained from UK's Office for National Statistics	Infant mortality - Congenital malformations- Quintile 5: 1.16 (1.06, 1.26)
Neoplasm cause-specific Infant deaths (death occurring in the first year of life) obtained from UK's Office for National Statistics	Infant mortality - Respiratory - Quintile 1: 1.00 (1.00, 1.00) Infant mortality - Respiratory - Quintile 2: 0.99 (0.76, 1.30) Infant mortality - Respiratory - Quintile 3: 1.06 (0.82, 1.37) Infant mortality - Respiratory - Quintile 4: 1.07 (0.83, 1.37) Infant mortality - Respiratory - Quintile 5: 0.92 (0.71, 1.18)
Blood cause-specific Infant deaths (death occurring in the first year of life) obtained from UK's Office for National Statistics	Infant mortality - Endocrine - Quintile 1: 1.00 (1.00, 1.00) Infant mortality - Endocrine - Quintile 2: 1.25 (0.85, 1.84) Infant mortality - Endocrine - Quintile 3: 1.66 (1.16, 2.37) Infant mortality - Endocrine - Quintile 4: 1.97 (1.39, 2.78)
Neonatal deaths (death occurring within the first 28 days of life, i.e., at age 0–27 days) obtained	Infant mortality - Endocrine - Quintile 5: 2.17 (1.54, 3.05) Infant mortality - Neoplasm - Quintile 1:

	from UK's Office for National Statistics	1.00 (1.00, 1.00) Infant mortality - Neoplasm - Quintile 2: 0.95 (0.60, 1.50) Infant mortality - Neoplasm - Quintile 3: 0.88 (0.56, 1.39) Infant mortality - Neoplasm - Quintile 4: 0.85 (0.54, 1.34) Infant mortality - Neoplasm - Quintile 5: 0.82 (0.52, 1.29)
	Post-neonatal deaths (death occurring from 28 days to 1 year of age) obtained from UK's Office for National Statistics	Infant mortality - Blood - Quintile 1: 1.00 (1.00, 1.00) Infant mortality -Blood - Quintile 2: 1.51 (0.63, 3.61) Infant mortality - Blood- Quintile 3: 1.44 (0.61, 3.41) Infant mortality - Blood - Quintile 4: 2.41 (1.09, 5.34) Infant mortality - Blood - Quintile 5: 3.20 (1.47, 6.94) Neonatal deaths - Quintile 1: 1.00 (1.00, 1.00) Neonatal deaths - Quintile 2: 1.01 (0.96, 1.06) Neonatal deaths - Quintile 3: 0.98 (0.93, 1.02) Neonatal deaths - Quintile 4: 1.03 (0.99, 1.08) Neonatal deaths - Quintile 5: 1.04 (1.00, 1.09) Post-neonatal deaths - Quintile 1: 1.00 (1.00, 1.00) Post-neonatal deaths - Quintile 2: 1.02 (0.95, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Post-neonatal deaths - Quintile 3: 1.00 (0.93, 1.07) Post-neonatal deaths - Quintile 4: 1.06 (1.00, 1.14) Post-neonatal deaths - Quintile 5: 1.11 (1.04, 1.18)

List of Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-14 Epidemiologic studies of oxides of nitrogen and birth outcomes of other birth outcomes

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Alderete et al. (2017)	Exclusion criteria included <18 years of age, HIV positive status, physical, mental, or cognitive disabilities that prevented participation, current incarceration, or multiple pregnancies.	AQS; Dispersion model: CALINE4 Averaging time: Other, NO ₂ – monthly; Other, NO _x - monthly Exposure years: 2012–2016	NO ₂ (ppb) Entire cohort Mean = 18.7±2.2 Females Mean = 18.9±2.3 Males Mean = 18.5±2.1 NO _x (ppb) Total: Entire cohort Mean = 13.7±8.7	Cord blood was collected and stored at room temperature for up to 24 hours until processing where serum was stored at –80°C until analysis. Plasma levels of leptin and HMW adiponectin were assayed in duplicate using	Linear regression Adjusted for: maternal age, gestational age, race/ethnicity, parity, annual family income, and maternal pre-pregnancy BMI	β (% difference) (95% CI) ^b Birth outcomes - Other birth outcomes: high molecular weight adiponectin levels for freeway NO _x exposure: 5.00 (-2.40, 12.80) Birth outcomes - Other birth outcomes: high molecular weight adiponectin levels for non-freeway NO _x exposure: 8.90 (-1.00, 19.80) Birth outcomes - Other birth outcomes: high molecular weight adiponectin levels for total NO _x exposure:

Maternal and Child Health Study (MACHS)

N = 136 mother-infant pairs
N with 6-month follow up data: 46

Los Angeles County, CA, U.S.

Recruitment: 2012–2016
Followed until 6 months after birth

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort			Females Mean = 13.7±7.9	ELISA (R&D Systems) and the average coefficient of variation for each assay was less than 10%. The ratio of leptin to HMW adiponectin (L/A) has been used as a marker of insulin resistance among children and adults. Adiponectin is a circulating protein produced by adipocytes that is present in high and low molecular weight oligomers. HMW adiponectin binds to its receptors with high affinity and is one of the key molecules mediating various metabolic actions.		5.80 (-1.30, 13.60)
			Males Mean = 13.6±9.4			Birth outcomes - Other birth outcomes: ratio of leptin to high molecular weight adiponectin (L/A ratio) levels for total NO _x exposure: 0.75 (-13.40, 17.20)
			Freeway: Entire cohort Mean = 10.4±8.4			Birth outcomes - Other birth outcomes: leptin levels for non-freeway NO _x exposure: 33.40 (8.90, 63.50)
			Females Mean = 10.4±7.5			Birth outcomes - Other birth outcomes: leptin levels for total NO _x exposure: 6.70 (-8.50, 24.40)
			Males Mean = 10.4±9.1			Birth outcomes - Other birth outcomes: ratio of leptin to high molecular weight adiponectin (L/A ratio) levels for freeway NO _x exposure: -2.10 (-16.30, 14.40)
			Non-freeway: Entire cohort Mean = 3.3±1.6			Birth outcomes - Other birth outcomes: leptin levels for freeway NO _x exposure: 2.80 (-12.40, 20.50)
			Females Mean = 3.3±1.7			Birth outcomes - Other birth outcomes: ratio of leptin to high molecular weight adiponectin (L/A ratio) levels for non-freeway NO _x exposure: 22.70 (0.20, 50.30)
			Males Mean = 3.3±1.5			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Ashley-Martin et al. (2016) Maternal-Infant Research on Environmental Chemicals (MIREC) Study N = 1,082 cord blood samples Toronto, Vancouver, Montreal, Edmonton, Winnipeg, Hamilton, Sudbury, Kingston, Halifax, Ottawa, Canada Enrollment: 2008–2011 Follow-up: each trimester, at birth, and up to 2 months after delivery Cohort	Pregnant women recruited in the first trimester from 10 Canadian cities between 2008 and 2011. Cord blood samples that were determined to be contaminated with maternal blood based on an elevated immunoglobulin A (IgA) concentration ($\geq 10\text{mg/mL}$) were excluded from the analysis. We excluded preterm infants and multiple births, as these infants have lower levels of the immune system biomarkers of interest in this study and children born preterm have been shown to have an increased risk of asthma in childhood. We excluded 171 samples from the NO₂ analysis due to residence beyond 25 km of a NAPs station.	LUR, Spatiotemporal/geospatial model, Fixed site monitor $r^2 = 0.73$ Averaging time: NO₂ - monthly NO₂ - pregnancy NO₂ - trimester Exposure years: 2008–2011	NO₂ (ppb) Duration of Pregnancy Median = 14.15 (IQR 12.99)	Immune system biomarkers were measured in the plasma of umbilical cord blood samples. TSLP concentrations were measured using a commercial antibody kit (Biolegend, San Diego, CA). IL-33 concentrations were analyzed using antibodies from an R & D systems duoset (Minneapolis, MN). Total IgE and total IgA concentrations were analyzed using ELISA kits (EBioscience, San Diego, CA).	Mixed effects linear regression Adjusted for: maternal age, household income (center and FSA are random effects)	OR (95% CI)^b Birth outcomes - Other birth outcomes: Cord blood immune system biomarker IL-33 $\geq 80\text{th}$ percentile for males: 1.01 (0.98, 1.04) Birth outcomes - Other birth outcomes: Cord blood immune system biomarker TSLP $\geq 80\text{th}$ percentile for males: 0.99 (0.96, 1.02) Birth outcomes - Other birth outcomes: Cord blood immune system biomarker IL-33/TSLP $\geq 80\text{th}$ percentile for males: 1.01 (0.98, 1.04) Birth outcomes - Other birth outcomes: Cord blood immune system biomarker IgE ≥ 0.5 ku/L for males: 1.00 (0.96, 1.04) Birth outcomes - Other birth outcomes: Cord blood immune system biomarker IL-33 $\geq 80\text{th}$ percentile for females: 1.04 (1.04, 1.08) Birth outcomes - Other birth outcomes: Cord blood immune system biomarker TSLP $\geq 80\text{th}$ percentile for females: 1.04 (1.01, 1.07) Birth outcomes - Other birth outcomes: Cord blood immune system biomarker IL-33/TSLP $\geq 80\text{th}$ percentile for females: 1.05 (1.02, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Birth outcomes - Other birth outcomes: Cord blood immune system biomarker IgE ≥ 0.5 ku/L for females: 1.01 (0.98, 1.04)
† Howe et al. (2018)	1 CHS participants enrolled at 5 to 7 years of age between 2002 and 2003 from public schools in 13 communities across southern California who could be matched to a California birth record and had complete information for at least 1 air pollutant across pregnancy. Further included singleton births and had plausible gestational age at birth values, including a 2-week buffer for late-term newborns (147-322 gestational days), and complete information for all other relevant covariates.	Fixed site monitor, Dispersion model Method validation NR Averaging time: NO ₂ - monthly NO _x - monthly Exposure years: 1995–1997	NO ₂ (ppb) Full-term and Late-term Mean = 30 $\pm$ 10.8 Median = 33 (IQR 14.5) P25 = 22.9 P75 = 37.4 Full Study Sample Mean = 30 $\pm$ 10.8 Median = 33 (IQR 14.6) P25 = 22.8 P75 = 37.4 NO _x (ppb) Full-term and Late-term Mean = 27.1 $\pm$ 23 Median = 21 (IQR 24.4) P25 = 11.7 P75 = 36.1 Full Study Sample Mean = 27.2 $\pm$ 23.5 Median = 21.1 (IQR 24.7)	Newborn heel-stick blood spot TT4 concentrations were measured by the California Department of Public Health (CDPH) using the Micromedic Concept 4 automated radioimmunological test (ICN Biomedical Inc). The CDPH also provided the newborn's age (in hours) at blood spot collection and the time (in days) from blood spot collection until TT4 measurement.	Linear regression (ordinary least squares) Adjusted for: newborn's sex, newborn's race/ethnicity, gestational age at birth, season of birth, maternal parity, maternal age, maternal education, maternal tobacco smoke use during pregnancy, age at newborn blood spot collection, and the community of the participant at recruitment	NO ₂ β (difference in total thyroxine (micrograms per deciliter)) (95% CI) ^b Birth outcomes - Other birth outcomes: Total thyroxine concentrations: 0.70 (0.10, 1.30) Birth outcomes - Other birth outcomes: Total thyroxine concentrations co-adjusted for PM ₁₀ : 0.30 (-0.40, 0.90) Birth outcomes - Other birth outcomes: Total thyroxine concentrations co-adjusted for O ₃ : 0.90 (0.30, 1.50) Birth outcomes - Other birth outcomes: Total thyroxine concentrations co-adjusted for PM _{2.5} : 0.40 (-0.20, 1.10) NO _x β (difference in total thyroxine (micrograms per deciliter)) (95% CI) ^b Birth outcomes - Other birth outcomes: Total thyroxine concentrations for freeway NO _x

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 11.6 P75 = 36.3			exposure: 0.00 (-0.40, 0.50) Birth outcomes - Other birth outcomes: Total thyroxine concentrations for non-freeway NO _x exposure: -0.10 (-0.50, 0.40) Birth outcomes - Other birth outcomes: Total thyroxine concentrations for total NO _x exposure: 0.00 (-0.40, 0.50)
† Lavigne et al. (2016a) Maternal-Infant Research on Environmental Chemicals (MIREC) Study N = 1,257 Toronto, Vancouver, Montreal, Edmonton, Winnipeg, Hamilton, Sudbury, Kingston, Halifax, Ottawa, Canada Recruitment: 2008–2011 Follow-up: each trimester, at delivery, post-delivery time points Cohort	Women were eligible for inclusion in the study if they were in the first trimester of pregnancy (<14 weeks of gestation), 18 years of age or older, able to communicate in French or English, and planning to deliver at a local participating hospital. Women were excluded from the study if they had any serious medical complications or if there were known fetal or chromosomal anomalies in the current pregnancy.	LUR This model explained 73% of the variation in NO ₂ measurements Averaging time: NO ₂ - trimester, whole-pregnancy, monthly Exposure years: 2006	NO ₂ (µg/m ³) Mean = 7.7±1.9	Stored umbilical cord blood samples were analyzed to measure levels of leptin and adiponectin using Meso Scale Discovery immunoassay kits (Meso Scale Diagnostics, Rockville, Maryland) at Mount Sinai Laboratory (Toronto, Ontario, Canada)	Mixed effects linear regression Adjusted for: maternal age, parity, pre-pregnancy body mass index, birth weight z score, and infant sex	β (% change) (95% CI) ^b Birth outcomes - Other birth outcomes: cord blood leptin levels: 12.00 (2.00, 23.00) Birth outcomes - Other birth outcomes: cord blood adiponectin levels: 13.00 (6.00, 20.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Seeni et al. (2019)	There were 223,385 singleton births in the Consortium on Safe Labor (2002–2008)	CMAQ	NO ₂ (ppb)	NICU admission was recorded in the neonate medical record or in discharge summaries	Logistic regression	NO ₂
N = 27,189 neonates	We excluded four infants with missing air pollution data	Method validation NR	Day Before Delivery IQR = 11.97993 Min = 0.844771 Max = 81.337503		Adjusted for: temperature (Celsius) and relative humidity	OR (95% CI) ^b Birth outcomes - Other birth outcomes: NICU admissions for day of delivery: 1.13 (1.10, 1.17)
Nationwide, U.S.		Averaging time: NO ₂ - 1-hour max, NO _x - 1-hour max, Other, NO ₂ - average week before delivery	Day of Delivery IQR = 12.10341 Min = 0.844771 Max = 81.37503			Birth outcomes - Other birth outcomes: NICU admissions for day before delivery: 1.13 (1.10, 1.17)
2002–2008		NO ₂ - day of delivery	Week Before Delivery			Birth outcomes - Other birth outcomes: NICU admissions for lag week 1: 1.03 (0.99, 1.07)
Case-crossover		NO ₂ - day before delivery	IQR = 10.18299			
		NO _x - average week before delivery	Min = 2.999747 Max = 48.82488			NO _x
		NO _x - day of delivery	NO _x (ppb)			OR (95% CI) ^b Birth outcomes - Other birth outcomes: NICU admissions for day before delivery: 1.04 (1.02, 1.08)
		NO _x - day before delivery	Day Before Delivery IQR = 26.21495 Min = 1.773109 Max = 258.3488			Birth outcomes - Other birth outcomes: NICU admissions for day of delivery: 1.08 (1.05, 1.10)
		Exposure years: 2002–2008	Day of Delivery IQR = 26.36542 Min = 1.773109 Max = 258.3488			Birth outcomes - Other birth outcomes: NICU admissions for lag week 1: 1.01 (0.98, 1.05)
			Week Before Delivery IQR = 25.13483 Min = 4.119 Max = 134.9031			

List of Abbreviations: BMI = body mass index; CI = confidence interval; CMAQ = Community Multiscale Air Quality; IQR = interquartile range; LUR = land use regression; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; P25 = 25th percentile; P75 = 75th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 7-15 Epidemiologic studies of oxides of nitrogen and birth outcomes of postnatal development

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Postnatal Growth						
[†] Alterman et al. (2023) n = 474,136 Israel 2011–2019 Cohort	Infants born during this timeframe at term (37–42 gestational weeks) with a birthweight ≥2500 g in the area covered by the exposure model in the central area of Israel.	Dispersion model 0.78 Averaging time: NO ₂ - weekly averages Exposure years: 2019	NO ₂ (ppb) Mean = 12.5 IQR = 7.3	Rapid weight gain during infancy was defined as being in the highest tertile of weight gain velocity, as measured by the SuperImposition by Translation and Rotation (SITAR) method specialized for modelling growth	Distributed-lag nonlinear models (DLNMs) with modified Poisson regression model Adjusted for: socioeconomic index sextile, population group, subdistrict, year, month of birth	NO ₂ RR (95% CI) ^c Postnatal Growth - Rapid weight gain in infants - Prenatal exposure period: 1.04 (1.02, 1.05) Postnatal Growth - Rapid weight gain in infants - Postnatal exposure period: 1.03 (1.02, 1.04) NO _x RR (95% CI) ^c Postnatal Growth - Rapid weight gain in infants - Prenatal exposure period: 1.05 (1.04, 1.06) Postnatal Growth - Rapid weight gain in infants - Postnatal exposure period: 1.02 (1.02, 1.03)
[†] Fossati et al. (2020) INMA, Infancia y Medio Ambiente N = 1,724 mother-child pairs	Inclusion criteria were at least 16 years, intention to give birth in the reference hospital, no problems in communication,	LUR Method validation NR Averaging time:	NO ₂ (µg/m ³) Asturias Cohort Median = 24.45 (IQR 11)	Age- and sex-standardized z-scores of height (zHeight), weight (zWeight) and	Linear regression Adjusted for: sub-cohort, season of birth, and maternal age at delivery, country of	β (Estimated change in zBMI) (95% CI) ^c Postnatal Growth - Growth, zBMI: -0.05 (-0.14, 0.03) β (Estimated change in zHeight) (95% CI) ^c

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Sabadell, Valencia, Asturias, Guipuzcoa, Spain Enrollment: 2003–2008 Follow-up: 4 years Cohort	singleton pregnancy, non-assisted conception.	NO ₂ - weekly averages Exposure years: 2003–2008	First Trimester of Pregnancy Median = 28.44 (IQR 20.19) P5 = 10.56 P95 = 61.44 Gipuzkoa Cohort Median = 16.97 (IQR 9.33) Sabadell Cohort Median = 35.4 (IQR 14.04) Valencia Cohort Median = 38.9 (IQR 25.16)	BMI (zBMI) were calculated using the World Health Organization (WHO) reference curves	origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet	Postnatal Growth - Growth, zHeight: -0.05 (-0.13, 0.03) β (Estimated change in zWeighth) (95% CI) ^c Postnatal Growth - Growth, zWeight: -0.07 (-0.15, 0.02)
† Ji et al. (2023) Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) n = 710 U.S. Enrollment: November 2015–September 2021 Cohort	Inclusion criteria: (1) less than 30 weeks gestation at the time of recruitment, (2) over 18 years of age, and (3) fluent English or Spanish speaker. Exclusion criteria were (1) HIV-positive status, (2) physical, mental, or cognitive disability that prevents participation or providing informed consent, (3) current incarceration, and (4) multiple gestations.	Spatiotemporal/geospatial model Averaging time: NO ₂ - Pregnancy average Exposure years: 2015–2021	NO ₂ (ppb) Mean = 16.4±2.9 Median = 16.5 (IQR 3.7) Min = 8.2 Max = 24.5 P10 = 12.9 P90 = 20.4	Weight measurements were collected from both interviewer-administered questionnaires and each in-person visit.	Linear mixed effect model Adjusted for: infant age, two spline terms, and interactions between air pollutants and age and spline terms, maternal education level, maternal race, pre-pregnancy BMI, hypertensive disorders, diabetic disorders, recruitment site, maternal age, parity, breastfeeding duration, postnatal air pollutant (same as the exposure),	β (Percent difference in growth) (95% CI) ^c Postnatal Growth - Percent difference in growth from 3rd trimester to 2 years: 1.04 (0.96, 1.11) Postnatal Growth - Percent difference in growth from 3rd trimester to 3 months: 1.56 (1.17, 2.07) Postnatal Growth - Percent difference in growth from 3 months to 6 months: 1.03 (0.8, 1.33) Postnatal Growth - Percent difference in growth from 6 months to 2 years: 0.9 (0.84, 0.98)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					and ambient temperature	β (Percent difference in infant attained weight) (95% CI) ^c Postnatal Growth - Infant attained weight at 3rd trimester: -10.94 (-16.44, -5.07) Postnatal Growth - Infant attained weight at birth: -6.45 (-10.47, -2.24) Postnatal Growth - Infant attained weight at 2 years: -7.79 (-12.00, -3.38) Postnatal Growth - Infant attained weight at 3rd trimester - multipollutant model with PM _{2.5} , PM ₁₀ , and O ₃ : -14.27 (-20.59, -7.45) Postnatal Growth - Infant attained weight at birth - multipollutant model with PM _{2.5} , PM ₁₀ , and O ₃ : -9.93 (-15.26, -4.28) Postnatal Growth - Infant attained weight at 2 years - multipollutant model with PM _{2.5} , PM ₁₀ , and O ₃ : -11.07 (-16.39, -5.41)
†Kim et al. (2018) Children's Health Study (CHS) n = 2,318 Southern California, U.S. Recruitment: 2002–2003 Follow-up: 4 years Cohort	Kindergarten students in southern California	Dispersion model Averaging time: In-utero NOx – nine-month average prior to birth First year of life NOx - 12 month average after birth Exposure years:	NOx (ppb) Freeway NOx Childhood Mean = 15.1±18.9 Median = 9.6 (IQR 22.7) Min = 0 Max = 351 P25 = 4.6 P75 = 18.1 First year of life	BMI was calculated by weight/height ² (kilograms/meter s ²)	Linear mixed effect model Adjusted for: age, sex, race/ethnicity, parental education, and Spanish baseline questionnaire	β (kg/m ²) (95% CI) ^c Postnatal Growth - BMI growth per year based on in utero exposure to freeway NOx: 0.05 (-0.02, 0.10) Postnatal Growth - BMI at age 10 years based on in utero exposure to freeway NOx: 0.10 (-0.30, 0.50) Postnatal Growth - BMI growth per year based on freeway NOx exposure for first year of life:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		2002–2007	Mean = 16.2±19.5 Median = 10.4 (IQR 17.8) Min = 0 Max = 304.2 P25 = 4.1 P75 = 21.9 In utero Mean = 16.7±20.1 Median = 10.8 (IQR 17.7) Min = 0 Max = 233.3 P25 = 4.4 P75 = 22.1 Non-Freeway NOx Childhood Mean = 6.2±4.7 Median = 5.2 (IQR 4.4) Min = 0.09 Max = 65.7 P25 = 3.2 P75 = 7.6 First year of life Mean = 9.3±6.7 Median = 7.9 (IQR 7.6) Min = 3e-04 Max = 77.4 P25 = 4.6 P75 = 12.2 In utero Mean = 10.3±7.4 Median = 8.7 (IQR 8.5)			0.10 (0.03, 0.20) Postnatal Growth - BMI at age 10 years per year based on freeway NOx exposure for first year of life: 0.50 (0.02, 0.90) Postnatal Growth - BMI growth per year based on in utero exposure to non-freeway NOx: 0.03 (-0.05, 0.10) Postnatal Growth - BMI at age 10 years based on in utero exposure to non-freeway NOx: 0.10 (-0.30, 0.60) Postnatal Growth - BMI growth per year based on non-freeway NOx exposure for first year of life: -0.02 (-0.10, 0.06) Postnatal Growth - BMI at age 10 years per year based on non-freeway NOx exposure for first year of life: -0.07 (-0.50, 0.40)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 3e-04 Max = 74 P25 = 5.2 P75 = 13.7			
† Patterson et al. (2021)	Maternal inclusion criteria include ≥ 18 years of age at delivery; healthy, term, singleton birth; enrollment by one month postpartum; self-identified Hispanic ethnicity; intention to breastfeed for at least three months postpartum; and ability to read at the 5th grade level in either English or Spanish in order to understand study procedures. Maternal exclusion criteria include medical conditions and/or medications known to potentially affect physical/mental health, nutritional status, or metabolism; tobacco use (defined as > 1 cigarette in the past week); recreational drug use; pre-term/low birth weight; and clinically diagnosed fetal abnormalities.	AQS 0.73 Averaging time: NO ₂ - Monthly average Exposure years: 2016–2020	NO ₂ (ppb) Mean = 18.05±2.34	Infant weight was twice calculated to the nearest 0.1 kg by subtraction of the weight of the mother holding the infant from the weight of the mother alone on a Tanita scale. Infant length was measured in duplicate to the nearest 0.1 centimeter (cm) using an infantometer. Infant umbilical circumference was measured to the nearest 0.1 cm in duplicate using a tape measure resistant to stretching. The sums of the four skinfold	Linear regression Adjusted for: infant sex, infant age, pre-pregnancy BMI, breastfeeding frequency, maternal age, and socioeconomic status	β (cm) (95% CI) ^c Postnatal Growth - Weight: 0.14 (0.02, 0.05) Postnatal Growth - Umbilical circumference: 0.25 (-0.25, 0.76) β (kg) (95% CI) ^c Postnatal Growth - Length: 0.23 (-0.09, 0.56) β (mm) (95% CI) ^c Postnatal Growth - Total subcutaneous fat (TSF): 1.69 (0.25, 3.12) β (95% CI) ^c Postnatal Growth - Central to total subcutaneous fat (CTSF): 0.00 (-0.01, 0.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				measures were calculated to create a proxy for total subcutaneous fat (TSF) at each time point.		
				The sum of the suprailiac and subscapular skinfold thicknesses (representing truncal fat) were calculated and divided by the sum of all four regions to generate a proxy for the ratio of central-to-total subcutaneous fat (CTSF).		
†Vrijheid et al. (2020)	Eligibility criteria for inclusion in the subcohort were: a) age 6–11 y at the time of the visit, with a preference for ages 7–9 y; b) sufficient stored pregnancy blood and urine samples available for analysis of prenatal exposure biomarkers; c) complete address	LUR, Personal monitor or sampler, Dispersion model		Height and weight were measured using regularly calibrated instruments and converted to BMI age-and-sex-standardized z-scores (zBMI) using the international	Linear regression Adjusted for: adjusted for cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, parental country of origin, breastfeeding and birth weight	β (zBMI change) (95% CI) ^c Postnatal Growth - zBMI change and outdoor NO ₂ : 0.23 (0.02, 0.43) Postnatal Growth - zBMI change and indoor NO ₂ : 0.11 (-0.04, 0.26)
Human Early-life Exposome project (HELIX)						
n = 1,301						
UK BiB cohort n = 205						
France EDEN cohort n = 198						
Spain INMA cohort n = 223						
Lithuania KANC cohort n = 204						
Norway MoBa cohort n = 272						
Greece Rhea cohort n = 199						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
France, U.K., Spain, Norway, Greece, Lithuania Follow-up: December 2013 and February 2016 Cohort	history available from first to last follow-up point; and d) no serious health problems that may affect the performance of the clinical testing or affect the volunteer's safety(e.g., acute respiratory infection).	February 2016		World Health Organization (WHO) reference curves		
Puberty						
† Zhao et al. (2021) German Infant Study on the Influence of Nutrition Intervention Plus Environmental and Genetic Influences on Allergy Development (GINIplus) + Influence of Life Style Factors on the Development of the Immune System and Allergies in East and West Germany (LISA) n = 1945 female n = 943 male n = 1002 Munich, Wesel, Leipzig, Bad Honnef, Germany Enrollment: 1995–1999 Follow-up: 2005–2009 Cross-Sectional	Healthy newborns delivered between 1995 and 1999 at a full gestational age (≥37 weeks) and with a normal birth weight (>2500 g).	LUR Averaging time: NO ₂ - annual average Exposure years: 2005–2009	NO ₂ (ppb) Mean = 11.71±2.05 (22.03±3.86 µg/m ³) Median = 11.6 (IQR 2.21) (21.9 µg/m ³) (IQR 4.16 µg/m ³) Min = 6.33 (11.91 µg/m ³) Max = 25.25 (47.51 µg/m ³)	The serum concentration of testosterone and estradiol was measured by the mechanized immunoassay system Modular.	Logistic regression Adjusted for: the exact age, sex, body mass index, time spent outside and in front of a screen, physical activity level, season and time of the blood sampling, household income, parental education, maternal age at birth, single parent, and income	OR (95% CI) ^b Puberty - Estradiol in females aged 10: 0.81 (0.36, 1.81) Puberty - Testosterone in males aged 10: 1.31 (0.61, 2.80)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Other Postnatal Development Outcomes						
† Bloemsma et al. (2021) Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study n = 1,027 Netherlands Recruited: 1996–1997 Follow-up: 2008–2010 Cohort	Children who participated in medical examination and had saliva samples. Children were excluded for whom ≥1 sample did not contain enough saliva to determine cortisol concentrations (n = 24), and children whose samples were unintentionally mixed or did not have a cap (n = 3) and if children had extremely high cortisol concentrations (n = 5), children with diabetes (n = 3), and children who used corticosteroids on the day of the saliva collection (n = 32).	LUR Averaging time: NO ₂ - annual average Exposure years: February 2009 - February 2010	NO ₂ (ppb) Median = 12.1 (IQR 4.5) (22.8 µg/m ³ (IQR 8.5 µg/m ³) P25 = 9.62 (18.1 µg/m ³) P75 = 14.1 (26.6 µg/m ³)	Children were asked to collect three saliva samples on one school day as part of a medical examination at age 12 years: immediately after awakening, 30 minutes after awakening (when cortisol levels are usually highest), and at 8.00 pm (in the evening).	GAM Adjusted for: sex, age, parental level of education, maternal smoking during pregnancy, smoking in the child's home, pubertal development, height, and season	β (nmol/L per hour) (95% CI) ^b Other Postnatal Development Outcomes - Diurnal Cortisol: 0.06 (-0.05, 0.16)

List of abbreviations in alphabetical order: AQS = Air Quality System; BiB = born in Brandford; BMI = body mass index; CI = confidence interval; CTSF = central to total subcutaneous fat; DLNM = distributed-lag nonlinear models; EDEN = Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant; HR = hazard ratio; INMA = Infancia y Medio Ambiente; IQR = interquartile range; IVF = *in vitro* fertilization; KANC = Kaunas cohort; LUR = land use regression; Max = maximum; Min = minimum; MoBa = Norwegian Mother and Child Cohort; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; O₃ = ozone; OR = odds ratio; P25 = 25th percentile; P75 = 75th percentile; PIAMA = Prevention and Incidence of Asthma and Mite Allergy; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; RR = rate ratio; SITAR = superimposition by translation and rotation; TSF = total subcutaneous fat; WHO = World Health Organization; zBMI = age-and-sex-standardized z-score of BMI, zHeight = age- and sex-standardized z-score of height, zWeight = age- and sex-standardized z-scores of weight.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

A.6. Metabolic Syndrome and Diabetes

Appendix Table 8-1 Epidemiologic studies of oxides of nitrogen exposure and diabetes mellitus

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Bai et al. (2018) Ontario Population Health and Environment Cohort (ONPHEC) n = Hypertension Cohort: 893, 499 Diabetes Cohort: 1, 056, 012 Toronto, Canada Enrollment: April 1, 1996 Follow-up: through December 31, 2012 Cohort	All Canadian-born residents, living in Toronto and were registered with Ontario's provincial health insurance plan. Restricted to ages 30–100, living in Toronto for at least three years before cohort entry, free of hypertension or diabetes at time of baseline.	LUR $r^2 = 50\%$ Averaging time: NO ₂ - annual average, Other, NO ₂ - 3-year moving averages Exposure years: 1996–2012	NO ₂ (ppb) Diabetes Cohort Mean = 21.4±3.5 Median = 21.1 (IQR 4) Min = 9.9 Max = 50.1	Incident physician-diagnoses from hospital discharge/claims: having at least one hospital admission with a diagnosis of the condition or two physician claims over a 2-year period using ICD-9 (250) and ICD-10 (E10–E14) revision diagnosis codes for diabetes	Random-effects Cox proportional hazards models Adjusted for: comorbid hypertension, COPD, asthma, congestive heart failure, acute myocardial infarction, cancer, neighborhood-level recent immigrants, unemployment rate, education, and annual household income	HR (95% CI) ^c Incident diabetes: 1.06 (1.05, 1.07)
†Cervantes-Martinez et al. (2022) Mexican Teachers Cohort N = 13, 669 Mexico	Included female public-school teachers; Excluded participants living or working outside of the 5-km radius of influence of the atmospheric monitoring network, participants who only responded to baseline questionnaire,	Spatiotemporal/geospatial model Carried out 10-fold cross validation and determined the predictive accuracy of each model based on its root mean square error (CV RMSE =	NO ₂ (ppb) Analytical subsample Mean = 34.6±7.3 Monthly mean across study period Incident Diabetes Mean = 29.8±5.3 No Diabetes	Incident T2D using self-report and two clinical datasets: physician-diagnosed diabetes, treatment, and date of diagnosis. Incident diabetes	Time-varying Cox models Adjusted for: time-dependent age, smoking status (passive and time-dependent active), time-dependent physical activity, SES, wood	HR (95% CI) ^c Incident T2D: 1.52 (1.37, 1.68)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 2006–2008 Follow-up: 2011–2013 and 2014–2020 Cohort	those who self-reported having diabetes at baseline, and those missing any data points needed to adjust statistical models	4.497) Averaging time: NO ₂ - 24-hour average, Other, NO ₂ - monthly Exposure years: 2007–2019	Mean = 28.6±5.4 Total Mean = 28.7±5.4 Monthly mean at baseline Incident Diabetes Mean = 35.3±7.5 No Diabetes Mean = 34.5±7.3 Total Mean = 34.6±7.3 Quartile 1 Median = 22.9 (IQR 3.5) Quartile 2 Median = 34.3 (IQR 2.9) Quartile 3 Median = 25.8 (IQR 3.1) Quartile 4 Median = 43.3 (IQR 3.5) Total population in study area Mean = 34.5±7.4	case by an affirmative response to two of the three following questions: 1) have you been diagnosed with diabetes or high blood sugar by a doctor (outside of pregnancy)? 2) do you receive treatment for diabetes? and 3) on what date did you receive a clinical diabetes diagnosis? Additionally defined diabetes cases based on the confirmation of the diagnosis, medication use, and/or control of diabetes through diet and exercise	smoking, and time spent outdoors	
† Clark et al. (2017) n = 380, 738	Adult residents 45-94 years old who were registered with the provincial health	LUR LUR validated in Wang et al. (2012)	NO ₂ (µg/m ³) Mean = 32.1 IQR = 8.4	Incident diabetes was determined using ICD codes (ICD-9 code 250,	Logistic Adjusted for: sex, age,	NO OR (95% CI) ^c Incident diabetes: 1.04 (1.01, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Vancouver, Canada Follow-up: January 1999–December 2002 Cohort	insurance plan and had lived in the study region during the 5-year exposure period. Individuals who had a diagnosis of diabetes before or during the exposure window were excluded.	https://doi.org/10.1016/j.atmosenv.2012.09.056 . Averaging time: NO ₂ - 5-year average; NO - 5-year average Exposure years: January 1994–December 2002	Min = 14.4 Max = 57.8 NO (µg/m ³) Mean = 32 IQR = 13.13 Min = 8.8 Max = 126	with ICD-10 coding back-translated to ICD-9 coding) pulled from the BC Medical Services Plan provided by the BC Ministry of Health. Type 1 diabetes could not be distinguished from Type 2 diabetes.	area-level household income	NO ₂ OR (95% CI) ^c Incident diabetes: 1.00 (0.98, 1.02)
† Coogan et al. (2016) Black Women's Health Study (BWHS) N = 43, 003 U.S. Enrollment: 1995 Follow-up: 1997–2011 Cohort	Black Women who lived in any of 56 metropolitan areas in the United States and had complete information on BMI. Women were excluded if they did not live in the metro areas, had prevalent diabetes,	LUR The R ² for the final spatiotemporal model is 0.80. Averaging time: NO ₂ - annual average Exposure years: 2000–2010	NO ₂ (ppb) LUR model: Min = 1.0 Max = 37.7 Mean = 18.6 SD = 6.5 P25 = 13.9 P75 = 23.6 Dispersion model for subset of 27 cities: Min = 5.1 Max = 40.7 Mean = 19.2 SD = 5.5 P25 = 14.6 P75 = 24.3 The distribution of NO ₂ across the U.S. and the location of the 56 cities is shown in the	Incident T2D: self-report of doctor-diagnosed diabetes at age 30 or older during follow-up through 2011	Cox proportional hazards model Adjusted for: age, questionnaire cycle, metro area, BMI, years of education, h/week vigorous exercise, vegetable/fruit diet pattern score and meat/fried foods diet pattern score, and smoking status	HR (95% CI) ^b Incident T2D: Dispersion model for subset of 27 cities: 0.94 (0.80, 1.11) Incident T2D: LUR model for 56 cities: 0.96 (0.87, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Supplementary Material.			
† Eze et al. (2017) Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) N = 2, 631 Aarau, Switzerland, Basel, Switzerland, Davos, Switzerland, Geneva, Switzerland, Lugano, Switzerland, Montana, Switzerland, Payerne, Switzerland, Wald, Switzerland, Switzerland Enrollment: 1991–2002 Follow-up: 2011 Cohort	Included participants who were not diabetic and had the same residence between 2002 and 2011	Dispersion model, LUR Final hybrid model having an adjusted R ² of 0.8 Averaging time: NO ₂ - annual average Exposure years: 2010–2011	NO ₂ (ppb) Incident Diabetes Median = 10.8 (IQR 8) (20.4 µg/m ³ (IQR 15 µg/m ³)) No Incident Diabetes Median = 11.2 (IQR 8.18) (21.1 µg/m ³ (IQR 15.4 µg/m ³))	Incident T2D: cases if they were not diabetic at SAP2 but reported physician-diagnosed diabetes or taking diabetes medication (including insulin, metformin, thiazolidinedione, gliflozin, incretin mimetic, acarbose or their combinations) or had HbA1c ≥6.5%, at SAP3	Mixed Poisson regression model with random intercepts Adjusted for: age, sex, educational level, neighbourhood SES index, smoking status and pack-years, consumption of alcohol, fruits and vegetables, physical activity, BMI, and change in BMI	RR (relative risk) (95% CI) ^b Incident T2D: 0.90 (0.61, 1.34)
† Gandini et al. (2018) Italian Longitudinal Study (ILS) N = 74, 989 Italy	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from	NO ₂ (ppb) Men Metropolitan Mean = 22.1±6.16 (41.5±11.6 µg/m ³) Rural Mean = 10.3±4 (19.3±8 µg/m ³)	Incident T2D: ICD-9 code 250; only the first hospital admission, excluding all subsequent hospitalization for the same cause	Cox proportional hazard model Adjusted for: age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status,	HR (95% CI) ^b Incident T2D: 0.96 (0.92, 1.01) Incident T2D: Restricted to Northern and Central Italy: 1.02 (0.95, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008 Cohort		monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity. Averaging time: NO ₂ - annual average Exposure years: 1999, 2003, 2005, 2007	Urban Mean = 13.9±5.2 (26.1±9.7 µg/m ³) Women Metropolitan Mean = 22.1±6.16 (41.6±11.6 µg/m ³) Rural Mean = 10.3±4.2 (19.3±7.9 µg/m ³) Urban Mean = 13.9±5.1 (26.1±9.6 µg/m ³)		type of municipality (rural, urban, metropolitan areas), and BMI	
†Hansen et al. (2016) Danish Nurse Cohort (DNC) N = 24, 174 Denmark Enrollment: 1993–1999 Follow-up: through December 31, 2013 Cohort	Excluded participants who died or emigrated between cohort entry and start of follow-up, who have diabetes, who had missing information on covariates, and who had missing address information.	Dispersion model Method validation NR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 1971–2013	NO ₂ (ppb) Diabetes Mean = 7.12±4.6 (13.4±8.7 µg/m ³) Non-Diabetic Mean = 6.64±4.2 (12.5±7.9 µg/m ³) Total Mean = 6.64±4.2 (12.5±7.9 µg/m ³) NO _x (µg/m ³) Diabetes Mean = 19.9±23.2 Non-Diabetic Mean = 18.3±22.6	Incident T2D: a minimum of one of the following criteria: 1) diabetes hospital discharge diagnosis since 1995 (ICD-10 code E10-14, DH36.0, DO24) in the Danish National Diabetes Register; 2) chiropody as a diabetic patient, 3) five blood-glucose measures within one year, or 4) two blood glucose measures per year in five coherent years in the	Cox proportional hazard model Adjusted for: age, calendar time, smoking (status, intensity), physical activity, alcohol consumption, fatty meat consumption, fruit and vegetable consumption, employment status, marital status, BMI, hypertension and myocardial infarction	NO ₂ HR (95% CI) ^b Incident T2D: 1.13 (0.97, 1.32) NO _x HR (95% CI) ^c Incident T2D: 1.01 (0.98, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Total Mean = 18.4±22.7	National Health Service Register; or 5) second purchase of insulin or oral anti-diabetic drugs within 6 months registered in Danish National Prescription Registry		
†Honda et al. (2017)	Double check	Fixed site monitor	NO ₂ (ppb)	Prevalent DM: one or more of the following: 1) HbA1c ≥6.5%, or 2) Participant self-reported taking anti-diabetic medication in one or more of the following categories: alpha-glucosidase inhibitors, anti-diabetic combinations, insulin, miscellaneous anti-diabetic agents, and/or sulfonylureas	Logistic regression Adjusted for: BMI, age, sex, race, education, tobacco use, physical activity, region, urbanicity, census tract data on median household income and percent of households living below the poverty line	POR (95% CI) ^b Prevalent DM: 1-year moving average exposure: 1.32 (1.11, 1.57) Prevalent DM: 2-year moving average exposure: 1.32 (1.11, 1.56) Prevalent DM: 3-year moving average exposure: 1.29 (1.10, 1.51) Prevalent DM: 4-year moving average exposure: 1.25 (1.06, 1.48) Prevalent DM: 5-year moving average exposure: 1.27 (1.09, 1.49)
National Social Life, Health, and Aging Project (NSHAP)		Averaging time: NO ₂ - annual average, Other, NO ₂ - 1-5 year moving averages	Total Cohort Mean = 5.53±2 (10.4±3 µg/m ³)			
N = 4, 121			With DM Mean = 5.69±1.5 (10.7±2.9 µg/m ³)			
U.S.		Exposure years: 1999–2007	Without DM Mean = 5.47±1.6 (10.3±3.1 µg/m ³)			
Enrollment: 2005–2006 and 2010–2011						
Cohort						
†Howell et al. (2019)	Restricted to ages 40-74, residence in study area, no previous hospital admission for stroke,	LUR Model R2 of 0.73	NO ₂ (ppb) Least Walkable Areas Mean = 15.2±4.9	Prevalent DM: any of the following criteria over a 2-year	Logistic regression Adjusted for: age, sex, ethnicity, immigration	OR (95% CI) ^b Prevalent DM: 1.11 (1.10, 1.13)
Cardiovascular Health in Ambulatory Care						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Research Team (CANHEART) N = 2, 469, 458 Ontario, Canada Enrollment: 1991–2007 Follow-up: 2008 Cohort	myocardial infarction, or congestive heart failure, or no previous percutaneous coronary intervention or coronary bypass graft during enrollment period, no residence in a long-term care facility at index or in previous 5 years, or those residing in Ontario during the preceding two years. Further excluded individuals living in neighborhoods missing air pollution exposures or who were missing information on area-level SES.	Averaging time: NO ₂ - annual average Exposure years: 2006	Most Walkable Areas Mean = 21.4±3.4	period: (i) two physician claims with diagnoses of diabetes; (ii) one physician claim with a fee code for insulin therapy support or diabetes management assessment; or (iii) one hospital admission with a diagnosis of diabetes	history, neighborhood median income	
† Hu et al. (2023) UK Biobank N = 390, 834 England, Scotland, Wales, U.K. Enrollment: 2006–2010 Follow-up: through February 20, 2020 Cohort	Participants aged 40-69 years; excluded those who had diabetes at baseline, who had hearing loss, and who had missing data on exposures or covariates, who had missing data on indicators for MetS.	LUR median r ² = 82% for NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Cases (with incident type 2 diabetes) Median = 14.4 (IQR 5) (27.1 µg/m ³ (IQR 9.4 µg/m ³)) Min = 6.86 (12.9 µg/m ³) Max = 56.28 (105.9 µg/m ³) Non-cases (without incident type 2 diabetes) Median = 13.7 (IQR 5.2) (25.8 µg/m ³ (IQR 9.8 µg/m ³)) Min = 6.86 (12.9 µg/m ³)	Incident T2D: ascertained through linkages to inpatient hospital records, which includes admissions and diagnoses (ICD-10 code of E11)	Cox proportional hazard model Adjusted for: stratified by age group and sex, plus adjustment for ethnicity, education, economic status, Townsend deprivation index, assessment center, length of time at residence, smoking status, alcohol intake frequency, sedentary time, sleep duration, physical activity, and healthy diet	HR (95% CI) ^b Incident T2D: 1.14 (1.05, 1.24) HR (95% CI) ^c Incident T2D (+ "cumulative risk Index": PM _{2.5} , NO ₂ , and noise): 1.06 (1.02, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Max = 57.66 (108.5 $\mu\text{g}/\text{m}^3$) NO ₂ ($\mu\text{g}/\text{m}^3$) Cases (with incident type 2 diabetes) Median = 27.1 (IQR 9.4) Min = 12.9 Max = 105.9 Non-cases (without incident type 2 diabetes) Median = 25.8 (IQR 9.8) Min = 12.9 Max = 108.5		score polygenic risk score for T2D	
† Kang et al. (2022) Henan Rural Cohort Study n = 38, 841 Henan Province, Suiping County, Yuzhou County, Xinxiang County, Tongxu County, Yima County, China 2015–2017 Cohort	Adults aged 18-79 recruited from five rural regions in the Henan province of China by multistage stratified cluster sampling. Participants were excluded if they had self-reported physician-diagnosed type 1 diabetes mellitus, or if they were missing obesity indicator or fasting blood glucose data.	Hybrid model A spatiotemporal model utilizing random forest methods estimated NO ₂ concentrations of each participant through combining daily satellite data, meteorological conditions, and land use data. The cross-validation (R ²) for NO ₂ was 72% (6.5 $\mu\text{g}/\text{m}^3$). Averaging time: NO ₂	NO ₂ ($\mu\text{g}/\text{m}^3$) Overall Mean = 39.87±3.6 Participants with T2DM Mean = 40.63±3.53 Participants without T2DM Mean = 39.79±3.6	T2DM assessed as: fasting blood glucose ≥ 7.0 mmol/L; previous Type 2 Diabetes Mellitus diagnosis by physician; usage of hypoglycemic drugs within the past two weeks	Logistic Adjusted for: age, gender, educational level, marital status, average monthly income, smoking, drinking status, activity, high-fat diet, fruits and vegetables intake, and history of T2DM	OR (95% CI) ^c T2D: 1.06 (1.05, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		- 3-year average				
		Exposure years: May 2014 - December 2016				
†Klompmaaker et al. (2019) Dutch Public Health Monitor 2012 (Dutch PHM 2012) n = 354, 827 Netherlands 2012 Cross-Sectional	Dutch citizens ≥19 years (older adults ≥ oversampled by design)	LUR leave-one-out cross-validation (LOOCV) R ² = 0.81 Averaging time: NO ₂ - annual average Exposure years: 2009	NO ₂ (ppb) Median = 12.4 (IQR 4.17) (23.4 µg/m ³ (IQR 7.85 µg/m ³))	Prevalent DM: self-report; "Do you have diabetes?" followed by a question "In the last 12 months, have you been treated for diabetes by a physician or a specialist?"	Logistic regression Adjusted for: sex, age, marital status, region of origin, education, work, standardized household income, smoking habits, number of cigarettes/day, alcohol consumption, number of alcohol glasses/week, physical activity, BMI, and neighborhood SES	OR (95% CI) ^b Prevalent DM: 1.15 (1.09, 1.22) Prevalent DM: coadjusted for NDVI 300m: 1.07 (1.01, 1.14) Prevalent DM: coadjusted for NDVI 1000m: 1.07 (1.01, 1.14) Prevalent DM: coadjusted for road-traffic noise: 1.15 (1.09, 1.22)
†Letellier et al. (2022) Community of Mine Study N = 552 San Diego, CA, U.S. 2014–2017 Cross-Sectional	Adults, aged 35-80, living for at least 6 months in selected census block groups. Restricted the population to participants with HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data. Participants with missing information on covariates and without air pollution exposure data were excluded.	Fixed site monitor Correlations between predicted and actual values at the location of the omitted point were used to assess validity of modeled estimates (with a min r of 0.55). Averaging time: NO ₂ - annual average Exposure years: 2014–2017	NO ₂ (ppb) Dynamic Exposure Hispanic/Latino Median = 0.0425 (IQR 0.02392) (0.08 µg/m ³ (IQR 0.045 µg/m ³)) Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 µg/m ³ (IQR 0.058 µg/m ³)) Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 µg/m ³ (IQR	Diabetes: blood glucose level higher than 126 mg/dl	Modified Poisson regression w/ GEE Adjusted for: sex, age, Hispanic/Latino ethnicity, income, smoking status, and BMI	RR (95% CI) ^c Diabetes, dynamic exposure (KDE): 1.05 (0.83, 1.31) Diabetes, static exposure (1, 600m buffer): 0.86 (0.67, 1.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			1.91 µg/m ³) Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 µg/m ³ (IQR 1.17 µg/m ³)) NO ₂ (µg/m ³) Dynamic Exposure Hispanic/Latino Median = 0.08 (IQR 0.045) Non-Hispanic Median = 0.092 (IQR 0.058) Static Exposure Hispanic/Latino Median = 9.77 (IQR 1.91) Non-Hispanic Median = 11.28 (IQR 1.17)			
† Li et al. (2021)	Included middle aged participants and those of European descent with complete genotyping data; excluded participants with T2D at baseline	LUR Method validation NR Averaging time: NO ₂ - annual average, NO _x - annual average, NO - annual average Exposure years: 2010	NO ₂ (µg/m ³) Quartile 1 Mean = 17.3±2.8 Quartile 2 Mean = 22.8±2.7 Quartile 3 Mean = 26.3±2.3 Quartile 4 Mean = 29.8±2.9	Incident T2D was defined by ICD-10 code E11	Cox proportional hazard models Adjusted for: age, ethnicity, sex, Townsend deprivation index, center, alcohol intake, smoking status, physical activity, sedentary hour, healthy diet score, BMI, systolic blood pressure, antihypertension meds,	HR (95% CI) ^c NO ₂ Incident T2DM (SD increment): 1.05 (1.02, 1.07) NO Incident T2DM (SD increment): 1.04 (1.02, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort			Quartile 5 Mean = 37±6.4 NO ₂ (µg/m ³) Quartile 1 Mean = 9.4±2.8 Quartile 2 Mean = 13.4±3.6 Quartile 3 Mean = 16±3.7 Quartile 4 Mean = 18.9±3.9 Quartile 5 Mean = 29.1±11.9		high cholesterol, and T2D GRS.	
† Li et al. (2022) UK Biobank N = 359, 153 England, Scotland, Wales, U.K. Enrollment: 2007–2010 Cohort	Excluded participants who withdrew from study, those has incomplete information, and those who had T2D at baseline	LUR Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2005–2007, 2010	NO ₂ (ppb) Physical Activity High Mean = 15.3±4.86 (28.8±9.15 µg/m ³) Low Mean = 15.52±4.78 (29.21±8.99 µg/m ³) Moderate Mean = 15.58±5.04 (29.32±9.49 µg/m ³) Total Mean = 15.49±4.9 (29.14±9.3 µg/m ³)	Age, sex race, education, household income, smoking status, alcohol consumption, body mass index, fruit and vegetable intake, family history of diabetes, hypertension, cardiovascular disease, depression,	Cox proportional hazard model Adjusted for: age, sex race, education, household income, smoking status, alcohol consumption, body mass index, fruit and vegetable intake, family history of diabetes, hypertension, cardiovascular disease, depression, cancer, physical activity	HR (95% CI) ^b Incident T2D: 1.16 (1.12, 1.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				cancer, physical activity		
† Luo et al. (2022)	Adults aged 40–69 years who were registered with the UK NHS and living near 1 of 22 study centers across England, Scotland, and Wales, without diabetes, stroke, IHD or cancer	LUR	NO ₂ (µg/m ³)	Incident T2D: Incidence of events was obtained from hospital inpatient visits; and coded according to the ICD-10, E11. Diabetes coded as E14 (unspecified diabetes) was also assigned as T2D.	Cox proportional hazard model	HR (95% CI) ^c T2D: 1.04 (1.02, 1.06)
UK Biobank		Median cross-validation $r^2 = 0.87$	CMD Free Median = 26 P25 = 21.2 P75 = 31.1		Adjusted for: age, sex, race, education, Townsend Deprivation Index, recruitment center	
N = 410, 494		Averaging time: NO ₂ - annual average	CMM Survivor Median = 27.3 P25 = 22.5 P75 = 32.1			
England, Scotland, Wales, U.K.		Exposure years: 2010–2011	Death with CMM Median = 27.4 P25 = 22.8 P75 = 32.5			
Enrollment: 2006–2010			Death with FCMD Median = 26.8 P25 = 22.1 P75 = 31.8			
Follow-up: through May 2021			Death without CMD Median = 26.2 P25 = 21.5 P75 = 31.3			
Cohort			FCMD Survivor Median = 26.5 P25 = 21.8 P75 = 31.4			
			Total Median = 26.1			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 21.3 P75 = 31.2			
† Zhang et al. (2021b) China Health and Retirement Longitudinal Study (CHARLS) N = 13, 013 China Enrollment: 2011–2012 Follow-up: 2015 Cross-Sectional	Participants who completed both questionnaires and blood tests	Hybrid model r ² = 0.78 Averaging time: NO ₂ - annual average Exposure years: 2015	NO ₂ (ppb) Overall Mean = 13 (24 µg/m ³) IQR = 6.579 (12.38 µg/m ³)	Prevalent DM: Self-reported diabetes was defined as answering "Yes" to the question "Have you been diagnosed with diabetes or high blood sugar?" Prevalent DM: following ADA recommendations; at least one of the following criteria: a fasting blood glucose >126 mg/dl, a non-fasting blood glucose >200 mg/dl, HbA1c >6.5%, or using antidiabetic medications including insulin, modern medicine or traditional Chinese medicine	Logistic regression Adjusted for: age, sex, educational level, BMI, smoking status, packyears for current smokers, drinking frequency, energy types for cooking and heating	OR (95% CI) ^b Prevalent Diabetes (self-report): 1.51 (1.31, 1.73) Prevalent Diabetes: 1.27 (1.14, 1.42)
† Nagrani et al. (2023) Identifications and prevention of dietary	All children attending kindergartens and primary schools were eligible, with at least one	LUR, Spatiotemporal/geospatial model	NO ₂ NR quantitatively, distribution shown in a	Prediabetes: assessed at the last follow-up examination in	Logistic regression Adjusted for: age, sex, study region, lifetime	OR (95% CI) ^c Prediabetes: Effects estimates provided in figure only

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
and lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study N = 5, 453 Sweden, Spain, Italy, Belgium, Germany, Hungary, Estonia, Cyprus Enrollment: 2009–2010 Follow-up: 2013–2014 Cohort	available metabolic measurement; excluded ever smokers, those who reported intake of anti-diabetic drugs at baseline or follow-up, those with history of diabetes, those with missing residential address, those with urine sample not available, randomly selected urine samples, and Estonia that did not have ELAPSE model available	Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010	figure	2013-14; defined as FG between 100 mg/dL to 125 mg/dL, or HbA1c between 5.7 and 6.4%, or both	alcohol status, membership in a sports club, screen time/week, parental education status, parental smoking, family history of diabetes	
† Paul et al. (2020b) Ontario Population Health and Environment Cohort (ONPHEC) N = 4, 774, 984 Ontario, Canada Enrollment: January 2001 Follow-up: through December 2015 Cohort	Ontario residents who were Canadian born, had lived in Ontario at least 5-year before cohort inception, were between 35–85 years of age, had record of birth date and sex, and were registered with provincial health insurance at enrollment. For mortality analyses, the cohort was restricted to those with diabetes diagnoses before January 1, 2001.	LUR Model was validated against NAPS ground monitor measurements in 2006 ($r^2 = 0.73$) Averaging time: NO ₂ - 3-year moving average Exposure years: 2006	NO ₂ (ppb) Cardiovascular Deaths IQR = 13.4 Min = 2.3 Max = 54.3 Cohort with Prevalent Diabetes IQR = 14.2 Min = 2.3 Max = 58.3 Cohort without Diabetes IQR = 13.8 Min = 2.7 Max = 71.4	Incident diabetes was ascertained using the Ontario Diabetes Database. Those who have had at least one hospital admission with a diagnosis of diabetes (ICD-9: code 250; ICD-10: codes E10–E14), or two or more physician claims related to diabetes (code 250) within a two-year period, and	Cox proportional hazard models Adjusted for: age, sex, SES, region, and healthcare access	HR (95% CI) ^c Incident diabetes: 1.04 (1.03, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Diabetes Deaths IQR = 13.2 Min = 2.3 Max = 52.4 Incident Diabetes Cases IQR = 14.2 Min = 2.7 Max = 71.4	who were diagnosed between cohort inception and the end of follow-up.		
† Paul et al. (2020a) Sacramento Area Latino Study on Aging (SALSA) N = 1, 564 Sacramento, CA, U.S. Enrollment: 1998–1999 Follow-up: through 2008 Cohort	Latino residents from California's Sacramento Valley area aged more than 60 years. Excluded participants who had CIND or dementia at baseline, did not participate in any follow-up interviews, or did not provide all necessary information.	Dispersion model With background pollutant levels in the model $r^2 = 0.95$ Without background pollutant levels in the model $r^2 = 0.90$ Averaging time: NO _x - annual average Exposure years: 2007–2008	NO _x (ppb) Mean = 2.59 SD = 2.2	Prevalent T2D: status based on reports of a physician diagnosis, inventory of antidiabetic medication use, or measured fasting glucose level ≥ 126 mg/dL (7.0 mmol/l) in a blood sample.	Logistic regression w/ GEE Adjusted for: baseline 3MSE score, baseline age, sex, years of education, primary language spoken, occupation for most of life (manual, non-manual, or other), NSES, cigarette smoking, a county indicator, and a rural/urban residential neighborhood indicator	OR (95% CI) ^c T2D: 1.24 (1.11, 1.38) T2D (≤ 2.68 ppb vs. ≤ 2.68 ppb): Referent T2D (> 2.68 ppb vs. ≤ 2.68 ppb): 1.62 (1.27, 2.05)
† Shin and Kim (2023) Cardiovascular Disease Association Study N = 14, 667 Wonju, Pyeongchang, Ganghwa, Goryeong,	Included community-dwelling adults aged 40-69 years; excluded those who reported a previous diagnosis of diabetes during baseline, those who reported 8-hour fasting plasma glucose levels ≥ 126 md/dL during baseline, those	Hybrid model, Chemical transport model The root mean square errors of NO ₂ levels were 6.9 ppb, 5.8 ppb, and 4.4 ppb on the daily, weekly, and annual scale,	NO ₂ (ppb) Diabetes Mean = 15.6 $\pm$ 4.9 No Diabetes Mean = 15.4 $\pm$ 5.1 Total Participants Mean = 15.4 $\pm$ 5.1	Incident DM: identified if participants reported physician-diagnosed diabetes in response to a structured questionnaire or	Cox proportional hazard model Adjusted for: sex, monthly household income, educational levels, cigarette smoking, alcohol consumption, regular physical activity, Mini	HR (95% CI) ^c Incident DM: 1.29 (1.12, 1.49)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Namwon, Yangpyeong, South Korea Enrollment: 2005–2011 Follow-up: 2016 Cohort	who did not participate in any follow-up surveys, those with missing data for BMI, and those who reported an implausible total energy intake (<500 or >5,000 kcal/day) at baseline.	respectively. Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly Exposure years: 2004–2016		had an 8-hour fasting plasma glucose level ≥126 mg/dL.	Dietary Assessment index score, BMI, with a random effect of survey sites	
† Strak et al. (2017) Public Health Monitor N = 289, 703 Netherlands 2012 Cross-Sectional	Dutch citizens, Ages ≥19, Excluded participants with missing potential confounders	LUR The models explained 86% of the variability in the annual NO ₂ concentrations Averaging time: NO ₂ - annual average Exposure years: 2012	NO ₂ (µg/m ³) Total Study Population Mean = 23.88±6.06 IQR = 7.76 Min = 9.11 Max = 138.11 P5 = 15.47 P25 = 19.6 P75 = 27.36 P95 = 34.69	Prevalent DM: “self-reported doctor-diagnosed diabetes” survey question with the information on diabetes medication prescription. If any of the two was positive, then the combined measure was assigned “yes”; if both were negative, then the combined measure was assigned “no”.	Logistic regression Adjusted for: sex, age, individual SES characteristics, neighborhood SES score, lifestyle risk factors	OR (95% CI) ^c Prevalent DM: 1.07 (1.05, 1.09)
† Sørensen et al. (2022b) Danish Civil Registration System N = 1, 922, 545	Included all Danish residents born after January 1, 1921, and living in Denmark from 1979 onwards. Excluded persons with prevalent diabetes and persons	Hybrid model Method validation NR Averaging time: NO ₂ - Monthly averages	NO ₂ (µg/m ³) Total Median = 15.2 P5 = 9.3 P95 = 27.2	Incident T2D: used the National Patient Register to identify all incident cases with T2D. Defined a T2D	Cox proportional hazards model Adjusted for: age, sex, calendar-year, civil status, individual and family income, country	HR (95% CI) ^c Incident T2D (NO ₂ traffic): 1.04 (1.04, 1.05) Incident T2D: 1.06 (1.05, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Denmark Enrollment: January 1, 2005 Follow-up: 11.2 years Cohort	missing information on one or more potential confounders.	Exposure years: 2000–2017	Traffic Median = 3.9 P5 = 1.1 P95 = 14.2	case as a person with two contacts to a hospital ICD-8 (250) or ICD-10 E11) and/or a pharmacy, defined using the Anatomical Therapeutic Chemical system (ATC) codes A10B (blood glucose lowering drugs, excluding insulins), A10AE54 (insulin glargine and lixisenatide) and A10AE56 (insulin degludec and liraglutide), though not including A10BJ02 (liraglutide: only Saxenda®) and women receiving A10BA02 (metformin) in combination with G03GB02 (clomifene) or G03HB (antiandrogens and estrogens) or a diagnosis of polycystic ovary	of origin, occupational status, education, and neighborhood-level percentage of population with low income, with only basic education, who are unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and who live in social housing	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				syndrome (ICD10: E282). Cases of T1D were excluded.		
† Sørensen et al. (2022a) Danish National Health Survey n = 246, 766 Denmark Enrollment: 2010–2013 Follow-up: 2017 Cohort	Population based sample in Denmark	Hybrid model Correlation coefficient = 0.87 Averaging time: 5-year running time-weighted average Exposure years: 2010–2017	NO ₂ (µg/m ³) NR quantitatively (The baseline distribution of 5-year exposure to NO ₂ is shown in the Supplement Material.)	Incident T2D: incident diabetes cases identified through linkage with the National Patient Register and the National Prescription Register. T2D cases defined as two contacts with either the hospital (ICD8: 250 or ICD10: E11) or pharmacy (ATC codes A10B (glucose lowering drugs (excl. insulin), excluding A10BJ02 (liraglutide) or a combination of A10AE54 (insulin glargine and lixisenatide) and A10AE56 (insulin degludec and liraglutide)) relating to type 2 diabetes. Cases of	Cox proportional hazards model Adjusted for: age, sex, year; register-based individual covariates: educational level, marital status, individual and household income, country of origin, occupational level; all area-level covariates: area-level (parish) proportion of inhabitants with only basic education, who were unemployed, with low income, with manual labor, with non-Western background, with a criminal record, proportion of single-parent families and families living in social housing; questionnaire-based information on lifestyle habits: smoking status and intensity, intake of fruit, intake of vegetables, intake, of red meat, physical activity and BMI	HR (95% CI) ^c Incident T2D: 1.14 (1.06, 1.23)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				T1D were excluded.		
† Wu et al. (2022b)	Free of diabetes and any diabetes-related events at baseline, no occurrences of the diabetes-related events before the diagnosis of T2D, no missing exposure data	Dispersion model	NO ₂ (ppb)	Diabetes complications were defined as the first occurrence of any diabetes complications events after the diagnosis of incident T2D [16].	Multi-state regression model	NO ₂
UK Biobank		Method validation NR	Baseline to Death Mean = 9.848±3.16 (18.53±5.94 µg/m ³)		Adjusted for: age, sex, ethnicity, residential area, smoking status, healthy diet, physical activity, and family history of diabetes	HR (95% CI) ^b Among those with T2D, complications from diabetes: 1.45 (1.31, 1.61)
N = 398, 993		Averaging time: NO ₂ - annual average, NO _x - annual average	Median = 9.577 (IQR 3.77) (18.02 µg/m ³ (IQR 7.09 µg/m ³))	Diabetes complications events after the diagnosis of incident T2D [16].		Incident T2D: 2.89 (2.76, 3.02)
England, Scotland, Wales, U.K.		Exposure years: 2002–2020	Min = 1.75 (3.29 µg/m ³) Max = 30.6 (57.6 µg/m ³) P25 = 7.701 (14.49 µg/m ³) P75 = 11.46 (21.57 µg/m ³)	Diabetes complications in this study included diabetic eye diseases, diabetic kidney diseases, diabetic neuropathy diseases, cardiovascular diseases (CVD), peripheral vascular diseases, and metabolic events		NO _x
Enrollment: 2006–2010			Baseline to T2D Mean = 9.88±3.17 (18.59±5.97 µg/m ³) Median = 9.598 (IQR 3.78) (18.06 µg/m ³ (IQR 7.11 µg/m ³)) Min = 1.75 (3.29 µg/m ³) Max = 30.6 (57.6 µg/m ³) P25 = 7.717 (14.52 µg/m ³) P75 = 11.5 (21.63 µg/m ³)			HR (95% CI) ^c Among those with T2D, complications from diabetes: 1.10 (1.06, 1.15)
Follow-up: through March 31, 2021			Complication to Death Mean = 9.965±3 (18.75±5.6 µg/m ³) Median = 9.789 (IQR	Cases of T2D were identified by ICD-10 code families E11. To exclude the prevalent diabetes cases, also collected cases of		Incident T2D: 1.39 (1.37, 1.42)
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			3.7) (18.42 µg/m ³ (IQR 6.96 µg/m ³)) Min = 2.88 (5.41 µg/m ³) Max = 27.45 (51.65 µg/m ³) P25 = 7.908 (14.88 µg/m ³) P75 = 11.61 (21.84 µg/m ³) T2D to Complication Mean = 10.52±3.21 (19.79±6.04 µg/m ³) Median = 10.24 (IQR 3.85) (19.26 µg/m ³ (IQR 7.25 µg/m ³)) Min = 2.9 (5.45 µg/m ³) Max = 28.81 (54.21 µg/m ³) P25 = 8.349 (15.71 µg/m ³) P75 = 12.2 (22.96 µg/m ³) T2D to Death Mean = 10.28±3.17 (19.35±5.96 µg/m ³) Median = 10 (IQR 3.81) (18.82 µg/m ³ (IQR 7.17 µg/m ³)) Min = 2.88 (5.41 µg/m ³) Max = 28.81 (54.21 µg/m ³) P25 = 8.147 (15.33 µg/m ³) P75 = 12 (22.5 µg/m ³)	diabetes identified through HbA1c ≥48mmol/mol, ICD-9 code 250 in hospital records, algorithmically defined outcome, and participants who ever used insulin or other hypoglycemic drugs before recruitment.		

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			The Whole Stage Mean = 9.688±3.15 (18.23±5.92 µg/m³) Median = 9.412 (IQR 3.76) (17.71 µg/m³ (IQR 7.08 µg/m³)) Min = 1.52 (2.86 µg/m³) Max = 30.78 (57.92 µg/m³) P25 = 7.531 (14.17 µg/m³) P75 = 11.29 (21.25 µg/m³) NO_x (µg/m³) Baseline to Death Mean = 27.79±11.04 Median = 26.32 (IQR 12.66) Min = 4.31 Max = 110.99 P25 = 20.21 P75 = 32.87 Baseline to T2D Mean = 27.88±11.09 Median = 26.39 (IQR 12.75) Min = 4.31 Max = 110.99 P25 = 20.24 P75 = 32.99 Complication to Death Mean = 28.11±10.44 Median = 26.88 (IQR			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			12.54) Min = 7.03 Max = 100.3 P25 = 20.78 P75 = 33.32 T2D to Complication Mean = 30.04±11.43 Median = 28.5 (IQR 13.38) Min = 7.09 Max = 105.14 P25 = 22.18 P75 = 35.56 T2D to Death Mean = 29.27±11.21 Median = 27.72 (IQR 13.08) Min = 7.03 Max = 105.14 P25 = 21.62 P75 = 34.7 The Whole Stage Mean = 27.27±10.92 Median = 25.81 (IQR 12.43) Min = 3.75 Max = 111.01 P25 = 19.79 P75 = 32.22			
† Wu et al. (2023)	Sample of half a million UK citizens	LUR	NO ₂ (µg/m ³)	Incident DM: defined as glycated hemoglobin	Cox proportional hazard model Adjusted for: age, sex,	NO ₂ HR (95% CI) ^c incident DM: 1.16 (1.08, 1.24)
UK Biobank		0.87 for NO ₂ , and 0.88 for NO _x	Mean = 26.65±7.74			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 162, 334			NO _x (µg/m ³)	(HbA1c) greater or equal to 48 mmol/mol at baseline, or a record of ICD-10 codes for diabetes (E10-E14), or any medication history of antihyperglycemic medications	ethnicity, body mass index, smoking status, physical activity, household income, Townsend deprivation index, green space	NO _x
Nationwide, U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 43.82±15.61			HR (95% CI) ^c
2006–2010		Exposure years: 2010–2011				incident DM: 1.11 (1.06, 1.16)
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Zhang et al. (2021b) China Health and Retirement Longitudinal Study (CHARLS) N = 13, 013 China Enrollment: 2011–2012 Follow-up: 2015 Cross-Sectional	Participants who completed both questionnaires and blood tests	Hybrid model $r^2 = 0.78$ Averaging time: NO ₂ - annual average Exposure years: 2015	NO ₂ (ppb) Overall Mean = 13 (24 µg/m ³) IQR = 6.579 (12.38 µg/m ³)	Prevalent DM: Self-reported diabetes was defined as answering "Yes" to the question "Have you been diagnosed with diabetes or high blood sugar?" Prevalent DM: following ADA recommendations; at least one of the following criteria: a fasting blood glucose >126 mg/dl, a non-fasting blood glucose >200 mg/dl, HbA1c >6.5%, or using antidiabetic medications including insulin, modern medicine or traditional Chinese medicine	Logistic regression Adjusted for: age, sex, educational level, BMI, smoking status, packyears for current smokers, drinking frequency, energy types for cooking and heating	OR (95% CI) ^b Prevalent Diabetes (self-report): 1.51 (1.31, 1.73) Prevalent Diabetes: 1.27 (1.14, 1.42)

List of abbreviations in alphabetical order: BMI = Body mass index; CI = Confidence interval; HR = Hazard ratio; ICD = International Classification of Disease; IQR = Interquartile Range; LUR = Land use regression; Max = maximum; Min = minimum; NO = Nitric oxide; NO₂ = Nitrogen dioxide; NO_x = Nitrogen oxides; O₃ = Ozone; OR = Odds ratio; P25 = 25th percentile; P75 = 75th percentile; PM_{2.5} = Particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = Particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; POR = prevalence odds ratio; ppb = Parts per billion; r² = Coefficient of determination; RR = Rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-2 Epidemiologic studies of exposure to oxides of nitrogen and MetS

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Eze et al. (2015) Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) n = 3769 Switzerland Enrollment: 1991 Follow-up: 2001–2002 Cohort	Random selection of participants from 8 Swiss communities, age 29–73	Hybrid model Averaging time: 10-year mean NO ₂ Exposure years: 1990–2000	NO ₂ No metabolic syndrome Mean = 14.46±6.01 (27.2±11.3 µg/m ³)	Adult Treatment Panel-III definition of MetS (defined using predicted waist circumference and North American cut-off for central obesity (≥102cm for men and ≥88 cm for women)) International Diabetes Federation definition of MetS (defined using predicted waist circumference and European cut-off for central obesity (≥94 cm for men and ≥80 cm for women)) WHO definition of MetS	Mixed logistic model Adjusted for: age, sex, educational attainment, neighborhood socioeconomic index, occupational exposure to vapors, gases, dusts or fumes, smoking status, smoked pack-years, exposure to passive smoke, consumption of fruits and raw vegetables, and physical activity, BMI	OR (95% CI) ^c MetS-W: 1.22 (1.02, 1.46) MetS-W coadjusted for PM ₁₀ : 0.94 (0.78, 1.13) MetS-A: 1.05 (0.95, 1.17) MetS-A coadjusted for PM ₁₀ : 0.93 (0.81, 1.08) MetS-I: 1.17 (1.04, 1.31) MetS-I coadjusted for PM ₁₀ : 1.04 (0.88, 1.23)
† Guo et al. (2022) China Health and Retirement Longitudinal Study (CHARLS) N = 6, 486	Participants aged over 45 years of age; excluded participants due to lacking information on PA and 71 participants	Spatiotemporal/geospatial model r ² = 0.84 Averaging time: NO ₂ - annual	NO ₂ (ppb) Overall Mean = 15.7±5.3 (29.5±10 µg/m ³) Median = 14.8 (27.9 µg/m ³) Min = 6.96 (13.1 µg/m ³)	The Joint Interim Societies' definition of MetS and using the cut points of WC from China	Logistic regression Adjusted for: sex, urbanity, educational level, status of marriage, cooking fuel, heating fuel, status of	NO ₂ OR (95% CI) ^b MetS: 1.44 (1.22, 1.71) MetS: Active group (physical activity): 1.22 (0.97, 1.55) MetS: Inactive group (physical

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
China 2015 Cross-Sectional	who lived at the survey site for less than one year	average Exposure years: 2015	Max = 27.7 (52.1 µg/m ³) P5 = 8.5 (16 µg/m ³) P25 = 11.3 (21.2 µg/m ³) P75 = 19.1 (35.9 µg/m ³) P95 = 25.4 (47.8 µg/m ³)		smoking, status of drinking, history of diseases, physical activity amount	activity): 1.52 (1.29, 1.81) MetS: Age group <60 yr : 1.32 (1.01, 1.72) MetS: Age group ≥60 yr: 1.54 (1.23, 1.93) MetS: Men: 1.64 (1.21, 2.22) MetS: Women: 1.33 (1.07, 1.65)
† Han et al. (2022) China Health and Retirement Longitudinal Study (CHARLS) N = 11, 838 China 2015 Cross-Sectional	Participants aged 45 years or older; excluded for missing data on age, for not keeping on an empty stomach, for missing information on smoking, exercise, or consumed alcohol within 30 minutes before examination, for missing data on waist circumference, SBP and/or DBP, TG, HDL, FBG or CRP, and for failing to assess air pollution exposure	Spatiotemporal/geospatial model r ² = 0.84 Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average Exposure years: 2013–2015	NO ₂ (µg/m ³) 3-year average Mean = 32.29±7.63 Median = 30.77 (IQR 11.28) P25 = 26.15 P75 = 37.43	The Joint Interim Societies' definition of MetS using their categorizations of WC for Chinese people	Generalized linear models Adjusted for: temperature, relative humidity, age, sex, residence, education, marital status, annual household expenditure, smoking status, and drinking status, physical activity	NO ₂ OR (95% CI) ^c MetS: 1.30 (1.21, 1.40)
† Letellier et al. (2022) Community of Mine Study N = 552	Adults, aged 35-80, living for at least 6 months in selected census block groups. Restricted the population to	Fixed site monitor Correlations between predicted and actual values at the location of the	NO ₂ (ppb) Dynamic Exposure Hispanic/Latino Median = 0.0425 (IQR 0.02392) (0.08 µg/m ³ (IQR	MetS: using NCEP ATP III definition; the presence of MetS (yes/no) was indicated based on having at least	Modified Poisson regression with GEE Adjusted for: sex, age, Hispanic/Latino	NO ₂ RR (95% CI) ^c MetS, dynamic exposure (KDE): 1.21 (1.12, 1.30) MetS, dynamic exposure (KDE):

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
San Diego, CA, U.S. 2014–2017 Cross-Sectional	participants with HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data. Participants with missing information on covariates and without air pollution exposure data were excluded.	omitted point were used to assess validity of modeled estimates (with a min r of 0.55). Averaging time: NO ₂ - annual average Exposure years: 2014–2017	0.045 µg/m ³) Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 µg/m ³ (IQR 0.058 µg/m ³)) Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 µg/m ³ (IQR 1.91 µg/m ³)) Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 µg/m ³ (IQR 1.17 µg/m ³)) NO ₂ (µg/m ³) Dynamic Exposure Hispanic/Latino Median = 0.08 (IQR 0.045) Non-Hispanic Median = 0.092 (IQR 0.058) Static Exposure Hispanic/Latino Median = 9.77 (IQR 1.91) Non-Hispanic Median = 11.28 (IQR 1.17)	three of the following risk determinants: increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); elevated triglycerides (≥150 mg/dl); low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); hypertension (≥130/≥80 mmHg); and impaired fasting glucose (≥110 mg/dl).	ethnicity, income, smoking status	Hispanic: 1.10 (0.92, 1.32) MetS, dynamic exposure (KDE): non-Hispanic: 1.23 (1.13, 1.33) MetS, static exposure (1, 600m buffer): 1.07 (0.98, 1.18) MetS, static exposure (1, 600m buffer): Hispanic: 1.13 (1.01, 1.27) MetS, static exposure (1, 600m buffer): non-Hispanic: 0.99 (0.86, 1.15)
[†] Liu et al. (2023) China Health and Retirement Longitudinal Study (CHARLS) N = 14, 097	Individuals aged 45 years or older; excluded participants who failed to provide fasting blood samples and whose	Spatiotemporal/geospatial model r ² = 72% Averaging time: NO ₂ - 24-hour	NO ₂ (ppb) Overall Mean = 16.8 (31.6 µg/m ³) Median = 16.5 (IQR 7.65) (31.1 µg/m ³ (IQR 14.4 µg/m ³))	MetS	Logistic regression Adjusted for: age, gender, education level, marital status, BMI, smoking, drinking, social activity	NO ₂ OR (95% CI) ^b MetS: 4.70 (4.21, 5.24) MetS: age 45-60 years (stratified models): 4.09 (3.55, 4.71) MetS: age 45-60 years: 1.43 (1.14,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
China	detailed information on sex, marital status, and habits of smoking and drinking were insufficient.	average, NO ₂ - annual average	Min = 7.65 (14.4 µg/m ³) Max = 35.8 (67.4 µg/m ³)		frequency, disability, health insurance, wage income and health status	1.78) MetS: age ≥60 years (stratified models): 5.77 (4.86, 6.86) MetS: age ≥60 years: 5.77 (4.87, 6.84) MetS: drinking status 0 (stratified models): 4.93 (4.32, 5.62) MetS: drinking status 0: 4.87 (4.31, 5.50) MetS: drinking status <1 time/month (stratified models): 5.71 (3.60, 9.04) MetS: drinking status <1 time/month: 4.92 (3.19, 7.59) MetS: drinking status >1 time/month (stratified models): 3.66 (2.75, 4.87) MetS: drinking status >1 time/month: 1.28 (0.77, 2.14) MetS: females (stratified models): 4.80 (4.21, 5.47) MetS: females: 4.72 (4.13, 5.39) MetS: health status fair (stratified models): 4.60 (3.96, 5.33) MetS: health status fair: 4.60 (3.97, 5.33) MetS: health status good/very good (stratified models): 4.38 (3.48, 5.51) MetS: health status good/very good: 1.06 (0.81, 1.39) MetS: health status poor/very poor (stratified models): 5.42 (4.31, 6.81) MetS: health status poor/very poor: 5.32 (4.24, 6.68) MetS: males (stratified models): 4.27 (3.50, 5.21) MetS: males: 1.02 (0.88, 1.17)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Nagrani et al. (2023) Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study N = 5, 453 Sweden, Spain, Italy, Belgium, Germany, Hungary, Estonia, Cyprus Enrollment: 2009–2010 Follow-up: 2013–2014 Cohort	All children attending kindergartens and primary schools were eligible, with at least one available metabolic measurement; excluded ever smokers, those who reported intake of anti-diabetic drugs at baseline or follow-up, those with history of diabetes, those with missing residential address, those with urine sample not available, randomly selected urine samples, and Estonia that did not have ELAPSE model available	LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO₂ - annual average Exposure years: 2010	NO₂ (µg/m³) NR	MetS: assessed at the last follow-up examination in 2013-14; children were categorized as cases of MetS if at least three of the components of MetS exceeded the 90th percentile (WC, HOMA-IR, HDL, TG, SBP or DBP)	logistic regression Adjusted for: age, study region, lifetime alcohol status, membership in a sports club, screen time/week, parental education status, parental smoking, family history of diabetes Adjusted for: age, sex, study region, lifetime alcohol status, membership in a sports club, screen time/week, parental education status, parental smoking, family history of diabetes	NO₂ OR (95% CI)^c MetS: Residential distance >250m to major road: 0.88 (0.71, 1.10) MetS: Residential distance ≤250m to major road: 1.06 (0.77, 1.47) MetS: sex: females: 1.09 (0.84, 1.41) MetS: sex: males: 0.82 (0.64, 1.06) MetS: Weight: normal weight: 0.91 (0.59, 1.40) MetS: Weight: overweight/obese: 0.90 (0.72, 1.14)
†Yu et al. (2020) Sacramento Area Latino Study on Aging (SALSA) N = 1, 554 Sacramento, CA, U.S.	Included if participants were 60+ years of age, resided in California Sacramento Valley, and self-identified at Latino. Excluded those who did not participate in	Dispersion model Method validation NR Averaging time: NO_x - annual average	NO_x (ppb) Abdominal Obesity Mean = 2.59±2.17 Median = 2 Min = 0.01 Max = 13.2 P5 = 0.45 P10 = 0.66 P25 = 1.15	MetS defined as the presence of three or more of these components: (1) abdominal obesity [waist circumference of ≥40 in. in men; ≥35 in. in women]; (2) borderline	Cox proportional hazards Adjusted for: baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life,	HR (95% CI)^b Metabolic Syndrome coadjusted for 24-hr noise: 0.84 (0.25, 2.76) Metabolic Syndrome coadjusted for nighttime noise: 0.84 (0.26, 2.66) Metabolic Syndrome: 1.41 (0.49, 4.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Recruitment: 1998–1999 Follow-up: 2007 Cohort	baseline visit, had no exposure estimates, already exhibited all 5 components of metabolic syndrome at baseline, who already met the criteria for the designated outcome at baseline, and lacked follow-up visits.	Exposure years: 1998–1999	P75 = 3.36 P90 = 5.15 P95 = 6.78 Hyperglycemia Mean = 2.5±2.14 Median = 1.81 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.65 P25 = 1.09 P75 = 3.12 P90 = 5.25 P95 = 6.8 Hypertension Mean = 2.55±2.15 Median = 1.85 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.66 P25 = 1.1 P75 = 3.33 P90 = 5.22 P95 = 7.15 Hypertriglyceridemia Mean = 2.57±2.14 Median = 1.86 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.67 P25 = 1.17 P75 = 3.29	elevation of blood glucose [fasting glucose ≥100 mg/dl, or use of glucose-lowering medications]; (3) elevated blood pressure [≥140/90 mmHg, or use of anti-hypertensive medication]; (4) elevated triglycerides [≥150 mg/dl, or use of statins]; and (5) low high-density lipoprotein (HDL) cholesterol [men: <40 mg/dl; women: <50 mg/dl, or use of statins].	baseline smoking status, baseline alcohol consumption status and physical activity level	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P90 = 5.31 P95 = 6.75 Low HDL-Cholesterol Mean = 2.64±2.19 Median = 1.95 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.68 P25 = 1.17 P75 = 3.56 P90 = 5.46 P95 = 6.82 Metabolic Syndrome Mean = 2.6±2.2 Median = 1.9 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.67 P25 = 1.16 P75 = 3.33 P90 = 5.46 P95 = 7 Total Mean = 2.6±2.17 Median = 1.9 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.67 P25 = 1.15 P75 = 3.44			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P90 = 5.3 P95 = 6.93			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Zhang et al. (2021a)	Participants older than 10 years	Spatiotemporal/geospatial model, Hybrid model	NO ₂ (ppb)	MetS	Generalized linear mixed models	NO ₂
Chinese Population			Total			OR (95% CI) ^b
N = 9, 897			Mean = 20.1 (37.8 µg/m ³)		Adjusted for: sex, age, weight status, temperature, relative humidity, parental education level achieved, parental smoking status, parental alcohol consumption, family histories of type 2 diabetes, hypertension, obesity, or cerebrovascular disease, outdoor physical activity time, diet of high fat, SSBs intake	MetS (Chinese criteria): 2.01 (1.32, 3.06)
Shanghai, Guangdong Province, Tianjin, Chongqing, China, Liaoning Province, Ningxia, Hunan, China		In cross validation, the r ² was 62% for daily estimates of NO ₂	Median = 20.9 (IQR 5) (39.4 µg/m ³ (IQR 9.5 µg/m ³)) Min = 9.99 (18.8 µg/m ³) Max = 31.5 (59.2 µg/m ³)			MetS (distinguish between the age groups 10- <16 years and 16+ years in IDF definition): 1.69 (1.02, 2.78)
2013		Averaging time: NO ₂ - 24-hour average				MetS (NCEP/ATP III): 1.37 (0.97, 1.92)
Cross-Sectional		Exposure years: 2013–2016				MetS: 1.71 (1.06, 2.77)
						MetS: Boy: 2.12 (1.17, 3.82)
						MetS: Girl: 1.26 (0.65, 2.43)
						MetS: PM ₁ +NO ₂ : 1.76 (0.62, 5.00)
						MetS: PM ₁ +PM _{2.5} +NO ₂ : 1.81 (0.25, 13.14)
						MetS: PM ₁ +PM ₁₀ +NO ₂ : 1.81 (0.31, 10.71)
						MetS: PM _{2.5} +NO ₂ : 1.81 (0.51, 6.39)
						MetS: PM _{2.5} +PM ₁₀ +NO ₂ : 1.78 (0.13, 24.18)
					(Models stratified by sex are not adjusted for sex)	MetS: PM ₁₀ +NO ₂ : 1.81 (0.58, 5.63)

List of Abbreviations: BMI = Body mass index; CI = Confidence interval; GEE = Generalized Estimating Equations; HDL = high-density lipoprotein; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; HR = Hazard ratio; IQR = Interquartile Range; KDE = Kernel Density Estimation; LUR = Land use regression; MetS = Metabolic syndrome; NO = Nitric oxide; NO₂ = Nitrogen dioxide; NO_x = Nitrogen oxides; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; O₃ = Ozone; OR = Odds ratio; PA = Physical activity; P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile; P90 = 90th percentile; P95 = 95th percentile; PM_{2.5} = Particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = Particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = Parts per billion; r² = Coefficient of determination; RR = Rate ratio; WC = Waist circumference; WHO = World Health Organization

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time

^cEstimates are not standardized

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-3 Epidemiologic studies of exposure to oxides of nitrogen and glucose and insulin homeostasis

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Eze et al. (2015) Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) n = 3,769 Switzerland Enrollment: 1991 Follow-up: 2001–2002 Cohort	Random selection of participants from 8 Swiss communities, age 29–73 yr	Hybrid model Averaging time: 10-year mean NO ₂ Exposure years: 1990–2000	NO ₂ (µg/m ³) No metabolic syndrome Mean = 27.2±11.3	IDF/ATP-III definition; IFG defined as fasting blood glucose ≥6.1 mmol/L and/or diagnosis of type 2 diabetes WHO definition; IFG defined as fasting blood glucose ≥6.1 mmol/L and/or diagnosis of type 2 diabetes	Mixed logistic model Adjusted for: age, sex, educational attainment, neighborhood socioeconomic index, occupational exposure to vapors, gases, dusts and fumes, smoking status, smoked pack-years, exposure to passive smoke, consumption of fruits and raw vegetables, physical activity, BMI	OR (95% CI) ^c Impaired fasting Glycaemia (IFG; IDF/ATP-III): 1.06 (0.93, 1.21) Impaired fasting Glycaemia (IFG;WHO): 1.15 (0.98, 1.34)
†Holliday et al. (2019) Women’s Health Initiative clinical trials (WHI CT) n = 3,915 U.S. Enrollment: 1993–1998 Follow-up: 1993–2004 Cohort	Postmenopausal female volunteers aged 50–79 yr from one of the 76 US examination centers. The present study examines a center- and race-stratified ~6% random, minority oversample of WHI CT participants with repeated measures of fasting glucose, fasting insulin, and geocoded address coordinates. Participants were eligible if they were	Spatiotemporal/geospatial model Averaging time: NO _x - 24-hour average Exposure years: 1993–2004	NO _x (ppb) Two-day Mean = 40.5 Median = 31.5 P5 = 12.1 P25 = 20.7 P75 = 49.1 P95 = 99.7 Annual Mean = 39.3 Median = 36.3 P5 = 18.9 P25 = 27.5	Fasting (>9 hours) serum and EDTA-treated plasma collected at the screening and annual visits 1, 3, or 6 (1993–2004) were frozen at -70°C and shipped to Medical Research Laboratories (MRC, Highland Heights, KY). Serum glucose	Multi-level, mixed effects models Adjusted for: clinical trial, sociodemographic, behavioral, clinical, temporal, and meteorological attributes: trial membership, treatment group, age (years), race/ethnicity, education, nSES, smoking, alcohol use, energy expenditure (MET-hours/week), BMI (kg/m ²), family	β (Percent change) (95% CI) ^c Fasting glucose (2-day mean) for all fasting glucose status: -0.20 (-0.70, -0.20) Fasting glucose (2-day mean) for impaired fasting glucose status: 0.00 (-0.40, 0.30) Fasting glucose (2-day mean) for normal fasting glucose status: -0.20 (-0.60, 0.30) Fasting glucose (365-day mean) for all fasting glucose status: -0.30 (-1.10, 0.50) Fasting glucose (365-day mean) for impaired fasting glucose status: 0.10 (-0.50, 0.70) Fasting glucose (365-day mean) for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	free of diabetes at their screening visit and underwent phlebotomy at the screening visit or annual visits 1, 3, or 6 (1993–2004). Participants were included through annual visit 6 unless their WHI follow-up ended or they developed diabetes.		P75 = 47.8 P95 = 71.5	and plasma lipids were assayed on a Hitachi 747 analyzer, glucose by the hexokinase method and HDL-C via isolation using heparin-manganese chloride. Serum insulin was measured by radioimmunoassay or on an ES 300 analyzer in a stepwise sandwich enzyme-linked immunosorbent assay. Results of the two methods were comparable insulin concentrations <60 µIU/ml. HOMA-IR was estimated as the product of insulin × glucose divided by 22.5. TyG was the natural log-	history of diabetes, season, day of the week, temperature (°C), dew point (°C), and barometric pressure (kPa)	normal fasting glucose status: -0.30 (-1.10, 0.40) Fasting insulin (2-day mean) for all fasting glucose status: -0.40 (-1.40, 0.70) Fasting insulin (2-day mean) for impaired fasting glucose status: 0.20 (-2.00, 2.40) Fasting insulin (2-day mean) for normal fasting glucose status: -0.40 (-1.40, 0.60) Fasting insulin (365-day mean) for all fasting glucose status: -0.90 (-3.30, 1.70) Fasting insulin (365-day mean) for impaired fasting glucose status: 0.40 (-2.70, 3.50) Fasting insulin (365-day mean) for normal fasting glucose status: -1.00 (-3.90, 1.90) HOMA-IR (2-day mean) for all fasting glucose status: -0.60 (-2.10, 0.90) HOMA-IR (2-day mean) for impaired fasting glucose status: -0.10 (-2.40, 2.20) HOMA-IR (2-day mean) for normal fasting glucose status: -0.40 (-1.90, 1.10) HOMA-IR (365-day mean) for all fasting glucose status: -1.20 (-3.80, 1.40) HOMA-IR (365-day mean) for impaired fasting glucose status: 0.00 (-3.20, 3.30) HOMA-IR (365-day mean) for normal fasting glucose status:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				transformed product of (TG × glucose × 0.5)		-1.10 (-4.20, 2.00) TyG (2-day mean) for all fasting glucose status: -0.40 (-1.60, 0.80) TyG (2-day mean) for impaired fasting glucose status: 0.00 (-2.60, 2.60) TyG (2-day mean) for normal fasting glucose status: -0.50 (-1.60, 0.70) TyG (365-day mean) for all fasting glucose status: -1.00 (-3.50, 1.50) TyG (365-day mean) for impaired fasting glucose status: -0.50 (-3.90, 3.00) TyG (365-day mean) for normal fasting glucose status: -1.20 (-4.00, 1.60)
† Honda et al. (2017)	Adults 57+ year who were community-dwelling Americans selected from eligible households identified in the Health and Retirement Study (HRS) in 2004	Fixed site monitor	NO ₂ (ppb)	HbA1c was collected via dried blood spots on filter paper.	Linear regression	β (NA) (95% CI) ^c
National Social Life, Health, and Aging Project (NSHAP)		Averaging time: NO ₂ - annual average, Other, NO ₂ - 1–5 year moving averages	Total Cohort Mean = 5.53±2 (10.4±3 µg/m ³)		Adjusted for: BMI, age, sex, race, education, diabetic medication use, tobacco use, physical activity, region, urbanicity, census tract data on median household income, and percent of households living below the poverty line	HbA1c (1-year moving average exposure): 2.00 (0.00, 0.00) HbA1c (Diabetic; 2-year moving average exposure): 1.90 (0.00, 0.00) HbA1c (Diabetic; 3-year moving average exposure): 1.90 (0.00, 0.00) HbA1c (Diabetic; 4-year moving average exposure): 1.70 (0.00, 0.00) HbA1c (Diabetic; 5-year moving average exposure): 1.90 (0.00, 0.00) HbA1c (Non-Diabetic; 2-year moving average exposure): 0.70 (0.00, 0.00) HbA1c (Non-Diabetic; 3-year moving average exposure): 0.60 (0.00, 0.00) HbA1c (Non-Diabetic; 4-year moving average exposure): 0.70
N = 4,121			With DM Mean = 5.69±1.5 (10.7±2.9 µg/m ³)			
U.S.		Exposure years: 1999–2007	Without DM Mean = 5.47±1.6 (10.3±3.1 µg/m ³)			
Enrollment: 2005–2006 and 2010–2011			NO ₂ (µg/m ³)			
Cohort			Total Cohort Mean = 10.4±3			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			With DM Mean = 10.7±2.9			(0.00, 0.00) HbA1c (Non-Diabetic; 5-year moving average exposure): 0.70 (0.00, 0.00)
			Without DM Mean = 10.3±3.1			
† Kang et al. (2022)	Adults aged 18–79 yr recruited from five rural regions in the Henan province of China by multistage stratified cluster sampling. Participants were excluded if they had self-reported physician-diagnosed type 1 diabetes mellitus, or if they were missing obesity indicator or fasting blood glucose data.	Hybrid model A spatiotemporal model utilizing random forest methods estimated NO ₂ concentrations of each participant through combining daily satellite data, meteorological conditions, and land use data. The cross-validation (r ²) for NO ₂ was 72% (6.5 µg/m ³). Averaging time: NO ₂ - 3-year average Exposure years: May 2014–December 2016	NO ₂ (µg/m ³) Overall Mean = 39.87±3.6 Participants with T2DM Mean = 40.63±3.53 Participants without T2DM Mean = 39.79±3.6	FBG was measured by the automatic biochemical analyzer using the glucose oxidative method	Logistic regression model Adjusted for: age, gender, educational level, marital status, average monthly income, smoking, drinking status, activity, high-fat diet, fruits and vegetables intake, and history of T2DM	β (mmol/L) (95% CI) ^c FBG: 0.04 (0.03, 0.04) FBG (NO ₂ ≥40 µg/m ³ vs. NO ₂ <40 µg/m ³): 0.32 (0.29, 0.35)
Henan Rural Cohort Study n = 38,841 Henan Province, Suiping County, Yuzhou County, Xinxiang County, Tongxu County, Yima County, China 2015–2017 Cohort						
† Letellier et al. (2022)	Adults, aged 35–80 yr, living for at least 6 months in selected census block groups. Restricted the	Fixed site monitor Correlations between predicted and actual values	NO ₂ (ppb) Dynamic Exposure Hispanic/Latino Median = 0.0425	Fasting plasma glucose (mg/dl) HbA1C (%)	Modified Poisson regression w/ GEE Adjusted for: sex, age, Hispanic/Latino	NO ₂ β (NA) (95% CI) ^c Fasting glucose, dynamic exposure (KDE): 0.01 (-0.01, 0.03)
Community of Mine Study N = 552						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
San Diego, CA, U.S. 2014–2017 Cross-Sectional	population to participants with HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data. Participants with missing information on covariates and without air pollution exposure data were excluded.	at the location of the omitted point were used to assess validity of modeled estimates (with a min r of 0.55). Averaging time: NO ₂ - annual average Exposure years: 2014–2017	(IQR 0.02392) (0.08 µg/m ³ (IQR 0.045 µg/m ³)) Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 µg/m ³ (IQR 0.058 µg/m ³)) Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 µg/m ³ (IQR 1.91 µg/m ³)) Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 µg/m ³ (IQR 1.17 µg/m ³)) NO ₂ (µg/m ³) Dynamic Exposure Hispanic/Latino Median = 0.08 (IQR 0.045) Non-Hispanic Median = 0.092 (IQR 0.058) Static Exposure Hispanic/Latino Median = 9.77 (IQR 1.91) Non-Hispanic	insulin resistance: HOMA-IR = fasting plasma insulin (mIU/L) * fasting plasma glucose (mg/dL)/22.5	ethnicity, income, smoking status, and BMI	Fasting glucose, static exposure (1,600m buffer): 0.01 (0.00, 0.03) HbA1C, dynamic exposure (KDE): 0.00 (-0.01, 0.01) HbA1C, static exposure (1,600m buffer): 0.00 (-0.01, 0.01) HOMA-IR, dynamic exposure (KDE): 0.08 (0.03, 0.13) HOMA-IR, dynamic exposure (KDE): Hispanic: 0.13 (0.03, 0.24) HOMA-IR, dynamic exposure (KDE): non-Hispanic: 0.06 (0.00, 0.11) HOMA-IR, static exposure (1,600m buffer): 0.01 (-0.04, 0.06) HOMA-IR, static exposure (1,600m buffer): Hispanic: -0.01 (-0.09, -0.07) HOMA-IR, static exposure (1,600m buffer): non-Hispanic: 0.03 (-0.03, 0.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 11.28 (IQR 1.17)			
† Liu et al. (2023)	Individuals aged 45 years or older; excluded participants who failed to provide fasting blood samples and whose detailed information on sex, marital status, and habits of smoking and drinking were insufficient.	Spatiotemporal/geospatial model r ² = 72% Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average Exposure years: 2011, 2012, 2015	NO ₂ (ppb) Overall Mean = 16.8 (31.6 µg/m ³) Median = 16.5 (IQR 7.65) (31.1 µg/m ³) (IQR 14.4 µg/m ³) Min = 7.65 (14.4 µg/m ³) Max = 35.8 (67.4 µg/m ³)	Elevated FG MetS	Logistic regression Adjusted for: age, gender, education level, marital status, BMI, smoking, drinking, social activity frequency, disability, health insurance, wage income and health status	NO ₂ OR (95% CI) ^b Elevated FG: 3.01 (2.75, 3.30) Elevated FG: Age 45-60 years (stratified models): 2.92 (2.59, 3.30) Elevated FG: Age 45-60 years: 1.10 (0.92, 1.31) Elevated FG: Age ≥60 years (stratified models): 3.16 (2.75, 3.63) Elevated FG: Age ≥60 years: 3.18 (2.78, 3.63) Elevated FG: Drinking status 0 time/month (stratified models): 3.08 (2.78, 3.41) Elevated FG: Drinking status 0: 3.08 (2.78, 3.41) Elevated FG: Drinking status <1 time/month (stratified models): 3.67 (2.51, 5.36) Elevated FG: Drinking status <1 time/month: 3.19 (2.23, 4.55) Elevated FG: Drinking status >1 time/month (stratified models): 2.52 (2.00, 3.17) Elevated FG: Drinking status >1 time/month: 1.21 (0.80, 1.84) Elevated FG: Females (stratified models): 3.16 (2.82, 3.54) Elevated FG: Females: 3.14 (2.81, 3.51) Elevated FG: Health status fair (stratified models): 2.87 (2.54, 3.25) Elevated FG: Health status fair:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						2.84 (2.52, 3.21) Elevated FG: Health status good/very good (stratified models): 2.81 (2.32, 3.41) Elevated FG: Health status good/very good: 1.01 (0.81, 1.25) Elevated FG: Health status poor/very poor (stratified models): 3.62 (1982.56, 0.01) Elevated FG: Health status poor/very poor: 3.67 (3.05, 4.42) Elevated FG: Males (stratified models): 2.74 (2.35, 3.19) Elevated FG: Males: 1.12 (0.93, 1.35)
†Mann et al. (2021) The Children's Health and Air Pollution Study (CHAPS) N = 299 California, U.S. 2015–2017 Cross-Sectional	Children ages 6–8 yr; residence in Fresno or Clovis for at least the past 3 months, residence within 20 km of the central air quality monitoring site, no plans to move from the Fresno/ Clovis area in the next 2 years, English- or Spanish-speaking, and no cancer, HIV, or autoimmune disease	Fixed site monitor, LUR Models for NO ₂ explain 99% of the observed temporal variance and 74% or the observed spatial variance Averaging time: NO ₂ - 1-hour max, NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages	NO ₂ (ppb) 1-Day Lag Mean = 6.98 Median = 5.07 (IQR 6.42) 1-Month Average Mean = 7.17 Median = 6.65 (IQR 6.46) 1-Week Average Mean = 7.19 Median = 6.01 (IQR 6.04) 1-Year Average Mean = 7.6 Median = 7.71 (IQR 1.74)	HbA1c	Generalized additive models Adjusted for: age, sex, SES, household smoking, diet, weight, race/ethnicity	β (%) (95% CI) ^c HbA1c (3-month exposure): 0.05 (0.00, 0.11) β (%) (95% CI) ^b HbA1c (1-year exposure): -0.02 (-0.29, 0.25) HbA1c (6-month exposure): 0.13 (-0.01, 0.27)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		Exposure years: 2013–2017	3-Month Average Mean = 7.3 Median = 6.88 (IQR 6.2)			
			6-Month Average Mean = 7.48 Median = 7.38 (IQR 3.42)			
† Nagrani et al. (2023)	All children attending kindergartens and primary schools were eligible, with at least one available metabolic measurement; excluded ever smokers, those who reported intake of anti-diabetic drugs at baseline or follow-up, those with history of diabetes, those with missing residential address, those with urine sample not available, randomly selected urine samples, and Estonia that did not have ELAPSE model available	LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ not reported quantitatively	HOMA-IR: assessed at the last follow-up examination in 2013–14; calculated as fasting insulin (μIU ml ⁻¹) × FG (mg/dl)/405 HbA1c: assessed at the last follow-up examination in 2013–14 FG: assessed at the last follow-up examination in 2013–14	Linear regression Adjusted for: age, sex, study region, lifetime alcohol status, membership in sport club, screen time/week, parental education status, parental smoking, family history of diabetes	NO ₂ β (%) (95% CI) ^c HbA1c: per IQR: 0.00 (-0.05, 0.05) β (mg/dL) (95% CI) ^c FG: per IQR: -0.03 (-0.08, 0.02) β (NA) (95% CI) ^c HOMA-IR: per IQR: 0.03 -0.04, 0.09)
Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study N = 5,453 Sweden, Spain, Italy, Belgium, Germany, Hungary, Estonia, Cyprus Enrollment: 2009–2010 Follow-up: 2013–2014 Cohort						
† Pedersen et al. (2019)	Random sample of children born mothers with and without GDM	Dispersion model Method validation NR	NO ₂ (μg/m ³) Postnatal Median = 10.7 P5 = 9.3	Clinical examination: HOMA-IR was calculated as follows:	Linear regression Adjusted for: child's age, sex, height, weight, maternal active smoking	β (mmol/L) (95% CI) ^c Plasma fasting glucose: In puberty: No [postnatal exposure]: -0.46 (-0.72, -0.20) Plasma fasting glucose: In puberty:
Danish National Birth Cohort (DNBC)						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 1,234		Averaging time:	P95 = 20.9	((fasting plasma insulin (pmol/L)	during pregnancy,	Yes [postnatal exposure]:
Denmark		Prenatal, 7-yr avg (postnatal)	Prenatal	× fasting plasma glucose (mmol/L))/22.5]	maternal education, household disposable income, area-income	-0.23 (-0.37, -0.09)
Enrollment: 1996–2002		Exposure years:	Median = 11.5			Plasma fasting glucose: Maternal education: High [postnatal exposure]: -0.22 (-0.35, -0.07)
Follow-up: Mar 2012–Apr 2014		1996–2014	P5 = 7.5	× 0.144)		Plasma fasting glucose: Maternal education: Low [postnatal exposure]: -0.29 (-0.66, 0.07)
Cohort			P95 = 28	Clinical examination: A fasting blood sample for glucose measurements was drawn in K-oxalat-Na-fluoride vials. Glucose levels were measured using standard laboratory methods on the Modular P-module.		Plasma fasting glucose: Maternal education: Middle [postnatal exposure]: -0.22 (-0.41, -0.03)
						Plasma fasting glucose: Maternal GDM: No [postnatal exposure]: -0.53 (-0.80, -0.25)
						Plasma fasting glucose: Maternal GDM: Yes [postnatal exposure]: -0.16 (-0.28, -0.04)
						Plasma fasting glucose: Maternal Pre-pregnancy BMI: ≥18.5-25 kg/m ² [postnatal exposure]: -0.32 (-0.53, -0.11)
						Plasma fasting glucose: Maternal Pre-pregnancy BMI: ≥25 kg/m ² [postnatal exposure]: -0.19 (-0.31, -0.06)
				Clinical examination: A fasting blood sample for glucose measurements was drawn in lithium-heparin vials for insulin. Insulin levels were measured using standard laboratory		Plasma fasting glucose: Q1 vs Q1 [REF] (postnatal exposure): 0.00 (0.00, 0.00)
						Plasma fasting glucose: Q1 vs Q1 [REF] (postnatal exposure, coadjusted for road traffic noise): 0.00 (0.00, 0.00)
						Plasma fasting glucose: Q1 vs Q1 [REF] (prenatal exposure): 0.00 (0.00, 0.00)
						Plasma fasting glucose: Q1 vs Q1 [REF] (prenatal exposure,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				methods on the Modular P-module.		coadjusted for road traffic noise): 0.00 (0.00, 0.00) Plasma fasting glucose: Q2 vs Q1 (postnatal exposure): -0.16 (-0.28, -0.04) Plasma fasting glucose: Q2 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.16 (-0.28, -0.04) Plasma fasting glucose: Q2 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -0.03 (-0.15, 0.09) Plasma fasting glucose: Q2 vs Q1 (prenatal exposure): -0.04 (-0.16, 0.08) Plasma fasting glucose: Q3 vs Q1 (postnatal exposure): -0.26 (-0.39, -0.14) Plasma fasting glucose: Q3 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.25 (-0.38, -0.12) Plasma fasting glucose: Q3 vs Q1 (prenatal exposure): -0.24 (-0.36, -0.11) Plasma fasting glucose: Q3 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -0.21 (-0.34, -0.07) Plasma fasting glucose: Q4 vs Q1 (postnatal exposure): -0.37 (-0.50, -0.24) Plasma fasting glucose: Q4 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.34 (-0.49, -0.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Plasma fasting glucose: Q4 vs Q1 (prenatal exposure): -0.34 (-0.47, -0.21) Plasma fasting glucose: Q4 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -0.29 (-0.44, -0.13) Plasma fasting glucose: Road traffic noise: High (>57.5 dB) [postnatal exposure]: -0.42 (-0.77, -0.07) Plasma fasting glucose: Road traffic noise: Low (≤57.5 dB) [postnatal exposure]: -0.15 (-0.27, -0.02) Plasma fasting glucose: Sex: Boys [postnatal exposure]: -0.26 (-0.42, -0.09) Plasma fasting glucose: Sex: Girls [postnatal exposure]: -0.20 (-0.34, -0.05) β (95% CI) ^c HOMA-IR (postnatal exposure): -0.37 (-0.58, -0.20) HOMA-IR: (postnatal exposure, coadjusted for road traffic noise): -0.33 (-0.57, -0.10) HOMA-IR: In puberty: No [postnatal exposure]: -0.38 (-0.88, 0.13) HOMA-IR: In puberty: Yes [postnatal exposure]: -0.41 (-0.68, -0.14) HOMA-IR: Maternal education: High [postnatal exposure]: -0.35 (-0.60, -0.10) HOMA-IR: Maternal education: Low [postnatal exposure]:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-0.71 (-1.36, -0.06)
						HOMA-IR: Maternal education: Middle [postnatal exposure]: -0.33 (-0.67, 0.01)
						HOMA-IR: Maternal GDM: No [postnatal exposure]: -0.54 (-1.04, -0.03)
						HOMA-IR: Maternal GDM: Yes [postnatal exposure]: -0.32 (-0.54, -0.11)
						HOMA-IR: Maternal Pre-pregnancy BMI: ≥ 18.5 -25 kg/m ² [postnatal exposure]: -0.56 (-0.94, -0.18)
						HOMA-IR: Maternal Pre-pregnancy BMI: ≥ 25 kg/m ² [postnatal exposure]: -0.29 (-0.52, -0.06)
						HOMA-IR: Q1 vs Q1 (postnatal exposure) [REF]: 0.00 (0.00, 0.00)
						HOMA-IR: Q1 vs Q1 (postnatal exposure, coadjusted for road traffic noise) [REF]: 0.00 (0.00, 0.00)
						HOMA-IR: Q1 vs Q1 (prenatal exposure) [REF]: 0.00 (0.00, 0.00)
						HOMA-IR: Q1 vs Q1 (prenatal exposure, coadjusted for road traffic noise) [REF]: 0.00 (0.00, 0.00)
						HOMA-IR: Q2 vs Q1 (postnatal exposure): -0.14 (-0.36, 0.09)
						HOMA-IR: Q2 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.13 (-0.36, 0.10)
						HOMA-IR: Q2 vs Q1 (prenatal exposure): 0.10 (-0.12, 0.33)
						HOMA-IR: Q2 vs Q1 (prenatal exposure, coadjusted for road traffic noise): 0.11 (-0.11, 0.33)
						HOMA-IR: Q3 vs Q1 (postnatal

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						exposure): -0.22 (-0.44, 0.01) HOMA-IR: Q3 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.19 (-0.42, 0.05) HOMA-IR: Q3 vs Q1 (prenatal exposure): -0.23 (-0.46, 0.01) HOMA-IR: Q3 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -0.20 (-0.44, 0.04) HOMA-IR: Q4 vs Q1 (postnatal exposure): -0.41 (-0.65, -0.18) HOMA-IR: Q4 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.36 (-0.62, -0.10) HOMA-IR: Q4 vs Q1 (prenatal exposure): -0.39 (-0.63, -0.15) HOMA-IR: Q4 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -0.35 (-0.61, -0.09) HOMA-IR: Road traffic noise: High (>57.5 dB) [postnatal exposure]: -0.55 (-1.19, 0.09) HOMA-IR: Road traffic noise: Low (≤57.5 dB) [postnatal exposure]: -0.38 (-0.61, -0.16) HOMA-IR: Sex: Boys [postnatal exposure]: -0.36 (-0.65, -0.06) HOMA-IR: Sex: Girls [postnatal exposure]: -0.39 (-0.64, -0.12) β (pmol/L) (95% CI) ^c Insulin (postnatal exposure): -2.42 (-4.47, -0.38) Insulin (prenatal exposure): -1.76 (-2.99, -0.53) Insulin: (postnatal exposure, coadjusted for road traffic noise): -2.26 (-4.61, 0.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Insulin: (prenatal exposure, coadjusted for road traffic noise): -1.78 (-3.32, -0.24) Insulin: In puberty: No [postnatal exposure]: -2.54 (-7.59, 2.51) Insulin: In puberty: Yes [postnatal exposure]: -3.44 (-6.13, -0.75) Insulin: Maternal education: High [postnatal exposure]: -2.22 (-4.74, 0.29) Insulin: Maternal education: Low [postnatal exposure]: -7.15 (-13.69, -0.60) Insulin: Maternal education: Middle [postnatal exposure]: -1.65 (-5.08, 1.78) Insulin: Maternal GDM: No [postnatal exposure]: -3.20 (-8.30, 1.89) Insulin: Maternal GDM: Yes [postnatal exposure]: -2.16 (4.35, 0.04) Insulin: Maternal Pre-pregnancy BMI: ≥ 18.5 -25 kg/m ² [postnatal exposure]: -4.16 (-8.02, -0.31) Insulin: Maternal Pre-pregnancy BMI: ≥ 25 kg/m ² [postnatal exposure]: -1.54 (-3.88, 0.79) Insulin: Q1 vs Q1 (postnatal exposure): REF Insulin: Q1 vs Q1 (postnatal exposure, coadjusted for road traffic noise): REF Insulin: Q1 vs Q1 (prenatal exposure): REF Insulin: Q1 vs Q1 (prenatal exposure, coadjusted for road traffic

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						noise): REF
						Insulin: Q2 vs Q1 (postnatal exposure): -0.61 (-2.91, 1.69)
						Insulin: Q2 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.55 (-2.86, 1.75)
						Insulin: Q2 vs Q1 (prenatal exposure): 0.07 (-2.16, 2.30)
						Insulin: Q2 vs Q1 (prenatal exposure, coadjusted for road traffic noise): 0.08 (-2.17, 2.33)
						Insulin: Q3 vs Q1 (postnatal exposure): -0.72 (-3.01, 1.56)
						Insulin: Q3 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -0.52 (-2.89, 1.85)
						Insulin: Q3 vs Q1 (prenatal exposure): -2.46 (-4.81, -0.11)
						Insulin: Q3 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -2.44 (-4.91, 0.03)
						Insulin: Q4 vs Q1 (postnatal exposure): -2.21 (-4.60, 0.18)
						Insulin: Q4 vs Q1 (postnatal exposure, coadjusted for road traffic noise): -1.83 (-4.47, 0.82)
						Insulin: Q4 vs Q1 (prenatal exposure): -3.23 (-5.66, -0.80)
						Insulin: Q4 vs Q1 (prenatal exposure, coadjusted for road traffic noise): -3.18 (-6.01, -0.34)
						Insulin: Road traffic noise: High (>57.5 dB) [postnatal exposure]: -4.15 (-10.58, 2.29)
						Insulin: Road traffic noise: Low (≤57.5 dB) [postnatal exposure]: -2.69 (-4.96, -0.41)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Insulin: Sex: Boys [postnatal exposure]: -1.48 (-4.45, 1.48) Insulin: Sex: Girls [postnatal exposure]: -3.13 (-5.72, -0.53)
† Yu et al. (2020)	Included if participants were 60+ years of age, resided in California Sacramento Valley, and self-identified at Latino. Excluded those who did not participate in baseline visit, had no exposure estimates, already exhibited all 5 components of metabolic syndrome at baseline, who already met the criteria for the designated outcome at baseline, and lacked follow-up visits.	Dispersion model Method validation NR Averaging time: NO _x - annual average Exposure years: 1998–1999	NO _x (ppb) Abdominal Obesity Mean = 2.59±2.17 Median = 2 Min = 0.01 Max = 13.2 P5 = 0.45 P10 = 0.66 P25 = 1.15 P75 = 3.36 P90 = 5.15 P95 = 6.78 Hyperglycemia Mean = 2.5±2.14 Median = 1.81 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.65 P25 = 1.09 P75 = 3.12 P90 = 5.25 P95 = 6.8 Hypertension Mean = 2.55±2.15 Median = 1.85 Min = 0.01 Max = 13.2 P5 = 0.42	Fasting blood draws were performed at baseline and most follow-up visits to assess lipid, triglyceride, glucose and other biomarkers. Borderline elevation of blood glucose [fasting glucose ≥100 mg/dl, or use of glucose-lowering medications]	Cox proportional hazards Adjusted for: baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level	HR (95% CI) ^b Hyperglycemia (coadjusted for 24-hr noise): 0.92 (0.27, 3.14) Hyperglycemia (coadjusted for nighttime noise): 0.92 (0.27, 3.14) Hyperglycemia: 1.09 (0.36, 3.34) OR (95% CI) ^b Hyperglycemia: 1.09 (0.36, 3.34) Hyperglycemia: adjusted for 24-hr noise: 0.92 (0.27, 3.14) Hyperglycemia: adjusted for nighttime noise exposure: 0.92 (0.27, 3.14)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P10 = 0.66 P25 = 1.1 P75 = 3.33 P90 = 5.22 P95 = 7.15 Hypertriglyceridemi a Mean = 2.57±2.14 Median = 1.86 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.67 P25 = 1.17 P75 = 3.29 P90 = 5.31 P95 = 6.75 Low HDL- Cholesterol Mean = 2.64±2.19 Median = 1.95 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.68 P25 = 1.17 P75 = 3.56 P90 = 5.46 P95 = 6.82 Metabolic Syndrome Mean = 2.6±2.2 Median = 1.9 Min = 0.01 Max = 13.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 0.42 P10 = 0.67 P25 = 1.16 P75 = 3.33 P90 = 5.46 P95 = 7 Total Mean = 2.6±2.17 Median = 1.9 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.67 P25 = 1.15 P75 = 3.44 P90 = 5.3 P95 = 6.93			
† Zhang et al. (2021a)	Participants older than 10 years	Spatiotemporal/geospatial model, Hybrid model	NO ₂ (ppb)	Elevated FG	Generalized linear mixed models	NO ₂
Chinese Population			Total	Blood glucose level		OR (95% CI) ^b
N = 9,897		In cross validation, the R ² was 62% for daily estimates of NO ₂	Mean = 20.1 (37.8 µg/m ³) Median = 20.9 (IQR 5) (39.4 µg/m ³ (IQR 9.5 µg/m ³)) Min = 9.99 (18.8 µg/m ³) Max = 31.5 (59.2 µg/m ³)		Adjusted for: age, sex, weight status, temperature, relative humidity, parental education level achieved, parental smoking status, parental alcohol consumption, family histories of type 2 diabetes, hypertension, obesity, or cerebrovascular disease, outdoor physical activity time, diet of high fat, SSBs intake	Blood glucose level: Q1: 1.00 (1.00, 1.00) Blood glucose level: Q2: 4.14 (0.01, 8.43) Blood glucose level: Q3: 9.62 (5.40, 14.01) Blood glucose level: Q4: 144.96 (78.68, 267.07) Elevated FG (Chinese criteria): 2.31 (1.16, 4.61) Elevated FG (NCEP/ATP-III): 0.87 (0.32, 2.41) Elevated FG: 2.31 (1.16, 4.61)
Shanghai, Guangdong Province, Tianjin, Chongqing, China, Liaoning Province, Ningxia, Hunan, China		Averaging time: NO ₂ - 24-hour average				
2013		Exposure years: 2013–2016				
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Zhang et al. (2021b) China Health and Retirement Longitudinal Study (CHARLS) N = 13,013 China Enrollment: 2011–2012 Follow-up: 2015 Cross-Sectional	Participants who completed both questionnaires and blood tests	Hybrid model r ² = 0.78 Averaging time: NO ₂ - annual average Exposure years: 2015	NO ₂ (ppb) Overall Mean = 13 (24 µg/m ³) IQR = 6.579 (12.38 µg/m ³)	HbA1c: Boronate affinity high-performance liquid chromatography method Fasting glucose: Standard enzymatic colorimetric methods (Hexokinase)	Linear regression Adjusted for: age, sex, educational level, BMI, smoking status, packyears for current smokers, drinking frequency, energy types for cooking and heating Copolutant models are additionally adjusted for the copollutant(s) evaluated (O ₃ , PM _{2.5} , or O ₃ and PM _{2.5})	β (%) (95% CI) ^b HbA1c (coadjusted for O ₃): 1.52 (0.83, 2.21) HbA1c (coadjusted for O ₃ +PM _{2.5}): 1.12 (0.29, 1.96) HbA1c (coadjusted for PM _{2.5}): 1.00 (0.17, 1.83) HbA1c: 1.29 (0.73, 1.85) β (mg/dL) (95% CI) ^b Fasting glucose (coadjusted for O ₃): 3.39 (2.15, 4.63) Fasting glucose (coadjusted for O ₃ +PM _{2.5}): 2.25 (0.77, 3.73) Fasting glucose (coadjusted for PM _{2.5}): 2.10 (0.64, 3.56) Fasting glucose: 3.42 (2.42, 4.42)

†Zhang et al. (2022)	Children aged 8–10 yr, residence in Fresno or Clovis for at least the past three months, residence within 20 km of the central air quality monitor site, no plans to move from study area for next two years, English or Spanish speaking, no cancer, HIV, or autoimmune disease	LUR, Fixed site monitor, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, NO _x - 24-hour average, NO _x - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages NO _x - weekly average NO _x - 1, 3, 6-month averages Exposure years: 2019	NO ₂ (ppb) 1-day average Median = 7.31 P25 = 4.12 P75 = 13.54 1-month average Median = 8.98 P25 = 4.33 P75 = 14.05 1-week average Median = 7.92 P25 = 4.53 P75 = 14.58 1-year average Median = 8.3 P25 = 7.23 P75 = 9.4 3-month average Median = 8.48 P25 = 4.46 P75 = 13.75 6-month average Median = 8.72 P25 = 5.64 P75 = 11.65 NO _x (ppb) 1-day average Median = 14.59 P25 = 10.06 P75 = 23.16	Blood specimens were collected by venipuncture by a trained phlebotomist, with serum collected in serum separator tubes and whole blood collected in EDTA vacutainers. % HbA1c measurements were retrieved at room temperature within 24 hr of draw and assayed by a commercial laboratory (LabCorp) using standard clinical laboratory techniques.	GAM Adjusted for: whether or not the child lives with a smoker, whether or not the child is Latinx, physical activity, household income, and a smoothed term for day of study	NO ₂ β (absolute changes in % HbA1c) (95% CI) ^c HbA1c: 1-month average: 0.03 (-0.16, 0.21) HbA1c: 1-week average: -0.08 (-0.17, 0.02) HbA1c: 3-month average: -0.11 (-0.37, 0.14) HbA1c: 6-month average: -0.07 (-0.27, 0.12) β (absolute changes in % HbA1c) (95% CI) ^b HbA1c: 1-day average: -0.13 (-0.30, 0.04) HbA1c: 1-year average: -0.23 (-0.64, 0.18) NO _x β (absolute changes in % HbA1c) (95% CI) ^c HbA1c: 1-month average: -0.01 (-0.17, 0.15) HbA1c: 1-week average: -0.07 (-0.16, 0.02) HbA1c: 3-month average: -0.11 (-0.27, 0.06) HbA1c: 6-month average: -0.06 (-0.19, 0.06) β (absolute changes in % HbA1c) (95% CI) ^b HbA1c: 1-day average: -0.07 (-0.24, 0.10) HbA1c: 1-year average: -0.17 (-0.49, 0.14)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			1-month average Median = 16.59 P25 = 10.79 P75 = 25.48			
			1-week average Median = 17.06 P25 = 10.53 P75 = 23.89			
			1-year average Median = 17.15 P25 = 15.36 P75 = 18.84			
			3-month average Median = 16 P25 = 11.47 P75 = 24.03			
			6-month average Median = 16.38 P25 = 13 P75 = 21.69			

List of Abbreviations: ATP-III = Adult Treatment Panel III; BMI = body mass index; CI = confidence interval; CT = clinical trial; DM = diabetes mellitus; FBG = fasting blood glucose; FG = fasting glucose; GAM = generalized additive model; GDM = gestational diabetes mellitus; GEE = generalized estimating equations; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; HR = hazard ratio; hr = hour; IFG = impaired fasting glycaemia; IQR = interquartile range; KDE = kernel density estimation; LUR = land use regression; max = maximum; MET-hours = metabolic-equivalent hours; MetS = metabolic syndrome; min = minimum; MRC = Medical Research Laboratories; NCEP = National Cholesterol Education Program; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; nSES = neighborhood socioeconomic status; O₃ = ozone; OR = odds ratio; P5 = 5th percentile; P10 = 10th percentile; P25 = 25th percentile; P75 = 75th percentile; P90 = 90th percentile; P95 = 95th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; ppb = parts per billion; Q1 = quartile 1; Q2 = quartile 2; Q3 = quartile 3; Q4 = quartile 4; RR = rate ratio; SES = socioeconomic status; T2DM = type 2 diabetes mellitus; TyG = triglyceride-glucose index; WHI = Women's Health Institute; WHO = World Health Organization.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-4 Animal toxicological studies of oxides of nitrogen exposure and glucose and insulin homeostasis

Study Details and Population	Exposure Details	Endpoints Examined*
† Guo et al. (2023)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6) age not reported, males and females n = 3–10/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	- Blood glucose (fasted) (♀↑) - Glucose tolerance test (AUC) (♀↑) - Insulin resistance index (HOMA-IR) (♀↑) - Insulin tolerance test (AUC) (NS) - Liver glycogen (PAS staining) (♀↓) - Serum insulin (fasted) (♀↑)
Takano et al. (2004)	Whole body inhalation with filtered air controls	0 d after exposure (LETO)
Rat (Otsuka Long-Evans Tokushima Fatty [OLETF] and Long-Evans Tokushima [LETO]) 8-wk-old, males n = 9–14/group	160 ppb (0.16 ppm) NO ₂ , continuous for 32 wk 800 ppb (0.8 ppm) NO ₂ , continuous for 32 wk 4,000 ppb (4.0 ppm) NO ₂ , continuous for 32 wk	0 d after exposure (OLETF) - Blood glucose (non-fasted) (NS) - Blood glucose (non-fasted) (NS)
† Yan et al. (2016)	Whole body inhalation with room air controls	1 d after exposure
Mouse (C57BL/6J) 2-mo-old, males n = 8–10/group	2,660 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 27 d	Serum insulin (fasted) (↑)

List of abbreviations in alphabetical order: AUC = area under curve; d = day; HOMA-IR = homeostasis model of insulin resistance; hr = hour; LETO = Long-Evans Tokushima; mg/m³ = milligrams per cubic meter; n = sample size; NO₂ = nitrogen dioxide; OLETF = Otsuka Long-Evans Tokushima Fatty; PAS = Periodic acid-Schiff; ppb = parts per billion; ppm = parts per million; wk = week

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ♀↑ = results were analyzed by sex and there was a statistically significant increase in at least one female experimental group and non-significant effect in males; ♀↓ = results were analyzed by sex and there was a statistically significant decrease in at least one female experimental group and a non-significant effect in males

†Studies published since the 2016 Oxides of Nitrogen ISA

Appendix Table 8-5 Epidemiologic studies of exposure to oxides of nitrogen and blood lipids

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Chen et al. (2021) n = 62 Research Triangle, NC, U.S. October 2016–September 2019 Panel	Healthy adults 25–55 years of age, with no history of respiratory or cardiovascular disease, non-smoker for year prior, not taking B-adrenergic receptor blockers or anti-inflammatory drugs	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2016–2019	NO ₂ (ppb) Mean = 5.3±3.8 IQR = 3.8 Min = 0.8 Max = 24.2	Total cholesterol LDL HDL	Linear mixed effect model Adjusted for: age, sex, race, BMI, long-term and seasonal trends, day of the week, temperature, and relative humidity	Percent change (95% CI) ^b HDL: high omega-3 group, 5dMA: -16.32 (-32.37, -0.26) HDL: high omega-3 group, 5dMA: -15.79 (-31.84, 0.26) HDL: high omega-3 group, 5dMA: -12.11 (-28.95, 4.74) HDL: high omega-3 group, lag 0: -7.89 (-17.89, 2.11) HDL: high omega-3 group, lag 0: -6.84 (-16.32, 2.63) HDL: high omega-3 group, lag 0: -4.74 (-14.47, 5.00) HDL: high omega-3 group, lag 1: -12.63 (-23.42, -1.84) HDL: high omega-3 group, lag 1: -10.00 (-21.05, 1.05) HDL: high omega-3 group, lag 1: -6.84 (-18.68, 5.00) HDL: high omega-3 group, lag 2: -10.53 (-20.26, -0.79) HDL: high omega-3 group, lag 2: -8.95 (-18.95, 1.05) HDL: high omega-3 group, lag 2: -8.42 (-18.68, 1.84) HDL: high omega-3 group, lag 3: 2.63 (-8.68, 13.95) HDL: high omega-3 group, lag 3: 3.16 (-8.42, 14.74) HDL: high omega-3 group, lag 3: 4.21 (-7.63, 16.05) HDL: high omega-3 group, lag 4: -5.26 (-16.05, 5.53) HDL: high omega-3 group, lag 4:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-4.74 (-15.79, 6.32)
						HDL: high omega-3 group, lag 4:
						-2.11 (-13.95, 9.74)
						HDL: low omega-3 group, 5dMA:
						-13.16 (-31.32, 5.00)
						HDL: low omega-3 group, 5dMA:
						-11.05 (-29.74, 7.63)
						HDL: low omega-3 group, 5dMA:
						-6.32 (-25.79, 13.16)
						HDL: low omega-3 group, lag 0:
						2.63 (-8.95, 14.21)
						HDL: low omega-3 group, lag 0:
						3.16 (-8.68, 15.00)
						HDL: low omega-3 group, lag 0:
						4.21 (-7.63, 16.05)
						HDL: low omega-3 group, lag 1:
						-3.16 (-13.68, 7.37)
						HDL: low omega-3 group, lag 1:
						-2.11 (-12.89, 8.68)
						HDL: low omega-3 group, lag 1:
						3.16 (-8.68, 15.00)
						HDL: low omega-3 group, lag 2:
						-11.58 (-23.16, 0.00)
						HDL: low omega-3 group, lag 2:
						-10.00 (-21.84, 1.84)
						HDL: low omega-3 group, lag 2:
						-9.47 (-21.58, 2.63)
						HDL: low omega-3 group, lag 3:
						-8.42 (-20.00, 3.16)
						HDL: low omega-3 group, lag 3:
						-8.42 (-19.74, 2.89)
						HDL: low omega-3 group, lag 3:
						-7.37 (-19.21, 4.47)
						HDL: low omega-3 group, lag 4:
						-0.53 (-11.05, 10.00)
						HDL: low omega-3 group, lag 4:
						-0.53 (-10.79, 9.74)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						HDL: low omega-3 group, lag 4: 1.58 (-8.95, 12.11) LDL: high omega-3 group, 5dMA: -8.42 (-30.00, 13.16) LDL: high omega-3 group, 5dMA: -7.37 (-28.95, 14.21) LDL: high omega-3 group, 5dMA: -4.21 (-26.58, 18.16) LDL: high omega-3 group, lag 0: -4.21 (-17.11, 8.68) LDL: high omega-3 group, lag 0: -3.68 (-16.58, 9.21) LDL: high omega-3 group, lag 0: -2.63 (-14.74, 9.47) LDL: high omega-3 group, lag 1: -2.63 (-17.37, 12.11) LDL: high omega-3 group, lag 1: 0.53 (-14.47, 15.53) LDL: high omega-3 group, lag 1: 5.79 (-10.26, 21.84) LDL: high omega-3 group, lag 2: -16.32 (-28.95, -3.68) LDL: high omega-3 group, lag 2: -15.26 (-28.16, -2.37) LDL: high omega-3 group, lag 2: -13.68 (-26.84, -0.53) LDL: high omega-3 group, lag 3: 5.26 (-10.53, 21.05) LDL: high omega-3 group, lag 3: 5.79 (-9.21, 20.79) LDL: high omega-3 group, lag 3: 6.32 (-8.42, 21.05) LDL: high omega-3 group, lag 4: -5.26 (-19.47, 8.95) LDL: high omega-3 group, lag 4: -4.74 (-18.95, 9.47) LDL: high omega-3 group, lag 4:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						-4.21 (-19.47, 11.05)
						LDL: low omega-3 group, 5dMA: -1.58 (-26.05, 22.89)
						LDL: low omega-3 group, 5dMA: 2.63 (-22.37, 27.63)
						LDL: low omega-3 group, 5dMA: 4.74 (-21.84, 31.32)
						LDL: low omega-3 group, lag 0: 4.74 (-11.05, 20.53)
						LDL: low omega-3 group, lag 0: 5.79 (-9.21, 20.79)
						LDL: low omega-3 group, lag 0: 6.32 (-9.21, 21.84)
						LDL: low omega-3 group, lag 1: 9.47 (-5.00, 23.95)
						LDL: low omega-3 group, lag 1: 11.05 (-3.42, 25.53)
						LDL: low omega-3 group, lag 1: 18.42 (2.37, 34.47)
						LDL: low omega-3 group, lag 2: -3.16 (-18.42, 12.11)
						LDL: low omega-3 group, lag 2: -0.53 (-16.32, 15.26)
						LDL: low omega-3 group, lag 2: 0.53 (-15.79, 16.84)
						LDL: low omega-3 group, lag 3: -10.00 (-24.74, 4.74)
						LDL: low omega-3 group, lag 3: -9.47 (-24.74, 5.79)
						LDL: low omega-3 group, lag 3: -8.42 (-23.42, 6.58)
						LDL: low omega-3 group, lag 4: -3.68 (-16.84, 9.47)
						LDL: low omega-3 group, lag 4: -3.16 (-16.32, 10.00)
						LDL: low omega-3 group, lag 4: -2.63 (-16.32, 11.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Total cholesterol: high omega-3 group, 5dMA: -9.47 (-25.00, 6.05)
						Total cholesterol: high omega-3 group, 5dMA: -8.95 (-24.47, 6.58)
						Total cholesterol: high omega-3 group, 5dMA: -4.74 (-21.05, 11.58)
						Total cholesterol: high omega-3 group, lag 0: -2.63 (-11.84, 6.58)
						Total cholesterol: high omega-3 group, lag 0: -1.05 (-10.00, 7.89)
						Total cholesterol: high omega-3 group, lag 0: -0.53 (-9.21, 8.16)
						Total cholesterol: high omega-3 group, lag 1: -2.63 (-12.89, 7.63)
						Total cholesterol: high omega-3 group, lag 1: -1.05 (-11.84, 9.74)
						Total cholesterol: high omega-3 group, lag 1: 3.16 (-8.16, 14.47)
						Total cholesterol: high omega-3 group, lag 2: -13.68 (-22.89, -4.47)
						Total cholesterol: high omega-3 group, lag 2: -13.16 (-22.37, -3.95)
						Total cholesterol: high omega-3 group, lag 2: -11.05 (-20.53, -1.58)
						Total cholesterol: high omega-3 group, lag 3: 0.00 (-10.26, 10.26)
						Total cholesterol: high omega-3 group, lag 3: 0.53 (-10.00, 11.05)
						Total cholesterol: high omega-3 group, lag 3: 1.58 (-9.47, 12.63)
						Total cholesterol: high omega-3 group, lag 4: -4.74 (-15.00, 5.53)
						Total cholesterol: high omega-3 group, lag 4: -3.68 (-13.95, 6.58)
						Total cholesterol: high omega-3 group, lag 4: -1.58 (-12.37, 9.21)
						Total cholesterol: low omega-3 group,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						5dMA: -3.68 (-20.79, 13.42) Total cholesterol: low omega-3 group, 5dMA: -1.05 (-18.42, 16.32) Total cholesterol: low omega-3 group, 5dMA: 3.68 (-14.74, 22.11) Total cholesterol: low omega-3 group, lag 0: 3.68 (-7.37, 14.74) Total cholesterol: low omega-3 group, lag 0: 4.21 (-6.58, 15.00) Total cholesterol: low omega-3 group, lag 0: 4.21 (-6.32, 14.74) Total cholesterol: low omega-3 group, lag 1: 5.26 (-4.74, 15.26) Total cholesterol: low omega-3 group, lag 1: 6.32 (-3.68, 16.32) Total cholesterol: low omega-3 group, lag 1: 11.58 (0.53, 22.63) Total cholesterol: low omega-3 group, lag 2: -5.79 (-16.32, 4.74) Total cholesterol: low omega-3 group, lag 2: -3.68 (-14.21, 6.84) Total cholesterol: low omega-3 group, lag 2: -2.63 (-13.68, 8.42) Total cholesterol: low omega-3 group, lag 3: -8.95 (-19.21, 1.32) Total cholesterol: low omega-3 group, lag 3: -7.89 (-18.16, 2.37) Total cholesterol: low omega-3 group, lag 3: -7.37 (-18.16, 3.42) Total cholesterol: low omega-3 group, lag 4: -1.05 (-10.53, 8.42) Total cholesterol: low omega-3 group, lag 4: -1.05 (-10.53, 8.42) Total cholesterol: low omega-3 group, lag 4: 1.05 (-8.68, 10.79)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Eze et al. (2015) Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) n = 3,769 Switzerland Enrollment: 1991 Followup: 2001–2002 Cohort	Random selection of participants from 8 Swiss communities, age 29–73	Hybrid model Averaging time: 10-year mean NO ₂ Exposure years: 1990–2000	NO ₂ (µg/m ³) No metabolic syndrome Mean = 27.2±11.3	IDF/ATP-III definition; Low HDL defined by IDF and ATP-III as <1.03 mmol/L (males), <1.29 mmol/L (females), or treatment for this condition High triglycerides defined as fasting triglycerides ≥1.7 mmol/L or treatment for this condition WHO definition; Low HDL defined by WHO as ≤0.9 mmol/L (males), ≤1.0 mmol/L (females).	Mixed logistic model Adjusted for: age, sex, educational attainment, neighbourhood socio-economic index, occupational exposure to vapours, gases, dusts and fumes, smoking status, exposure to passive smoke, consumption of fruits and raw vegetables, physical activity, BMI	OR (95% CI) ^c High triglycerides: 0.94 (0.85, 1.03) Low high-density lipoproteins (IDF/ATP-III): 0.95 (0.87, 1.05) Low high-density lipoproteins (WHO): 0.88 (0.76, 1.01)
† Fossati et al. (2020) INMA, Infancia y Medio Ambiente N = 1,724 mother-child pairs Sabadell, Valencia, Asturias, Guipuzcoa, Spain Enrollment: 2003–2008 Follow-up: 4 years Cohort	Inclusion criteria were at least 16 years, intention to give birth in the reference hospital, no problems in communication, singleton pregnancy, non-assisted conception.	LUR Method validation NR Averaging time: NO ₂ - weekly averages Exposure years: 2003–2008	NO ₂ (µg/m ³) Asturias Cohort Median = 24.45 (IQR 11) First Trimester of Pregnancy Median = 28.44 (IQR 20.19) P5 = 10.56 P95 = 61.44 Gipuzkoa Cohort Median = 16.97 (IQR 9.33) Sabadell Cohort Median = 35.4 (IQR 14.04)	Lipids z score: TG and HDL levels were measured in blood samples using standard analytical techniques. Age-, sex-, and subcohort-specific z-scores of TG (zTG) and HDL (zHDL) were calculated. A lipid score was computed as the mean of zTG and zHDL, the latter multiplied by –1 due to the inverse association with the cardio-metabolic risk.	Linear regression Adjusted for: sub-cohort, season of birth, and maternal age at delivery, country of origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet	β (z score) (95% CI) ^c Lipid score (1 st trimester): -0.03 (-0.14, 0.07) Lipids score (2 nd trimester): -0.07 (-0.17, 0.03) Lipids score (3 rd trimester): -0.06 (-0.16, 0.05) Lipids score (pregnancy): -0.07 (-0.19, 0.04) Lipids score (1 st year of life): -0.05 (-0.13, 0.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Valencia Cohort Median = 38.9 (IQR 25.16)			
† Gui et al. (2020)	Children aged 7–12 yr; adolescents aged 13–18 yr; excluded those without information on key demographic characteristics and lifestyles	Spatiotemporal/geo spatial model	NO ₂ (ppb)	Hypoalphalipoproteinemia	Generalized linear mixed models	Percent change (95% CI) ^b HDL-C: 1.41 (-1.10, 3.92)
Chinese Population			Chongqing	TC		HDL-C: 6-12 yr: -0.11 (-2.64, 2.42)
N = 12,814		The 10-fold cross validation showed R ² of 62% for daily prediction of NO ₂	Mean = 24±4 (45±8 µg/m ³)	Hypercholesterolemia	Adjusted for: sex, age, body mass index, parental education, parental smoking, outdoor exercise, weight-loss practices, spermathe/menarche, humidity, temperature, season, urban residency (urban or rural), region (south or north), and residuals from regression model of highly correlated pollutants	HDL-C: 13-18 yr: 2.99 (-2.38, 8.36) HDL-C: Additional adjustment for dietary intake: 1.47 (-1.02, 3.95) HDL-C: Additional adjustment for short-term air pollutant levels: 3.41 (-0.08, 6.90)
Shanghai, Guangdong Province, Tianjin, Chongqing, China, Liaoning Province, Ningxia, Hunan, China		Averaging time: NO ₂ - 24-hour average	Guangdong Mean = 23±0.5 (44±1 µg/m ³)	Hypertriglyceridemia		HDL-C: exposure 3 yr average (2011–13): 1.41 (-1.10, 3.92)
2013			Hunan Mean = 11±0.5 (20±1 µg/m ³)	TG		HDL-C: Female: 2.20 (-0.45, 4.85) HDL-C: Male: 0.24 (-2.16, 2.65)
Cross-Sectional		Exposure years: 2013	Liaoning Mean = 15±4 (29±8 µg/m ³)	HDL-C		HDL-C: Normal weight: 1.62 (-1.07, 4.31) HDL-C: Overweight/obesity: -0.09 (-2.78, 2.60)
			Ningxia Mean = 19±2 (36±3 µg/m ³)	LDL-C		Hyperbetalipoproteinemia: 1.45 (0.70, 2.20) Hyperbetalipoproteinemia: 6–12 yr: 1.86 (1.10, 2.62)
			Overall Mean = 21±5 (40±9 µg/m ³) Median = 23 (IQR 4) (44 µg/m ³ (IQR 8 µg/m ³)) Min = 10 (19 µg/m ³) Max = 31 (59 µg/m ³)		Additional adjustment for diet: dietary intake (including sugar-sweetened beverages intake, fried food intake, and meat intake)	Hyperbetalipoproteinemia: 13–18 yr: 0.87 (0.02, 1.71) Hyperbetalipoproteinemia: Female: 1.34 (0.47, 2.20) Hyperbetalipoproteinemia: Male: 1.83 (0.89, 2.76)
			Shanghai		Additional adjustment for short-term air pollutant levels: short-term air pollutant levels (or residuals from regression	Hyperbetalipoproteinemia: Normal weight: 1.43 (0.54, 2.32) Hyperbetalipoproteinemia: Overweight/obesity: 1.64 (0.79, 2.48)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 23±0.5 (44±1 µg/m ³) Tianjin Mean = 25±2 (47±3 µg/m ³)		model of highly correlated short- and long-term pollutants levels)	Hypercholesterolemia: 2.69 (1.86, 3.52) Hypercholesterolemia: 6–12 yr: 2.56 (1.66, 3.46) Hypercholesterolemia: 13–18 yr: 3.50 (1.06, 5.94) Hypercholesterolemia: female: 2.77 (1.77, 3.76) Hypercholesterolemia: male: 2.56 (1.37, 3.74) Hypercholesterolemia: Normal weight: 2.63 (1.74, 3.53) Hypercholesterolemia: Overweight/obesity: 2.58 (1.35, 3.80) Hypertriglyceridemia: 1.49 (1.06, 1.91) Hypertriglyceridemia: 6–12 yr: 2.01 (1.22, 2.80) Hypertriglyceridemia: 13–18 yr: 1.20 (0.83, 1.58) Hypertriglyceridemia: Female: 1.41 (0.96, 1.86) Hypertriglyceridemia: Male: 1.54 (0.93, 2.15) Hypertriglyceridemia: Normal weight: 1.20 (0.82, 1.59) Hypertriglyceridemia: Overweight/obesity: 1.79 (1.26, 2.31) Hypoalphalipoproteinemia: 1.64 (1.29, 1.99) Hypoalphalipoproteinemia: 6–12 yr: 1.77 (1.41, 2.13) Hypoalphalipoproteinemia: 13–18 yr: 1.49 (1.04, 1.93) Hypoalphalipoproteinemia: Female:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						1.49 (1.09, 1.88) Hypoalphalipoproteinemia: Male: 1.81 (1.38, 2.23) Hypoalphalipoproteinemia: Normal weight: 1.56 (1.19, 1.94) Hypoalphalipoproteinemia: Overweight/obesity: 1.88 (1.47, 2.30) LDL-C: -3.54 (-8.59, 1.51) LDL-C: 6-12 yr: -2.60 (-6.64, 1.45) LDL-C: 13-18 yr: -6.15 (-13.76, 1.46) LDL-C: Additional adjustment for dietary intake: -3.50 (-8.61, 1.61) LDL-C: Additional adjustment for short-term air pollutant levels: -5.10 (-11.33, 1.13) LDL-C: exposure three-year average (2011–13): -3.54 (-8.59, 1.51) LDL-C: female: -3.27 (-8.26, 1.71) LDL-C: male: -1.77 (-5.48, 1.95) LDL-C: Normal weight: -3.56 (-8.70, 1.59) LDL-C: Overweight/obesity: -1.58 (-4.93, 1.77) TC: 6–12 yr: 6.60 (0.23, 12.98) TC: 9.88 (2.81, 16.94) TC: 13–18 yr: 11.87 (0.83, 22.92) TC: Additional adjustment for dietary intake: 8.73 (0.36, 17.10) TC: Additional adjustment for short-term air pollutant levels: 10.99 (-0.05, 22.02) TC: Exposure three-year average (2011–13): 9.88 (2.81, 16.94) TC: Female: 10.14 (2.74, 17.55) TC: Male: 9.50 (3.83, 15.18) TC: Normal weight:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						10.10 (2.95, 17.25) TC: Overweight/obesity: 7.30 (1.99, 12.61) TG: -3.20 (-7.28, 0.88) TG: 6–12 yr: -2.31 (-8.37, 3.74) TG: 13–18 yr: -7.96 (-14.25, -1.67) TG: Additional adjustment for dietary intake: -3.31 (-7.24, 0.62) TG: Additional adjustment for short-term air pollutant levels: -0.49 (-6.64, 5.66) TG: exposure three-year average (2011–13): -3.20 (-7.28, 0.88) TG: Female: -3.71 (-7.94, 0.53) TG: Male: -1.32 (-5.20, 2.57) TG: Normal weight: -4.05 (-8.37, 0.28) TG: Overweight/obesity: 1.90 (-3.51, 7.31)
† Holliday et al. (2019) Women’s Health Initiative clinical trials (WHICT) n = 3,915 U.S. Enrollment: 1993–1998 Follow-up: 1993–2004 Cohort	Postmenopausal female volunteers aged 50–79 yr from one of the 76 U.S. examination centers. The present study examines a center- and race-stratified ~6% random, minority oversample of WHI CT participants with repeated measures of fasting glucose, fasting insulin, and geocoded address coordinates. Participants were eligible if they were free	Spatiotemporal/geospatial model Averaging time: NO _x - 24-hour average Exposure years: 1993–2004	NO _x (ppb) Two-day Mean = 40.5 Median = 31.5 P5 = 12.1 P25 = 20.7 P75 = 49.1 P95 = 99.7 Annual Mean = 39.3 Median = 36.3 P5 = 18.9 P25 = 27.5 P75 = 47.8 P95 = 71.5	TG:HDL-C	Linear mixed effect models Adjusted for: clinical trial, sociodemographic, behavioral, clinical, temporal, and meteorological attributes: trial membership, treatment group, age (years), race/ethnicity, education, nSES, smoking, alcohol use, energy expenditure (MET-hours/week), BMI (kg/m ²), family history of diabetes, season, day of	Percent change (95% CI) ^b TG:HDL-C: -0.59 (-3.15, 1.97) TG:HDL-C: -0.21 (-1.43, 1.00) TG:HDL-C: Fasting glucose impaired: -0.11 (-2.54, 2.32) TG:HDL-C: Fasting glucose impaired: 0.00 (-3.99, 3.99) TG:HDL-C: Fasting glucose normal: -0.79 (-3.55, 1.97) TG:HDL-C: Fasting glucose normal: -0.42 (-2.01, 1.16)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	of diabetes at their screening visit and underwent phlebotomy at the screening visit or annual visits 1, 3, or 6 (1993–2004). Participants were included through annual visit 6 unless their WHI follow-up ended or they developed diabetes.				the week, temperature (°C), dew point (°C), and barometric pressure (kPa)	
† Letellier et al. (2022)	Adults, aged 35–80, living for at least 6 months in selected census block groups. Restricted the population to participants with HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data. Participants with missing information on covariates and without air pollution exposure data were excluded.	Fixed site monitor	NO ₂ (ppb)	Triglycerides (mg/dL)	Modified Poisson regression w/ GEE	NO ₂
Community of Mine Study		Correlations between predicted and actual values at the location of the omitted point were used to assess validity of modeled estimates (with a min ρ of 0.55).	Dynamic Exposure Hispanic/Latino Median = 0.0425 (IQR 0.02392) (0.08 $\mu\text{g}/\text{m}^3$ (IQR 0.045 $\mu\text{g}/\text{m}^3$))	Dyslipidemia: presence of one of more of the following conditions: TC ≥ 200 mg/dL, TG ≥ 150 mg/dL, LDL-C ≥ 130 mg/dL or HDL-C < 40 mg/dL	Adjusted for: sex, age, Hispanic/Latino ethnicity, income, smoking status, BMI	RR (95% CI) ^b
N = 552			Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 $\mu\text{g}/\text{m}^3$ (IQR 0.058 $\mu\text{g}/\text{m}^3$))			Dyslipidemia, dynamic exposure (KDE): 1.28 (1.12, 1.46)
San Diego, CA, U.S.						Dyslipidemia, dynamic exposure (KDE): Hispanic: 1.24 (0.96, 1.59)
2014–2017				Cholesterol (mg/dL)		Dyslipidemia, dynamic exposure (KDE): non-Hispanic: 1.28 (1.08, 1.51)
Cross-Sectional		Averaging time: NO ₂ - annual average	Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 $\mu\text{g}/\text{m}^3$ (IQR 1.91 $\mu\text{g}/\text{m}^3$))	LDL cholesterol (mg/dL)		Dyslipidemia, static exposure (1,600 m buffer): 1.02 (0.85, 1.22)
		Exposure years: 2014–2017	Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 $\mu\text{g}/\text{m}^3$ (IQR 1.17 $\mu\text{g}/\text{m}^3$))			Dyslipidemia, static exposure (1,600 m buffer): Hispanic: 1.02 (0.82, 1.27)
			NO ₂ ($\mu\text{g}/\text{m}^3$)			Dyslipidemia, static exposure (1,600 m buffer): non-Hispanic: 0.98 (0.75, 1.28)
						β (mg/dL) (95% CI) ^b
						cholesterol, dynamic exposure (KDE): 9.67 (3.71, 15.64)
						cholesterol, static exposure (1,600 m buffer): 2.69 (-3.12, 8.50)
						LDL cholesterol, dynamic exposure (KDE): 9.03 (3.63, 14.43)
						LDL cholesterol, static exposure

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Dynamic Exposure Hispanic/Latino Median = 0.08 (IQR 0.045) Non-Hispanic Median = 0.092 (IQR 0.058) Static Exposure Hispanic/Latino Median = 9.77 (IQR 1.91) Non-Hispanic Median = 11.28 (IQR 1.17)			(1,600 m buffer): 2.65 (-2.71, 8.02) Triglycerides, dynamic exposure (KDE): 0.13 (0.05, 0.22) Triglycerides, static exposure (1,600 m buffer): 0.09 (0.03, 0.16)
† Liu et al. (2023)	Individuals aged 45 yr or older; excluded participants who failed to provide fasting blood samples and whose detailed information on sex, marital status, and habits of smoking and drinking were insufficient.	Spatiotemporal/geospatial model r ² = 72% Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average Exposure years: 2011, 2012, 2015	NO ₂ (ppb) Overall Mean = 16.8 (31.6 µg/m ³) Median = 16.5 (IQR 7.65) (31.1 µg/m ³) (IQR 14.4 µg/m ³) Min = 7.65 (14.4 µg/m ³) Max = 35.8 (67.4 µg/m ³)	Low HDL-C High TG MetS	Logistic regression Adjusted for: age, gender, education level, marital status, BMI, smoking, drinking, social activity frequency, disability, health insurance, wage income and health status	OR (95% CI) ^b High TG: 2.45 (2.23, 2.69) High TG: Age 45-60 yr (stratified models): 2.14 (1.89, 2.42) High TG: Age 45-60 yr: 1.43 (1.19, 1.72) High TG: Age ≥60 yr (stratified models): 2.92 (2.52, 3.39) High TG: Age ≥60 yr: 3.01 (2.61, 3.48) High TG: Drinking status 0 time/month (stratified models): 2.56 (2.30, 2.85) High TG: Drinking status 0 time/month: 2.56 (2.30, 2.84) High TG: Drinking status <1

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						time/month (stratified models): 2.26 (1.53, 3.33) High TG: Drinking status <1 time/month: 2.01 (1.39, 2.90) High TG: Drinking status >1 time/month (stratified models): 1.98 (1.55, 2.54) High TG: Drinking status >1 time/month: 0.95 (0.61, 1.46) High TG: Females (stratified models): 2.39 (2.13, 2.68) High TG: Females: 2.37 (2.12, 2.66) High TG: Health status fair (stratified models): 2.45 (2.15, 2.79) High TG: Health status fair: 2.45 (2.16, 2.78) High TG: Health status good/very good (stratified models): 2.54 (2.07, 3.12) High TG: Health status good/very good: 0.97 (0.77, 1.22) High TG: Health status poor/very poor (stratified models): 2.37 (1.96, 2.87) High TG: Health status poor/very poor: 2.39 (1.99, 2.87) High TG: Males (stratified models): 2.46 (2.07, 2.91) High TG: Males: 0.91 (0.74, 1.10) Low HDL-C: 3.20 (2.91, 3.52)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Low HDL-C: age 45-60 yr (stratified models): 2.78 (2.45, 3.16) Low HDL-C: Age 45-60 yr: 1.37 (1.14, 1.66) Low HDL-C: Age ≥60 yr (stratified models): 3.93 (3.39, 4.56) Low HDL-C: Age ≥60 years: 3.84 (3.32, 4.45)
						Low HDL-C: Drinking status 0 time/month (stratified models): 3.26 (2.93, 3.63) Low HDL-C: Drinking status 0: 3.23 (2.90, 3.59) Low HDL-C: Drinking status <1 time/month (stratified models): 3.30 (2.23, 4.90) Low HDL-C: Drinking status <1 time/month: 3.05 (2.10, 4.42) Low HDL-C: Drinking status >1 time/month (stratified models): 3.06 (2.34, 4.01) Low HDL-C: Drinking status >1 time/month: 0.98 (0.63, 1.54)
						Low HDL-C: Females (stratified models): 3.05 (2.72, 3.42) Low HDL-C: Females: 2.98 (2.66, 3.34)
						Low HDL-C: Health status fair (stratified models): 3.14 (2.76, 3.58) Low HDL-C: Health status fair: 3.20 (2.82, 3.64)
						Low HDL-C: Health status good/very

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						good (stratified models): 2.94 (2.40, 3.61) Low HDL-C: Health status good/very good: 1.09 (0.86, 1.38) Low HDL-C: Health status poor/very poor (stratified models): 3.68 (3.03, 4.49) Low HDL-C: Health status poor/very poor: 3.47 (2.86, 4.20) Low HDL-C: Males (stratified models): 3.58 (3.01, 4.26) Low HDL-C: Males: 0.80 (0.66, 0.98)
†Nagrani et al. (2023) Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study N = 5,453 Sweden, Spain, Italy, Belgium, Germany, Hungary, Estonia, Cyprus Enrollment: 2009–2010 Follow-up: 2013–2014 Cohort	All children attending kindergartens and primary schools were eligible, with at least one available metabolic measurement; excluded ever smokers, those who reported intake of anti-diabetic drugs at baseline or follow-up, those with history of diabetes, those with missing residential address, those with urine sample not available, randomly selected urine samples, and Estonia that did not have ELAPSE model available	LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ not reported quantitatively	HDL: assessed at the last follow-up examination in 2013–2014 TG: assessed at the last follow-up examination in 2013–2014	Linear regression Adjusted for: age, sex, study region, lifetime alcohol status, membership in sport club, screen time/week, parental education status, parental smoking, family history of diabetes	β (mg/dL) (95% CI) ^c HDL: per IQR: 0.00 (-0.05, 0.05) TG: per IQR: -0.02 (-0.7, 0.03)
†Yu et al. (2020)	Included if participants were 60+ yr of age,	Dispersion model	NO _x (ppb)	Elevated triglycerides ≥150 mg/dL, or use of	Cox proportional hazards	HR (95% CI) ^b Hypertriglyceridemia:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Sacramento Area Latino Study on Aging (SALSA)	resided in California Sacramento Valley, and self-identified as Latino.	Method validation NR	Abdominal Obesity Mean = 2.59±2.17 Median = 2	statins]	Adjusted for: baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation	0.84 (0.23, 3.06) Hypertriglyceridemia: 0.84 (0.23, 3.06)
N = 1,554	Excluded those who did not participate in baseline visit, had no exposure estimates, already exhibited all 5 components of metabolic syndrome at baseline, who already met the criteria for the designated outcome at baseline, and lacked follow-up visits.	Averaging time: NO _x - annual average	Min = 0.01 Max = 13.2 P5 = 0.45 P10 = 0.66 P25 = 1.15 P75 = 3.36 P90 = 5.15 P95 = 6.78	low high-density lipoprotein (HDL) cholesterol [men: <40 mg/dL; women: <50 mg/dL, or use of statins]	during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level	Hypertriglyceridemia: 1.29 (0.40, 4.22) Low HDL-cholesterol: 3.14 (1.15, 8.54) Low HDL-cholesterol: 3.14 (1.15, 8.54) Low HDL-cholesterol: 3.39 (1.37, 8.39)
Sacramento, CA, U.S.		Exposure years: 1998–1999				
Recruitment: 1998–1999						
Follow-up: 2007						
Cohort			Hyperglycemia Mean = 2.5±2.14 Median = 1.81 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.65 P25 = 1.09 P75 = 3.12 P90 = 5.25 P95 = 6.8 Hypertension Mean = 2.55±2.15 Median = 1.85 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.66 P25 = 1.1 P75 = 3.33 P90 = 5.22 P95 = 7.15 Hypertriglyceridemia			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 2.57±2.14 Median = 1.86 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.67 P25 = 1.17 P75 = 3.29 P90 = 5.31 P95 = 6.75			
			Low HDL-Cholesterol Mean = 2.64±2.19 Median = 1.95 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.68 P25 = 1.17 P75 = 3.56 P90 = 5.46 P95 = 6.82			
			Metabolic Syndrome Mean = 2.6±2.2 Median = 1.9 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.67 P25 = 1.16 P75 = 3.33 P90 = 5.46 P95 = 7			
			Total			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 2.6±2.17 Median = 1.9 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.67 P25 = 1.15 P75 = 3.44 P90 = 5.3 P95 = 6.93			
† Zhang et al. (2021a)	Participants older than 10 years	Spatiotemporal/geospatial model, Hybrid model	NO ₂ (ppb)	Low HDL	Generalized linear mixed models	OR (95% CI) ^b
Chinese Population			Total	High TG		High TG (Chinese criteria): 1.04 (0.72, 1.50)
N = 9,897		In cross validation, the r ² was 62% for daily estimates of NO ₂	Mean = 20.1 (37.8 µg/m ³) Median = 20.9 (IQR 5) (39.4 µg/m ³ (IQR 9.5 µg/m ³)) Min = 9.99 (18.8 µg/m ³) Max = 31.5 (59.2 µg/m ³)		Adjusted for: age, sex, weight status, temperature, relative humidity, parental education level achieved, parental smoking status, parental alcohol consumption, family histories of type 2 diabetes, hypertension, obesity, or cerebrovascular disease, outdoor physical activity time, diet of high fat, SSBs intake	High TG (NCEP/ATP-III): 0.89 (0.65, 1.22) High TG: 1.18 (0.76, 1.82) Low HDL (Chinese criteria): 1.00 (0.63, 1.59) Low HDL (NCEP/ATP-III): 1.14 (0.73, 1.76) Low HDL: 1.12 (0.71, 1.74)
Shanghai, Guangdong Province, Tianjin, Chongqing, China, Liaoning Province, Ningxia, Hunan, China		Averaging time: NO ₂ - 24-hour average				
2013		Exposure years: 2013–2016				
Cross-Sectional						
† Zhang et al. (2021b)	Participants who completed both questionnaires and blood tests	Hybrid model	NO ₂ (ppb)	Triglyceride: Standard enzymatic colorimetric methods (Oxidase method)	linear regression	OR (95% CI) ^b
China Health and Retirement Longitudinal Study (CHARLS)		r ² = 0.78	Overall		Adjusted for: age, sex, educational level, BMI, smoking status, packyears for current smokers, drinking	Dyslipidemia: Age: 21-64 yr: 1.16 (0.92, 1.45) Dyslipidemia: Age: ≥65 yr: 1.47 (1.14, 1.90) Dyslipidemia: Drinking status: Non-drinker: 1.27 (1.04, 1.55)
N = 13,013		Averaging time: NO ₂ - annual average	Mean = 13 (24 µg/m ³) IQR = 6.579 (12.38 µg/m ³)	LDL: Standard enzymatic colorimetric methods (Direct method)		

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
China Enrollment: 2011–2012 Follow-up: 2015 Cross-Sectional		Exposure years: 2015		Dyslipidemia, male	frequency, energy types for cooking and heating	Dyslipidemia: Sex: Female: 1.17 (0.16, 8.51)
				Dyslipidemia, Non-smoker	Copolutant models are additionally adjusted for the copollutant(s) evaluated (O ₃ , PM _{2.5} , or O ₃ and PM _{2.5})	Dyslipidemia: Sex: Male: 1.39 (1.08, 1.78)
				Dyslipidemia, non-drinker		Dyslipidemia: Drinking status: Drinker: 1.29 (0.95, 1.74)
				Dyslipidemia, BMI 18.5–24.9		Dyslipidemia: Age: Smoking status: non-smoker: 1.17 (0.93, 1.48)
				Dyslipidemia, BMI ≥25	Logistic regression	Dyslipidemia: BMI: 18.5-24.9 kg/m ² : 1.29 (1.00, 1.65)
				Dyslipidemia, female	Adjusted for: age, sex, educational level, BMI, smoking status, packyears for current smokers, drinking frequency, energy types for cooking and heating	Dyslipidemia: BMI: <18.5 kg/m ² : 1.27 (0.33, 4.92)
				Prevalent Dyslipidemia: the ratio of cholesterol to HDL ≥5.0 or using lipid-lowering medications.		Dyslipidemia: BMI: ≥25 kg/m ² : 1.25 (1.00, 1.58)
				Cholesterol: Standard enzymatic colorimetric methods (Oxidase method)		Dyslipidemia: smoking status: smoker: 1.39 (1.08, 1.78)
				Dyslipidemia, BMI <18.5	Copolutant models are additionally adjusted for the copollutant(s) evaluated (O ₃ , PM _{2.5} , or O ₃ and PM _{2.5})	Prevalent Dyslipidemia (self-report): 1.51 (1.28, 1.77)
				Dyslipidemia, drinker		Prevalent Dyslipidemia (self-report): 1.56 (1.32, 1.84)
				Dyslipidemia, Smoker		Prevalent Dyslipidemia (self-report): 1.65 (1.47, 1.85)
				Dyslipidemia, ≥65		Prevalent Dyslipidemia (self-report): 1.74 (1.53, 1.99)
				Prevalent Dyslipidemia: Self-reported dyslipidemia was evaluated based on the question: "Have you ever been diagnosed with dyslipidemia?"		Prevalent Dyslipidemia: 1.20 (1.02, 1.42)
						Prevalent Dyslipidemia: 1.22 (1.09, 1.37)
						Prevalent Dyslipidemia: 1.27 (1.07, 1.50)
						Prevalent Dyslipidemia: 1.42 (1.24, 1.63)
						β (mg/dL) (95% CI) ^b
						Cholesterol: -2.75 (-3.53, -1.98)
						Cholesterol: -0.99 (-2.14, 0.17)
						Cholesterol: -0.12 (-1.30, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				HDL: Standard enzymatic colorimetric methods (Direct method)		Cholesterol: -0.09 (-1.06, 0.88) HDL: -4.74 (-5.78, -3.71) HDL: -4.50 (-5.76, -3.24) HDL: -4.19 (-5.43, -2.96) HDL: -3.91 (-4.76, -3.05)
				Dyslipidemia, 21–64 yrs		LDL: -2.83 (-3.99, -1.66) LDL: 0.12 (-1.63, 1.87) LDL: 0.93 (-0.54, 2.39) LDL: 1.29 (-0.49, 3.08) Triglyceride: 0.74 (-1.36, 2.85) Triglyceride: 5.20 (2.53, 7.87) Triglyceride: 5.82 (2.62, 9.02) Triglyceride: 7.02 (3.75, 10.29)

† Zhang et al. (2022)	Children aged 8–10 years, residence in Fresno or Clovis for at least the past three months, residence within 20 km of the central air quality monitor site, no plans to move from study area for next two years, English or Spanish speaking, no cancer, HIV, or autoimmune disease	LUR, Fixed site monitor, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average, NO _x - 24-hour average, NO _x - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages NO _x - weekly average NO _x - 1, 3, 6-month averages Exposure years: 2019	NO ₂ (ppb) 1-day average Median = 7.31 P25 = 4.12 P75 = 13.54 1-month average Median = 8.98 P25 = 4.33 P75 = 14.05 1-week average Median = 7.92 P25 = 4.53 P75 = 14.58 1-year average Median = 8.3 P25 = 7.23 P75 = 9.4 3-month average Median = 8.48 P25 = 4.46 P75 = 13.75 6-month average Median = 8.72 P25 = 5.64 P75 = 11.65 NO _x (ppb) 1-day average Median = 14.59 P25 = 10.06 P75 = 23.16	HDL	GAM Adjusted for: living with a smoker, whether or not the child is hispanic, physical activity, household income, and a smoothed term for day of study	β (mg/dL) (95% CI) ^c HDL: -15.40 (-27.40, -3.40) HDL: -7.90 (-15.40, -0.40) HDL: -3.10 (-6.30, 0.10)
The Children's Health and Air Pollution Study (CHAPS)						
N = 218						
Fresno, CA, U.S.						
2015–2017						
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			1-month average Median = 16.59 P25 = 10.79 P75 = 25.48			
			1-week average Median = 17.06 P25 = 10.53 P75 = 23.89			
			1-year average Median = 17.15 P25 = 15.36 P75 = 18.84			
			3-month average Median = 16 P25 = 11.47 P75 = 24.03			
			6-month average Median = 16.38 P25 = 13 P75 = 21.69			

List of Abbreviations: 5dMA = 5-day moving average; ATP-III = Adult Treatment Panel III; BMI = body mass index; CI = confidence interval; GAM = generalized additive model; HDL = high-density lipoproteins; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; IDF = International Diabetes Federation; IQR = interquartile range; KDE = kernel density estimation; LDL = low-density lipoproteins; LDL-C = low-density lipoprotein cholesterol; LUR = land use regression; max = maximum; MetS = metabolic syndrome; MET-hours = metabolic equivalent hours; min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; nSES = neighborhood socioeconomic status; O₃ = ozone; OR = odds ratio; P5 = 5th percentile; P10 = 10th percentile; P25 = 25th percentile; P75 = 75th percentile; P90 = 90th percentile; P95 = 95th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; ppb = parts per billion; RR = rate ratio; TC = total cholesterol; TG = triglycerides; WHO = World Health Organization; yr = year; zHDL = z-score of high-density lipoproteins; zTG = z-score of triglycerides.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-6 Animal toxicological studies of oxides of nitrogen exposure and blood lipids

Study Details and Population	Exposure Details	Endpoints Examined*
† Farraj et al. (2016)	Whole body inhalation with filtered air controls	24 hr after exposure
Rat (Spontaneously Hypertensive) 12-wk-old, males n = 6/group	500 ppb (0.5 ppm) NO ₂ , continuous for 3 hr	• Serum HDL cholesterol (↓) • Serum LDL cholesterol (NS) • Serum triglycerides (NS)
† Guo et al. (2023)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6) age not reported, males and females n = 3–10/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	• Liver free fatty acids (♀↑) • Liver lipids (oil red O staining) (♀↑) • Liver total cholesterol (♀↑) • Liver triglycerides (♀↑) • Serum VLDL (♀↑) • Serum total cholesterol (♀↑) • Serum triglycerides (♀↑)
Takano et al. (2004)	Whole body inhalation with filtered air controls	0 d after exposure (LETO)
Rat (Otsuka Long-Evans Tokushima Fatty [OLETF] and Long-Evans Tokushima [LETO]) 8-wk-old, males n = 9–14/group	160 ppb (0.16 ppm) NO ₂ , continuous for 32 wk 800 ppb (0.8 ppm) NO ₂ , continuous for 32 wk 4,000 ppb (4.0 ppm) NO ₂ , continuous for 32 wk	• Blood HDL cholesterol (↓) • Blood HDL/total cholesterol ratio (NS) • Blood total cholesterol (NS) • Blood triglycerides (NS)
		0 d after exposure (OLETF)
		• Blood HDL cholesterol (↓) • Blood HDL/total cholesterol ratio (↓) • Blood total cholesterol (NS) • Blood triglycerides (↑)

List of abbreviations in alphabetical order: d = day; HDL = high-density lipoprotein; hr = hour; n = sample size; LDL = low-density lipoprotein; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; VLDL = very-low-density lipoprotein; wk = week.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ♀↑ = results were analyzed by sex and there was a statistically significant increase in at least one female experimental group and non-significant effect in males.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-7 Epidemiologic studies of exposure to oxides of nitrogen and adiposity and weight gain

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Eze et al. (2015) Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) n = 3769 Switzerland Enrollment: 1991 Follow-up: 2001–2002 Cohort	Random selection of participants from 8 Swiss communities, age 29-73	Hybrid model Averaging time: 10-year mean NO₂ Exposure years: 1990–2000	NO₂ (µg/m³) No metabolic syndrome Mean = 27.2±11.3	Defined using the predicted waist circumference and European cut-offs (≥94cm for males and ≥80cm for females) BMI >30kg/m²	Mixed logistic model Adjusted for: age, sex, educational attainment, neighbourhood socio-economic index, occupational exposure to vapours, gases, dusts and fumes, smoking status, smoked pack-years, exposure to passive smoke, consumption of fruits and raw vegetables, physical activity	OR (95% CI)^c Central obesity (BMI >30kg/m²): 1.01 (0.89, 1.14) Central obesity: 1.06 (0.90, 1.26)
†Fossati et al. (2020) INMA, Infancia y Medio Ambiente N = 1, 724 mother-child pairs Sabadell, Valencia, Asturias, Guipuzcoa, Spain Enrollment: 2003–2008 Follow-up: 4 years Cohort	Inclusion criteria were at least 16 years, intention to give birth in the reference hospital, no problems in communication, singleton pregnancy, non-assisted conception.	LUR Method validation NR Averaging time: NO₂ - weekly averages Exposure years: 2003–2008	NO₂ (µg/m³) Asturias Cohort Median = 24.45 (IQR 11) First Trimester of Pregnancy Median = 28.44 (IQR 20.19) P5 = 10.56 P95 = 61.44 Gipuzkoa Cohort Median = 16.97 (IQR 9.33)	zWC	Linear regression Adjusted for: sub-cohort, season of birth, and maternal age at delivery, country of origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet	β (score) (95% CI)^c zWC (1st year of life): 0.02 (-0.08, 0.12) zWC (2nd trimester): -0.05 (-0.16, 0.07) zWC (3rd trimester): -0.08 (-0.20, 0.05) zWC (pregnancy): -0.05 (-0.18, 0.09) zWC: 0.02 (-0.11, 0.15)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Sabadell Cohort Median = 35.4 (IQR 14.04)			
			Valencia Cohort Median = 38.9 (IQR 25.16)			
† Letellier et al. (2022)	Adults, aged 35-80, living for at least 6 months in selected census block groups. Restricted the population to participants with HOMA-IR, diabetes, hypertension, obesity, dyslipidemia, and MetS data. Participants with missing information on covariates and without air pollution exposure data were excluded.	Fixed site monitor Correlations between predicted and actual values at the location of the omitted point were used to assess validity of modeled estimates (with a min ρ of 0.55). Averaging time: NO ₂ - annual average Exposure years: 2014–2017	NO ₂ (ppb) Dynamic Exposure Hispanic/Latino Median = 0.0425 (IQR 0.02392) (0.08 $\mu\text{g}/\text{m}^3$ (IQR 0.045 $\mu\text{g}/\text{m}^3$)) Non-Hispanic Median = 0.04889 (IQR 0.03082) (0.092 $\mu\text{g}/\text{m}^3$ (IQR 0.058 $\mu\text{g}/\text{m}^3$)) Static Exposure Hispanic/Latino Median = 5.19 (IQR 1.02) (9.77 $\mu\text{g}/\text{m}^3$ (IQR 1.91 $\mu\text{g}/\text{m}^3$)) Non-Hispanic Median = 5.995 (IQR 0.622) (11.28 $\mu\text{g}/\text{m}^3$ (IQR 1.17 $\mu\text{g}/\text{m}^3$)) NO ₂ ($\mu\text{g}/\text{m}^3$) Dynamic Exposure Hispanic/Latino	BMI (kg/m^2) Obesity: BMI >30 kg/m^2	Modified Poisson regression w/ GEE Adjusted for: sex, age, Hispanic/Latino ethnicity, income, smoking status	NO ₂ RR (95% CI) ^c Obesity, dynamic exposure (KDE): 1.21 (1.10, 1.33) Obesity, dynamic exposure (KDE): Hispanic: 1.22 (1.05, 1.42) Obesity, dynamic exposure (KDE): non-Hispanic: 1.18 (1.03, 1.35) Obesity, static exposure (1, 600m buffer): 0.90 (0.79, 1.02) Obesity, static exposure (1, 600m buffer): Hispanic: 0.93 (0.77, 1.11) Obesity, static exposure (1, 600m buffer): non-Hispanic: 0.90 (0.72, 1.13) β (kg/m^2) (95% CI) ^c BMI, dynamic exposure (KDE): 0.65 (0.18, 1.12) BMI, static exposure (1, 600m buffer): -0.25 (-0.72, 0.22)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 0.08 (IQR 0.045) Non-Hispanic Median = 0.092 (IQR 0.058) Static Exposure Hispanic/Latino Median = 9.77 (IQR 1.91) Non-Hispanic Median = 11.28 (IQR 1.17)			
† Liu et al. (2023)	Individuals aged 45 years or older; excluded participants who failed to provide fasting blood samples and whose detailed information on sex, marital status, and habits of smoking and drinking were insufficient.	Spatiotemporal/geospatial model r ² = 72% Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average Exposure years: 2011, 2012, 2015	NO ₂ (ppb) Overall Mean = 16.8 (31.6 µg/m ³) Median = 16.5 (IQR 7.65) (31.1 µg/m ³) (IQR 14.4 µg/m ³) Min = 7.65 (14.4 µg/m ³) Max = 35.8 (67.4 µg/m ³)	Central obesity MetS	Logistic regression Adjusted for: age, gender, education level, marital status, BMI, smoking, drinking, social activity frequency, disability, health insurance, wage income and health status	NO ₂ OR (95% CI) ^b Central obesity: 2.65 (2.33, 3.01) Central obesity: age 45-60 years (stratified models): 2.46 (2.07, 2.92) Central obesity: age 45-60 years: 1.15 (0.89, 1.49) Central obesity: age ≥60 years (stratified models): 2.89 (2.38, 3.52) Central obesity: age ≥60 years: 2.86 (2.35, 3.48) Central obesity: drinking status 0 (stratified models): 2.56 (2.21, 2.96) Central obesity: drinking status 0: 2.53 (2.18, 2.93) Central obesity: drinking status <1 time/month (stratified models): 4.03 (2.29, 7.09) Central obesity: drinking status <1 time/month: 3.59 (2.18, 5.92) Central obesity: drinking status >1 time/month (stratified models): 2.81

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						(2.03, 3.89) Central obesity: drinking status >1 time/month: 1.25 (0.70, 2.26) Central obesity: females (stratified models): 2.84 (2.41, 3.34) Central obesity: females: 2.80 (2.37, 3.30) Central obesity: health status fair (stratified models): 2.89 (2.42, 3.45) Central obesity: health status fair: 2.86 (2.40, 3.42) Central obesity: health status good/very good (stratified models): 2.47 (1.88, 3.24) Central obesity: health status good/very good: 1.15 (0.84, 1.58) Central obesity: health status poor/very poor (stratified models): 2.41 (1.85, 3.14) Central obesity: health status poor/very poor: 2.35 (1.81, 3.05) Central obesity: males (stratified models): 2.35 (1.89, 2.90) Central obesity: males: 1.15 (0.88, 1.49)
†Mann et al. (2021)	Children ages 6–8; residence in Fresno or Clovis for at least the past 3 months, residence within 20 km of the central air quality monitoring site, no plans to move from the Fresno/ Clovis area in the next 2 years, English- or Spanish-	Fixed site monitor, LUR Models for NO ₂ explain 99% of the observed temporal variance and 74% or the observed spatial variance Averaging time:	NO ₂ (ppb) 1-Day Lag Mean = 6.98 Median = 5.07 (IQR 6.42) 1-Month Average Mean = 7.17 Median = 6.65 (IQR 6.46)	Waist-Height Ratio Percent Body Fat BMI	Generalized additive models Adjusted for: age, sex, SES, household smoking, diet, weight, race/ethnicity	% change (95% CI) ^c BMI (3-month exposure): 3.49 (-1.80, 9.05) % change (95% CI) ^b BMI (1-year exposure): 9.10 (-13.22, 31.43) BMI (6-month exposure): 11.69 (-0.81, 24.18) β (%) (95% CI) ^c
The Children’s Health and Air Pollution Study (CHAPS)						
N = 299						
California, U.S.						
2015–2017						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cross-Sectional	speaking, and no cancer, HIV, or autoimmune disease	NO ₂ - 1-hour max, NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages Exposure years: 2013–2017	1-Week Average Mean = 7.19 Median = 6.01 (IQR 6.04) 1-Year Average Mean = 7.6 Median = 7.71 (IQR 1.74) 3-Month Average Mean = 7.3 Median = 6.88 (IQR 6.2) 6-Month Average Mean = 7.48 Median = 7.38 (IQR 3.42)			Percent Body Fat (3-month exposure): 0.55 (-1.77, 2.87) β (%) (95% CI) ^b Percent Body Fat (1-year exposure): 2.30 (-9.30, 13.91) Percent Body Fat (6-month exposure): 1.73 (-4.26, 7.71) β (ratio) (95% CI) ^c Waist-Height Ratio (3-month exposure): 0.01 (-0.01, 0.02) β (ratio) (95% CI) ^b Waist-Height Ratio (1-year exposure): 0.10 (0.00, 0.20) Waist-Height Ratio (6-month exposure): 0.01 (-0.03, 0.06)
†Nagrani et al. (2023) Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS) and I. Family Study N = 5, 453 Sweden, Spain, Italy, Belgium, Germany, Hungary, Estonia, Cyprus Enrollment: 2009–2010 Follow-up: 2013–2014	All children attending kindergartens and primary schools were eligible, with at least one available metabolic measurement; excluded ever smokers, those who reported intake of anti-diabetic drugs at baseline or follow-up, those with history of diabetes, those with missing residential address, those with urine sample not available, randomly	LUR, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ not reported quantitatively	WC: assessed at the last follow-up examination in 2013–14	linear regression Adjusted for: age, sex, study region, lifetime alcohol status, membership in sport club, screen time/week, parental education status, parental smoking, family history of diabetes	NO ₂ β (cm) (95% CI) ^c WC: per IQR: -0.02 (-0.08, 0.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort	selected urine samples, and Estonia that did not have ELAPSE model available					
† White et al. (2016) Black Women's Health Study (BWHS) N = 38, 374 U.S. Enrollment: 1995 Follow-up: 1997–2011 Cohort	Black women, aged 21–69 years; women were excluded at baseline if they were >55 years, did not live in any of 56 metropolitan areas in the US, had a history of cancer at baseline or during follow-up, reported baseline weight <80 pounds or >300 pounds, had a history of gastric bypass surgery, had no follow-up, or had no pollutant data.	Hybrid model r ² = 0.80 Averaging time: NO ₂ - annual average Exposure years: 2000–2010	NO ₂ (ppb) Overall Mean = 18.5±6.5	Mean weight change	Linear mixed models Adjusted for: diet (Western and prudent), menopausal status, education level, smoking status, vigorous activity, everyday racism, height, age, neighborhood SES, weight at age 18 years, and time Adjusted for: diet (Western and prudent), menopausal status, education level, smoking status, vigorous activity, everyday racism, lifetime racism, height, age, neighborhood SES, weight at age 18 years, and time	β (kg) (95% CI) ^b Mean weight change: -0.52 (-0.79, -0.24) Mean weight change: BMI, 25 to <30: -0.06 (-0.60, 0.47) Mean weight change: BMI, <25: -0.79 (-0.88, -0.71) Mean weight change: BMI, ≥30: -0.57 (-1.10, -0.04) Mean weight change: Neighborhood SES, at median: -0.54 (-0.93, -0.14) Mean weight change: Neighborhood SES, at Q1: -0.69 (-1.08, -0.30) Mean weight change: Neighborhood SES, at Q3: -0.37 (-0.76, 0.02) Mean weight change: SES and NO ₂ correlation, high r >0.5: -1.43 (-2.97, 0.10) Mean weight change: SES and NO ₂ correlation, low r ≤0.3: -0.29 (-0.77, 0.20) Mean weight change: SES and NO ₂ correlation, moderate 0.3 <r ≤0.5: -0.80 (-1.45, -0.16)
† Yu et al. (2020) Sacramento Area Latino Study on Aging (SALSA) N = 1, 554	Included if participants were 60+ years of age, resided in California Sacramento Valley, and self-identified at Latino. Excluded those who did not participate	Dispersion model Method validation NR Averaging time: NO _x - annual	NO _x (ppb) Abdominal Obesity Mean = 2.59±2.17 Median = 2 Min = 0.01 Max = 13.2	abdominal obesity [waist circumference of ≥40 in. in men; ≥35 in. in women]	Cox proportional hazards Adjusted for: baseline age, gender, years of education, neighborhood	HR (95% CI) ^b Abdominal Obesity: 0.30 (0.07, 1.26) Abdominal Obesity coadjusted for 24-hour noise exposure: 0.30 (0.06, 1.45) Abdominal Obesity coadjusted for

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Sacramento, CA, U.S. Recruitment: 1998–1999 Follow-up: 2007 Cohort	in baseline visit, had no exposure estimates, already exhibited all 5 components of metabolic syndrome at baseline, who already met the criteria for the designated outcome at baseline, and lacked follow-up visits.	average Exposure years: 1998–1999	P5 = 0.45 P10 = 0.66 P25 = 1.15 P75 = 3.36 P90 = 5.15 P95 = 6.78 Hyperglycemia Mean = 2.5±2.14 Median = 1.81 Min = 0.01 Max = 13.2 P5 = 0.37 P10 = 0.65 P25 = 1.09 P75 = 3.12 P90 = 5.25 P95 = 6.8 Hypertension Mean = 2.55±2.15 Median = 1.85 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.66 P25 = 1.1 P75 = 3.33 P90 = 5.22 P95 = 7.15 Hypertriglyceridemi a Mean = 2.57±2.14 Median = 1.86 Min = 0.01 Max = 13.2		socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level	Nighttime noise exposure: 0.30 (0.06, 1.45)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 0.37 P10 = 0.67 P25 = 1.17 P75 = 3.29 P90 = 5.31 P95 = 6.75 Low HDL-Cholesterol Mean = 2.64±2.19 Median = 1.95 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.68 P25 = 1.17 P75 = 3.56 P90 = 5.46 P95 = 6.82 Metabolic Syndrome Mean = 2.6±2.2 Median = 1.9 Min = 0.01 Max = 13.2 P5 = 0.42 P10 = 0.67 P25 = 1.16 P75 = 3.33 P90 = 5.46 P95 = 7 Total Mean = 2.6±2.17 Median = 1.9 Min = 0.01 Max = 13.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 0.42 P10 = 0.67 P25 = 1.15 P75 = 3.44 P90 = 5.3 P95 = 6.93			
[†] Zhang et al. (2021a)	Participants older than 10 years	Spatiotemporal/geospatial model, Hybrid model	NO ₂ (ppb)	Abdominal obesity	Generalized linear mixed models	NO ₂
Chinese Population			Total			OR (95% CI) ^b
N = 9, 897		In cross validation, the R ² was 62% for daily estimates of NO ₂	Mean = 20.1 (37.8 µg/m ³) Median = 20.9 (IQR 5) (39.4 µg/m ³ (IQR 9.5 µg/m ³)) Min = 9.99 (18.8 µg/m ³) Max = 31.5 (59.2 µg/m ³)	Waist circumference	Adjusted for: age, sex, weight status, temperature, relative humidity, parental education level achieved, parental smoking status, parental alcohol consumption, family histories of type 2 diabetes, hypertension, obesity, or cerebrovascular disease, outdoor physical activity time, diet of high fat, SSBs intake	Abdominal obesity (Chinese criteria): 1.99 (1.45, 2.73) Abdominal obesity (distinguish between the age groups 10- <16 years and 16+ years in IDF definition): 1.71 (1.26, 2.33) Abdominal obesity (NCEP/ATP III): 1.99 (1.45, 2.73) Abdominal obesity: 1.99 (1.45, 2.73) Waist circumference: Q1: 1.00 (1.00, 1.00) Waist circumference: Q2: -0.07 (-1.48, 1.34) Waist circumference: Q3: 2.41 (1.04, 3.78) Waist circumference: Q4: 2.44 (1.08, 3.81)
Shanghai, Guangdong Province, Tianjin, Chongqing, China, Liaoning Province, Ningxia, Hunan, China		Averaging time: NO ₂ - 24-hour average				
2013		Exposure years: 2013–2016				
Cross-Sectional						

List of Abbreviations: BMI = Body mass index; CI = Confidence interval; HR = Hazard ratio; IQR = Interquartile Range; LUR = Land use regression; MetS = Metabolic syndrome; NO = Nitric oxide; NO₂ = Nitrogen dioxide; NO_x = Nitrogen oxides; O₃ = Ozone; OR = Odds ratio; PA = Physical activity; P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile; P95 = 95th percentile; PM_{2.5} = Particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = Particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = Parts per billion; r² = Coefficient of determination; RR = Rate ratio; WC = Waist circumference.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-8 Epidemiologic studies of exposure to oxides of nitrogen and cause-specific mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Diabetes Mortality						
† Brunekreef et al. (2021) ; Strak et al. (2021)	Pooled analysis of data from eight well-established ESCAPE cohorts and analysis of seven large administrative cohorts in Europe.	LUR, Chemical transport model, Hybrid model r ² = 58% Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) CEANS-SALT Cohort Mean = 11.31±3.28 (21.29±6.18 µg/m ³) Median = 11.17 (IQR 3.9) (21.02 µg/m ³ (IQR 7.33 µg/m ³)) Min = 1.58 (2.98 µg/m ³) Max = 26.85 (50.53 µg/m ³) P5 = 5.958 (11.21 µg/m ³) P25 = 9.327 (17.55 µg/m ³) P75 = 13.22 (24.88 µg/m ³) P95 = 16.94 (31.87 µg/m ³) CEANS-SDPP Cohort Mean = 8.259±2.28 (15.54±4.29 µg/m ³) Median = 8.269 (IQR 2.86) (15.56 µg/m ³ (IQR 5.38 µg/m ³)) Min = 1.57 (2.96 µg/m ³) Max = 19.71 (37.09 µg/m ³) P5 = 4.15 (7.81 µg/m ³) P25 = 6.792 (12.78 µg/m ³) P75 = 9.651 (18.16 µg/m ³)	Diabetes mortality: 249–250 (ICD-9) and E10–E14 (ICD-10)	Cox proportional hazard model Adjusted for: age, sex (strata), year of enrolment, smoking status, duration and intensity of smoking, body mass index, marital status, employment status, neighbourhood or municipal level mean income in 2001	HR (95% CI) ^b Belgian cohort: 0.81 (0.76, 0.87) Danish cohort: 1.20 (1.13, 1.28) Diabetes mortality: 1.49 (1.22, 1.83) Dutch cohort: 0.95 (0.89, 1.02) English cohort: 0.99 (0.78, 1.27) Meta-analysis of administrative cohorts: 1.02 (0.92, 1.14) Norwegian cohort: 1.08 (1.00, 1.16) Rome cohort: 1.01 (0.94, 1.08) Swiss cohort: 1.15 (1.07, 1.24)
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), E3N cohort, European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Heinz Nixdorf Recall study (HNR), KORA, Danish Nurse Cohort (DNC), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese						
n = Unsure						
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands						
Recruitment: 1992–2011 Follow-up: 2011–2017						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m ³) P95 = 11.94 (22.46 µg/m ³) CEANS-SIXTY Cohort Mean = 10.99±3.26 (20.68±6.13 µg/m ³) Median = 10.92 (IQR 4) (20.54 µg/m ³ (IQR 7 µg/m ³)) Min = 1.42 (2.68 µg/m ³) Max = 25.45 (47.88 µg/m ³) P5 = 5.69 (10.7 µg/m ³) P25 = 9.051 (17.03 µg/m ³) P75 = 12.77 (24.03 µg/m ³) P95 = 16.62 (31.28 µg/m ³) CEANS-SNACK Cohort Mean = 14.56±2.71 (27.39±5.09 µg/m ³) Median = 15.1 (IQR 3.92) (28.5 µg/m ³ (IQR 7.38 µg/m ³)) Min = 6.176 (11.62 µg/m ³) Max = 22.65 (42.61 µg/m ³) P5 = 9.71 (18.27 µg/m ³) P25 = 12.52 (23.56 µg/m ³) P75 = 16.45 (30.95 µg/m ³) P95 = 18.04 (33.94			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) DCH Cohort Mean = 14.9±3.64 (28.04±6.84 µg/m³) Median = 15.05 (IQR 5.3) (28.32 µg/m³ (IQR 10 µg/m³)) Min = 3.4 (6.4 µg/m³) Max = 38.39 (72.23 µg/m³) P5 = 8.79 (16.54 µg/m³) P25 = 12.36 (23.26 µg/m³) P75 = 17.68 (33.26 µg/m³) P95 = 20.31 (38.22 µg/m³) DNC-1999 Cohort Mean = 13.74±4.5 (25.85±8.47 µg/m³) Median = 12.63 (IQR 7.345) (23.76 µg/m³ (IQR 13.82 µg/m³)) Min = 3.41 (6.42 µg/m³) Max = 28.84 (54.26 µg/m³) P5 = 7.286 (13.71 µg/m³) P25 = 10.32 (19.42 µg/m³) P75 = 17.67 (33.24 µg/m³) P95 = 20.7 (38.95 µg/m³) DNC-1993 Cohort Mean = 11.6±4 (21.9±8			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) Median = 10.83 (IQR 5.591) (20.37 µg/m³ (IQR 10.52 µg/m³)) Min = 2.41 (4.54 µg/m³) Max = 38.39 (72.23 µg/m³) P5 = 5.41 (10.18 µg/m³) P25 = 8.689 (16.35 µg/m³) P75 = 14.28 (26.87 µg/m³) P95 = 19.7 (37.07 µg/m³)			
			E3N Cohort Mean = 14.01±5.18 (26.36±9.75 µg/m³) Median = 13.06 (IQR 6.664) (24.57 µg/m³ (IQR 12.54 µg/m³)) Min = 1.84 (3.46 µg/m³) Max = 43.06 (81.02 µg/m³) P5 = 7.12 (13.4 µg/m³) P25 = 10.27 (19.32 µg/m³) P75 = 16.93 (31.86 µg/m³) P95 = 24.23 (45.59 µg/m³)			
			EPIC-NL-MORGEN Cohort Mean = 18.36±3.22 (34.55±6.05 µg/m³) Median = 17.9 (IQR 4.77) (33.6 µg/m³ (IQR			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			8.97 µg/m ³) Min = 5.8 (11 µg/m ³) Max = 36.49 (68.66 µg/m ³) P5 = 13.91 (26.18 µg/m ³) P25 = 15.93 (29.97 µg/m ³) P75 = 20.69 (38.94 µg/m ³) P95 = 23.8 (44.8 µg/m ³)			
			EPIC-NL-PROSPECT Cohort Mean = 19.11±2.88 (35.96±5.41 µg/m ³) Median = 18.85 (IQR 3.86) (35.46 µg/m ³ (IQR 7.27 µg/m ³)) Min = 10.41 (19.58 µg/m ³) Max = 33.03 (62.15 µg/m ³) P5 = 14.6 (27.4 µg/m ³) P25 = 17.28 (32.52 µg/m ³) P75 = 21.15 (39.79 µg/m ³) P95 = 23.72 (44.63 µg/m ³)			
			HNR Cohort Mean = 20.08±2.48 (37.78±4.66 µg/m ³) Median = 19.95 (IQR 2.67) (37.54 µg/m ³ (IQR 5.03 µg/m ³)) Min = 13.41 (25.23			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m ³) Max = 39.9 (75.07 µg/m ³) P5 = 16.61 (31.26 µg/m ³) P25 = 18.53 (34.87 µg/m ³) P75 = 21.2 (39.9 µg/m ³) P95 = 24.36 (45.83 µg/m ³) KORA-S3 Cohort Mean = 11.23±1.8 (21.13±3.3 µg/m ³) Median = 11.14 (IQR 2.3) (20.97 µg/m ³ (IQR 4.32 µg/m ³)) Min = 5.538 (10.42 µg/m ³) Max = 22.17 (41.72 µg/m ³) P5 = 8.66 (16.3 µg/m ³) P25 = 10.03 (18.88 µg/m ³) P75 = 12.34 (23.21 µg/m ³) P95 = 14.04 (26.41 µg/m ³) KORA-S4 Cohort Mean = 11.19±1.8 (21.05±3.39 µg/m ³) Median = 11.06 (IQR 2.39) (20.82 µg/m ³ (IQR 4.49 µg/m ³)) Min = 5.14 (9.68 µg/m ³) Max = 22.17 (41.72 µg/m ³) P5 = 9.97 (18.76 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 12.35 (23.24 $\mu\text{g}/\text{m}^3$) P75 = 14.1 (26.5 $\mu\text{g}/\text{m}^3$) P95 = 22.17 (41.72 $\mu\text{g}/\text{m}^3$) Pooled Cohort Mean = 13 $\pm$ 4.28 (25 $\pm$ 8.05 $\mu\text{g}/\text{m}^3$) Median = 12.83 (IQR 5.394) (24.14 $\mu\text{g}/\text{m}^3$ (IQR 10.15 $\mu\text{g}/\text{m}^3$)) Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$) P5 = 6.861 (12.91 $\mu\text{g}/\text{m}^3$) P25 = 10.37 (19.52 $\mu\text{g}/\text{m}^3$) P75 = 15.77 (29.68 $\mu\text{g}/\text{m}^3$) P95 = 21.01 (39.53 $\mu\text{g}/\text{m}^3$) VHM&PP Cohort Mean = 11.67 $\pm$ 2.84 (21.96 $\pm$ 5.34 $\mu\text{g}/\text{m}^3$) Median = 11.94 (IQR 3.71) (22.46 $\mu\text{g}/\text{m}^3$ (IQR 6.99 $\mu\text{g}/\text{m}^3$)) Min = 2.05 (3.85 $\mu\text{g}/\text{m}^3$) Max = 25.66 (48.28 $\mu\text{g}/\text{m}^3$) P5 = 6.532 (12.29 $\mu\text{g}/\text{m}^3$) P25 = 9.901 (18.63 $\mu\text{g}/\text{m}^3$) P75 = 13.62 (25.62 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P95 = 15.8 (29.7 µg/m ³)			
			NO ₂ (µg/m ³)			
			CEANS-SALT Cohort			
			Mean = 21.29±6.18			
			Median = 21.02 (IQR 7.33)			
			Min = 2.98			
			Max = 50.53			
			P5 = 11.21			
			P25 = 17.55			
			P75 = 24.88			
			P95 = 31.87			
			CEANS-SDPP Cohort			
			Mean = 15.54±4.29			
			Median = 15.56 (IQR 5.38)			
			Min = 2.96			
			Max = 37.09			
			P5 = 7.81			
			P25 = 12.78			
			P75 = 18.16			
			P95 = 22.46			
			CEANS-SIXTY Cohort			
			Mean = 20.68±6.13			
			Median = 20.54 (IQR 7)			
			Min = 2.68			
			Max = 47.88			
			P5 = 10.7			
			P25 = 17.03			
			P75 = 24.03			
			P95 = 31.28			
			CEANS-SNACK Cohort			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 27.39±5.09 Median = 28.5 (IQR 7.38) Min = 11.62 Max = 42.61 P5 = 18.27 P25 = 23.56 P75 = 30.95 P95 = 33.94 DCH Cohort Mean = 28.04±6.84 Median = 28.32 (IQR 10) Min = 6.4 Max = 72.23 P5 = 16.54 P25 = 23.26 P75 = 33.26 P95 = 38.22 DNC-1999 Cohort Mean = 25.85±8.47 Median = 23.76 (IQR 13.82) Min = 6.42 Max = 54.26 P5 = 13.71 P25 = 19.42 P75 = 33.24 P95 = 38.95 DNC-1993 Cohort Mean = 21.9±8 Median = 20.37 (IQR 10.52) Min = 4.54 Max = 72.23			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 10.18 P25 = 16.35 P75 = 26.87 P95 = 37.07 E3N Cohort Mean = 26.36±9.75 Median = 24.57 (IQR 12.54) Min = 3.46 Max = 81.02 P5 = 13.4 P25 = 19.32 P75 = 31.86 P95 = 45.59 EPIC-NL-MORGEN Cohort Mean = 34.55±6.05 Median = 33.6 (IQR 8.97) Min = 11 Max = 68.66 P5 = 26.18 P25 = 29.97 P75 = 38.94 P95 = 44.8 EPIC-NL-PROSPECT Cohort Mean = 35.96±5.41 Median = 35.46 (IQR 7.27) Min = 19.58 Max = 62.15 P5 = 27.4 P25 = 32.52			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 39.79 P95 = 44.63 HNR Cohort Mean = 37.78±4.66 Median = 37.54 (IQR 5.03) Min = 25.23 Max = 75.07 P5 = 31.26 P25 = 34.87 P75 = 39.9 P95 = 45.83 KORA-S3 Cohort Mean = 21.13±3.3 Median = 20.97 (IQR 4.32) Min = 10.42 Max = 41.72 P5 = 16.3 P25 = 18.88 P75 = 23.21 P95 = 26.41 KORA-S4 Cohort Mean = 21.05±3.39 Median = 20.82 (IQR 4.49) Min = 9.68 Max = 41.72 P5 = 18.76 P25 = 23.24 P75 = 26.5 P95 = 41.72 Pooled Cohort			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 25±8.05 Median = 24.14 (IQR 10.15) Min = 2.68 Max = 81.02 P5 = 12.91 P25 = 19.52 P75 = 29.68 P95 = 39.53 VHM&PP Cohort Mean = 21.96±5.34 Median = 22.46 (IQR 6.99) Min = 3.85 Max = 48.28 P5 = 12.29 P25 = 18.63 P75 = 25.62 P95 = 29.7			
† Brunekreef et al. (2021) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), E3N cohort, European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Heinz Nixdorf Recall study (HNR), KORA, Danish Nurse Cohort (DNC), EPIC Monitoring Project on Risk Factors and Chronic	Pooled analysis of data from eight well-established ESCAPE cohorts and analysis of seven large administrative cohorts in Europe.	LUR, Chemical transport model, Hybrid model $r^2 = 58\%$ Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) CEANS-SALT Cohort Mean = 11.31±3.28 (21.29±6.18 µg/m ³) Median = 11.17 (IQR 3.9) (21.02 µg/m ³ (IQR 7.33 µg/m ³)) Min = 1.58 (2.98 µg/m ³) Max = 26.85 (50.53 µg/m ³) P5 = 5.958 (11.21 µg/m ³) P25 = 9.327 (17.55 µg/m ³) P75 = 13.22 (24.88 µg/m ³)	diabetes mortality: 249-250 (ICD-9) and E10-E14 (ICD-10)	Cox proportional hazard model Adjusted for: age, sex (strata), year of enrolment, smoking status, duration and intensity of smoking, body mass index, marital status, employment status, neighbourhood or municipal level mean income in 2001	HR (95% CI) ^b Belgian cohort: 0.81 (0.76, 0.87) Danish cohort: 1.20 (1.13, 1.28) Diabetes mortality: 1.49 (1.22, 1.83) Dutch cohort: 0.95 (0.89, 1.02) English cohort: 0.99 (0.78, 1.27) Meta-analysis of administrative cohorts: 1.02 (0.92, 1.14) Norwegian cohort: 1.08 (1.00, 1.16) Rome cohort: 1.01 (0.94, 1.08) Swiss cohort: 1.15 (1.07, 1.24)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese			P95 = 16.94 (31.87 $\mu\text{g}/\text{m}^3$)			
n = Unsure			CEANS-SDPP Cohort Mean = 8.259 $\pm$ 2.28 (15.54 $\pm$ 4.29 $\mu\text{g}/\text{m}^3$) Median = 8.269 (IQR 2.86) (15.56 $\mu\text{g}/\text{m}^3$ (IQR 5.38 $\mu\text{g}/\text{m}^3$)) Min = 1.57 (2.96 $\mu\text{g}/\text{m}^3$) Max = 19.71 (37.09 $\mu\text{g}/\text{m}^3$) P5 = 4.15 (7.81 $\mu\text{g}/\text{m}^3$) P25 = 6.792 (12.78 $\mu\text{g}/\text{m}^3$) P75 = 9.651 (18.16 $\mu\text{g}/\text{m}^3$) P95 = 11.94 (22.46 $\mu\text{g}/\text{m}^3$)			
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands			CEANS-SIXTY Cohort Mean = 10.99 $\pm$ 3.26 (20.68 $\pm$ 6.13 $\mu\text{g}/\text{m}^3$) Median = 10.92 (IQR 4) (20.54 $\mu\text{g}/\text{m}^3$ (IQR 7 $\mu\text{g}/\text{m}^3$)) Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 25.45 (47.88 $\mu\text{g}/\text{m}^3$) P5 = 5.69 (10.7 $\mu\text{g}/\text{m}^3$) P25 = 9.051 (17.03 $\mu\text{g}/\text{m}^3$) P75 = 12.77 (24.03 $\mu\text{g}/\text{m}^3$) P95 = 16.62 (31.28 $\mu\text{g}/\text{m}^3$)			
Recruitment: 1992–2011 Follow-up: 2011–2017						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			CEANS-SNACK Cohort Mean = 14.56±2.71 (27.39±5.09 µg/m ³) Median = 15.1 (IQR 3.92) (28.5 µg/m ³ (IQR 7.38 µg/m ³)) Min = 6.176 (11.62 µg/m ³) Max = 22.65 (42.61 µg/m ³) P5 = 9.71 (18.27 µg/m ³) P25 = 12.52 (23.56 µg/m ³) P75 = 16.45 (30.95 µg/m ³) P95 = 18.04 (33.94 µg/m ³)			
			DCH Cohort Mean = 14.9±3.64 (28.04±6.84 µg/m ³) Median = 15.05 (IQR 5.3) (28.32 µg/m ³ (IQR 10 µg/m ³)) Min = 3.4 (6.4 µg/m ³) Max = 38.39 (72.23 µg/m ³) P5 = 8.79 (16.54 µg/m ³) P25 = 12.36 (23.26 µg/m ³) P75 = 17.68 (33.26 µg/m ³) P95 = 20.31 (38.22 µg/m ³)			
			DNC-1999 Cohort Mean = 13.74±4.5			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			(25.85±8.47 µg/m ³) Median = 12.63 (IQR 7.345) (23.76 µg/m ³ (IQR 13.82 µg/m ³)) Min = 3.41 (6.42 µg/m ³) Max = 28.84 (54.26 µg/m ³) P5 = 7.286 (13.71 µg/m ³) P25 = 10.32 (19.42 µg/m ³) P75 = 17.67 (33.24 µg/m ³) P95 = 20.7 (38.95 µg/m ³)			
			DNC-1993 Cohort Mean = 11.6±4 (21.9±8 µg/m ³) Median = 10.83 (IQR 5.591) (20.37 µg/m ³ (IQR 10.52 µg/m ³)) Min = 2.41 (4.54 µg/m ³) Max = 38.39 (72.23 µg/m ³) P5 = 5.41 (10.18 µg/m ³) P25 = 8.689 (16.35 µg/m ³) P75 = 14.28 (26.87 µg/m ³) P95 = 19.7 (37.07 µg/m ³)			
			E3N Cohort Mean = 14.01±5.18 (26.36±9.75 µg/m ³) Median = 13.06 (IQR 6.664) (24.57 µg/m ³ (IQR 12.54 µg/m ³)) Min = 1.84 (3.46 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$) P5 = 7.12 (13.4 $\mu\text{g}/\text{m}^3$) P25 = 10.27 (19.32 $\mu\text{g}/\text{m}^3$) P75 = 16.93 (31.86 $\mu\text{g}/\text{m}^3$) P95 = 24.23 (45.59 $\mu\text{g}/\text{m}^3$) EPIC-NL-MORGEN Cohort Mean = 18.36 $\pm$ 3.22 (34.55 $\pm$ 6.05 $\mu\text{g}/\text{m}^3$) Median = 17.9 (IQR 4.77) (33.6 $\mu\text{g}/\text{m}^3$ (IQR 8.97 $\mu\text{g}/\text{m}^3$)) Min = 5.8 (11 $\mu\text{g}/\text{m}^3$) Max = 36.49 (68.66 $\mu\text{g}/\text{m}^3$) P5 = 13.91 (26.18 $\mu\text{g}/\text{m}^3$) P25 = 15.93 (29.97 $\mu\text{g}/\text{m}^3$) P75 = 20.69 (38.94 $\mu\text{g}/\text{m}^3$) P95 = 23.8 (44.8 $\mu\text{g}/\text{m}^3$) EPIC-NL-PROSPECT Cohort Mean = 19.11 $\pm$ 2.88 (35.96 $\pm$ 5.41 $\mu\text{g}/\text{m}^3$) Median = 18.85 (IQR 3.86) (35.46 $\mu\text{g}/\text{m}^3$ (IQR 7.27 $\mu\text{g}/\text{m}^3$)) Min = 10.41 (19.58 $\mu\text{g}/\text{m}^3$) Max = 33.03 (62.15 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) P5 = 14.6 (27.4 µg/m³) P25 = 17.28 (32.52 µg/m³) P75 = 21.15 (39.79 µg/m³) P95 = 23.72 (44.63 µg/m³) HNR Cohort Mean = 20.08±2.48 (37.78±4.66 µg/m³) Median = 19.95 (IQR 2.67) (37.54 µg/m³ (IQR 5.03 µg/m³)) Min = 13.41 (25.23 µg/m³) Max = 39.9 (75.07 µg/m³) P5 = 16.61 (31.26 µg/m³) P25 = 18.53 (34.87 µg/m³) P75 = 21.2 (39.9 µg/m³) P95 = 24.36 (45.83 µg/m³) KORA-S3 Cohort Mean = 11.23±1.8 (21.13±3.3 µg/m³) Median = 11.14 (IQR 2.3) (20.97 µg/m³ (IQR 4.32 µg/m³)) Min = 5.538 (10.42 µg/m³) Max = 22.17 (41.72 µg/m³) P5 = 8.66 (16.3 µg/m³) P25 = 10.03 (18.88			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			$\mu\text{g}/\text{m}^3$ P75 = 12.34 (23.21 $\mu\text{g}/\text{m}^3$) P95 = 14.04 (26.41 $\mu\text{g}/\text{m}^3$)			
			KORA-S4 Cohort Mean = 11.19 $\pm$ 1.8 (21.05 $\pm$ 3.39 $\mu\text{g}/\text{m}^3$) Median = 11.06 (IQR 2.39) (20.82 $\mu\text{g}/\text{m}^3$ (IQR 4.49 $\mu\text{g}/\text{m}^3$)) Min = 5.14 (9.68 $\mu\text{g}/\text{m}^3$) Max = 22.17 (41.72 $\mu\text{g}/\text{m}^3$) P5 = 9.97 (18.76 $\mu\text{g}/\text{m}^3$) P25 = 12.35 (23.24 $\mu\text{g}/\text{m}^3$) P75 = 14.1 (26.5 $\mu\text{g}/\text{m}^3$) P95 = 22.17 (41.72 $\mu\text{g}/\text{m}^3$)			
			Pooled Cohort Mean = 13 $\pm$ 4.28 (25 $\pm$ 8.05 $\mu\text{g}/\text{m}^3$) Median = 12.83 (IQR 5.394) (24.14 $\mu\text{g}/\text{m}^3$ (IQR 10.15 $\mu\text{g}/\text{m}^3$)) Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$) P5 = 6.861 (12.91 $\mu\text{g}/\text{m}^3$) P25 = 10.37 (19.52 $\mu\text{g}/\text{m}^3$) P75 = 15.77 (29.68 $\mu\text{g}/\text{m}^3$) P95 = 21.01 (39.53 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) VHM&PP Cohort Mean = 11.67±2.84 (21.96±5.34 µg/m³) Median = 11.94 (IQR 3.71) (22.46 µg/m³ (IQR 6.99 µg/m³)) Min = 2.05 (3.85 µg/m³) Max = 25.66 (48.28 µg/m³) P5 = 6.532 (12.29 µg/m³) P25 = 9.901 (18.63 µg/m³) P75 = 13.62 (25.62 µg/m³) P95 = 15.8 (29.7 µg/m³) NO₂ (µg/m³) CEANS-SALT Cohort Mean = 21.29±6.18 Median = 21.02 (IQR 7.33) Min = 2.98 Max = 50.53 P5 = 11.21 P25 = 17.55 P75 = 24.88 P95 = 31.87 CEANS-SDPP Cohort Mean = 15.54±4.29 Median = 15.56 (IQR 5.38) Min = 2.96 Max = 37.09			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 7.81 P25 = 12.78 P75 = 18.16 P95 = 22.46 CEANS-SIXTY Cohort Mean = 20.68±6.13 Median = 20.54 (IQR 7) Min = 2.68 Max = 47.88 P5 = 10.7 P25 = 17.03 P75 = 24.03 P95 = 31.28 CEANS-SNACK Cohort Mean = 27.39±5.09 Median = 28.5 (IQR 7.38) Min = 11.62 Max = 42.61 P5 = 18.27 P25 = 23.56 P75 = 30.95 P95 = 33.94 DCH Cohort Mean = 28.04±6.84 Median = 28.32 (IQR 10) Min = 6.4 Max = 72.23 P5 = 16.54 P25 = 23.26 P75 = 33.26 P95 = 38.22 DNC-1999 Cohort			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 25.85±8.47 Median = 23.76 (IQR 13.82) Min = 6.42 Max = 54.26 P5 = 13.71 P25 = 19.42 P75 = 33.24 P95 = 38.95 DNC-1993 Cohort Mean = 21.9±8 Median = 20.37 (IQR 10.52) Min = 4.54 Max = 72.23 P5 = 10.18 P25 = 16.35 P75 = 26.87 P95 = 37.07 E3N Cohort Mean = 26.36±9.75 Median = 24.57 (IQR 12.54) Min = 3.46 Max = 81.02 P5 = 13.4 P25 = 19.32 P75 = 31.86 P95 = 45.59 EPIC-NL-MORGEN Cohort Mean = 34.55±6.05 Median = 33.6 (IQR 8.97)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 11 Max = 68.66 P5 = 26.18 P25 = 29.97 P75 = 38.94 P95 = 44.8			
			EPIC-NL-PROSPECT Cohort Mean = 35.96±5.41 Median = 35.46 (IQR 7.27) Min = 19.58 Max = 62.15 P5 = 27.4 P25 = 32.52 P75 = 39.79 P95 = 44.63			
			HNR Cohort Mean = 37.78±4.66 Median = 37.54 (IQR 5.03) Min = 25.23 Max = 75.07 P5 = 31.26 P25 = 34.87 P75 = 39.9 P95 = 45.83			
			KORA-S3 Cohort Mean = 21.13±3.3 Median = 20.97 (IQR 4.32) Min = 10.42 Max = 41.72 P5 = 16.3			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 18.88 P75 = 23.21 P95 = 26.41 KORA-S4 Cohort Mean = 21.05±3.39 Median = 20.82 (IQR 4.49) Min = 9.68 Max = 41.72 P5 = 18.76 P25 = 23.24 P75 = 26.5 P95 = 41.72 Pooled Cohort Mean = 25±8.05 Median = 24.14 (IQR 10.15) Min = 2.68 Max = 81.02 P5 = 12.91 P25 = 19.52 P75 = 29.68 P95 = 39.53 VHM&PP Cohort Mean = 21.96±5.34 Median = 22.46 (IQR 6.99) Min = 3.85 Max = 48.28 P5 = 12.29 P25 = 18.63 P75 = 25.62 P95 = 29.7			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Crouse et al. (2015) Canadian Census Health and Environment Cohort (CanCHEC) n = 301,115 Nationwide, Canada Enrollment: 1991 Follow-up: 1991–2006 Cohort	Non-institutionalized individuals 25 years of age and older and residing in Canada in 1991.	LUR $r^2 = 0.43$ Averaging time: NO ₂ - 7-yr MA; 1-yr lag Exposure years: 1984–2006	NO ₂ (ppb) Mean = 11.6 Median = 10.4 (IQR 10.5) Min = 0 Max = 51.5 P25 = 6 P75 = 16.5	ICD-9: 250; ICD-10: E10–E14	Cox proportional hazard models Adjusted for: age, sex, Aboriginal ancestry, visible minority status, highest level of education, employment status, occupational class, immigrant status, marital status, income quintile. Census division and census tract–census division percent of immigrants, percent of adults without high school diploma, percent of subjects in lowest income quintile	HR (95% CI) ^b Diabetes mortality: 1.05 (1.00, 1.10)
†Gariazzo et al. (2023) n = 1,769, 660 Italy 2013–2015 Time-series	Daily mortality counts (natural, cardiovascular, cardiac, ischemic, cerebrovascular, respiratory, mental, nervous, metabolic, diabetes) classified using ICD-10 codes from the Italian National Institute of Statistics	Hybrid model Cross-validation at $R^2 = 0.6$ Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2015	NO ₂ (ppb) Rural Mean = 6.27 (11.8 µg/m ³) Median = 5 (IQR 3.9 (9.5 µg/m ³ (IQR 7.3 µg/m ³)) Min = 1.4 (2.7 µg/m ³) Max = 39.2 (73.7 µg/m ³) P25 = 3.8 (7.1 µg/m ³) P75 = 7.65 (14.4 µg/m ³) Suburban Mean = 10.5 (19.8 µg/m ³) Median = 9.35 (IQR 6.01) (17.6 µg/m ³ (IQR 11.3 µg/m ³))	Mortality data retrieved from the Italian National Institute of Statistics (diabetes [E10–E14])	Over-dispersed Poisson generalized additive model Adjusted for: municipality-specific long-term seasonal time trends and day of the week, as well as province-specific air temperature, bank holidays, summer population decreases and influenza epidemics	IR (converted from %IR) (95% CI) ^b lag: 0-5: 1.14 (0.65, 1.99) lag: 0-1: 1.28 (0.50, 3.33) lag: 2-5: 1.01 (0.59, 1.73)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 2.3 (4.4 µg/m ³) Max = 56.02 (105.4 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 12.9 (24.2 µg/m ³) Urban Mean = 15.8 (29.7 µg/m ³) Median = 14.7 (IQR 8.29) (27.6 µg/m ³ (IQR 15.6 µg/m ³)) Min = 3.2 (6.1 µg/m ³) Max = 61.6 (115.9 µg/m ³) P25 = 11.2 (21.1 µg/m ³) P75 = 19.5 (36.7 µg/m ³) Mean = 7.81 (14.7 µg/m ³) Median = 6.32 (IQR 5.74) (11.9 µg/m ³ (IQR 10.8 µg/m ³)) Min = 1.4 (2.7 µg/m ³) Max = 61.6 (115.9 µg/m ³) P25 = 4 (8 µg/m ³) P75 = 9.99 (18.8 µg/m ³)			
†Kang et al. (2023) National Health Information Databases (NHID), Korea n = 121, 423 South Korea Enrollment: January 2009–December 2009 Follow-up: January 2010–	All patients aged ≥40 years with diagnosis of COPD at enrollment	Spatiotemporal/geo spatial model 10-fold cross-validation (r ² of NO ₂ in 2009 was 0.50). Averaging time: NO ₂ - annual average	NO ₂ (ppb) 1-year Median = 19.6 (36.9 µg/m ³) P25 = 16 (30 µg/m ³) P75 = 25.6 (48.2 µg/m ³) 3-year Median = 19.9 (37.5 µg/m ³) P25 = 16.2 (30.4 µg/m ³)	Diabetes mellitus (E10-14); cause of death from the South Korean NHIS-NHID database was linked to the death certificate information from the	Cox proportional hazard models Adjusted for: baseline age, sex, income level, BMI (continuous), smoking status, Charlson Comorbidity Index (CCI) at the time of COPD diagnosis, and the presence of	HR (95% CI) ^b 1 year: 1.06 (0.94, 1.20) 3 year: 1.13 (0.99, 1.28) 5 year: 1.12 (0.94, 1.32)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
December 2018 Cohort		Exposure years: January 1, 2009– December 31, 2013	P75 = 26.5 (49.8 µg/m ³) 5-year Median = 20.5 (38.5 µg/m ³) P25 = 16.2 (30.5 µg/m ³) P75 = 27.7 (52.1 µg/m ³)	National Statistical Office	exacerbation (none, moderate, and severe)	
† Lim et al. (2018) NIH-AARP Diet and Health Study N = 50, 700 Atlanta, GA, Pennsylvania, California, North Carolina, Florida, Louisiana, New Jersey, Detroit, MI, U.S. Enrollment: 1995 Follow-up: 1995–2011 Cohort	Members of AARP, 50-71 years of age; excluded participants with missing data	LUR $r^2 = 0.89-0.95$ Averaging time: NO ₂ - annual average, Other, NO ₂ - Monthly averages Exposure years: 2000–2010	NO ₂ (ppb) Age <65 Mean = 12.3±5.5 ≥65 Mean = 12±5.6 BMI 18.5-25 Mean = 12.2±5.6 25-30 Mean = 12.1±5.5 30-35 Mean = 12.2±5.5 <18.5 Mean = 12±5.7 >35 Mean = 12.6±5.6 Fat Consumption, Grams Per Day Quartile 1 Mean = 12.5±5.6 Quartile 2 Mean = 12.3±5.5 Quartile 3 Mean = 12.1±5.5 Quartile 4	ICD-9: 250; ICD-10: E10– E14	Cox proportional hazard models Adjusted for: age, sex, and location as strata; and race, BMI, education, smoking, and marriage at individual- level; and median income and % with high school education at census-tract level	HR (95% CI) ^b Diabetes mortality: 1.09 (1.01, 1.18)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 12±5.5			
			Fruit Consumption, Pyramid Servings Per Day			
			Quartile 1			
			Mean = 11.9±5.5			
			Quartile 2			
			Mean = 12±5.4			
			Quartile 3			
			Mean = 12.2±5.5			
			Quartile 4			
			Mean = 12.7±5.6			
			Overall			
			Mean = 12.2±5.5			
			Race			
			Asian, Pacific Islander, or American Indian/Alaskan Native			
			Mean = 15.7±6.5			
			Black			
			Mean = 15.3±5.9			
			Hispanic			
			Mean = 14.8±7			
			White			
			Mean = 11.9±5.4			
			Sex			
			Female			
			Mean = 12.4±5.6			
			Male			
			Mean = 12±5.4			
			Smoking			
			Less than a pack, 1+ year			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			quit Mean = 12.2±5.5 Less than a pack, stopped less than a year/current Mean = 12.4±5.7 More than a pack, 1+ year quit Mean = 11.8±5.5 More than a pack, stopped less than a year or current Mean = 11.7±5.6 Never Mean = 12.4±5.5 Vegetable Consumption, Pyramid Servings Per Day Quartile 1 Mean = 12±5.6 Quartile 2 Mean = 12±5.6 Quartile 3 Mean = 12±5.6 Quartile 4 Mean = 12.6±5.6			
†Paul et al. (2020b) Ontario Population Health and Environment Cohort (ONPHEC) N = 4,774, 984 Ontario, Canada Enrollment: January 2001	Ontario residents who were Canadian born, had lived in Ontario at least 5-year before cohort inception, were between 35–85 years of age, had record of birth	LUR Model was validated against NAPS ground monitor measurements in 2006 ($r^2 = 0.73$) Averaging time:	NO ₂ (ppb) Cardiovascular Deaths IQR = 13.4 Min = 2.3 Max = 54.3 Cohort with Prevalent Diabetes IQR = 14.2	Diabetes mortality among persons with prevalent diabetes was ascertained using records from death certificates and considering the	Cox proportional hazard models Adjusted for: age, sex, SES, region, and healthcare access	HR (95% CI) ^c 3 year: 1.08 (1.02, 1.13)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow-up: through December 2015 Cohort	date and sex, and were registered with provincial health insurance at enrollment. For mortality analyses, the cohort was restricted to those with diabetes diagnoses before January 1, 2001.	NO ₂ - 3-year moving average Exposure years: 2006	Min = 2.3 Max = 58.3 Cohort without Diabetes IQR = 13.8 Min = 2.7 Max = 71.4 Diabetes Deaths IQR = 13.2 Min = 2.3 Max = 52.4 Incident Diabetes Cases IQR = 14.2 Min = 2.7 Max = 71.4	underlying cause of death; diabetes mortality (ICD-9: 250; ICD-10: E10–E14).		
† So et al. (2020) Danish Nurse Cohort (DNC) N = 24,541 Denmark Enrollment: 1993 and 1999 Follow-up: through December 2013 Cohort	Female nurses (aged >44 years) of the Danish Nurse Organization who could be linked to the Danish Civil Registration System.	Hybrid model Method validation NR Averaging time: NO ₂ - 3-year moving average; 1-year lag Exposure years: 1990–2012	NO ₂ (ppb) Cohort Baseline (1993 or 1999) Mean = 7.12 (13.4 µg/m ³)	Mortality data retrieved from Danish Register of Causes of Death diabetes (ICD-10: E10–E14)	Cox proportional hazard model Adjusted for: adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy	HR (95% CI) ^b Diabetes mortality: 1.43 (0.87, 2.35)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†So et al. (2022) Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) n = 3,083,227 Nationwide, Denmark Enrollment: January 2000 Follow-up: through December 2017 Cohort	Cohort of individuals 30 years or older	LUR, Chemical transport model 0.58 Averaging time: NO ₂ - annual average Exposure years: 1999–2017	NO ₂ (ppb) Mean = 10.8±4.22 (20.3±7.94 µg/m ³) IQR = 5.47 (10.3 µg/m ³) Min = 2 (3.7 µg/m ³) Max = 38.4 (72.2 µg/m ³) P5 = 5 (9.4 µg/m ³) P25 = 7.76 (14.6 µg/m ³) P75 = 13.2 (24.9 µg/m ³) P95 = 19 (35.7 µg/m ³)	Mortality data retrieved from Danish Register of Causes of Death diabetes (ICD-10: E10–E14)	Cox proportional hazard model Adjusted for: age, sex, parish level (cluster term), household income in decile, occupational status, immigrant status, marital status, highest completed education level, regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region	HR (95% CI) ^b Diabetes mortality: 1.04 (0.99, 1.09)
Metabolic Mortality						

† Gariazzo et al. (2023)	Daily mortality counts (natural, cardiovascular, cardiac, ischemic, cerebrovascular, respiratory, mental, nervous, metabolic, diabetes) classified using ICD-10 codes from the Italian National Institute of Statistics	Hybrid model Cross-validation at $r^2 = 0.6$ Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2015	NO ₂ (ppb) Rural Mean = 6.27 (11.8 µg/m ³) Median = 5 (IQR 3.9) (9.5 µg/m ³ (IQR 7.3 µg/m ³)) Min = 1.4 (2.7 µg/m ³) Max = 39.2 (73.7 µg/m ³) P25 = 3.8 (7.1 µg/m ³) P75 = 7.65 (14.4 µg/m ³) Suburban Mean = 10.5 (19.8 µg/m ³) Median = 9.35 (IQR 6.01) (17.6 µg/m ³ (IQR 11.3 µg/m ³)) Min = 2.3 (4.4 µg/m ³) Max = 56.02 (105.4 µg/m ³) P25 = 6.9 (13 µg/m ³) P75 = 12.9 (24.2 µg/m ³) Urban Mean = 15.8 (29.7 µg/m ³) Median = 14.7 (IQR 8.29) (27.6 µg/m ³ (IQR 15.6 µg/m ³)) Min = 3.2 (6.1 µg/m ³) Max = 61.6 (115.9 µg/m ³) P25 = 11.2 (21.1 µg/m ³) P75 = 19.5 (36.7 µg/m ³) Mean = 7.81 (14.7 µg/m ³) Median = 6.32 (IQR 5.74) (11.9 µg/m ³ (IQR 10.8 µg/m ³)) Min = 1.4 (2.7 µg/m ³) Max = 61.6 (115.9 µg/m ³)	Mortality data retrieved from the Italian National Institute of Statistics (metabolic [E00–E99])	Over-dispersed Poisson generalized additive models Adjusted for: municipality-specific long-term seasonal time trends and day of the week, as well as province-specific air temperature, bank holidays, summer population decreases and influenza epidemics	IR (converted from %IR) (95% CI) ^b lag: 0-5 - age - 0–64 y: 1.24 (0.11, 13.88) lag: 0-5 - age - 65–74 y: 1.28 (0.62, 2.60) lag: 0-5 - age - 75–84 y: 1.54 (0.78, 3.04) lag: 0-5 - age - 85+ y: 1.36 (1.00, 1.87) lag: 0-5 - gender - female: 0.98 (0.75, 1.28) lag: 0-5 - gender - male: 2.04 (1.28, 3.26) lag: 0-5: 1.30 (1.04, 1.63) lag: 0-1: 1.35 (0.95, 1.90) lag: 2-5: 1.13 (0.96, 1.34)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 4 (8 µg/m ³) P75 = 9.99 (18.8 µg/m ³)			
Cardiomatabolic Mortality						
† Brunekreef et al. (2021) ; Strak et al. (2021)	Pooled analysis of data from eight well-established ESCAPE cohorts and analysis of seven large administrative cohorts in Europe.	LUR, Chemical transport model, Hybrid model r ² = 58% Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) CEANS-SALT Cohort Mean = 11.31±3.28 (21.29±6.18 µg/m ³) Median = 11.17 (IQR 3.9) (21.02 µg/m ³ (IQR 7.33 µg/m ³)) Min = 1.58 (2.98 µg/m ³) Max = 26.85 (50.53 µg/m ³) P5 = 5.958 (11.21 µg/m ³) P25 = 9.327 (17.55 µg/m ³) P75 = 13.22 (24.88 µg/m ³) P95 = 16.94 (31.87 µg/m ³) CEANS-SDPP Cohort Mean = 8.259±2.28 (15.54±4.29 µg/m ³) Median = 8.269 (IQR 2.86) (15.56 µg/m ³ (IQR 5.38 µg/m ³)) Min = 1.57 (2.96 µg/m ³) Max = 19.71 (37.09 µg/m ³) P5 = 4.15 (7.81 µg/m ³) P25 = 6.792 (12.78 µg/m ³) P75 = 9.651 (18.16	defined as mortality due to either cardiovascular disease or diabetes (diabetes mortality: 249–250 (ICD-9) and E10-E14 (ICD-10); cardiovascular disease mortality: 400–440 (ICD-9) and I10–I70 (ICD-10))	Cox proportional hazard model Adjusted for: age, sex (strata), year of enrolment, smoking status, duration and intensity of smoking, body mass index, marital status, employment status, neighbourhood or municipal level mean income in 2001 Adjusted for: cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity2), BMI, marital status, employment status and 2001 neighbourhood-level mean income	HR (95% CI) ^c Cardiomatabolic disease mortality: 10.6 ppb (< 20 µg/m ³): 1.18 (1.07, 1.31) Cardiomatabolic disease mortality: 15.9 ppb (<30 µg/m ³): 1.13 (1.08, 1.17) Cardiomatabolic disease mortality: 21.3 ppb (<40 µg/m ³): 1.11 (1.08, 1.15) HR (95% CI) ^b Cardiomatabolic disease mortality - road-traffic noise: 1.12 (1.01, 1.23) Cardiomatabolic disease mortality: 1.13 (1.04, 1.23) Cardiomatabolic disease mortality: 1.19 (1.13, 1.25) Cardiomatabolic disease mortality: Meta-analysis of administrative cohorts: 1.05 (1.01, 1.09)
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), E3N cohort, European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Heinz Nixdorf Recall study (HNR), KORA, Danish Nurse Cohort (DNC), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese						
n = Unsure						
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands						
Recruitment: 1992–2011 Follow-up: 2011–2017						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort			$\mu\text{g}/\text{m}^3$ P95 = 11.94 (22.46 $\mu\text{g}/\text{m}^3$)			
			CEANS-SIXTY Cohort Mean = 10.99 ± 3.26 (20.68 ± 6.13 $\mu\text{g}/\text{m}^3$) Median = 10.92 (IQR 4) (20.54 $\mu\text{g}/\text{m}^3$ (IQR 7 $\mu\text{g}/\text{m}^3$)) Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 25.45 (47.88 $\mu\text{g}/\text{m}^3$) P5 = 5.69 (10.7 $\mu\text{g}/\text{m}^3$) P25 = 9.051 (17.03 $\mu\text{g}/\text{m}^3$) P75 = 12.77 (24.03 $\mu\text{g}/\text{m}^3$) P95 = 16.62 (31.28 $\mu\text{g}/\text{m}^3$)			
			CEANS-SNACK Cohort Mean = 14.56 ± 2.71 (27.39 ± 5.09 $\mu\text{g}/\text{m}^3$) Median = 15.1 (IQR 3.92) (28.5 $\mu\text{g}/\text{m}^3$ (IQR 7.38 $\mu\text{g}/\text{m}^3$)) Min = 6.176 (11.62 $\mu\text{g}/\text{m}^3$) Max = 22.65 (42.61 $\mu\text{g}/\text{m}^3$) P5 = 9.71 (18.27 $\mu\text{g}/\text{m}^3$) P25 = 12.52 (23.56 $\mu\text{g}/\text{m}^3$) P75 = 16.45 (30.95 $\mu\text{g}/\text{m}^3$) P95 = 18.04 (33.94 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) DCH Cohort Mean = 14.9±3.64 (28.04±6.84 µg/m³) Median = 15.05 (IQR 5.3) (28.32 µg/m³ (IQR 10 µg/m³)) Min = 3.4 (6.4 µg/m³) Max = 38.39 (72.23 µg/m³) P5 = 8.79 (16.54 µg/m³) P25 = 12.36 (23.26 µg/m³) P75 = 17.68 (33.26 µg/m³) P95 = 20.31 (38.22 µg/m³) DNC-1999 Cohort Mean = 13.74±4.5 (25.85±8.47 µg/m³) Median = 12.63 (IQR 7.345) (23.76 µg/m³ (IQR 13.82 µg/m³)) Min = 3.41 (6.42 µg/m³) Max = 28.84 (54.26 µg/m³) P5 = 7.286 (13.71 µg/m³) P25 = 10.32 (19.42 µg/m³) P75 = 17.67 (33.24 µg/m³) P95 = 20.7 (38.95 µg/m³) DNC-1993 Cohort Mean = 11.6±4 (21.9±8			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) Median = 10.83 (IQR 5.591) (20.37 µg/m³ (IQR 10.52 µg/m³)) Min = 2.41 (4.54 µg/m³) Max = 38.39 (72.23 µg/m³) P5 = 5.41 (10.18 µg/m³) P25 = 8.689 (16.35 µg/m³) P75 = 14.28 (26.87 µg/m³) P95 = 19.7 (37.07 µg/m³)			
			E3N Cohort Mean = 14.01±5.18 (26.36±9.75 µg/m³) Median = 13.06 (IQR 6.664) (24.57 µg/m³ (IQR 12.54 µg/m³)) Min = 1.84 (3.46 µg/m³) Max = 43.06 (81.02 µg/m³) P5 = 7.12 (13.4 µg/m³) P25 = 10.27 (19.32 µg/m³) P75 = 16.93 (31.86 µg/m³) P95 = 24.23 (45.59 µg/m³)			
			EPIC-NL-MORGEN Cohort Mean = 18.36±3.22 (34.55±6.05 µg/m³) Median = 17.9 (IQR 4.77) (33.6 µg/m³ (IQR			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			8.97 µg/m ³) Min = 5.8 (11 µg/m ³) Max = 36.49 (68.66 µg/m ³) P5 = 13.91 (26.18 µg/m ³) P25 = 15.93 (29.97 µg/m ³) P75 = 20.69 (38.94 µg/m ³) P95 = 23.8 (44.8 µg/m ³)			
			EPIC-NL-PROSPECT Cohort Mean = 19.11±2.88 (35.96±5.41 µg/m ³) Median = 18.85 (IQR 3.86) (35.46 µg/m ³ (IQR 7.27 µg/m ³)) Min = 10.41 (19.58 µg/m ³) Max = 33.03 (62.15 µg/m ³) P5 = 14.6 (27.4 µg/m ³) P25 = 17.28 (32.52 µg/m ³) P75 = 21.15 (39.79 µg/m ³) P95 = 23.72 (44.63 µg/m ³)			
			HNR Cohort Mean = 20.08±2.48 (37.78±4.66 µg/m ³) Median = 19.95 (IQR 2.67) (37.54 µg/m ³ (IQR 5.03 µg/m ³)) Min = 13.41 (25.23			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m ³ Max = 39.9 (75.07 µg/m ³) P5 = 16.61 (31.26 µg/m ³) P25 = 18.53 (34.87 µg/m ³) P75 = 21.2 (39.9 µg/m ³) P95 = 24.36 (45.83 µg/m ³) KORA-S3 Cohort Mean = 11.23±1.8 (21.13±3.3 µg/m ³) Median = 11.14 (IQR 2.3) (20.97 µg/m ³ (IQR 4.32 µg/m ³)) Min = 5.538 (10.42 µg/m ³) Max = 22.17 (41.72 µg/m ³) P5 = 8.66 (16.3 µg/m ³) P25 = 10.03 (18.88 µg/m ³) P75 = 12.34 (23.21 µg/m ³) P95 = 14.04 (26.41 µg/m ³) KORA-S4 Cohort Mean = 11.19±1.8 (21.05±3.39 µg/m ³) Median = 11.06 (IQR 2.39) (20.82 µg/m ³ (IQR 4.49 µg/m ³)) Min = 5.14 (9.68 µg/m ³) Max = 22.17 (41.72 µg/m ³) P5 = 9.97 (18.76 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 12.35 (23.24 $\mu\text{g}/\text{m}^3$) P75 = 14.1 (26.5 $\mu\text{g}/\text{m}^3$) P95 = 22.17 (41.72 $\mu\text{g}/\text{m}^3$) Pooled Cohort Mean = 13 $\pm$ 4.28 (25 $\pm$ 8.05 $\mu\text{g}/\text{m}^3$) Median = 12.83 (IQR 5.394) (24.14 $\mu\text{g}/\text{m}^3$ (IQR 10.15 $\mu\text{g}/\text{m}^3$)) Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$) P5 = 6.861 (12.91 $\mu\text{g}/\text{m}^3$) P25 = 10.37 (19.52 $\mu\text{g}/\text{m}^3$) P75 = 15.77 (29.68 $\mu\text{g}/\text{m}^3$) P95 = 21.01 (39.53 $\mu\text{g}/\text{m}^3$) VHM&PP Cohort Mean = 11.67 $\pm$ 2.84 (21.96 $\pm$ 5.34 $\mu\text{g}/\text{m}^3$) Median = 11.94 (IQR 3.71) (22.46 $\mu\text{g}/\text{m}^3$ (IQR 6.99 $\mu\text{g}/\text{m}^3$)) Min = 2.05 (3.85 $\mu\text{g}/\text{m}^3$) Max = 25.66 (48.28 $\mu\text{g}/\text{m}^3$) P5 = 6.532 (12.29 $\mu\text{g}/\text{m}^3$) P25 = 9.901 (18.63 $\mu\text{g}/\text{m}^3$) P75 = 13.62 (25.62 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P95 = 15.8 (29.7 µg/m ³)			
			NO ₂ (µg/m ³)			
			CEANS-SALT Cohort Mean = 21.29±6.18 Median = 21.02 (IQR 7.33) Min = 2.98 Max = 50.53 P5 = 11.21 P25 = 17.55 P75 = 24.88 P95 = 31.87			
			CEANS-SDPP Cohort Mean = 15.54±4.29 Median = 15.56 (IQR 5.38) Min = 2.96 Max = 37.09 P5 = 7.81 P25 = 12.78 P75 = 18.16 P95 = 22.46			
			CEANS-SIXTY Cohort Mean = 20.68±6.13 Median = 20.54 (IQR 7) Min = 2.68 Max = 47.88 P5 = 10.7 P25 = 17.03 P75 = 24.03 P95 = 31.28			
			CEANS-SNACK Cohort			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 27.39±5.09 Median = 28.5 (IQR 7.38) Min = 11.62 Max = 42.61 P5 = 18.27 P25 = 23.56 P75 = 30.95 P95 = 33.94			
			DCH Cohort Mean = 28.04±6.84 Median = 28.32 (IQR 10) Min = 6.4 Max = 72.23 P5 = 16.54 P25 = 23.26 P75 = 33.26 P95 = 38.22			
			DNC-1999 Cohort Mean = 25.85±8.47 Median = 23.76 (IQR 13.82) Min = 6.42 Max = 54.26 P5 = 13.71 P25 = 19.42 P75 = 33.24 P95 = 38.95			
			DNC-1993 Cohort Mean = 21.9±8 Median = 20.37 (IQR 10.52) Min = 4.54 Max = 72.23			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 10.18 P25 = 16.35 P75 = 26.87 P95 = 37.07 E3N Cohort Mean = 26.36±9.75 Median = 24.57 (IQR 12.54) Min = 3.46 Max = 81.02 P5 = 13.4 P25 = 19.32 P75 = 31.86 P95 = 45.59 EPIC-NL-MORGEN Cohort Mean = 34.55±6.05 Median = 33.6 (IQR 8.97) Min = 11 Max = 68.66 P5 = 26.18 P25 = 29.97 P75 = 38.94 P95 = 44.8 EPIC-NL-PROSPECT Cohort Mean = 35.96±5.41 Median = 35.46 (IQR 7.27) Min = 19.58 Max = 62.15 P5 = 27.4 P25 = 32.52			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P75 = 39.79 P95 = 44.63 HNR Cohort Mean = 37.78±4.66 Median = 37.54 (IQR 5.03) Min = 25.23 Max = 75.07 P5 = 31.26 P25 = 34.87 P75 = 39.9 P95 = 45.83 KORA-S3 Cohort Mean = 21.13±3.3 Median = 20.97 (IQR 4.32) Min = 10.42 Max = 41.72 P5 = 16.3 P25 = 18.88 P75 = 23.21 P95 = 26.41 KORA-S4 Cohort Mean = 21.05±3.39 Median = 20.82 (IQR 4.49) Min = 9.68 Max = 41.72 P5 = 18.76 P25 = 23.24 P75 = 26.5 P95 = 41.72 Pooled Cohort			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 25±8.05 Median = 24.14 (IQR 10.15) Min = 2.68 Max = 81.02 P5 = 12.91 P25 = 19.52 P75 = 29.68 P95 = 39.53 VHM&PP Cohort Mean = 21.96±5.34 Median = 22.46 (IQR 6.99) Min = 3.85 Max = 48.28 P5 = 12.29 P25 = 18.63 P75 = 25.62 P95 = 29.7			
† Brunekreef et al. (2021) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), E3N cohort, European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Heinz Nixdorf Recall study (HNR), KORA, Danish Nurse Cohort (DNC), EPIC Monitoring Project on Risk Factors and Chronic	Pooled analysis of data from eight well-established ESCAPE cohorts and analysis of seven large administrative cohorts in Europe.	LUR, Chemical transport model, Hybrid model $r^2 = 58\%$ Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) CEANS-SALT Cohort Mean = 11.31±3.28 (21.29±6.18 µg/m ³) Median = 11.17 (IQR 3.9) (21.02 µg/m ³ (IQR 7.33 µg/m ³)) Min = 1.58 (2.98 µg/m ³) Max = 26.85 (50.53 µg/m ³) P5 = 5.958 (11.21 µg/m ³) P25 = 9.327 (17.55 µg/m ³) P75 = 13.22 (24.88 µg/m ³)	Defined as mortality due to either cardiovascular disease or diabetes (diabetes mortality: 249–250 (ICD-9) and E10–E14 (ICD-10); cardiovascular disease mortality: 400–440 (ICD-9) and	Cox proportional hazard model Adjusted for: age, sex (strata), year of enrolment, smoking status, duration and intensity of smoking, body mass index, marital status, employment status, neighbourhood or municipal level mean income in 2001 Adjusted for: cohort id,	HR (95% CI) ^c Cardiometabolic disease mortality: 10.6 ppb (< 20 µg/m ³): 1.18 (1.07, 1.31) Cardiometabolic disease mortality: 15.9 ppb (<30 µg/m ³): 1.13 (1.08, 1.17) Cardiometabolic disease mortality: 21.3 ppb (<40 µg/m ³): 1.11 (1.08, 1.15) HR (95% CI) ^b Cardiometabolic disease mortality - road-traffic noise: 1.12 (1.01, 1.23) Cardiometabolic disease mortality: 1.13 (1.04, 1.23)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese			P95 = 16.94 (31.87 $\mu\text{g}/\text{m}^3$)	I10–I70 (ICD-10))	age, sex, year of baseline visit, smoking (status, duration, intensity, intensity2), BMI, marital status, employment status and 2001 neighbourhood-level mean income	Cardiometabolic disease mortality: 1.19 (1.13, 1.25) Cardiometabolic disease mortality: Meta-analysis of administrative cohorts: 1.05 (1.01, 1.09)
n = Unsure			CEANS-SDPP Cohort Mean = 8.259 $\pm$ 2.28 (15.54 $\pm$ 4.29 $\mu\text{g}/\text{m}^3$) Median = 8.269 (IQR 2.86) (15.56 $\mu\text{g}/\text{m}^3$ (IQR 5.38 $\mu\text{g}/\text{m}^3$)) Min = 1.57 (2.96 $\mu\text{g}/\text{m}^3$) Max = 19.71 (37.09 $\mu\text{g}/\text{m}^3$) P5 = 4.15 (7.81 $\mu\text{g}/\text{m}^3$) P25 = 6.792 (12.78 $\mu\text{g}/\text{m}^3$) P75 = 9.651 (18.16 $\mu\text{g}/\text{m}^3$) P95 = 11.94 (22.46 $\mu\text{g}/\text{m}^3$)			
Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands			CEANS-SIXTY Cohort Mean = 10.99 $\pm$ 3.26 (20.68 $\pm$ 6.13 $\mu\text{g}/\text{m}^3$) Median = 10.92 (IQR 4) (20.54 $\mu\text{g}/\text{m}^3$ (IQR 7 $\mu\text{g}/\text{m}^3$)) Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 25.45 (47.88 $\mu\text{g}/\text{m}^3$) P5 = 5.69 (10.7 $\mu\text{g}/\text{m}^3$) P25 = 9.051 (17.03 $\mu\text{g}/\text{m}^3$) P75 = 12.77 (24.03 $\mu\text{g}/\text{m}^3$) P95 = 16.62 (31.28 $\mu\text{g}/\text{m}^3$)			
Recruitment: 1992–2011 Follow-up: 2011–2017						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			CEANS-SNACK Cohort Mean = 14.56±2.71 (27.39±5.09 µg/m ³) Median = 15.1 (IQR 3.92) (28.5 µg/m ³ (IQR 7.38 µg/m ³)) Min = 6.176 (11.62 µg/m ³) Max = 22.65 (42.61 µg/m ³) P5 = 9.71 (18.27 µg/m ³) P25 = 12.52 (23.56 µg/m ³) P75 = 16.45 (30.95 µg/m ³) P95 = 18.04 (33.94 µg/m ³)			
			DCH Cohort Mean = 14.9±3.64 (28.04±6.84 µg/m ³) Median = 15.05 (IQR 5.3) (28.32 µg/m ³ (IQR 10 µg/m ³)) Min = 3.4 (6.4 µg/m ³) Max = 38.39 (72.23 µg/m ³) P5 = 8.79 (16.54 µg/m ³) P25 = 12.36 (23.26 µg/m ³) P75 = 17.68 (33.26 µg/m ³) P95 = 20.31 (38.22 µg/m ³)			
			DNC-1999 Cohort Mean = 13.74±4.5			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			(25.85±8.47 µg/m ³) Median = 12.63 (IQR 7.345) (23.76 µg/m ³ (IQR 13.82 µg/m ³)) Min = 3.41 (6.42 µg/m ³) Max = 28.84 (54.26 µg/m ³) P5 = 7.286 (13.71 µg/m ³) P25 = 10.32 (19.42 µg/m ³) P75 = 17.67 (33.24 µg/m ³) P95 = 20.7 (38.95 µg/m ³)			
			DNC-1993 Cohort Mean = 11.6±4 (21.9±8 µg/m ³) Median = 10.83 (IQR 5.591) (20.37 µg/m ³ (IQR 10.52 µg/m ³)) Min = 2.41 (4.54 µg/m ³) Max = 38.39 (72.23 µg/m ³) P5 = 5.41 (10.18 µg/m ³) P25 = 8.689 (16.35 µg/m ³) P75 = 14.28 (26.87 µg/m ³) P95 = 19.7 (37.07 µg/m ³)			
			E3N Cohort Mean = 14.01±5.18 (26.36±9.75 µg/m ³) Median = 13.06 (IQR 6.664) (24.57 µg/m ³ (IQR 12.54 µg/m ³)) Min = 1.84 (3.46 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Max = 43.06 (81.02 $\mu\text{g}/\text{m}^3$) P5 = 7.12 (13.4 $\mu\text{g}/\text{m}^3$) P25 = 10.27 (19.32 $\mu\text{g}/\text{m}^3$) P75 = 16.93 (31.86 $\mu\text{g}/\text{m}^3$) P95 = 24.23 (45.59 $\mu\text{g}/\text{m}^3$) EPIC-NL-MORGEN Cohort Mean = 18.36 $\pm$ 3.22 (34.55 $\pm$ 6.05 $\mu\text{g}/\text{m}^3$) Median = 17.9 (IQR 4.77) (33.6 $\mu\text{g}/\text{m}^3$ (IQR 8.97 $\mu\text{g}/\text{m}^3$)) Min = 5.8 (11 $\mu\text{g}/\text{m}^3$) Max = 36.49 (68.66 $\mu\text{g}/\text{m}^3$) P5 = 13.91 (26.18 $\mu\text{g}/\text{m}^3$) P25 = 15.93 (29.97 $\mu\text{g}/\text{m}^3$) P75 = 20.69 (38.94 $\mu\text{g}/\text{m}^3$) P95 = 23.8 (44.8 $\mu\text{g}/\text{m}^3$) EPIC-NL-PROSPECT Cohort Mean = 19.11 $\pm$ 2.88 (35.96 $\pm$ 5.41 $\mu\text{g}/\text{m}^3$) Median = 18.85 (IQR 3.86) (35.46 $\mu\text{g}/\text{m}^3$ (IQR 7.27 $\mu\text{g}/\text{m}^3$)) Min = 10.41 (19.58 $\mu\text{g}/\text{m}^3$) Max = 33.03 (62.15 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) P5 = 14.6 (27.4 µg/m³) P25 = 17.28 (32.52 µg/m³) P75 = 21.15 (39.79 µg/m³) P95 = 23.72 (44.63 µg/m³) HNR Cohort Mean = 20.08±2.48 (37.78±4.66 µg/m³) Median = 19.95 (IQR 2.67) (37.54 µg/m³ (IQR 5.03 µg/m³)) Min = 13.41 (25.23 µg/m³) Max = 39.9 (75.07 µg/m³) P5 = 16.61 (31.26 µg/m³) P25 = 18.53 (34.87 µg/m³) P75 = 21.2 (39.9 µg/m³) P95 = 24.36 (45.83 µg/m³) KORA-S3 Cohort Mean = 11.23±1.8 (21.13±3.3 µg/m³) Median = 11.14 (IQR 2.3) (20.97 µg/m³ (IQR 4.32 µg/m³)) Min = 5.538 (10.42 µg/m³) Max = 22.17 (41.72 µg/m³) P5 = 8.66 (16.3 µg/m³) P25 = 10.03 (18.88			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) P75 = 12.34 (23.21 µg/m³) P95 = 14.04 (26.41 µg/m³) KORA-S4 Cohort Mean = 11.19±1.8 (21.05±3.39 µg/m³) Median = 11.06 (IQR 2.39) (20.82 µg/m³ (IQR 4.49 µg/m³)) Min = 5.14 (9.68 µg/m³) Max = 22.17 (41.72 µg/m³) P5 = 9.97 (18.76 µg/m³) P25 = 12.35 (23.24 µg/m³) P75 = 14.1 (26.5 µg/m³) P95 = 22.17 (41.72 µg/m³) Pooled Cohort Mean = 13±4.28 (25±8.05 µg/m³) Median = 12.83 (IQR 5.394) (24.14 µg/m³ (IQR 10.15 µg/m³)) Min = 1.42 (2.68 µg/m³) Max = 43.06 (81.02 µg/m³) P5 = 6.861 (12.91 µg/m³) P25 = 10.37 (19.52 µg/m³) P75 = 15.77 (29.68 µg/m³) P95 = 21.01 (39.53			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			µg/m³) VHM&PP Cohort Mean = 11.67±2.84 (21.96±5.34 µg/m³) Median = 11.94 (IQR 3.71) (22.46 µg/m³ (IQR 6.99 µg/m³)) Min = 2.05 (3.85 µg/m³) Max = 25.66 (48.28 µg/m³) P5 = 6.532 (12.29 µg/m³) P25 = 9.901 (18.63 µg/m³) P75 = 13.62 (25.62 µg/m³) P95 = 15.8 (29.7 µg/m³) NO₂ (µg/m³) CEANS-SALT Cohort Mean = 21.29±6.18 Median = 21.02 (IQR 7.33) Min = 2.98 Max = 50.53 P5 = 11.21 P25 = 17.55 P75 = 24.88 P95 = 31.87 CEANS-SDPP Cohort Mean = 15.54±4.29 Median = 15.56 (IQR 5.38) Min = 2.96 Max = 37.09			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 7.81 P25 = 12.78 P75 = 18.16 P95 = 22.46 CEANS-SIXTY Cohort Mean = 20.68±6.13 Median = 20.54 (IQR 7) Min = 2.68 Max = 47.88 P5 = 10.7 P25 = 17.03 P75 = 24.03 P95 = 31.28 CEANS-SNACK Cohort Mean = 27.39±5.09 Median = 28.5 (IQR 7.38) Min = 11.62 Max = 42.61 P5 = 18.27 P25 = 23.56 P75 = 30.95 P95 = 33.94 DCH Cohort Mean = 28.04±6.84 Median = 28.32 (IQR 10) Min = 6.4 Max = 72.23 P5 = 16.54 P25 = 23.26 P75 = 33.26 P95 = 38.22 DNC-1999 Cohort			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 25.85±8.47 Median = 23.76 (IQR 13.82) Min = 6.42 Max = 54.26 P5 = 13.71 P25 = 19.42 P75 = 33.24 P95 = 38.95 DNC-1993 Cohort Mean = 21.9±8 Median = 20.37 (IQR 10.52) Min = 4.54 Max = 72.23 P5 = 10.18 P25 = 16.35 P75 = 26.87 P95 = 37.07 E3N Cohort Mean = 26.36±9.75 Median = 24.57 (IQR 12.54) Min = 3.46 Max = 81.02 P5 = 13.4 P25 = 19.32 P75 = 31.86 P95 = 45.59 EPIC-NL-MORGEN Cohort Mean = 34.55±6.05 Median = 33.6 (IQR 8.97)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 11 Max = 68.66 P5 = 26.18 P25 = 29.97 P75 = 38.94 P95 = 44.8			
			EPIC-NL-PROSPECT Cohort Mean = 35.96±5.41 Median = 35.46 (IQR 7.27) Min = 19.58 Max = 62.15 P5 = 27.4 P25 = 32.52 P75 = 39.79 P95 = 44.63			
			HNR Cohort Mean = 37.78±4.66 Median = 37.54 (IQR 5.03) Min = 25.23 Max = 75.07 P5 = 31.26 P25 = 34.87 P75 = 39.9 P95 = 45.83			
			KORA-S3 Cohort Mean = 21.13±3.3 Median = 20.97 (IQR 4.32) Min = 10.42 Max = 41.72 P5 = 16.3			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P25 = 18.88 P75 = 23.21 P95 = 26.41 KORA-S4 Cohort Mean = 21.05±3.39 Median = 20.82 (IQR 4.49) Min = 9.68 Max = 41.72 P5 = 18.76 P25 = 23.24 P75 = 26.5 P95 = 41.72 Pooled Cohort Mean = 25±8.05 Median = 24.14 (IQR 10.15) Min = 2.68 Max = 81.02 P5 = 12.91 P25 = 19.52 P75 = 29.68 P95 = 39.53 VHM&PP Cohort Mean = 21.96±5.34 Median = 22.46 (IQR 6.99) Min = 3.85 Max = 48.28 P5 = 12.29 P25 = 18.63 P75 = 25.62 P95 = 29.7			

† Crouse et al. (2015)	Non-institutionalized individuals 25 years of age and older and residing in Canada in 1991.	LUR $r^2 = 0.43$ Averaging time: NO ₂ - 7-yr MA; 1-yr lag	NO ₂ (ppb) Mean = 11.6 Median = 10.4 (IQR 10.5) Min = 0 Max = 51.5 P25 = 6 P75 = 16.5	ICD-9: 390–459, 250; ICD-10: I00–I99, E10–E14	Cox proportional hazard models Adjusted for: age, sex, Aboriginal ancestry, visible minority status, highest level of education, employment status, occupational class, immigrant status, marital status, income quintile. Census division and census tract–census division percent of immigrants, percent of adults without high school diploma, percent of subjects in lowest income quintile	HR (95% CI) ^b Cardiometabolic disease mortality (coadjusted for PM _{2.5} +O ₃): 1.04 (1.03, 1.05) Cardiometabolic disease mortality (immigrant status: immigrant): 1.08 (1.05, 1.11) Cardiometabolic disease mortality (immigrant status: non-immigrant): 1.04 (1.03, 1.06) Cardiometabolic disease mortality (income: bottom quintile): 1.13 (1.11, 1.16) Cardiometabolic disease mortality (income: top quintile): 0.96 (0.93, 1.00) Cardiometabolic disease mortality (men - 60-69): 1.07 (1.02, 1.11) Cardiometabolic disease mortality (men - 70-79): 1.06 (1.03, 1.09) Cardiometabolic disease mortality (men - 80-89): 1.04 (1.01, 1.07) Cardiometabolic disease mortality (men - all ages): 1.05 (1.03, 1.07) Cardiometabolic disease mortality (men - less than 60): 1.04 (0.98, 1.09) Cardiometabolic disease mortality (overall, per 10 ppb): 1.05 (1.04, 1.06) Cardiometabolic disease mortality (women - 60-69): 1.05 (0.98, 1.12) Cardiometabolic disease mortality (women - 70-79): 1.07 (1.03, 1.11) Cardiometabolic disease mortality (women - 80-89): 1.02 (0.99, 1.05) Cardiometabolic disease mortality (women - all ages): 1.05 (1.03, 1.07) Cardiometabolic disease mortality
Canadian Census Health and Environment Cohort (CanCHEC)						
n = 301, 115						
Nationwide, Canada		Exposure years: 1984–2006				
Enrollment: 1991						
Follow-up: 1991–2006						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						(women - less than 60): 1.23 (1.13, 1.33) Cardiometabolic disease mortality: 1.05 (1.04, 1.06)

List of Abbreviations: BMI = Body mass index; CI = Confidence interval; HR = Hazard ratio; IQR = Interquartile Range; LUR = Land use regression; MetS = Metabolic syndrome; NO = Nitric oxide; NO₂ = Nitrogen dioxide; NO_x = Nitrogen oxides; O₃ = Ozone; OR = Odds ratio; P25 = 25th percentile; P75 = 75th percentile; P95 = 95th percentile; PM_{2.5} = Particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = Particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = Parts per billion; r² = Coefficient of determination; RR = Rate ratio; WC = Waist circumference; WHO = World Health Organization.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 8-9 Epidemiologic studies of exposure to oxides of nitrogen and other indicators of metabolic function

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Fossati et al. (2020) INMA, Infancia y Medio Ambiente N = 1, 724 mother-child pairs Sabadell, Valencia, Asturias, Guipuzcoa, Spain Enrollment: 2003–2008 Follow-up: 4 years Cohort	Inclusion criteria were at least 16 years, intention to give birth in the reference hospital, no problems in communication, singleton pregnancy, non-assisted conception.	LUR Method validation NR Averaging time: NO ₂ - weekly averages Exposure years: 2003–2008	NO ₂ (µg/m ³) Asturias Cohort Median = 24.45 (IQR 11) First Trimester of Pregnancy Median = 28.44 (IQR 20.19) P5 = 10.56 P95 = 61.44 Gipuzkoa Cohort Median = 16.97 (IQR 9.33) Sabadell Cohort Median = 35.4 (IQR 14.04) Valencia Cohort Median = 38.9 (IQR 25.16)	CMR score	Linear regression Adjusted for: sub-cohort, season of birth, and maternal age at delivery, country of origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet	β (score) (95% CI) ^c CMR score (1st year of life): -0.03 (-0.19, 0.12) CMR score (2nd trimester): -0.13 (-0.31, 0.06) CMR score (3rd trimester): -0.13 (-0.38, 0.07) CMR score (pregnancy): -0.09 (-0.31, 0.13) CMR score: 0.06 (-0.15, 0.26)
† Mann et al. (2021) The Children’s Health and Air Pollution Study (CHAPS) N = 299 California, U.S. 2015–2017	Children ages 6–8; residence in Fresno or Clovis for at least the past 3 months, residence within 20 km of the central air quality monitoring site, no plans to move from the Fresno/Clovis area in the next 2 years, English-	Fixed site monitor, LUR Models for NO ₂ explain 99% of the observed temporal variance and 74% or the observed spatial variance Averaging time: NO ₂ -	NO ₂ (ppb) 1-Day Lag Mean = 6.98 Median = 5.07 (IQR 6.42) 1-Month Average Mean = 7.17 Median = 6.65 (IQR 6.46) 1-Week Average	Leptin Adiponectin	Generalized additive models Adjusted for: age, sex, SES, household smoking, diet, weight, race/ethnicity	% change (95% CI) ^c Adiponectin (3-month exposure): 8.83 (-12.81, 34.29) Leptin (3-month exposure): -2.34 (-16.82, 14.66) % change (95% CI) ^b Adiponectin (1-year exposure): 3.53 (-103.07, 110.12) Adiponectin (6-month exposure): 15.62 (-42.16, 73.41)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cross-Sectional	or Spanish-speaking, and no cancer, HIV, or autoimmune disease	1-hour max, NO ₂ - 24-hour average, NO ₂ - annual average, Other, NO ₂ - weekly average NO ₂ - 1, 3, 6-month averages Exposure years: 2013–2017	Mean = 7.19 Median = 6.01 (IQR 6.04)			Leptin (1-year exposure): 17.21 (-64.88, 99.29)
			1-Year Average Mean = 7.6 Median = 7.71 (IQR 1.74)			Leptin (6-month exposure): 3.35 (-38.78, 45.49)
			3-Month Average Mean = 7.3 Median = 6.88 (IQR 6.2)			
			6-Month Average Mean = 7.48 Median = 7.38 (IQR 3.42)			

†Wu et al. (2022a)						
Henan Rural Cohort Study	Ages 18-79; excluded participants with cancer, coronary heart disease, stroke, and with missing data on T2DM, hypertension, dyslipidemia, and cardiometabolic risk predictors, and who were omitted information needed.	Hybrid	NO ₂ (ppb)	Cardiometabolic risk	Linear regression	β (score) (95% CI) ^b
N = 33, 638		Averaging time: NO ₂ - 3 year averages	Cardiometabolic Risk Score Mean = 21.23±1.93 (39.95±3.63 µg/m ³) Median = 21.41 (IQR 4.12) (40.29 µg/m ³ (IQR 7.76 µg/m ³)) Min = 16 (31 µg/m ³) Max = 26.47 (49.81 µg/m ³) P25 = 19.4 (36.5 µg/m ³) P75 = 23.53 (44.27 µg/m ³)		Model 2 Adjusted for: age, gender, marital status, educational level, and personal averaged monthly income	Cardiometabolic risk (model 2): 2.20 (1.95, 2.46) Cardiometabolic risk (model 3): 1.93 (1.68, 2.18) Cardiometabolic risk: age <65 years: 1.89 (1.60, 2.18) Cardiometabolic risk: age ≥65 years: 2.23 (1.73, 2.74) Cardiometabolic risk: diet high: 1.59 (1.28, 1.90) Cardiometabolic risk: diet low: 2.24 (1.80, 2.67) Cardiometabolic risk: drinking high: 2.72 (1.80, 3.64) Cardiometabolic risk: drinking low: 1.69 (1.43, 1.95) Cardiometabolic risk: educational level ≤primary school: 2.05 (1.68, 2.43) Cardiometabolic risk: educational level >primary school: 1.89 (1.55, 2.23) Cardiometabolic risk: men: 2.63 (2.21, 3.04)
Suiping County, Yuzhou County, Xinxiang County, Tongxu County, Yima County, China		Exposure years: 2015–2017			Model 3 Adjusted for: age, gender, marital status, educational level, personal averaged monthly income, smoking status, alcohol intake, the diet score, family history of CHD, family history of Stroke, family history of T2DM, and family history of hypertension	Cardiometabolic risk: Personal averaged monthly income 500-999 RMB: 1.44 (1.01, 1.88) Cardiometabolic risk: Personal averaged monthly income <500 RMB: 2.22 (1.79, 2.64) Cardiometabolic risk: Personal averaged monthly income ≥1000 RMB: 2.16 (1.70, 2.61) Cardiometabolic risk: physical activity high: 1.84 (1.36, 2.32) Cardiometabolic risk: physical activity low: 1.74 (1.45, 2.04) Cardiometabolic risk: smoking high: 1.73 (1.33, 2.12) Cardiometabolic risk: smoking low:
2015–2017					Stratified models are adjusted for the same covariates as Model 3 minus whatever factor is being stratified	
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						1.75 (1.43, 2.08) Cardiometabolic risk: women: 1.51 (1.20, 1.83)

List of abbreviations in alphabetical order: BMI = Body mass index; CI = Confidence interval; CMR = cardiometabolic risk; GEE = Generalized Estimating Equations; HR = Hazard ratio; IQR = Interquartile Range; LUR = Land use regression; Max = maximum; Min = minimum; NO = Nitric oxide; NO₂ = Nitrogen dioxide; NO_x = Nitrogen oxides; O₃ = Ozone; OR = Odds ratio; P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile; P95 = 95th percentile; PM_{2.5} = Particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = Particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = Parts per billion; r² = Coefficient of determination; RR = Rate ratio.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

A.7. Nervous System Effects

Appendix Table 9-14 Epidemiologic studies of oxides of nitrogen exposure and cognitive function

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Binter et al. (2022)	Mother-child pairs (singleton births) during prenatal care visits, general population	LUR, Hybrid model	NO ₂ (ppb)	Nonverbal abilities	linear regression	β (points) (95% CI) ^b
HELIX			Childhood			Nonverbal abilities-pregnancy: 0.20 (-1.18, 1.57)
n = 5403		ESCAPE LUR methodology	Mean = 13.3±6.2 (25.1±11.6 µg/m ³)	Verbal abilities	Adjusted for: age at recruitment, maternal smoking, maternal pre-pregnancy BMI, paternal BMI at recruitment, parity, maternal and paternal educational levels, child sex, and child age at assessment	Verbal abilities-pregnancy: -0.39 (-1.67, 0.88)
European Region, France, U.K., Spain, Greece		Beelen et al. (2013) ; Eeftens et al. (2012)	Pregnancy			Nonverbal abilities-childhood: 0.54 (-0.65, 1.72)
Enrollment: 2003–2010 (trimester 1–3)		Hybrid (dispersion)	Mean = 11.5±5.47 (21.7±10.3 µg/m ³)			Verbal abilities-childhood: -0.75 (-1.83, 0.32)
Follow-up: 5 yr		Rahmalia et al. (2012)				
Cohort		Averaging time: Pregnancy, childhood				
		Exposure yr: 2003–2015				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Clark et al. (2012) RANCH N = 719 London, U.K. Enrollment: 2001–2003 Cross-sectional	School children from 22 schools surrounding Heathrow Airport Age: 9–10 yr old	Hybrid (emission- dispersion/ regression) Averaging time: annual avg Exposure yr: 2000	Mean: 22.7±5.6 (42.73±10.60 µg/m ³)	Reading comprehension (Suffolk Reading Scale, Child Memory Scale, Search and Memory Task)	Multi-level linear and logistic models Adjusted for: age, sex, employment status, crowding, home ownership, mother's educational level, long- standing illness, main language spoken at home, parental support for schoolwork, and classroom window glazing type.	β (score) (95% CI: Reading Comprehension: 0.01 (-1.43, 1.45) Recognition Memory: -0.09 (-0.77, 0.58) Information Recall: 0.23 (-0.69, 1.14) Conceptual Recall: -0.04 (-0.28, 0.21) Working Memory: 0.68 (-3.27, 4.63)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Compa et al. (2023)	School children (10–13 yr old) from randomly selected schools in Poland with and without ADHD	LUR, Fixed site monitor	NO ₂ (ppb)	ANT	Linear regression	RR (95% CI) ^b
NeuroSmog			long-term	CPT		NA (results reported in figures only)
n = 652		LUR model was validated using 5-fold cross-validation	Mean = 9.6 (18 µg/m ³)		Adjusted for: age, sex, parental education, and time spent outdoors	Annual average NO ₂ exposure was associated with less efficient orienting of attention on the ANT and improved performance (more correct rejections) on the CPT among those with ADHD.
Nationwide, Poland		(adjusted r ² = 0.85)				NO ₂ exposure from 1 to 7 days was associated with worse executive attention on the ANT and faster response time and fewer omission errors in the neurotypical group.
October 2020–July 2022		Averaging time: NO ₂ - annual average, Other, NO ₂ -1–7 day average				
Case-Control		Exposure yr: 2018 for long-term. 2020–2022 for short-term.				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Guilbert et al. (2023) EDEN and PELAGIE n = 1,271 France Enrollment: 2002–2006 Cohort	Randomly selected from the live-born singletons in France	Chemical transport model bias not exceeding 3.5% in urban areas, lower performance in rural areas with an overestimation by 60–80% depending on the yr (relatively few monitoring stations) Averaging time: multiyear Exposure yr: NR	NO ₂ (µg/m ³) Median = 16.9 P25 = 15.5 P75 = 19.7	Score based on WPPSI-III and NEPSY-II	Distributed Lag Non-linear Models Adjusted for: recruitment center, maternal education, age at conception, pre-pregnancy BMI, maternal fish consumption before pregnancy, parity, child prenatal tobacco exposure, breastfeeding, child stimulation through maternal interactions, HOME score, method of childcare, age at the cognitive test and the French European Deprivation Index	NR (95% CI) ^e Cognitive function: Increasing NO ₂ exposure in early pregnancy associated with small increases in general cognitive abilities. Associations negative (i.e., increases in NO ₂ exposure were associated with decreases in cognitive abilities) during later periods of pregnancy, but confidence overlapped with the null value.

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Guxens et al. (2012) INMA N = 2,644 Gipuzkoa, Sabadell, Valencia, Asturias, Spain Enrollment: 2003–2008 Follow-up: birth to 2 yr of age Cohort	Pregnant women enrolled during first trimester at public primary health care centers or public hospitals, ≥16 yr of age, intention to deliver at the reference hospital, no problems of communication, singleton pregnancy, no assisted conception.	LUR, Fixed site monitor, Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ - duration of pregnancy Exposure yr: 2003–2008	NO ₂ (µg/m ³) Asturias Mean = 23.2±0.1 Gipuzkoa Mean = 20.1±6.5 Overall Mean = 29±11.2 Sabadell Mean = 32.1±8.8 Valencia Mean = 36.8±11	Various tests of general cognition	Linear regression Adjusted for: psychologist, child's sex, age at assessment, maternal education, age, height, pre-pregnancy BMI, alcohol use during pregnancy, large fatty and lean fish consumption at first trimester, season-specific maternal circulating vitamin D level at pregnancy, use of gas stove at home during pregnancy, and number of siblings at birth	β (score) (95% CI) ^c Bayley MDI: -0.95 (-3.90, 1.89)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Guxens et al. (2014)	Pregnant women (population-based birth cohort)	LUR	NO ₂ (ppb)	BSID	Linear regression	NO ₂
ESCAPE		r ² NO ₂ : 55–92% (median 82%)	Min = 6.11 (11.5 µg/m ³)		Adjusted for: maternal education, country of birth, age at delivery, pre-pregnancy BMI, height, smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at outcome, evaluator, quality of the cognitive or psychomotor development test	β (score) (95% CI) ^b
n = 9482		r ² NO _x : 49–91% (median 78%)	Max = 23.3 (43.9 µg/m ³)			General Cognition: -0.43 (-1.81, 0.94)
European Region, France, Spain, Italy, Germany, Greece, Netherlands		Reported in Beelen et al. (2013)				NO _x
Enrollment: 1997–2008		Averaging time: Pregnancy period				β (score) (95% CI) ^b
Follow-up: 1–6 yr						General Cognition: -0.16 (-0.71, 0.39)
Cohort		Exposure yr: 2002–2005 (EDEN-France), 2008–2011 (other)				
†Lertxundi et al. (2019)	Mother/infant pairs (population-based sample)	LUR	NO ₂ (ppb)	McCarthy GCI	Linear regression	β (score) (95% CI) ^b
INMA		r ² = 0.60–0.88 (annual avg concentration)	Mean = 17.2±0.21 (32.3±0.4 µg/m ³)		Adjusted for: maternal education, age at delivery, smoking during pregnancy, parity, child's sex, parity, SES, child's age at neurodevelopment assessment, rural/urban place of residence.	McCarthy GCI: -1.32 (-3.20, 0.56)
n = 1119						
Spain		Averaging time: pregnancy exposure				
Enrollment: 2004–2008						
Follow-up: 4–6 yr						
Cohort		Exposure yr: 2003–2008				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Loftus et al. (2019) CANDLE cohort n = 1,005 Shelby County, TN, U.S. Enrollment: 2006–2011 Follow-up: 4–6 yr Cohort	Birth cohort of mother-child pairs with uncomplicated pregnancies enrolled at 16–28 weeks gestation intending to deliver at 1 of 4 participating hospitals.	Spatiotemporal/geospatial model 10-fold cross-validation (r^2 ranged between 0.79 and 0.89) Averaging time: NO ₂ - annual average Exposure yr: 2006	NO ₂ (ppb) Mean = 12.06±2.34 Median = 11.96 (IQR 3.81) Min = 5.71 Max = 16.81	FSIQ, Stanford Binet	Linear regression Adjusted for: age, sex, maternal education, insurance status, Childhood Opportunity index, maternal age, race, IQ prenatal depression, smoking birth order, breastfeeding, child sleep, prenatal vitamin, marital status, paternal education pre pregnancy BMI, Knowledge of Infant Development survey score	β (score) (95% CI) ^b FSIQ: 2.30 (-1.90, 6.50)
†Lu et al. (2021) Stanford Education Data Archive (SEDA) n = 10,878 U.S. 2010–2016 Quasi-experimental	U.S. children, grades 3–8	Ensemble machine learning model C-V r^2 = 0.788, spatial r^2 of 0.844, temporal r^2 of 0.72 Di et al. (2020) Averaging time: NO ₂ - annual average Exposure yr: 2000–2016.	NO ₂ (ppb) Mean = 13.2 ± 6.3 Median = 11.5 Min = 1.9 Max = 42.8 P25 = 8.9 P75 = 15.8	Standardized Test Score	Generalized DID Adjusted for: PM _{2.5} , Ozone, student racial/ethnic compositions, student-level SES, urbanicity, and Geographic School District-level SES	β (score) (95% CI) ^c Math Score: 0.00 (-0.01, 0.00) ELA Score: -0.01 (-0.01, -0.01)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Morgan et al. (2023) Southern California Mother's Milk Study n = 161 Southern California, U.S. Enrollment: 2016–end date Study yr: NR Follow-up: 2 yr Cohort	Latino mother infant pairs.	Other Averaging time: Pregnancy mo and 1–9 mo total pregnancy avg Exposure yr: NR	NO ₂ (ppb) 1–9 mo average Mean = 17.89±2.43 IQR = 9	BDI-cognitive	multivariate linear regression, distributed lag linear models Adjusted for: SES, breast feedings per day, gestational age, pre-pregnancy BMI, infant birthweight, and infant sex	β (score) (95% CI) ^c Composite cognitive score BDI: -1.76 (-3.50, 2.43) β (score) (95% CI) ^b Composite language score BDI: -1.36 (-8.31, 5.60) Composite cognitive score BDI: -2.88 (-10.78, 5.02) Composite motor score BDI: 2.26 (-4.59, 9.12)
van Kempen et al. (2012) RANCH N = 553 Netherlands Enrollment: NR	School children from 24 schools surrounding Schiphol-Amsterdam Airport Age: 9–11 yr old	LUR Averaging time: annual avg Exposure yr: 2001	Mean (home): 16.5±2.9 (31±5.5 μg/m ³) Mean (school): 16.4±2.7 (30.8±5.1 μg/m ³)	SRTT, SAT, HECT, SDST, DMST	Multilevel linear regression Adjusted for: age, sex, employment status, crowding, homeownership, mother's education, long-standing illness, main language spoken at home, parental support, type of window glazing at school	<u>School</u> β (DMST span length) (95% CI): -0.30 (-0.54, -0.07) β (SRTT ms) (95% CI): -0.17 (-18.71, 18.37): β (HECT pixels): 0.11 (-0.03, 0.25) β (SDST latency) (95% CI): 0.09 (-0.13, 0.32) <u>Home</u> β (DMST span length) (95% CI): 0.17 (0.12, 0.22) β (SRTT ms) (95% CI): -3.78 (-21.73, 14.17) β (HECT pixels): 0.04 (-0.10, 0.18) β (SDST latency) (95% CI): 0.00 (-0.20, 0.20)

List of abbreviations in alphabetical order: ADHD = Attention Deficit Hyperactivity Disorder; ANT = attention network test; avg = average; BDI = Bayley's Development Index; BMI = body mass index; BSID = Bayley Scales of Infant Development; CANDLE = Conditions Affecting Neurocognitive Development in Early Childhood; CI = confidence interval; CPT = continuous performance test; DID = difference-in-difference; DMST = Digit Memory Span Test; ELA = English Language Arts; EDEN = 'Etude des D'eterminants pr'e-et postnatals du d'eveloppement et de la sant'e de l'Enfant; ESCAPE = European Study of Cohorts for Air Pollution Effects; FSIQ = Full Scale Intelligence Quotient; GCI = General Cognitive Index; HECT = Hand-Eye Coordination Test; HELIX = Human Early-life Exposome project; INMA = Infancia y Medio Ambiente; IQR = Interquartile Range; LUR = land use regression; Max = maximum; Min = minimum; NA = not applicable; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; NR = not reported; P = percentile; PELAGIE = Perturbateurs Endocriniens, 'Etude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; ppb = parts per billion; RANCH = Road Traffic and Aircraft Noise Exposure and Children's Cognition and Health; RR = rate ratio; SAT = Switching Attention Test; SDST = Symbol Digit Substitution Test; SES = Socioeconomic Status; SRTT = simple Reaction Time Test; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-2 Toxicological studies of oxides of nitrogen exposure and cognitive function

Study Details and Population	Exposure Details	Endpoints Examined*
[†] Yan et al. (2016b)	Whole body inhalation with room air controls	Timing unclear (C57BL/6J Mice)
Mouse (C57BL/6J and APP/PS1) 2, 5-mo-old, males n = 2–14/group	1,330 ppb (2.5 mg/m ³) (C57BL/6J mice only) NO ₂ , 5 hr/d for 28 d 2,660 ppb (5.0 mg/m ³) NO ₂ , 5 hr/d for 28 d	• MWM—acquisition (latency to platform) (↑) • MWM—probe trial (target annulus crossovers) (↓) • MWM—probe trial (time in target quadrant) (↓)
[†] Yan et al. (2020)	Whole body inhalation with room air controls	22–26 d after exposure
Mouse (C57BL/6) developmental exposure (GD 0 to PND 0), males and females n = 8–20/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	• MWM—acquisition (distance traveled) (♂↑) • MWM—acquisition (latency to platform) (♂↑) • MWM—acquisition (thigmotaxis %) (♂↑)
		27 d after exposure
		• MWM—probe trial (distance traveled in target quadrant) (♂↓) • MWM—probe trial (entries in target quadrant) (♂↓) • MWM—probe trial (frequency crossing platform zone) (♂↓) • MWM—probe trial (time in target quadrant) (♂↓)

List of abbreviations in alphabetical order: d = day; GD = gestational day; hr = hour; mo = month(s); MWM = Morris water maze; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million.

*Simplified results interpreted as: ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females; ♂↓ = results were analyzed by sex and there was a statistically significant decrease in at least one male experimental group and a non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-3 Epidemiologic studies of oxides of nitrogen exposure and motor function

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ahmed et al. (2022)	Women born 1973–1978 and participated in ALSWH	LUR	NO ₂ (ppb)	Motor Delay-ASQ	logistic regression	OR (95% CI) ^c
MatCH		Model explained 81% of spatial variation (RMSE: 1.4 ppb) (2006–2011), 66% (RMSE: 2 ppb) (2006–2014), 57% (RMSE: 2.3 ppb) and 80% (RMSE: 1.8 ppb) (1996 onwards)	Pregnancy Mean = 6.8±2.9 Median = 6.7 Min = 1.3 Max = 18.9		Adjusted for: sex, child's age at the time of survey, maternal education, family composition, mother's ability to manage on income available, Accessibility/Remoteness Index of Australia, SES	Pregnancy-Moderate vs. Low: 1.12 (0.60, 2.07)
n = 5,471, from 2,948 women (SDQ)						Child 1st yr-High vs. Low: 0.59 (0.26, 1.33)
n = 1,265, from 978 women (ASQ)						Child LTA-Moderate vs. Low: 0.96 (0.52, 1.79)
Australia			NO ₂ (ppb)			Pregnancy-High vs. Low: 0.77 (0.39, 1.54)
Enrollment: 1996 (born 1973–1978), 2012–2013			Child lifetime Mean = 6±2.5 Median = 5.8 Min = 1.3 Max = 22.3			Child 1st yr-Moderate vs. Low: 1.29 (0.65, 2.54)
Follow-up: 2017						Child yr before survey-High vs. Low: 0.78 (0.39, 1.58)
Cohort		Averaging time: Estimated annual average for each year from enrollment to end of follow-up and derived 6 metrics - mothers long-term, pregnancy, first year of child's life, age 1–4 yr, child lifetime, year leading up to survey.	First year of life Mean = 6.6±2.8 Median = 6.4 Min = 1.4 Max = 17.7			Pregnancy-Moderate vs. Low: 1.07 (0.56, 2.02)
			Mother long-term Mean = 7.9±2.3 Median = 7.9 Min = 2.6 Max = 7.9			Child LTA-High vs. Low: 0.65 (0.33, 1.28)
						Child yr before survey-Moderate vs. Low: 1.31 (0.70, 2.46)
						Child 1st yr-High vs. Low: 0.50 (0.21, 1.17)
						Child LTA-Moderate vs. Low: 0.89 (0.47, 1.67)
						Child LTA-High vs. Low: 0.56 (0.28, 1.12)
						Child yr before survey-Moderate vs. Low: 1.21 (0.63, 2.34)
		Exposure yr: 1996–2017				Child yr before survey-High vs. Low: 0.68 (0.32, 1.43)
						Pregnancy-High vs. Low:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						0.70 (0.33, 1.49) Child 1st yr-Moderate vs. Low: 1.17 (0.58, 2.38)
† Binter et al. (2022)	Mother-child pairs (singleton births) during prenatal care visits, general population	LUR, Hybrid model ESCAPE LUR methodology Beelen et al. (2013) ; Eeftens et al. (2012) Hybrid (dispersion) Rahmalia et al. (2012) Averaging time: Pregnancy, childhood Exposure yr: 2003–2015	NO ₂ (ppb) Childhood Mean = 13.3±6.2 (25.1±11.6 µg/m ³) Pregnancy Mean = 11.5±5.47 (21.7±10.3 µg/m ³)	Clinical Kinematic Assessment Tool/Peg moving task	linear regression Adjusted for: age at recruitment, maternal smoking, maternal pre-pregnancy BMI, paternal BMI at recruitment, parity, maternal and paternal educational levels, child sex, and child age at assessment	β (points) (95% CI) ^b Fine Motor-Childhood: 0.43 (-0.75, 1.61) Gross Motor-Childhood: -0.75 (-2.04, 0.54) Fine Motor-Pregnancy: -1.37 (-2.84, 0.10) Gross Motor-Pregnancy: 0.00 (-1.47, 1.47)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Guxens et al. (2014)	Pregnant women (population-based birth cohort)	LUR	NO ₂ (ppb)	BSID-Global Psychomotor	linear regression	NO ₂
ESCAPE		r ² NO ₂ : 55–92% (median 82%)	Min = 6.11 (11.5 µg/m ³)		Adjusted for: maternal education, country of birth, age at delivery, pre-pregnancy BMI, maternal height, maternal smoking during pregnancy, parity	β (points) (95% CI) ^b
n = 9482		r ² NO _x : 49–91% (median 78%)	Max = 23.3 (43.9 µg/m ³)		Child's sex, season at child's birth date, urbanicity at child's birth address, age at the cognitive or motor development assessment, evaluator, and quality of the cognitive or psychomotor development test.	Global Psychomotor-Pregnancy: -1.28 (-2.35, -0.21)
European Region, France, Spain, Italy, Germany, Greece, Netherlands		Reported in Beelen et al. (2013)				NO _x
Enrollment: 1997–2008		Averaging time: Pregnancy period				β (points) (95% CI) ^c
Follow-up: 1–6 yr						Global Psychomotor-Pregnancy: -0.44 (-1.25, -0.11)
Cohort		Exposure yr: 2002–2005 (EDEN-France), 2008–2011 (other)				
† Lertxundi et al. (2019)	Mother/infant pairs (population-based sample)	LUR	NO ₂ (µg/m ³)	McCarthy Motor	linear regression	β (points) (95% CI) ^c
INMA		r ² = 0.60–0.88 (annual avg concentration)	Mean = 32.3±0.4		Adjusted for: Maternal education, age at delivery, smoking during pregnancy, parity, child's sex, parity, SES, child's age at neurodevelopment assessment, rural/urban place of residence.	Motor-Pregnancy: -0.07 (-0.21, 0.07)
n = 1119						Male-Pregnancy: -0.10 (-0.24, 0.04)
Spain		Averaging time: pregnancy exposure				Female-Pregnancy: -0.07 (-0.33, 0.20)
Enrollment: 2004–2008						<4 mo breastfeeding or only bottle-Pregnancy: -0.09 (-0.23, 0.06)
Follow-up: 4–6 yr		Exposure yr: 2003–2008				≥4 mo breastfeeding-Pregnancy: -0.07 (-0.28, 0.14)
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Morgan et al. (2023) Southern California Mother's Milk Study n = 161 Southern California, U.S. Enrollment: 2016–end date Study yr NR Follow-up: 2 yr Cohort	Latino mother infant pairs.	Other Averaging time: Pregnancy mo and 1–9 mo total pregnancy avg Exposure yr: NR	NO ₂ (ppb) 1–9 mo average Mean = 17.89±2.43 IQR = 9	BSID	multivariate linear regression, distributed lag linear models Adjusted for: SES, breast feedings per day, gestational age, pre-pregnancy BMI, infant birthweight, and infant sex	β (points) (95% CI) ^c Composite motor-1st mo pregnancy: -0.35 (-0.69, 0.00) β (points) (95% CI) ^b Composite motor- pregnancy: 2.26 (-4.59, 9.12)

List of abbreviations in alphabetical order: ASQ = Ages and Stages Questionnaires; ALSWH = Australian Longitudinal Study on Women's Health; avg = average; BMI = body mass index; BSID = Bayley Scales of Infant Development; CI = confidence interval; EDEN = 'Etude des D'eterminants pr'e-et postnatals du d'eveloppement et de la sant'e de l'Enfant; ESCAPE = European Study of Cohorts for Air Pollution Effects; HELIX = Human Early-life Exposome project; INMA = Infancia y Medio Ambiente; IQR = interquartile range; LUR = land use regression; LTA = lifetime average; MatCH = Mothers and their Children's Health; Max = maximum; Min = minimum; mo = month(s); NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; OR = odds ratio; ppb = parts per billion; RMSE = Root Mean Square Error; SDQ = Strengths and Difficulties Questionnaire; SES = socioeconomic status; vs. = versus; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-4 Toxicological studies of oxides of nitrogen exposure and motor function

Study Details and Population	Exposure Details	Endpoints Examined*
Di Giovanni et al. (1994)	Whole body inhalation with room air controls	14 d after exposure
Rat (Wistar)	1,500 ppb (1.5 ppm) NO ₂ , continuous for 20 d	• Locomotor activity (NS)
developmental exposure (GD 0 to GD 20), males	3,000 ppb (3.0 ppm) NO ₂ , continuous for 20 d	21 d after exposure
n = 6–7/group		• Locomotor activity (NS)
†Li et al. (2021)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	• OFT (distance traveled) (NS)
7-wk-old, males and females		
n = 3–15/group		
†Li et al. (2022a)	Whole body inhalation with room air controls	21–23 d after exposure
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	• OFT (distance traveled) (NS)
developmental exposure (GD 0 to PND 0), males and females		
n = 3–15/group		

Study Details and Population	Exposure Details	Endpoints Examined*
Tabacova et al. (1985)	Whole body inhalation with room air controls	7 d after exposure • Surface righting (% success <2 sec) (↓)
Rat (Wistar)	27 ppb (0.05 mg/m ³) NO ₂ , 6 hr/d for 21 d	9 d after exposure • Negative geotaxis (% success) (↓) • Negative geotaxis (latency) (↑) • OFT (passivity, postural and gait defects) (↑) • OFT (squares entered, head raisings) (↓)
developmental exposure (GD 0 to GD 21), males and females	53 ppb (0.1 mg/m ³) NO ₂ , 6 hr/d for 21 d	14 d after exposure • Air righting (% success) (↓) • Auditory startle (% success) (↓) • OFT (postural and gait defects) (↑) • OFT (squares entered, head raisings, passivity) (NS)
n = 4–20/group	532 ppb (1.0 mg/m ³) NO ₂ , 6 hr/d for 21 d	18 d after exposure • Air righting (% success) (↓) • Auditory startle (% success) (NS) • Hindlimb support (% success) (↓) • Hindlimb support (latency) (↑)
	5,318 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 21 d	21 d after exposure • OFT (squares crossed, rearings) (NS)
		30 d after exposure • OFT (squares crossed, rearings) (♂↓)
		60 d after exposure • OFT (rearings) (NS) • OFT (squares crossed) (♂↓)

Study Details and Population	Exposure Details	Endpoints Examined*
† Ye et al. (2022)	Whole body inhalation with room air controls	During exposure (day 3, 6, 9, 12, 15)
Rat (Sprague Dawley)	500 ppb (0.5 ppm) NO ₂ , 4 hr/d for 15 d	• Spontaneous activity (↑)
7-wk-old, females	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 15 d	
n = 10/group		

List of abbreviations in alphabetical order: d = day; GD = gestational day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; OFT = open field test; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week(s).

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase; ↓ = at least one experimental group had a statistically significant decrease; ♂↓ = results were analyzed by sex and there was a statistically significant decrease in at least one male experimental group and a non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-5 Epidemiologic studies of oxides of nitrogen exposure and autism spectrum disorder

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Volk et al. (2013)	Children aged 24–60 mo at recruitment born in California and residing in a catchment area near one of the study regional centers	Dispersion model, Central site monitor	NO ₂ (ppb)	ADOS and ADI-R clinical Dx	Additive logistic regression	OR (95% CI) ^c
CHARGE			1st trimester			ASD Dx - 1st Trimester: 1.44 (1.05, 1.20)
n = Cases: 279		Averaging time:	Mean = 17 ± 8.1		Adjusted for: child sex, child ethnicity	ASD Dx - 2nd Trimester: 1.61 (1.15, 2.25)
Controls: 245		Dispersion model - NO _x -pregnancy; NO _x -1st postnatal yr	2nd trimester		(Hispanic vs. white; Black/Asian/other vs. white), maximum education of parents	ASD Dx - 3rd Trimester: 1.64 (1.18, 2.29)
California, U.S.		Central site monitors - NO ₂ - pregnancy; NO ₂ - 1st postnatal yr; NO ₂ - trimester	3rd trimester		(parent with highest of 4 levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 yr vs. ≤35 yr), and prenatal smoking (self-report of ever vs. never smoked while pregnant).	ASD Dx - Pregnancy: 1.81 (1.23, 2.65)
1997–2008 (birth)			Mean = 17 ± 8.1			ASD Dx - 1st postnatal yr: 2.06 (1.37, 3.09)
Case-Control			Pregnancy			
		Exposure yr: Dispersion model (NO _x): 1997–2008.	Mean = 17 ± 7.1			
		Central site monitors (NO ₂): 1997–2009	1st postnatal year			
			Mean = 16 ± 6.8			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Volk et al. (2014) CHARGE n = Cases: 251 Controls: 156 California, U.S. 1997–2008 (birth) Case-Control	Children aged 24–60 mo at recruitment born in California and residing in a catchment area near one of the study regional centers	Dispersion model, Central site monitor Averaging time: NO ₂ - pregnancy Exposure yr: Dispersion model (NO _x): 1997–2008. Central site monitors (NO ₂): 1997–2009	NO ₂ (ppb) Median = 14.9 P75 = 17.5	ADOS and ADI-R clinical Dx	Logistic regression Adjusted for: child sex, child ethnicity (Hispanic vs. white, Black/Asian/other vs. white), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 yr vs. ≤35 yr), prenatal smoking (self-report of ever- vs. never-smoked while pregnant), and home ownership (owner vs. renter).	OR (95% CI) ^c ASD Dx - Pregnancy. Quartiles 1-3 (<17.5 ppb) x CG/GG MET Genotypes (ref) ASD Dx - Pregnancy. Quartiles 1–3 (<17.5 ppb) x CC MET Genotype: 0.72 (0.41, 1.30) ASD Dx - Pregnancy. Quartile 4 (≥17.5 ppb) x CC MET Genotype: 3.60 (1.30, 12.70) ASD Dx - Pregnancy. Quartile 4 (≥17.5 ppb) x CG/GG MET Genotypes: 1.20 (0.71, 2.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Bragg et al. (2024)	US pregnant mothers who previously had a child with autism, aged ≥18 yr, living within 2 hr of a study site, and <29 wk pregnant at enrollment	Ensemble machine learning model Averaging time: NO ₂ - pregnancy NO ₂ - trimester Exposure yr: 2009–2012	NO ₂ (ppb) Pregnancy Median = 22.8 (IQR 8.8)	SRS	Quantile regression Adjusted for: study site, maternal age, maternal race and ethnicity, maternal socioeconomic deprivation index, and child sex	OR (95% CI) ^c ASD Dx: 1.00 (0.92, 1.08) β (Total Score) (95% CI) ^c Autistic Traits Score: -0.01 (-0.77, 0.83)
EARLI N = 126 mother-child pairs Baltimore, MD; Sacramento, CA; San Francisco, CA; Philadelphia, PA, U.S. Enrollment: 2009–2012 Follow-up: age 36 mos Cohort						
† Goodrich et al. (2017)	Children aged 24–60 mo at recruitment born in California and residing in a catchment area near one of the study regional centers	Fixed site monitor Averaging time: NO ₂ - trimester Exposure yr: 1997–2009	NO ₂ (ppb) Median = 14.18	ADOS and ADI-R clinical Dx	Logistic regression Adjusted for: self-reported financial hardship between 3 mo before pregnancy to time of interview (yes/no), child's year of birth, vitamin A and zinc intake during the first mo of pregnancy.	OR (95% CI) ^c ASD Dx - Low Folate 1st Trimester: 1.53 (0.91, 2.56) ASD Dx - High Folate 1st Trimester: 0.74 (0.46, 1.19) ASD Dx - Low Folate 2nd Trimester: 1.25 (0.73, 2.14) ASD Dx - High Folate 2nd Trimester: 0.88 (0.57, 1.38) ASD Dx - Low Folate 3rd Trimester: 1.04 (0.64, 1.71) ASD Dx - High Folate 3rd Trimester: 1.19 (0.74, 1.92)
CHARGE n = 297 autism cases 143 ASD cases 236 controls California, U.S. Enrollment: 2003–Study yr NR Case-Control						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Guxens et al. (2015) GASPII, CATSS, Generation R, INMA n = 11,310 Italy, Sweden, The Netherlands, Spain Enrollment: 1992–2008 Follow-up: age 4–10 yr Cohort	Mother-child pairs from population-based birth cohorts and one twin study in European countries.	LUR Averaging time: NO ₂ - pregnancy; NO _x - pregnancy Exposure yr: 2008–2011	NO ₂ (ppb) Median = cohort-specific medians ranged 9.5–22.4 (17.9–42.2 µg/m ³) NO _x (µg/m ³) Median = cohort-specific medians ranged 35–70 (estimated from figure)	A-TAC (age 9 or 12 yr in Swedish cohort), PDP subscale of CBCL1½–5 (age 6 yr in Dutch cohort and age 4 yr in Italian cohort), 18-item SRS (age 6 yr in Dutch cohort), CAST (age 4–5 yr in Spanish cohorts)	Logistic regression Adjusted for: maternal characteristics (education, country of birth, age at delivery, prepregnancy BMI, height, prenatal smoking, and parity), child's sex, season at child's birth, urbanicity at child's birth address, and child's age at autistic traits assessment, and evaluator of the autistic traits	NO ₂ OR (95% CI) ^b Autistic Traits Score within Clinical Range: 0.77 (0.47, 1.27) Autistic Traits Score within Borderline/Clinical Range: 0.91 (0.68, 1.21) NO _x OR (95% CI) ^c Autistic Traits Score within Borderline/Clinical Range: 0.98 (0.88, 1.09) Autistic Traits Score within Clinical Range: 0.93 (0.78, 1.11)
†Kim et al. (2017) CHARGE n = 158 cases 147 controls California, U.S. Enrollment: 2003–Study yr NR Case-Control	Children aged 24–60 mo at recruitment born in California and residing in a catchment area near one of the study regional centers	Fixed site monitor Averaging time: NO ₂ - pregnancy NO ₂ - conception to 2nd birthday Exposure yr: 1997–2009	NO ₂ (ppb) SD = 5.7	ADOS and ADI-R clinical Dx	Logistic regression Adjusted for: maximum education level of parents, child's sex and child's ethnicity	OR (95% CI) ^b ASD Dx - Total CNV Burden: 1.63 (1.02, 2.61) ASD Dx - Deletions: 1.90 (1.12, 3.21) ASD Dx - Duplications: 1.54 (0.97, 2.44)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Li et al. (2023b)	Children 10–12 yr at enrollment in five urban and rural municipalities in the north of the Netherlands. The majority were part of a cohort representative of the general population and a quarter consisted of a high-risk cohort defined by contact with mental health outpatient clinics before age 11.	LUR Averaging time: NO ₂ - annual average Exposure yr: 2000–2018	NO ₂ (ug/m ³) Wave T1 Mean = 17.25 ± 3.04 Wave T2 Mean = 17.74 ± 3.76 Wave T3 Mean = 15.52 ± 3.37 Wave T4 Mean = 16.68 ± 4.5 Wave T5 Mean = 16.63 ± 4.83 Wave T6 Mean = 15.87 ± 5.41	CSBQ or ASBQ item mean scores scaled from 0–2, with higher scores indicating more severe ASD symptoms	Linear regression - mixed effects Adjusted for: follow-up time, the interaction between follow-up time and environmental exposures, age at baseline, sex, socioeconomic status, children’s use of psychostimulant medication, the interaction between follow-up time and sex, the interaction between follow-up time and children’s use of psychostimulant medication, problematic pregnancy or child delivery, maternal smoking during pregnancy, mothers’ age at child delivery, pregnancy duration, and lifetime parental psychopathology	β (Scale (0–2)) (95% CI) ^c ASD Symptoms: -0.0120 (-0.0210, -0.0032)

† Murphy et al. (2024)	Full-term singleton children (≥37 wk gestation) born in Ontario matched on maternal age at delivery, race/ethnicity, parity prenatal care provider, substance use, pre-existing health conditions, and mental health at personal level, neighborhood education and income, and infant birth year with matching ratios ranging from 1:1 to 1:5 case to controls. Cases were diagnosed after 2 yr of age	LUR LOOCV $r^2 = 0.73$ Averaging time: NO ₂ - weekly Exposure yr: 2012–2016	NO ₂ (ppb) T0: 13 weeks preconception to conception Mean = 11.9 ± 5.4 Median = 11.7 (IQR 7.3) T1: 1st trimester Mean = 12.1 ± 5.5 Median = 12.1 (IQR 7.7) T2: 2nd trimester Mean = 12 ± 5.4 Median = 11.8 (IQR 7.5) T3: 3rd trimester Mean = 11.6 ± 5.2 Median = 11.4 (IQR 7) T4: conception to delivery Mean = 11.9 ± 4.8 Median = 12.4 (IQR 6.9) T5: 13 weeks preconception to delivery Mean = 11.9 ± 4.7 Median = 12.6	Health records clinical Dx after age 2 yr	Distributed lag non-linear model (DLNM) Adjusted for: maternal age, birth season (Fall, Winter, Spring, Summer) Logistic regression Adjusted for: maternal age, birth season (Fall, Winter, Spring, Summer), infant sex (male, female), mode of delivery (vaginal delivery, caesarean delivery), residential community type (urban, rural)	OR (95% CI) ^c ASD Dx - wk 13 Gestation: 1.9 (1.7, 2.1) ASD Dx - wk 27 Gestation: 1.7 (1.5, 1.9) ASD Dx - wk 40 Gestation: 1.8 (1.6, 2.0) ASD Dx - 13 wk Preconception; DLNM: 1.2 (1.1, 1.2) ASD Dx - Pregnancy; DLNM: 2.5 (2.2, 2.8) ASD Dx - 13 wk Preconception: 1.8 (1.6, 2.0) ASD Dx - wk 1 Gestation: 1.8 (1.7, 2.0)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			(IQR 6.9)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† O'Sharkey et al. (2024) CDPH birth registry n = 444,651 Cases: 10,369 Controls: 434,282 Southern California, U.S. January 2016–December 2019 (enrollment) Case-Control	Singleton children within a boundary composed largely of Los Angeles, north Orange County, and western San Bernardino County, with gestational age between 140–315 days, birth weights within 500–6,800 g, and complete covariate data.	Ensemble machine learning model Averaging time: NO ₂ - entire pregnancy Exposure yr: 2016–2019	NO ₂ (ppb) ASD Case Mean = 12.11 ± 3.03 Median = 11.81 P25 = 10.03 P75 = 13.78 Non-ASD Control Mean = 11.95 ± 2.95 Median = 11.68 P25 = 9.91 P75 = 13.62	California Department of Developmental Services Client Development Evaluation Report clinical Dx	Logistic regression Adjusted for: child sex, parity, and maternal age, race/ethnicity, nativity, education, method of prenatal care payment, and smoking	OR (95% CI) ^b ASD Dx: 1.14 (1.07, 1.22)

† Pagalan et al. (2018)	All single, twin, and triplet births to mothers aged 15–49 yr who were registered with the provincial health insurance plan for at least 275 days and residing in metropolitan Vancouver during their pregnancy, with at least 20 weeks of gestation or 500 g birth weight. Infants were excluded if they died younger than 1 yr of age.	LUR	NO (ppb)	ADOS and ADI-R clinical Dx	Logistic regression	NO
British Columbia Provincial Health Insurance Program		Averaging time: NO ₂ -monthly; NO-monthly	Monthly average		Adjusted for: child sex, birth mo, birth year, maternal age, maternal birthplace, and neighborhood-level urbanicity and income band.	OR (95% CI) ^c
n = 132,256		Exposure yr: 2003–2014	1st trimester			ASD Dx - Pregnancy: 1.07 (1.01, 1.13)
			Median = 17.4			ASD Dx - 3rd Trimester: 1.04 (0.98, 1.09)
			P25 = 10			ASD Dx - 1st Trimester: 1.06 (1.01, 1.11)
			P75 = 28.3			ASD Dx - 2nd Trimester: 1.04 (0.99, 1.08)
			2nd trimester			
			Median = 16.6			
			P25 = 9.5			
			P75 = 27.8			
			3rd trimester			
			Median = 15.3			
			P25 = 9.1			
			P75 = 26.5			
			Pregnancy			
			Median = 18.3			
			P25 = 14			
			P75 = 24.7			
			NO ₂ (ppb)			
			Monthly average			
			1st trimester			
			Median = 14.5			
			P25 = 12.1			
			P75 = 17.6			
			2nd trimester			
			Median = 14.3			
			P25 = 11.9			
			P75 = 17.5			
			3rd trimester			
			Median = 14			
			P25 = 11.6			
			P75 = 17.2			
			Pregnancy			
			Median = 14.3			
			P25 = 12.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
P75 = 17						
† Rahman et al. (2022)	Singleton children born at 37–44 wk of gestation at Kaiser Permanente Southern California hospitals covered by the KPSC health plan at age 1 yr	Ensemble machine learning model 10-fold cross-validation ($r^2 = 0.79$). Averaging time: NO ₂ - weekly Exposure yr: 2001–2014	NO ₂ (ppb) Dry season (Apr–Oct) Mean = 32.2 P25 = 26 P75 = 43.2 Entire year Mean = 35.4 P25 = 26 P75 = 43.4 Wet season (Nov–Mar) Mean = 40.1 P25 = 26 P75 = 43.3	ICD-9 codes 299.0, 299.1, 299.8, and 299.9, ICD-10 codes F84.0, F84.3, F84.5, F84.8, and F84.9	Cox proportional hazards model with a distributed lag model (DLM) Adjusted for: child sex, maternal race/ethnicity, maternal age at delivery, parity, education, maternal comorbidities, medical centers, household income, birth year, and season	HR (95% CI) ^c ASD Dx: 0.99 (0.90, 1.09)
KPSC n = 294,937 Southern California, U.S. Enrollment: January 2001–December 2014 Follow-up: Age 18 mo through December 2019 Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ritz et al. (2018)	All singleton cases of ASD born in Denmark and controls individually matched on birth year and gender from Danish medical registers, using a 1:5 ratio.	Hybrid model	NO ₂ (ppb)	Danish National Patient Register and the Danish Psychiatric Central Register (ICD-10 codes F84.0, F84.1, F84.5, F84.8, or F84.9) clinical Dx	Logistic regression	OR (95% CI) ^b
Danish Medical Birth Registry	Included children had gestation period between 21–46 weeks, birth weight between 500–6800 g, mothers residing in Denmark throughout pregnancy, and children residing in Denmark from birth to index date.	Correlation (r) between modeled and measured half-year mean NO ₂ at 204 locations in metro Copenhagen was 0.90. Correlations between modeled and measured 1-mo mean concentrations of NO _x and NO ₂ over 1995–2006 on a busy street in Copenhagen were 0.88 and 0.67, respectively.	Pregnancy Median = 10.4 (19.57 ug/m ³) Min = 2.35 (4.43 ug/m ³) Max = 42.96 (80.84 ug/m ³) P25 = 7.605 (14.31 ug/m ³) P75 = 13.73 (25.83 ug/m ³)		Adjusted for: maternal age, paternal age, location of birth, neighborhood SES employment, neighborhood SES housing, and maternal smoking during pregnancy. Matched on child gender and birth year.	ASD Dx - Pregnancy: 1.17 (1.11, 1.23) ASD Dx - 9 mo Postnatal: 1.19 (1.13, 1.25)
n = Cases: 15,387 Controls: 68,139		Averaging time: NO ₂ -9 mo prenatal; NO ₂ -entire pregnancy; NO ₂ -each trimester; NO ₂ -9 mo postnatal; NO _x -9 mo prenatal; NO _x -entire pregnancy; NO _x -each trimester; NO _x -9 mo postnatal;	9 mo postnatal Median = 10.09 (18.98 ug/m ³) Min = 2.19 (4.12 ug/m ³) Max = 41.81 (78.67 ug/m ³) P25 = 7.43 (13.98 ug/m ³) P75 = 13.36 (25.13 ug/m ³)			
Nationwide, Denmark		Exposure yr: 1989–2013				
1996–2016 (enrollment) 1989–2013 (birth)						
Case-Control						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wang et al. (2021a)	Random sample of live births between 1996–2000	Spatiotemporal/geospatial model	NO ₂ (ppb)	Health Insurance records clinical Dx: autistic disorder (ICD-9-CM code: 299.0), Asperger syndrome (299.8), and PDD-NOS (299.9)	Cox proportional hazards model with a distributed lag model (DLM)	HR (95% CI) ^c
LHID2000	covered by the national health insurance system in Taiwan in 2000.	Averaging time: NO ₂ -entire pregnancy; NO ₂ -first trimester; NO ₂ -second trimester; NO ₂ -third trimester;	ASD Mean = 25.47 ± 6.12			ASD Dx - 1st Trimester: 1.34 (1.19, 1.52)
n = 62,919					Adjusted for: sex and calendar year of birth	ASD Dx - 2nd Trimester: 1.22 (1.07, 1.38)
Nationwide, Taiwan		Exposure yr: 1995–2000	non-ASD Mean = 24.34 ± 6.01			ASD Dx - 3rd Trimester: 1.18 (1.04, 1.34)
Enrollment: 2000 (born 1996–2000)						ASD Dx - Pregnancy: 1.39 (1.19, 1.62)
Follow-up: through December 2013						
Cohort						

List of abbreviations in alphabetical order: A-TAC = Autism-Tics, AD/HD and other Comorbidities inventory; ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; ASBQ = Adult Social Behavior Questionnaire; ASD = autism spectrum disorder; BMI = body mass index; BORN = Better Outcomes Registry & Network; CANS-ASP = Ontario Ministry of Children and Youth Services' Child and Adolescent Needs and Strengths - Autism Spectrum Profile; CANUE = Canadian Urban Environmental Health Consortium; CAST = Childhood Autism Spectrum Test; CATSS = Child and Adolescent Twin Study in Sweden; CBCL = Child Behavior Checklist; CDPH = California Department of Public Health; CHARGE = Childhood Autism Risks from Genetics and Environment; CI = confidence interval; CNV = copy number variation; CSBQ = Children's Social Behavior Questionnaire; DLM = distributed lag model; DLNM = distributed lag non-linear model; Dx = diagnosis; EARLI = Early Autism Risk Longitudinal Investigation; GASPII = Gene and Environment Prospective Study on Infancy in Italy; HR = hazard ratio; hr = hour(s); ICD = International Classification of Diseases; INMA = Infancia y Medio Ambiente; IQR = interquartile range; KPSC = Kaiser Permanente Southern California; LHID2000 = Longitudinal Health Insurance Database 2000; LOOCV = leave-one-out cross-validation; LUR = land use regression; Max = maximum; Min = minimum; mo = month; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; NO = nitric oxide; NR = not reported; OR = odds ratio; P = percentile; PDD = pervasive developmental disorder; PDP = pervasive developmental problems; ppb = parts per billion; SRS = Social Responsiveness Scale; T = timepoint; TRAILS = TRacking Adolescents' Individual Lives Survey; vs. = versus; wk = week(s); yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-6 Toxicological studies of oxides of nitrogen exposure and autism spectrum disorder

Study Details and Population	Exposure Details	Endpoints Examined*
Di Giovanni et al. (1994)	Whole body inhalation with room air controls	5 d after exposure
Rat (Wistar)	1,500 ppb (1.5 ppm) NO ₂ , continuous for 20 d	• Ultrasonic vocalizations (total duration) (NS)
developmental exposure (GD 0 to GD 20), males	3,000 ppb (3.0 ppm) NO ₂ , continuous for 20 d	10 d after exposure
n = 6–7/group		• Ultrasonic vocalizations (total duration) (↓)
		15 d after exposure
		• Ultrasonic vocalizations (total duration) (↓)
†Li et al. (2021)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	• Marble burying (♂↑)
7-wk-old, males and females		
n = 3–15/group		

List of abbreviations in alphabetical order: d = day; GD = gestational day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week(s).

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↓ = at least one experimental group had a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-7 Epidemiologic studies of oxides of nitrogen exposure and externalizing behaviors

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
ADHD						
† Li et al. (2023b)	Children 10–12 yr at enrollment in five urban and rural municipalities in the north of the Netherlands. The majority were part of a cohort representative of the general population and a quarter consisted of a high-risk cohort defined by contact with mental health outpatient clinics before age 11 yr	LUR	NO ₂ (ug/m ³)	CBCL or ABCL	Linear regression - mixed effects	β (Scale (0–2)) (95% CI) ^c ADHD symptoms: -0.02 (-0.03, 0.00)
TRAILS n = 2,750 Northern region, The Netherlands Enrollment: March 2001–July 2002 Follow-up: 14–16 yr Cohort		Averaging time: NO ₂ - annual average Exposure yr: 2000–2018	Wave T1 Mean = 17.25±3.04 Wave T2 Mean = 17.74±3.76 Wave T3 Mean = 15.52±3.37 Wave T4 Mean = 16.68±4.5 Wave T5 Mean = 16.63±4.83 Wave T6 Mean = 15.87±5.41		Adjusted for: follow-up time, the interaction between follow-up time and environmental exposures, age at baseline, sex, socioeconomic status, children's use of psychostimulant medication, the interaction between follow-up time and sex, the interaction between follow-up time and children's use of psychostimulant medication, problematic pregnancy or child delivery, maternal smoking during pregnancy, mothers' age at child delivery, pregnancy duration, and lifetime parental psychopathology	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Lofthus et al. (2020) CANDLE n = 975 Shelby County, TN, U.S. Enrollment: 2006–2011 Follow-up: age 4–6 yr Cohort	Women aged 16–40 yr, in the second trimester of a singleton pregnancy, intent to deliver at one of five health care settings in Shelby County, and with no pregnancy complications (e.g. Dx of gestational diabetes, high blood pressure or other condition)	Spatiotemporal/geospatial model Cross-validation r ² = 0.79–0.89 Averaging time: NO ₂ - annual average Exposure yr: 2006 for prenatal exposures, 2011 for postnatal exposures	NO ₂ (ppb) postnatal Mean = 8.6±1.8 Median = 8.6 (IQR 2.8) P25 = 8.1 P75 = 10.7 prenatal Mean = 12±2.4 Median = 11.9 (IQR 3.8) P25 = 10.3 P75 = 14.1	CBCL	Linear regression Adjusted for: child age, child sex, recruitment site, temporal splines, maternal characteristics (age, race, education, prenatal smoking, prenatal depression, IQ), breastfeeding, neighborhood COI (postnatal economics score & educational score), insurance status, adjusted household income, child sleep score at assessment, and birth order.	RR (95% CI) ^b Externalizing Behavior-Prenatal: 1.34 (1.06, 1.69) Externalizing Behavior-Postnatal: 1.47 (1.01, 2.13)
† Min and Min (2016) NHIS-NSC, Korea n = 8,936 Nationwide, South Korea Enrollment: January 2002–December 2002 Follow-up: Through 2012 Cohort	Infants born in South Korea in 2002 who visited hospitals during the follow-up period and did not have low birthweight, respiratory distress, encephalitis, and jaundice at birth. Infants with ADHD Dx before age 2 yr were excluded.	Spatiotemporal/geospatial model Averaging time: NO ₂ - annual average Exposure yr: 2002–2012		Medical claims data (ICD-10 code F90.0)	Cox proportional hazards regression Adjusted for: gender, metropolitan area, and household income relative to the median	HR (95% CI) ^c ADHD Dx - 3rd Tertile (≥57.56 µg/m ³) vs. 1st Tertile ≤40.58 µg/m ³): 2.12 (1.56, 2.89) ADHD Dx - 2nd Tertile (40.59–57.55 µg/m ³) vs. 1st Tertile ≤40.58 µg/m ³): 1.44 (1.31, 2.43) HR (95% CI) ^b ADHD Dx - Continuous: 1.74 (1.45, 2.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Thygesen et al. (2020) Danish Civil Registration System n = 809,654 Nationwide, Denmark Enrollment: January 1992–December 2007 Follow-up: age 5 yr through July 2013 Cohort	All singletons who were alive and resident in Denmark on their 5th birthday, whose parents were both born in Denmark, and whose mothers were residents in Denmark at time of conception	Dispersion model Averaging time: NO ₂ – birth to 5 yr Exposure yr: 1992–2007	NO ₂ (ppb) Min = 2.33 (4.39 ug/m ³) Max = 30.62 (57.62 ug/m ³) NO ₂ (ug/m ³) Min = 4.39 Max = 57.62	Hospital records ICD-10 codes F90x or F98.8	Poisson regression Adjusted for: age, calendar year, sex, and mother's and father's level of education and income	IRR (95% CI) ^c ADHD Dx – Quintile 2 vs. Quintile 1: 1.22 (1.16, 1.28) ADHD Dx - Quintile 3 vs. Quintile 1: 1.30 (1.24, 1.37) ADHD Dx - Quintile 4 vs. Quintile 1: 1.47 (1.40, 1.55) ADHD Dx - Quintile 5 vs. Quintile 1: 1.70 (1.61, 1.78) IRR (95% CI) ^b ADHD Dx: 1.83 (1.75, 1.92)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Yorifuji et al. (2016) Longitudinal Survey of Babies in the 21st Century n = 46,039 Nationwide, Japan Enrollment: January 2001 or July 2001 Follow-up: 2009 (age 8 yr) Cohort	Singleton births representing 1/20 of babies born in Japan	Fixed-site monitor Averaging time: NO ₂ -entire pregnancy Exposure yr: 2000–2001	NO ₂ (ppb) Mean = 17.7±8	CBCL/4–18 Japanese Edition	Logistic regression Adjusted for: individual characteristics (sex, birth mo, maternal age at delivery, parity, maternal smoking status, maternal educational attainment, and paternal income) and municipality-level variables (residential area, per capita tax income, and density).	OR (95% CI) ^c Failure to Pay Attention When Crossing a Street – Quartile 4 vs. Quartile 1: 1.17 (1.00, 1.37) Failure to Pay Attention When Crossing a Street - Quartile 2 vs. Quartile 1: 1.08 (0.97, 1.20) Failure to Pay Attention When Crossing a Street - Quartile 3 vs. Quartile 1: 1.17 (1.05, 1.31) OR (95% CI) ^b Failure to Pay Attention When Crossing a Street: 1.09 (1.02, 1.17) Interrupting People: 1.02 (0.96, 1.09) Inability to Wait His/Her Turn During Play: 1.00 (0.88, 1.13)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yuchi et al. (2022) n = 1,217 Vancouver metropolitan region, Canada Enrollment: 2000–2001 (birth) Follow-up: age 3–2010 Cohort	Birth cohort of all live singleton births in metropolitan Vancouver registered in the mandatory health insurance program in British Columbia	LUR r ² = 0.73 Averaging time: NO ₂ - annual average Exposure yr: 2006	NO ₂ (ppb) Median = 16.4 (IQR 5.9)	Hospital records, physician visits, and prescriptions	Cox proportional hazards regression Adjusted for: Maternal age, paternal age, maternal body mass index, maternal parity, birth weight, season of birth, gestational age, infant sex, education, household income, residential instability, material deprivation, dependency and ethnic concentration	HR (95% CI) ^b ADHD Dx: 1.02 (0.93, 1.11)
Aggression						
† Jorcano et al. (2019) GASPII, Generation R, INMA, ABCD, GINIplus, EDEN, LISA, REPRO_PL n = 13,182 Nationwide, France, Spain, Italy, Poland, Germany, Netherlands Enrollment: Ranged 1995–2008 Follow-up: age 7–10 yr (CBCL) or 7–11 yr (SDQ)	Population-based birth cohorts of singletons born in European countries.	LUR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: ESCAPE: 2008–2011; REPRO_PL: 2006–2016; INMA-Gipuzkoa: 2006–2007	NO ₂ (ppb) Prenatal: Cohort-specific means ranged 8.5–23.1 (15.9–43.5 µg/m ³) Postnatal: Cohort-specific means ranged 7.4–23.1 (14.0–43.5 µg/m ³) NO _x (ppb) NR	CBCL/6-18 rule-breaking syndrome and aggression scales (>P93) or SDQ conduct problems scale (>3)	Logistic regression Adjusted for: maternal characteristics (education level, country of birth, age at delivery, pre-pregnancy, BMI, height, prenatal smoking, prenatal alcohol use, parity), paternal characteristics (education level, country of birth, age at delivery), household status during pregnancy, and child's sex and age at assessment	NO ₂ OR (95% CI) ^b Aggressive Symptoms (borderline/clinical) - Prenatal: 1.14 (0.94, 1.38) Aggressive Symptoms (borderline/clinical) - Postnatal: 0.87 (0.69, 1.11) NO _x OR (95% CI) ^b Aggressive Symptoms (borderline/clinical) - Prenatal: 1.04 (0.94, 1.15) Aggressive Symptoms (borderline/clinical) - Postnatal: 0.89 (0.74, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort						
† Yorifuji et al. (2016)	Singleton births representing 1/20 of babies born in Japan.	Fixed site monitor	NO ₂ (ppb)	CBCL/4–18 Japanese Edition	Logistic regression	OR (95% CI) ^b
Longitudinal Survey of Babies in the 21st Century		Averaging time: NO ₂ - pregnancy	Mean = 17.7±8		Adjusted for: individual characteristics (sex, birth mo, maternal age at delivery, parity, maternal smoking status, maternal educational attainment, and paternal income) and municipality-level variables (residential area, per capita tax income, and density).	Causing Disturbances in Public: 1.00 (0.93, 1.08) Lying - Continuous: 1.06 (1.00, 1.14) Destroying Toys and/or Books: 1.06 (0.96, 1.18) Hurting Other People: 0.93 (0.84, 1.02)
n = 46,039		Exposure yr: 2000–2001				
Nationwide, Japan						
Enrollment: January 2001 or July 2001						OR (95% CI) ^c
Follow-up: 2009 (age 8 yr)						Lying - Quartile 2 vs. Quartile 1: 1.10 (1.01, 1.20) Lying – Quartile 3 vs. Quartile 1: 1.12 (1.02, 1.23) Lying - Quartile 4 vs. Quartile 1: 1.09 (0.95, 1.25) Destroying Toys and/or Books - Quartile 2 vs. Quartile 1: 1.11 (0.98, 1.26) Destroying Toys and/or Books - Quartile 3 vs. Quartile 1: 1.14 (0.99, 1.32) Destroying Toys and/or Books - Quartile 4 vs. Quartile 1: 1.12 (0.90, 1.40)
Cohort						

List of abbreviations in alphabetical order: ABCD = Amsterdam-Born Children and Their Development Study; ABCL = Adult Behavior Checklist; ADHD = attention deficit hyperactivity disorder; BMI = body mass index; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CBCL = Child Behavior Checklist; CI = confidence interval; COI = child opportunity index; Dx = diagnosis; HR = hazard ratio; hr = hour(s); ICD = International Classification of Diseases; INMA = Infancia y Medio Ambiente; IQ = intelligence quotient; IQR = interquartile range; IRR = incidence rate ratio; LISA = Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Childhood; LUR = land use regression; Max = maximum; Min = minimum; mo = month; NHIS-NSC = National Health Insurance Service-National Sample Cohort; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; OR = odds ratio; P = percentile; ppb = parts per billion; REPRO_PL = Polish Mother and Child Cohort Study; RR = risk ratio; SDQ = Strengths and Difficulties Questionnaire; T = timepoint; TRAILS = TRacking Adolescents' Individual Lives Survey; vs. = versus; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-8 Toxicological studies of oxides of nitrogen exposure and externalizing behaviors

Study Details and Population	Exposure Details	Endpoints Examined*
Di Giovanni et al. (1994)	Whole body inhalation with room air controls	14 d after exposure
Rat (Wistar)	1,500 ppb (1.5 ppm) NO ₂ , continuous for 20 d	Locomotor activity (NS)
developmental exposure (GD 0 to GD 20), males	3,000 ppb (3.0 ppm) NO ₂ , continuous for 20 d	21 d after exposure
n = 6–7/group		Locomotor activity (NS)
†Li et al. (2021)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	OFT (distance travelled) (NS)
7-wk-old, males and females		
n = 3–15/group		
†Li et al. (2022a)	Whole body inhalation with room air controls	21–23 d after exposure
Mouse (C57BL/6J)	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	OFT (distance travelled) (NS)
developmental exposure (GD 0 to PND 0), males and females		
n = 3–15/group		

Study Details and Population	Exposure Details	Endpoints Examined*
Tabacova et al. (1985)	Whole body inhalation with room air controls	9 d after exposure - OFT (passivity) (↑) - OFT (squares entered, head raisings) (↓) 14 d after exposure - OFT (squares entered, head raisings, passivity) (NS) 21 d after exposure - OFT (squares crossed, rearings) (NS) 30 d after exposure - OFT (squares crossed, rearings) (♂↓) 60 d after exposure - OFT (rearings) (NS) - OFT (squares crossed) (♂↓)
†Ye et al. (2022)	Whole body inhalation with room air controls	During exposure (Day 3, 6, 9, 12, 15) Spontaneous activity (↑)
Rat (Wistar)	27 ppb (0.05 mg/m ³) NO ₂ , 6 hr/d for 21 d	
developmental exposure (GD 0 to GD 21), males and females	53 ppb (0.1 mg/m ³) NO ₂ , 6 hr/d for 21 d	
n = 4–20/group	532 ppb (1.0 mg/m ³) NO ₂ , 6 hr/d for 21 d	
	5,318 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 21 d	
Rat (Sprague Dawley)	500 ppb (0.5 ppm) NO ₂ , 4 hr/d for 15 d	
7-wk-old, females	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 15 d	
n = 10/group		

List of abbreviations in alphabetical order: d = day; GD = gestational day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; OFT = open field test; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week(s).

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↓ = at least one experimental group had a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-9 Epidemiologic studies of oxides of nitrogen exposure and anxiety, depression, and psychological distress

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Long-Term Exposure in Children and Adolescents						
† Jiang et al. (2023) n = 15,331 Nationwide, China September 2017–October 2017 Cross-Sectional	Grade 7–11 students from middle schools, general high schools, and vocational high schools were selected using multistage stratified cluster random sampling of 15 districts/counties from 11 cities in 11 provinces across China	Ensemble machine learning model Cross-validation r^2 = 0.84 Averaging time: NO ₂ - annual average Exposure yr: 2016–2017	NO ₂ (ppb) Mean = 19.99±4.47 (37.62±8.42 ug/m ³) Median = 20.6 (IQR 3.9) (38.7 ug/m ³) P25 = 15.1 (28.5 ug/m ³) P75 = 24.5 (46.1 ug/m ³)	CES-D GAD-7	Generalized linear mixing effect model Adjusted for: age, gender, ethnicity, urbanization, whether the only child, parent's education, geographical location, area-level gross domestic product (GDP), area-level normalized difference vegetation index (NDVI400), and area-level average annual temperature	OR (95% CI) ^b Depressive Symptoms-Score ≥10: 1.00 (0.97, 1.03) Anxiety Symptoms-Score ≥5: 0.97 (0.95, 1.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					birth order.	
Long-Term Exposure in Adults						
† Abed Al Ahad et al. (2022)	Adults aged ≥16 yr from England, Wales, Scotland, and Northern Ireland.	Dispersion model	NO ₂ (ppb)	GHQ-12 (0–12) score ≥2	Logistic regression	OR (95% CI) ^b
UKHLS		Averaging time: NO ₂ - annual average	Mean = ranged 13.1–18.8 µg/m ³ during 2009–2019 (estimated from figure)	GHQ-12 (0–12) score ≥4	Adjusted for: age, gender, ethnicity, country of birth, marital status, education, occupation, perceived financial situation, smoking status and year dummies (2009–2019)	Psychological Distress - LSOAs Level: 1.28 (1.22, 1.34)
n = 60,146		Exposure yr: 2009–2019				Psychological Distress - Local Authority Level: 1.26 (1.19, 1.33)
Nationwide, U.K.						Severe Psychological Distress - LSOAs Level: 1.24 (1.17, 1.31)
Wave 1: 2009–2010						Severe Psychological Distress - Local Authority Level: 1.20 (1.12, 1.28)
Follow-up: 2019						
Panel						
† Feng et al. (2023)	Adults aged 40–69 yr who were registered with the UK NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales.	Spatiotemporal/geospatial model	NO ₂ (ppb)	Hospital records (ICD-10 codes F32–33)	Cox proportional hazards regression	NO ₂
UK Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 9.73±3.2 (18.3±6.1 µg/m ³)	Hospital records (ICD-10 codes F40–41)	Adjusted for: age, sex, ethnicity, household income, physical activity, Townsend deprivation index, time spent outdoors, residential area, percentage of green space, and ambient temperature	HR (95% CI) ^b
n = 72,908		Exposure yr: 2006–2021	NO _x (µg/m ³)	Hospital records (ICD-10 codes F00–99)		Depressive Disorders Dx - IPW: 1.12 (1.05, 1.20)
Nationwide, U.K.			Mean = 27.4±11.2			Anxiety Disorders Dx - IPW: 1.21 (1.13, 1.29)
Enrollment: 2006–2010	Participants with MDD at baseline or had missing information on air pollution were excluded.					Mental Disorders Dx - IPW: 1.18 (1.15, 1.19)
Follow-up: Baseline survey–December 2019						NO _x
Cohort						HR (95% CI) ^c
						Depressive Disorders Dx - IPW: 1.05 (0.98, 1.12)
						Anxiety Disorders Dx - IPW: 1.18 (1.11, 1.25)
						Mental Disorders Dx - IPW: 1.16 (1.13, 1.19)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Fu et al. (2022)	Adults aged 40–69 yr who were registered with the UK NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales. Participants with MDD at baseline or had missing information on air pollution were excluded.	LUR	NO ₂ (ppb)	Hospital records (ICD-10 code F32)	Cox proportional hazards regression	NO ₂
UK Biobank n = 490,780		LOOCV = r^2 = 0.87 for NO ₂ and 0.88 for NO _x	NR		Adjusted for: age (continuous), sex (male/female), race (white/Mixed/Asian or Asian British/Black or Black British), alcohol consumption (never/previous/current/missing), smoking status (never/previous/current/missing), body mass index (<25 kg/m ² /25 to 29.9 kg/m ² /≥30 kg/m ² /missing), physical activity (continuous, MET-min/week), diabetes at baseline (yes/no) and hypertension at baseline (yes/no).	HR (95% CI) ^b Depression Dx: 1.14 (1.09, 1.19)
Nationwide, U.K. Enrollment: 2006–2010 Follow-up: Baseline survey–December 2019 Cohort		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: 2005–2007 and 2010 for NO ₂ ; 2010 for NO _x	NR			HR (95% CI) ^c Depression Dx - Tertile 2 vs. Tertile 1: 1.11 (1.06, 1.16) Depression Dx - Tertile 3 vs. Tertile 1: 1.14 (1.09, 1.19) NO _x HR (95% CI) ^c Depression Dx: 1.04 (1.03, 1.05) Depression Dx - Tertile 2 vs. Tertile 1: 1.10 (1.06, 1.15) Depression Dx - Tertile 3 vs. Tertile 1: 1.16 (1.12, 1.21)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Gandini et al. (2018)	Individuals from families residing in 1442 municipalities across Italy	Hybrid model	NO ₂ (ppb)	Hospital and mortality records (ICD-9 codes 290–319)	Cox proportional hazards regression	HR (95% CI) ^b
ILS		CTM fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity.	Men Metropolitan Mean = 22.1±6.16 (41.5±11.6 ug/m ³) Rural Mean = 10.3±4 (19.3±8 ug/m ³) Urban Mean = 13.9±5.2 (26.1±9.7 ug/m ³)		Adjusted for: age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality (rural, urban, metropolitan areas) and BMI	Hospital Admissions for Mental, Behavioral and Neurodevelopmental Disorders: 0.98 (0.88, 1.09)
N = 74,989			Women Metropolitan Mean = 22.1±6.16 (41.6±11.6 ug/m ³) Rural Mean = 10.3±4.2 (19.3±7.9 ug/m ³) Urban Mean = 13.9±5.1 (26.1±9.6 ug/m ³)			
Italy		Averaging time: NO ₂ - annual average				
Enrollment: 1999–2000		Exposure yr: 1999, 2003, 2005, 2007				
Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Gao et al. (2023)	Adults aged 37–73 yr who were registered with the UK NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales	LUR	NO ₂ (ppb)	PHQ-4 or hospital records (ICD-9 code 300 or ICD-10 codes F40–F41)	Logistic regression	NO ₂
UK Biobank n = 398,241		LOOCV $r^2 = 0.87$ for NO ₂ and 0.88 for NO _x	Mean = 15.42±4.87 (29.01±9.17 ug/m ³) IQR = 5.777 (10.87 ug/m ³)		Adjusted for: age, sex, BMI, race, smoking status, healthy alcohol intake status, healthy physical activity status, yr of education, FEV ₁ , FVC, Townsend deprivation index, urbanicity, and prevalent hypertension, CHD, and diabetes.	OR (95% CI) ^b Anxiety Dx or Symptoms - Baseline: 1.05 (1.03, 1.08) Depression Dx or Symptoms - Baseline: 1.14 (1.12, 1.17) Anxiety Dx or Symptoms - Follow-Up: 1.12 (1.07, 1.18) Depression Dx or Symptoms - Follow-Up: 1.09 (1.04, 1.14)
Nationwide, U.K. Enrollment: 2006–2010 Follow-up: 2016–2017 Cohort		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: 2005–2007 and 2010 for NO ₂ ; 2010 for NO _x	Min = 4.71 (8.86 ug/m ³) Max = 66.501 (125.13 ug/m ³) P25 = 12.09 (22.75 ug/m ³) P75 = 17.87 (33.62 ug/m ³) NO _x (ug/m ³) Mean = 43.68±15.54 IQR = 16.53 Min = 19.74 Max = 265.94 P25 = 22.75 P75 = 33.62	PHQ-4 or hospital records (ICD-9 code 311 or ICD-10 codes F32–F33)		NO _x OR (95% CI) ^c Anxiety Dx or Symptoms - Baseline: 1.04 (1.03, 1.06) Depression Dx or Symptoms - Baseline: 1.06 (1.05, 1.08) Anxiety Dx or Symptoms - Follow-Up: 1.04 (1.01, 1.06) Depression Dx or Symptoms - Follow-Up: 1.03 (1.00, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Hautekiet et al. (2022) BHIS n = 16,455 Nationwide, Belgium 2008, 2013, 2018 Cross-Sectional	Participants ≥15 yr who completed the mental health modules and lived at least one yr at the current address. BHIS participants were sampled from the Belgian National Register based on a multistage stratified sampling design.	Spatiotemporal/geospatial model LOOCV $r^2 = 0.78$ Averaging time: NO ₂ - annual average Exposure yr: 2009–2010, 2013, 2018	NO ₂ (ppb) Mean = 11.6 (21.8 ug/m ³) Median = 10.8 (IQR 5.74) (20.3 ug/m ³) (IQR 10.8 ug/m ³) P25 = 8.61 (16.2 ug/m ³) P75 = 14 (27 ug/m ³)	GHQ-12 (0–12) score ≥4 SCL-90-R BHIS question SF-36 GHQ-12 (0–12) score ≥2	Logistic regression Adjusted for: age, gender, year, region, highest education of the household, household composition, country of birth, smoking status and the quadratic term of age when both the linear and quadratic term were significant	OR (95% CI) ^b Psychological Distress: 1.11 (0.98, 1.25) Severe Psychological Distress: 1.07 (0.92, 1.24) Depressive Disorder: 1.13 (0.93, 1.36) Suicidal Ideation: 1.05 (0.83, 1.33) Suboptimal Vitality: 1.24 (1.06, 1.44) Poor Self-Rated Health: 1.26 (1.11, 1.42) Generalized anxiety Disorder: 1.11 (0.87, 1.41)
† Kim et al. (2020) EPINEF n = 2,729 Seoul, Incheon, Wonju, Pyeongchang, South Korea March 2014–November 2017 Cross-Sectional	Adults aged ≥50 yr with no Dx of dementia, movement disorders, and stroke	Spatiotemporal/geospatial model 5-fold cross-validation $r^2 = 0.82$ Averaging time: NO ₂ -5-year Exposure yr: 2010	NO ₂ (ppb) Men Mean = 11.64±6.32 (21.91±11.9 ug/m ³) Women Mean = 14.02±6.207 (26.38±11.68 ug/m ³)	SGDS-K	Linear regression Adjusted for: age, gender, systolic blood pressure, BMI, smoking status and alcohol drinking, education level, income, physical activity, daily life condition, and disease morbidities	β (Score) (95% CI) ^b Depressive Symptoms: 0.0120 (0.0060, 0.0181)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Klompaker et al. (2019)	Dutch citizens ≥19 yr	LUR	NO ₂ (ppb)	Prescriptions from national obligatory health insurance database	Logistic regression	OR (95% CI) ^b
PHM		LOOCV (r ² Method validation NR)	Median = 12.4 (IQR 4.17) (23.4 ug/m ³ (IQR 7.85 ug/m ³)		Adjusted for: sex, age, marital status, region of origin, education, paid occupation, household income, neighborhood SES, smoking status, alcohol use and degree of urbanization	Hypnotics and Sedatives: 1.34 (1.17, 1.54) Psychological Distress - K10 ≥30: 1.20 (1.13, 1.29) Anxiolytics: 1.37 (1.25, 1.50) Antidepressants: 1.07 (1.01, 1.14)
n = 354,827						
Nationwide, Netherlands		Averaging time: NO ₂ - annual average		K10 score ≥30		
2012						
Cross-Sectional		Exposure yr: NR				
† Li et al. (2023a)	Adults aged 40–69 yr who were registered with the UK NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales. Participants with MDD at baseline or had missing information on genetic data and air pollution were excluded	LUR	NO ₂ (ppb)	Hospital and mortality records (ICD-10 codes F32 and F33)	Cox proportional hazards regression	NO ₂
UK Biobank		LOOCV r ² = 0.87 for NO ₂ and 0.88 for NO _x	Mean = 14.04±4.03 (26.41±7.59 ug/m ³)		Adjusted for: age, gender, ethnicity, education level, employment status, household income, and Townsend deprivation index	HR (95% CI) ^c
n = 354,897			NO _x (ug/m ³)			MDD Dx - NO ₂ Q2 vs. Q1: 1.02 (0.98, 1.07) MDD Dx - NO ₂ Q3 vs. Q1: 1.02 (0.98, 1.07) MDD Dx - NO ₂ Q4 vs. Q1: 0.99 (0.94, 1.04) HR (95% CI) ^b MDD Dx - Continuous: 1.00 (0.96, 1.04)
Nationwide, U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 43.68±15.55			NO _x
Enrollment: 2006–2010 Follow-up: 2011–2021						HR (95% CI) ^c MDD Dx - NO _x Q2 vs. Q1: 1.06 (1.01, 1.12) MDD Dx - NO _x Q3 vs. Q1: 1.05 (1.00, 1.11) MDD Dx - NO _x Q4 vs. Q1: 1.07 (1.02, 1.13) MDD Dx - Continuous: 1.02 (1.01, 1.05)
Cohort		Exposure yr: 2010				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Petkus et al. (2021a) WHIMS n = 6,118 Nationwide, U.S. Enrollment: 1996–1999 Follow-up: 1 yr Cohort	Postmenopausal women aged ≥65 yr across 48 states and free of dementia at baseline	Spatiotemporal/geospatial model Cross-validation r ² = 0.84. Averaging time: NO ₂ - annual average Exposure yr: 1993–1996	NO ₂ (ppb) Mean = 16.1±6.9 Median = 15.6 P25 = 10.9 P75 = 19.9	Latent emotional distress factor (combined scores from the 6-item CES-D and the 5-item emotional wellbeing scale from SF-36)	Structural equation model Adjusted for: initial age at WHIMS-ECHO, race/ethnicity, geographic region of residence, employment status, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, and hypertension, diabetes, and history of cardiovascular disease).	β (Score) (95% CI) ^b Depressive Symptoms - Recent Exposure: -0.028 (-0.061, 0.005)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Petkus et al. (2021b) WHIMS-ECHO n = 1,583 Nationwide, U.S. Enrollment: 2008 Follow-up: 2008–2016 Cohort	Community-dwelling women ≥80 yr and dementia-free at baseline	Spatiotemporal/geospatial model Averaging time: NO ₂ -3-year Exposure yr: 1995–1997 for remote exposure; 2005–2007 for recent exposure	NO ₂ (ppb) Remote exposure (10 yr before baseline) Mean = 16.22±7.28 Median = 15.3 (IQR 9.55) P25 = 10.9 P75 = 20.4	GDS-15	Structural equation model Adjusted for: initial age at WHIMS-ECHO, race/ethnicity, geographic region of residence, employment status, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, and hypertension, diabetes, and history of cardiovascular disease), and neighborhood socioeconomic characteristics.	β (Score) (95% CI) ^b Depressive Symptoms - Remote Exposure: 0.301 (0.109, 0.492) Depressive Symptoms - Recent Exposure: 0.238 (-0.038, 0.513)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Petkus et al. (2022) WHIMS-MRI n = 764 Nationwide, U.S. Enrollment: 2008 Follow-up: 2008–2018 Cohort	Community-dwelling women ≥80 yr and dementia-free at baseline	Spatiotemporal/geospatial model cross-validation r ² = 0.85 for NO ₂ Averaging time: NO ₂ -3-year Exposure yr: 2002–2005	NO ₂ (ppb) Mean = 12.47±6.25 Median = 11.1 (IQR 7.8) P25 = 8.1 P75 = 15.3	GDS-15	Structural equation model Adjusted for: age at MRI, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking; alcohol use; physical activities), neighborhood socioeconomic characteristics, and clinical characteristics (any prior hormone use, hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease) Adjusted for: education, region of residence, race/ethnicity, and cardiovascular disease	β (z-score standardized (based on initial WHIMS-ECHO mean and standard deviation) 3-quantile-spline transformed GDS-15 scores) (95% CI) ^b Depressive Symptoms - Baseline: -0.094 (-0.210, 0.022) Depressive Symptoms - Annual Linear Change: 0.029 (0.004, 0.054)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Qiu et al. (2023a) Medicare denominator and Medicare CCW n = 8,907,422 Nationwide, U.S. Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr) Cohort	All continuously enrolled Medicare beneficiaries in the contiguous U.S. without prevalent depression 5 yr after first enrollment	Ensemble machine learning model Cross-validation r^2 ranged 0.692–0.804 for yr 2000–2016 ($r^2 = 0.788$ total) Averaging time: NO ₂ - annual average, NO ₂ - 5-year moving average Exposure yr: 2000–2016	NO ₂ (ppb) Median = 15.4 P25 = 10.4 P75 = 23.1	CCW algorithm combining Medicare claims and ICD-9/10 codes	Cox proportional hazards regression Adjusted for: calendar year, region, temperature, precipitation, Normalized Difference Vegetation Index, population density, community poverty, low education rate, nearest hospital distance, percentage ambulatory visit level, percentage Black individuals, percentage Asian individuals, percentage Hispanic individuals, community smoking rate, percentage renting, and income extreme index (community psychosocial stress proxy).	HR (95% CI) ^b Depression Dx - lag0: 1.008 (1.003, 1.013) Depression Dx - lag1: 1.006 (1.000, 1.012) Depression Dx - lag3: 1.010 (1.005, 1.015) Depression Dx - lag5: 1.014 (1.010, 1.018) Depression Dx - 5-yr MA: 1.016 (1.010, 1.022)

† Sakhvidi et al. (2022)	Adults aged 18–69 randomly selected from 22 health screening centers in 20 departments distributed over a large area of metropolitan France, including both urban and rural areas	LUR	NO ₂ (ppb)	CES-D	Logistic regression	IRR (95% CI) ^b
CONSTANCES		Hold-out validation $r^2 = 0.575$.	Female Mean = 14.1±6.558 (26.6±12.34 ug/m ³)	CES-D score ≥ 19	Adjusted for: age, sex, education, income, alcohol drinking habits, smoking status, neighborhood deprivation, the mo of completion of the questionnaire, day of the week of completion of the questionnaire, recruitment center, body mass index, non-occupational physical activity, perceived health status, self-reported cardiovascular diseases, and type-2 diabetes	Depressive Symptoms - Total Score: 1.030 (1.017, 1.044) Depressed Affect: 1.087 (1.061, 1.113) Disturbed Interpersonal Relationships: 1.032 (0.994, 1.072) Low Positive Affect: 1.013 (0.999, 1.027) Somatic Complaints: 1.017 (1.003, 1.032)
n = 123,754						
Nationwide, France		Averaging time: NO ₂ - annual average	Male Mean = 14.12±6.558 (26.56±12.34 ug/m ³)			
2012–2020						
Cross-Sectional		Exposure yr: 2010	Total Mean = 14.13±6.558 (26.58±12.34 ug/m ³)		Negative binomial regression Adjusted for: age, sex, education, income, alcohol drinking habits, smoking status, neighborhood deprivation, the mo of completion of the questionnaire, day of the week of completion of the questionnaire, recruitment center, body mass index, non-occupational physical activity, perceived health status, self-reported cardiovascular diseases, and type-2 diabetes	OR (95% CI) ^b Clinically Significant Elevated Depressive Symptoms: 1.085 (1.037, 1.135)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					diabetes	
† Wu et al. (2023)	Individuals aged ≥60 yr residing in the Kungsholmen district, Stockholm, Sweden, without prevalent dementia, intellectual disability, schizophrenia, prevalent depression or depressive symptoms	Dispersion model	NO _x (ug/m ³)	CPRS	Cox proportional hazards regression	HR (95% CI) ^c Depression Dx: 1.26 (1.01, 1.58)
SNAC-K		Model validated using linear regression against measurements at three traffic monitoring places and one urban background place (r ² =0.99)	Mean = 32.2±11.4		Adjusted for: age (timescale), sex, education, neighborhood household mean income, baseline year, birth year (strata), SES, smoking, alcohol consumption, number of medications, 3-year average levels of green space at 100 m buffer and road traffic noise before baseline	
n = 2,812						
Nationwide, Sweden						
Enrollment: March 2001–June 2004						
Follow-up: 6 yr (aged <78 yr) or 3 yr (aged ≥78 yr)						
Cohort		Averaging time: NO _x - annual average				
		Exposure yr: 1990, 1995, 2000, 2005, 2011				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yang et al. (2023)	Adults aged 40–69 yr who were registered with the UK NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales.	LUR	NO ₂ (ug/m ³)	Hospital records (ICD-10 codes F32–33)	Cox proportional hazards regression	NO HR (95% CI) ^c
UK Biobank n = 389,185	Participants with MDD at baseline or had missing information on air pollution were excluded	Models validated using LOOCV $r^2 = 0.82$ for NO ₂ ; $r^2 = 0.78$ for NO _x	Median = 26 P25 = 21.3 P75 = 31.1	Hospital records (ICD-10 codes F40–48)	Adjusted for: age, sex, assessment center, ethnicity, length of time at residence, Townsend deprivation index, education level, employment status, 24-h weighted average noise, and proximity to major roads.	Anxiety Dx Quartile 2 vs. Quartile 1: 1.13 (1.01, 1.18) Quartile 3 vs. Quartile 1: 1.08 (1.03, 1.15) Quartile 4 vs. Quartile 1: 1.08 (1.03, 1.14)
Nationwide, U.K. Enrollment: 2006–2010 Follow-up: Baseline survey–February 2020 Cohort		Averaging time: NO ₂ - annual average, NO - annual average	Median = 15.9 P25 = 11.6 P75 = 20.6			Depression Dx Quartile 2 vs. Quartile 1: 1.07 (1.02, 1.13) Quartile 3 vs. Quartile 1: 1.11 (1.06, 1.17) Quartile 4 vs. Quartile 1: 1.12 (1.06, 1.18)
		Exposure yr: 2008–2011				NO ₂ HR (95% CI) ^c Anxiety Dx Quartile 2 vs. Quartile 1: 1.06 (1.01, 1.11) Quartile 3 vs. Quartile 1: 1.09 (1.04, 1.14) Quartile 4 vs. Quartile 1: 1.10 (1.05, 1.15) Depression Dx Quartile 2 vs. Quartile 1: 1.11 (1.06, 1.17) Quartile 3 vs. Quartile 1: 1.15 (1.09, 1.22) Quartile 4 vs. Quartile 1: 1.14 (1.07, 1.21)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Short-Term Exposure						
† Gu et al. (2020)	Urban employees, retirees, and residents, including children, students, older adults without previous employment, and the unemployed, residing in 75 cities prefecture-level and above in mainland China	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure yr: 2014–2017	NO ₂ (ppb) Northern region Mean = 19.9±10.7 (37.5±20.2 ug/m ³) Median = 18.1 (IQR 13.9) (34.1 ug/m ³) (IQR 26.2 ug/m ³) Min = 0.69 (1.3 ug/m ³) Max = 111.2 (209.3 ug/m ³) Southern region Mean = 16.7±9.19 (31.5±17.3 ug/m ³) Median = 14.9 (IQR 11.6) (28.1 ug/m ³) (IQR 21.9 ug/m ³) Min = 0.5 (1 ug/m ³) Max = 152.3 (286.6 ug/m ³) Total Mean = 18.4±10.2 (34.6±19.1 ug/m ³) Median = 16 (IQR 12.9) (31 ug/m ³) (IQR 24.3 ug/m ³) Min = 0.5 (1 ug/m ³) Max = 152.3 (286.6 ug/m ³)	Hospital admissions (ICD-10 codes F32 and F33)	Generalized additive model with quasi-Poisson regression Adjusted for: day of week, public holidays, temperature, relative humidity, and calendar time	β (percent change) (95% CI) ^b HA for Depression - lag 01: 6.70 (2.75, 10.65)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Lu et al. (2020) n = 111,842 Shenzhen, Changsha, Guangzhou, Changchun, Chengde, Fuzhou, Hohhot, Jinan, Lanzhou, Nanjing, Qingdao, Suzhou, Xining, China January 2013–December 2015 Case-crossover	Patients with outpatient visits for mental disorders from the largest hospitals in 13 Chinese cities	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure yr: 2013–2015	NO ₂ (ppb) Jinan (highest) Mean = 28.29 (53.23 ug/m ³) Fuzhou (lowest) Mean = 17.43 (32.79 ug/m ³)	Hospital outpatient visits for anxiety, depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, ADHD, and autism	Logistic regression Adjusted for: daily temperature, relative humidity and wind speed	β (percent change) (95% CI) ^b Hospital Outpatient Visit for Mental Disorders (Depression, Anxiety, Others) - lag 05: 14.214 (10.443, 17.985)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ma et al. (In Press) UEBMI and URBMI n = 84,207 Nationwide, China January 2013–December 2017 Time-series	Urban employees, retirees, and residents, including children, students, older adults without previous employment, and the unemployed, residing in 75 cities prefecture-level and above in mainland China	Central site monitor Averaging time: NO _x - 24-hour average Exposure yr: 2013–2017	NO ₂ (ppb) Northern Region Mean = 21.2±10.8 (39.8±20.3 ug/m ³) Median = 19.3 (IQR 14) (36.3 ug/m ³) (IQR 26.3 ug/m ³) P5 = 6.06 (11.4 ug/m ³) P95 = 38.6 (72.6 ug/m ³) Overall Mean = 19.0±10.3 (36±19.4 ug/m ³) Median = 17.1 (IQR 13) (32.2 ug/m ³) (IQR 25 ug/m ³) P5 = 5.37 (10.1 ug/m ³) P95 = 35.2 (66.2 ug/m ³) Southern Region Mean = 17.1±9.35 (32.1±17.6 ug/m ³) Median = 15.2 (IQR 11.9) (28.6 ug/m ³) (IQR 22.4 ug/m ³) P5 = 7.28 (13.7 ug/m ³) P95 = 41.3 (77.7 ug/m ³)	Hospital admissions (ICD-10 codes F32 and F33)	Generalized additive model with quasi-Poisson regression Adjusted for: day of week, public holidays, temperature, relative humidity, and calendar time	β (percent change) (95% CI) ^b HA for Depression - lag 02: 7.15 (2.92, 11.38)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Qiu et al. (2022) Medicare n = Depression case days: 458,492 Depression control days: 1,552,408 Nationwide, U.S. January 2000–December 2016 Case-crossover	All patients aged ≥65 yr enrolled in Medicare with a primary Dx of identified psychiatric disorder	Ensemble machine learning model 10-fold cross- validation r ² = 0.79. Averaging time: NO ₂ - 24-hour average Exposure yr: 2000–2016	NO ₂ (ppb) Depression Median = 18.24 P25 = 10.7 P75 = 29.25	Hospital admissions (ICD-9 codes 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, and 311.xx; ICD-10 codes F32.xx, F33.xx, F34.1x, F39.xx, and F43.21)	Logistic regression Adjusted for: precipitation	β (percent change) (95% CI) ^b HA for Depression - lag 02: 1.40 (0.14, 2.66)

† Szyszkowicz et al. (2016)	All patients in Ontario hospitals admitted to the ED for depression	Central site monitor	NO ₂ (ppb)	Hospital admissions (ICD-10 codes F32 and F33)	Logistic regression	OR (95% CI) ^b
NACRS			City: Algoma		Adjusted for: daily temperature and humidity	ED Visit for Depression - lag 0, Male:
n = 118,602 visits		Averaging time: NO ₂ - 24-hour average	Mean = 5.1 IQR = 4 Min = 0 Max = 24			1.034 (0.972, 1.099) ED Visit for Depression - lag 1, Male:
Ontario, Canada						0.982 (0.924, 1.045) ED Visit for Depression - lag 5, Male:
April 2004–December 2011		Exposure yr: 2004–2011	City: Halton Mean = 12.9 IQR = 7.7 Min = 1 Max = 51.2			0.991 (0.933, 1.053) ED Visit for Depression - lag 8, Male:
Case-crossover						0.967 (0.911, 1.027) ED Visit for Depression - lag 0, Female:
			City: Hamilton Mean = 13.9 IQR = 9.5 Min = 1.7 Max = 63			1.059 (1.006, 1.114) ED Visit for Depression - lag 1, Female:
						1.029 (0.978, 1.082) ED Visit for Depression - lag 5, Female:
			City: London Mean = 10.9 IQR = 7 Min = 0 Max = 51			0.974 (0.927, 1.023) ED Visit for Depression - lag 8, Female:
						1.000 (0.952, 1.050)
			City: Ottawa Mean = 8.7 IQR = 7 Min = 1 Max = 47			
			City: Peel Mean = 13.2 IQR = 9.5 Min = 2 Max = 54			
			City: Toronto			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 18.5 IQR = 9.4 Min = 4.5 Max = 62.1			
			City: Windsor Mean = 15.6 IQR = 8.1 Min = 2.4 Max = 55.5			
			City: York Mean = 8.2 IQR = 7 Min = 0 Max = 47			
			Pooled all cities IQR = 9			

List of abbreviations in alphabetical order: ABCD = Amsterdam-Born Children and Their Development Study; ADHD = attention-deficit/hyperactivity disorder; BHIS = Belgian Health Interview Survey; BMI = body mass index; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CBCL = Child Behavior Checklist; CCW = Chronic Conditions Warehouse; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; CONSTANCES = Cohorte des consultants des Centres d'examens de santé; COI = child opportunity index; CPRS = Comprehensive Psychopathological Rating Scale; CTM = chemical transport model; DLM = distributed lag model; Dx = diagnosis; ED = emergency department; EDEN = Etude des Determinants pre-et postnatals du developpement et de la sante de l'Enfant; EPINEF = Environmental Pollution-Induced Neurological Effects; ESCAPE = European Study of Cohorts for Air Pollution Effects; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GAD-7 = General Anxiety Disorder-7; GASPII = Gene and Environment Prospective Study on Infancy in Italy; GDS = Geriatric Depression Scale; GHQ = General Health Questionnaire; GINIplus = German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy; HA = hospital admission; HR = hazard ratio; ICD = International Classification of Diseases; ILS = Italian Longitudinal Study; INMA = Infancia y Medio Ambiente; IPW = inverse probability weighting; IQR = interquartile range; IRR = incidence rate ratio; K10 = Kessler psychological distress scale; LISA = Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Childhood; LOOCV = leave-one-out cross-validation; LSOAS = Lower layer Super Output Areas; LUR = land use regression; Max = maximum; Min = minimum; MDD = major depressive disorder; mo = month; NACRS = National Ambulatory Care Reporting System; NHS = National Health Service; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; NR = not reported; OR = odds ratio; P = percentile; PHM = Dutch Public Health Monitor; ppb = parts per billion; RR = risk ratio; REPRO_PL = Polish Mother and Child Cohort Study; RMSE = root mean square error; SCL-90-R = Symptom Checklist-90-Revised; SDQ = Strengths and Difficulties Questionnaire; SF-36 = Short-Form-36; SGDS-K = Geriatric Depression Scale-Short Form Korean Version; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; UEBMI = Urban Employee-Based Basic Medical Insurance; UKHLS = Understanding Society: The UK Household Longitudinal Study; URBMI = Urban Resident-Based Basic Medical Insurance; vs. = versus; WHIMS = Women's Health Initiative Memory Study; WHIMS-ECHO = Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; WHIMS-MRI = Women's Health Initiative Memory Study Magnetic Resonance Imaging; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-10 Toxicological studies of oxides of nitrogen exposure and anxiety, depression, and psychological distress

Study Details and Population	Exposure Details	Endpoints Examined*
† Li et al. (2021)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J) 7-wk-old, males and females n = 3–15/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	- EPM (time in closed arms) (NS) - EPM (time in open arms) (♂↓) - FST (immobility) (♂↑) - OFT (time in center) (♂↓)
† Li et al. (2022a)	Whole body inhalation with room air controls	21–23 d after exposure
Mouse (C57BL/6J) developmental exposure (GD 0 to PND 0), males and females n = 3–15/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	- EPM (time in closed arms) (♂↑) - EPM (time in open arms) (♂↓) - FST (immobility) (♂↑) - OFT (time in center) (♂↓)
Tabacova et al. (1985)	Whole body inhalation with room air controls	21 d after exposure
Rat (Wistar) developmental exposure (GD 0 to GD 21), males and females n = 4–20/group	27 ppb (0.05 mg/m ³) NO ₂ , 6 hr/d for 21 d 53 ppb (0.1 mg/m ³) NO ₂ , 6 hr/d for 21 d 532 ppb (1.0 mg/m ³) NO ₂ , 6 hr/d for 21 d 5,318 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 21 d	21 d after exposure - OFT (objects explored, rearings, self-grooming, defecation) (NS) 30 d after exposure - OFT (objects explored, self-grooming, defecation) (NS) - OFT (rearings) (♂↓) 60 d after exposure - OFT (rearings, objects explored, self-grooming, defecation) (NS)

List of abbreviations in alphabetical order: d = day; EPM = elevated plus maze; FST = forced swim test; GD = gestational day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; OFT = open field test; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week(s).

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↓ = at least one experimental group had a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-11 Epidemiologic studies of oxides of nitrogen exposure and schizophrenia

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Long-Term Exposure						
† Antonsen et al. (2020)	National register of all people born in Denmark between 1980–1984, residing in Denmark at age 10 yr and has two Danish-born parents.	Dispersion model	NO ₂ (ppb)	Psychiatric Central Research Register, which includes information on inpatient psychiatric HA or outpatient episode when the Dx was assigned	Poisson regression	NO ₂
Danish Civil Registration System		Averaging time: NO ₂ -10-year	Capital Mean = 16.2±1.3 (30.4±2.5 ug/m ³)		Adjusted for: age, calendar year, gender, parental mental illness, parental socioeconomic position, and degree of urbanization at tenth birthday	IRR (95% CI) ^b Schizophrenia Dx: 1.41 (1.17, 1.70)
n = 230,844		Exposure yr: birth–10 yr	Capital suburb Mean = 15±1.5 (28.3±2.9 ug/m ³)			NO _x
Nationwide, Denmark			Provincial city Mean = 12.3±2 (23.1±3.7 ug/m ³)			IRR (95% CI) ^c Schizophrenia Dx: 1.06 (1.02, 1.10)
Enrollment: January 1980–December 1984			Provincial town Mean = 10±2.9 (18.9±5.4 ug/m ³)			
Cohort			Rural area Mean = 8.82±2.3 (16.6±4.3 ug/m ³)			
			NO _x (ug/m ³)			
			Capital Mean = 44.1±5.2			
			Capital suburb Mean = 42.1±5.8			
			Provincial city Mean = 41.3±14.1			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Provincial town Mean = 26.5±13.7			
			Rural area Mean = 21.9±8.8			
† Newbury et al. (2019)	Nationally representative birth cohort of monozygotic and dizygotic twin pairs born between January 1, 1994, and December 4, 1995, across England and Wales.	CMAQ	NO ₂ (ug/m ³)	Parent interview at 12 yr of age on seven symptoms drawing from instruments used in previous studies in other cohorts.	Ordinal logistic regression	NO ₂
E-Risk Longitudinal Twin Study n = 2063		Model validated against central site monitors (r ² = 0.81 for NO ₂ ; r ² = 0.79 for NO _x).	Mean = 20.18±9.68 Min = 2.31 Max = 67.89		Adjusted for: family socioeconomic status, family psychiatric history, maternal psychosis, childhood psychotic symptoms, adolescent smoking, cannabis dependence, alcohol dependence, neighborhood socioeconomic status, neighborhood crime, and neighborhood social conditions	OR (95% CI) ^c Clinically Verified Psychotic Symptoms: 1.76 (0.82, 3.79) Psychotic Experiences: 1.01 (1.00, 1.03) Psychotic Experiences, Quartile 2 vs. Quartile 1: 0.70 (0.50, 0.99) Psychotic Experiences, Quartile 4 vs. Quartile 1: 1.41 (0.98, 2.03) Psychotic Experiences, Quartile 4 vs. Quartile 1–Quartile 3: 1.71 (1.28, 2.28)
Nationwide, England, Wales		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 25.79±16.28 Min = 2.48 Max = 151.08	Interview at 18 yr of age on prodromal psychotic experiences occurring between 12–18 yr drawing from the Prevention through Risk Identification, Management and Education (PRIME)-screen and the Structured Interview for Psychosis-Risk Syndromes (SIPS)		NO _x
Enrollment: January 1999–December 2000 (age 5 yr) Follow-up: 2012–2014 (age 18 yr)		Exposure yr: 2012				OR (95% CI) ^c Clinically Verified Psychotic Symptoms: 1.79 (0.84, 3.83) Psychotic Experiences, Quartile 4 vs. Quartile 1: 1.37 (0.97, 1.92) Psychotic Experiences, Quartile 2 vs. Quartile 1: 0.65 (0.46, 0.91) Psychotic Experiences:
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						1.01 (1.00, 1.02) Psychotic Experiences, Quartile 4 vs. Quartile 1–Quartile 3: 1.72 (1.30, 2.29)
† Qiu et al. (2023b)	Inpatient admissions with a primary Dx of psychotic disorders (ICD 9, 10) with hospital and residential addresses located in the same state	Ensemble machine learning model Averaging time: NO ₂ - annual average Exposure yr: 2002–2016	NO ₂ (ppb) Median = 15.8 (IQR 14.6) P25 = 10.5 P75 = 25.1	Primary Dx of psychotic disorders (using ICD-9 and -10 codes) in State Inpatient Databases	Zero-inflated negative binomial regression Adjusted for: ambient temperature, cumulative precipitation, solar radiation, area-level SES (poverty, education, ambulatory visit level, smoking rates, racial income disparities), population density, admission state, admission year, and individual demographics (age, sex, race/ethnicity, primary Dx	RR (95% CI) ^b HA for Psychotic Disorder: 1.18 (1.16, 1.20)
HCUP n = 1,211,100 New York, North Carolina, Michigan, New Jersey, Maryland, Arizona, Rhode Island, Washington, U.S. 2002–2016 Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Short-Term Exposure						
† Qiu et al. (2022)	All patients aged ≥65 yr enrolled in Medicare with a primary Dx of identified psychiatric disorder	Ensemble machine learning model	NO ₂ (ppb)	HA (ICD-9 code 295.xx; ICD-10 codes F20.xx, F25.0x, and F25.1x)	Logistic regression	β (percent change) (95% CI) ^b
Medicare			Schizophrenia		Adjusted for:	HA for schizophrenia - lag 02:
Schizophrenia case days: 165,572		10-fold cross-validation r ² = 0.79.	Median = 21.25		precipitation	2.56 (0.80, 4.32)
Schizophrenia control days: 562,745			P25 = 12.4			
Nationwide, U.S.		Averaging time: NO ₂ - 24-hour average	P75 = 32.93			
January 2000–December 2016		Exposure yr: 2000–2016				
Case-crossover						

List of abbreviations in alphabetical order: CI = confidence interval; CMAQ = Community Multiscale Air Quality; Dx = diagnosis; E-Risk = Environmental Risk; HA = hospital admission; HCUP = Health Cost and Utilization Project; ICD = International Classification of Diseases; IQR = interquartile range; IRR = incidence rate ratio; Max = maximum; Min = minimum; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; OR = odds ratio; P = percentile; ppb = parts per billion; RR = risk ratio; vs. = versus; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-12 Epidemiologic studies of oxides of nitrogen exposure and general cognitive decline

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)	
† Cullen et al. (2018)	Adults aged 40–69 yr registered with the NHS, living within 25 miles study assessment centers across England, Scotland, and Wales	LUR, Hybrid model	NO ₂ (ppb)	Reasoning	β estimates were obtained using linear regression, Rate Ratios (RR) were obtained using linear regression with log transformed values (i.e., reaction time) or negative binomial regression (i.e., pairs matching). ORs were obtained using logistic regression. Prospective analyses adjusted for: age, baseline age (longitudinal only), gender, ethnic group, Townsend deprivation score, education, smoking status, physical activity, time outdoors, proximity to nearest major road, traffic intensity on nearest major road, population density category, and time between baseline and follow-up (longitudinal only). Logistic regression	NO ₂ (cross-sectional analysis)	
UK Biobank		(LOOCV r ² = 0.87 for NO ₂ and 0.88 for NO _x)	Cross-sectional sample: Median = 17.6 (33.2 μg/m ³)	Reaction Time		β (95% CI): 0.60 (0.57, 0.64)	
n = Cross-sectional analysis: 86,759			P25 = 13.9 (26.2 μg/m ³)	Numeric Memory		RR (95% CI): 1.00 (2.42, 0.41)	
Longitudinal analysis: 2,913		Averaging time: NO ₂ - annual average, NO _x - annual average	P75 = 21.21 (39.91 μg/m ³)	Pairs Matching		β (95% CI): -0.21 (-0.57, 0.16)	
Nationwide, U.K.			Longitudinal sample: Median = 13.47 (25.35 μg/m ³)	Prospective Memory		RR (95% CI): 1.02 (1.01, 1.02)	
Enrollment: 2006–2010		Exposure yr: 2005 for NO ₂ and 2010 for NO _x	P25 = 10.92 (20.54 μg/m ³)			OR (95% CI): 1.04 (1.00, 1.09)	
Follow-up: 2012–2013			P75 = 15.96 (30.04 μg/m ³)			NO _x (cross-sectional analysis):	
Cohort							β (95% CI): -0.002 (-0.003, -0.000)
							RR (95% CI): 1.0002 (1.0001, 1.0003)
							β (95% CI): -0.007 (-0.014, -0.001)
							RR (95% CI): 1.001 (1.000, 1.002)
	OR (95% CI): 0.999 (0.997, 1.000)						
					NO ₂ (longitudinal analysis):		
					β (95% CI): 0.21 (-0.07, 0.49)		
					β (95% CI): -11.06 (-27.37, 5.26)		
					β (95% CI): -0.47 (-1.17, 0.22)		
					OR (95% CI): 1.83 (0.78, 4.30)		
					NO _x (longitudinal analysis):		
					β (95% CI): 0.0015 (-0.0056, 0.0087)		
					β (95% CI): -0.2785 (-0.6955, 0.1384)		
					β (95% CI): -0.0007 (-0.0171, 0.0157)		

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
						OR (95% CI): 1.01 (0.99, 1.03)
† Franz et al. (2023)	Randomly selected male veterans from Vietnam Era Twin Registry	Spatiotemporal/geospatial model	NO ₂ (ppb)	Episodic Memory	GEE	β (Change) (95% CI) ^b
VETSA			Average decrease		Adjusted for:	Episodic Memory -Past:
n = 1,124		C-V r ² = 0.87	Mean = 1.18±3.36	Speed	rural/urban, education, APOE-ε4 allele carrier, race/ethnicity, smoking status, alcohol, history of cvd, diabetes, high cholesterol, depressive symptoms, stroke	0.0070 (-0.1085, 0.1225)
U.S.		Averaging time: multi-year exposure using residential histories	Past Mean = 11.14 Min = 1.6 Max = 44.74	Executive Function		Speed - Past: 0.0220 (-0.0740, 0.1180)
Exposure: 1993–2000						Executive Function - Past: -0.0380 (-0.1255, 0.0495)
Outcome assessment: 2003–2007				Working Memory		Working Memory - Past: -0.0460 (-0.1360, 0.0440)
Cohort		Exposure yr: 1993–2017	Recent Mean = 9.28 Min = 1.72 Max = 37.37	General Verbal Fluency		General Verbal Fluency - Past: -0.0980 (-0.2130, 0.0170)
						Semantic Fluency - Past: -0.1370 (-0.2500, -0.0240)
						Semantic Fluency - Recent: -0.1950 (-0.3265, -0.0635)
				Semantic Fluency		Speed - Recent: 0.0240 (-0.0950, 0.1430)
						Executive Function - Recent: -0.0200 (-0.1345, 0.0945)
						Working Memory - Recent: -0.0410 (-0.1625, 0.0805)
						Episodic Memory -Recent: -0.0200 (-0.1550, 0.1150)
						General Verbal Fluency - Recent: -0.1150 (-0.2520, 0.0220)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Huels et al. (2018) SALIA n = 587 Ruhr, Germany Baseline: 1985–1994 Follow-up: 2007–2010 Cohort	Women aged 55 yr at enrollment	LUR C-V $r^2 = 0.88$ Averaging time: NO ₂ - annual average Exposure yr: 2008–2009	NO ₂ (ppb) Mean = 17.8 (33.5 μg/m ³) IQR = 7.33 (13.8 μg/m ³) Min = 10.8 (20.3 μg/m ³) Max = 44.7 (84.1 μg/m ³)	VCP	Adjusted for: age, height, BMI, SES, current and former smoking habits, exposure to second-hand smoke, living in an urban area vs. a rural area, APOE-ε4 incidence, physical activity and depression	β (change) (95% CI) ^b VCP: -0.35 (-0.67, -0.03)
† Kulick et al. (2020b) WHICAP N = 5,330 NOMAS N = 1,093 New York City, NY, U.S. WHICAP - Enrollment: 1992, 1999, 2010 - Follow-up: every 18–24 mo NOMAS - Enrollment: 1993–2001 - Follow-up: 2003–2008 Cohort		Fixed site monitor Method validation NR Averaging time: NO ₂ - annual average Exposure yr: 2003–2008	NO ₂ (ppb) NOMAS Mean = 30.51 IQR = 3.16 WHICAP Mean = 31.88 IQR = 12.32	Cognitive decline SD change in GCI	linear mixed models Adjusted for: age, education, sex, race/ethnicity), neighborhood sociodemographic variables (Census-based SES) and cohort	β (Difference in SD score) (95% CI) ^b Decline on GCI: -0.05 (-0.06, -0.03) GCI: -0.18 (-0.24, -0.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Nußbaum et al. (2020)	Participants from the HNR study aged 45–75 yr at baseline who were physically able and have no medical contraindications for MRI.	Hybrid model	NO ₂ (ppb)	Neuro-psychological tests Difference in test score rank	linear regression	NO ₂
1000BRAINS		Method validation	Mean = 15.7±2.5 (29.6±4.7 µg/m ³)		Adjusted for: age, sex, SES	β (score rank difference) (95% CI) ^b
n = 615		NR	IQR = 2.8 (5.3 µg/m ³)			Selective Attention: 0.00 (-0.18, 0.18)
Bochum, Essen, Mülheim/Ruhr, Germany		Averaging time: NO ₂ - annual average, NO _x - annual average	Min = 10.5 (19.8 µg/m ³) Max = 33.2 (62.4 µg/m ³)			Verbal Working Memory: 0.18 (0.00, 0.36)
Enrollment: December 2000–August 2003	Cohort	Exposure yr: 2008–2009	NO _x (µg/m ³)			Visual-Spatial Working Memory: 0.11 (-0.07, 0.28)
Follow-up: 2011–2015						Cognitive: Language: 0.00 (-0.12, 0.12)
						Processing Speed: 0.04 (-0.14, 0.21)
						NO _x
			Mean = 49.3±11.3 IQR = 14.2 Min = 24.3 Max = 107.7			β (score rank) (95% CI) ^c Cognitive: Language: -0.01 (-0.05, 0.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Petkus et al. (2021b) WHIMS-ECHO n = 1,583 Nationwide, U.S. Enrollment: 2008 Follow-up: 2008–2016 Cohort	Community-dwelling women ≥80 yr and dementia-free at baseline.	Spatiotemporal/geospatial model Method validation NR Averaging time: NO ₂ -3-year Exposure yr: 1995–1997 for remote exposure; 2005–2007 for recent exposure	NO ₂ (ppb) Remote exposure (10 yr before baseline) Mean = 16.22±7.28 Median = 15.3 (IQR 9.55) P25 = 10.9 P75 = 20.4	Latent factor consisting of the immediate and delayed recall from the East Boston Memory Test and the world list memory from the TICS	Structural equation model Adjusted for: initial age at recruitment, race/ethnicity, geographic region of residence, employment status, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease), and neighborhood SES	β (Score) (95% CI) ^b Episodic memory-remote exposure: -0.08 (-0.28, 0.12) Episodic memory-recent exposure: -0.17 (-0.46, 0.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zare Sakhvidi et al. (2022)	Representative sample, adults ≥45 yr old	LUR	NO ₂ (ppb)		Linear regression	β (Change) (95% CI) ^b
French CONSTANCES study		Explained 59% of spatial variation in NO ₂	Median = 13.57 (IQR 7.403) (25.54 μg/m ³ (IQR 13.93 μg/m ³))		Adjusted for: age, education, sex, center, smoking status, alcohol drinking, familial situation, BMI, history of Alzheimer's disease	global cognition: 0.419 (0.370, 0.467)
n = 61,462						β (change) (95% CI) ^b
France		Averaging time: NO ₂ - annual average			in parents, non-occupational physical activity, living alone at home, country of origin, depression symptoms, hypertension, type-2 diabetes, CVDs, hearing loss, income, living area (urban, suburban, isolated city, or rural), and French Deprivation Index	semantic fluency: -0.527 (-0.797, -0.257)
2012–upper range NR						
Cross-Sectional		Exposure yr: 2012–upper range NR				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Tzivian et al. (2017)	Randomly selected men and women (50–80 yr)	LUR	NO ₂ (ppb)	GCS	Linear regression	NO ₂
HNR study		Explained 89% of variation for NO ₂ , and 88% NO _x (ESCAPE model: Beelen et al. 2013)	Mean = 16±2.57 (30.1±4.84 µg/m ³) Median = 15.66 (29.46 µg/m ³) Min = 10.53 (19.81 µg/m ³)		Adjusted for: age, sex, SES, alcohol consumption, smoking status, ETS, any regular physical activity, and BMI	β (Change) (95% CI) ^b GCS (High NO ₂ /Noise): -0.37 (-0.61, -0.13)
n = 3885						
Germany						NO _x
2006–2008		Averaging time: NO ₂ - annual average, NO _x - annual average	Max = 33.18 (62.44 µg/m ³) P25 = 14.23 (26.78 µg/m ³) P75 = 17.5 (32.9 µg/m ³)			β (Change) (95% CI) ^b GCS (High NO _x /Noise): -0.16 (-0.24, -0.07)
Cross-Sectional		Exposure yr: 2008–2009	NO _x (µg/m ³) Mean = 50.43±11.61 Median = 49.27 Min = 24.3 Max = 126.63 P25 = 41.96 P75 = 57.61			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wang et al. (2021b) WHIMS-ECHO n = 2,056 U.S. Enrollment: 1995/98–2008 Follow-up: 2018 Cohort	Community dwelling women	Other C-V r ² 0.85 for NO ₂ Averaging time: 3-yr average at enrollment and remote 3-yr avg lagged 10 yr from enrollment Exposure yr: 1998–2008	NO ₂ (ppb) Recent Mean = 5.564±2.65 (10.47±4.98 µg/m ³) Remote Mean = 8.408±3.86 (15.82±7.26 µg/m ³)	CVLT	Latent class mixed models Adjusted for: age, follow-up time, interaction of age with follow-up time, and time-varying propensity scores	β (points/yr) (95% CI) ^b ≤80 yr, slow decliners: -0.002 (-0.082, 0.078) ≤80 yr, fast decliners: -0.34 (-0.74, 0.06) >80 yr, slow decliners: -0.18 (-0.39, 0.04) >80 yr, fast decliners: -0.18 (-0.42, 0.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wang et al. (2023b) (MESA) n = 4,208 Chicago, IL; Baltimore, MD; Winston-Salem, NC; St. Paul, MN; New York City, NY; Los Angeles County, CA, U.S. Enrollment: July 2000–July 2002 Follow-up: July 2010–July 2012 Cohort	Men and women aged 45–84 yr and free of clinical CVD at baseline, including four racial/ethnic groups from six US communities.	Spatiotemporal/geo spatial model Model performance differed regionally; the C-V coefficient of determination (r ²) varied from 0.45–0.90 for NO ₂ and 0.50–0.92 for NO _x . Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: 1993–2013	NO ₂ (ppb) Mean = 14.6±7.8 NO _x (ppb) Mean = 25.7±15.8	CASI lowest 10th percentile of CASI score distribution	Linear regression/ Logistic regression Adjusted for: age, gender, race, height, weight, BMI, smoking status, pack-year, environment smoking, alcohol uses, physical activity, education, social economic index, systolic and diastolic blood pressure	NO ₂ OR (95% CI) ^b Low Cognitive Function: 1.32 (1.10, 1.58) β (Score) (95% CI) ^b CASI score: -1.08 (-1.59, -0.57) Working memory DS: 0.00 (0.00, 0.00) β (score) (95% CI) ^b Processing speed DSC: 0.00 (0.00, 0.00) NO _x OR (95% CI) ^b Low Cognitive Function: 1.27 (1.08, 1.49) β (Score) (95% CI) ^b CASI score: -0.92 (-1.40, -0.43) Processing speed DSC: -2.07 (-3.61, -0.54) Working memory DS: -0.41 (-0.81, -0.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Younan et al. (2022)	Older women residing in the U.S., 74–92 yr	Other	NO ₂ (ppb)	TICS-M	linear mixed effects	β (points/yr) (95% CI) ^b
WHIMS-ECHO		C-V r ² = 0.85	Recent Mean = 10.4±4.9	CVLT	Adjusted for: spatial random effect, enrollment year, age, follow-up year, age x follow-up year, time-varying propensity scores, geographic region and race/ethnicity, education, income, and employment status, neighborhood characteristics, lifestyle factors (smoking, drinking, and physical activities, prior hormone use, hormone therapy assignment, CVD risk factors depression, BMI, and CVD histories	TICS-M: 0.087 (0.023, 0.151) CVLT: 0.151 (0.008, 0.295)
n = TICS-M: 2232 CVLT: 1721		Averaging time: 3-yr avg	Remote (10 yr earlier) Mean = 15.7±7.2			
U.S.		Exposure yr: 1996–2012				
Enrollment: 2008–2012 Follow-up: 2008–2018						
Quasi-experimental						

List of abbreviations in alphabetical order: APOE = Apolipoprotein E; BMI = body mass index; CASI = Cognitive Abilities Screening Instrument; CI = confidence interval; C-V = cross-validation; CVD = cardiovascular disease; CVLT = California Verbal Learning Test; DS = Digit Span; DSC = Digit Symbol Coding; ETS = environmental tobacco smoke; GCI = General Cognitive Index; GCS = global cognitive score; GEE = generalized estimating equation; HNR = Heinz Nixdorf Recall study; IQR = interquartile range; LOOCV = leave one out cross-validation; LUR = land use regression; Max = Maximum; MESA = Multiethnic Study of Atherosclerosis; Min = minimum; MRI = magnetic resonance imaging; NHS = National Health Service; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; NOMAS = Northern Manhattan Study; OR = odds ratio; P = percentile; RR = rate ratio; SALIA = Study on the influence of Air pollution on Lung function, Inflammation and Aging; SD = standard deviation; SES = socioeconomic status; TICS-M = Telephone Interview for Cognitive Status-Modified; VCP = Visuo-construction Performance; VETSA = Vietnam Era Twin Study of Aging; vs. = versus; WHICAP = Washington Heights–Inwood Community Aging Project; WHIMS-ECHO = Women’s Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-13 Epidemiologic studies of oxides of nitrogen exposure and Alzheimer's disease and dementia

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Chang et al. (2014) n = 29,547 Taiwan 2000–2010 Cohort	Aged 50 yr or older for whom air pollution data were available and did not present a history of head injury, stroke, or dementia	Fixed site monitor Averaging time: NO ₂ - annual average Exposure yr: 1998–2010	NR	NHIRD claim records, ICD 9-CM	Cox proportional hazards Adjusted for: age, sex, monthly income, diabetes, IHD, hypertension, COPD, alcoholism and urbanization.	HR (95% CI) ^c Dementia Q4 vs. Q1: 1.54 (1.34, 1.77) Dementia Q3 vs. Q1: 1.01 (0.87, 1.17) Dementia Q2 vs. Q1: 1.10 (0.96, 1.26)
† Chen et al. (2017) n = 2,066,639 Ontario, Canada 2001–2013 Cohort	All Ontario residents aged 55–85 yr, Canadian-born, and free of physician-diagnosed dementia	LUR 73% variability explained for NO ₂ Averaging time: NO ₂ - annual average Exposure yr: 1994–2013	NO ₂ (ppb) Mean = 16.2 IQR = 14.2 Min = 2.4 Max = 65.3	ICD9/10 codes, physician visits or dementia medication	Random effects Cox model Adjusted for: Age, sex, and region; neighborhood-level income, education, unemployment rate, and immigrants; urban residency and a North/South indicator; Preexisting brain injury, stroke, diabetes, hypertension, coronary heart disease, heart failure, and arrhythmia; indirect adjustment for smoking, physical activity, obesity, and education	HR (95% CI) ^b Dementia 10-yr lag: 1.04 (1.02, 1.06) Dementia 5-yr lag: 1.06 (1.05, 1.07) Dementia 2-yr lag: 1.07 (1.06, 1.08)
† Chen et al. (2023) UK Biobank	Adults (age: 40–69 yr)	LUR NO ₂ and NO _x : 87% and 88%,	NO ₂ (ppb) Q1 Median = 10.5 (IQR	HA records, ICD-9/10 codes	Cox proportional hazards Adjusted for: age, sex,	NO ₂ HR (95% CI) ^b Vascular dementia:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
n = 459,844		respectively	3) (19.7 µg/m ³ (IQR 5 µg/m ³)		ethnicity, household income level, smoking status, diet quality score, alcohol consumptions, total sedentary time, body mass index, systolic and diastolic blood pressure, use of antihypertensive medications, histories of diabetes and respiratory disease, aspirin use, and APOE genotype	1.19 (1.08, 1.33) All cause dementia: 1.21 (1.15, 1.27) AD: 1.23 (1.14, 1.32)
U.K.		Averaging time:	P25 = 9 (17 µg/m ³) P75 = 12 (22 µg/m ³)			
2006–2010		NO ₂ - annual average, NO _x - annual average	Q2 Median = 14 (IQR 2) (26 µg/m ³ (IQR 4 µg/m ³) P25 = 13 (24 µg/m ³) P75 = 15 (28 µg/m ³)			
Cohort		Exposure yr: 2005–2010	Q3 Median = 16.4 (IQR 2.6) (30.8 µg/m ³ (IQR 4.9 µg/m ³) P25 = 15.1 (28.4 µg/m ³) P75 = 17.7 (33.3 µg/m ³)			NO _x HR (95% CI) ^b Vascular dementia: 1.06 (1.01, 1.12) All cause dementia: 1.07 (1.04, 1.09) AD: 1.09 (1.05, 1.14)
			Q4 Median = 20.8 (IQR 5.2) (39.1 µg/m ³ (IQR 9.8 µg/m ³) P25 = 19 (35 µg/m ³) P75 = 23.8 (44.8 µg/m ³)			
			NO _x (µg/m ³)			
			Q1 Median = 28.4 (IQR 9) P25 = 23.9 P75 = 32.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Q2 Median = 38.9 (IQR 6.7) P25 = 35.6 P75 = 42.3			
			Q3 Median = 46 (IQR 7.4) P25 = 42.4 P75 = 49.8			
			Q4 Median = 57.7 (IQR 16.3) P25 = 51.4 P75 = 67.7			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Gandini et al. (2018)	Individuals from families residing in 1442 municipalities across Italy	Hybrid model	NO ₂ (ppb)	ICD-9 codes NS disease/AD (NHIS records)	Cox proportional hazards	HR (95% CI) ^b
ILS		Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity.	Men Metropolitan Mean = 22.1±6.16 (41.5±11.6 µg/m ³) Urban Mean = 13.9±5.2 (26.1±9.7 µg/m ³) Rural Mean = 10.3±4 (19.3±8 µg/m ³)		Adjusted for: by age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality (rural, urban, metropolitan areas) and BMI	1st HA for NS disease: 1.10 (1.02, 1.18) 1st HA for AD: 1.12 (0.93, 1.34)
N = 74,989						
Italy						
Enrollment: 1999–2000						
Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008						
Cohort						
		Averaging time: NO ₂ - annual average	Mean = 13.9±5.1 (26.1±9.6 µg/m ³) Rural Mean = 10.3±4.2 (19.3±7.9 µg/m ³)			
		Exposure yr: 1999, 2003, 2005, 2007				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ilango et al. (2020) Canadian Community Health Survey n = 34,391 Ontario, Canada Participants who participated in the 1996–2003 Canadian Community Health Surveys were followed through 2013 or until dementia diagnosis Cohort	Canadian-born Ontario residents who lived in Ontario for at least 5 yr, aged 45 or older at baseline, who participated in NPHS (National Population Health Survey) or CCHS.	LUR 73% Averaging time: NO ₂ - 3-year running average (w/ 5-year lags) Exposure yr: 1993–2013	NO ₂ (ppb) Mean = 10.4 IQR = 7.6 Min = 2.2 Max = 54.4	ICD9/10 codes, physician visits or dementia medication	Cox proportional hazards Adjusted for: age, sex, education, marital status, income quintile, smoking status, body mass index, physical activity, rural residence and northern region; area level: recent immigrants, unemployment and education.	HR (95% CI) ^b Dementia 3 yr avg: 1.42 (1.18, 1.70)
† Ilango et al. (2023) GEMS n = 2,564 U.S. 2000–2008 Cohort	Older adults (>75 yr)	Spatiotemporal/geospatial model NO ₂ range from 0.78 to 0.88 Averaging time: NO ₂ - annual average Exposure yr: 1980–1990	NO ₂ (ppb) Median = 16.62 (IQR 6.67)	ICD9/10 codes, physician visits or dementia medication	Cox proportional hazards Adjusted for: sex, education, race/ethnicity, living situation, study site, treatment assignment, neighborhood deprivation and census tract.	HR (95% CI) ^b Dementia 10 yr avg: 1.39 (1.04, 1.87)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ma et al. (2023) UK Biobank n = 164,447 U.K. 2006–2010 Cohort	Adults aged ≥60 yr at baseline. Excluded those with dementia at baseline and those with incomplete data.	LUR For a LUR model, the cross-validation r^2 for NO ₂ was 87% Averaging time: NO ₂ - annual average Exposure yr: 2005–2010	NO ₂ (ppb) Mean = 14.9±4.6 (28.1±8.7 µg/m ³)	UK Biobank algorithm/ICD codes	Cox proportional hazards Adjusted for: age, sex, assessment centres and calendar year of cohort entry, Townsend deprivation index, yr of education, moderating drinking, current smoking, regular physical activity, healthy diet score, depression and social isolation, hearing problems, traumatic brain injury, obesity, diabetes, hypertension, high cholesterol, cardiovascular disease, or high overall genetic susceptibility, the first 10 genetic principal components, relatedness and genotyping array	HR (95% CI) ^b Dementia: 1.39 (1.19, 1.63)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Mortamais et al. (2021) Three-City Study (3C Study) n = 7,066 Bordeaux, Dijon, Montpellier, France Enrollment: 1999 and 2001 Follow up: 12 yr Cohort	Participants aged ≥65 yr	LUR 59% spatial variation measured for NO ₂ Averaging time: NO ₂ - annual average Exposure yr: 1999–2013	NO ₂ (ppb) Mean = 18.2±4 (34.2±7.5 µg/m ³) Median = 17.4 (32.8 µg/m ³) Min = 6.8 (12.8 µg/m ³) Max = 48.8 (91.8 µg/m ³)	Physician adjudicated	Cox proportional hazards Adjusted for: delayed entry with age as the basic timescale and birth as the time origin, sex, centre, education, APOE genotype, deprivation index, alcohol intake, and smoking habits	HR (95% CI) ^b AD: 1.04 (0.88, 1.23) All-cause dementia: 1.04 (0.82, 1.32) Vascular dementia: 1.04 (0.61, 1.77)
† Parra et al. (2022) UK Biobank n = 187,194 England, Scotland, Wales, U.K. 2006–2010 Cohort	Individuals aged 60–69 yr living without dementia	LUR LUR model explained variances from 55% to 92% (median 83%) for NO ₂ and 49% to 91% (median 78%) for NO _x Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: 2010–2011	NO ₂ (ppb) Any Dementia Median = 14.2 (IQR 4.99) (26.72 µg/m ³) (IQR 9.39 µg/m ³) No Dementia Median = 13.53 (IQR 5.03) (25.45 µg/m ³) (IQR 9.47 µg/m ³) NO _x (µg/m ³) Any Dementia Median = 43.04 (IQR 16.02) No Dementia Median = 41.2 (IQR 15.88)	NHS HA records, ICD9/10 codes: AD, VAD FTD	Cox proportional hazards Adjusted for: age, sex, college enrolled, smoking status, income, urban, research center/county, APOE-ε4	NO ₂ HR (95% CI) ^b AD: 1.32 (1.07, 1.63) All-cause Dementia: 1.39 (1.23, 1.58) Vascular dementia: 1.39 (1.06, 1.83) NO _x HR (95% CI) ^c AD: 1.11 (1.03, 1.20) Vascular dementia: NA All-cause Dementia: 1.11 (1.06, 1.17)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Paul et al. (2020) SALSA N = 1,564 Sacramento, CA, U.S. Enrollment: 1998–1999 Follow-up: through 2008 Cohort	Latino residents from California's Sacramento Valley area aged more than 60 yr. Excluded participants who had CIND or dementia at baseline, did not participate in any follow-up interviews, or did not provide all necessary information.	Dispersion model With background pollutant levels in the model $r^2 = 0.95$ Without background pollutant levels in the model $r^2 = 0.90$ Averaging time: NO _x - annual average Exposure yr: 2007–2008		In-home cognitive/clinical assessment	Cox proportional hazards Adjusted for: age, sex, education, primary language, occupation, smoking, neighborhood ses, urbanicity, county indicators, and baseline cognitive function	HR (95% CI) ^c CIND (>2.68 ppb vs. lowest tertile): 1.45 (1.07, 1.96) Dementia: 1.20 (0.98, 1.47) Dementia (>2.68 ppb vs. lowest tertile): 1.55 (1.04, 2.33) CIND: 1.21 (1.05, 1.40)
†Shi et al. (2021) Medicare CCW n = 12.2 and 12.4 million people in dementia and AD cohorts, respectively U.S. 2000–2018 Cohort	Individuals aged ≥65 from the Medicare Chronic Conditions Warehouse	Ensemble machine learning model NO ₂ 0.84 Averaging time: NO ₂ - annual average Exposure yr: 2000–2016	NO ₂ (ppb) Mean = 17.1 IQR = 11.6	Medicare claims/ICD codes	Cox proportional hazards Adjusted for: age, Sex, Race, neighborhood-level socioeconomic status, county-level behavioral risk factors, Adjusted for: individual characteristics, copollutants, neighborhood-level socioeconomic status, and other	HR (95% CI) ^b Dementia 5 yr avg: 1.03 (1.02, 1.04) AD 5 yr avg): 1.04 (1.04, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wang et al. (2023a)	Individuals aged 37–73 in England, Scotland, and Wales who self-reported prevalent cognitive impairment, Alzheimer's disease, dementia, chronic degenerative neurological problems were excluded.	Spatiotemporal/geospatial model	NO ₂ (ppb)	ICD-10 (AD, FTD, vascular, other dementia)	Cox proportional hazards	NO ₂
UK Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Median = 9.311 (IQR 3.9) (17.52 µg/m ³ (IQR 7.4 µg/m ³))		Adjusted for: age, sex, qualification, Townsend Deprivation Index, sleep duration, smoking status, social isolation, drinking status, BMI, hypertension, diabetes, stroke, depression, hearing impairment, family history of dementia.	HR (95% CI) ^b Dementia (Model 3): 1.00 (0.63, 1.60) Dementia (Model 1): 1.45 (1.32, 1.59)
n = 498,660		Exposure yr: 2006–2019	NO _x (µg/m ³)			NO _x
U.K.			Median = 25.49 (IQR 12.53)		Adjusted for: age, sex, qualification, Townsend Deprivation Index	HR (95% CI) ^c Dementia (Model 3): 1.00 (0.99, 1.01) Dementia (Model 1): 1.01 (1.00, 1.01)
Baseline: 2006–2010						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wang et al. (2022) WHIMS-ECHO n = 2,239 Nationwide, U.S. Enrollment: 2008 Follow-up: 2008–2018 Cohort	Community-dwelling women aged 74-92 yr and dementia-free at baseline	Spatiotemporal/geospatial model Cross-validation r^2 = 0.85 for NO ₂ Averaging time: NO ₂ - 3-year average Exposure yr: 1996-1998 (remote) and 2006-2008 (recent)	NO ₂ (ppb) Recent Mean = 10.43±4.89 IQR = 6.19 Remote Mean = 15.69±7.15 IQR = 9.42	Dementia Questionnaire interview of proxies and DSM-IV	Cox proportional hazards with IPW Adjusted for: enrollment year, demographic variables (age, geographic region/spatial random effect, and race/ethnicity), socioeconomic factors (education, income, and employment status) and neighborhood characteristics, lifestyle factors (smoking, drinking, and physical activities), hormone use, hormone therapy assignment, cardiovascular risk factors (hypertension, diabetes, and hypercholesterolemia), depression, BMI, and CVD histories	HR (95% CI) ^b Dementia – Recent NO ₂ : 1.02 (0.88, 1.17) Dementia – Remote NO ₂ : 0.86 (0.73, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wood et al. (2022)	Adults aged 50 yr and older	Other	NO ₂ (ppb)	self-reported, doctor dx	Cox proportional hazards	HR (95% CI) ^b Dementia: 0.99 (0.96, 1.02)
English Longitudinal Study of Aging		$r^2 = 0.78$ for NO ₂	Baseline Age Brand 50–59		Adjusted for: baseline age, gender, physical activity, and smoking status	
n = 8,525		Averaging time: NO ₂ - annual average	Mean = 13.7 (25.8 µg/m ³)			
England		Exposure yr: 2004	60–69 Mean = 13.6 (25.5 µg/m ³)			
2002–2017			70–79 Mean = 13.4 (25.2 µg/m ³)			
Cohort			80–89 Mean = 13.3 (25.1 µg/m ³)			
			90+ Mean = 12.5 (23.5 µg/m ³)			
			Total Mean = 13.6±7.28 (25.5±13.7 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wu et al. (2022)	Individuals aged ≥60 yr residing in the Kungsholmen district, Stockholm, Sweden, without prevalent dementia, intellectual disability, schizophrenia, prevalent depression or depressive symptoms	Dispersion model Model validated using linear regression against measurements at three traffic monitoring places and one urban background place (r ² =0.99) Averaging time: NO _x – 3-year moving average, NO _x – 1-year moving average Exposure yr: 1990, 1995, 2000, 2005, 2011	NO _x (ug/m ³) Mean = 29.4±10.4	Physician-diagnosed dementia based on DSM-IV following a 3-step procedure CIND Dx based on absence of dementia and scoring 1.5 SD below age-specific means based on baseline SNAC-K cohort on cognitive tests (Free recall, TMTB, Category and Letter Fluency, mental rotation, digit cancellation, and pattern comparison)	Cox proportional hazards Adjusted for: age, sex, SES, education, smoking, physical activity, early retirement, neighborhood household mean income, and the number of cognitive test occasions Considers death as the competing risk event	HR (95% CI) ^c Dementia following CIND – 3-yr MA: 1.15 (0.91, 1.44) Dementia following CIND – 1-yr MA, 1-yr lag: 1.43 (1.15, 1.76) CIND – 3-yr MA: 1.15 (1.03, 1.29) CIND – 1-yr MA, 1-yr lag: 1.34 (1.21, 1.50)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Yu et al. (2020) SALSA N = 1,789 n = 1,612 Sacramento, California, U.S. 1998–2007 Cohort	Mexican-Americans aged 60 yr and older	Dispersion model Averaging time: NO _x - annual average Exposure yr: "Decades" before and after 1998– 2007	NO _x (ppb) Mean = 2.6±2.2	Clinical Exams/MRI	Cox proportional hazards Adjusted for: baseline age, sex, education, occupation held during most of the life, NSES, smoking status, alcohol status, residential county, physical activity and household income, and baseline cognition function	HR (95% CI) ^c Dementia: 1.20 (1.00, 1.40)
†Yuan et al. (2023) UK Biobank n = 437,932 U.K. Baseline: 2006–2010 Follow-up: 2010–2023 Cohort	Individuals aged 40–69 yr without a pre- existing diagnosis of all-cause dementia, Alzheimer's disease, or vascular dementia at baseline.	LUR Averaging time: NO _x - annual average Exposure yr: 2010	NO _x (µg/m ³) All-cause dementia Median = 43.4 (IQR 16.6) P25 = 35.4 P75 = 52 Alzheimer's Disease Median = 43.4 (IQR 16.8) P25 = 35.2 P75 = 52 Non-Alzheimer's disease Median = 42.1 (IQR 116.5) P25 = 34.1 P75 = 50.6 Non-dementia Median = 42.1 (IQR	UK Biobank algorithm/ICD codes	Cox proportional hazards Adjusted for: educational level, household income, employment status, body mass index, smoking, alcohol drinking, physical activity, fruit and vegetable intake, environmental tobacco smoke exposure (at home), head injury, depression, family history of dementia, first 20 principal components of ancestry, urban residency, Townsend deprivation index, polygenic risk score	HR (mutually adjusted PM _{2.5} , PM ₁₀) (95% CI) ^c Vascular dementia (NO _x ≥50 µg/m ³): 0.94 (0.75, 1.19) AD: 1.26 (1.08, 1.48) All-cause dementia (NO _x ≥50 µg/m ³): 1.14 (1.02, 1.26)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			16.5) P25 = 34.1 P75 = 50.6			
			Non-vascular dementia Median = 42.1 (IQR 16.5) P25 = 34.1 P75 = 50.6			
			Vascular dementia Median = 43.5 (IQR 15.2) P25 = 36.7 P75 = 51.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zhang et al. (2023b)	Adults aged 50 yr and older	LUR	NO ₂ (ppb)	Physician, HA records ICD codes	Cox proportional hazards	NO ₂
UK Biobank		r ² for NO ₂ = 87% r ² for NO _x = 88%	Mean = 15±4.7 (28.2±8.8 µg/m ³) Median = 14.5 (IQR 5.58) (27.2 µg/m ³) (IQR 10.5 µg/m ³) P25 = 11.8 (22.2 µg/m ³) P75 = 17.4 (32.7 µg/m ³)		Adjusted for: educational level, household income, employment status, body mass index, smoking, alcohol drinking, physical activity, fruit and vegetable intake, environmental tobacco smoke exposure (at home), head injury, depression, family history of dementia, first 20 principal components of ancestry, urban residency, Townsend deprivation index, polygenic risk score	HR (95% CI) ^b Dementia: 1.28 (1.17, 1.40) AD: 1.32 (1.13, 1.55) Vascular dementia: 1.22 (0.97, 1.55)
n = 227,840		Averaging time: NO ₂ - annual average, NO _x - annual average				
U.K.		Exposure yr: 2005–2007, 2010 (NO ₂); 2010 (NO _x)	NO _x (µg/m ³) Mean = 42.5±14.9 Median = 40.9 (IQR 16.1) P25 = 32.9 P75 = 49.1			NO _x HR (95% CI) ^c Dementia: 1.03 (0.99, 1.07) HR (95% CI) ^b AD: 1.06 (0.99, 1.14) Vascular dementia: 0.98 (0.88, 1.08)
2006–2010						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Zhang et al. (2023a) n = 7,715,057 California, New York, North Carolina, New Jersey, Missouri, U.S. 2005–2015 Case-crossover	Patients 45 yr and older with ED visits recorded in hospital associations or state health departments in five US states: California (2005–2015), Missouri (2005–2015), North Carolina (2011–2015), New Jersey (2005–2015), and New York (2005–2015).	Ensemble machine learning model The ensemble model produced a C-V R-squared value of 0.79 overall, a spatial R-squared value of 0.84, and a temporal R-squared value of 0.73. Averaging time: NO ₂ - 1-hour max Exposure yr: 2000–2016	NO ₂ (ppb) 5-state Mean = 17.94±13.4 IQR = 17.11 California Mean = 20.65±14.19 IQR = 20.26 Missouri Mean = 12.06±8.4 IQR = 8.84 New Jersey Mean = 25.29±12.67 IQR = 18.01 New York Mean = 18.08±14.65 IQR = 16.7 North Carolina Mean = 12.47±8.2 IQR = 9.5	ED visits, Medicare/Medic aid algorithm	Conditional logistic regression Adjusted for: temperature (6df for all-year, 3 df for warm-season ozone), humidity, sociodemographic characteristics, federal holidays, day-of-year time trends (4 df natural cubic splines) and patient-matched controls by ZIP code, day of the week, and yr/mo	OR (95% CI) ^b AD/ADRD ED visits: 1.01 (1.00, 1.01) AD/ADRD ED visits: 1.01 (1.00, 1.01)

List of abbreviations in alphabetical order: AD = Alzheimer’s disease; ADRD = Alzheimer’s Disease Related Dementia; APOE = Apolipoprotein E; BMI = body mass index; CCW = Chronic Conditions Warehouse; CI = confidence interval; CCHS = Canadian Community Health Survey; CIND = cognitive impairment non-dementia; COPD = chronic obstructive pulmonary disease; C-V = cross-validation; df = degrees of freedom; DSM = Diagnostic and Statistical Manual; Dx = diagnosis; ED = emergency department; FTD = Frontotemporal Dementia; GEMS = Ginkgo Evaluation of Memory Study; HA = Hospital Admission; HR = hazard ratio; ICD-(CM) = International Classification of Diseases-(Clinical Modification); IHD = ischemic heart disease; ILS = Italian Longitudinal Study; IQR = interquartile range; LUR = Land Use Regression; Max = Maximum; Min = Minimum; MRI = magnetic resonance imaging; NHS = National Health Service; NHIRD = National Health Insurance Database; NHIS = National Health Interview Survey; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; OR = odds ratio; P = percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; Q = quartile; RMSE = root mean square error; SALSA = Sacramento Area Latino Study on Aging; SES = socioeconomic status; TMTB = Trail Making Test Part B; VAD = Vascular Dementia; vs. = versus; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.
[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-14 Toxicological studies of oxides of nitrogen exposure and Alzheimer’s disease and dementia		
Study Details and Population	Exposure Details	Endpoints Examined*
[†] Yan et al. (2016b)	Whole body inhalation with room air controls	Timing unclear (APP/PS1 Mice)
Mouse (C57BL/6J and APP/PS1)	1,330 ppb (2.5 mg/m ³) (C57BL/6J mice only) NO ₂ , 5 hr/d for 28 d	• Amyloid-β deposition in cortex and hippocampus (↑) • Amyloid-β protein expression in cortex and hippocampus (↑) • MWM—acquisition (latency to platform) (↑) • MWM—probe trial (time in target quadrant) (↓) • MWM—probe trial (target annulus crossovers) (↓) • Neurodegeneration (fluoro-jade c stain) in cortex and hippocampus (↑)
2, 5-mo-old, males	2,660 ppb (5.0 mg/m ³) NO ₂ , 5 hr/d for 28 d	Timing unclear (C57BL/6J Mice)
n = 2–14/group		• APP and BACE1 protein expression in hippocampus and cortex (↑) • Amyloid-β deposition in cortex and hippocampus (↑)
[†] Yan et al. (2016a)	Whole body inhalation with room air controls	0 d after exposure
Mouse (C57BL/6J)	1,330 ppb (2.5 mg/m ³) NO ₂ , 5 hr/d for 4 wk	• Phosphorylated tau protein expression in cortex and hippocampus (↑)
2-mo-old, males	2,660 ppb (5 mg/m ³) NO ₂ , 5 hr/d for 4 wk	• Tau protein expression in cortex and hippocampus (NS)
n = 10/group		

List of abbreviations in alphabetical order: APP = amyloid precursor protein; BACE1 = beta-secretase 1; d = day; GD = gestational day; hr = hour; MWM = Morris water maze; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week(s)
*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↓ = at least one experimental group had a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females.
[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-15 Epidemiologic studies of oxides of nitrogen exposure and Parkinson's disease

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Gandini et al. (2018) ILS N = 74,989 Italy Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008 Cohort	Individuals from families residing in 1442 municipalities across Italy	Hybrid model Chemical transport model fed by emission data and meteorological prognostic fields, fused with ground observation data from monitors with >80% data availability. The RMSE of hourly NO ₂ ranged from 16.51 to 27.95 µg/m ³ by urbanicity. Averaging time: NO ₂ - annual average Exposure yr: 1999, 2003, 2005, 2007	NO ₂ (ppb) Men Metropolitan Mean = 22.1±6.16 (41.5±11.6 µg/m ³) Rural Mean = 10.3±4 (19.3±8 µg/m ³) Urban Mean = 13.9±5.2 (26.1±9.7 µg/m ³) Women Metropolitan Mean = 22.1±6.16 (41.6±11.6 µg/m ³) Rural Mean = 10.3±4.2 (19.3±7.9 µg/m ³) Urban Mean = 13.9±5.1 (26.1±9.6 µg/m ³)	NIS Hospital records	Cox proportional hazards Adjusted for: by age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality (rural, urban, metropolitan areas) and BMI	HR (95% CI) ^b 1st HA PD: 1.16 (0.89, 1.50)
† Goria et al. (2021) n = 196,479 Paris, Bordeaux, Clermont-Ferrand, Dijon, Grenoble, Le Havre, Lens-Douai, Lille, Lyon, Marseille, Montpellier, Nancy, Nantes, Nice, Rennes, Rouen, Strasbourg, Toulouse, France	Patients who were admitted to hospitals in 18 urban areas across France, with data obtained from the National Health Data System	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure yr: 2009–2017	NO ₂ (ppb) Bordeaux Mean = 10 (18.9 µg/m ³) Min = 0.5 (1 µg/m ³) Max = 36 (68 µg/m ³) Clermont Mean = 12.6 (23.7	Hospital Discharge	Generalized additive Poisson Adjusted for: penalized spline function for season and long-term temporal trends, temperature	RR (95% CI) ^b PD All year: 1.04 (1.02, 1.06)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
2009–2017			$\mu\text{g}/\text{m}^3$ Min = 1 (2 $\mu\text{g}/\text{m}^3$) Max = 58.5 (110 $\mu\text{g}/\text{m}^3$)			
Time-series			Dijon Mean = 11 (21 $\mu\text{g}/\text{m}^3$) Min = 1 (2 $\mu\text{g}/\text{m}^3$) Max = 45 (85 $\mu\text{g}/\text{m}^3$)			
			Grenoble Mean = 12.7 (23.9 $\mu\text{g}/\text{m}^3$) Min = 1 (2 $\mu\text{g}/\text{m}^3$) Max = 48 (90 $\mu\text{g}/\text{m}^3$)			
			Le Havre Mean = 11.5 (21.6 $\mu\text{g}/\text{m}^3$) Min = 1 (2 $\mu\text{g}/\text{m}^3$) Max = 46 (86 $\mu\text{g}/\text{m}^3$)			
			Lens Mean = 11.6 (21.8 $\mu\text{g}/\text{m}^3$) Min = 0.5 (1 $\mu\text{g}/\text{m}^3$) Max = 42 (79 $\mu\text{g}/\text{m}^3$)			
			Lille Mean = 13.1 (24.6 $\mu\text{g}/\text{m}^3$) Min = 2 (3 $\mu\text{g}/\text{m}^3$) Max = 43 (80 $\mu\text{g}/\text{m}^3$)			
			Lyon Mean = 16.1 (30.3 $\mu\text{g}/\text{m}^3$)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			µg/m ³) Min = 2 (4 µg/m ³) Max = 75.5 (142 µg/m ³)			
			Marseille Mean = 17.8 (33.5 µg/m ³) Min = 2 (4 µg/m ³) Max = 44 (82 µg/m ³)			
			Montpellier Mean = 13.9 (26.1 µg/m ³) Min = 0.5 (1 µg/m ³) Max = 42 (79 µg/m ³)			
			Nancy Mean = 14.5 (27.2 µg/m ³) Min = 3 (5 µg/m ³) Max = 44 (83 µg/m ³)			
			Nantes Mean = 8.88 (16.7 µg/m ³) Min = 0.5 (1 µg/m ³) Max = 39 (73 µg/m ³)			
			Nice Mean = 15.5 (29.1 µg/m ³) Min = 3 (6 µg/m ³) Max = 37 (70 µg/m ³)			
			Paris Mean = 18.5 (34.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			µg/m ³) Min = 4 (7 µg/m ³) Max = 64.8 (122 µg/m ³)			
			Rennes Mean = 10 (19 µg/m ³) Min = 0 (0 µg/m ³) Max = 45 (84 µg/m ³)			
			Rouen Mean = 13.2 (24.8 µg/m ³) Min = 26 (48 µg/m ³) Max = 46 (86 µg/m ³)			
			Strasbourg Mean = 14 (26.3 µg/m ³) Min = 2 (4 µg/m ³) Max = 64.3 (121 µg/m ³)			
			Toulouse Mean = 11.1 (20.8 µg/m ³) Min = 1 (2 µg/m ³) Max = 43 (81 µg/m ³)			
[†] Huang et al. (2024)	Included initially PD-free participants with complete genotyping data.	Hybrid model	NO ₂ (ppb)	Patient and hospital records, ICD codes	Cox proportional hazards	NO ₂
N = 312,009		Method validation	Individuals with PD		Adjusted for: age, sex, BMI, alcohol consumption, smoking status, education level,	HR (95% CI) ^c
China		NR	Mean = 15.11±4.52 (28.43±8.51 µg/m ³)			Q3 vs. Q1 (ref): 1.06 (0.93, 1.21)
Follow-up mean: 12.07 yr		Averaging time: NO ₂ - annual	Individuals without			Q2 vs. Q1 (ref): 0.98 (0.86, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Cohort		average, NO _x - annual average	PD Mean = 14.96±4.45 (28.14±8.38 µg/m ³)		employment status, household income, and Townsend deprivation index, number of long-term morbidities	Q4 vs. Q1 (ref): 1.24 (1.09, 1.42) HR (95% CI) ^b PD (continuous exposure): 1.17 (1.04, 1.30)
		Exposure yr: 2010	Overall Mean = 14.96±4.45 (28.14±8.38 µg/m ³)			NO _x
			NO ₂ (µg/m ³)			HR (95% CI) ^c PD (continuous exposure): 1.02 (0.96, 1.09)
			Individuals with PD Mean = 28.43±8.51			Q2 vs. Q1 (ref): 0.98 (0.86, 1.11)
			Individuals without PD Mean = 28.14±8.38			Q4 vs. Q1 (ref): 1.05 (0.92, 1.21)
			Overall Mean = 28.14±8.38			Q3 vs. Q1 (ref): 1.03 (0.90, 1.17)
			NO _x (µg/m ³)			
			Individuals with PD Mean = 43±14.48			
			Individuals without PD Mean = 42.97±14.88			
			Overall Mean = 42.97±14.87			
† Lee et al. (2016a)	PD (ICD-9-CM) patients with age- and gender- matched controls	Other	NO _x (ppb)	Incident PD cases (ID-9-CM code 332.0) from NHIRD	Logistic Regression	OR (95% CI) ^b ≥75th vs. <25th: 1.10 (1.04, 1.17)
n = 55,585		Averaging time: NO _x - annual average	Cases Mean = 29.32±11.6		Adjusted for: age at index, sex, year of diagnosis, CCI,	50–75th vs. <25th: 0.91 (0.86, 0.97)
Taiwan						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
2007–2009 Case-Control		Exposure yr: 1998–date of diagnosis	Controls Mean = 29.11±11.4	Incident PD (ICD-9-CM code 332.0) from NHIRD	insurance premium, urbanization	PD (continuous exposure): 1.00 (0.96, 1.04) 25–50th vs. <25th: 1.03 (0.97, 1.09)
† Lee et al. (2016b) Parkinson’s Disease in Denmark (PASIDA) n = 1,476 cases 1,537 controls Nationwide, Denmark Enrollment: January 2008– December 2010 Case-Control	Patients aged 35 yr or more with a first hospital or outpatient clinic contact for PD (ICD-8 code 342 and ICD-10 code G20) between 1996 and mid- 2009 from the Danish National Hospital Register and randomly sampled controls without PD diagnosis before index date matched to cases on sex and year of birth from the Danish Central Population Register.	Spatiotemporal/ge ospatial model Method validation NR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: 1995–2006	NO ₂ (ppb) Mean = 7.27±2.06 (13.68±3.88 µg/m ³) Median = 6.5 (IQR 1.56) (12.23 µg/m ³) (IQR 2.94 µg/m ³) Min = 5.2 (9.8 µg/m ³) Max = 22.99 (43.26 µg/m ³) P25 = 6.027 (11.34 µg/m ³) P75 = 7.589 (14.28 µg/m ³) P95 = 11.28 (21.23 µg/m ³) NO _x (µg/m ³) Mean = 20.88±12.73 Median = 16.42 (IQR 7.13) Min = 13.46 Max = 181.55 P25 = 14.71 P75 = 21.84 P95 = 41.59	ICD codes from hospital/outpatie nt records with medical review	Logistic regression Adjusted for: age at first cardinal symptom, gender, education, smoking status (never, ex-smoker, current smoker), pack-yr of smoking, family history of PD, and year of birth, and job history	NO ₂ OR (95% CI) ^b Incident PD: 1.07 (0.48, 2.36) PD: 1.45 (0.98, 2.15) NO _x OR (95% CI) ^c Incident PD: 1.01 (0.92, 1.11) PD: 1.05 (1.00, 1.10)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Liu et al. (2016) PAGE n = 566,398 Atlanta, GA, Pennsylvania, California, North Carolina, Florida, Louisiana, New Jersey, Detroit, MI, U.S. Enrollment: 1985–2000 Follow-up: 2004–2006 Nested case-control	AARP members who were 5–71 years old and resided in one of six U.S. states old and resided in one of the study locations.	LUR Averaging time: NO₂ - annual average Exposure years: 2006	NO₂ (ppb) Min = 1 Max = 34.2	Self-reported, physician dx	Logistic Regression Adjusted for: age at baseline, sex, race, caffeine intake, smoking status, caffeine intake, and physical activity	OR (95% CI)^c PD ≥75th vs. 25th (ref): 0.99 (0.81, 1.20) OR (95% CI)^b PD: 1.01 (0.90, 1.14)
†Lomme et al. (2023) Dutch European Investigation into Cancer and Nutrition (EPIC-NL), Arbeid, Milieu en Gezondheid Onderzoek (AMIGO) n = Controls: 35,106 Cases: 168 Nationwide, The Netherlands Enrollment: 1993–1997 (EPIC-NL) and 2011–2012 (AMIGO) Follow-up: 1998–2003 and 2010–2011 (EPIC-NL) and 2015 (AMIGO) Case-Cohort	General population adults aged 21–64 years in 3 Dutch cities (EPIC-MORGEN), women aged 49–70 years in a breast cancer screening program in Utrecht (EPIC-Prospect), and general population adults aged 31–63 years recruited via a Dutch national general practitioners network (AMIGO).	LUR Method validation NR Averaging time: NO₂ - annual average, NO_x - annual average Exposure years: 2009	NO₂ (ppb) Q1 Median = 7.92 (14.9 µg/m³) Min = 5.47 (10.3 µg/m³) Max = 10.4 (19.6 µg/m³) Q2 Median = 11.35 (21.35 µg/m³) Min = 10.4 (19.6 µg/m³) Max = 12.3 (23.2 µg/m³) Q3 Median = 13.7 (25.8 µg/m³)	Self-reported PD dx, relevant medication, Tanner PD screening quex, hospital and medical records	Logistic regression Adjusted for: baseline age (continuous), education (low, medium, high), sex and cohort (in combined analyses)	NO₂ OR (95% CI)^b PD - Q2 vs. Q1: 1.03 (0.67, 1.59) PD - Q3 vs. Q1: 1.34 (0.90, 2.02) PD - Q4 vs. Q1: 1.48 (0.99, 2.25) NO_x OR (95% CI)^b PD Q2 vs. Q1: 1.27 (0.82, 1.99) PD- Q3 vs. Q1: 1.53 (1.00, 2.37) PD Q4 vs. Q1: 2.08 (1.37, 3.22)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Min = 12.3 (23.2 µg/m ³) Max = 15.1 (28.4 µg/m ³) Q4 Median = 25.7 (48.4 µg/m ³) Min = 15.1 (28.4 µg/m ³) Max = 36.4 (68.4 µg/m ³) NO _x (µg/m ³) Q1 Median = 22.75 Min = 17.3 Max = 28.1 Q2 Median = 30.75 Min = 28.1 Max = 33.4 Q3 Median = 37.3 Min = 33.4 Max = 41.2 Q4 Median = 75.1 Min = 41.2 Max = 109			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Ritz et al. (2015)	PD patients	Dispersion model	NO ₂ (ppb)	Hospital register with medical review	Logistic Regression	NO ₂
n = 3,496 n cases = 1,696 n controls = 1,800		PM _{2.5} and NO ₂ : 0.62	Mean = 7.286±2.1 (13.71±3.9 µg/m ³)		Adjusted for: birth year, sex, age at first symptom, education, smoking, family history of PD, and job history of air pollution exposure	OR (95% CI) ^b PD: 1.73 (1.18, 2.52)
Denmark		PM ₁₀ and NO ₂ : 0.58	Median = 6.505 (IQR 1.58) (12.24 µg/m ³ (IQR 2.97 µg/m ³)			PD (5-yr lag): 1.54 (1.14, 2.06)
1996–2009		Averaging time: 1971 until date of diagnosis	Min = 5.2 (9.8 µg/m ³)			PD (10-yr lag): 1.63 (1.21, 2.18)
Case-Control		Exposure years: 1971–2009	Max = 22.99 (43.26 µg/m ³) P25 = 6.032 (11.35 µg/m ³) P75 = 7.61 (14.32 µg/m ³) P95 = 11.39 (21.44 µg/m ³)			NO _x
			NO _x (µg/m ³)			OR (95% CI) ^b PD: 1.06 (1.02, 1.11)
			Mean = 21±13.02 Median = 16.49 (IQR 7.1) Min = 13.46 Max = 181.55 P25 = 14.73 P75 = 21.83 P95 = 42.12			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Salimi et al. (2020)	Adults aged 45 years and over in NSW, Australia.	LUR	NO ₂ (ppb)	Self-reported physician dx	Logistic Regression	OR (95% CI) ^b
45 and Up Study		Models captured up to 69% of spatial variability in NO ₂ at urban near-traffic and urban background locations, and up to 58% of variability at all validation sites, including roadside locations	Mean = 6.335±3.06 (11.92±5.76 µg/m ³) Median = 5.623 (IQR 4.49) (10.58 µg/m ³) (IQR 8.44 µg/m ³) Min = 2.24 (4.21 µg/m ³) Max = 37.8 (71.2 µg/m ³) P10 = 3.02 (5.68 µg/m ³) P25 = 3.84 (7.22 µg/m ³) P75 = 8.323 (15.66 µg/m ³) P90 = 10.62 (19.98 µg/m ³)		Adjusted for: NA	PD: 1.12 (0.93, 1.34)
N = 267,153 n = 236,390		Averaging time: NO ₂ - annual average				
New South Wales, Australia		Exposure years: 2006–2009				
2006–2009						
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Shin et al. (2018) n = 2,194,519 Ontario, Canada Individuals followed from April 2001 until March 2013 Cohort	All adults aged 55–85 yr, free of PD, and who lived in Ontario	LUR This model explained 73% of the variation in NO ₂ measurements. Averaging time: NO ₂ - annual average Exposure yr: 2001–2013	NO ₂ (ppb) Mean = 14.7±8 Median = 13.5 (IQR 12.9) Min = 2.2 Max = 53.2 P25 = 7.9 P75 = 20.8	Physician claims (2 or more in 2 yr) or relevant prescription within 6 mo	Cox proportional hazards Adjusted for: age, sex, neighborhood-level factors, region, and comorbidities (hypertension, diabetes, stroke, dementia, etc.)	HR (95% CI) ^b PD: 1.03 (1.00, 1.06)

†Toro et al. (2019)						
n = 1,290 cases n = 436 controls n = 854	Individuals were eligible as cases if they were initially diagnosed with PD between January 2006 to December 2011 and were still alive at time of recruitment. Controls were patients diagnosed with non-neurodegenerative and peripheral neurological diseases (i.e. median nerve neuropathy, ulnar nerve neuropathy, thoracic and lumbar disc disease and sciatica), which were assumed to not share the same pathological mechanisms as PD.	LUR	NO ₂ (ppb)	Hospital medical w neurologist review	Logistic Regression	NO ₂
Rotterdam, Groningen, Tilburg, Nijmegen, Netherlands		The final models each pollutants included three to seven predictor variables and explained 86% (NO ₂), 87% (NO _x) of concentration variability.	Cases Mean = 14±2.9 (26.4±5.4 µg/m ³) P10 = 9.99 (18.8 µg/m ³) P90 = 17.9 (33.6 µg/m ³)		Adjusted for: educational level, smoking status and family history of PD, area level SES	OR (95% CI) ^c Q3 (>26.9–≤30.4) vs. ≤22.8 (ref): 0.94 (0.61, 1.44) Q4 (>30.4) vs. ≤22.8 (ref): 0.92 (0.57, 1.48) Q2 (>22.8–≤26.9) vs. ≤22.8 (ref): 1.17 (0.78, 1.74) OR (95% CI) ^b PD (continuous exposure): 0.82 (0.45, 1.51)
April 2010– June 2012		Averaging time: NO ₂ - annual average, NO _x - annual average	Controls Mean = 14.1±2.8 (26.6±5.3 µg/m ³) P10 = 10.4 (19.5 µg/m ³) P90 = 17.5 (32.9 µg/m ³)			NO _x
Case-Control		Exposure yr: 1992–2011	NO ₂ (µg/m ³) Cases Mean = 26.4±5.4 P10 = 18.8 P90 = 33.6 Controls Mean = 26.6±5.3 P10 = 19.5 P90 = 32.9			OR (95% CI) ^c Q2 (>22.8–≤26.9) vs. ≤22.8 (ref): 0.93 (0.62, 1.38) Q4 (>30.4) vs. ≤22.8 (ref): 0.98 (0.64, 1.52) PD (continuous exposure): 0.93 (0.67, 1.30) Q3 (>26.9–≤30.4) vs. ≤22.8 (ref): 0.79 (0.51, 1.20)
			NO _x (µg/m ³) Cases Mean = 43.2±8.6 P10 = 33.2 P90 = 53.4 Controls Mean = 43.4±8.7			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P10 = 33.5 P90 = 53.1			

List of abbreviations in alphabetical order: AARP = American Association of Retired People; AMIGO = Arbeid, Milieu en Gezondheid Onderzoek; BMI = body mass index; CI = confidence interval; EPIC-NL = Dutch European Investigation into Cancer and Nutrition; HA = Hospital Admission; HR = hazard ratio; ICD-(CM) = International Classification of Diseases-(Clinical Modification); ILS = Italian Longitudinal Study; IQR = interquartile range; LUR = Land Use Regression; Min = Minimum; Max = Maximum; MRI = magnetic resonance imaging; NHIRD = National Health Insurance Database; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; OR = odds ratio; P = percentile; ppb = parts per billion; PAGE study = Parkinson’s, Genes, and Environment study; PASIDA = Parkinson’s Disease in Denmark; PD = Parkinson’s disease; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; Q = quartile; RR = rate ratio; SES = socioeconomic status; vs. = versus; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA

Appendix Table 9-16 Epidemiologic studies of oxides of nitrogen exposure and other neurodegenerative diseases

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
†Bai et al. (2018) ONPHEC n = 2,824,478 Ontario, Canada Subjects were followed from cohort entry in April 1, 2001 until December 31, 2013 to determine incident cases of MS Cohort	Canadian-born adults who resided in Ontario for 5 or more yr and were registered with Ontario's provincial health insurance plan - Subjects were 20–40 yr old and free of physician-diagnosed MS at the time of entry	LUR The exposure assessment was based on a 5-year moving window of past exposures to NO₂ with a 2-year lag. Sensitivity analyses were performed to incorporate adjustments for population density and individual level factors. This model explained 73% of the variability in NO₂ measurements at fixed-site monitors with a root mean square error of 2.9 ppb Averaging time: NO₂ - annual average Exposure yr: 1994–2013	NO₂ (ppb) Mean = 14.8±7.5 Median = 13.7 (IQR 11.6) Min = 1 Max = 11.6	MS HA (ICD-9 CM 340/ICD-10 G35) or 5 physician claims in 1 yr	Cox proportional hazards Adjusted for: age as the time-scale, stratified by an indicator for living in the Greater Toronto Area or not, adjusted for sex, history of hypertension, diabetes, traumatic brain injury, infectious mononucleosis, income quintile, urban/rural indicator, latitude, and neighborhood-level race	HR (95% CI)^b MS: 0.92 (0.83, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Hedström et al. (2023) Epidemiologic Investigation of Multiple Sclerosis, Genes and Environment in Multiple Sclerosis n = 15,515 Sweden 1993–2018 Case-Control	Swedish general population aged 16–70 yr	Chemical transport model Averaging time: NO _x - annual average Exposure yr: 1990, 2000, 2011, 2015		MS registry, neurologist dx using McDonald criteria	Logistic Regression Adjusted for: study, age, region, ancestry, smoking, passive smoking, sun exposure and adolescent body mass index.	OR (95% CI) ^c MS: 1.03 (1.02, 1.05) 50–75% (9.93–16.42 µg/m ³): 1.19 (1.07, 1.32) 75–90% (16.42–24.6 µg/m ³): 1.23 (1.09, 1.39) >90% (>24.58 µg/m ³): 1.37 (1.20, 1.57) 25–50% (5.92–9.93 µg/m ³): 1.16 (1.06, 1.28)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Parks et al. (2022)	Patients with ALS diagnosis identified using ICD-8 (348.0) and ICD-10 (G12.2) codes. Controls without ALS diagnosis.	Spatiotemporal/geospatial model	NO _x (µg/m ³)	ALS Registry (ICD-8 348.0 and ICD-10 G12.2)	Conditional logistic regression	% OR (95% CI) ^c
Danish National Patient Register		(R) in the range 0.45–0.96	Cases			ALS - 5 year window:
n = 23,270			1-yr avg		Adjusted for: NA	-0.03 (-0.14, 0.10)
Denmark		Averaging time: NO _x - annual average	Mean = 26±20			
1989–2013			5-yr avg			
Case-Control		Exposure yr: 1989–2013	Mean = 28±21			
			10-yr avg			
			Mean = 29±22			
			Controls			
			1-yr avg			
			Mean = 26±19			
			5-yr avg			
			Mean = 27±20			
			10-yr avg			
			Mean = 29±20			
			Overall			
			1-yr avg			
			Mean = 26±19			
			5-yr avg			
			Mean = 27±20			
			10-yr avg			
			Mean = 29±20			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Seelen et al. (2017)	ALS cases from ESCAPE, All patients newly diagnosed as possible, probable (laboratory supported), or definite ALS, according to the revised El Escorial Criteria	LUR NO ₂ 80% Averaging time: NO ₂ - annual average, NO _x - annual average Exposure yr: 2009–2013	NO ₂ (µg/m ³) Cases Mean = 26.9±5.6 Controls Mean = 26±5.2 NO _x (µg/m ³) Cases Mean = 44.7±9.6 Controls Mean = 43.6±8.9	Incident ALS cases (possible, probable (laboratory supported), or definite ALS per revised El Escorial Criteria)	Conditional logistic regression Adjusted for: age, sex education, BMI, smoking, alcohol consumption, area SES, urbanization degree	NO ₂ OR (95% CI) ^c ALS Q3 (>42.2–≤47.3 µg/m ³) Q1 ≤22.5 µg/m ³ : 1.25 (0.97, 1.63) ALS Q4 (>47.3 µg/m ³) Q1 ≤22.5 µg/m ³ : 1.74 (1.32, 2.30) ALS Q2 (>38.2–≤44.2) Q1 ≤22.5 µg/m ³ : 1.38 (1.09, 1.76) Non-bulbar onset (Q4 vs. Q1): 1.35 (0.95, 1.91) Bulbar onset (Q4 vs. Q1): 1.74 (1.23, 2.46) NO _x OR (95% CI) ^c ALS Q3 (>42.2–≤47.3) vs. Q1 ≤22.5 µg/m ³ : 1.12 (0.87, 1.43) ALS Q2 (>38.2–≤44.2) vs. Q1 ≤22.5 µg/m ³ : 0.98 (0.78, 1.24) Bulbar onset (Q4 vs. Q1): 1.48 (1.05, 2.09) ALS Q4 (>47.3) vs. Q1 ≤22.5 µg/m ³ : 1.38 (1.07, 1.77) Non-bulbar onset (Q4 vs. Q1): 1.22 (0.87, 1.70)

List of abbreviations in alphabetical order: ALS = Amyotrophic lateral sclerosis; BMI = body mass index; CI = confidence interval; HA = Hospital Admission; HR = hazard ratio; ICD = International Classification of Diseases; IQR = interquartile range; LUR = Land Use Regression; Min = Minimum; Max = Maximum; MS = Multiple sclerosis; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; ONPHEC = Ontario Population Health and Environment Cohort; OR = odds ratio; P = percentile; ppb = parts per billion; Q = quartile; SES = socioeconomic status; vs. = versus; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-17 Epidemiologic studies of oxides of nitrogen exposure and other nervous system effects

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Hjortebjerg et al. (2018) DNBC n = 51,465 Denmark Recruitment: 1996–2002 Follow-up: 7 yr Cohort	Women who spoke Danish and intended to carry their pregnancy to term. Excluded 2374 who were not singletons, 949 with missing exposure information, 2494 with missing information on one or more potential confounders.	Dispersion model r = 0.90 half-year NO ₂ (1994–1995) was found to be. r = 0.67 1-mo mean NO ₂ (1995–2006) Averaging time: NO ₂ - annual average Exposure yr: 1994–1995, 1995–2006	NO ₂ (ppb) Febrile Seizure Cases Median = 5.8 (11 µg/m ³) P5 = 3.8 (7.1 µg/m ³) P95 = 14.1 (26.5 µg/m ³) Total Population Median = 5.79 (10.9 µg/m ³) P5 = 3.8 (7.1 µg/m ³) P95 = 13.9 (26.1 µg/m ³)	ICD-10 codes from DNPR (out- and inpatients records from 1994 onward)	Cox proportional hazards Adjusted for: sex, maternal age at birth, household income at birth, maternal education at birth, parity at birth, smoking and alcohol consumption during pregnancy, calendar-year (time-dependent, mutual noise/NO ₂ adjustment.	IRR (95% CI) ^b Febrile seizures - Childhood exposure: 1.15 (0.98, 1.35) Febrile seizures - Prenatal exposure: 1.00 (0.86, 1.17)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Li et al. (2022b)	Population based cohort of adults 40–69 at baseline.	LUR	NO ₂ (ppb)	Microvascular disease	Cox proportional hazards	NO ₂
UK Biobank		C-V $r^2 = 0.87$ (LUR-ESCAPE)	With incident microvascular disease		Adjusted for: age, sex, ethnicity, average total household income, center address, distance to the coast, smoking status, BMI, healthy diet score, alcohol consumption, sedentary time, SBP, DBP, antihypertensive medication use, diabetes, respiratory disease, and statin use	HR (95% CI) ^b
n = 396,020		Averaging time: NO ₂ - annual avg NO _x - annual avg	Mean = 15.7±4.9 (29.6±9.2 µg/m ³)			Peripheral neuropathy: 1.17 (1.11, 1.24)
U.K.			Without incident microvascular disease			Retinopathy: 1.01 (0.94, 1.09)
Baseline: 2006–2010		Exposure yr: 2005–2007, 2010	Mean = 15.5±4.9 (29.2±9.3 µg/m ³)			NO _x
Follow-up: 2020			NO _x (µg/m ³)			HR (95% CI) ^c
Cohort			With Incident microvascular disease			Peripheral neuropathy: 1.05 (1.00, 1.10)
			Mean = 44.8±15.8			Retinopathy: 0.99 (0.94, 1.04)
			Without incident microvascular disease			
			Mean = 43.8±15.6			

List of abbreviations in alphabetical order: Avg = average; BMI = body mass index; CI = confidence interval; C-V = cross-validation; DBP = diastolic blood pressure; DNBC = Danish National Birth Cohort; DNPR = Danish National Patient Register; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ratio; ICD = international classification of diseases; IRR = Incidence Rate Ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; P = percentile; ppb = parts per billion; SBP = systolic blood pressure; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-18 Toxicological studies of oxides of nitrogen exposure and other nervous system effects

Study Details and Population	Exposure Details	Endpoints Examined*
†Ye et al. (2022)	Whole body inhalation with room air controls	During exposure (Day 3, 6, 9, 12, 15)
Rat (Sprague Dawley)	500 ppb (0.5 ppm) NO ₂ , 4 hr/d for 15 d	• Mechanical pain threshold (↓) • Rat grimace scale score (↑)
7-wk-old, females	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 15 d	
n = 10/group		
†Ye et al. (2024)	Whole body inhalation with ambient air controls	During exposure (Day 3, 6, 9, 12, 15)
Rat (Sprague Dawley)	5,000 ppb (5 ppm) NO ₂ , 4 hr/d for 15 d	• Mechanical pain threshold (↓) • Rat grimace scale score (↑)
7-wk-old, females		
n = 20/group		

List of abbreviations in alphabetical order: d = day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week(s).

* Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↓ = at least one experimental group had a statistically significant decrease; ♂↑ = results were analyzed by sex and there was a statistically significant increase in at least one male experimental group and non-significant effect in females.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-19 Epidemiologic studies of oxides of nitrogen exposure and mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Andersen et al. (2022) ELAPSE n = 271,720 Sweden, France, Denmark, Germany, Austria, Netherlands Varied by cohorts, enrollment ranged from 1985 to 2005, and follow-up ranged from 2011 to 2015. Cohort	Adults enrolled in seven European cohorts.	LUR 59% spatial variation for NO ₂ Averaging time: NO ₂ - annual average Exposure yr: 2010	Med: 12.2 (23 µg/m ³) (estimated from Figure 1)	ICD 9/10 codes for dementia, psychiatric disorders, vascular dementia, mood disorders, and neurotic disorders	Cox proportional hazards Adjusted for: age (time axis), sex (strata), sub-cohort (strata), and calendar yr of baseline smoking (status, duration, intensity, and intensity2), body mass index (category), marital status, and employment status, area-level mean yr income	HR (95% CI) ^b Dementia mortality: 0.89 (0.73, 1.09)
† Cole-Hunter et al. (2023) ELAPSE n = 271,720 Sweden, France, Denmark, Germany, Austria The start of follow-up was the yr of enrolment in individual cohorts which ranged from 1985 to 2001. The pooled cohorts were followed until 2010.	Participants from the ELAPSE study who were adults aged ≥ 30 yr, based on data from population or census registries	LUR Annual mean concentrations were estimated from hybrid LUR models estimated from fixed site monitors, satellite data, and chemical transport models, capturing 58% of NO ₂ spatial variation at a 10 0m x 100 m scale. Averaging time: NO ₂ - annual average	Med: 12.2 (23 µg/m ³) (estimated from Figure 1)	PD mortality ICD9: 332; and, ICD-10: G20, G21 (secondary Parkinsonism), G22 (Parkinsonism not elsewhere classified), and F02.3 (dementia in PD).	Cox proportional hazards Adjusted for: age (time axis), sex (strata), sub-cohort (strata), and calendar yr of baseline; smoking (status, duration, intensity, and intensity), BMI (category), marital status, and employment status;	HR (Two pollutant model) (95% CI) ^b PD Mortality: 1.26 (0.91, 1.74)

Cohort		Exposure yr: 1985–2010			area-level mean yr income	
† Gariazzo et al. (2023)	Daily mortality counts Italian National Institute of Statistics	Hybrid model	NO ₂ (ppb)	ICD-10, nervous disease (G00-G99)	Poisson regression	IRR (95% CI) ^b
n = 1,769,660		Cross-validation at r ² =0.6	Rural		Adjusted for:	Lag 0-1 days- nervous disease mortality:
Italy			Mean = 6.27 (11.8 µg/m ³)		municipality-specific long-term	0.77 (0.71, 0.83)
2013-2015		Averaging time: NO ₂ - 24-hour average	Median = 5 (IQR 3.9) (9.5 µg/m ³ (IQR 7.3 µg/m ³)		seasonal time trends and day of the week, as well as	Lag 2-5 days: 0.71 (0.53, 0.94)
Time-series		Exposure yr: 2013-2015	Min = 1.4 (2.7 µg/m ³)		province-specific air temperature, bank holidays, summer population decreases and	Lag 0-5 days: 0.84 (0.65, 1.08)
			Max = 39.2 (73.7 µg/m ³)		influenza epidemics	
			P25 = 3.8 (7.1 µg/m ³)			
			P75 = 7.65 (14.4 µg/m ³)			
			Suburban			
			Mean = 10.5 (19.8 µg/m ³)			
			Median = 9.35 (IQR 6.01) (17.6 µg/m ³ (IQR 11.3 µg/m ³)			
			Min = 2.3 (4.4 µg/m ³)			
			Max = 56.02 (105.4 µg/m ³)			
			P25 = 6.9 (13 ug/m3)			
			P75 = 12.9 (24.2 µg/m ³)			
			Urban			
			Mean = 15.8 (29.7 µg/m ³)			
			Median = 14.7			

			(IQR 8.29) (27.6 $\mu\text{g}/\text{m}^3$ (IQR 15.6 $\mu\text{g}/\text{m}^3$) Min = 3.2 (6.1 $\mu\text{g}/\text{m}^3$) Max = 61.6 (115.9 $\mu\text{g}/\text{m}^3$) P25 = 11.2 (21.1 $\mu\text{g}/\text{m}^3$) P75 = 19.5 (36.7 $\mu\text{g}/\text{m}^3$) Mean = 7.81 (14.7 $\mu\text{g}/\text{m}^3$) Median = 6.32 (IQR 5.74) (11.9 $\mu\text{g}/\text{m}^3$ (IQR 10.8 $\mu\text{g}/\text{m}^3$) Min = 1.4 (2.7 $\mu\text{g}/\text{m}^3$) Max = 61.6 (115.9 $\mu\text{g}/\text{m}^3$) P25 = 4 (8 $\mu\text{g}/\text{m}^3$) P75 = 9.99 (18.8 $\mu\text{g}/\text{m}^3$)			
† Kang et al. (2023) n = 121,423 South Korea Follow-up: January 1, 2010, until death or the end of the study period (December 31, 2018), whichever was first. Cohort	All patients ≥ 40 yr who met the definition of COPD during January 1, 2009 to December 31, 2009 were included. Individuals who died in 2009 or did not undergo a health screening exam between January 1, 2007 and	Spatiotemporal/geospatial model The performance of the kriging model was evaluated using 10-fold cross-validation (r^2 of NO_2 in 2009 was 0.50). Averaging time: NO_2 - annual average Exposure yr: January 1,	NO_2 (ppb) 1-yr Median = 19.6 (36.9 $\mu\text{g}/\text{m}^3$) P25 = 16 (30 $\mu\text{g}/\text{m}^3$) P75 = 25.6 (48.2 $\mu\text{g}/\text{m}^3$) 3-yr Median = 19.9 (37.5 $\mu\text{g}/\text{m}^3$) P25 = 16.2 (30.4	ICD10: hospital admissions, outpatient visits, treatments and procedures reimbursed by the NHIS and prescriptions.	Cox proportional hazards Adjusted for: age (40–49, 50–59, 60–69, 70–79, 80–89, and ≥ 90 yr), sex, income percentile (≤ 30 th, 30–70th, and > 70 th), BMI (continuous), smoking status (never, former, and current), Charlson	HR (95% CI) ^b ALS Mortality: 1- yr average: 1.08 (0.95, 1.23) ALS Mortality: 5-yr average: 0.97 (0.93, 1.01) ALS Mortality: 3-yr average: 0.88 (0.82, 0.96)

	December 31, 2009 were excluded. Additionally, participants with missing information on smoking status, BMI, or area of residence as well as participants whose air pollutant levels in their area of residence could not be estimated were excluded.	2009–December 31, 2013	$\mu\text{g}/\text{m}^3$ P75 = 26.5 (49.8 $\mu\text{g}/\text{m}^3$) 5-yr Median = 20.5 (38.5 $\mu\text{g}/\text{m}^3$) P25 = 16.2 (30.5 $\mu\text{g}/\text{m}^3$) P75 = 27.7 (52.1 $\mu\text{g}/\text{m}^3$)		Comorbidity Index at the time of COPD diagnosis (continuous), and the presence of exacerbation (none, moderate, and severe) and stratified by Seoul, metropolitan cities, and other	
† Klompaker et al. (2021) n = 10,481,566 Netherlands Follow-up period: January 1, 2013–December 31, 2018 Cohort	Dutch populations aged 30+	Hybrid model, LUR, Dispersion model Averaging time: NO ₂ - annual average Exposure yr: 2010	NO ₂ (ppb) Median = 14 (IQR 4.4) (26.3 $\mu\text{g}/\text{m}^3$ (IQR 8.3 $\mu\text{g}/\text{m}^3$)	Statistics Netherlands (CBS) using ICD-10	Cox proportional hazards Adjusted for: sex stratified, adjusted for marital status, region of origin, standardized household income, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region, percentage of immigrants region, NDVI 300 m	HR (95% CI) ^b Neurodegenerative Disease Mortality: 0.98 (0.95, 1.02)

† Klompmaaker et al. (2020)	Dutch citizens 19 yr or older	LUR	NO ₂ (ppb)	National health survey (Public Health Monitor)	Cox proportional hazards	HR (95% CI) ^b
Public Health Monitor		Averaging time: NO ₂ - annual average	Complete case population		Adjusted for: age as underlying time scale, adjusted for marital status, region of origin, education, paid occupation, standardized household income, physical activity, BMI, smoking, alcohol consumption, PC4 composite SES, mean income (neighborhood/region), unemployment (neighborhood/region), % immigrants (neighborhood/region)	Neurodegenerative Disease Mortality:
full (imputed) population		Exposure yr: 2013	Median = 12.27 (IQR 4.01) (23.08 µg/m ³ (IQR 7.54 µg/m ³))			1.05 (0.86, 1.29)
n = 339,633			Full population			Neurodegenerative Disease Mortality:
complete case population n = 244,814			Median = 12.23 (IQR 4.04) (23.01 µg/m ³ (IQR 7.61 µg/m ³))			1.05 (0.86, 1.29)
Netherlands						Older adults:
Enrollment: September–November 2012						1.54 (0.62, 3.83)
Follow-up: 2013–2017						Non-older adults:
Cohort						0.69 (0.27, 1.74)
† Malek et al. (2023)	Postmenopausal women aged 50-79	AQS	NO ₂ (ppb)	WHI, death certificate data	Conditional logistic regression	NO ₂
WHI		Method validation NR	5-yr		Adjusted for: smoking, education, and total energy expenditure from recreational physical activity	OR (95% CI) ^b
N = 161,808		Averaging time: NO ₂ - 24-hour average, NO _x - 24-hour average	Cases			ALS Mortality: 5-yr average:
U.S.			Controls			0.90 (0.58, 1.42)
Baseline: 1993–1998		Exposure yr: 2010	Mean = 15±5			ALS Mortality: 7.5 yr average:
Case-Control			7.5-yr			0.82 (0.54, 1.23)
			Cases			ALS Mortality: 10 yr average:
			Mean = 15.2±5			0.74 (0.46, 1.17)
			Controls			
			Mean = 15.3±5			NO _x

			10-yr Cases Mean = 15.4±4.6 Controls Mean = 15.6±4.8 NOx (ppb) 5-yr Cases Mean = 26.9±13.1 Controls Mean = 27.2±12.6 7.5-yr Cases Mean = 27.4±12.7 Controls Mean = 28±12.6 10-yr Cases Mean = 27.5±11.4 Controls Mean = 28.7±12.3			OR (95% CI) ^b ALS Mortality: 5-yr average: 0.82 (0.60, 1.11) ALS Mortality: 7.5 yr average: 0.82 (0.60, 1.11) ALS Mortality: 10 yr average: 0.67 (0.44, 1.00)
† So et al. (2022) ELAPSE n = 3,083,227 Nationwide, Denmark Enrollment: January 2000 Follow-up: through December 2017 Cohort	Cohort of individuals 30 yr or older	LUR, Chemical transport model 0.58 Averaging time: NO ₂ - annual average Exposure yr: 1999-2017	NO ₂ (ppb) Mean = 10.8±4.22 (20.3±7.94 µg/m ³) IQR = 5.47 (10.3 µg/m ³) Min = 2 (3.7 µg/m ³) Max = 38.4 (72.2 µg/m ³) P5 = 5 (9.4 µg/m ³) P25 = 7.76 (14.6 µg/m ³) P75 = 13.2 (24.9	Danish Register of Cause of Death (Helweg- Larsen 2011) using the following International Classification of Disease 10th revision definitions: chronic kidney disease (N18),	Cox proportional hazards Adjusted for: age, sex, and parish level occupational status, immigrant status, marital status, and highest completed education, mean household income, regional percentage of unemployment,	HR (95% CI) ^b Psychiatric disorder mortality: 1.48 (1.38, 1.58) Dementia mortality: 1.10 (1.06, 1.14)

	$\mu\text{g}/\text{m}^3$ P95 = 19 (35.7 $\mu\text{g}/\text{m}^3$)	dementia (F00- F03, G30, G31.8–9), and psychiatric disorders (excluding dementia) (F04-F99)	and the difference of mean household income and percentage of unemployment, between parish and region

List of abbreviations in alphabetical order: ALS = amyotrophic lateral sclerosis; AQS = Air Quality System; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IRR = incidence rate ratio; ICD = International Classification of Diseases; LUR = land use regression; Max = maximum; Min = minimum; NDVI = Normalized Difference Vegetation Index; NHIS = National Health Insurance Service; NO₂ = nitrogen dioxide; NO_x = oxides of nitrogen; NR = not reported; OR = odds ratio; P = percentile; PC4 = four digit postal code level; PD = Parkinson's disease; ppb = parts per billion; SES = socioeconomic status; WHI = Women's Health Initiative; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-20 Epidemiologic studies of oxides of nitrogen exposure and overt nervous system effects

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Erickson et al. (2020)	U.K. population-based registry sample, adults 44–80 yr	LUR	NO ₂ (µg/m ³)	MRI	Linear regression	NO ₂
UK Biobank n = 18,292		ESCAPE LUR (Beelen et al. 2013)	Mean = 25.61±6.86 Min = 12.93 Max = 89.55		Adjusted for: age, sex, race, education, income, overall health, BMI, smoking status and frequency of drinking alcohol	β (mm ³) (95% CI) ^c Gray matter vol: -103.00 (-180.00, -26.00) White matter vol: -72.00 (-155.00, 12.00)
U.K. 2014		Averaging time: NO ₂ - annual average, NO _x - annual average	NO _x (µg/m ³) Mean = 42.33±14.02 Min = 19.74 Max = 231.89			NO _x
Cross-Sectional		Exposure yr: 2010				β (mm ³) (95% CI) ^c White matter vol: -26.00 (-67.00, 15.00) Gray matter vol: -42.00 (-79.00, -4.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Gale et al. (2020)	Adults 40–69 yr (community-based sample using registries)	LUR	NO ₂ (µg/m ³)	MRI	Linear regression	NO ₂
UK Biobank n = 18,288		ESCAPE LUR, see Beelen et al. 2013	Mean = 25.61±6.86 Min = 12.93 Max = 89.55		Adjusted for: age, gender, race, educational attainment, household income, self-rated health, body-mass index, smoking status, drinking frequency	β (mm ³) (95% CI) ^c Left Pole Vol: -5.12 (-10.24, 0.00) Right Pole Vol: -6.25 (-11.96, -0.54)
U.K. 2006–2010		Averaging time: NO ₂ - annual average, NO _x - annual average	NO _x (µg/m ³) Mean = 42.32±14.02 Min = 19.74 Max = 231.89			Left Operculum Cortex: -0.58 (-1.10, -0.06) Right Operculum Cortex: 0.05 (-0.46, 0.56)
Cross-Sectional		Exposure yr: 2010				NO _x β (mm ³) (95% CI) ^c Right Operculum Cortex: -0.07 (-0.33, 0.18) Left Pole Vol: -2.92 (-5.51, -0.34) Right Pole Vol: -3.93 (-6.80, -1.05) Left Operculum Cortex: -0.39 (-0.66, -0.13)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Guxens et al. (2018)	Children oversampled for maternal exposures, depression drugs/symptoms, behavioral and developmental problems.	LUR	NO ₂ (µg/m ³)	MRI	Linear regression	β (mm ³) (95% CI) ^c
Generation R		MSE r ² for back extrapolation: 0.52–0.55	Mean = 39.3 Min = 25.3 Max = 73.3		Adjusted for: parental educational levels; monthly household income; parental countries of birth; parental ages; maternal prenatal smoking, maternal prenatal alcohol use; parental BMIs and heights; maternal parity; marital status; maternal psychological distress; maternal IQ; and child gender, age, and genetic ancestry	Total Brain Vol: 124.00 (-1118.00, 1375.00) Cortical GM Vol: -60.00 (-853.00, 733.00) Cortical WM Vol: 199.00 (-287.00, 685.00) Subcortical GM Vol: 36.00 (-17.00, 89.00) Ventricular Vol: 4.00 (-57.00, 64.00)
n = 783						
Rotterdam, Netherlands						
Enrollment: 2002–2006 Follow-up: 6–10 yr		Averaging time: Pregnancy period				
Cohort		Exposure yr: 2009–2010				
† Hedges et al. (2020)	Population-based registry sample of adults (44–80 yr)	LUR	NO ₂ (ppb)	MRI	Linear regression	NO ₂
UK Biobank		ESCAPE LUR (see Beelen et al. 2013)	Mean = 13.61±3.65 (25.61±6.86 µg/m ³) Min = 6.872 (12.93 µg/m ³) Max = 47.59 (89.55 µg/m ³)		Adjusted for: total brain volume, inverse distance to nearest major road, age, gender, race, education, income, overall health, BMI, smoking status and frequency of drinking alcohol.	β (mm ³) (95% CI) ^b Left Thalamus Vol: 0.00 (-25.50, 25.50) Right Thalamus Vol: -5.08 (-29.45, 19.29)
n = 18,278						
U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average				
2010			NO _x (µg/m ³)			NO _x
Cross-Sectional		Exposure yr: 2010	Mean = 42.32±14.02 Min = 19.74 Max = 231.89			β (mm ³) (95% CI) ^c Right Thalamus Vol: -0.52 (-1.17, 0.13) Left Thalamus Vol: -0.31 (-1.00, 0.37)
† Kulick et al. (2017)	Older adults (≥50 yr)	Other	NO ₂ (ppb)	MRI	Linear and logistic regression	NO ₂

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Northern Manhattan Study (NOMAS)	free of clinical stroke	Method validation NR	Mean = 29.9 IQR = 3.6		Adjusted for: age at MRI, sex, race-ethnicity, education, insurance status, socioeconomic status	OR (95% CI) ^b SBI: 0.97 (0.63, 1.49) β (mm ³) (95% CI) ^b log-WMHV: -0.04 (-0.17, 0.08) TCBV: -0.01 (-0.51, 0.49)
n = 1075		Averaging time: NO ₂ - annual	NO _x (ppb)			
U.S.		average, NO _x - annual average	Mean = 69.1 IQR = 14			
2003–2008		Exposure yr: 2003–2008				
Cross-Sectional						NO _x OR (95% CI) ^b SBI: 0.99 (0.77, 1.26) β (mm ³) (95% CI) ^b log-WMHV: -0.02 (-0.10, 0.05) TCBV: -0.02 (-0.31, 0.28)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Nußbaum et al. (2020)	Participants from the HNR study aged 45–75 yr at baseline who were physically able and have no medical contraindications for MRI.	Hybrid model	NO ₂ (ppb)	MRI	multiple linear regression	NO ₂
1000BRAINS		Method validation	Mean = 15.7±2.5 (29.6±4.7 µg/m ³)			β (Change in LGI) (95% CI) ^b
n = 615		NR	IQR = 2.8 (5.3 µg/m ³)		Adjusted for: age, sex, education level, alcohol consumption, smoking status, cumulative pack-yr, environmental tobacco, smoke, weekly calorie expenditure by performing regular physical activity, and neighborhood unemployment rate	Right IPL: -0.04 (-0.09, 0.02)
Bochum, Essen, Mülheim/Ruhr, Germany		Averaging time: NO ₂ - annual average, NO _x - annual average	Min = 10.5 (19.8 µg/m ³) Max = 33.2 (62.4 µg/m ³)			Right PCC/P: -0.07 (-0.14, 0.00)
Enrollment: December 2000–August 2003		Exposure yr: 2008–2009	NO _x (µg/m ³)			Right DLPFC: -0.04 (-0.09, 0.02)
Follow-up: 2011–2015						NO _x
Cohort			Mean = 49.3±11.3 IQR = 14.2 Min = 24.3 Max = 107.7			β (Change in LGI) (95% CI) ^c Right DLPFC: -0.01 (-0.02, 0.01) Right PCC/P: -0.02 (-0.04, -0.01) β (Change in LGI) (95% CI) ^b Right IPL: -0.02 (-0.03, 0.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Petkus et al. (2022) WHIMS-ECHO/WHIMS-MRI studies n = 764 Nationwide, U.S. Enrollment: 2008 Follow-up: 2008–2018 Cohort	Community-dwelling women ≥80 yr and dementia-free at baseline.	Spatiotemporal/geospatial model C-V $r^2 = 0.85$ for NO_2 Averaging time: NO_2 -3-yr Exposure yr: 2002–2005	NO_2 (ppb) Mean = 12.47 ± 6.25 Median = 11.1 (IQR 7.8) P25 = 8.1 P75 = 15.3	MRI	Structural equation model Adjusted for: Age at MRI, intracranial volume, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking; alcohol use; physical activities), neighborhood socioeconomic characteristics, and clinical characteristics (any prior hormone use ever, hypercholesterolemia, hypertension, diabetes, and history of CVD)	β (z-score) (95% CI) ^b Brain vol-anterior cingulate: -0.17 (-0.27, -0.08) Brain vol-amygdala: -0.12 (-0.21, -0.03) Brain vol-prefrontal cortex: -0.16 (-0.24, -0.08) Brain vol-insula: -0.18 (-0.28, -0.08) Brain vol-thalamus: -0.03 (-0.12, 0.07) Brain vol-basal ganglia: -0.14 (-0.24, -0.03) Brain vol-limbic medial temporal lobe: -0.16 (-0.25, -0.08) Brain vol-hippocampus: -0.04 (-0.14, 0.06)

List of abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; C-V = cross-validation; CVD = cardiovascular disease; DLPFC = dorsolateral pre-frontal cortex; ESCAPE = European Study of Cohorts for Air Pollution Effects; GM = gray matter; HNR = Heinz Nixdorf Recall; IPL = inferior parietal lobule; IQ = intelligence quotient; LGI = local gyrification index; LUR = land use regression; Max = maximum; Min = minimum; mm = millimeter; MRI = Magnetic Resonance Imaging; MSE = mean square error; NO_2 = nitrogen dioxide; NO_x = oxides of nitrogen; NOMAS = Northern Manhattan Study; OR = odds ratio; P = percentile; PCC/P = posterior cingulate cortex/precuneus; ppb = parts per billion; Q = quartile; SBI = subclinical brain infarcts; TCBV = total cerebral brain volume; WHIMS-ECHO = Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes; vol = volume; WHIMS-MRI = Women's Health Initiative Memory Study-Magnetic Resonance Imaging; WM = white matter; WMHV = white matter hyperintensity volume; yr = year(s).

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO_2 for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO_2 for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO_2 for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO_2 for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 9-21 Toxicological studies of oxides of nitrogen exposure and overt nervous system effects

Study Details and Population	Exposure Details	Endpoints Examined*
Li et al. (2012)	Whole body inhalation with fresh air controls	18 hr after exposure
Rat (Wistar) 280–300 g, males n = 6/group	2,660 ppb (5 mg/m ³) NO ₂ , 6 hr/d for 7 d 5, 318 ppb (10 mg/m ³) NO ₂ , 6 hr/d for 7 d	- Brain-to-body weight ratio (↓) - Pallium histopathology (Damaged neurons with pyknotic nuclei and eosinophilic cytoplasm)
†Li et al. (2021)	Whole body inhalation with room air controls	Timing unclear
Mouse (C57BL/6J) 7-wk-old, males and females n = 3–15/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	- Brain-to-body weight ratio (NS) - Myelin structure (Damages to the ultrastructure of myelin sheaths in male mice)
†Li et al. (2022a)	Whole body inhalation with room air controls	7, 14, 21 d after exposure
Mouse (C57BL/6J) developmental exposure (GD 0 to PND 0), males and females n = 3–15/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	Myelin structure (Altered myelination and changes in myelin ultrastructure in male offspring)
†Yan et al. (2020)	Whole body inhalation with room air controls	1 d after exposure
Mouse (C57BL/6) developmental exposure (GD 0 to PND 0), males and females n = 8–20/group	2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 20 d	Brain weight (NS)

List of abbreviations in alphabetical order: d = day; GD = gestational day; g = gram; hr = hour; n = sample size; NO₂ = nitrogen dioxide; PND = postnatal day; ppb = parts per billion; ppm = parts per million; wk = week(s).

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↓ = at least one experimental group had a statistically significant decrease.

†Studies published since the 2016 Oxides of Nitrogen ISA.

A.8. Total Mortality– Short-term Exposure

Appendix Table 10-1 Epidemiologic studies of short-term exposure to oxides of nitrogen and total mortality

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Chen et al. (2018)	NR	Fixed site monitor	NO ₂ (µg/m ³)	The causes of deaths evaluated in the present study were total (coded by the International Classification of Disease, 10th revision [ICD-10]: A00–R99)	2-stage Bayesian hierarchical model	HR (95% CI) ^c Total mortality - lag 0–1: 0.90 (0.70, 1.10) Total mortality - lag 0: 0.60 (0.50, 0.80) Total mortality - lag 1: 0.70 (0.60, 0.90) Total mortality - lag 2: 0.50 (0.60, 0.90) Total mortality - lag 3: 0.30 (0.10, 0.40)
N = ~290,000,000		Method validation NR	Overall Mean = 31±11 Median = 30			
China		Averaging time: NO ₂ - annual average	Min = 10 Max = 66 P25 = 22 P75 = 38			
2013–2015		Exposure years: 2013–2015				
Time-series						
† Corso et al. (2020)	Daily mortality (total nonaccidental and cardiovascular) data classified by ICD-10 codes	Central site monitor	NO ₂ (ppb)	ICD codes	Generalized additive Poisson regression models	RR (95% CI) ^b Non-accidental mortality- warm period: 10.34 (7.04, 13.75) Non-accidental mortality - cold period: 0.04 (-1.51, 1.61) Non-accidental mortality, ≥75 years: 4.36 (2.38, 6.38) Non-accidental mortality, cold period, ≥75 years: 0.75 (-1.14, 2.68) Non-accidental mortality, warm period, ≥75 years: 12.05 (7.62, 16.67) Non-accidental mortality: 2.85 (1.52, 4.21)
n = NR		Averaging time: NO ₂ - 24-hour average	Bordeaux Mean = 10.4 (19.6 µg/m ³) Min = 1 (2 µg/m ³) Max = 36.1 (67.9 µg/m ³)		Adjusted for: Daily temperature, day of the week, bank holiday, seasonality	
Paris, Bordeaux, Clermont-Ferrand, Dijon, Grenoble, Le Havre, Lens-Douai, Lille, Lyon, Marseille, Montpellier, Nancy, Nantes, Nice, Rennes, Rouen, Strasbourg, Toulouse, France		Exposure years: 2010–2014	Clermont-Ferrand Mean = 13 (24 µg/m ³) Min = 1.1 (2.1 µg/m ³) Max = 55.32 (104.1 µg/m ³) Dijon Mean = 12 (22.5 µg/m ³) Min = 1.3 (2.4 µg/m ³) Max = 38.8 (73.1 µg/m ³)			
2010–2014						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Time-series			Grenoble Mean = 12.6 (23.8 µg/m ³) Min = 1.4 (2.7 µg/m ³) Max = 42.9 (80.8 µg/m ³)			
			Le Havre Mean = 11.9 (22.4 µg/m ³) Min = 1 (2 µg/m ³) Max = 42 (79 µg/m ³)			
			Lens-Douai Mean = 11.5 (21.7 µg/m ³) Min = 0.5 (1 µg/m ³) Max = 43 (81 µg/m ³)			
			Lille Mean = 13.4 (25.3 µg/m ³) Min = 1.9 (3.5 µg/m ³) Max = 42.7 (80.3 µg/m ³)			
			Lyon Mean = 16.5 (31.1 µg/m ³) Min = 2.3 (4.3 µg/m ³) Max = 51.2 (96.3 µg/m ³)			
			Marseille Mean = 17.4 (32.7 µg/m ³) Min = 2.4 (4.5 µg/m ³) Max = 43.7 (82.3 µg/m ³)			
			Montpellier Mean = 13.8 (25.9 µg/m ³) Min = 0.58 (1.1 µg/m ³) Max = 42.3 (79.5 µg/m ³)			
			Nancy			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 13 (24.4 µg/m ³) Min = 2.5 (4.7 µg/m ³) Max = 35.7 (67.1 µg/m ³)			
			Nantes Mean = 9.51 (17.9 µg/m ³) Min = 0.96 (1.8 µg/m ³) Max = 39 (73.4 µg/m ³)			
			Nice Mean = 13.2 (24.9 µg/m ³) Min = 3 (5 µg/m ³) Max = 29 (55 µg/m ³)			
			Paris Mean = 19 (36 µg/m ³) Min = 4.4 (8.3 µg/m ³) Max = 49 (93 µg/m ³)			
			Rennes Mean = 9.94 (18.7 µg/m ³) Min = 0.37 (0.7 µg/m ³) Max = 44.88 (84.45 µg/m ³)			
			Rouen Mean = 13.7 (25.7 µg/m ³) Min = 2 (3.7 µg/m ³) Max = 40 (75 µg/m ³)			
			Strasbourg Mean = 14 (27 µg/m ³) Min = 2.5 (4.7 µg/m ³) Max = 39.1 (73.5 µg/m ³)			
			Toulouse Mean = 11.2 (21.1 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 1.2 (2.3 µg/m ³) Max = 40.8 (76.8 µg/m ³)			
† Gariazzo et al. (2023) n = 1,769,660 Italy 2013–2015 Time-series	Daily mortality counts (natural, cardiovascular, cardiac, ischemic, cerebrovascular, respiratory, mental, nervous, metabolic, diabetes) classified using ICD-10 codes from the Italian National Institute of Statistics	Hybrid model Cross-validation at r ² = 0.6 Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2015	NO ₂ (µg/m ³) Rural Mean = 11.8 Median = 9.5 (IQR 7.3) Min = 2.7 Max = 73.7 P25 = 7.1 P75 = 14.4 Suburban Mean = 19.8 Median = 17.6 (IQR 11.3) Min = 4.4 Max = 105.4 P25 = 13 P75 = 24.2 Urban Mean = 29.7 Median = 27.6 (IQR 15.6) Min = 6.1 Max = 115.9 P25 = 21.1 P75 = 36.7 Overall Mean = 14.7 Median = 11.9 (IQR 10.8) Min = 2.7 Max = 115.9 P25 = 8 P75 = 18.8	ICD codes	Time series and pooled analysis Adjusted for: municipality, year, month, day of the week, holidays, summer population decrease and influenza epidemics	HR (95% CI) ^c Total (natural) mortality, lag 0–1: -0.88 (-1.49, -0.26) Total (natural) mortality, lag 2–5: -0.14 (-0.80, 0.54)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Huang et al. (2023) n = NR Canada 2001–2018 (Hospitalizations) 2001–2015 (Mortality) Time-series	Daily mortality and hospitalizations (non-accidental all-cause, circulatory, and respiratory) using ICD-10 codes	Central site monitor Averaging time: 3-hour max Exposure years: 2001–2018	NO ₂ (ppb) Mean = 16.7 Median = 16.9 Min = 7.1 Max = 30 P25 = 12.9 P75 = 19.5	ICD codes	Bayesian hierarchical model	HR (95% CI) ^c All cause mortality - Adults (<65 years): 0.17 (0.00, 0.79) All-cause mortality - Older adult (>65 years): 0.91 (0.16, 1.01) All-cause mortality: 0.64 (0.15, 0.74)
†Lanzinger et al. (2016) UFIREG n = 4,894,169 Dresden, Augsburg, Germany; Prague, Czech Republic; Ljubljana, Slovenia; Chernivtsi, Ukraine Augsburg and Dresden: January 2011–December 2012; Ljubljana and Prague: January 2012–December 2013; Chernivtsi: January 2013–March 2014	Daily mortality (natural causes, cardiovascular, respiratory) of residents who died in study cities classified by ICD-10 codes. Infants aged <1 year were excluded.	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2011–2013	NO ₂ (ppb) Augsburg Mean = 15±6.27 (28±11.8 µg/m ³) Median = 14.3 (IQR 8.56) (26.9 µg/m ³ (IQR 16.1 µg/m ³) Min = 2.2 (4.2 µg/m ³) Max = 39 (74 µg/m ³) Dresden Mean = 11.9±5.3 (22.3±10 µg/m ³) Median = 10.8 (IQR 6.86) (20.4 µg/m ³ (IQR 12.9 µg/m ³) Min = 2.1 (3.9 µg/m ³) Max = 35.8 (67.3 µg/m ³) Ljubljana Mean = 13.3±7.87 (25.1±14.8 µg/m ³) Median = 11.8 (IQR 8.72)	ICD codes	Poisson regression Adjusted for: dummy variables for day of the week (Monday to Sunday), a dummy variable for public holidays referring to single days (holidays vs. non-holidays), a dummy variable for the decrease of the populations present in the city during longer vacation periods with high travel activities for example during school vacation (Christmas, Easter, summer vacation), a dummy variable for influenza epidemics (where available), air temperature (average	HR (95% CI) ^c Total (natural) mortality, lag 0–5: 0.40 (-3.10, 4.10) Total (natural) mortality, lag 0–1: 0.50 (-1.60, 2.80) Total (natural) mortality, lag 2–5: 0.10 (-3.40, 3.70)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Time-series			(22.2 µg/m³ (IQR 16.4 µg/m³) Min = 0.96 (1.8 µg/m³) Max = 63.46 (119.4 µg/m³) Prague Mean = 11.6±6.22 (21.9±11.7 µg/m³) Median = 10.4 (IQR 8.61) (19.5 µg/m³ (IQR 16.2 µg/m³) Min = 2.4 (4.5 µg/m³) Max = 39.4 (74.2 µg/m³) NO₂ (µg/m³) Augsburg Mean = 28±11.8 Median = 26.9 (IQR 16.1) Min = 4.2 Max = 74 Dresden Mean = 22.3±10 Median = 20.4 (IQR 12.9) Min = 3.9 Max = 67.3 Ljubljana Mean = 25.1±14.8 Median = 22.2 (IQR 16.4) Min = 1.8 Max = 119.4 Prague Mean = 21.9±11.7		of lags 0–1 [lag 0: same-day; lag 1: one day before the event] to represent effects of high temperatures and average of lags 2–13 [lag 2: two days prior to the event; lag 13: 13 days prior to the event] to represent effects of low temperatures), and relative humidity (average of lags 0–1 and average of lags 2–13)	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Median = 19.5 (IQR 16.2) Min = 4.5 Max = 74.2			
† Li et al. (2021) n = 9.6 million 28 provinces of mainland China January 2013–December 2017 Time-series	Death Register and Report Information System of Chinese Center for Disease Control and Prevention	Monitors (China's National Urban Air Quality Real-time Publishing Platform of the China National Environmental Monitoring Center Averaging time: NO ₂ - 24-hour average Exposure years: 2013–2017	NO ₂ (ppb) Mean = 39.7±9.5 Median = 38.0 (IQR 16.4) Min = 22.8 Max = 60.6	ICD 10 codes for total, nonaccidental case codes A00 to R99	Generalized additive model with overdispersion	HR (95% CI) ^b Daily mortality: 2.47 (1.90, 3.04) Year of Life Lost: 2.43 (1.78, 3.08)
† Liu et al. (2022) n = 3,063,192 Georgia, Massachusetts, Michigan, New Jersey, Indiana, Kansas, Ohio, U.S. 2000–2015 Case-crossover	Daily mortality (all-cause, cardiovascular, respiratory) classified by ICD-10 codes	Hybrid model Out-of-sample predicted $r^2 = 0.79$ Averaging time: NO ₂ - 24-hour average Exposure years: 2000–2015	NO ₂ (ppb) Mean = 21.2±12.1	ICD codes	Conditional logistic regression	HR (95% CI) ^c All-cause mortality - 65-75: 0.07 (-0.26, 0.40) All-cause mortality - ≥75: 0.14 (-0.17, 0.44) All-cause mortality - female: 0.07 (-0.05, 0.20) All-cause mortality - <high school education (ref): 0.00 (0.00, 0.00) All-cause mortality - >high school education: -0.01 (-0.20, 0.17) All-cause mortality - age group: 45-65: 0.04 (-0.29, 0.37) All-cause mortality - age group: <45 (ref): 0.00 (0.00, 0.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						All-cause mortality - high school education: -0.01 (-0.17, 0.16) All-cause mortality - male (ref): 0.00 (0.00, 0.00)
† Meng et al. (2021) n = 62,800,000 United States, Sweden, China, United Kingdom, Canada, Spain, Japan, South Korea, Taiwan, Brazil, Switzerland, Colombia, Thailand, Germany, Czech Republic, Greece, Australia, Finland, Chile, Estonia, Portugal, Romania 1973–2018 Time-series	Mortality data (total, cardiovascular, and respiratory) obtained from local authorities within each selected country/region using ICD-9 and 10 codes	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1973–2018	NO ₂ (ppb) Pooled Median = 14.3 (26.9 µg/m ³) P25 = 10.4 (19.5 µg/m ³) P75 = 19.2 (36.2 µg/m ³) United States Median = 15.3 (28.7 µg/m ³) P25 = 11.1 (20.8 µg/m ³) P75 = 20.5 (38.6 µg/m ³)	ICD codes	QuasiPoisson generalised linear regression model & meta-analytic approach Adjusted for: year, day of the week, temperature, humidity,	HR (95% CI) ^b Total mortality, pooled for 398 cities of 22 countries/regions: 1.74 (1.34, 2.14) Total mortality, United States: 2.16 (1.74, 2.58)
† Perez et al. (2015) n = 2,240,694 Switzerland 1995–2010 Time-series	ED admissions and deaths (all cause, cardiovascular, respiratory) classified using ICD-10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1995–2010	NO ₂ (ppb) Region AG/BE/LU/SO Mean = 21 (39 µg/m ³) Region AG/BL/BS/SO Mean = 14.1 (26.6 µg/m ³) Region AI/AR/FL/SG Mean = 9.62 (18.1 µg/m ³)	ICD codes	Poisson regression Adjusted for: indicator variables for the days of the week and for holidays, temperature (T), relative humidity (RH) and barometric pressure (P), influenza incidence for the day of the event	HR (95% CI) ^b Daily mortality - Ages ≥65: 1.20 (-0.10, 2.52) Daily mortality - Ages ≥75: 1.20 (0.00, 2.42)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Region AI/AR/SG/TG Mean = 8.18 (15.4 µg/m ³)		(t) and the two preceding days	
			Region BE Mean = 14.6 (27.5 µg/m ³)		temperature (T), relative humidity (RH) and barometric pressure (P)	
			Region BE/FR/SO Mean = 8.61 (16.2 µg/m ³)		for the day of the event (t) and the two preceding days	
			Region GR Mean = 16.6 (31.3 µg/m ³)		temperature (T), relative humidity (RH) and barometric pressure (P)	
			Region LU/NW/OW/SZ/UR Mean = 12.6 (23.7 µg/m ³)		for the day of the event (t) and the two preceding days	
			Region LU/ZG Mean = 14.3 (26.9 µg/m ³)			
			Region SG/SH/SZ/ZH Mean = 19.1 (35.9 µg/m ³)			
			Region TISopracceneri/GR Mean = 13 (24 µg/m ³)			
			Region TISottoceneri Mean = 20.4 (38.4 µg/m ³)			
			Region VS Mean = 18.9 (35.6 µg/m ³)			
† Schwartz et al. (2017) n = NR	Women who had singleton deliveries in the county of Scandia from 1999–1995.	Other Averaging time: NO ₂ - 24-hour average	NO ₂ (ppb) Mean = 18.4±6.4 Min = 4 Max = 46.9	ICD codes	Instrument variable	HR (95% CI) ^c Daily deaths: 0.62 (-0.12, 1.64)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Boston, Massachusetts, U.S. 2000–2009 Time-series	Inclusion was automatic unless otherwise requested.	Exposure years: NR				
† Schwartz et al. (2018) n = 7,277,274 Nationwide, United States 1999–2010 Other (Specify in notes box)	Only specified that mortality data were used from 135 U.S. cities	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1999–2010	NO ₂ (ppb) Mean = 15.3 P25 = 9.5 P75 = 19.8	ICD codes	Marginal structure model Marginal structure model with negative control Time series	HR (95% CI) ^c Daily mortality - marginal structural model: 2.59 (1.78, 3.40) Daily mortality - marginal structure model with negative control: 2.62 (1.81, 3.43) HR (95% CI) ^b Daily mortality- time series: 0.76 (0.15, 1.38)
† Shin et al. (2022) n = NR Montreal, Halton, Ontario, London, Ontario, Toronto, Ontario, Windsor, Ontario, Edmonton, Winnipeg, Hamilton, Sudbury, Halifax, Saint John, Quebec City, Ottawa, Durham, York, Peel, Niagara, Waterloo, Sarnia, Sault Sainte Marie, Regina,	Mortality and hospitalization daily counts (all-cause, circulatory, and respiratory) classified by ICD-9 and 10 codes	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 1984–2012	NO ₂ (ppb) Population-weighted Cold season Mean = 20±4 Warm season Mean = 16±4 Year Mean = 18 Min = 8 Max = 28	ICD codes	Generalized additive quasi-Poisson model with a Bayesian hierarchical model Adjusted for: calendar time and temperature	HR (95% CI) ^c All-cause mortality, females, cold season, lag year 0: 1.40 (0.90, 1.80) All-cause mortality, females, cold season, lag year 1: 0.10 (-0.20, 0.30) All-cause mortality, females, cold season, lag year 2: -0.30 (-0.60, 0.00) All-cause mortality, females, lag year 0: 1.60 (1.20, 1.90) All-cause mortality, females, lag year 1: 0.20 (0.00, 0.40) All-cause mortality, females, lag year 2: -0.20 (-0.40, 0.10) All-cause mortality, females,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Saskatoon, Calgary, Canada						warm season, lag year 0: 2.00 (1.30, 2.80)
1984–2012						All-cause mortality, females, warm season, lag year 1: -0.40 (-0.90, 0.10)
Time-series						All-cause mortality, females, warm season, lag year 2: -0.50 (-1.00, 0.00)
						All-cause mortality, males, cold season, lag year 0: 1.30 (0.80, 1.80)
						All-cause mortality, males, cold season, lag year 1: 0.40 (-0.10, 0.80)
						All-cause mortality, males, cold season, lag year 2: -0.30 (-0.90, 0.40)
						All-cause mortality, males, lag year 0: 1.80 (1.30, 2.30)
						All-cause mortality, males, lag year 1: 0.40 (0.10, 0.70)
						All-cause mortality, males, lag year 2: -0.10 (-0.40, 0.30)
						All-cause mortality, males, warm season, lag year 0: 2.50 (1.80, 3.20)
						All-cause mortality, males, warm season, lag year 1: -0.70 (-1.30, 0.00)
						All-cause mortality, males, warm season, lag year 2: -0.50 (-1.00, 0.10)
†Wei et al. (2021)	Medicare enrollment records between January 1, 2000–December	Hybrid model 0.79	NO ₂ (ppb) Long term Mean = 20.4±8.3	All-cause mortality	Linear probability model/weighted least squares	Beta (95% CI) ^c Annual number of early deaths with LPM/WLS method, below standard (<100 ppb) analysis:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 1,503,572 Massachusetts, U.S. 2000–2012 Other (Specify in notes box)	31, 2012, for beneficiaries aged 65 years and above residing in Massachusetts from the Centers for Medicare and Medicaid Services	Averaging time: NO ₂ - 24-hour average, NO ₂ - annual average Exposure years: January 1, 1999, and December 31, 2012	Median = 19.2 Min = 3.2 Max = 64.6 P5 = 8.6 P25 = 14.1 P75 = 26.1 P95 = 35 Short term Mean = 20.5±11.6 Median = 18.7 Min = 0.2 Max = 119 P5 = 5.3 P25 = 11.3 P75 = 27.9 P95 = 41.6		Adjusted for: sex (male or female), race (White, Black, or Other), age group (65–69, 70–74, 75–79, 80–84, or ≥85 years), and Medicaid eligibility (as a marker of socioeconomic status), air surface temperature, dew point temperature, and relative humidity, median household income, median house value, percent of owner-occupied homes, percent of population living in poverty, percent of population below high school education, population density, percent of Blacks, and percent of Hispanics M-out-of-n random forests (moonRF) Adjusted for: sex (male or female), race (White, Black, or Other), age group (65–69, 70–74, 75–79, 80–84, or ≥85 years), and Medicaid eligibility (as	168.00 (156.00, 179.00) Annual number of early deaths with LPM/WLS method: 167.00 (156.00, 179.00) Annual number of early deaths with moonRF method, below standard (<100 ppb) analysis: 163.00 (151.00, 174.00) Annual number of early deaths with moonRF method: 163.00 (151.00, 174.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
					a marker of socioeconomic status), air surface temperature, dew point temperature, and relative humidity, median household income, median house value, percent of owner-occupied homes, percent of population living in poverty, percent of population below high school education, population density, percent of Blacks, and percent of Hispanics	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
[†] Zhao et al. (2021)	Mortality data from 2014–2016 across 954 municipal districts and 1897 counties in China	Spatiotemporal/geospatial model Averaging time: NO ₂ - 24-hour average Exposure years: 2014–2016	NO ₂ (ppb) Min = 7.435 (13.99 µg/m ³) Max = 24.81 (46.69 µg/m ³)	ICD codes	Logistic regression Adjusted for: Sunlight, humidity and temperature	OR (95% CI) ^b All-cause mortality in urban areas: 1.02 (1.01, 1.04)
n = NR						
China						
2014–2016						
Time-series						

List of Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; ICD = International Classification of Disease; IQR = interquartile range; LPM = Linear probability model; LUR = land use regression; Max = maximum; Min = minimum; NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NR = not reported; OR = odds ratio; P# = #th percentile; ppb = parts per billion; R² = coefficient of determination; RR = relative risk; WLS = weighted least squares.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

A.9. Total Mortality – Long-term Exposure

Study Reference	Participant Description	Exposure Assessment	Concentration Examination^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Beelen et al. (2008) Brunekreef et al. (2009) NLCS N = 117,528 Netherlands Enrollment: September 1986 Follow-up: 1987–1996 Cohort	Adults aged 55–69 yrs living in 204 municipalities throughout the Netherlands	Hybrid model Averaging time: NO ₂ - annual average Exposure years: 1987–1996	NO ₂ (ppb) Background NO ₂ Mean = 18.3±3.9 (34.5±7.3 µg/m ³) Min = 7.76 (14.6 µg/m ³) Max = 28.1 (52.8 µg/m ³) Overall NO ₂ Mean = 19.6±4.4 (36.9±8.2 µg/m ³) Min = 7.76 (14.6 µg/m ³) Max = 35.4 (66.7 µg/m ³)	Cancer registries	Cox proportional hazards Adjusted for: Age, sex, smoking status, area level indicators of SES	NO ₂ RR (95% CI) ^b Nonaccidental Mortality: 1.05 (1.00, 1.10)
Beelen et al. (2014) EPIC-Umea, FINRISK, HUBRO, SNAC-K, SALT/Twin gene, 60-y/IMPROVE, SDPP, DCH, EPIC-	Adults from general population in 13 countries across Europe	LUR The model explained 58–90% of the variability in the annual average concentrations for NO ₂ and 49–91% of the variability in the annual average concentrations for NO _x Averaging time: NO ₂ -	NO ₂ (ppb) 60-y/IMPROVE Mean = 5.69±2.2 (10.7±4.2 µg/m ³) DCH Mean = 8.66±4 (16.3±7 µg/m ³) E3N Mean = 16.2±6.75	Mortality registries	Cox proportional hazards Adjusted for: sex, calendar time, smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetables intake, alcohol consumption, BMI, educational level, occupational class, employment status, marital	NO ₂ HR (95% CI) ^b Nonaccidental Mortality: 1.02 (0.98, 1.06) NO _x HR (95% CI) ^c Nonaccidental

MORGEN, EPIC-Prospect, SALIA, EPIC- Oxford, KORA, VHM&PP, SAPALDIA, E3N, EPIC- Varese, EPIC- Turin, SIDRIA- Rome, EPIC-San Sebastian, EPIC- Athens	annual average, NO _x - annual average Exposure years: 2008– 2011	(30.5±12.7 µg/m ³) EPIC-Athens Mean = 20.1±7.28 (37.9±13.7 µg/m ³) EPIC-MORGEN Mean = 12.6±4 (23.8±7 µg/m ³) EPIC-Oxford Mean = 13±4.2 (24.4±7.9 µg/m ³) EPIC-San Sebastian Mean = 12.6±3.5 (23.8±6.6 µg/m ³) EPIC-Turin Mean = 28.2±5.74 (53.1±10.8 µg/m ³) EPIC-Umea Mean = 2.8±1.3 (5.2±2.5 µg/m ³) EPIC-Varese Mean = 23.2±9.19 (43.7±17.3 µg/m ³) EPIC_PROSPECT Mean = 14.2±2.4 (26.7±4.6 µg/m ³) FINRISK Mean = 8.13±2.6 (15.3±4.8 µg/m ³) HUBRO Mean = 11.1±4	status, and area-level socioeconomic status	Mortality: 1.02 (1.00, 1.04)
N = 367,251				
Sweden, France, United Kingdom, Denmark, Spain, Italy, Switzerland, Norway, Germany, Greece, Austria, Netherlands				
EPIC-Umea: Enrollment = 1992–1996; Follow-up = 12.7 mean yrs				
FINRISK: Enrollment = 1992, 1997, 2002, 2007; Follow-up = 10.6 mean yrs				
HUBRO:				

Enrollment = 2000–2001; Follow-up = 9.6 mean yrs SNAC-K:	(20.9±8 µg/m ³)
Enrollment = 2001–2004; Follow-up = 6.5 mean yrs SALT/Twin gene: Enrollment = 1998–2002; Follow-up = 8.7 mean yrs 60-y/IMPROVE: Enrollment = 1997–1999; Follow-up = 11.2 mean yrs SDPP: Enrollment = 1992–1998; Follow-up: 13.9 mean yrs DCH: Enrollment = 1993–1997; Follow-up: 13.2 mean yrs EPIC- MORGEN: Enrollment = 1993–1997; Follow-up: 13.2 mean yrs EPIC- PROSPECT: Enrollment = 1993–1997; Follow-up =	KORA Mean = 9.94±2.1 (18.7±3.9 µg/m ³) SALIA Mean = 16±4.1 (30±7.8 µg/m ³) SALT/Twin gene Mean = 5.79±2.2 (10.9±4.2 µg/m ³) SAPALDIA Mean = 15.3±3.2 (28.8±6.1 µg/m ³) SDPP Mean = 4.5±0.9 (8.4±1.7 µg/m ³) SIDRIA-Rome Mean = 20.8±4.8 (39.1±9.1 µg/m ³) SIDRIA-Turin Mean = 31.8±5.58 (59.8±10.5 µg/m ³) SNAC-K Mean = 9.19±2.6 (17.3±4.8 µg/m ³) VHM&PP Mean = 10.6±2.9 (19.9±5.5 µg/m ³) NO _x (µg/m ³)

12.9 mean yrs	60-y/IMPROVE
SALIA:	Mean = 18.6±9.4
Enrollment =	
1985–1987 and	DCH
1990–1994;	Mean = 26.6±18.3
Follow-up: 18.6	
mean yrs	E3N
EPIC-Oxford:	Mean = 55.6±28.2
Enrollment =	
1993–2001;	EPIC-Athens
Follow-up: 12.6	Mean = 75.2±40.8
mean yrs	
KORA:	EPIC-MORGEN
Enrollment =	Mean = 36.5±11.8
1994–1995 and	
1999–2001;	EPIC-Oxford
Follow-up =	Mean = 40.8±15.6
10.5 mean yrs	
VHM&PP:	EPIC-PROSPECT
Enrollment =	Mean = 39.6±10.5
1985–2005;	
Follow-up =	EPIC-San Sebastian
17.3 mean yrs	Mean = 47.1±12.5
SAPALDIA:	
Enrollment =	EPIC-Turin
1991; Follow-up	Mean = 96.1±21
= 16.1 mean yrs	
E3N: Enrollment	EPIC-Umea
= 1993–1996;	Mean = 8.7±5.7
Follow-up =	
13.5 mean yrs	EPIC-Varese
EPIC-Varese:	Mean = 86.6±41.9
Enrollment =	
1993–1997;	FINRISK
Follow-up =	Mean = 24.2±8.8
11.3 mean yrs	
EPIC-Turin:	HUBRO
Enrollment =	Mean = 38.2±15.4
1993–1998;	
Follow-up =	KORA

13.4 yrs			Mean = 32.6±7.4			
SIDRIA-Turin:						
Enrollment =			SALIA			
1999; Follow-up			Mean = 50.7±20.4			
= 11 mean yrs						
SIDRIA-Rome:			SALT/Twin gene			
Enrollment =			Mean = 18.9±9.3			
1999; Follow-up						
= 11.2 mean yrs			SAPALDIA			
EPIC-San			Mean = 48.7±13.6			
Sebastian:						
Enrollment =			SDPP			
1992–1995;			Mean = 14.4±3.2			
Follow-up =						
12.5 mean yrs			SIDRIA-Rome			
EPIC-Athens:			Mean = 82.1±23.9			
Enrollment =						
1994–1999;			SIDRIA-Turin			
Follow-up =			Mean = 107.3±24.1			
11.2 mean yrs						
Cohort			SNAC-K			
			Mean = 33.2±12.3			
			VHM&PP			
			Mean = 40±9.6			
Carey et al. (2013)	Adults aged 40–89 yrs registered with the U.K. NHS for at least one year	Dispersion model, Fixed site monitor	NO ₂ (ppb)	Death registration records	Cox proportional hazards	HR (95% CI) ^b
Clinical Practice Research Datalink		r ² = 0.57–0.80	London Region		Adjusted for: age, sex, smoking, BMI, education	All-Cause Mortality:
N = 835,607		Averaging time: NO ₂ - annual average	Mean = 17.7±2.4 (33.3±4.5 µg/m ³)			1.06 (1.03, 1.08)
England, Scotland, Wales, U.K.		Exposure years: 2002	North Region			
Enrollment:			Mean = 12.4±3.3 (23.4±6.3 µg/m ³)			
			Overall			
			Mean = 12±3.9 (22.5±7.4 µg/m ³)			
			IQR = 5.69 (10.7			

January 2003 Follow-up: 2003–2007 Cohort			$\mu\text{g}/\text{m}^3$ Min = 2.4 (4.5 $\mu\text{g}/\text{m}^3$) Max = 32.3 (60.8 $\mu\text{g}/\text{m}^3$) South Region Mean = 10.3±3.2 (19.4±6.1 $\mu\text{g}/\text{m}^3$)			
Hart et al. (2013) Nurses' Health Study n = 84,562 Nationwide, U.S. Enrollment: 1988 Follow-up: through 2006 Cohort	Married female U.S. registered nurses aged 30–55 yrs in 1976 with home addresses in 1988–2006 within the continental United States and geocoded to the street segment level. Women were excluded if they reported CHD or cancer before the start of follow-up	Spatiotemporal/geospatial model Averaging time: NO ₂ - annual average Exposure years: 2000	NO ₂ (ppb) Median = 13.9 (IQR 7.5) Min = 0 Max = 80.4	National Death Index	Cox proportional hazards Adjusted for: age, race, calendar year, BMI, physical activity, healthy diet score, alcohol consumption, hypercholesterolemia, high blood pressure, diabetes, family history of MI, smoking status and pack-years, overall mental health status, mother and father's occupations, marital status, husband's education, nurses' education level, employment status, and census. tract median income and median home value (at current address and difference from previous address)	HR (95% CI) ^b All-Cause Mortality: 1.03 (0.99, 1.06)
Hoek et al. (2002) NLCS n = 4,492 Nationwide, Netherlands	Participants aged 55–69 yrs at enrollment from 204 (29%) of 714 municipalities with computerized population registries and were covered by	Spatiotemporal/geospatial model CV RMSE ranged 0.15 for the regional background model to 0.25 for the urban background model	NO ₂ (ppb) Background (regional and urban background only) Mean = 19.2±4.2 (36.1±7.9 $\mu\text{g}/\text{m}^3$) Median = 19.3 (36.4 $\mu\text{g}/\text{m}^3$)	National Mortality registries	Cox proportional hazards Adjusted for: age, sex, education, Quetelet-index, occupation, active and passive cigarette smoking, neighborhood socioeconomic score	RR (95% CI) ^b All-Cause Mortality, Background: 1.14 (0.89, 1.47) All-Cause Mortality, Background and

Enrollment: 1986 Follow-up: through 1994 Cohort	cancer registries in 1986	Averaging time: NO ₂ - 4- year Exposure years: 1987– 1990	Min = 7.81 (14.7 µg/m ³) Max = 31.6 (59.5 µg/m ³) P5 = 10.8 (20.3 µg/m ³) P25 = 17.2 (32.4 µg/m ³) P75 = 21.7 (40.8 µg/m ³) P95 = 25.6 (48.2 µg/m ³) Background and Local (including distance to major roadways) Mean = 19.5±4.4 (36.6±8.3 µg/m ³) Median = 19.5 (36.6 µg/m ³) Min = 7.81 (14.7 µg/m ³) Max = 35.7 (67.2 µg/m ³) P5 = 10.8 (20.3 µg/m ³) P25 = 17.3 (32.6 µg/m ³) P75 = 22.1 (41.5 µg/m ³) P95 = 26.9 (50.7 µg/m ³)			local: 1.21 (0.96, 1.54)
Jerrett et al. (2009) Toronto Western Hospital	Residents of Ontario with health insurance program number who attended a	LUR r ² = 0.7 Averaging time: NO ₂ - annual average	NO ₂ (ppb) Overall Median = 22.9	National Mortality registries	Cox proportional hazards Adjusted for: sex, age, smoking status, BMI, BMI- squared, FVC (% predicted), neighborhood deprivation	RR (95% CI) ^b Nonaccidental Mortality: 1.48 (1.01, 2.17)

N = 2,360	respiratory disease clinic	Exposure years: 2002, 2004	P25 = 20.8 P75 = 24.8		index, clustering on census. tract	
Toronto, Canada						
Enrollment: 1992–1999 Follow-up: 1992–2002						
Cohort						
Jerrett et al. (2013)	Subjects with valid postal addresses, residents of California, and excluded those with missing data on key covariates	LUR	NO ₂ (ppb)	Medical records	Cox proportional hazards	RR (95% CI) ^b
CPS-II		Averaging time: NO ₂ - monthly	Overall Mean = 12.27 Median = 12.12		Adjusted for: individual-level covariates, consolidated metropolitan statistical area city indicators, 1990 ecologic covariates stratifying the baseline hazard function by age, gender, and race	All-Cause Mortality: 1.077 (1.018, 1.140)
N = 73,711		Exposure years: 1988–2002	P5 = 7.93 P10 = 8.81 P25 = 10.21 P75 = 14.33 P90 = 16.22 P95 = 17.09			
California, U.S.						
Enrollment: 1982 Follow-up: 1982–2000						
Cohort						
Krewski et al. (2000)	HSC: White adults aged 25–74 yrs residing in 1 of 6 U.S. cities. ACS CPS-II: Adults aged ≥30 yrs residing in the 50 U.S. states, Puerto Rico, and DC.	Central site monitor	NO ₂ (ppb)	Death certificates	Cox proportional hazards	RR (95% CI) ^b
HSC, CPS-II		Averaging time: NO ₂ - annual average	All cities IQR = 15.8		Adjusted for: age (5-yr groupings), sex, current-smokers, pack-yrs for current smokers, former-smokers, pack-yrs for former-smokers, high school education, BMI, and occupational exposure to dust or fumes	Nonaccidental Mortality: 1.15 (1.04, 1.27) Nonaccidental Mortality - April–September: 0.98 (0.96, 1.01) Nonaccidental Mortality -
n = 8,111		Exposure years: 1977–1985	Harriman Mean = 14.1			
St. Louis, MO; Steubenville, OH; Portage, WI; Topeka, KS; Watertown, MA;						
			Portage Mean = 6.1			
			St. Louis		Adjusted for: tobacco	

Kingston-Harriman, TN; U.S.			Mean = 19.7			
			Steubenville Mean = 21.9		consumption, education level, occupational exposure, BMI, marital status, alcohol consumption, interaction with gender	October–March: 0.97 (0.96, 0.99)
Enrollment: 1974–1977 (HSC), 1982 (CPS-II)			Topeka Mean = 10.6			
Follow-up: 1974–1989 (HSC), 1982–1989 (CPS-II)			Watertown Mean = 18.1			
Cohort						
Lipfert et al. (2000)	U.S. male veterans with hypertension receiving all or most of their medical care at a one of 32 VA clinics participating in the Hypertension Screening and Treatment Program.	Fixed site monitor	NO ₂ (ppb)	National Center for Health Statistics	Cox proportional hazards	HR (95% CI) ^b
VCMS		Averaging time: NO ₂ - annual average	1960–74 Mean = 30.32±14.24 Median = 28.19		Adjusted for: age, systolic and diastolic blood pressure, BMI, race, smoking, height, interactions of zip-code-average racial distribution and income, and county-level factors (education, income <75% of poverty, percent black, heating degree days)	All-Cause Mortality: 1.07 (1.04, 1.10)
N = 90,070		Exposure years: 1975–1996	Min = 5 Max = 64.88			
Nationwide, U.S.			1975–81 Mean = 27.22±8.54 Median = 27.75 Min = 2.65 Max = 58.37			
Enrollment: 1976						
Follow-up: 1976–1981, 1982–1988, 1989–1996			1982–88 Mean = 23.65±6.51 Median = 22.6 Min = 2.7 Max = 46			
Cohort			1989–96 Mean = 21.45±6.14 Median = 21.6			

			Min = 1 Max = 42.5			
Lipfert et al. (2006b)	U.S. male veterans with hypertension receiving all or most of their medical care at one of 32 VA clinics participating in the Hypertension Screening and Treatment Program.	Fixed site monitor Averaging time: NO ₂ - annual average Exposure years: 1976-2001	NO ₂ (ppb) 1976–81 Mean = 27.2±8.5 1982–88 Mean = 23.7±6.5 1989–96 Mean = 21.5±6.1 1997–2001 Mean = 19.8±5.5	National Center for Health Statistics	Cox proportional hazards Adjusted for: age, systolic and diastolic blood pressure, BMI, race, smoking, height, interactions of zip-code-average racial distribution and income, and county-level factors (education, income <75% of poverty, percent black, heating degree days)	RR (95% CI) ^b All-Cause Mortality: 1.025 (0.983, 1.069)
VCMS 1976–81 n = 67,108 1982–88 n = 55,323 1989–96 n = 41,598 1997–2001 n = 28,635 Nationwide, U.S. Enrollment: 1976 Follow-up: through 2001 Cohort						
Lipfert et al. (2006a)	U.S. male veterans with hypertension receiving all or most of their medical care at one of 32 VA clinics participating in the Hypertension Screening and Treatment Program.	AQS Averaging time: NO ₂ - annual average, NO _X - annual average Exposure years: 1999–2001	NO ₂ (ppb) Overall Mean = 13.6±7.1 Min = 3 Max = 40.8 Overall, only sites with STN data Mean = 16.3±7 Min = 3.6 Max = 40.8	National Center for Health Statistics	Cox proportional hazards Adjusted for: age, systolic and diastolic blood pressure, BMI, race, smoking, height, interactions of zip-code-average racial distribution and income, and county-level factors (education, income <75% of poverty, percent black, heating degree days)	HR (95% CI) ^b All-Cause Mortality: 1.04 (0.96, 1.12)
VCMS N = ~70,000 Nationwide, U.S. Enrollment: 1976 Follow-up:						

1997–2001						
Cohort						
† Bouma et al. (2023)	Adults aged ≥30 yrs	Dispersion model	NO ₂ (ppb)	Dutch digital municipal population register	Cox proportional hazards	HR (95% CI) ^b
Dutch administrative cohort		r ² = 0.60	Overall		Adjusted for: stratified by sex and adjusted for individual-level covariates (standardized household income, region of origin, marital status), and area-level covariates (mean income per income recipient, unemployment rate, social assistance, percentage non-western immigrants, and percentage of low education level) on the neighborhood and regional level	Nonaccidental Mortality: 1.053 (1.040, 1.067)
N = 10,735,734		Averaging time: NO ₂ - annual average	Mean = 10.52±2.64 (19.79±4.97 µg/m ³)			
Netherlands		Exposure years: 2016	Median = 10.4 (IQR 3.47) (19.5 µg/m ³)			
Enrollment: 2013			P25 = 8.806 (16.57 µg/m ³)			
Follow-up: 2013–2019			P75 = 12.27 (23.09 µg/m ³)			
Cohort						
† Brauer et al. (2019)	Non-institutionalized Canadian residents aged 25–90 yrs	LUR	NO ₂ (ppb)	Death records	Cox proportional hazards	HR (95% CI) ^b
CanCHEC, CCHS		Averaging time: NO ₂ - 3-yr MA; 1-yr lag	Mean = 8.6±5.9		Adjusted for: age at baseline, sex, immigrant status, four Can-Marg index dimensions, urban form, community size, airshed, marital status, education, income quintile, indigenous. status, visible minority status, employment status, and occupational class	Nonaccidental Mortality - CanCHEC pooled cohorts: 1.008 (1.003, 1.012)
n = CanCHEC: 8.5 million		Exposure years: 2006	IQR = 6.63			Nonaccidental Mortality - CCHS pooled cohorts: 1.05 (1.02, 1.07)
CCHS: 540,900						
Nationwide, Canada						
Enrollment: CanCHEC: 1991, 1996, 2001; CCHS: 2001, 2003,						

2005, 2007,
2008, 2009,
2010, 2011, and
2012
Follow-up:
Through
December 2016

Cohort

†Brunckreef et al. (2021)	General population adults aged ≥30 yrs	LUR, CTM, Europe-wide LUR	NO ₂ (ppb)	National Mortality databases	Cox proportional hazards	HR (95% CI) ^b
†Stafoggia et al. (2022)		r ² = 0.58	8 Pooled ESCAPE Cohorts		Adjusted for: cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income	Nonaccidental Mortality; 8 pooled ESCAPE cohorts:
†Strak et al. (2021)		Averaging time: NO ₂ - annual average	Mean = 13±4.28 (25±8.05 µg/m ³)			1.168 (1.136, 1.201)
8 ESCAPE cohorts: CEANS, DCH, E3N, VHM&PP, HNR, KORA, DNC, EPIC-MORGEN, EPIC-Prospect		Exposure years: 2010	Median = 12.83 (IQR 5.394) (24.14 µg/m ³ (IQR 10.15 µg/m ³)			ELAPSE administrative cohorts meta-analysis:
			Min = 1.42 (2.68 µg/m ³)			1.084 (1.037, 1.134)
			Max = 43.06 (81.02 µg/m ³)			Belgian Administrative Cohort:
			P5 = 6.861 (12.91 µg/m ³)			1.002 (0.991, 1.013)
			P25 = 10.37 (19.52 µg/m ³)			Danish Administrative Cohort:
N = 325,367			P75 = 15.77 (29.68 µg/m ³)			1.211 (1.188, 1.234)
			P95 = 21.01 (39.53 µg/m ³)			Dutch Administrative Cohort:
Copenhagen, Aarhus, Vorarlberg, Ruhr, Augsburg, Stockholm County, Sweden, France, Denmark, Germany,			CEANS-SALT Cohort			1.057 (1.036, 1.079)
			Mean = 11.31±3.28 (21.29±6.18 µg/m ³)			English Administrative
			Median = 11.17 (IQR 3.9) (21.02 µg/m ³)			

Austria, Netherlands	$\mu\text{g}/\text{m}^3$ (IQR 7.33 $\mu\text{g}/\text{m}^3$) Min = 1.58 (2.98 $\mu\text{g}/\text{m}^3$) Max = 26.85 (50.53 $\mu\text{g}/\text{m}^3$) P5 = 5.958 (11.21 $\mu\text{g}/\text{m}^3$) P25 = 9.327 (17.55 $\mu\text{g}/\text{m}^3$) P75 = 13.22 (24.88 $\mu\text{g}/\text{m}^3$) P95 = 16.94 (31.87 $\mu\text{g}/\text{m}^3$)	Cohort: 1.059 (1.013, 1.107) Norwegian Administrative Cohort: 1.120 (1.105, 1.135) Roman Administrative Cohort: 1.053 (1.034, 1.073) Swiss Administrative Cohort: 1.096 (1.079, 1.114)
Enrollment: 1985–2005 Follow-up: 2015 7 administrative cohorts: N = 29,912,322 Belgian n = 6,491,801 Danish n = 3,323,612 Dutch n = 10,532,360 English n = 1,491,124 Norwegian n = 2,516,192 Italian n = 1,263,712 Swiss n = 4,293,521 Sweden, France, England, Denmark, Italy, Belgium, Switzerland, Norway, Germany, Austria, Netherlands Enrollment: 1992–2011	CEANS-SDPP Cohort Mean = 8.259±2.28 (15.54±4.29 $\mu\text{g}/\text{m}^3$) Median = 8.269 (IQR 2.86) (15.56 $\mu\text{g}/\text{m}^3$ (IQR 5.38 $\mu\text{g}/\text{m}^3$) Min = 1.57 (2.96 $\mu\text{g}/\text{m}^3$) Max = 19.71 (37.09 $\mu\text{g}/\text{m}^3$) P5 = 4.15 (7.81 $\mu\text{g}/\text{m}^3$) P25 = 6.792 (12.78 $\mu\text{g}/\text{m}^3$) P75 = 9.651 (18.16 $\mu\text{g}/\text{m}^3$) P95 = 11.94 (22.46 $\mu\text{g}/\text{m}^3$) CEANS-SIXTY Cohort Mean = 10.99±3.26 (20.68±6.13 $\mu\text{g}/\text{m}^3$)	

Follow-up: 2011–2017	Median = 10.92 (IQR 4) (20.54 $\mu\text{g}/\text{m}^3$ (IQR 7 $\mu\text{g}/\text{m}^3$)
Cohort	Min = 1.42 (2.68 $\mu\text{g}/\text{m}^3$) Max = 25.45 (47.88 $\mu\text{g}/\text{m}^3$) P5 = 5.69 (10.7 $\mu\text{g}/\text{m}^3$) P25 = 9.051 (17.03 $\mu\text{g}/\text{m}^3$) P75 = 12.77 (24.03 $\mu\text{g}/\text{m}^3$) P95 = 16.62 (31.28 $\mu\text{g}/\text{m}^3$) CEANS-SNACK Cohort Mean = 14.56$\pm$2.71 (27.39$\pm$5.09 $\mu\text{g}/\text{m}^3$) Median = 15.1 (IQR 3.92) (28.5 $\mu\text{g}/\text{m}^3$ (IQR 7.38 $\mu\text{g}/\text{m}^3$) Min = 6.176 (11.62 $\mu\text{g}/\text{m}^3$) Max = 22.65 (42.61 $\mu\text{g}/\text{m}^3$) P5 = 9.71 (18.27 $\mu\text{g}/\text{m}^3$) P25 = 12.52 (23.56 $\mu\text{g}/\text{m}^3$) P75 = 16.45 (30.95 $\mu\text{g}/\text{m}^3$) P95 = 18.04 (33.94 $\mu\text{g}/\text{m}^3$) DCH Cohort Mean = 14.9$\pm$3.64 (28.04$\pm$6.84 $\mu\text{g}/\text{m}^3$) Median = 15.05

(IQR 5.3) (28.32
 $\mu\text{g}/\text{m}^3$ (IQR 10
 $\mu\text{g}/\text{m}^3$)
Min = 3.4 (6.4
 $\mu\text{g}/\text{m}^3$)
Max = 38.39 (72.23
 $\mu\text{g}/\text{m}^3$)
P5 = 8.79 (16.54
 $\mu\text{g}/\text{m}^3$)
P25 = 12.36 (23.26
 $\mu\text{g}/\text{m}^3$)
P75 = 17.68 (33.26
 $\mu\text{g}/\text{m}^3$)
P95 = 20.31 (38.22
 $\mu\text{g}/\text{m}^3$)

DNC-1999 Cohort
Mean = 13.74 ± 4.5
($25.85 \pm 8.47 \mu\text{g}/\text{m}^3$)
Median = 12.63
(IQR 7.345) (23.76
 $\mu\text{g}/\text{m}^3$ (IQR 13.82
 $\mu\text{g}/\text{m}^3$)
Min = 3.41 (6.42
 $\mu\text{g}/\text{m}^3$)
Max = 28.84 (54.26
 $\mu\text{g}/\text{m}^3$)
P5 = 7.286 (13.71
 $\mu\text{g}/\text{m}^3$)
P25 = 10.32 (19.42
 $\mu\text{g}/\text{m}^3$)
P75 = 17.67 (33.24
 $\mu\text{g}/\text{m}^3$)
P95 = 20.7 (38.95
 $\mu\text{g}/\text{m}^3$)

DNC-1993 Cohort
Mean = 11.6 ± 4
($21.9 \pm 8 \mu\text{g}/\text{m}^3$)
Median = 10.83

(IQR 5.591) (20.37
µg/m³ (IQR 10.52
µg/m³)
Min = 2.41 (4.54
µg/m³)
Max = 38.39 (72.23
µg/m³)
P5 = 5.41 (10.18
µg/m³)
P25 = 8.689 (16.35
µg/m³)
P75 = 14.28 (26.87
µg/m³)
P95 = 19.7 (37.07
µg/m³)

E3N Cohort
Mean = 14.01±5.18
(26.36±9.75 µg/m³)
Median = 13.06
(IQR 6.664) (24.57
µg/m³ (IQR 12.54
µg/m³)
Min = 1.84 (3.46
µg/m³)
Max = 43.06 (81.02
µg/m³)
P5 = 7.12 (13.4
µg/m³)
P25 = 10.27 (19.32
µg/m³)
P75 = 16.93 (31.86
µg/m³)
P95 = 24.23 (45.59
µg/m³)

EPIC-NL-MORGEN
Cohort
Mean = 18.36±3.22
(34.55±6.05 µg/m³)

Median = 17.9 (IQR
4.77) (33.6 $\mu\text{g}/\text{m}^3$
(IQR 8.97 $\mu\text{g}/\text{m}^3$)
Min = 5.8 (11 $\mu\text{g}/\text{m}^3$)
Max = 36.49 (68.66
 $\mu\text{g}/\text{m}^3$)
P5 = 13.91 (26.18
 $\mu\text{g}/\text{m}^3$)
P25 = 15.93 (29.97
 $\mu\text{g}/\text{m}^3$)
P75 = 20.69 (38.94
 $\mu\text{g}/\text{m}^3$)
P95 = 23.8 (44.8
 $\mu\text{g}/\text{m}^3$)

EPIC-NL-
PROSPECT Cohort
Mean = 19.11 $\pm$ 2.88
(35.96 $\pm$ 5.41 $\mu\text{g}/\text{m}^3$)
Median = 18.85
(IQR 3.86) (35.46
 $\mu\text{g}/\text{m}^3$ (IQR 7.27
 $\mu\text{g}/\text{m}^3$)
Min = 10.41 (19.58
 $\mu\text{g}/\text{m}^3$)
Max = 33.03 (62.15
 $\mu\text{g}/\text{m}^3$)
P5 = 14.6 (27.4
 $\mu\text{g}/\text{m}^3$)
P25 = 17.28 (32.52
 $\mu\text{g}/\text{m}^3$)
P75 = 21.15 (39.79
 $\mu\text{g}/\text{m}^3$)
P95 = 23.72 (44.63
 $\mu\text{g}/\text{m}^3$)

HNR Cohort
Mean = 20.08 $\pm$ 2.48
(37.78 $\pm$ 4.66 $\mu\text{g}/\text{m}^3$)
Median = 19.95

(IQR 2.67) (37.54
µg/m³ (IQR 5.03
µg/m³)
Min = 13.41 (25.23
µg/m³)
Max = 39.9 (75.07
µg/m³)
P5 = 16.61 (31.26
µg/m³)
P25 = 18.53 (34.87
µg/m³)
P75 = 21.2 (39.9
µg/m³)
P95 = 24.36 (45.83
µg/m³)

KORA-S3 Cohort
Mean = 11.23±1.8
(21.13±3.3 µg/m³)
Median = 11.14
(IQR 2.3) (20.97
µg/m³ (IQR 4.32
µg/m³)
Min = 5.538 (10.42
µg/m³)
Max = 22.17 (41.72
µg/m³)
P5 = 8.66 (16.3
µg/m³)
P25 = 10.03 (18.88
µg/m³)
P75 = 12.34 (23.21
µg/m³)
P95 = 14.04 (26.41
µg/m³)

KORA-S4 Cohort
Mean = 11.19±1.8
(21.05±3.39 µg/m³)
Median = 11.06

(IQR 2.39) (20.82
µg/m³ (IQR 4.49
µg/m³)
Min = 5.14 (9.68
µg/m³)
Max = 22.17 (41.72
µg/m³)
P5 = 9.97 (18.76
µg/m³)
P25 = 12.35 (23.24
µg/m³)
P75 = 14.1 (26.5
µg/m³)
P95 = 22.17 (41.72
µg/m³)

VHM&PP Cohort
Mean = 11.67±2.84
(21.96±5.34 µg/m³)
Median = 11.94
(IQR 3.71) (22.46
µg/m³ (IQR 6.99
µg/m³)
Min = 2.05 (3.85
µg/m³)
Max = 25.66 (48.28
µg/m³)
P5 = 6.532 (12.29
µg/m³)
P25 = 9.901 (18.63
µg/m³)
P75 = 13.62 (25.62
µg/m³)
P95 = 15.8 (29.7
µg/m³)

Belgium
Mean = 16.2±3.9

			(30.4±7.3 µg/m ³)			
			Denmark Mean = 10.8±4.2 (20.3±7.9 µg/m ³)			
			Italy Mean = 17.5±3.2 (32.9±6.1 µg/m ³)			
			Norway Mean = 8.13±4.1 (15.3±7.8 µg/m ³)			
			Switzerland Mean = 12.6±3.9 (23.7±7.4 µg/m ³)			
			The Netherlands Mean = 16.7±3.8 (31.4±7.1 µg/m ³)			
† Chen et al. (2016) n = 39,054 Tianjin, Shenyang, Taiyuan, Rizhao, China January 1998– December 2009 Cohort	Chinese adults born prior to January 1, 1975, and a resident in the defined area since January 1, 1998	Central site monitor Averaging time: NO ₂ - annual average Exposure years: 1998–2008	NO ₂ (ppb) Mean = 21.61±0.834 (40.66±1.57 µg/m ³) Median = 20.29 (IQR 13.8) (38.18 µg/m ³ (IQR 25.96 µg/m ³) Min = 9.6 (18 µg/m ³) Max = 41.77 (78.59 µg/m ³) P25 = 14.42 (27.13 µg/m ³) P75 = 28.21 (53.09 µg/m ³)	Family report on questionnaire or CDC death certificates (ICD-10: A00–R99)	Cox proportional hazards Adjusted for: age (continuous variable), gender (male or female), marital status (single/separated/divorced/widowed or married), education (high school or more, less than high school), BMI (b20, 20–25, 25–30, N30 kg/m ²), smoking status (with cigarette amounts per day, 0, 1–10, 11–20, N20), alcohol consumption (yes or no), occupational exposures (self-reported exposure to dust and fumes in the	HR (95% CI) ^b Nonaccidental Mortality - Time-varying exposure: 0.957 (0.948, 0.966) 1998 exposure: 0.864 (0.818, 0.911) Average pollution for surviving period; Ensemble machine learning model: 0.801 (0.748, 0.858)

					workplace, yes or no) and leisure exercise (active or non-active).	
†Chen et al. (2023)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales, with IBD and excluding those who died within 1 year of follow-up, those with cancer at baseline or 1 year of follow-up, and those who moved to another address at repeat assessments	LUR CV-r ² = 0.87 for NO ₂ ; CV-r ² = 0.88 for NO _x Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2005–2007, 2010	NO ₂ (ppb) NO ₂ Mean = 15±4.7 (29±8.9 µg/m ³) Median = 14.8 (IQR 5.53) (27.9 µg/m ³) (IQR 10.4 µg/m ³) Min = 5.3 (10 µg/m ³) Max = 46 (86.6 µg/m ³) NO _x (µg/m ³) NO _x Mean = 43.9±15.2 Median = 42 (IQR 15.6) Min = 19.7 Max = 247.5	Self-reports, primary care, hospital inpatient data	Cox proportional hazards Adjusted for: age, sex, ethnicity, assessment centers, household income, smoking status, education, BMI, physical activity, healthy diet, alcohol consumption, baseline related surgery history, medication	NO ₂ HR (95% CI) ^b Nonaccidental Mortality; IBD: 1.31 (1.07, 1.60) Nonaccidental Mortality; CD: 1.33 (0.96, 1.85) Nonaccidental Mortality; UC: 1.25 (0.97, 1.61) NO _x HR (95% CI) ^c Nonaccidental Mortality; IBD: 1.10 (1.01, 1.20) Nonaccidental Mortality; CD: 1.04 (0.89, 1.21) Nonaccidental Mortality; UC: 1.14 (1.01, 1.29)
†Chen et al. (2024)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales, who moved to a new	Dispersion model Model validated against central site monitors (r ² = 0.85) for NO ₂ . Averaging time: NO ₂ - annual average, NO _x - annual average	NO ₂ (µg/m ³) History of high NO ₂ exposure Median = 26.6 P25 = 24.3 P75 = 30.5 History of high NO _x exposure	NHS	Cox proportional hazards with IPW Adjusted for: age, sex, race, setting (rural or urban), income, education, TDI, BMI, vegetable consumption, fruit consumption, red meat consumption, oily fish	NO ₂ HR (95% CI) ^c All-Cause Mortality; low to low exposure: 1 All-Cause Mortality; low to moderate

Enrollment: 2006–2010	location for at least one year at least	Exposure years: 2002–2021	Median = 42.2 P25 = 37.6 P75 = 50.5	consumption, non-oily fish consumption, smoking status, heavy drinking, physical activity, and use of medication	exposure: 1.21 (1.06, 1.39) All-Cause Mortality; low to high exposure: 1.29 (1.09, 1.53)
Follow-up: through October 2021	once during follow-up.		History of low NO ₂ exposure Median = 14.1 P25 = 11.9 P75 = 15.7	Adjusted for: age, sex, race, setting (rural or urban), income, education, TDI, BMI, vegetable consumption, fruit consumption, red meat consumption, oily fish consumption, non-oily fish consumption, smoking status, heavy drinking, physical activity, and use of medication	All-Cause Mortality; moderate to low exposure: 1.10 (0.95, 1.27) All-Cause Mortality; moderate to moderate exposure: 1.23 (1.08, 1.41) All-Cause Mortality; moderate to high exposure: 1.34 (1.17, 1.54) All-Cause Mortality; high to low exposure: 0.89 (0.75, 1.06) All-Cause Mortality; high to moderate exposure: 1.05 (0.90, 1.23) All-Cause Mortality; high to high exposure: 1.34 (1.18, 1.51)
Quasi-experimental			History of low NO _x exposure Median = 20		
			History of moderate NO ₂ exposure Median = 19.9 P25 = 18.6 P75 = 21.2		
			History of moderate NO _x exposure Median = 29.6 P25 = 27.5 P75 = 32		
					NO _x
					HR (95% CI) ^c All-Cause

Mortality; low to
low exposure:
1
All-Cause
Mortality; low to
moderate
exposure:
1.21 (1.06, 1.39)
All-Cause
Mortality; low to
high exposure:
1.29 (1.08, 1.53)
All-Cause
Mortality;
moderate to low
exposure:
1.10 (0.95, 1.28)
All-Cause
Mortality;
moderate to
moderate
exposure:
1.21 (1.06, 1.39)
All-Cause
Mortality;
moderate to high
exposure:
1.29 (1.13, 1.49)
All-Cause
Mortality; high to
low exposure:
0.84 (0.70, 1.00)
All-Cause
Mortality; high to
moderate
exposure:
1.08 (0.93, 1.27)
All-Cause
Mortality; high to

						high exposure: 1.36 (1.21, 1.53)
† Crouse et al. (2015)	Non-institutionalized individuals aged ≥25 yrs and residing in Canada in 1991.	LUR r ² = 0.43 Averaging time: NO ₂ - 7-yr MA; 1-yr lag Exposure years: 1984–2006	NO ₂ (ppb) Mean = 11.6 Median = 10.4 (IQR 10.5) Min = 0 Max = 51.5 P25 = 6 P75 = 16.5	Canadian Mortality Database	Cox proportional hazards Adjusted for: aboriginal ancestry, visible minority status, highest level of education, employment status, occupational class, immigrant status, marital status, income quintile, census. division and census. tract-census. division percent of immigrants, percent of adults without high school diploma, percent of subjects in lowest income quintile	HR (95% CI) ^b Nonaccidental Mortality: 1.065 (1.056, 1.073)
CanCHEC n = 301,115 Nationwide, Canada Enrollment: 1991 Follow-up: 1991–2006 Cohort						
† Dimakopoulou et al. (2023)	Adults aged ≥37 yrs	LUR CV-r ² = 0.58 Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Catalonia Median = 19.5 (IQR 10.8) (36.7 µg/m ³ (IQR 20.4 µg/m ³)) CEANS Median = 10.2 (IQR 4.4) (19.2 µg/m ³ (IQR 8.2 µg/m ³)) EPIC-NL Median = 18.2 (IQR 4) (34.3 µg/m ³ (IQR 8 µg/m ³)) Greece Median = 12.2 (IQR 12.6) (22.9 µg/m ³ (IQR 23.7 µg/m ³))	Mortality registries (ICD-9: 001–799; ICD-10: A00–R99)	Cox proportional hazards Adjusted for: age, sex and subcohort, if applicable (both as strata variables), baseline year, individual lifestyle and socioeconomic information at baseline: marital status. (single, married or living with partner, divorced or separated, or widowed); BMI; smoking status. and smoking duration; intensity of smoking among current and former smokers (cigarettes per day) and smoking intensity squared; employment status. (yes or no); level of education (primary or less, secondary,	HR (95% CI) ^b Nonaccidental Mortality - Administrative cohorts pooled: 1.063 (1.017, 1.111) Catalonia: 1.053 (1.035, 1.072) Greece: 1.023 (1.016, 1.029) Netherlands: 1.051 (1.044, 1.059) Rome: 1.030 (1.014, 1.047) Sweden:
Administrative cohorts: RoLS, SNC, Catalanian administrative cohort, Dutch administrative cohort, SIMSAM, GRAD, Traditional cohorts: CEANS, EPIC-NL, KORA n = 27,731,158						

(administrative) n = 57,653 (traditional) Rome, Catalonia, Sweden, Spain, Italy, Switzerland, Greece, Netherlands Enrollment: 2010–2014 (administrative), 1992–2004 (traditional) Follow-up: through 2018– 2019 (administrative), through 2011– 2015 (traditional) Cohort			KORA Median = 12 (IQR 3.5) (23 $\mu\text{g}/\text{m}^3$ (IQR 6.6 $\mu\text{g}/\text{m}^3$) Netherlands Median = 16.6 (IQR 4.6) (31.3 $\mu\text{g}/\text{m}^3$ (IQR 8.7 $\mu\text{g}/\text{m}^3$) Rome Median = 17.4 (IQR 4.1) (32.7 $\mu\text{g}/\text{m}^3$ (IQR 7.8 $\mu\text{g}/\text{m}^3$) Sweden Median = 7.6 (IQR 3) (14.3 $\mu\text{g}/\text{m}^3$ (IQR 6 $\mu\text{g}/\text{m}^3$) Switzerland Median = 12 (IQR 4.7) (22.6 $\mu\text{g}/\text{m}^3$ (IQR 8.8 $\mu\text{g}/\text{m}^3$)	or tertiary, as per country- specific definitions); and area-level socioeconomic status.		1.148 (1.140, 1.156) Switzerland: 1.077 (1.065, 1.088) Traditional cohorts pooled: 0.983 (0.669, 1.444) CEANS: 1.049 (0.927, 1.188) EPIC-NL: 1.084 (0.846, 1.390) KORA: 0.801 (0.632, 1.016)
†Eum et al. (2019) Medicare n = 14,100,000 Nationwide, U.S. Enrollment: December 2000– December 2008	Medicare enrollees aged 65–120 yrs living in the conterminous U.S.	AQS Averaging time: NO ₂ - 12-mo MA Exposure years: 2000– 2008	NO ₂ (ppb) Median = 14.23 P25 = 9.69 P75 = 18.63	National Death Index	Poisson Adjusted for: age, gender, race, and state of residence	RR (95% CI) ^b Nonaccidental Mortality: 1.055 (1.053, 1.057) 1-yr MA: 1.056 (1.054, 1.058) 2-yr MA: 1.054 (1.052, 1.056) 3-yr MA: 1.052 (1.050,

Follow-up: December 2000– December 2008						1.054) 4-yr MA: 1.049 (1.047, 1.051) 5-yr MA: 1.046 (1.044, 1.048)
Cohort						
† Eum et al. (2022)	Open cohort of Medicare beneficiaries aged ≥65 yrs residing in the conterminous U.S. between 2001 and 2008	LUR Model performance was lower in rural ($r^2 = 0.69$) as compared to urban ($r^2 = 0.80$) areas, suggesting greater exposure error for rural ZIP codes Averaging time: NO ₂ - 12-mo MA Exposure years: 2000–2008	NO ₂ (ppb) Mean = 10.9±6.44 Median = 9.14 (IQR 7.85) Min = 1.03 Max = 47.04 P25 = 6.16 P75 = 13.98	National Death Index	Poisson Adjusted for: age, gender, race, and state of residence	RR (95% CI) ^b Nonaccidental Mortality: 1.14 (1.14, 1.14)
Medicare n = 49,712,702 Nationwide, U.S. Enrollment: 2001–2008 Follow-up: 2001–2008						
Cohort						
† Gariazzo et al. (2021)	Aged ≥30 yrs and resided in same address for ≥5 yrs before enrollment	CTM, Ensemble machine learning model, Dispersion model CTM $r^2 = 0.49$ Ensemble machine learning 10-fold CV- $r^2 = 0.62$ Dispersion $r^2 = 0.44$ Averaging time: NO ₂ - annual average Exposure years: 2015	NO ₂ (ppb) CTM: 1 km resolution Mean = 15.5±2 (29.2±3.7 µg/m ³) Median = 15.5 (IQR 19.1) (29.2 µg/m ³) (IQR 35.9 µg/m ³) Min = 8.34 (15.7 µg/m ³) Max = 19.1 (35.9 µg/m ³) P5 = 12 (22 µg/m ³) P25 = 14.2 (26.7	Rome Municipal Register	Cox proportional hazards Adjusted for: sex, marital status, place of birth, education, occupation, area-based socioeconomic position	HR (95% CI) ^b Nonaccidental Mortality; Dispersion 4m: 1.008 (1.002, 1.013) Dispersion 200m: 1.012 (1.005, 1.019) Ensemble 200m: 1.011 (1.004, 1.019) CTM 1km:
Rome Longitudinal Study n = 482,259 Rome, Italy Enrollment: 2001 Follow-up: 2015						

Cohort	µg/m³) P75 = 16.9 (31.8 µg/m³) P95 = 19 (35.7 µg/m³) Dispersion: 4 m resolution Mean = 23.2±7.17 (43.6±13.5 µg/m³) Median = 22.3 (IQR 8.88) (41.9 µg/m³ (IQR 16.7 µg/m³) Min = 5.2 (9.8 µg/m³) Max = 108.7 (204.5 µg/m³) P5 = 13.6 (25.5 µg/m³) P25 = 18.1 (34.1 µg/m³) P75 = 27.1 (50.9 µg/m³) P95 = 35.7 (67.2 µg/m³) 200m resolution Mean = 22.7±5.58 (42.8±10.5 µg/m³) Median = 22.7 (IQR 7.92) (42.8 µg/m³ (IQR 14.9 µg/m³) Min = 5.9 (11.1 µg/m³) Max = 45 (84.6 µg/m³) P5 = 14 (26.3 µg/m³) P25 = 19 (35 µg/m³) P75 = 26.5 (49.9 µg/m³) P95 = 32.4 (60.9	1.036 (1.016, 1.056)

			µg/m ³)			
			Ensemble: 200 m resolution Mean = 23.3±5.2 (43.8±9.7 µg/m ³) Median = 22.2 (IQR 7.65) (41.7 µg/m ³) (IQR 14.4 µg/m ³) Min = 10.9 (20.5 µg/m ³) Max = 35.9 (67.6 µg/m ³) P5 = 15.7 (29.6 µg/m ³) P25 = 19.5 (36.6 µg/m ³) P75 = 27.2 (51.1 µg/m ³) P95 = 32.8 (61.7 µg/m ³)			
[†] Guyatt et al. (2024)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living within 25 miles of 1 of 22 study assessment centers across England, Scotland, and Wales. Participants with prevalent cardiovascular disease events or hospital admissions from multiple nations were excluded.	LUR CV-r ² = 0.87 in the Greater London area (remained >0.5 across the rest of the U.K.) Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Median = 13.6 (IQR 5.2) (25.6 µg/m ³) (IQR 9.7 µg/m ³) P25 = 11 (21 µg/m ³) P75 = 16.3 (30.7 µg/m ³)	NHS	Cox proportional hazards Adjusted for: sex; height; BMI; average household income before tax; education level; and passive smoking. In ever-smokers, results were further adjusted for smoking intensity, using “pack-years”	HR (95% CI) ^b Nonaccidental Mortality; never smoker: 1.08 (0.96, 1.21) Nonaccidental Mortality; ever smoker: 1.10 (0.98, 1.23)
U.K. Biobank n = 208,998 (total and CVD mortality) n = 199,577 (incident CVD) Nationwide, U.K. Enrollment: 2006–2010 Follow-up: through						

November 2015 (Scotland), January 2016 (England and Wales)						
Cohort						
† Hamroun et al. (2024)	Individuals aged ≥18 yrs with end-stage kidney disease who began maintenance dialysis in France between January 1, 2012–December 31, 2020.	Spatiotemporal/geospatial model	NO ₂ (ppb)	REIN	Cox proportional hazards	HR (95% CI) ^b
REIN		Cross-validated against central site monitors in rural, suburban, and urban areas (Pearson r =0.55–0.70; RMSE: <25% of the annual mean concentration).	Mean = 7.116±1.41 (13.39±2.65 µg/m ³) Median = 6.893 (12.97 µg/m ³) Min = 4.57 (8.59 µg/m ³) Max = 19.1 (35.93 µg/m ³) P25 = 6.064 (11.41 µg/m ³) P75 = 7.81 (14.7 µg/m ³)		Adjusted for: age, sex, BMI, smoking status, comorbidities, mobility, dialysis care model (including peritoneal dialysis, in-center hemodialysis, self-care/home hemodialysis, and training center), conditions of dialysis initiation (functional dialysis access and emergency start), hemoglobin level and albumin level, the distance to the nearest dialysis center, the municipality population density, and the social deprivation index. Stratified by year (2012–2020) and dialysis center.	All-Cause Mortality; 1-yr lag: 1.078 (1.019, 1.140)
n = 90,373						
Nationwide, France						
Enrollment: January 2012–December 2020 Follow-up: December 2022		Averaging time: NO ₂ - annual average Exposure years: 2009–2020				
Cohort						
† Hartiala et al. (2016)	Patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography	Spatiotemporal/geospatial model		Medical records and annual in-person, phone, or proxy follow-up	Cox proportional hazards	HR (95% CI) ^b
Cleveland Clinic GeneBank		Averaging time: NO ₂ - 3-yr average after enrollment	Mean = 19.1±1.8 Min = 7.8 Max = 23.3 Mean = 18.2±2 Min = 4.9 Max = 22.1		Adjusted for: age, sex, education level, current smoking, Framingham Adult Treatment Panel III risk score	All-Cause Mortality: 1.00 (0.58, 1.74)
n = ~4,600		Exposure years: 1998–2010				
Cleveland, OH,						

U.S.

Enrollment:
2001–2007
Follow-up: 3 yrs

Cohort

†Huang et al. (2023)	Participants were randomly selected from small neighborhoods, born prior to January 1, 1975 and lived in the defined area since January 1, 1998	Ensemble machine learning model Averaging time: NO ₂ - annual average Exposure years: 2013–2019	NO ₂ (ppb) 1998 Mean = 20.8±8.56 (39.2±16.1 µg/m ³) 2019 Mean = 23.56±2.7 (44.34±5.1 µg/m ³)	Family report on questionnaire or CDC death certificates (ICD-10: A00–R99)	Cox proportional hazards Adjusted for: age, sex, BMI, level of education, income, occupational exposure, physical exercise and status of marital, smoking, and drinking	HR (95% CI) ^b Nonaccidental Mortality: 1.50 (1.43, 1.57)
n = 37,442						
Tianjin, Shenyang, Taiyuan, Rizhao, China						
January 1998–December 2019						

Cohort

†Hvidtfeldt et al. (2019)	Adults aged 50–64 yrs who lived in the areas of Copenhagen and Aarhus and were born in Denmark, without cancer	Hybrid model Averaging time: NO ₂ - annual average Exposure years: 1979–2015	NO ₂ (ppb) Median = 13 (25 µg/m ³) P5 = 9.51 (17.9 µg/m ³) P95 = 20.9 (39.4 µg/m ³)	Danish Register of Causes of Death	Cox proportional hazards Adjusted for: age, sex, calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, fruit and vegetable consumption, neighborhood level SES	HR (95% CI) ^b All-Cause Mortality: 1.14 (1.08, 1.20)
Danish DCH						
N = 49,564						
Copenhagen, Aarhus, Denmark						
Enrollment: 1993–1997 Follow-up: through 2015						

Cohort

† Kang et al. (2023)	Adults aged ≥40 yrs with a health screening exam and diagnosed with COPD during January 1, 2009–December 31, 2009, who did not die in 2009	Spatiotemporal/geospatial model	NO ₂ (ppb)	NHIS-NHID	Cox proportional hazards	HR (95% CI) ^b
Korean NHID		10-fold CV-r ² of NO ₂ in 2009 = 0.50	1-year Median = 19.6 (36.9 µg/m ³) P25 = 16 (30 µg/m ³) P75 = 25.6 (48.2 µg/m ³)		Adjusted for: age, sex, income percentile, BMI, smoking status, CCI, presence of exacerbation	All-Cause Mortality, 1-year: 0.987 (0.970, 1.004)
n = 121,423		Averaging time: NO ₂ - annual average				All-Cause Mortality, 3-year: 0.991 (0.973, 1.009)
South Korea		Exposure years: January 1, 2009–December 31, 2013	3-year Median = 19.9 (37.5 µg/m ³) P25 = 16.2 (30.4 µg/m ³) P75 = 26.5 (49.8 µg/m ³)			All-Cause Mortality, 5-year: 0.981 (0.961, 1.002)
Follow-up: January 1, 2010, until death or the end of the study period (December 31, 2018), whichever was first.			5-year Median = 20.5 (38.5 µg/m ³) P25 = 16.2 (30.5 µg/m ³) P75 = 27.7 (52.1 µg/m ³)			
Cohort						
† Klompmaaker et al. (2020)	Dutch citizens aged ≥19 yrs	LUR	NO ₂ (ppb)	Dutch longitudinal mortality database	Cox proportional hazards	HR (95% CI) ^b
PHM		Averaging time: NO ₂ - annual average	Complete case population Median = 12.27 (IQR 4.01) (23.08 µg/m ³ (IQR 7.54 µg/m ³)		Adjusted for: sex, marital status, region of origin, education, paid occupation, household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses	Nonaccidental Mortality: 0.98 (0.93, 1.03)
full (imputed) population n = 339,633 complete case population n = 244,814		Exposure years: 2013	Full population Median = 12.23 (IQR 4.04) (23.01 µg/m ³ (IQR 7.61 µg/m ³)		alcohol, PC4 composite SES, mean income neighborhood, unemployment	
Netherlands					neighborhood, percentage of immigrants neighborhood, mean income region,	
Enrollment:						

September– November 2012 Follow-up: 2013–2017					unemployment region, percentage of immigrants region	
Cohort						
†Klompmaaker et al. (2021b)	Dutch citizens aged ≥30 yrs	LUR, Dispersion model, Hybrid model	NO ₂ (ppb) Median = 14 (IQR 4.4) (26.3 µg/m ³ (IQR 8.3 µg/m ³)	Dutch longitudinal mortality database	Cox proportional hazards Adjusted for: sex, marital status, region of origin, education, paid occupation, household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses alcohol, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrant neighborhoods, mean income region, unemployment region, percentage of immigrants region	HR (95% CI) ^b Nonaccidental Mortality: 1.051 (1.038, 1.063)
Dutch national administrative cohort n = 10,481,566 Netherlands Enrollment: 2009–2011 Follow-up: January 2013– December 2018 Cohort		Averaging time: NO ₂ - annual average Exposure years: 2010				
†Klompmaaker et al. (2021a)	Dutch citizens aged ≥29 yrs	LUR, Dispersion model, Hybrid model		Dutch longitudinal mortality database	Cox proportional hazards Adjusted for: age, strata(sex), random (neighborhood), standardized household income, region of origin, marital status, socio- economic composite score region, mean income per income recipient region, unemployment rate region, percentage non-western immigrants region, and the difference between	HR (95% CI) ^b Nonaccidental Mortality Europe-wide LUR: 1.057 (1.036, 1.079) LUR: 1.006 (0.987, 1.025) Dispersion:
Dutch administrative cohort N = 10,532,360 Netherlands Enrollment: January 2008 Follow-up:		LUR: Explained variance for 86% NO ₂ Hybrid: Explained variance for 59% NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2007– 2010				

through December 2012					neighborhood and region of mean income, unemployment rate, non- western immigrants and the composite SES score	1.028 (1.010, 1.047)
Cohort						
†Lefler et al. (2019)	Adults aged 18–84 yrs	LUR	NO ₂ (ppb)	NHIS	Cox proportional hazards	HR (95% CI) ^b All-Cause Mortality:
NHIS		Averaging time: NO ₂ - annual average	17-yr average (1999–2015) Mean = 10.69±5.73 IQR = 6.72		Adjusted for: age, sex, and race-ethnicity by allowing each combination of age (in one-yr increments), sex, and race-ethnicity (Hispanic, non-Hispanic black, non- Hispanic white, other or unknown)	1.018 (1.003, 1.033)
N = 635,539		Exposure years: 1979– 2015				
Nationwide, U.S.						
Enrollment: 1987–2014 Follow-up: through 2015						
Cohort						
†Li et al. (2023b)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales, without CVD or cancer	LUR	NO ₂ (ppb)	U.K. NHS	Cox proportional hazards	NO ₂
U.K. Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Decedents Mean = 15.77±4.8 (29.67±9.04 µg/m ³)		Adjusted for: sex, ethnicity, assessment center, education, alcohol consumption status, smoking status, BMI, average total household income, physical activity, prevalent diabetes, prevalent hypertension	HR (95% CI) ^b All-Cause Mortality: 1.24 (1.20, 1.28)
N = 400,259		Exposure years: 2005– 2007, 2010	Survivors Mean = 15.56±4.92 (29.28±9.26 µg/m ³)			NO _x
England, Scotland, Wales, U.K.			Total Mean = 15.6±4.92 (29.3±9.25 µg/m ³)			HR (95% CI) ^c All-Cause Mortality: 1.04 (1.03, 1.05)
Enrollment: 2006–2010 Follow-up: through February 2020			NO _x (µg/m ³) Decedents			

Cohort			Mean = 45.18±16.22			
			Survivors			
			Mean = 43.94±15.58			
			Total			
			Mean = 44.01±15.62			
† Li et al. (2023a)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, Wales, and U.K.	LUR	NO ₂ (ppb)	Hospital and mortality records	Cox proportional hazard	NO ₂
U.K. Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Overall		Adjusted for: age, sex, ethnicity, educational level, residential area, TDI, smoking status, alcohol consumption, BMI, mean time spent outdoors, hypertension, diabetes mellitus, cardiovascular disease, estimated glomerular filtration rate, urine albumin to creatine ratio	HR (95% CI) ^b
N = 453,347		Exposure years: 2010–2011	Median = 13.96 (IQR 5.19) (26.27 µg/m ³ (IQR 9.76 µg/m ³)			All-Cause Mortality: 1.00 (0.96, 1.04)
Baseline: 2010	ESKD, malignant tumors, or exposure outlier (threshold: mean±5 SD)		NO _x (µg/m ³)			NO _x
Follow-up: median 11.87 years			Overall			HR (95% CI) ^c
			Median = 42.46 (IQR 16.35)			All-Cause Mortality: 1.01 (1.00, 1.03)
Cohort						
† Lim et al. (2019)	Members of AARP aged 50–71 yrs who responded to a mailed questionnaire	Hybrid model	NO ₂ (ppb)	U.S. Social Security Administration Death Master File and the National Death Index	Cox proportional hazards	HR (95% CI) ^b
NIH-AARP Diet and Health Study		Averaging time: NO ₂ - annual average	Mean = 11.1±5.6		Adjusted for: age, sex, and location, as strata; for race, BMI, education, smoking, diet, and marital status, at individual level; and for median income and percentage with high school education at census-tract level	All-Cause Mortality: 1.04 (1.02, 1.05)
N = 566,398		Exposure years: 1990–2012	Min = 1.5			
n = 548,780 (96.9% of cohort)			Max = 31.7			
California, Florida,						

Louisiana, New
Jersey, North
Carolina,
Pennsylvania,
Atlanta, GA;
Detroit, MI, U.S.

Enrollment:
1995–1996
Follow-up:
through
December 2011

Cohort

†Lipfert and Wyzga (2018)	Male U.S. military veterans receiving care at one of 32 VA health centers.	Fixed site monitor, Dispersion model	NO ₂ (ppb)	Death records	Washington University Proportional Hazard	RR (95% CI) ^b All-Cause Mortality:
VCMS		Averaging time: NO ₂ - annual average	1976–1981 exposure period Mean = 27		Adjusted for: age, smoking	1.052 (1.015, 1.091)
N = ~90,000		Exposure years: 1976–2001	1982–1988 exposure period Mean = 24			
Nationwide, U.S.			1989–1996 exposure period Mean = 21			
Enrollment: 1976 Follow-up: 1976–2001			1997–2001 exposure period Mean = 16			
Cohort			≥1975 exposure period Mean = 30			
			NO ₂ (ppb)			
			Nationwide			

			Dispersion Modeling 1997–2001 Mean = 19.5			
† Liu et al. (2024)	Elders aged ≥65 yrs, focusing on those aged ≥80 yrs, in urban and rural areas in 23 provinces of China.	LUR	NO ₂ (ppb)	Family report on questionnaire validated by death certificates when available	Cox proportional hazards	HR (95% CI) ^b Nonaccidental Mortality:
CLHLS n = 13,207		Model performance differed regionally, r ² = 0.52 in Asia	Mean = 10±7.33 (19±13.8 µg/m ³) Median = 8.61 (16.2 µg/m ³) Min = 0.648 (1.22 µg/m ³) Max = 57.9 (109 µg/m ³)		Adjusted for: age, sex, education, household income, marriage, residence, exercise, smoking, alcohol drinking, housework frequency, social activity frequency, residence, region, temperature annual mean, temperature annual SD, elevation, season, road density, city GDP per capita, city population density, BMI, MMSE score, ADL score	1.41 (1.32, 1.50)
Nationwide, China		Averaging time: NO ₂ - annual average				
Enrollment: 2008–2009 Follow-up: through 2018		Exposure years: 2008–2018				
Cohort						
† Luo et al. (2022)	Adults aged 40-69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales, without diabetes, stroke, IHD or cancer	LUR	NO ₂ (ppb)	Hospital inpatient visits	Cox proportional hazards	HR (95% CI) ^b All-Cause Mortality:
U.K. Biobank N = 410,494		r ² = 0.87	CMD Free Median = 14 (26 µg/m ³) P25 = 11.3 (21.2 µg/m ³) P75 = 16.5 (31.1 µg/m ³)		Adjusted for: age, race, sex, education, TDI, recruitment center	1.14 (1.10, 1.18)
England, Scotland, Wales, U.K.		Averaging time: NO ₂ - annual average				
Enrollment: 2006–2010 Follow-up: through May 31, 2021		Exposure years: 2010–2011	CMM Survivor Median = 14.5 (27.3 µg/m ³) P25 = 12 (22.5 µg/m ³) P75 = 17.1 (32.1 µg/m ³)			
Cohort			Death with CMM			

Median = 14.6 (27.4
 $\mu\text{g}/\text{m}^3$)
P25 = 12.1 (22.8
 $\mu\text{g}/\text{m}^3$)
P75 = 17.3 (32.5
 $\mu\text{g}/\text{m}^3$)

Death with FCMD
Median = 14.2 (26.8
 $\mu\text{g}/\text{m}^3$)
P25 = 11.7 (22.1
 $\mu\text{g}/\text{m}^3$)
P75 = 16.9 (31.8
 $\mu\text{g}/\text{m}^3$)

Death without CMD
Median = 13.9 (26.2
 $\mu\text{g}/\text{m}^3$)
P25 = 11.4 (21.5
 $\mu\text{g}/\text{m}^3$)
P75 = 16.6 (31.3
 $\mu\text{g}/\text{m}^3$)

FCMD Survivor
Median = 14.1 (26.5
 $\mu\text{g}/\text{m}^3$)
P25 = 11.6 (21.8
 $\mu\text{g}/\text{m}^3$)
P75 = 16.7 (31.4
 $\mu\text{g}/\text{m}^3$)

Total
Median = 13.9 (26.1
 $\mu\text{g}/\text{m}^3$)
P25 = 11.3 (21.3
 $\mu\text{g}/\text{m}^3$)
P75 = 16.6 (31.2
 $\mu\text{g}/\text{m}^3$)

† Paul et al. (2020)	Ontario residents who were Canadian born, had lived in Ontario at least 5-yr before cohort inception, were between 35–85 yrs of age, had record of birth date and sex, and were registered with provincial health insurance at enrollment. For mortality analyses, the cohort was restricted to those with diabetes diagnoses before January 1, 2001.	LUR	NO ₂ (ppb)	ONPHEC	Cox proportional hazards	HR (95% CI) ^b Nonaccidental Mortality:
ONPHEC		Model was validated against NAPS ground monitor measurements in 2006 ($r^2 = 0.73$)	Cardiovascular Deaths IQR = 13.4 Min = 2.3 Max = 54.3		Adjusted for: age, sex, region classification, area-level socioeconomic status (SES), and healthcare access. Stratified by Greater Toronto Area residence.	1.038 (1.024, 1.051)
N = 4,774,984		Averaging time: NO ₂ - 3-yr MA	Cohort with Prevalent Diabetes IQR = 14.2 Min = 2.3 Max = 58.3			
Ontario, Canada		Exposure years: 2006	Cohort without Diabetes IQR = 13.8 Min = 2.7 Max = 71.4			
Enrollment: January 2001			Diabetes Deaths IQR = 13.2 Min = 2.3 Max = 52.4			
Follow-up: through December 2015			Incident Diabetes Cases IQR = 14.2 Min = 2.7 Max = 71.4			
Cohort						
† Pu et al. (2024)	Adults aged 37–73 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales	LUR	NO ₂ (ppb)	NHS	Cox proportional hazards	NO ₂
U.K. Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	General lifestyle Mean = 13.96±4.01 (26.26±7.55 µg/m ³)		Adjusted for: age, gender, ethnicity, education level, income, BMI, depression, dementia, diabetes, cancer, cardiovascular disease,	HR (95% CI) ^b Nonaccidental Mortality:
n = 271,075		Exposure years: 2010	Healthy lifestyle Mean = 13.74±4 (25.86±7.53 µg/m ³)			1.206 (1.162, 1.252)
Nationwide, U.K.						NO _x

Cohort						
† Raaschou-Nielsen et al. (2020)	All persons who have lived in Denmark at one point in time since April 2, 1968, who were born between 1921 and 1985, and aged 30–85 yrs	CTM	NO ₂ (ppb)	Danish Civil Registration system	Logistic	IRR (95% CI) ^b
n = 4,401,348		Averaging time: NO ₂ - time-weighted average	Cases		Adjusted for: age, sex, calendar time, marital status, educational level, occupational status, income, country of origin, number of children, car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent households, immigrants, and criminal records	Nonaccidental Mortality: 1.10 (1.08, 1.12)
Denmark		Exposure years: 1991–2015	Mean = 9.51 (17.9 µg/m ³)			
Enrollment: April 1968			Median = 8.98 (IQR 5) (16.9 µg/m ³ (IQR 9.5 µg/m ³)			
Follow-up: January 1991–December 2015			Min = 2.5 (4.7 µg/m ³)			
Case-Control			Max = 38.8 (73.1 µg/m ³)			
			P5 = 4.7 (8.9 µg/m ³)			
			P25 = 6.86 (12.9 µg/m ³)			
			P75 = 11.9 (22.4 µg/m ³)			
			P95 = 15.5 (29.1 µg/m ³)			
			P99 = 17.4 (32.7 µg/m ³)			
			Controls			
			Mean = 9.3 (17.5 µg/m ³)			
			Median = 8.77 (IQR 4.9) (16.5 µg/m ³ (IQR 9.2 µg/m ³)			
			Min = 2.5 (4.7 µg/m ³)			
			Max = 44.8 (84.3 µg/m ³)			
			P5 = 4.7 (8.8 µg/m ³)			
			P25 = 6.75 (12.7 µg/m ³)			
			P75 = 11.6 (21.9 µg/m ³)			

			P95 = 15.3 (28.7 µg/m ³) P99 = 17.2 (32.3 µg/m ³)			
† Shi et al. (2022)	Medicare beneficiaries aged ≥65 yrs in the continuous U.S.	Ensemble machine learning model	NO ₂ (ppb)	Centers for Medicare and Medicaid Services	Cox proportional hazards	HR (95% CI) ^b
Medicare		CV-r ² = 0.84	Overall		Adjusted for: age, sex, race/ethnicity, healthcare capacity variables, land-use variable, demographic and SES variables, behavioral risk factors	All-Cause Mortality, full cohort: 1.025 (1.023, 1.028)
N = 68,721,015		Averaging time: NO ₂ - annual average	Long-term Mean = 16.4±9.4			≤53 ppb: 1.032 (1.029, 1.036)
Nationwide, U.S.		Exposure years: 2000–2016	Low-exposure cohorts Mean = 19.1±9.45 Median = 17.28 Min = 0.01 Max = 53 P5 = 6.7 P25 = 11.58 P75 = 25.15 P95 = 37.18		IPW	Conditional poisson regression: 1.028 (1.025, 1.031)
Enrollment: 2001–2017 Follow-up: through 2017					Adjusted for: age, sex, race/ethnicity, healthcare capacity variables, land-use variable, demographic and SES variables, behavioral risk factors	IPW: 1.016 (1.013, 1.019)
Cohort					Poisson	
					Adjusted for: age, sex, race/ethnicity, healthcare capacity variables, land-use variable, demographic and SES variables, behavioral risk factors	
† So et al. (2020)	Female nurses (aged >44 yrs) of the Danish Nurse Organization who could be linked to the Danish Civil Registration System	Hybrid model	NO ₂ (ppb)	Danish Register of Causes of Death	Cox proportional hazards	HR (95% CI) ^b
DNC		Averaging time: NO ₂ - 3-yr MA; 1-yr lag	Cohort Baseline (1993 or 1999) Mean = 7.12 (13.4 µg/m ³)		Adjusted for: age, BMI, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status,	Nonaccidental Mortality: 0.95 (0.88, 1.03)
N = 24,541		Exposure years: 1990–2012				<15 µg/m ³ : 1.13 (0.89, 1.45)
Denmark						

Enrollment: 1993 and 1999 Follow-up: through December 2013					marital status, use of hormone therapy	
Cohort						
†So et al. (2022)	General population adults ≥30 yrs	LUR, CTM	NO ₂ (ppb)	Danish Register of Causes of Death	Cox proportional hazards	HR (95% CI) ^b
Danish Administrative Cohort		r ² = 0.58	Mean = 10.8±4.22 (20.3±7.94 µg/m ³)		Adjusted for: age, sex, parish level, household income, occupational status,	Nonaccidental Mortality: 1.12 (1.10, 1.14)
n = 3,083,227		Averaging time: NO ₂ - annual average	IQR = 5.47 (10.3 µg/m ³)		immigrant status, marital status, highest completed education level, regional mean household income,	<20 µg/m ³ : 1.39 (1.35, 1.42)
Nationwide, Denmark		Exposure years: 1999– 2017	Min = 2 (3.7 µg/m ³) Max = 38.4 (72.2 µg/m ³) P5 = 5 (9.4 µg/m ³) P25 = 7.76 (14.6 µg/m ³) P75 = 13.2 (24.9 µg/m ³) P95 = 19 (35.7 µg/m ³)		percentage of unemployment, difference of mean household income and percentage of unemployment, between parish and region	Time-varying exposure: 1.08 (1.07, 1.09)
Enrollment: January 2000 Follow-up: through December 2017						
Cohort						
†Tao et al. (2024)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales	LUR	NO ₂ (µg/m ³)	NHS	Cox proportional hazards	HR (95% CI) ^c
U.K. Biobank		Averaging time: NO ₂ - annual average	Advantaged neighborhood Mean = 23.2		Adjusted for: age, gender, race, BMI, smoking status, alcohol consumption,	Nonaccidental Mortality: 1.034 (1.020, 1.049)
n = 421,650		Exposure years: 2005– 2007, 2010	Median = 22.87 P5 = 14.77 P25 = 19.42 P75 = 26.76 P95 = 32.23		healthy diet score, educational level, income level, neighborhood environment	
Nationwide, England			Disadvantaged neighborhood			
Enrollment: 2006–2010 Follow-up:						

through September 2021			Mean = 37.87 Median = 35.97 P5 = 25.48 P25 = 31.67 P75 = 43.12 P95 = 55.8			
Cohort			Intermediate neighborhood Mean = 28.47 Median = 28.01 P5 = 16.73 P25 = 23.73 P75 = 32.6 P95 = 41.07			
†Thomson et al. (2020)	Non-institutionalized Canadian residents aged 30–89 yrs at enrollment. Person-yrs where the respondent reached age 90 years, were recent immigrants (<10 yrs before survey), or had missing or invalid postal codes were excluded.	LUR Averaging time: NO ₂ - 3-yr MA; 1-yr lag Exposure years: 2006	NO ₂ (ppb) Overall Mean = 8.06 Median = 6.52 Min = 0.01 Max = 69.08 P5 = 2.19 P10 = 2.83 P25 = 4.23 P75 = 10.22 P90 = 15.67 P95 = 19.36 P99 = 27.37	Surveys, vital statistics	Cox proportional hazards Adjusted for: age, sex, CCHS survey cycle, visible minority status, Indigenous identity, marital status, educational attainment, income quintile, alcohol consumption, smoking status, fruit and vegetable intake, exercise behaviors, neighborhood marginalization, airshed, CMA/CA size	HR (95% CI) ^b Nonaccidental Mortality, poor or fair self-rated mental health: 1.26 (1.10, 1.45) Excellent or very good self-rated mental health: 1.08 (1.03, 1.15)
CCHS N = 392,300 Nationwide, Canada Enrollment: 2000–2012 Follow-up: December 2016 Cohort						
†Turner et al. (2016)	Adults aged ≥30 yrs with a family member aged ≥45 yrs	LUR r ² = 0.78 Averaging time: NO ₂ - annual average	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 (IQR 6) Min = 1 Max = 37.6	ICD 9 code 162; ICD 10 code C33–C34	Cox proportional hazards Adjusted for: age, race, sex stratified and adjusted for education; marital status; BMI; BMI squared; cigarette smoking status; cigarettes	HR (95% CI) ^b All-Cause Mortality: 1.04 (1.03, 1.06)
CPS-II n = 669,046						

U.S.		Exposure years: 2006	P5 = 5.1 P25 = 8.1 P95 = 21.2			per day and cigarettes per day squared; yrs smoked and yrs smoked squared; age started smoking < 18 years; passive smoking; vegetable, fruit, fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index, 1990 ecological covariates: median household income, and percent African American, Hispanic, post-secondary education, unemployment, and poverty
Enrollment: 1982 Follow-up: through 2004 Cohort						
†Wang et al. (2022)	Adults aged 40–69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, Wales, and Wales, without cancer or CVD	LUR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2005–2007, 2010	NO ₂ (ppb) Overall Mean = 15.5±4.9 (29.2±9.2 µg/m ³) NO _x (µg/m ³) Overall Mean = 43.8±15.5	NHS Information Center	Cox proportional hazards Adjusted for: age, sex, race, assessment center, TDI, alcohol consumption status, smoking status, BMI, physical activity, healthy diet score, diabetes, hypertension	NO ₂ HR (95% CI) ^b All-Cause Mortality: 1.10 (1.03, 1.17) NO _x HR (95% CI) ^c All-Cause Mortality: 1.02 (1.01, 1.03)
U.K. Biobank N = 386,937 England, Scotland, Wales, U.K. Enrollment: 2006–2010 Follow-up: 2018 Cohort						
†Wang et al. (2023)	Adults aged ≥45 yrs in mainland China	Fixed site monitor CV-r ² = 0.72 Averaging time: NO ₂ - annual average	NO ₂ (ppb) Overall Mean = 11.3±3.3 (21.2±6.3 µg/m ³) Median = 10.8 (20.3 µg/m ³)	Survey data	Cox proportional hazards Adjusted for: age, sex, education level, marital status, BMI, smoking status, drinking status, residence, regional distribution,	HR (95% CI) ^b All-Cause Mortality: 1.454 (1.202, 1.758)
CHARLS N = 15,440						

Nationwide, China		Exposure years: 2005– 2018	Min = 3.9 (7.4 µg/m ³) Max = 23.8 (44.7 µg/m ³) P25 = 8.77 (16.5 µg/m ³) P75 = 13.4 (25.2 µg/m ³)		cardiovascular disease, respiratory disease	
Baseline: June 2011–March 2012 Follow-up: every 2–3 yrs after baseline						
Cohort						
†Wei et al. (2021)	Open cohort of Medicare beneficiaries aged ≥65 yrs residing in the continuous U.S. between 2000 and 2016	Ensemble machine learning model CV-r ² = 0.84 Averaging time: NO ₂ - annual average Exposure years: 2000– 2016	NO ₂ (ppb) Overall Mean = 17.3±9.66	Medicare records	Log linear regression Adjusted for: age, sex, medicaid enrollment	RR (95% CI) ^c All-Cause Mortality, 6th decile (16.23 ppb) vs. 1st decile (5.53 ppb): 1.005 (1.002, 1.018) All-Cause Mortality, 10th decile (37.79 ppb) vs. 1st decile (5.53 ppb): 1.024 (1.021, 1.027)
Medicare N = 74,537,533 Nationwide, U.S. Enrollment: 2000–2016 Follow-up: through 2016						
Cohort						
†Weichenthal et al. (2017)	Non- institutionalized, non-immigrant Canadian citizens aged 25-90 yrs linked to annual postal code histories and Social Insurance Numbers	LUR Model validated against 2006 NAPS monitoring data (r ² = 0.73) Averaging time: NO ₂ - 3- yr MA; 1-yr lag Exposure years: 1981– 2012	NO ₂ (ppb) Mean = 11.47 Median = 10.31 Max = 64.78 P5 = 3.36 P25 = 6.44 P75 = 15.1 P95 = 24.52	Canadian Mortality Database	Cox proportional hazards Adjusted for: stratified by age (5-yr categories), sex, airshed, and population center size, adjusted for individual-level covariates (visible minority status, aboriginal status, marital status, educational attainment, income quintile,	HR (95% CI) ^b Nonaccidental Mortality: 1.068 (1.057, 1.080)
CanCHEC n = 2,448,500 Nationwide, Canada Enrollment: May						

2011 Follow-up: May–December 2011 Cohort					and labour force status) and neighbourhood-level covariates (percent unemployed (aged ≥ 25 yrs), percent not graduated from high school (aged ≥ 25 yrs), percent low-income status within census divisions, and population density (per km ²) within dissemination areas)	
†Xu et al. (2023) RHINE III n = 9,135 Reykjavík, Iceland; Bergen, Norway; Umeå, Gothenburg, Uppsala, Sweden; Aarhus, Denmark; Tartu, Estonia Enrollment: 2010 Follow-up: through December 2021 Cohort	Participants aged 40–65 yrs living near one of seven study centers in Northern Europe.	Dispersion model DEHM/UBM model validated against central site monitors (r = 0.70, 0.60, and 0.73 in Denmark, Norway, and Sweden, respectively). Airviro model validated against central site monitors in Tartu, Estonia. Averaging time: NO ₂ - annual average Exposure years: 1990–2010	NO ₂ (ppb) 1990-2010 Mean = 7.605±3.73 (14.31±7.01 µg/m ³) 1990 Mean = 8.328±4.2 (15.67±7.9 µg/m ³) 2000 Mean = 7.43±3.81 (13.98±7.17 µg/m ³) 2010 Mean = 7.116±4.03 (13.39±7.58 µg/m ³)	National Mortality registries	Cox proportional hazards Adjusted for: age (as timescale), sex (strata) and study center (strata), smoking status, pack-yrs of smoking, BMI, education, physical activity and marital status	HR (95% CI) ^b All-Cause Mortality; 1990 exposure: 1.34 (0.85, 2.13) All-Cause Mortality; 2000 exposure: 1.06 (0.67, 1.66) All-Cause Mortality; 2010 exposure: 1.06 (0.72, 1.55)
†Yazdi et al. (2021) Medicare n = 72,769,408	Medicare beneficiaries aged ≥ 65 yrs in the continuous U.S. exposed to ≤ 53 ppb	Ensemble machine learning model CV-r ² = 0.84 Averaging time: NO ₂ -	NO ₂ (ppb) Mean = 19.8 Median = 17.96 Min = 5.93 Max = 53	Medicare denominator file	IPW Adjusted for: warm-season and cold-season temperatures, year, age, race, sex, Medicaid eligibility,	β (% change) (95% CI) ^b All-Cause Mortality, ≤ 53 ppb:

Nationwide, U.S.	of NO ₂ for all study years.	annual average Exposure years: 2000– 2016	P10 = 8.96 P25 = 12.2 P75 = 25.9 P90 = 33.41		region of residence, distance to nearest hospital, percentage of people who had an A1c exam, percentage of people who had an ambulatory care visit, percentage of people who had a cholesterol exam, percentage of people who had an eye exam, percentage of women who had a mammogram, percentage of the population who are Black, percentage of the population who are Hispanic, population density per square mile, percentage of the population living below the poverty line, percentage of the housing occupied by the owners, median value of housing occupied by the owners, median household income, percentage of the population who did not graduate from high school, mean BMI, rate of smoking, and rate of lung cancer	0.030 (0.025, 0.035)
Enrollment: January 2000– January 2016 Follow-up: through December 2016 Cohort						
†Yu et al. (2024)	General population in 108 municipalities across the continental U.S.	Fixed site monitor Averaging time: NO ₂ - annual average Exposure years: 1987– 2000	NO ₂ (ppb) Mean = 30.88±6.65 Median = 20.35 (IQR 7.98) Min = 3.98 Max = 45.4 P25 = 16.86 P75 = 24.84	U.S. National Center for Health Statistics	Poisson Adjusted for: city-level population variation, calendar year, spatial unit, and mean summer and winter temperatures	RR (95% CI) ^b Nonaccidental Mortality: 1.068 (1.046, 1.091) Nonaccidental Mortality; 1-yr lag: 1.054 (1.032, 1.077) Nonaccidental
NMMAPS N = 10,794,553 Nationwide, U.S. 1987–2000						

Time-series						Mortality; 2-yr lag: 1.063 (1.040, 1.086) Nonaccidental Mortality; 3-yr lag: 1.014 (0.991, 1.037)
† Zhang et al. (2021)	Ontario residents aged ≥30 yrs	LUR	NO ₂ (ppb)	Ontario Registrar General Death Database	Cox proportional hazards	HR (95% CI) ^b Nonaccidental Mortality; 5-yr MA: 1.305 (1.225, 1.391) Nonaccidental Mortality; <19.5 ppb: 1.255 (1.172, 1.344) Nonaccidental Mortality; <17.0 ppb: 1.231 (1.138, 1.331) Nonaccidental Mortality; 4-yr MA: 1.397 (1.306, 1.495) Nonaccidental Mortality; 3-yr MA: 1.466 (1.364, 1.576)
OHS		Model validated against NAPS ground monitor measurements in 2006 ($r^2 = 0.73$).	Baseline Mean = 10.9±5.3 Median = 10 (IQR 7.9) P25 = 6.5 P75 = 14.4		Adjusted for: whether born in Canada, educational level, marital status, household income, BMI, fruit & vegetable intake, smoking, alcohol drinking, physical activity, environmental exposure to tobacco smoke at home and working place, rural/urban, north/south and neighborhood-level socio-economic factors, including percentage of recent immigrants, percentage of population aged ≥15 yrs without employment and percentage of population aged ≥15 yrs with educational level lower than high school, and income quintile	
N = 88,615						
Ontario, Canada		Averaging time: NO ₂ - 3, 4, and 5-yr MA				
Enrollment: 2009–2013		Exposure years: 2006				
Follow-up: through December 2017						
Cohort						
† Zhang et al. (2022)	Excluded those who had no follow-up data during 2012–	Spatiotemporal/geospatial model, Ensemble machine learning model	NO ₂ (ppb) 2010	Survey data and follow-up investigations	Cox proportional hazards Adjusted for: sex, age,	HR (95% CI) ^b All-Cause Mortality:

CFPS N = 30,843 Nationwide, China Baseline: April 2010–February 2011 Follow-up: 2012–2020 Cohort	2018 (n = 2549) and objects whose information on death date was invalid or logically erroneous (n = 25). To avoid bias from selection of participants, we also excluded participants who died within the first year from the baseline interview (n = 183).	$r^2 = 0.72$ Averaging time: NO ₂ - annual average Exposure years: 2005– 2018	Mean = 12.1±4.1 (22.8±7.8 µg/m ³) Median = 11.5 (21.6 µg/m ³) Min = 4.7 (8.9 µg/m ³) Max = 23.3 (43.9 µg/m ³) P25 = 8.72 (16.4 µg/m ³) P75 = 14.6 (27.5 µg/m ³) 2018 Mean = 10.2±3.3 (19.1±6.2 µg/m ³) Median = 9.62 (18.1 µg/m ³) Min = 3.7 (6.9 µg/m ³) Max = 20.8 (39.2 µg/m ³) P25 = 7.76 (14.6 µg/m ³) P75 = 12 (22.6 µg/m ³)	smoking, alcohol consumption, physical activity	1.127 (1.042, 1.219)
[†] Zhang et al. (2023) AIRCODEN N = 3,721,810 Nationwide, Denmark Enrollment: March–July 2020 and August	Danish residents aged ≥30 yrs who had lived in Denmark for ≥1 yr by March 1, 2020, without a positive SARS-CoV-2 test before enrollment	CTM, LUR ELAPSE LUR model 5- fold hold-out validation r^2 = 0.59 Averaging time: NO ₂ - annual average Exposure years: 1979– 2019 (CTM); 2010 (LUR)	NO ₂ (ppb) All-Cause Mortality Mean = 5.63±1.2 (10.6±2.3 µg/m ³) COVID-19 Hospitalization Mean = 6.06±1.2 (11.4±2.3 µg/m ³) COVID-19 Incidence	National COVID-19 Surveillance System Cox proportional hazards Adjusted for: calendar time, sex, age at baseline, region, marital status, household size, individual wealth, family income, education and occupational status, parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate,	HR (95% CI) ^b All-Cause Mortality: 1.23 (1.06, 1.43)

2020–April 2021 Follow-up: through April 2021 Cohort			Mean = 6.11±1.3 (11.5±2.4 µg/m ³) COVID-19 Mortality Mean = 6.11±1.2 (11.5±2.3 µg/m ³) Total Population Mean = 5.69±1.3 (10.7±2.4 µg/m ³)			different of those variables between parish and municipality, and municipality-level access to healthcare
† Zhu et al. (2024) U.K. Biobank n = 461,112 England, Scotland, Wales, U.K. Enrollment: 2006–2010 Follow-up: through October 2021 Cohort	Adults aged 40–69 yrs who were registered with the U.K. NHS and living near 1 of 22 study centers across England, Scotland, and Wales Exposure years: 2010	LUR CV-r ² = 0.87 for NO ₂ ; CV-r ² = 0.88 for NO _x Averaging time: NO ₂ - annual average, NO _x - annual average	NO ₂ (ppb) Mean = 14.17±4.06 (26.66±7.63 µg/m ³) IQR = 5.23 (9.85 µg/m ³) Min = 6.872 (12.93 µg/m ³) Max = 57.658 (108.49 µg/m ³) P25 = 11.37 (21.39 µg/m ³) P75 = 16.6 (31.24 µg/m ³) NO _x (µg/m ³) Mean = 44.02±15.65 IQR = 16.55 Min = 19.74 Max = 265.94 P25 = 34.22 P75 = 50.77	NHS	Cox proportional hazards Adjusted for: Age, sex, race, education level, income, TDI, smoking status, pack- year of smoking, drinking status, drinking consumption, physical activity, MET minutes per week, dietary behaviors	NO ₂ HR (95% CI) ^b Nonaccidental Mortality: 1.12 (1.08, 1.16) NO _x HR (95% CI) ^c Nonaccidental Mortality: 1.05 (1.04, 1.06)

List of abbreviations in alphabetical order: 60YO/IMPROVE = Stockholm 60 y old/IMPROVE Study; AIRCODEN = Danish population-based nationwide cohort; AQS = Air Quality System; BMI = body mass index; CanCHEC = Canadian Census Health and Environment Cohort; CCHS=Canadian Community Health Survey; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CFPS = China Family Panel Studies; CHARLS = China Health and Retirement Longitudinal Study; CI = confidence interval; CLHLS = Chinese Longitudinal Healthy Longevity Survey; CPS-II = American Cancer Society Cancer Prevention Study-II; CTM = chemical transport model; CTS = California Teachers Study; CV = cross-validation; DCH = Danish Diet, Cancer, and Health; DNC = Danish Nurse Cohort; E3N = Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale; EE = effect estimate; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; EPIC-MORGEN = EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands; EPIC-NL = European Prospective Investigation into Cancer and Nutrition in the Netherlands; ESCAPE = European Study of Cohorts for Air Pollution Effects; GRAD = Greek administrative cohort; HNR = Heinz Nixdorf Recall study; HR = hazard ratio; hrs = hours; HSC = Harvard Six Cities study; HUBRO = Oslo Health Study; ICD = International Classification of Diseases; IPW = inverse probability weighting; IQR = interquartile range; IRR = incidence rate ratio; km = kilometer; KORA = Cooperative Health Research in the Region of Augsburg; LUR = land use regression; m = meter; MA = moving average; max = maximum; min = minimum; mo = month; NAPS = National Air Pollution Surveillance program; NHID = National Health Information Database; NHIS = National Health Interview Survey; NHS = National Health Service; NIH-AARP = National Institutes of Health American Association of Retired Persons; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; NLCS = Netherlands Cohort Study on Diet and Cancer; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; NR = not reported; OHS = Ontario Health Study; ONPHEC=Ontario Population Health and Environment Cohort; OR = odds ratio; P = percentile; PHM = Public Health Monitor; ppb = parts per billion; r = correlation coefficient; REIN = Renal Epidemiology and Information Network; RHINE = Respiratory Health in Northern Europe; RoLS = Rome Longitudinal Study; RMSE = root mean square error; SALIA = Study on the influence of Air pollution on Lung function, Inflammation and Ageing; SALT/TwinGene = Stockholm Screening Across the Lifespan Twin study and TwinGene; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; SDPP = Stockholm Diabetes Prevention Program; SES = socioeconomic status; SIDRIA = Italian Studies of Respiratory Disorders in Childhood and Environment; SIMSAM = Swedish administrative cohort; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; SNC = Swiss National Cohort; TDI = Townsend Deprivation Index; VCMS = Veterans' Cohort Mortality Study; VHM&PP = Austrian Vorarlberg Health Monitoring and Prevention Programme; yr = year.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

A.10. Cancer

Appendix Table 12-1 Epidemiologic studies of oxides of nitrogen exposure and lung cancer

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Lung Cancer Incidence						
† Bai et al. (2019) Ontario Population Health and Environment Cohort (ONPHEC) Entire lung cancer cohort n = 4,952,022 Incident lung cancer cohort n = 100,146 Entire breast cancer cohort n = 2,564,340 Incidence breast cancer cohort n = 91,146 Canada 2001–2015 Cohort	All long-term residents who lived in Ontario and were registered with Ontario's provincial health insurance plan on April 1, 1996, aged 35–85 years with no previous	LUR Averaging time: 3-year moving average with 4-year time lag Exposure years: 2006	NO ₂ (ppb) Mean = 17.9 IQR = 13.9	Ontario Cancer Registry	Cox proportional hazard model Adjusted for: age, sex, region, census tract-level recent immigrants (arrived in the 5 years prior to census), unemployment rate, education, and annual household income	HR (95% CI) ^b Lung cancer incidence: 1.04 (1.02, 1.05) Lung cancer incidence - 10-year exposure lag: 1.03 (1.01, 1.04)
† Chen et al. (2023) UK Biobank n = 187,912 United Kingdom Baseline: 2006–2010	Participants aged 39–72 years at baseline, enrolled in 22 assessment centers throughout the United Kingdom Participants were excluded if they had a cancer diagnosis	LUR Averaging time: NO ₂ - annual average, NO _x - annual average	NR	Cancer diagnoses were obtained through linkages to the national cancer and death registries with ICD-10 codes	Cox proportional hazard model Adjusted for: age at recruitment, sex, education level, Townsend deprivation index, family history of lung cancer, diabetes at	NO ₂ HR (95% CI) ^b Lung cancer incidence: 1.07 (0.98, 1.16) NO _x HR (95% CI) ^c

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow-up: through September 30, 2021 for England and Wales Follow-up: through October 31, 2021 for Scotland Cohort	excluding non-melanoma skin cancer at baseline (n = 38,066), no acceptable 24-hour dietary assessment (n = 268,619), implausible energy intake from dietary assessment (n = 2,576), incomplete covariate data (n = 2,299), and/or missing NO _x data (n = 2,939).	Exposure years: 2010		C33–C34 for incident lung cancer	baseline, body mass index, pack years of smoking, energy intake, Vitamin A retinol equivalents intake, Vitamin D intake, fish oil supplementation habit	Lung cancer incidence: 1.04 (1.01, 1.08)
† Cheng et al. (2022) The Multiethnic Cohort Study (MEC) N = 215,251 (96,810 males and 118,441 females) n = 97,288 United States Enrollment: 1993–1996 Follow-up: end of December 2013 Cohort	Adults 45–75 years of age largely from self-reported racial and ethnic groups (African American, European American, Japanese American, Latino American, and Native Hawaiian), residing in Hawaii or California (primarily Los Angeles County). Participants were excluded if missing smoking information or had an invalid address.	LUR, Spatiotemporal/geospatial model Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2006–2007	NO ₂ (ppb) Kriging African Americans Mean = 28.27±5.61 Min = 7.97 Max = 50.59 European Americans Mean = 28.5±5.47 Min = 7.15 Max = 50.09 Japanese Americans Mean = 27.57±4.49 Min = 6.44 Max = 47.77 Latino Americans Mean = 29.73±4.56 Min = 6.86 Max = 54.06 LUR African Americans Mean = 27.22±5.48	California Cancer Registry, Hawaii Tumor Registry, National Death Index, and state death certificate files	Cox proportional hazard model Adjusted for: race/ethnicity (among all), sex, education, marital status, smoking intensity and duration, family history of lung cancer, occupation, neighborhood socioeconomic status, nonsteroidal anti-inflammatory drug use, body mass index, drinking, physical activity, energy intake, red meat intake, and processed meat intake with age at cohort entry as the stratum variable	NO ₂ HR (95% CI) ^b Lung cancer incidence: 1.06 (0.97, 1.15) NO _x HR (95% CI) ^b Lung cancer incidence: 1.06 (1.00, 1.12)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Min = 7.32 Max = 75.82 European Americans Mean = 28.33±6.91 Min = 6.96 Max = 73.54 Japanese Americans Mean = 27.12±5.93 Min = 7.83 Max = 67.61 Latino Americans Mean = 30.36±5.61 Min = 6.77 Max = 65.63 NO _x (ppb) Kriging African Americans Mean = 64.69±16.33 Min = 8.44 Max = 178.95 European Americans Mean = 59.72±14.16 Min = 12.29 Max = 138.03 Japanese Americans Mean = 59.48±11.56 Min = 10.1 Max = 137.39 Latino Americans Mean = 62.36±12.41 Min = 10.49 Max = 188.69 LUR African Americans			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 59.28±15.78 Min = 15.94 Max = 221.75 European Americans Mean = 55.77±19.21 Min = 7.99 Max = 182.59 Japanese Americans Mean = 54.9±17.82 Min = 9.91 Max = 179.61 Latino Americans Mean = 61.3±17.05 Min = 8.19 Max = 198.15			
†Gowda et al. (2019) Women's Health Initiative (WHI) n = 65,419 non-cases n = 65,154 cases n = 265 United States Recruitment: 1993–1998 Follow-up: October 1993–April 2012 Cohort	Post-menopausal women, aged 50–79 at enrollment. Participants were excluded if they had a history of any cancer diagnosis (except nonmelanoma skin cancer) at baseline, had missing BMI data, history of emphysema, history of asthma, missing neighborhood socioeconomic status, no follow-up data, or missing air pollution data.	Spatiotemporal/geospatial model r ² = 0.85 Averaging time: NO ₂ - annual average Exposure years: 1999-2013	NO ₂ (ppb) cases Mean = 15.7±5.7 non-cases Mean = 15.8±6.8	Cancers were identified as part of medical update questionnaires administered at least annually to participants.	Cox proportional hazard model Adjusted for: study arm and models adjusted for age at baseline, race, BMI, U.S. region, history of emphysema, history of asthma, and neighborhood socioeconomic status (NSES)	HR (95% CI) ^b Lung cancer incidence - Adenocarcinoma: 0.93 (0.71, 1.22) Lung cancer incidence - All lung cancer: 0.92 (0.74, 1.15)
†Huang et al. (2021) UK Biobank	Participants aged 40–69 years and visited one of 22 assessment centers in the UK,	LUR Averaging time: NO ₂ - annual	NO ₂ (ppb) Mean = 15.49±4.84 (29.14±9.11 µg/m ³)	National cancer registries with	Cox proportional hazard model Adjusted for: age, sex,	NO ₂ HR (95% CI) ^b Lung cancer incidence: 1.10 (1.05,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 449,219 lung cancer cases n = 2,020 United Kingdom Baseline: 2006–2010 Cohort	without previous diagnosis of cancer at baseline. Participants were excluded if individuals were missing air pollution (n = 6,755), missing genetic data (n = 13,174), individuals with sex mismatch (n = 132)	average, NO _x - annual average Exposure years: 2010	IQR = 5.729 (10.78 µg/m ³) Min = 4.43 (8.34 µg/m ³) Max = 66.496 (125.12 µg/m ³) NO _x (µg/m ³) Mean = 44.19±15.57 IQR = 16.42 Min = 19.74 Max = 265.94	ICD-10 codes of C33–C34	BMI, household income, education level, smoking status, and pack-years of smoking	1.15) NO _x HR (95% CI) ^c Lung cancer incidence: 1.13 (1.07, 1.18)
† Hvidtfeldt et al. (2021) Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) n = 307,550 Sweden, France, Denmark, Germany, Austria, Netherlands 1985–2005 Follow-up: 2011–2017 Cohort	Participants of ELAPSE cohorts who had complete information at baseline for sex, age, smoking status, BMI, employment status, and area-level SES and did not have a cancer diagnosis at baseline.	LUR Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Mean = 13±4 (25±8 µg/m ³)	Bronchus and lung cancers ICD 9 codes 162.2-162.9 and ICD 10 C34; adenocarcinoma s ICDO3 8140-8384, fifth digit morphology code 3; squamous-cell carcinomas ICDO3 8050-8084, fifth digit morphology code 5 Bronchus and lung cancers ICD 9 codes 162.2-162.9 and ICD 10 C34;	Cox proportional hazard model Adjusted for: age, sex, study (ELAPSE), year of baseline visit, smoking status, duration, intensity, intensity2, BMI, marital status, employment status, 2001 mean income at neighborhood level	HR (95% CI) ^b Lung cancer incidence - Squamous-cell: 0.94 (0.76, 1.18) Lung cancer incidence - All lung cancers: 1.04 (0.95, 1.14) Lung cancer incidence - Adenocarcinoma: 1.04 (0.90, 1.20)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				adenocarcinoma s ICFO3 8140-8384, fifth digit morphology code 3; squamous-cell carcinomas ICDO3 8050-8084, fifth digit morphology code 3		
				Bronchus and lung cancers ICD 9 codes 162.2-162.9 and ICD 10 C34; adenocarcinoma s ICFO ₃ 8140-8384, fifth digit morphology code 3; squamous-cell carcinomas ICDO3 8050-8084, fifth digit morphology code 4		
[†] Letellier et al. (2022)	Patients with a primary non-small cell lung cancer (NSCLC) diagnosis who were treated at City of Hope Comprehensive Cancer Center (COH) who also	Spatiotemporal/geospatial model Averaging time: NO ₂ - 5-year NO ₂ - 10-year	NO ₂ (µg/m ³) 5-years before diagnosis Mean = 17 P25 = 14.8 P75 = 18.3 KRAS G12C/V	Somatic genomic tests were ordered as part of usual clinical care and sequencing results were obtained from	Logistic regression Adjusted for: age, sex, race/ethnicity, educational level, insurance status, area deprivation index, smoking status, cancer	OR (95% CI) ^c Lung cancer incidence - Exposure 10-yrs before diagnosis for TP53 mutation: 1.30 (0.97, 1.76) Lung cancer incidence - Exposure 5-yrs before diagnosis for KRAS mutation: 0.93 (0.69, 1.26) Lung cancer incidence - Exposure 5-
N = 695 n = 435 Durante, CA, U.S. 2013–2018						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort	had air pollution exposure data.	Exposure years: NR	negative mutation status Mean = 17.1 P25 = 15.1 P75 = 18.3 KRAS G12C/V positive mutation status Mean = 16.9 P25 = 14.3 P75 = 18.1 KRAS negative mutation status Mean = 17 P25 = 15.2 P75 = 18.2 KRAS positive mutation status Mean = 17.1 P25 = 14.3 P75 = 18.6 TP53 negative mutation status Mean = 16.9 P25 = 14.6 P75 = 18.6 TP53 positive mutation status Mean = 17.2 P25 = 15 P75 = 18.3 10-years before diagnosis Mean = 18.9 P25 = 136.3 P75 = 20.5	the COH EMR, which contains test results from both internal and external laboratories.	stage, cancer histology, and year of diagnosis	yrs before diagnosis for KRAS G12C/V mutation: 0.95 (0.65, 1.42) Lung cancer incidence - Exposure 10-yrs before diagnosis for KRAS G12C/V mutation: 0.94 (0.62, 1.44) Lung cancer incidence - Exposure 10-yrs before diagnosis for KRAS mutation: 0.96 (0.69, 1.33) Lung cancer incidence - Exposure 5-yrs before diagnosis for TP53 mutation: 1.30 (0.99, 1.71)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			KRAS G12C/V negative mutation status Mean = 19.1 P25 = 16.7 P75 = 20.6 KRAS G12C/V positive mutation status Mean = 18.7 P25 = 15.6 P75 = 20.3 KRAS negative mutation status Mean = 19 P25 = 16.9 P75 = 20.5 KRAS positive mutation status Mean = 19 P25 = 15.9 P75 = 21.1 TP53 negative mutation status Mean = 18.9 P25 = 16.4 P75 = 20.9 TP53 positive mutation status Mean = 19.4 P25 = 16.9 P75 = 20.6			
† Liang et al. (2023)	Individual aged 37–73 years recruited from 22 assessment centers in the UK. Participants	LUR Averaging time: NO ₂ - annual	NO ₂ (ppb) Median = 14 (IQR 5.27) (26 µg/m ³)	ICD-10 codes C33-C34 from self-report, hospital	Cox proportional hazard model Adjusted for: age, sex,	NO ₂ HR (95% CI) ^b Lung cancer incidence: 1.19 (1.10,

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n = 367,623 incident lung cancer n = 1,306 no lung cancer n = 366,317 United Kingdom Baseline: 2006–2010 End of follow-up: October 2021 Cohort	were excluded if they had a history of lung cancer at baseline (n = 256), lifestyle (n = 101,177), pollution (n = 33,449) information was inaccessible, missing genetic information (n = 8,213) and sex mismatch (n = 258)	average, NO _x - annual average Exposure years: 2010	(IQR 9.92 µg/m ³) NO _x (µg/m ³) Median = 42.01 (IQR 16.64)	admissions data, primary care and death register	race, educational level, household income, region, BMI, alcohol status, smoking status, physical activity and diet	1.27) NO _x HR (95% CI) ^c Lung cancer incidence: 1.14 (1.09, 1.20)
† Weichenthal et al. (2017) Ontario Population Health and Environment Cohort (ONPHEC) Total cohort population N = 1,039,128 Incident cases of lung cancer n = 12,908 Canada Enrollment start: April 1, 1996 Start of follow-up: April 1, 2001 End of follow-up: December 31, 2012 Cohort	Adults residing in Toronto, Ontario, Canada between ages 30–100 years, free of conditions under investigation (asthma, COPD, lung cancer).	LUR r ² = 0.69 Averaging time: NO ₂ - annual average Exposure years: 2004	NO ₂ (ppb) Mean = 21.4±3.5 Median = 21.1 (IQR 4.1) Min = 9.9 Max = 48.9 P5 = 16.4 P25 = 19.1 P75 = 23.2 P95 = 32.8	Institute for Clinical and Evaluative Sciences (ICES) databases, specifically Ontario Cancer Registry for incident lung cancer with ICF-O-3 codes C34.0-C34.9	Cox proportional hazard model Adjusted for: age, sex, percentage of the population 15 years of age and older with less than a high school education, percentage of the population 15 years of age and older without employment, percentage of recent immigrants, average household income, diabetes, congestive heart failure, hypertension, and acute myocardial infarction	HR (95% CI) ^b Lung cancer incidence: 1.18 (1.10, 1.26)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Wong et al. (2021)	Participants were adults aged 40–69 years old who resided within 40 km of 22 assessment centers across the UK. Participants were excluded for data quality issues (n = 304), discrepancy in genetic vs. reported sex (n = 14,634), had an immunologic or hematologic disorder at baseline (n = 6,210), cancer diagnosis at baseline (n = 43,801), withdrew from the study (n = 64), resided in a sparse or remote geographic region (n = 36,150), were not working and did not have commuting data (n = 164,020), and/or did not have NO ₂ data (n = 3,309).	LUR Averaging time: NO ₂ - annual average Exposure years: 2005-2007	NO ₂ (ppb) 2005 Median = 15.06 (IQR 6.154) (28.33 µg/m ³ (IQR 11.58 µg/m ³) P25 = 12.27 (23.08 µg/m ³) P75 = 18.42 (34.66 µg/m ³) 2006 Median = 14.8 (IQR 5.57) (27.84 µg/m ³ (IQR 10.48 µg/m ³) P25 = 12.11 (22.79 µg/m ³) P75 = 17.68 (33.27 µg/m ³) 2007 Median = 15.33 (IQR 6) (28.85 µg/m ³ (IQR 11.29 µg/m ³) P25 = 12.55 (23.61 µg/m ³) P75 = 18.5 (34.9 µg/m ³)	ICD 10 codes C34.0-C34.9; ICD-O-3 code 8140 was used to define adenocarcinoma, while 8052, 8084, 8073, and 8083 were used for squamous cell carcinoma (SCC)	Cox regression models Adjusted for: commute mode, frequency, and distance, along with age, sex-smoking status, smoking duration, study site, race/ethnicity, body mass index, alcohol, and income	HR (95% CI) ^b Lung cancer incidence: 1.04 (1.01, 1.07)
Lung Cancer Mortality						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Chen et al. (2016) n = 39,054 Tianjin, Shenyang, Taiyuan, Rizhao, China January 1998 to December 2009 Cohort	Eligible participants must have been born prior to January 1, 1975, and had to be a resident in the defined area since January 1, 1998.	Central site monitor Averaging time: NO ₂ - annual average Exposure years: 1998-2008	NO ₂ (ppb) Mean = 21.61±0.834 (40.66±1.57 µg/m ³) Median = 20.29 (IQR 13.8) (38.18 µg/m ³ (IQR 25.96 µg/m ³) Min = 9.6 (18 µg/m ³) Max = 41.77 (78.59 µg/m ³) P25 = 14.42 (27.13 µg/m ³) P75 = 28.21 (53.09 µg/m ³)	ICD-10 C33 and C34	Cox proportional hazard model Adjusted for: age at baseline, gender, BMI, education, marital status, smoking status, passive smoking, household income, alcohol consumption, occupation, diet, and leisure exercise Cox proportional hazard model co-adjusted for PM ₁₀ Adjusted for: age at baseline, gender, BMI, education, marital status, smoking status, passive smoking, household income, alcohol consumption, occupation, diet, and leisure exercise	HR (95% CI) ^b Lung cancer mortality - average NO ₂ for the surviving period: 0.72 (0.58, 0.89) Lung cancer mortality - time-varying exposures for both deaths and controls: 0.94 (0.91, 0.97) Lung cancer mortality - time-varying exposures for both deaths and controls with PM ₁₀ : 1.01 (0.97, 1.05) Lung cancer mortality - assigned 1998 air pollution exposure: 0.82 (0.69, 0.97) Lung cancer mortality - average NO ₂ for the surviving period with PM ₁₀ : 1.65 (1.30, 2.09) Lung cancer mortality - assigned 1998 air pollution exposure with PM ₁₀ : 0.80 (0.68, 0.95)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Eckel et al. (2016) n = 352,053 California, U.S. 1988–2009 Cohort	California residents with lung cancer diagnosed in 1988–2009. Participants were excluded if diagnosis was in situ cancer or non-carcinoma histology.	AQS r ² = 0.73 Averaging time: NO ₂ - Monthly Exposure years: 1988-2012	NO ₂ (ppb) Distant site(s) Mean = 22±10.4 Localised only Mean = 20.6±9.3 Regional Mean = 21.4±9.7 Total Mean = 21.9±10.2 Unknown Mean = 24.5±11.3	ICD-9 code 1629 for 1988–1998 deaths and ICD-10 code C349 deaths after 1998	Cox proportional hazard model Adjusted for: age, sex, race/ethnicity, marital status, education index, socioeconomic status, rural–urban commuting area, distance to primary interstate highway, distance to primary US and state highways, histology at diagnosis, month of diagnosis, year of diagnosis and initial treatment	HR (95% CI) ^b Lung cancer mortality - Overall: 1.25 (1.24, 1.26) Lung cancer mortality - Regional (stage of diagnosis): 1.38 (1.35, 1.42) Lung cancer mortality - Distant sites (stage of diagnosis): 1.14 (1.12, 1.16) Lung cancer mortality - Localised only (stage of diagnosis): 1.70 (1.65, 1.75)
† Eum et al. (2019) Medicare n = 14,100,000 Nationwide, U.S. Enrollment: December 2000–December 2008 Follow-up: December 2000–December 2008 Cohort	Medicare enrollees aged 65–120 years living in the conterminous United States.	AQS Averaging time: NO ₂ - 12-month moving average Exposure years: 2000–2008	NO ₂ (ppb) Median = 14.23 P25 = 9.69 P75 = 18.63	ICD-10 code C34	Poisson regression models Adjusted for: Age, gender, and race-stratified and state-adjusted	MRR (95% CI) ^b Lung cancer mortality: 0.98 (0.98, 0.99) Lung cancer mortality - East Region: 0.99 (0.98, 1.00) Lung cancer mortality - West Region: 0.95 (0.94, 0.96) Lung cancer mortality - Center Region: 1.06 (1.03, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†(Eum et al., 2022) Medicare n = 49,712,702 Nationwide, U.S. Enrollment: 2001–2008 Cohort	Open cohort of Medicare beneficiaries aged ≥65 years residing in the contiguous US between 2001 and 2008.	LUR 81% of the spatial ($r^2 = 0.81$), 73% of temporal ($r^2 = 0.73$), and 84% of the spatiotemporal variation ($r^2 = 0.84$) in monthly mean NO₂ concentrations from 2000 to 2010, with an absolute average bias of 2.4 ppb; the model performance was lower in rural ($r^2 = 0.69$) as compared to urban ($r^2 = 0.80$) areas, suggesting greater exposure error for rural ZIP codes Averaging time: NO₂ - 12-month moving average Exposure years: 2000–2008	NO₂ (ppb) Mean = 10.9±6.44 Median = 9.14 (IQR 7.85) Min = 1.03 Max = 47.04 P25 = 6.16 P75 = 13.98	ICD-10 code C34	Cox proportional hazard model Adjusted for: strata for sex (male, female), race (white, non-white), age (1 year age categories with 90+ years old as one category), ZIP code and adjusted for ZIP code- and state-level SES by including the two SES variables as covariates	HR (95% CI)^b Lung cancer mortality: 1.04 (1.02, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Huang et al. (2023) n = 37,442 Tianjin, Shenyang, Taiyuan, Rizhao, China January 1998–December 2019 Cohort	Participants were randomly selected from small neighborhoods, born prior to January 1, 1975 and lived in the defined area since January 1, 1998.	Ensemble machine learning model Averaging time: NO ₂ - annual average Exposure years: 2013–2019	NO ₂ (ppb) 1998 Mean = 20.8±8.56 (39.2±16.1 µg/m ³) 2019 Mean = 23.56±2.7 (44.34±5.1 µg/m ³)	ICD-10 code C34	Cox proportional hazard model Adjusted for: age, sex, BMI, level of education, income, occupational exposure, physical exercise and status of marital, smoking and drinking Cox proportional hazard model with adjustment for O ₃ Adjusted for: age, sex, BMI, level of education, income, occupational exposure, physical exercise and status of marital, smoking and drinking	HR (95% CI) ^b Lung cancer mortality: 1.32 (1.17, 1.49) Lung cancer mortality - lag 0–1 years: 1.37 (1.17, 1.59) Lung cancer mortality - lag 0–3 years: 1.48 (1.27, 1.72) Lung cancer mortality - lag 0–4 years: 1.41 (1.21, 1.65) Lung cancer mortality - lag 0–5 years: 1.39 (1.18, 1.63) Lung cancer mortality - lag 0–2 years: 1.41 (1.21, 1.65) Lung cancer mortality - O ₃ : 1.39 (1.20, 1.60)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Hvidtfeldt et al. (2019) Danish Diet, Cancer and Health (DCH) N = 49,564 Copenhagen, Aarhus, Denmark Enrollment: 1993–1997 Follow-up: through 2015 Cohort	Men and women aged 50–64 who lived in the areas of Copenhagen and Aarhus and were born in Denmark. Exclusion criteria included having cancer at or prior to baseline, having unavailable residential address history (therefore exposure history), and those who had missing confounder information.	Hybrid model Method validation NR Averaging time: NO ₂ - annual average Exposure years: 1979–2015	NO ₂ (ppb) Median = 13 (25 µg/m ³) P5 = 9.51 (17.9 µg/m ³) P95 = 20.9 (39.4 µg/m ³)	ICD-10 code C34	Cox proportional hazard model Adjusted for: age, sex, calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, and fruit and vegetable consumption, and neighborhood level SES	HR (95% CI) ^b Lung cancer mortality: 1.08 (0.92, 1.26)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Kang et al. (2023) n = 121,423 South Korea Follow-up: January 1, 2010, until death or the end of the study period (December 31, 2018), whichever was first. Cohort	All patients ≥40 years who met the definition of COPD during January 1, 2009 to December 31, 2009 were included. Individuals who died in 2009 or did not undergo a health screening exam between January 1, 2007 and December 31, 2009 were excluded. Additionally, participants with missing information on smoking status, BMI, or area of residence as well as participants whose air pollutant levels in their area of residence could not be estimated were excluded.	Spatiotemporal/geospatial model The performance of the kriging model was evaluated using 10-fold cross-validation (r^2 of NO ₂ in 2009 was 0.50). Averaging time: NO ₂ - annual average Exposure years: January 1, 2009–December 31, 2013	NO ₂ (ppb) 1-year Median = 19.6 (36.9 µg/m ³) P25 = 16 (30 µg/m ³) P75 = 25.6 (48.2 µg/m ³) 3-year Median = 19.9 (37.5 µg/m ³) P25 = 16.2 (30.4 µg/m ³) P75 = 26.5 (49.8 µg/m ³) 5-year Median = 20.5 (38.5 µg/m ³) P25 = 16.2 (30.5 µg/m ³) P75 = 27.7 (52.1 µg/m ³)	ICD-10 code C34	Cox proportional hazard models Adjusted for: age (40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years), sex, income percentile (≤30th, 30–70th, and >70th), BMI (continuous), smoking status (never, former, and current), Charlson Comorbidity Index at the time of COPD diagnosis (continuous), and the presence of exacerbation (none, moderate, and severe) and stratified by Seoul, metropolitan cities, and others	HR (95% CI) ^b Lung cancer mortality - 1-year exposure lag: 0.98 (0.94, 1.03) Lung cancer mortality - 5-year exposure lag: 0.99 (0.94, 1.04) Lung cancer mortality - 3-year exposure lag: 0.97 (0.93, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Klompmaaker et al. (2020)	Dutch citizens 19 years or older	LUR	NO ₂ (ppb)	ICD 10 code C34	Cox proportional hazard model	HR (95% CI) ^b
Public Health Monitor		Averaging time: NO ₂ - annual average	Complete case population Median = 12.27 (IQR 4.01) (23.08 µg/m ³ (IQR 7.54 µg/m ³)		Adjusted for: age as underlying time scale, stratified by sex and adjusted for marital status, region of origin, education, paid occupation, standardized household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses alcohol, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region and percentage of immigrants region	Lung cancer mortality - greenness (NDVI 300 m): 1.13 (0.92, 1.38) Lung cancer mortality: 1.08 (0.90, 1.29) Lung cancer mortality - road traffic noise: 1.13 (0.91, 1.39)
full (imputed) population n = 339,633 complete case population n = 244,814		Exposure years: 2013				
Netherlands			Full population Median = 12.23 (IQR 4.04) (23.01 µg/m ³ (IQR 7.61 µg/m ³)			
Enrollment: September–November 2012 Follow-up: 2013–2017						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Klompaker et al. (2021b) n = 10,481,566 Netherlands Follow-up period: January 1, 2013–December 31, 2018 Cohort	Dutch populations aged 30+	Hybrid model, LUR, Dispersion model Averaging time: NO ₂ - annual average Exposure years: 2010	NO ₂ (ppb) Median = 14 (IQR 4.4) (26.3 µg/m ³ (IQR 8.3 µg/m ³)	ICD-10 C34	Cox proportional hazard model Adjusted for: age as underlying time scale, stratified by sex and adjusted for marital status, region of origin, standardized household income, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region and percentage of immigrants region	HR (95% CI) ^b Lung cancer mortality: 1.18 (1.13, 1.22) Lung cancer mortality - LUR model: 1.13 (1.09, 1.17) Lung cancer mortality - Hybrid model: 1.14 (1.10, 1.18) Lung cancer mortality - Dispersion model: 1.10 (1.07, 1.14)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Klompaker et al. (2021a) Statistics Netherlands (CBS) N = 10,532,360 Netherlands Enrollment: January 1, 2008 Follow-up: through December 31, 2012 Cohort	Full Dutch population aged 29+	LUR, Dispersion model, Hybrid model LUR: Explained variance for 86% NO ₂ Hybrid: Explained variance for 59% NO ₂ Averaging time: NO ₂ - annual average Exposure years: 2007–2010		ICD-10 C34	Cox proportional hazard model Adjusted for: age, strata(sex), random (neighborhood), standardized household income, region of origin, marital status, socio-economic composite score region, mean income per income recipient region, unemployment rate region, percentage non-western immigrants region, and the difference between neighborhood and region of mean income, unemployment rate, non-western immigrants and the composite SES score (4 digit postal code)	HR (95% CI) ^b Lung cancer mortality - Dispersion model: 1.15 (1.11, 1.20) Lung cancer mortality - LUR model: 1.17 (1.13, 1.22) Lung cancer mortality - hybrid model: 1.18 (1.13, 1.22)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Lim et al. (2019) NIH-AARP Diet and Health Study N = 566,398 n = 548,780 (96.9% of cohort) CA, FL, LA, NJ, NC, PA, Atlanta GA, Detroit MI, U.S. Enrollment: 1995–1996 Follow-up: through December 2011 Cohort	Members of AARP aged 50–71 years who responded to a mailed questionnaire.	Hybrid model Method validation NR Averaging time: NO₂ - annual average Exposure years: 1990-2012	NO₂ (ppb) Mean = 11.1±5.6 Min = 1.5 Max = 31.7	Death records	Cox proportional hazard model Adjusted for: Age, sex, and location, as strata; for race, body mass index, education, smoking, diet, and marital status, at individual level; and for median income and percentage with high school education at census-tract level	HR (95% CI)^b Lung cancer mortality: 1.00 (0.97, 1.04)

† Raaschou-Nielsen et al. (2020)	All persons who have lived in Denmark at one point in time since April 2, 1968, who were born between 1921 and 1985, and aged 30 to 85 years.	Chemical transport model	NO ₂ (ppb)	(ICD-8: 162.1; ICD-10: C34)	Logistic regression	MRR (95% CI) ^b
n = 4,401,348			Cases		Adjusted for: sex, age, and calendar time, by match, and individual factors: marital status, educational level, occupational status, income, country of origin, and number of children	Lung cancer mortality: 1.34 (1.31, 1.38)
Denmark		Averaging time: NO ₂ - time-weighted average	Mean = 9.51 (17.9 µg/m ³) Median = 8.98 (IQR 5) (16.9 µg/m ³ (IQR 5) (16.9 µg/m ³) Min = 2.5 (4.7 µg/m ³) Max = 38.8 (73.1 µg/m ³) P5 = 4.7 (8.9 µg/m ³) P25 = 6.86 (12.9 µg/m ³) P75 = 11.9 (22.4 µg/m ³) P95 = 15.5 (29.1 µg/m ³) P99 = 17.4 (32.7 µg/m ³)			
Enrollment: April 2, 1968 Follow-up: January 1, 1991 to December 31, 2015		Exposure years: 1991–2015	Controls Mean = 9.3 (17.5 µg/m ³) Median = 8.77 (IQR 4.9) (16.5 µg/m ³ (IQR 9.2 µg/m ³) Min = 2.5 (4.7 µg/m ³) Max = 44.8 (84.3 µg/m ³) P5 = 4.7 (8.8 µg/m ³) P25 = 6.75 (12.7 µg/m ³) P75 = 11.6 (21.9 µg/m ³) P95 = 15.3 (28.7 µg/m ³)			
Case-Control						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P99 = 17.2 (32.3 µg/m ³)			
† Turner et al. (2016) Cancer Prevention Study II n = 669,046 United States Enrollment: 1982 Follow-up: through 2004 Cohort	Participants were at least 30 years of age and had a family member aged 45 years or older with complete data on residence and covariates.	LUR r ² = 0.78 Averaging time: NO ₂ - annual average Exposure years: 2006	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 (IQR 6) Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P95 = 21.2	ICD 9 code 162; ICD 10 code C33-C34	Cox proportional hazard model Adjusted for: age, race, sex stratified and adjusted for education; marital status; BMI; BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; age started smoking <18 years; passive smoking; vegetable, fruit, fiber intake; fat intake; beer, wine, and liquor intake; industrial exposures; an occupational dirtiness index, 1990 ecological covariates: median household income, and percent African American, Hispanic, post-secondary education, unemployment, and poverty	HR (95% CI) ^b Lung cancer mortality: 0.99 (0.95, 1.03)

List of abbreviations in alphabetical order: AQS = Air Quality System; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; EMR = electronic medical records; ETS = environmental tobacco smoke; ICD = international classification of diseases; IQR = interquartile range; HR = hazard ratio; LUR = land use regression; Max = maximum; min = minimum; MRR = mortality risk ratio; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; NR = not reported; NSES = neighborhood socioeconomic status; NVDI = Normalized Difference Vegetation Index; ppb = parts per billion; P25 = 25th percentile; P75 = 75th percentile; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; O₃ = ozone; ONPHEC = Ontario Population Health and Environment Cohort; OR = odds ratio; SES = socioeconomic status.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 12-2 Toxicological studies of oxides of nitrogen exposure and lung cancer

Study Details and Population	Exposure Details	Endpoints Examined*
Adkins et al. (1986) Mouse (A/J) 8, 10-wk-old, females n = 30/group	Whole body inhalation with conditioned air controls 1,000 ppb (1 ppm) NO ₂ , 6 hr/d for 6 mo 5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 6 mo	0 d after exposure Tumors/tumor-bearing mouse lung (NS)
Han et al. (2013) Rat (Wistar) 3-mo-old, males n = 6/group	Whole body inhalation with filtered air controls 2,660 ppb (2.66 ppm) NO ₂ , 6 hr/d for 7 d 5,320 ppb (5.32 ppm) NO ₂ , 6 hr/d for 7 d 10,640 ppb (10.64 ppm) NO ₂ , 6 hr/d for 7 d	0 d after exposure - Comet assay (DNA damage) (↑) - DNA-protein adduct formation (↑) - Micronucleus assay (micronuclei formation) (↑)
Ichinose et al. (1991) Rat (Wistar) 6-wk-old, males n = 40/group	Whole body inhalation with filtered air controls 40 ppb (0.04 ppm) NO ₂ , continuous for 17 mo 400 ppb (0.4 ppm) NO ₂ , continuous for 17 mo 4,000 ppb (4 ppm) NO ₂ , continuous for 17 mo	0 d after exposure (followed by injection with carcinogen BHPN) Incidence of BHPN-induced lung tumors (adenoma or adenocarcinoma) (NS)
Isomura et al. (1984) Rat (Sprague Dawley) 3-wk-old, males n = 5/group	Whole body inhalation with filtered air controls 8,000 ppb (8 ppm) NO ₂ , continuous for 3 hr 15,000 ppb (15 ppm) NO ₂ , continuous for 3 hr 27,000 ppb (27 ppm) NO ₂ , continuous for 3 hr 27,000 ppb (27 ppm) NO, continuous for 3 hr 9,000 ppb (9 ppm) NO, continuous for 3 hr	18 hr after exposure (NO ₂) - Chromosome aberrations (dose-dependently increased mutation frequency) - Ouabain-resistant mutations (dose-dependently increased mutation frequency) 18 hr after exposure (NO)

Study Details and Population	Exposure Details	Endpoints Examined*
	19,000 ppb (19 ppm) NO, continuous for 3 hr 21,000 ppb (21 ppm) NO ₂ , continuous for 3 hr	Ouabain-resistant mutations (increased mutation frequency)
Ohyama et al. (1999) Rat (F344/Jcl) 6-wk-old, males n = 3/group	Whole body inhalation with filtered air controls 600 ppb (6 ppm) NO ₂ , 16 hr/d for 10 mo	0 d after exposure Adduct formation (increased DNA adduct formation in 2 of 3 rats)
Richters and Kuraitis (1981) Mouse (C57BL/6J and Swiss Webster) age not reported, males n = 24–90/group	Whole body inhalation with room air controls 400 ppb (0.40 ppm) NO ₂ , 8 hr/d for 10 wk 800 ppb (0.80 ppm) NO ₂ , 8 hr/d for 10 wk 400 ppb (0.40 ppm) NO ₂ , 8 hr/d for 12 wk 800 ppb (0.80 ppm) NO ₂ , 8 hr/d for 12 wk	0 d after exposure Facilitation of lung tumor metastasis (↑)
Richters and Kuraitis (1983) Mouse (C57BL/6J) age not reported, sex not reported n = 23–51/group	Whole body inhalation with filtered air controls 500 ppb (0.5 ppm) NO ₂ , 7 hr/d for 8 wk 300 ppb (0.3 ppm) NO ₂ , 7 hr/d for 12 wk 400 ppb (0.4 ppm) NO ₂ , 7 hr/d for 12 wk	3 wk after exposure (8 wk exposure) - Mean number of nodules per lung (NS) 3 wk after exposure (12 wk exposure) - Mean number of nodules per lung (↑)
Richters and Damji (1990) Mouse (AKR/cum) age not reported, females n = 18–50/group	Whole body inhalation with filtered air controls 250 ppb (0.25 ppm) NO ₂ , 7 hr/d for 37 d 250 ppb (0.25 ppm) NO ₂ , 7 hr/d for 71 d 250 ppb (0.25 ppm) NO ₂ , 7 hr/d for 111 d 250 ppb (0.25 ppm) NO ₂ , 7 hr/d for 141 d 250 ppb (0.25 ppm) NO ₂ , 7 hr/d for 181 d 250 ppb (0.25 ppm) NO ₂ , 7 hr/d for 10 mo	0 d after exposure (10 mo exposure) - Survival (↑) 0 d after exposure (37–181 d exposure) - T cell lymphoma (some animals in the exposed group showed decreased progression of spontaneous T cell lymphoma)
Wagner et al. (1965) Mouse (CAF1/Jax) age not reported, males n = 20/group	Whole body inhalation with filtered air controls 5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 12 mo 5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 14 mo 5,000 ppb (5 ppm) NO ₂ , 6 hr/d for 16 mo	0 d after exposure Lung tumors (↑)

List of abbreviations in alphabetical order: d = day; hr = hour; min = minute; mo = month; n = sample size; NO = nitric oxide; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million; wk = week.

* Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase.

Appendix Table 12-3 Epidemiologic studies of oxides of nitrogen exposure and cancers of sites outside the lung

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cancers outside the Lungs: Leukemia						
† Puett et al. (2020)	All citizens of Denmark 20 years of age or older, excluded cases prior cancer diagnoses (except non-melanoma skin cancer). For each case, four controls were selected at random, matched on sex, and birth month and year, who did not have a prior cancer diagnosis (except non-melanoma skin cancer) and were alive and had a Danish residential address at the date of leukemia diagnosis for the case (index date). Cases and controls were excluded if they did not reside in Denmark at index date, were missing a geocodable residential address for 20% or more of the ten years prior to the index date, and those missing information on the covariates of interest.	Dispersion model Averaging time: NO ₂ - time-weighted 1 year average; NO ₂ - time-weighted 5-year average; NO ₂ - time-weighted 10-year average Exposure years: 1968–2014	NO ₂ (ppb) Cases Mean = 11.1±4.5 (20.8±8.5 µg/m ³) Controls Mean = 11±4.5 (21±8.5 µg/m ³)	All leukemia ICD-10 Codes 90-95; Acute lymphoblastic leukemia ICD-10 code: 91.0; Chronic lymphoblastic leukemia ICD-10 code: 91.1; Acute lymphoblastic leukemia ICD-10 code: 92.0; Chronic myeloid leukemia ICD-10 code: 92.1	Logistic regression Adjusted for: Controls matched to cases by sex, birth month and year; individual level occupation, marital status, and individual level disposable income (quartiles); area level education, income, home ownership, and retirement	OR (95% CI) ^b Leukemia Incidence - 1-yr time weighted average: 1.02 (0.96, 1.08) Leukemia Incidence - 5-yr time weighted average: 1.02 (0.95, 1.09) Leukemia Incidence - 10-yr time weighted average: 1.00 (0.95, 1.06) Leukemia Incidence - Chronic myeloid - 1-yr time weighted average: 0.98 (0.81, 1.19) Leukemia Incidence - Chronic myeloid - 5-yr time weighted average: 0.96 (0.80, 1.16) Leukemia Incidence - Chronic myeloid - 10-yr time weighted average: 0.93 (0.76, 1.13) Leukemia Incidence - Chronic lymphoblastic - 1-yr time weighted average: 1.00 (0.92, 1.09) Leukemia Incidence - Chronic lymphoblastic - 5-yr time weighted average: 1.00 (0.92, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Leukemia Incidence - Chronic lymphoblastic - 10-yr time weighted average: 0.98 (0.90, 1.07)
						Leukemia Incidence - Acute myeloid - 1-yr time weighted average: 1.04 (0.93, 1.16) Leukemia Incidence - Acute myeloid - 5-yr time weighted average: 1.04 (0.93, 1.16) Leukemia Incidence - Acute myeloid - 10-yr time weighted average: 1.02 (0.91, 1.14)
						Leukemia Incidence - Acute lymphoblastic - 1-yr time weighted average: 0.93 (0.66, 1.30) Leukemia Incidence - Acute lymphoblastic - 5-yr time weighted average: 1.06 (0.76, 1.48) Leukemia Incidence - Acute lymphoblastic - 10-yr time weighted average: 1.12 (0.80, 1.55)
						Leukemia Incidence - 1-yr time weighted average; Age <69: 0.95 (0.87, 1.04) Leukemia Incidence - 5-yr time weighted average; Age <69: 0.96 (0.87, 1.05) Leukemia Incidence - 10-yr time weighted average; Age <69:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						0.95 (0.86, 1.04)
						Leukemia Incidence - 1-yr time weighted average; Age $\geq$ 70: 1.06 (0.98, 1.15) Leukemia Incidence - 5-yr time weighted average; Age $\geq$ 70: 1.05 (0.97, 1.14) Leukemia Incidence - 10-yr time weighted average; Age $\geq$ 70: 1.03 (0.95, 1.12)
[†] Raaschou-Nielsen et al. (2015)	Eligible cases were aged 30-84 years with lymphocytic leukemia (ICD-10: C91) or myeloid leukemia (ICD-10: C92), had no previous diagnosis of cancer (except for nonmelanoma skin cancer), had been born in Denmark and lived at a geocodable address in Denmark at the time of diagnosis. For each case, two controls matched on sex and year of birth were randomly selected from the Danish Civil Registration System.	Dispersion model Averaging time: NO ₂ - 5-year exposure NO ₂ - 10-year exposure NO ₂ - mean exposure since 1971 NO _x - 5-year exposure NO _x - 10 year exposure NO _x - mean exposure since 1971 Exposure years: 1971–2010	NO ₂ (ppb) Lymphocytic leukemia cases Median = 6.7 (12.6 $\mu\text{g}/\text{m}^3$) P5 = 5.47 (10.3 $\mu\text{g}/\text{m}^3$) P95 = 11.5 (21.7 $\mu\text{g}/\text{m}^3$) Lymphocytic leukemia controls Median = 6.75 (12.7 $\mu\text{g}/\text{m}^3$) P5 = 5.47 (10.3 $\mu\text{g}/\text{m}^3$) P95 = 12.1 (22.7 $\mu\text{g}/\text{m}^3$) Myeloid leukemia cases Median = 6.8 (12.8 $\mu\text{g}/\text{m}^3$)	ICD-10 codes: C91 and C92	Logistic regression Adjusted for: matched on sex and year of birth with adjustment for disposable income, level of education, cohabitation status and comorbidity	NO ₂ HR (95% CI) ^b Leukemia Incidence - Acute myeloid leukemia; 10-year exposure: 1.32 (0.92, 1.90) Leukemia Incidence - Myeloid leukemia; 10-year exposure: 1.10 (0.81, 1.48) Leukemia Incidence - Chronic myeloid leukemia; 10-year exposure: 0.69 (0.36, 1.31) Leukemia Incidence - Lymphocytic; Mean exposure since 1971: 0.94 (0.66, 1.35) Leukemia Incidence - Chronic myeloid leukemia; Mean exposure since 1971: 0.80 (0.35, 1.83) Leukemia Incidence - Chronic myeloid leukemia; 5-year exposure: 0.74 (0.39, 1.38) Leukemia Incidence - Lymphocytic; 10-year exposure:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 5.47 (10.3 μg/m ³) P95 = 12.2 (22.9 μg/m ³)			0.91 (0.68, 1.21) Leukemia Incidence - Myeloid leukemia; 5-year exposure: 1.16 (0.87, 1.54) Leukemia Incidence - Acute myeloid leukemia; Mean exposure since 1971: 1.66 (1.04, 2.66) Leukemia Incidence - Myeloid leukemia; Mean exposure since 1971: 1.32 (0.90, 1.95) Leukemia Incidence - Lymphocytic; 5-year exposure: 0.94 (0.78, 1.14) Leukemia Incidence - Acute myeloid leukemia; 5-year exposure: 1.34 (0.95, 1.90)
			Myeloid leukemia controls Median = 6.75 (12.7 μg/m ³) P5 = 5.47 (10.3 μg/m ³) P95 = 12 (22.6 μg/m ³)			
			NO _x (μg/m ³)			
			Lymphocytic leukemia cases Median = 16.8 P5 = 13.5 P95 = 45.3			OR (95% CI) ^b Leukemia incidence - All leukemia; 1-year TWA; age 70 and above: 1.06 (0.98, 1.15) Leukemia incidence - All leukemia; 5-year TWA; age 69 years or less: 0.96 (0.87, 1.05) Leukemia incidence - All leukemia; 1-year TWA; age 69 years or less: 0.95 (0.87, 1.04) Leukemia incidence - All leukemia; 5-year TWA: 1.02 (0.95, 1.09) Leukemia incidence - All leukemia; 5-year TWA; age 70 and above: 1.05 (0.97, 1.14) Leukemia incidence - All leukemia; 10-year TWA; age 69 years or less: 0.95 (0.86, 1.04)
			Lymphocytic leukemia controls Median = 17.3 P5 = 13.5 P95 = 48.1			
			Myeloid leukemia cases Median = 17.3 P5 = 13.6 P95 = 55.6			
			Myeloid leukemia controls Median = 17.3			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			P5 = 13.6 P95 = 48.4			Leukemia incidence - All leukemia; 10-year TWA: 1.00 (0.95, 1.06) Leukemia incidence - All leukemia; 10-year TWA; age 70 and above: 1.03 (0.95, 1.12) Leukemia incidence - All leukemia; 1-year TWA: 1.02 (0.96, 1.08) NO_x HR (95% CI)^c Leukemia Incidence - Lymphocytic; Mean exposure since 1971: 0.97 (0.87, 1.09) Leukemia Incidence - Chronic myeloid leukemia; 5-year exposure: 0.92 (0.76, 1.13) Leukemia Incidence - Myeloid leukemia; Mean exposure since 1971: 1.11 (0.99, 1.24) Leukemia Incidence - Myeloid leukemia; 10-year exposure: 1.04 (0.94, 1.14) Leukemia Incidence - Lymphocytic; 5-year exposure: 0.97 (0.87, 1.04) Leukemia Incidence - Acute myeloid leukemia; Mean exposure since 1971: 1.20 (1.04, 1.38) Leukemia Incidence - Lymphocytic; 10-year exposure: 0.96 (0.87, 1.06) Leukemia Incidence - Myeloid leukemia; 5-year exposure: 1.05 (0.96, 1.16)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Leukemia Incidence - Acute myeloid leukemia; 10-year exposure: 1.09 (0.97, 1.23) Leukemia Incidence - Chronic myeloid leukemia; Mean exposure since 1971: 0.93 (0.73, 1.19) Leukemia Incidence - Chronic myeloid leukemia; 10-year exposure: 0.91 (0.75, 1.11) Leukemia Incidence - Acute myeloid leukemia; 5-year exposure: 1.10 (0.98, 1.24)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 yr old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 codes: 204-208; ICD-10 codes: C91-C95 ICD-9 code: 203; ICD-10 code: C88, C90	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Leukemia mortality: 1.00 (0.91, 1.10)
Cancers outside the Lungs: Bladder Cancer						

†Chen et al. (2022)	Excluded due to fail in logical checks, cancer diagnosis before baseline, missing exposure, missing individual-level covariates, or area-level mean income	LUR	NO ₂ (ppb)	National cancer registries, self-reports, death certificates	Cox proportional hazard model	HR (95% CI) ^b Bladder cancer incidence: 1.02 (0.84, 1.24)
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Dutch European Investigation into Cancer and Nutrition (EPIC-NL), Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N), Danish Nurse Cohort (DNC)		$r^2 = 0.58$	CEANS-SALT Mean = 11.28±3.31 (21.22±6.22 µg/m ³) Median = 11.16 (20.99 µg/m ³) P5 = 5.867 (11.04 µg/m ³) P25 = 9.306 (17.51 µg/m ³) P75 = 13.17 (24.78 µg/m ³) P95 = 16.94 (31.88 µg/m ³)		Adjusted for: subcohort, age, sex, year of baseline visit, smoking, BMI, marital status, employment status, 2001 area-level mean income	
N = 302,493			CEANS-SDPP Mean = 8.195±2.27 (15.42±4.27 µg/m ³) Median = 8.259 (15.54 µg/m ³) P5 = 4.15 (7.81 µg/m ³) P25 = 6.792 (12.78 µg/m ³) P75 = 9.635 (18.13 µg/m ³) P95 = 11.9 (22.39 µg/m ³)			
Stockholm, Vorarlberg, Sweden, France, Denmark, Austria, Netherlands			CEANS-SIXTY Mean = 10.96±3.25 (20.63±6.11 µg/m ³) Median = 10.88 (20.48 µg/m ³) P5 = 5.708 (10.74 µg/m ³) P25 = 9 (17 µg/m ³) P75 = 12.68 (23.85 µg/m ³)			
Enrollment: 1985–2005 Follow-up 18 years						
Cohort						

$\mu\text{g}/\text{m}^3$)
P95 = 16.58 (31.19
 $\mu\text{g}/\text{m}^3$)

CEANS-SNACK
Mean = 14.57 ± 2.69
($27.42 \pm 5.07 \mu\text{g}/\text{m}^3$)
Median = 15.2 (28.6
 $\mu\text{g}/\text{m}^3$)
P5 = 9.72 (18.29
 $\mu\text{g}/\text{m}^3$)
P25 = 12.61 (23.73
 $\mu\text{g}/\text{m}^3$)
P75 = 16.45 (30.95
 $\mu\text{g}/\text{m}^3$)
P95 = 18.04 (33.95
 $\mu\text{g}/\text{m}^3$)

DCH
Mean = 14.93 ± 3.66
($28.09 \pm 6.88 \mu\text{g}/\text{m}^3$)
Median = 15.13
($28.46 \mu\text{g}/\text{m}^3$)
P5 = 8.774 (16.51
 $\mu\text{g}/\text{m}^3$)
P25 = 12.34 (23.22
 $\mu\text{g}/\text{m}^3$)
P75 = 17.73 (33.36
 $\mu\text{g}/\text{m}^3$)
P95 = 20.33 (38.25
 $\mu\text{g}/\text{m}^3$)

DNC-1999
Mean = 13.73 ± 4.51
($25.84 \pm 8.49 \mu\text{g}/\text{m}^3$)
Median = 12.6
($23.71 \mu\text{g}/\text{m}^3$)
P5 = 7.265 (13.67
 $\mu\text{g}/\text{m}^3$)
P25 = 10.32 (19.42

$\mu\text{g}/\text{m}^3$)
P75 = 17.68 (33.27
 $\mu\text{g}/\text{m}^3$)
P95 = 20.7 (38.95
 $\mu\text{g}/\text{m}^3$)

DNC-1993
Mean = 11.6 ± 4.23
($21.8 \pm 7.96 \mu\text{g}/\text{m}^3$)
Median = 10.78
($20.28 \mu\text{g}/\text{m}^3$)
P5 = 5.405 (10.17
 $\mu\text{g}/\text{m}^3$)
P25 = 8.647 (16.27
 $\mu\text{g}/\text{m}^3$)
P75 = 14.22 (26.75
 $\mu\text{g}/\text{m}^3$)
P95 = 19.64 (36.95
 $\mu\text{g}/\text{m}^3$)

E3N
Mean = 13.99 ± 5.18
($26.33 \pm 9.74 \mu\text{g}/\text{m}^3$)
Median = 13.04
($24.53 \mu\text{g}/\text{m}^3$)
P5 = 7.12 (13.4
 $\mu\text{g}/\text{m}^3$)
P25 = 10.3 (19.3
 $\mu\text{g}/\text{m}^3$)
P75 = 16.93 (31.85
 $\mu\text{g}/\text{m}^3$)
P95 = 24.21 (45.56
 $\mu\text{g}/\text{m}^3$)

EPIC-NL-
MORGEN
Mean = 18.36 ± 3.22
($34.54 \pm 6.05 \mu\text{g}/\text{m}^3$)
Median = 17.84
($33.57 \mu\text{g}/\text{m}^3$)

P5 = 13.91 (26.18
μg/m³)
P25 = 15.93 (29.97
μg/m³)
P75 = 20.69 (38.93
μg/m³)
P95 = 23.86 (44.89
μg/m³)

EPIC-NL-
PROSPECT
Mean = 19.09±2.88
(35.92±5.41 μg/m³)
Median = 18.83
(35.43 μg/m³)
P5 = 14.54 (27.35
μg/m³)
P25 = 17.27 (32.49
μg/m³)
P75 = 21.13 (39.75
μg/m³)
P95 = 23.69 (44.58
μg/m³)

Pooled Cohort
Mean = 13.21±4.23
(24.86±7.96 μg/m³)
Median = 12.8
(24.09 μg/m³)
P5 = 6.8 (12.8
μg/m³)
P25 = 10.35 (19.47
μg/m³)
P75 = 15.66 (29.46
μg/m³)
P95 = 10.22 (19.23
μg/m³)

VHM&PP
Mean = 11.67±2.84

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			(21.95±5.34 µg/m ³) Median = 11.93 (22.45 µg/m ³) P5 = 6.526 (12.28 µg/m ³) P25 = 9.896 (18.62 µg/m ³) P75 = 13.62 (25.62 µg/m ³) P95 = 15.77 (29.68 µg/m ³)			

†Pedersen et al. (2018)						
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Oslo Health Study (HUBRO), Dutch European Investigation into Cancer and Nutrition (EPIC-NL), EPIC-Oxford, European Prospective Investigation into Cancer and Nutrition (EPIC)-Umeå, Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese, EPIC-Turin, EPIC-San Sebastian, Italian Studies of Respiratory Disorders in Childhood and Environment (SIDRIA-Rome)	Participants with a cancer (except nonmelanoma skin cancer) before enrollment were excluded as were participants for whom information about exposure to air pollution and the most important potential confounders could not be obtained.	LUR	NO ₂ (ppb)	ICD-9 code 1880-1889 and ICD-10 code C67	Cox proportional hazard model	NO ₂
		Averaging time: NO ₂ - annual average	CEANS Mean = 5.74±2.4 (10.8±4.6 µg/m ³)		Adjusted for: Age, sex, calendar time, smoking, occupation, employment, education, area-level SES	HR (95% CI) ^b Bladder cancer incidence - Overall: 0.96 (0.80, 1.15)
		Exposure years: 2008–2011	DCH Mean = 8.72±4 (16.4±7 µg/m ³)			NO _x
			EPIC NL Mean = 13.4±3.3 (25.2±6.2 µg/m ³)			HR (95% CI) ^c Bladder cancer incidence - Overall: 0.99 (0.91, 1.09)
			EPIC Oxford Mean = 13±4 (24.5±8 µg/m ³)			
			EPIC San Sebastian Mean = 12.6±3.5 (23.8±6.6 µg/m ³)			
			EPIC Turin Mean = 28.3±5.74 (53.2±10.8 µg/m ³)			
			EPIC Umea Mean = 2.8±1.3 (5.2±2.5 µg/m ³)			
			EPIC Varese Mean = 23.1±9.19 (43.5±17.3 µg/m ³)			
			HUBRO Mean = 11.1±4 (20.9±8 µg/m ³)			
			SIDRIA Rome			

N = 303,431

Stockholm, Rome, Oslo, Umea, Turin, Italy, Varese, Italy,

Vorarlberg, Oxford, UK, San Sebastian, Spain, Sweden, England, Denmark, Spain, Italy, Norway, Austria, Netherlands	Mean = 20.8±4.8 (39.1±9.1 µg/m ³)
Enrollment: 1985–2005	VHM&PP Mean = 10.6±2.9 (19.9±5.5 µg/m ³)
Follow-up: 14 years	NO _x (µg/m ³)
Cohort	CEANS Mean = 19±10.2
	DCH Mean = 26.8±18.4
	EPIC NL Mean = 37.9±11.3
	EPIC Oxford Mean = 40.9±15.6
	EPIC San Sebastian Mean = 47.2±12.5
	EPIC Turin Mean = 96.4±21
	EPIC Umea Mean = 8.7±5.8
	EPIC Varese Mean = 86.1±41.8
	HUBRO Mean = 38.3±15.4
	SIDRIA Rome Mean = 82±23.9

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			VHM&PP Mean = 39.9±9.5			
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code 188; ICD-10 code: C67	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Bladder cancer mortality: 1.05 (0.91, 1.20)

†Turner et al. (2019)						
Spanish Bladder Cancer Study	Cases were histologically confirmed and aged between 21 and 80 years. Controls were patients admitted to the hospital for conditions unrelated to the exposures under study and were individually matched to cases by hospital, 5-year age at diagnosis/interview, sex, ethnicity, and region of residence	LUR $r^2 = 0.56$	NO ₂ (ppb) Age Group 60-69 Mean = 14.8±5.42 (27.8±10.2 µg/m ³) 70+ Mean = 15.3±5.47 (28.8±10.3 µg/m ³) <60 Mean = 15.6±5.3 (29.3±9.9 µg/m ³)	Hospital registries, clinical records, pathology lists	Logistic Regression Adjusted for: Age group, sex, region, smoking pack years, high risk occupations	OR (95% CI) ^b Bladder cancer incidence: 0.91 (0.57, 1.46)
Cases n = 938 Controls n = 973		Averaging time: NO ₂ - annual average				
Asturias, Barcelona, Alicante, Tenerife, Valles, Bages, Spain		Exposure years: 2008-2011	Region Asturias Mean = 13.7±4.9 (25.7±9.2 µg/m ³) Barcelona Mean = 18.5±3.7 (34.9±6.9 µg/m ³) Elche Mean = 18.2±5.95 (34.2±11.2 µg/m ³) Tenerife Mean = 11.3±5 (21.3±9.5 µg/m ³) Valles Mean = 16.5±4.8 (31.1±9.1 µg/m ³)			
1998–2001			Sex Female Mean = 15.4±5.42 (28.9±10.2 µg/m ³) Male Mean = 15.1±5.42 (28.5±10.2 µg/m ³)			
Case-Control						
Cancers outside the Lungs: Female Reproductive Cancer - Breast Cancer						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Amadou et al. (2023) Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'éducation Nationale (E3N) N = 98,995 n = 10,444 cases n = 5,222 controls n = 5,222 France Baseline: 1990 Follow-up: 1997, 2000, 2002, 2005, 2008, and 2011 Nested case-control	French women, between 40 and 65 years of age at inclusion in 1990, and insured by the national health insurance covering employees from the French National Education System.	LUR, Chemical transport model Averaging time: NO₂ - annual average Exposure years: LUR model: 2010-2010 and then back-extrapolated until 1990; Chemical transport model: 1990–2010	NO₂ (ppb) Chemical transport model Postmenopausal Cases Mean = 13.2±9.35 (24.9±17.6 µg/m³) Postmenopausal Controls Mean = 12.8±9 (24.1±17 µg/m³) Premenopausal Cases Mean = 13.6±9.6 (25.6±18 µg/m³) Premenopausal Controls Mean = 13.5±9.3 (25.4±17.5 µg/m³) LUR model Postmenopausal Cases Mean = 16.2±8.18 (30.4±15.4 µg/m³) Postmenopausal Controls Mean = 15.9±8 (29.9±15 µg/m³) Premenopausal Cases Mean = 16.6±8.5 (31.3±16 µg/m³) Premenopausal Controls	Cases identified through self-reports or death certificates.	Logistic regression Adjusted for: age, date, department of residence, and menopausal status at blood collection or at baseline, and existence of a biological sample, body mass index, previous family history of breast cancer, history of personal benign breast disease, age at menarche, parity and age at first full-term pregnancy, breastfeeding, oral contraceptive use, and menopausal hormone therapy use	OR (95% CI)^b Breast cancer - Overall, Chemical transport model (CHIMERE): 1.16 (1.08, 1.25) Breast cancer - Overall, LUR: 1.07 (0.99, 1.17)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			Mean = 16.4±8.18 (30.9±15.4 µg/m ³)			
† Andersen et al. (2016) Danish Nurse Cohort N = 22,877 Breast cancer cases n = 1,145 No breast cancer cases n = 21,732 Denmark Recruitment: 1993 and 1999 Follow-up: 2013 Cohort	Of the 28,731 nurses, we excluded 1,924 with cancer and 3 with inactive vital status before cohort baseline, and 3,927 with missing data on address or confounder, leaving 22,877 for final analyses.	Dispersion model Averaging time: NO ₂ - annual average Exposure years: 1990–2013		Central Population Register, Danish Cancer Register	Cox proportional hazard model Adjusted for: Age, smoking status and intensity, alcohol use, BMI, physical activity, parity, age at first birth, age at menarche, hormone therapy use, oral contraceptive use, menopausal status	HR (95% CI) ^b Breast cancer incidence: 1.00 (0.85, 1.18)
† Andersen et al. (2017b) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Oslo Health Study (HUBRO), Dutch European Investigation into Cancer and Nutrition (EPIC-NL), Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N),	Analyses were restricted to women who were postmenopausal or who were older than 55 yr at the cohort baseline and who did not have cancer before the study baseline (excluding nonmelanoma skin cancers).	LUR LUR models for the other elements performed moderately with average cross validation r ² generally between 50% and 60% Averaging time: NO ₂ - annual average Exposure years: 1990s–2010	NO ₂ (ppb) CEANS Mean = 6.27±3 (11.8±5 µg/m ³) Min = 3 (6 µg/m ³) Max = 19 (35.8 µg/m ³) DCH Mean = 8.77±4 (16.5±7 µg/m ³) Min = 3 (5.6 µg/m ³) Max = 23 (43.3 µg/m ³) EPIC-E3N Mean = 16.4±6.75 (30.9±12.7 µg/m ³)	ICD-10 code C50; ICD-9 code 174; and ICD-7 code 170	Cox proportional hazard model Adjusted for: Age, year of enrollment, smoking status, smoking duration among ever smokers, smoking intensity among ever smokers, alcohol use, physical activity, BMI, educational level, employment, age at first birth, parity, hormone therapy use, hormone therapy duration, socioeconomic status	NO ₂ HR (95% CI) ^b Breast cancer incidence: 1.04 (0.96, 1.13) NO _x HR (95% CI) ^c Breast cancer incidence: 1.04 (1.00, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
EPIC-Oxford, European Prospective Investigation into Cancer and Nutrition (EPIC)-Umea, Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese, EPIC-Turin, EPIC-San Sebastian			Min = 4.6 (8.7 $\mu\text{g}/\text{m}^3$) Max = 49.8 (93.7 $\mu\text{g}/\text{m}^3$) EPIC-NL Mean = 14 $\pm$ 3 (26.3 $\pm$ 5 $\mu\text{g}/\text{m}^3$) Min = 7.23 (13.6 $\mu\text{g}/\text{m}^3$) Max = 29 (54.6 $\mu\text{g}/\text{m}^3$) EPIC-Oxford Mean = 12.2 $\pm$ 4 (22.9 $\pm$ 7 $\mu\text{g}/\text{m}^3$) Min = 6.86 (12.9 $\mu\text{g}/\text{m}^3$) Max = 47 (89 $\mu\text{g}/\text{m}^3$) EPIC-San Sebastian Mean = 12.8 $\pm$ 3.6 (24.1 $\pm$ 6.7 $\mu\text{g}/\text{m}^3$) Min = 5.2 (9.8 $\mu\text{g}/\text{m}^3$) Max = 24 (45.1 $\mu\text{g}/\text{m}^3$) EPIC-Turin Mean = 28 $\pm$ 5.47 (53 $\pm$ 10.3 $\mu\text{g}/\text{m}^3$) Min = 7.92 (14.9 $\mu\text{g}/\text{m}^3$) Max = 44 (83 $\mu\text{g}/\text{m}^3$)			
N = 74,750 Breast cancer cases n = 3,612						
Stockholm, Oslo, Kungsholmen, Copenhagen, Turin, Italy, Varese, Italy, Vorarlberg, Oxford, UK, San Sebastian, Spain, Umeå, Sweden, France, United Kingdom, Denmark, Spain, Italy, Norway, Austria, Netherlands						
Enrollment: 1992–2005 Follow-up: 2013						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			EPIC-Umea Mean = 2.9±1.3 (5.4±2.5 µg/m ³) Min = 1.9 (3.5 µg/m ³) Max = 9.67 (18.2 µg/m ³)			
			EPIC-Varese Mean = 23.5±9.25 (44.2±17.4 µg/m ³) Min = 0.8 (1.5 µg/m ³) Max = 45.5 (85.7 µg/m ³)			
			HUBRO Mean = 10.4±3.8 (19.6±7.2 µg/m ³) Min = 3.7 (6.9 µg/m ³) Max = 25.9 (48.7 µg/m ³)			
			VHM&PP Mean = 10.8±2.9 (20.4±5.5 µg/m ³) Min = 1.5 (2.9 µg/m ³) Max = 22.3 (41.9 µg/m ³)			
† Bai et al. (2019)	All long-term residents who lived in Ontario and were registered with Ontario's provincial health	LUR Averaging time: 3-year moving average with 4-	NO ₂ (ppb) Mean = 17.9 IQR = 13.9	Ontario Cancer Registry	Cox proportional hazard model Adjusted for: age, sex, region, census tract-	HR (95% CI) ^c Breast cancer incidence: 1.02 (1.00, 1.04) Breast cancer incidence - 10-year exposure lag:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Entire lung cancer cohort n = 4,952,022 Incident lung cancer cohort n = 100,146 Entire breast cancer cohort n = 2,564,340 Incidence breast cancer cohort n = 91,146 Canada 2001–2015 Cohort	insurance plan on April 1, 1996, aged 35–85 years with no previous	year time lag Exposure years: 2006			level recent immigrants (arrived in the 5 years prior to census), unemployment rate, education, and annual household income	1.03 (1.01, 1.05)
† Cheng et al. (2020) The Multiethnic Cohort Study (MEC) n = 57,589 United States Recruitment: 1993–1996 Follow-up through 2010 Cohort	Men and women aged 45–75 years from five self-reported racial/ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians, and white people), residing in Hawaii (HI) or CA (primarily Los Angeles County)	Dispersion model, Spatiotemporal/geospatial model, LUR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 1993–2010	NR	Participants were followed prospectively for diagnosis of incident invasive breast cancer through routine linkage with the CA and HI statewide cancer registries, which are a part of the National Cancer Institute’s Surveillance, Epidemiology and End Results Program, and for vital status through linkages to the National Death Index and	Cox proportional hazard model Adjusted for: age at entry (as a strata variable, 5-year categories), race/ethnicity for all women, BMI, family history of breast cancer, age at first live birth, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity, energy intake, alcohol use, smoking, education, neighborhood SES	NO ₂ HR (95% CI) ^b Breast cancer incidence - Kriging - White: 1.00 (0.80, 1.26) Breast cancer incidence - LUR - White: 0.99 (0.85, 1.16) Breast cancer incidence - LUR: 1.02 (0.95, 1.10) Breast cancer incidence - Kriging - Latinos: 1.06 (0.84, 1.34) Breast cancer incidence - Kriging - Japanese American: 1.24 (0.90, 1.70) Breast cancer incidence - Kriging - Black (author reported African American): 1.09 (0.91, 1.30) Breast cancer incidence - Kriging:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
				death certificate files.		1.05 (0.94, 1.18) Breast cancer incidence - LUR - Japanese American: 1.17 (0.96, 1.42) Breast cancer incidence - LUR - Black (author reported African American): 1.07 (0.93, 1.24) Breast cancer incidence - LUR - Latinos: 0.93 (0.81, 1.08) NO _x HR (95% CI) ^b Breast cancer incidence - Kriging: 1.05 (0.98, 1.11) Breast cancer incidence - CALINE4 - Black (author reported African American): 1.27 (0.39, 4.11) Breast cancer incidence - LUR - Black (author reported African American): 1.11 (1.00, 1.22) Breast cancer incidence - Kriging - White: 0.99 (0.86, 1.15) Breast cancer incidence - LUR - Japanese American: 1.17 (1.02, 1.33) Breast cancer incidence - CALINE4 - White: 1.24 (0.30, 5.21) Breast cancer incidence - Kriging - Latinos: 1.10 (0.97, 1.24)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Breast cancer incidence - LUR: 1.03 (0.98, 1.09) Breast cancer incidence - LUR - White: 0.96 (0.86, 1.08) Breast cancer incidence - LUR - Latinos: 1.00 (0.90, 1.10) Breast cancer incidence - Kriging - Japanese American: 1.10 (0.88, 1.39) Breast cancer incidence - CALINE4: 0.93 (0.50, 1.75) Breast cancer incidence - Kriging - Black (author reported African American): 1.07 (0.97, 1.18) Breast cancer incidence - CALINE4 - Latinos: 0.33 (0.11, 0.97) Breast cancer incidence - CALINE4 - Japanese American: 4.75 (0.98, 23.11)
†Goldberg et al. (2017) N = 1,277 Cases n = 681 Controls n = 596 Canada 2008–2011 Case-control	Women were eligible if they fulfilled criteria for being menopausal (i.e., the WHO criteria for menopausal status, accounting for hormone replacement therapy, hysterectomy, and bilateral oophorectomy)(WHO, 1981; WHO scientific group on research on the menopause in the,	LUR 80% of variability Averaging time: NO ₂ - annual average Exposure years: 2005-2006	NO ₂ (ppb) Breast Cancer Cases Mean = 12.16±2.75 Median = 11.78 (IQR 3.75) Min = 6.22 Max = 22.34 P25 = 10.08 P75 = 13.83 Breast Cancer Controls	Pathology records or face-to-face or telephone interviews	Logistic regression mode Adjusted for: age, family history, education, age at menarche, age at first full term pregnancy, body mass index, alcohol status, number of full-term pregnancy, immigrants, unemployment rate, low	OR (95% CI) ^b Breast cancer incidence - Overall: 1.14 (0.71, 1.82) Breast cancer incidence - ER+/PR+ Overall 1.20 (0.72, 1.98) Breast cancer incidence - ER+/PR+ Living at current dwelling at least 10 years 1.38 (0.72, 2.65) Breast cancer incidence - Overall, Living at recruitment address 10 years

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	1990, 1996), had never had a previous occurrence of any type of cancer, were between 50 and 70 years of age, lived on the Island of Montreal, were registered with the universal Provincial Electoral List, and were alive at time of interview.		Mean = 11.96±2.62 Median = 11.61 (IQR 3.79) Min = 6.16 Max = 19.53 P25 = 9.95 P75 = 13.74		education, median household income	prior to study entry 1.22 (0.66, 2.25) Breast cancer incidence - Overall, Not living at recruitment address 10 years prior to study entry 0.82 (0.31, 2.16)
†Goldberg et al. (2019)	The Canadian National Breast Screening Study included a non-random sample of 89,835 women between 40 and 59 years of age recruited mostly from urban centres in Canada between 1980 and 1985. Women were excluded if they had a breast cancer beforehand.	LUR r ² = 0.73 with root mean square error 2.9 ppb Averaging time: NO ₂ - annual average Exposure years: 2006	NO ₂ (ppb) Postmenopausal Cohort Mean = 15.3±6.5 Median = 15.2 (IQR 9.7) Min = 0.1 Max = 48.9 P25 = 10.6 P75 = 20.3 Premenopausal Cohort Mean = 15.2±6.3 Median = 14.9 (IQR 9.6) Min = 0.1 Max = 48.6 P25 = 10.5 P75 = 20.1	Canadian Mortality Database and Canadian Cancer Registry	Cox proportional hazard model Adjusted for: age, occupation, marital status, attained education, BMI, cigarette pack-years, ever pregnant, oral contraceptive use, hormone replacement therapy, age at menarche, breast self-examination, and family history of breast cancer	RR (95% CI) ^b Breast cancer - Premenopausal, Age 52 cut-off: 1.20 (1.06, 1.36) Breast cancer - Postmenopausal, Age 50 cut-off: 1.03 (0.99, 1.08) Breast cancer - Premenopausal, Age 50 cut-off: 1.15 (0.99, 1.35) Breast cancer - Postmenopausal, Age 52 cut-off: 1.03 (0.99, 1.07)
Canadian National Breast Cancer Screening Study N = 89,247 Postmenopausal Cohort: 88,389 Postmenopausal Cases: 5,851 Premenopausal Cohort: 38,210 Premenopausal Cases: 652 Canada Enrollment: 1980–1985 Follow-up: 20 yrs (2005) Cohort						
†Poulsen et al. (2023)	All women living in Denmark and	Dispersion model	NO ₂ (ppb)	Danish Civil Registration	Logistic regression model	OR (95% CI) ^b Breast cancer incidence - Overall:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Denmark National Administrative and Health Registers	diagnosed with a primary breast cancer (ICD10: C50) between 2000 and 2014. We did not include women with other prior cancer diagnoses (except non-melanoma skin cancer). in Denmark (excluding Greenland and the Faroe Islands) at index date. Subjects for whom >20% of the address history, 20 years prior to index date, could not be geocoded or who had missing information on marital status, country of origin or area of residence (parish) were also excluded.	Averaging time: NO ₂ - annual average Exposure years: 2000–2014	All Cases Mean = 11.27 (21.21 µg/m ³) Median = 10.65 (IQR 5.45) (20.03 (IQR 10.25) µg/m ³) Min = 3.23 (6.08 µg/m ³) Max = 41.65(78.36 µg/m ³) P5 = 5.99 (11.27 µg/m ³) P10 = 6.73 (12.66 µg/m ³) P25 = 8.20 (15.43 µg/m ³) P75 = 13.65 (25.68 µg/m ³) P90 = 16.33 (30.72 µg/m ³) P95 = 18.57 (34.93 µg/m ³) P99 = 24.33 (45.78 µg/m ³) All Controls Mean = 11.12 (20.92 µg/m ³) Median = 10.47 (IQR 5.36) (19.69 (IQR 10.09) µg/m ³) Min = 3.23 (6.07 µg/m ³) Max = 41.56 (78.20 µg/m ³) P5 = 5.87 (11.05 µg/m ³) P10 = 6.63 (12.48	System, Statistics Denmark, Danish National Prescription Register	Adjusted for: Age, month of birth, marital status, education, occupational status, personal income, region of origin, use of HT, use of oral contraceptives, use of Aspirin, use of non-aspirin NSAIDs, use of anti-allergy medication, income in lowest quartile, unemployed, manual labor, retired, basic education, living in social housing, owning their own dwelling, single parent families, previous convicted, of Danish origin	1.06 (1.01, 1.11) Breast cancer incidence – Overall, Diagnosis age greater than or equal to 55 years: 1.06 (1.01, 1.11) Breast cancer incidence – Overall, Diagnosis age less than 55 years: 1.10 (1.01, 1.19) Breast cancer incidence – Overall, including PM _{2.5} : 1.00 (0.95, 1.06) Breast cancer incidence – Overall, including EC 1.10 (0.77, 1.56) Breast cancer incidence – TWA period of 5 years, all cases 1.04 (1.00, 1.08) Breast cancer incidence – TWA period of 5 years, age of diagnosis greater than or equal to 55 years 1.04 (0.98, 1.10) Breast cancer incidence – TWA period of 5 years, age of diagnosis less than 55 years 1.04 (0.95, 1.14) Breast cancer incidence – TWA period of 5 years, age of diagnosis less than 45 years 0.89 (0.76, 1.04) Breast cancer incidence – TWA period of 10 years, all cases

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			$\mu\text{g}/\text{m}^3$ P25 = 8.10 (15.24 $\mu\text{g}/\text{m}^3$ P75 = 13.46 (25.33 $\mu\text{g}/\text{m}^3$ P90 = 16.16 (30.41 $\mu\text{g}/\text{m}^3$ P95 = 18.25 (34.33 $\mu\text{g}/\text{m}^3$ P99 = 24.41 (45.92 $\mu\text{g}/\text{m}^3$			1.06 (1.01, 1.11) Breast cancer incidence – TWA period of 10 years, age of diagnosis greater than or equal to 55 years 1.06 (1.01, 1.11) Breast cancer incidence – TWA period of 10 years, age of diagnosis less than 55 years 1.06 (0.96, 1.16) Breast cancer incidence – TWA period of 10 years, age of diagnosis less than 45 years 0.93 (0.79, 1.08) Breast cancer incidence – TWA period of 20 years, all cases 1.06 (1.01, 1.11) Breast cancer incidence – TWA period of 20 years, age of diagnosis greater than or equal to 55 years 1.06 (1.01, 1.11) Breast cancer incidence – TWA period of 20 years, age of diagnosis less than 55 years 1.10 (1.01, 1.19) Breast cancer incidence – TWA period of 20 years, age of diagnosis less than 45 years 1.00 (0.86, 1.16)
† Reding et al. (2015)	U.S. women between ages 35 to 74 whose sister had breast cancer.	Spatiotemporal/geospatial model	NO ₂ (ppb)		Cox proportional hazard model	HR (95% CI) ^b
Sister Study cohort		r ² = 0.85	Cases - All Mean = 10.3±4.7		Adjusted for: age at diagnosis, race, educational attainment,	Breast cancer incidence: 1.03 (0.95, 1.13)
N = 50,884 n cases: 1,749		Averaging time:	Cases - ER-/PR-			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
n controls: 47,591 United States August 2003 to July 2009 Cohort		NO ₂ - annual average Exposure years: 2006	Mean = 9.8±4.5 Cases - ER+/PR+ Mean = 10.4±4.7 Controls Mean = 10.1±4.7		smoking status, and menopausal hormone therapy	
† Smotherman et al. (2023) UK Biobank N = 155,235 England, Scotland, Wales, U.K. Enrollment: 2006–2010 Follow-up: 2019 Cohort	Women aged 40-69 years, only postmenopausal women were included in this study, women without a history of breast cancer or any other type of cancer (except non-melanoma skin). Participants were excluded if they had missing information on all air pollution assessments and selected breast cancer risk factors	LUR Averaging time: NO ₂ - annual average Exposure years: 2005, 2006, 2007, 2010	NO ₂ (ppb) 2005 Mean = 15.71±5.28 (29.56±9.93 µg/m ³) Median = 14.9 (28.04 µg/m ³) Min = 3.54 (6.66 µg/m ³) Max = 67.319 (126.67 µg/m ³) P25 = 12.15 (22.87 µg/m ³) P75 = 18.24 (34.33 µg/m ³) 2006 Mean = 15.22±4.8 (28.63±9.03 µg/m ³) Median = 14.7 (27.6 µg/m ³) Min = 3.6 (6.77 µg/m ³) Max = 68.792 (129.44 µg/m ³) P25 = 12 (22.6 µg/m ³) P75 = 17.52 (32.97 µg/m ³)	A breast cancer diagnosis invasive and in-situ) was identified based on diagnostic codes according to the 9th revision of the International Classification of Diseases (ICD-9: 174, 2330) or the 10th revision (ICD-10: C50, D05).	Cox proportional hazard model Adjusted for: Age, BMI, race, age at menopause, age at menarche, parity/age at first birth, postmenopausal hormone use, family history of breast cancer, alcohol consumption, and smoking	HR (95% CI) ^b Breast cancer incidence - Cumulative average, analyses without exposure lag per 2.66 ppb increase: 1.00 (0.95, 1.06) Breast cancer incidence - Cumulative average, analyses with 2-year exposure lag per 2.66 ppb increase: 1.00 (0.95, 1.06) Breast cancer incidence - Cumulative average, analyses without exposure lag per 5.31 ppb increase: 1.00 (0.95, 1.06) Breast cancer incidence - Cumulative average, analyses with 2-year exposure lag per 5.31 ppb increase: 1.02 (0.95, 1.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			2007 Mean = 16.13±5.602 (30.36±10.54 µg/m ³) Median = 15.19 (28.58 µg/m ³) Min = 3.71 (6.99 µg/m ³) Max = 73.548 (138.39 µg/m ³) P25 = 12.4 (23.4 µg/m ³) P75 = 18.38 (34.59 µg/m ³)			
			2010 Mean = 14.04±3.96 (26.41±7.45 µg/m ³) Median = 13.79 (25.95 µg/m ³) Min = 6.872 (12.93 µg/m ³) Max = 57.116 (107.47 µg/m ³) P25 = 11.29 (21.24 µg/m ³) P75 = 16.43 (30.91 µg/m ³)			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 codes 174-175; ICD-10 code C50	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Breast cancer mortality: 1.05 (0.96, 1.14)
Cancers outside the Lungs: Female Reproductive Cancers – Cervical, Ovarian, and Uterine Cancers						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code: 179, 182; ICD-10 codes: C54-C55 ICD-9 code: 180; ICD-10 code: C53 ICD-9 cod: 183; ICD-10 code: C56	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Cervical cancer mortality: 1.38 (0.87, 2.18) Ovarian cancer mortality: 1.05 (0.89, 1.22) Uterine cancer mortality: 1.11 (0.91, 1.36)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Villanueva et al. (2021) California Cancer Registry (CCR) N = 29,844 California, U.S. Enrollment: 1996–2014 Follow-up: 2016 Cohort	To be eligible for the study, women had to be 18 years or older at diagnosis. Women were then excluded if their case was obtained through death record, had unknown stage, or had a germ cell or stromal tumor classification.	Central site monitor Averaging time: NO ₂ - Other Exposure years: 1996–2016	NO ₂ (ppb) Early Stage Mean = 15.5±5.8 Median = 14.4 P25 = 11 P75 = 19 Overall Mean = 16.1±6.6 Median = 15.1 P25 = 11.2 P75 = 19.6 Stage III Mean = 16.2±6.7 Median = 15 P25 = 11.2 P75 = 19.6 Stage IV Mean = 16.8±7.3 Median = 15.8 P25 = 11.4 P75 = 20.3	California Cancer Registry	Cox proportional hazard model Adjusted for: Age at diagnosis, race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis, tumor grade, tumor histology, tumor size, comorbidity status, treatment adherence, year of diagnosis	HR (95% CI) ^c Ovarian cancer mortality - Overall, T1 (<20 ppb), Reference: 1.00 (1.00, 1.00) Ovarian cancer mortality - Overall, T2 (20-30 ppb): 1.30 (1.25, 1.36) Ovarian cancer mortality - Overall, T3 (>30 ppb): 2.48 (2.32, 2.66)
Cancers outside the Lungs: Male Reproductive Cancers						
†Taj et al. (2022) Danish Cancer Registry, Danish Civil Registration System N = 25,387 Cases n = 6,390 Controls n = 18,997	All patients diagnosed with testicular cancer between 1989 and 2014, aged 20 years or older at the time of diagnosis, and without a previous cancer diagnosis, including a previous testicular	Hybrid model Comparisons between model predictions and measured concentrations show correlation coefficients	NO ₂ (ppb) Cases Mean = 11.51±4.3 (21.66±8.09 µg/m ³) Median = 10.87 (IQR 5.8) (20.46 µg/m ³ (IQR 11 µg/m ³))	Danish Civil Registration System, Danish Cancer Registry	Logistic Regression Adjusted for: age and calendar time by matched design, marital status, personal income, labor market attachment, neighborhood level	OR (95% CI) ^b Testicular cancer incidence - 10-20 years before diagnosis (10-year lag): 0.96 (0.87, 1.07) Testicular cancer incidence - 10 years before diagnosis: 0.98 (0.89, 1.08) Testicular cancer incidence - First 10 years of life:

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Denmark 1989–2014 Case-Control	cancer, in the Danish Cancer Registry; accepted a previous diagnosis of nonmelanoma skin cancer. Four age-matched controls, free of previous cancer diagnosis (except nonmelanoma skin cancer), and alive at the date of diagnosis of their cases, were randomly selected and matched to each case. Controls were selected from all eligible male individuals in the Danish Civil Registration System.	between 0.62 and 0.92 for the different pollutants. Averaging time: NO ₂ - annual average Exposure years: 1979-2014	Min = 2.97 (5.58 µg/m ³) Max = 35.54 (66.87 µg/m ³) P5 = 5.83 (10.97 µg/m ³) P95 = 19.16 (36.06 µg/m ³) Controls Mean = 11.56±4.26 (21.75±8.02 µg/m ³) Median = 10.91 (IQR 5.74) (20.52 µg/m ³ (IQR 10.8 µg/m ³) Min = 3.1 (5.83 µg/m ³) Max = 40.63 (76.45 µg/m ³) P5 = 5.894 (11.09 µg/m ³) P95 = 19.2 (36.12 µg/m ³)		characteristics (manual labor, income, and home ownership)	0.84 (0.68, 1.03) Testicular cancer incidence - Year before birth: 0.77 (0.62, 0.96)
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in	NO ₂ (ppb) CPS-II NO ₂ Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code 185; ICD-10 code C61 ICD-9 code 185; ICD-10 code C62	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age	HR (95% CI) ^b Prostate cancer mortality: 1.02 (0.87, 1.18)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort	base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2		started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates Cox proportional hazard model with co-adjustment for PM _{2.5} Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates Cox proportional hazard model with co-adjustment for PM _{2.5} and O ₃	

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Adjusted for: NA						
† Youogo et al. (2022)	All cancers were histologically confirmed diagnoses of cancer and classified using the ICD-9 rubrics. Controls were selected during the same time period as the cases from a random sample of individuals from each of the participating provinces. Analysis was restricted to cases and controls 50 years of age and older.	LUR, Chemical transport model, Fixed site monitor The final LUR model explained 73% of the variation in NAPS measurements with a RMSE of 2.9 ppb and matches well with city-specific NO ₂ LUR models which typically have r ² values between 0.54 and 0.81. The LUR model provided a highly spatially resolved surface that could better capture smaller within-city variations in exposure but lacked the temporal component. The satellite measurements were able to cover large geographical	NO ₂ (ppb) NO ₂ National LUR Cases Mean = 19.8±11.6 Controls Mean = 18.8±11.8 NO ₂ Satellite Cases Mean = 1.4±1.2 Controls Mean = 1.4±1.3 NO ₂ Scaled Cases Mean = 16.3±9 Controls Mean = 15.5±8.9	Provincial health insurance plans, Ministry of Finance Property Assessment, random digit dialing	Logistic Regression Adjusted for: Age, province, ethnicity, pack-years, alcohol, BMI, years of education, moderate physical activity, strenuous physical activity, total caloric intake, exposure to pesticides, exposure to cadmium, neighborhood SES index, neighborhood greenness	OR (95% CI) ^b Prostate cancer incidence - Scaled model: 1.13 (1.01, 1.27) Prostate cancer incidence - Satellite model: 1.81 (0.72, 4.54) Prostate cancer incidence - National LUR model: 1.12 (1.02, 1.23)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
		areas including those not covered by ground-based fixed-site monitors. The satellite-derived exposure metric was limited in that the spatial resolution was modest. Averaging time: NO₂ - annual average Exposure years: 1975–1994, 2005–2007				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cancers outside the Lungs: Overall						
† Cohen et al. (2016)	Individuals aged ≤65 years who were hospitalized for incident MI between 1992–1993 in one of eight hospitals in central Israel.	LUR	NO _x (ppb)	International Classification of Diseases for Oncology (ICDO) codes: incidence cases of cancers of all sites (C00.0–C80.9); cancers located in the bronchus and the lung (ICDO codes: C34.0–C34.9), prostate gland (C61.9), kidney (C64.9) and bladder (C67.9)	Cox proportional hazards model	HR (95% CI) ^b
Isreal Study of First Acute Myocardial Infarction		Leave-one-out cross-validation r^2 = 0.74	Mean = 23.7 Min = 9.3 Max = 84.1		Adjusted for: Adjusted for age, sex, ethnicity, nSES, obesity at baseline, past smoker and smoking coded as a categorical time-dependent variable, incorporating assessments at baseline and follow-up interviews, 5 and 10–13 years post-MI (three categories: none-smoker, smoking up to 20 cigarettes per day and smoking more than 20 cigarettes per day	Cancer Incidence: 1.17 (0.94, 1.44) Cancer Mortality: 1.17 (0.86, 1.58) Lung, Prostate, Kidney, or Bladder Cancer Incidence: 1.35 (1.01, 1.79) Cancer Incidence - Excluding heavy smokers: 1.12 (0.91, 1.38) Cancer Mortality - Excluding heavy smokers: 1.23 (0.91, 1.67) Lung, Prostate, Kidney, or Bladder Cancer Incidence - Excluding heavy smokers: 1.37 (1.02, 1.84)
n = 1393		Averaging time: NO _x - annual average				
Israel		Exposure years: 1992–2011				
Enrollment: 1992–1993 Follow-up: 1997–1998; 2002–2005						
Cohort				International Classification of Diseases for Oncology (ICDO) codes: cancer mortality were identified through codes 140.0 to 239.9 (ICD-09) until 1998, or C00.0 to D48.0 (ICD-10) since 1999		

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Eum et al. (2019)	Medicare enrollees aged 65–120 years living in the conterminous United States	AQS	NO ₂ (ppb)	ICD-10 code C-D	Poisson regression model	MRR (95% CI) ^b
Medicare		Averaging time: NO ₂ - 12-month moving average	Median = 14.23 P25 = 9.69 P75 = 18.63		Adjusted for: Age, gender, and race-stratified and state-adjusted	All cancer: 1.02 (1.02, 1.03)
n = 14,100,000						All cancer - Center Region: 1.09 (1.08, 1.10)
Nationwide, U.S.		Exposure years: 2000–2008				All cancer - Center Region - Adjusted for PM _{2.5} : 1.09 (1.08, 1.11)
Enrollment: December 2000–December 2008						All cancer - West Region - Adjusted for PM _{2.5} : 0.97 (0.96, 0.98)
Follow-up: December 2000–December 2008						All cancer - West Region: 0.98 (0.98, 0.99)
Cohort						All cancer - East Region: 1.04 (1.03, 1.04)
						All cancer - Adjusted for PM _{2.5} : 1.02 (1.01, 1.02)
						All cancer - East Region - Adjusted for PM _{2.5} : 1.01 (1.01, 1.02)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Eum et al. (2022) Medicare n = 49,712,702 Nationwide, U.S. Enrollment: 2001–2008 Cohort	Open cohort of Medicare beneficiaries aged ≥65 years residing in the contiguous US between 2001 and 2008.	LUR 81% of the spatial ($r^2 = 0.81$), 73% of temporal ($r^2 = 0.73$), and 84% of the spatiotemporal variation ($r^2 = 0.84$) in monthly mean NO ₂ concentrations from 2000 to 2010, with an absolute average bias of 2.4 ppb; the model performance was lower in rural ($r^2 = 0.69$) as compared to urban ($r^2 = 0.80$) areas, suggesting greater exposure error for rural ZIP codes Averaging time: NO ₂ - 12-month moving average Exposure years: 2000–2008	NO ₂ (ppb) Mean = 10.9±6.44 Median = 9.14 (IQR 7.85) Min = 1.03 Max = 47.04 P25 = 6.16 P75 = 13.98	ICD-10 code C34	Cox proportional hazard model Adjusted for: strata for sex (male, female), race (white, non-white), age (1 year age categories with 90+ years old as one category), ZIP code and adjusted for ZIP code- and state-level SES by including the two SES variables as covariates	HR (95% CI) ^b All Cancer Mortality: 1.04 (1.03, 1.06) All cancer mortality - BC: 1.04 (1.03, 1.06) All cancer mortality - PM _{2.5} : 1.04 (1.03, 1.05)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Kang et al. (2023) n = 121,423 South Korea Follow-up: January 1, 2010, until death or the end of the study period (December 31, 2018), whichever was first. Cohort	All patients ≥40 years who met the definition of COPD during January 1, 2009 to December 31, 2009 were included. Individuals who died in 2009 or did not undergo a health screening exam between January 1, 2007 and December 31, 2009 were excluded. Additionally, participants with missing information on smoking status, BMI, or area of residence as well as participants whose air pollutant levels in their area of residence could not be estimated were excluded.	Spatiotemporal/geospatial model The performance of the kriging model was evaluated using 10-fold cross-validation (R ² of NO ₂ in 2009 was 0.50). Averaging time: NO ₂ - annual average Exposure years: January 1, 2009–December 31, 2013	NO ₂ (ppb) 1-year Median = 19.6 (36.9 µg/m ³) P25 = 16 (30 µg/m ³) P75 = 25.6 (48.2 µg/m ³) 3-year Median = 19.9 (37.5 µg/m ³) P25 = 16.2 (30.4 µg/m ³) P75 = 26.5 (49.8 µg/m ³) 5-year Median = 20.5 (38.5 µg/m ³) P25 = 16.2 (30.5 µg/m ³) P75 = 27.7 (52.1 µg/m ³)	ICD-10 code C34	Cox proportional hazard models Adjusted for: age (40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years), sex, income percentile (≤30th, 30–70th, and >70th), BMI (continuous), smoking status (never, former, and current), Charlson Comorbidity Index at the time of COPD diagnosis (continuous), and the presence of exacerbation (none, moderate, and severe) and stratified by Seoul, metropolitan cities, and others	HR (95% CI) ^b All cancer mortality - 1-year exposure lag: 0.90 (0.83, 0.99) All cancer mortality - 3-year exposure lag: 0.87 (0.79, 0.96) All cancer mortality - 5-year exposure lag: 0.88 (0.79, 0.99)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Li et al. (2023)	Middle-aged individuals from 22 centers in the UK were recruited for the UK Biobank study. Participants were excluded if they had incomplete air pollution data, cardiovascular disease or cancer at baseline, or subsequently dropped out of the study.	LUR, Hybrid model Method validation NR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2005–2007, 2010	NO ₂ (ppb) Decedents Mean = 15.77±4.8 (29.67±9.04 µg/m ³) Survivors Mean = 15.56±4.92 (29.28±9.26 µg/m ³) Total Mean = 15.6±4.92 (29.3±9.25 µg/m ³) NO _x (µg/m ³) Decedents Mean = 45.18±16.22 Survivors Mean = 43.94±15.58 Total Mean = 44.01±15.62	ICD-10 cancer codes C00-C97	Cox proportional hazard models Adjusted for: age, sex, ethnicity, UK Biobank assessment centre, education, alcohol consumption status, smoking status, BMI, average total household income, physical activity, prevalent diabetes, and prevalent hypertension	NO ₂ HR (95% CI) ^b Cancer Mortality: 1.16 (1.10, 1.22) NO _x HR (95% CI) ^c Cancer Mortality: 1.03 (1.01, 1.04)
Cancers outside the Lungs: Brain Cancer						

†Andersen et al. (2017a)	Participants who did not have cancer before cohort baseline (excluding nonmelanoma skin cancers)	LUR	NO ₂ (ppb)	National or regional cancer registries	Cox proportional hazard model	NO ₂
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Oslo Health Study (HUBRO), European Prospective Investigation into Cancer and Nutrition (EPIC)-Umeå, Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese, EPIC-Turin		Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2008–2011	CEANS Mean = 5.74±2.4 (10.8±4.6 µg/m ³) DCH Mean = 8.77±4 (16.5±7 µg/m ³) EPIC-NL Mean = 13.4±3.3 (25.2±6.2 µg/m ³) EPIC-Turin Mean = 28±5.47 (53±10.3 µg/m ³) EPIC-Umea Mean = 2.8±1.3 (5.3±2.5 µg/m ³) EPIC-Varese Mean = 23.1±9.19 (43.4±17.3 µg/m ³) HUBRO Mean = 11.1±4 (20.9±8 µg/m ³) VHM&PP Mean = 11±2.9 (20±5.5 µg/m ³) NO _x (µg/m ³) CEANS Mean = 19.1±10.2		Adjusted for: Age, sex, year of enrollment, education, occupation in petrochemical industry, area level SES Meta-analysis - DerSimonian-Laird Method Adjusted for: Age, sex, year of enrollment, education, occupation in petrochemical industry, area level SES	HR (95% CI) ^b Brain Cancer Incidence - Total Brain Tumor: 1.08 (0.70, 1.65) Brain Cancer Incidence - Benign Brain Tumor: 0.91 (0.53, 1.55) Brain Cancer Incidence - Overall: 1.08 (0.69, 1.67) NO _x HR (95% CI) ^b Brain Cancer Incidence - Total Brain Tumor: 1.01 (0.84, 1.22) Brain Cancer Incidence - Overall: 1.05 (0.86, 1.28) Brain Cancer Incidence - Benign Brain Tumor: 0.97 (0.75, 1.25)
N = 282,194						
Stockholm, Oslo, Umea, Copenhagen, Turin, Italy, Varese, Italy, Vorarlberg, Sweden, Denmark, Italy, Norway, Austria, Netherlands						
Recruitment: 1985–2005						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow-up: 12 years Cohort			DCH Mean = 27.2±18.5			
			EPIC-NL Mean = 37.9±12.3			
			EPIC-Turin Mean = 96.1±96.1			
			EPIC-Umea Mean = 8.8±5.8			
			EPIC-Varese Mean = 85.9±41.9			
			HUBRO Mean = 38.2±15.5			
			VHM&PP Mean = 40.1±9.6			

†Hvidtfeldt et al. (2023a)	Included all participants who were free of cancer at baseline (except non-melanoma skin cancer).	LUR	NO ₂ (ppb)	National cancer registries, death certificates, medical records, self-reports	Cox proportional hazard model	HR (95% CI) ^b Brain Cancer Incidence - Overall: 1.14 (0.90, 1.43)
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Dutch European Investigation into Cancer and Nutrition (EPIC-NL), Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N), Danish Nurse Cohort (DNC), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect		Averaging time: NO ₂ - annual average	DCH Cohort Mean = 14.9±3.7 (28.1±6.9 µg/m ³)		Adjusted for: Age, sex, year of baseline visit, smoking status, duration, intensity, BMI, marital status, employment status	
		Exposure years: 2010	DNC-1999 Cohort Mean = 13.7±4.5 (25.8±8.5 µg/m ³)			
			DNC-1993 Cohort Mean = 11.6±4 (21.8±8 µg/m ³)			
			E3N Cohort Mean = 14±5.2 (26.3±9.7 µg/m ³)			
			EPIC-MORGEN Cohort Mean = 18.3±3.2 (34.5±6.1 µg/m ³)			
			EPIC-Prospect Cohort Mean = 19.1±2.9 (35.9±5.4 µg/m ³)			
			Pooled Cohort Mean = 13.2±4 (24.9±8 µg/m ³)			
			SALT Cohort Mean = 11.3±3.3 (21.2±6.2 µg/m ³)			
			SDPP Cohort Mean = 8.18±2.3 (15.4±4.3 µg/m ³)			
N = 302,493						
Stockholm, Kungsholmen, Copenhagen, Aarhus, Vorarlberg, Sweden, France, Denmark, Austria, Netherlands						
Recruitment: 1985–2005						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow up: 2011–2015						
Cohort			SIXTY Cohort Mean = 10.9±3.2 (20.6±6.1 µg/m ³)			
			SNAC-K Cohort Mean = 14.6±2.7 (27.4±5.1 µg/m ³)			
			VHM&PP Cohort Mean = 12±2.8 (22±5.3 µg/m ³)			

†Jørgensen et al. (2016)	Participants were excluded due to cancer diagnosis before cohort baseline and missing address or geocode. Participants needed to be linked to the Central Population Register.	Dispersion model	NO ₂ (ppb)	ICD-10 codes for brain tumors, defined as primary tumors of the brain, meninges, and cranial nerves: C70.0, C71.0-C71.9, C72.2-C72.5, D32.0, D33.0-D33.2, D33.3, D42.0, D43.0-D43.2, D43.3; ICD-10 codes for subtypes by the location of the tumor: tumors of the brain ICD10: C71.0-C71.9, D33.0-D33.2, D43.0-D43.2, tumors of meninges: C70.0, D32.0 and D42.0; malignancy of tumours: malignant C70.0, C71.0-C71.9, C72.2-C72.5 and nonmalignant D32.0, D33.0-D33.2, D33.3, D42.0, D43.0-D43.2, D43.3	Cox proportional hazard model	NO ₂
Danish Nurse Cohort (DNC)		Averaging time: NO ₂ - annual average, NO _x - annual average	Brain Tumor - Cases Mean = 7.02±4.1 (13.2±7.8 µg/m ³)		Adjusted for: Age, other cancer diagnoses, date of death, emigration	HR (95% CI) ^b Brain Cancer Incidence - Type by location; Meninges: 1.55 (0.83, 2.90) Brain Cancer Incidence - Type by malignancy; Benign: 1.52 (0.93, 2.47) Brain Cancer Incidence - Type by location: Brain: 1.05 (0.53, 2.09) Brain Cancer Incidence - Type by malignancy; Malignant: 0.72 (0.28, 1.90) Brain Cancer Incidence - Overall: 1.24 (0.80, 1.93)
N = 28,731 n = 25,143 n brain tumor = 121 n no brain tumor = 25,022		Exposure years: 1971–2013	No Brain Tumor Mean = 6.7±4.3 (12.6±8.1 µg/m ³)			
Denmark			Total Mean = 6.7±4.3 (12.6±8.1 µg/m ³)			NO _x
Enrollment: 1993 or 1999 Follow-up: 2013			NO _x (µg/m ³)			HR (95% CI) ^c Brain Cancer Incidence- Overall: 1.02 (0.93, 1.12) Brain Cancer Incidence - Type by location; Brain: 1.01 (0.88, 1.16) Brain Cancer Incidence - Type by malignancy; Malignant: 0.98 (0.82, 1.18) Brain Cancer Incidence - Type by location; Meninges: 1.04 (0.91, 1.19) HR (95% CI) ^b Brain Cancer Incidence - Type by malignancy; Benign: 1.04 (0.93, 1.15)
Cohort			Brain Tumor - Cases Mean = 19.4±22.9			
			No Brain Tumor Mean = 19±24.3			
			Total Mean = 19±24.3			

† Poulsen et al. (2016)	Cases: identified from the Danish Cancer Registry; were all Danes, aged 18–85 years, registered with a benign or malignant tumor of the brain proper in the years 2000–2009. Inclusion of only first, primary tumors, thus excluding any with preceding tumors as well as metastases. It was required that cases had been born in Denmark and had a known address in Denmark at time of diagnosis	Dispersion model	NO _x (µg/m ³)	ICD10: C71, D330–D332, D430–D433	Logistic Regression	OR (95% CI) ^c
N = 12,201 Cases n = 4,183 Controls n = 8,018		Method validation NR	Cases Mean = 22 Median = 17		Adjusted for: Sex and year of birth	Brain Cancer Incidence - 10 years latency period: 1.01 (0.79, 1.28)
Denmark		Averaging time: NO _x - annual average	Min = 12 Max = 261 P5 = 14 P95 = 45	ICD10: C71, D330–D332, D430–D432	Adjusted for: Sex, year of birth, years of living in a major urban municipality	Brain Cancer Incidence - All Brain Tumors: 1.08 (0.84, 1.40)
Enrollment: 2000–2009		Exposure years: 1971–2009	Controls Mean = 22 Median = 17 Min = 12 Max = 250 P5 = 14 P95 = 46	ICD10: C71, D330–D332, D430–D434		Brain Cancer Incidence - Only exposure in the last 10 years prior to diagnosis - Urban adjusted: 1.24 (0.97, 1.59)
Case-Control	Controls: for each case, two random controls, matched on gender and year of birth, were selected from the CPR. Controls that were dead, emigrated or diagnosed with cancer before the diagnosis data of their matched case were excluded and substitute controls were sampled from surplus controls from the present study. All controls in the final sample were required to be born in Denmark and to be alive, cancer					Brain Cancer Incidence - Only exposure in the last 10 years prior to diagnosis: 1.20 (0.96, 1.52) Brain Cancer Incidence- 10 years latency period - Urban adjusted: 1.02 (0.79, 1.33) Brain Cancer Incidence - All Brain Tumors - Urban adjusted: 1.11 (0.84, 1.46)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
	free, and living at a known address in Denmark at time of diagnosis of their matched case.					

†Poulsen et al. (2020)	Identified all Danes aged 20 years or above with primary intracranial tumor in the period 1989 to 2014. Cases were not allowed to have other cancer diagnoses except nonmelanoma skin cancer, prior to their brain tumor.	Hybrid model	NO ₂ (ppb)	ICD-10 codes for all	Logistic Regression	NO ₂
Danish Cancer Registry, Danish Civil Registration System		Averaging time: NO ₂ - annual average	Cases Median = 13.6 (IQR 5.745) (25.6 µg/m ³ (IQR 10.81 µg/m ³) Min = 3.01 (5.66 µg/m ³) Max = 42 (79 µg/m ³) P5 = 5.522 (10.39 µg/m ³) P10 = 6.298 (11.85 µg/m ³) P25 = 7.86 (14.79 µg/m ³) P75 = 10.28 (19.35 µg/m ³) P90 = 16.59 (31.22 µg/m ³) P95 = 18.99 (35.74 µg/m ³) P99 = 25.65 (48.26 µg/m ³)	intracranial CNS tumor C70.0, C71.0-C71.9, C72.2, C72.5, D32.0,D33.0-D33.3,D42.0,D43.0-D43.3) and for the following subgroups: malignant tumors (prefix C), non-malignant tumors (prefix D), cranial nerves (C72.2, C72.5,D33.3,D43.3), meningioma (C70.0,D32.0,D42.0), glioma (morphology codes 9380/0–9480/9 within ICD10: C71.0-C71.9, D33.0-D33.3, D43.0-D43.2), malignant non-glioma brain tumors (all other morphologies within ICD10: C71.0-C71.9) and non-malignant non-glioma brain	Adjusted for: Matched on age, sex and month of birth and adjusted for marital status, occupational status, personal income, region of origin and area level information on percentage of parish population with income in lowest quartile, unemployed, manual labor, retired, basic education, living in social housing, owning their own dwelling, single parent families, previously convicted, of Danish origin	OR (95% CI) ^b Brain Cancer Incidence - Non-malignant: 1.04 (0.96, 1.13) Brain Cancer Incidence - Meningioma: 1.15 (1.03, 1.28) Brain Cancer Incidence - Non-malignant non-glioma tumors of the brain: 0.95 (0.82, 1.10) Brain Cancer Incidence - Intracranial CNS Tumors: 1.05 (0.99, 1.12) Brain Cancer Incidence - Glioma: 1.05 (0.95, 1.16) Brain Cancer Incidence - Cranial Nerves: 0.92 (0.76, 1.10) Brain Cancer Incidence - Malignant: 1.07 (0.99, 1.17) Brain Cancer Incidence - Malignant non-glioma tumors of the brain: 1.15 (0.97, 1.36)
N = 67,362 Cases: 22,454 Controls: 44,908	Cases and controls were excluded if they have no recorded address in Denmark at index date, less than 80% geocodable address history for the 10-year period preceding index date, and missing information on marital status, employment status, household disposable income or area of residence.	Exposure years: 1979–2014	Controls Median = 13.47 (IQR 5.729) (25.35 µg/m ³ (IQR 10.78 µg/m ³) Min = 3.02 (5.68 µg/m ³) Max = 39.25 (73.86 µg/m ³) P5 = 5.501 (10.35 µg/m ³) P10 = 6.266 (11.79 µg/m ³) P25 = 7.743 (14.57			NO _x
Denmark						OR (95% CI) ^c Brain Cancer Incidence - Meningioma: 1.01 (0.97, 1.05) Brain Cancer Incidence - Malignant non-glioma tumors of the brain: 1.05 (1.00, 1.11) Brain Cancer Incidence - Cranial Nerves: 0.97 (0.91, 1.04)
1989–2014						
Case-Control						

	$\mu\text{g}/\text{m}^3$ P75 = 10.19 (19.18 $\mu\text{g}/\text{m}^3$ P90 = 16.51 (31.06 $\mu\text{g}/\text{m}^3$ P95 = 18.98 (35.72 $\mu\text{g}/\text{m}^3$ P99 = 25.69 (48.33 $\mu\text{g}/\text{m}^3$ NO _x ($\mu\text{g}/\text{m}^3$) Cases Median = 25.15 (IQR 19.01) Min = 6.15 Max = 330.91 P5 = 11.48 P10 = 13.26 P25 = 17.34 P75 = 36.35 P90 = 51.35 P95 = 67.22 P99 = 115.37 Controls Median = 24.83 (IQR 18.86) Min = 6.13 Max = 270.31 P5 = 11.42 P10 = 13.17 P25 = 17.06 P75 = 35.92 P90 = 51.01 P95 = 67.33 P99 = 116.69	tumors (all other morphologies within ICD10:D33.0- D33.3, D43.0- D43.2)	Brain Cancer Incidence - Malignant: 1.03 (1.00, 1.06) Brain Cancer Incidence - Non- malignant: 1.00 (0.97, 1.03) Brain Cancer Incidence - Glioma: 1.02 (0.98, 1.05) Brain Cancer Incidence - Intracranial CNS Tumors: 1.01 (0.99, 1.03) Brain Cancer Incidence - Non- malignant non-glioma tumors of the brain: 1.00 (0.95, 1.04)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 Code 191; ICD-10 Code C71	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Brain Cancer Mortality: 0.98 (0.87, 1.11)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Weichenthal et al. (2020) Canadian Census Health and Environment Cohort (CanCHEC) N = 1,938,100 Toronto, Montreal, Canada Enrollment: 1991, 1996, 2001, 2006 Follow up: 2001–2016 Cohort	Included noninstitutionalized respondents under the age of 90 who lived in Toronto or Montreal for at least 1 year between 1998 and the end of follow up in 2016.	LUR Montreal $r^2 = 0.6$ Toronto $r^2 = 0.5$ Averaging time: NO ₂ - annual average Exposure years: 2006	NO ₂ (ppb) Mean = 20.2±8.43	ICD-10 code C71.0-C71.9	Cox proportional hazard model Adjusted for: Age, sex, immigrant status, census year, smoking, BMI, SES Adjusted for: Age, sex, immigrant status, census year	HR (95% CI) ^b Brain Cancer Incidence - Overall: 0.96 (0.89, 1.03) Brain Cancer Incidence - Co-adjusted for PM _{2.5} : 0.98 (0.90, 1.07) Brain Cancer Incidence - Co-adjusted for UFPs: 0.93 (0.83, 1.04) Brain Cancer Incidence - Co-adjusted for PM _{2.5} and UFPs: 0.94 (0.84, 1.05) Brain Cancer Incidence - All SES + PM _{2.5} + UFP + indirect adjustment for smoking and BMI: 0.99 (0.84, 1.16)

† Wu et al. (2020)	Men and women aged 45–75 years from five racial and ethnic groups residing in California. Participants were excluded who had a brain cancer or meningioma diagnosis before cohort entry and those with questionable address data and other invalid entry of exit dates	LUR, Spatiotemporal/geospatial model, Dispersion model	NR	State cancer registries, National death index, death certificates, Medicare	Cox proportional hazard model	NO ₂
The Multiethnic Cohort Study (MEC)					Adjusted for: Age, race, ethnicity, education, baseline BMI, hypertension, SES at baseline, current SES, smoking, occupation	HR (95% CI) ^c Brain Cancer Incidence - Latino Women - Kriging: 1.31 (0.27, 6.40) Brain Cancer Incidence - Overall - Kriging: 1.09 (0.56, 2.11) Brain Cancer Incidence - Women - LUR: 0.62 (0.31, 1.25) Brain Cancer, Malignant Glioma Incidence - Men - Kriging: 3.37 (0.99, 11.50) Brain Cancer, Meningioma Incidence - Women - Kriging: 0.99 (0.63, 1.56) Brain Cancer Incidence - Men - Kriging: 2.21 (0.77, 6.38) Brain Cancer, Meningioma Incidence - Men - Kriging: 1.02 (0.46, 2.25) Brain Cancer, Meningioma Incidence - Overall - LUR: 1.06 (0.75, 1.50) Brain Cancer Incidence - Latino Men - Kriging: 3.40 (0.56, 20.70) Brain Cancer, Meningioma Incidence - Men - LUR: 1.00 (0.50, 1.97) Brain Cancer, Malignant Glioma Incidence - Overall - Kriging: 1.65 (0.77, 3.58) Brain Cancer, Meningioma Incidence - Overall - Kriging: 1.02 (0.69, 1.50)
N = 103,308		Averaging time: NO _x month NO ₂ month				
California, U.S.		Exposure years: 1993–2013				
Enrollment: 1993–1996						
Follow-up: 2013						
Cohort						

Brain Cancer, Malignant Glioma
Incidence - Women - Kriging:
0.95 (0.35, 2.55)
Brain Cancer Incidence - Women -
Kriging:
0.64 (0.27, 1.48)
Brain Cancer Incidence - All Latino -
Kriging:
2.09 (0.64, 6.88)
Brain Cancer Incidence - Overall -
LUR:
0.86 (0.51, 1.43)
Brain Cancer, Meningioma Incidence
- Women - LUR:
1.09 (0.73, 1.62)
Brain Cancer Incidence - Men - LUR:
1.18 (0.56, 2.49)

NO_x

HR (95% CI)^c
Brain Cancer Incidence - Overall -
Kriging:
0.87 (0.51, 1.51)
Brain Cancer, Malignant Glioma
Incidence - Men - Kriging:
1.31 (0.52, 3.33)
Brain Cancer Incidence - Latino Men
- Kriging:
0.82 (0.22, 3.13)
Brain Cancer Incidence - Overall -
CALINE4:
0.89 (0.29, 2.73)
Brain Cancer, Malignant Glioma
Incidence - Overall - Kriging:
1.15 (0.61, 2.15)
Brain Cancer, Malignant Glioma
Incidence - Women - Kriging:
1.02 (0.43, 2.41)
Brain Cancer Incidence - Men -

Kriging:
 1.14 (0.49, 2.67)
 Brain Cancer Incidence - All Latino -
 Kriging:
 1.34 (0.52, 3.48)
 Brain Cancer Incidence - Latino
 Women - Kriging:
 2.09 (0.52, 8.46)
 Brain Cancer, Meningioma Incidence
 - Men - CALINE4:
 1.23 (0.30, 5.11)
 Brain Cancer Incidence - Men -
 CALINE4:
 1.05 (0.20, 5.46)
 Brain Cancer, Meningioma Incidence
 - Overall - CALINE4:
 1.52 (0.78, 2.98)
 Brain Cancer, Meningioma Incidence
 - Overall - Kriging:
 0.88 (0.63, 1.22)
 Brain Cancer, Meningioma Incidence
 - Men - Kriging:
 0.73 (0.39, 1.39)
 Brain Cancer, Meningioma Incidence
 - Women - Kriging:
 0.93 (0.63, 1.37)
 Brain Cancer Incidence - Overall -
 LUR:
 0.82 (0.52, 1.27)
 Brain Cancer Incidence - Women -
 Kriging:
 0.70 (0.34, 1.45)
 Brain Cancer Incidence - Women -
 CALINE4:
 0.79 (0.17, 3.65)
 Brain Cancer, Meningioma Incidence
 - Women - LUR:
 1.02 (0.73, 1.43)
 Brain Cancer Incidence - Men - LUR:
 0.94 (0.49, 1.82)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Brain Cancer, Meningioma Incidence - Women - CALINE4: 1.63 (0.76, 3.48) Brain Cancer, Meningioma Incidence - Men - LUR: 0.70 (0.42, 1.42) Brain Cancer Incidence - Women - LUR: 0.71 (0.39, 1.30) Brain Cancer, Meningioma Incidence - Overall - LUR: 0.95 (0.70, 1.27)
Cancers outside the Lungs: Childhood Cancers						

†Hall et al. (2019)	Childhood cancer cases diagnosed less than 6 years were gathered. Cancer-free controls were frequency matched to childhood cancer cases by birth year, but otherwise randomly selected from birth records.	Monitor data - California Air Resources Board Air Toxics Program monitoring data	NO ₂ (ppb)	Germ cell tumor cases were classified based on the International Classification of Childhood Cancer, Version 3 (ICCC-3) codes 101–105; histological subtypes of GCTs were identified via the International Classification of Diseases for Oncology, Version 3 (ICD-O-3) yolk sac tumors (ICD-O-3 code 9071	Logistic Regression	NO
California Cancer Registry (CCR)			Mean = 25.385±11.556		Adjusted for: Birth year, maternal age, maternal race, neighborhood-level SES	OR (95% CI) ^c
n = Cases: 243			IQR = 17.157			Childhood Cancer - Incidence of germ cell tumors - First trimester:
Controls: 147,100			Min = 1.35			0.98 (0.79, 1.23)
California, U.S.		Averaging time:	Max = 65.76			Childhood Cancer - Incidence of germ cell tumors - Second trimester:
1988–2013		NO ₂ - first trimester	P10 = 12.545			1.05 (0.86, 1.29)
Case-Control		NO ₂ - second trimester	P25 = 16.519			Childhood Cancer - Incidence of germ cell tumors - Entire Pregnancy:
		NO ₂ - entire pregnancy	P75 = 33.676			1.00 (0.74, 1.34)
		NO _x - first trimester	P90 = 42.269			NO ₂
		NO _x - second trimester	NO (ppm)			OR (95% CI) ^c
		NO _x - entire pregnancy	Mean = 28.136±21.537			Childhood Cancer - Incidence of germ cell tumors - Second trimester:
		NO - first trimester	IQR = 26.005			0.89 (0.62, 1.27)
		NO - second trimester	Min = 0.304			Childhood Cancer - Incidence of Yolk Sac Tumors - Entire pregnancy:
		NO - entire pregnancy	Max = 141.767			0.57 (0.33, 0.99)
			P10 = 7.182			Childhood Cancer - Incidence of germ cell tumors - First trimester:
			P25 = 12.293			0.87 (0.61, 1.24)
			P75 = 38.298			Childhood Cancer - Incidence of Yolk Sac Tumors - First trimester:
			P90 = 61.405			0.77 (0.47, 1.16)
			NO _x (ppb)			Childhood Cancer - Incidence of germ cell tumors - Entire Pregnancy:
		Exposure years: 1998–2013	Mean = 53.788±31.778			0.81 (0.56, 1.19)
			IQR = 41.94			Childhood Cancer - Incidence of Yolk Sac Tumors - Second trimester:
			Min = 3.137			0.69 (0.42, 1.14)
			Max = 202.484			NO _x
			P10 = 20.728			OR (95% CI) ^c
			P25 = 29.347			Childhood Cancer - Incidence of Yolk
			P75 = 71.286			
			P90 = 103.316			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Sac Tumors - First trimester: 0.97 (0.71, 1.31) Childhood Cancer - Incidence of Yolk Sac Tumors - Second trimester: 0.95 (0.66, 1.36) Childhood Cancer - Incidence of germ cell tumors - Entire Pregnancy: 0.95 (0.68, 1.33) Childhood Cancer - Incidence of Yolk Sac Tumors - Entire pregnancy: 0.78 (0.51, 1.20) Childhood Cancer - Incidence of Yolk Sac Tumors - First trimester: 0.93 (0.65, 1.35) Childhood Cancer - Incidence of Yolk Sac Tumors - Second trimester: 1.00 (0.75, 1.33) Childhood Cancer - Incidence of Yolk Sac Tumors - Entire pregnancy: 0.73 (0.46, 1.17) Childhood Cancer - Incidence of germ cell tumors - First trimester: 0.96 (0.73, 1.26) Childhood Cancer - Incidence of germ cell tumors - Second trimester: 1.03 (0.79, 1.33)

†Janitz et al. (2016)	Included children	LUR	NO ₂ (ppb)	International	Logistic Regression	OR (95% CI) ^c
Oklahoma Central Cancer Registry (OCCR)	diagnosed with acute leukemia under 20 years of age between the years of 1997 and 2012 in Oklahoma.	The authors observed high correlation between the data used to build the model (90%) and the model testing data (10%) ($r^2 = 0.78$ for model building data, $r^2 = 0.76$ for model testing data).	Mean = 6.65 Min = 1 Max = 23.27	Classification of Diseases of Oncology, Third Edition histology codes for both acute lymphoid leukemia (ALL) (9820, 9823, 9826, 9827, 9831–9837, 9940, 9948) and acute myeloid leukemia (AML) (9840, 9861, 9866, 9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9931)	Adjusted for: Maternal education	Childhood Cancer - All Leukemia Incidence, Q1 (1.00–7.04 ppb): Reference Childhood Cancer - All Leukemia Incidence, Q2 (7.05–8.82 ppb): 0.88 (0.61, 1.27) Childhood Cancer - All Leukemia Incidence, Q3 (8.83–11.18 ppb): 0.75 (0.52, 1.09) Childhood Cancer - All Leukemia Incidence, Q4 (11.19–19.89 ppb): 1.08 (0.75, 1.55)
Cases n = 307 Controls n = 1,013	Controls were selected from birth certificate records and matched to cases on week of birth.					Childhood Cancer - Acute myeloid leukemia incidence, Q1 (1.00–7.04 ppb): Reference Childhood Cancer - Acute myeloid leukemia incidence, Q2 (7.05–8.82 ppb): 1.17 (0.54, 2.56) Childhood Cancer - Acute myeloid leukemia incidence, Q3 (8.83–11.18 ppb): 1.28 (0.60, 2.71) Childhood Cancer - Acute myeloid leukemia incidence, Q4 (11.19–19.89 ppb): 1.28 (0.59, 2.80)
Oklahoma, U.S.		Averaging time: NO ₂ - annual average				Childhood Cancer - Acute lymphoid leukemia incidence, Q1 (1.00–7.04 ppb): Reference Childhood Cancer - Acute lymphoid
1997–2012		Exposure years: 2000–2010				
Case-Control						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						leukemia Incidence, Q2 (7.05–8.82 ppb): 0.85 (0.56, 1.29) Childhood Cancer - Acute lymphoid leukemia incidence, Q3 (8.83–11.18 ppb): 0.65 (0.42, 1.01) Childhood Cancer - Acute lymphoid leukemia incidence, Q4 (11.19–19.89 pb): 1.09 (0.72, 1.64)
†Kreis et al. (2022)	Included all incident cases of cancer diagnosed under the age of 16 years between 1990 and 2015 who were resident in Switzerland at time of diagnosis and could be linked to a record in the SNC. Children diagnosed with cancer prior to the first census of their lifetime were excluded.	Hybrid model The average adjusted r^2 of the annual models fitting model predictions against measurements was 0.69. Averaging time: NO ₂ - annual average Exposure years: 1990–2015	NO ₂ (ppb) Median = 11.9 (22.4 µg/m ³)	ICCC-3	Logistic Regression Adjusted for: neighborhood socio-economic position, level of urbanization, background ionizing radiation	HR (95% CI) ^b Childhood Cancer - All cancers incidence: 1.04 (0.93, 1.16) Childhood Cancer - Lymphoma incidence: 1.06 (0.80, 1.39) Childhood Cancer - Soft Tissue Sarcomas Incidence: 1.10 (0.70, 1.71) Childhood Cancer - Acute myeloid leukemia incidence: 1.66 (1.00, 2.75) Childhood Cancer - Leukemia incidence: 1.12 (0.91, 1.37) Childhood Cancer - Acute lymphoblastic leukemia incidence: 1.00 (0.79, 1.27) Childhood Cancer - CNS incidence: 0.93 (0.72, 1.18) Childhood Cancer - Malignant Bone Tumors Incidence: 0.89 (0.56, 1.40)

†Lavigne et al. (2017)	Pregnancies with postal codes of residence outside Ontario were excluded. Excluded subjects with missing date of birth, sex, 6-digit postal code value and/or exposure estimates.	LUR	NO ₂ (ppb)	International Classification of Childhood Cancer, 3rd Edition (ICCC-3): code 011 for ALL; code 0.32 for astrocytoma; code 061 for Wilms tumor	Cox proportional hazard model	HR (95% CI) ^c
Mother-Baby Linked (MOMBABY)		This model explained 73% of the variation in annual 2006 NO ₂ NAPS measurements.	Child's first year Mean = 20.7±9 IQR = 13.4		Adjusted for: Maternal age at delivery, infant sex, parity, year of birth, maternal cigarette smoking during pregnancy, census tract median family income, census tract proportion of population who are visibly minority and census tract proportion of the adult female population aged 25-64 years old who completed postsecondary education	Childhood Cancer - Wilms Tumor Incidence, Child's First Year: 0.93 (0.63, 1.39) Childhood Cancer - Acute Lymphoid Leukemia Incidence, Second Trimester: 1.11 (0.91, 1.36) Childhood Cancer - Acute Lymphoid Leukemia Incidence, Child's First Year: 0.98 (0.80, 1.21) Childhood Cancer - Acute Lymphoid Leukemia Incidence, Third Trimester: 0.95 (0.77, 1.17) Childhood Cancer - Acute Lymphoid Leukemia Incidence: 1.06 (0.94, 1.20) Childhood Cancer - Wilms Tumor Incidence, Third Trimester: 0.93 (0.63, 1.39) Childhood Cancer - Acute Lymphoid Leukemia Incidence, First Trimester: 1.20 (1.02, 1.41) Childhood Cancer - Astrocytoma Incidence, Second Trimester: 1.28 (0.83, 1.97) Childhood Cancer - Wilms Tumor Incidence: 1.06 (0.83, 1.34) Childhood Cancer - Wilms Tumor Incidence, First Trimester: 1.01 (0.70, 1.50) Childhood Cancer - Wilms Tumor Incidence, Second Trimester: 1.08 (0.74, 1.59) Childhood Cancer - Astrocytoma Incidence: 1.07 (0.84, 1.37)
N = 2,350,898						
Ontario, Canada			Entire pregnancy Mean = 20.7±8.3 IQR = 13.4			
1988–2012		Averaging time:				
Cohort		NO ₂ - first trimester	First trimester Mean = 21.1±9 IQR = 13.3			
		NO ₂ - second trimester				
		NO ₂ - third trimester	Second trimester Mean = 21.1±9 IQR = 13.2			
		NO ₂ - entire pregnancy				
		NO ₂ - child's 1st year	Third trimester Mean = 20.9±9 IQR = 13.3			
		Exposure years: 2005–2011				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
						Childhood Cancer - Astrocytoma Incidence, Third Trimester: 1.55 (1.02, 2.37) Childhood Cancer - Astrocytoma Incidence, First Trimester: 1.11 (0.72, 1.72) Childhood Cancer - Astrocytoma, Child's First Year: 1.31 (0.93, 1.84)

† Lavigne et al. (2020)	Children diagnosed with cancer between birth and 14 years of age. Excluded if pregnancies with residential postal codes outside Toronto or missing, as well as those without a valid health card number, with multiple births, or missing sex information.	LUR	NO ₂ (ppb)	ICCC-3 codes: code 011 for acute lymphoid leukemia, code 012 for acute myeloid leukemia, code 022-023 for non-Hodgkin lymphoma, code 031 for ependymoma, code 032 for astrocytoma, code 041 for neuroblastoma, code 050 for bilateral retinoblastoma, code 061 for Wilms tumors, code 071 for hepatoblastoma, code 091 for rhabdomyosarcoma, code 101-105 for germ cell tumors; ICD-O codes 9470-9472, 9474, and 9480 for medulloblastoma, and code 9473 for primitive neuroectodermal tumors	Cox proportional hazard model Adjusted for: distributed lag weekly exposures during the pregnancy period, distributed lag monthly exposures after birth, maternal age at delivery, infant sex, parity, year of birth, maternal cigarette smoking during pregnancy using multiple imputation, dissemination area median family income, dissemination area proportion of population who are visible minority and dissemination are proportion of the adult female population aged 25-64 years old who completed postsecondary education	HR (95% CI) ^c Childhood Cancer - Acute lymphoblastic leukemia incidence, childhood exposure: 1.24 (0.73, 2.10) Childhood Cancer - Acute lymphoblastic leukemia incidence, entire pregnancy: 0.84 (0.49, 1.46) Childhood Cancer - All cancers incidence, Childhood Exposure: 1.06 (0.85, 1.33) Childhood Cancer - All cancers incidence, childhood exposure - UFPs + NO ₂ : 0.97 (0.92, 1.03) Childhood Cancer - Acute myeloid leukemia incidence, entire pregnancy: 1.16 (0.35, 3.89) Childhood Cancer - All cancers incidence, Entire Pregnancy: 0.88 (0.69, 1.12) Childhood Cancer - All cancers incidence, entire pregnancy - UFPs + NO ₂ : 1.00 (0.91, 1.12) Childhood Cancer - Acute myeloid leukemia incidence, childhood exposure: 1.37 (0.44, 4.28) Childhood Cancer - All cancers, childhood exposure – UFPs + NO ₂ + PM _{2.5} : 0.97 (0.92, 1.04) Childhood Cancer - All cancers, entire pregnancy – UFPs + NO ₂ + PM _{2.5} : 1.01 (0.92, 1.13)
Better Outcomes Registry Network (BORN) Ontario, Mother-Baby Linked (MOMBABY)		Averaging time: Other - Weekly	IQR = 11.4			
N = 653,702		Exposure years: 2010–2011				
Toronto, Ontario, Canada						
1998–2017						
Cohort						
Cancers outside the Lungs: Gastrointestinal Cancer						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Chen et al. (2023)	Included 5,747 individuals with IBD and excluded participants with missing air pollutants data, participants who died within the first year of follow-up, participants who had any cancer at baseline or had GI cancer within the first-year follow-up, or participants who moved to another address at repeat assessments.	LUR	NO ₂ (ppb)	Longitudinal medical records via linkage to external national data including inpatient data, cancer registry data and death data	Cox proportional hazard model	NO ₂
UK Biobank		The LUR showed good model performance in London, with cross-validation R ² of 87% for NO ₂ and 88% for NO _x	NO ₂ Mean = 15±4.7 (29±8.9 µg/m ³) Median = 14.8 (IQR 5.53) (27.9 µg/m ³) Min = 5.3 (10 µg/m ³) Max = 46 (86.6 µg/m ³)		Adjusted for: Age, sex, ethnicity, assessment centers, household income, smoking status, education, BMI, physical activity, healthy diet, alcohol consumption, baseline related surgery history, medication	HR (95% CI) ^b Gastrointestinal Cancer - Overall incidence for CD: 0.84 (0.37, 1.92) Gastrointestinal Cancer - Overall incidence for UC: 1.17 (0.77, 1.78) Gastrointestinal Cancer - Overall incidence for IBD: 1.05 (0.73, 1.53)
N = 4,708		Averaging time: NO ₂ - annual average	NO _x (µg/m ³)			NO _x
England, Scotland, Wales, U.K.		Exposure years: 2005–2007, 2010	NO _x Mean = 43.9±15.2 Median = 42 (IQR 15.6) Min = 19.7 Max = 247.5			HR (95% CI) ^b Gastrointestinal Cancer - Overall incidence for UC: 1.03 (0.83, 1.28) Gastrointestinal Cancer - Overall incidence for CD: 0.86 (0.56, 1.31) Gastrointestinal Cancer - Overall incidence for IBD: 0.98 (0.81, 1.18)
Recruitment: 2006–2010						
Follow-up: mean of 12 years						
Cohort						

†Nagel et al. (2018)	Lymphomas/myelomas/leukemias were excluded according to the ICDO-3.	LUR	NO ₂ (ppb)	ICD-9 and ICD-10 codes: gastric cancer C16 [ICD10] and 151 [ICD9], and for UADT cancers: C01–06 and 141–145 (oral cavity), C09, C10 (oropharynx), C12, C13 (hypopharynx) and 146 (pharynx), C14, C32, and 161 (larynx), C15 and 150 (esophagus). Lymphomas/myelomas/leukemias were excluded according to the International Classification of Diseases for Oncology (ICDO-3) 9590–9989	Cox Proportional Regression	NO ₂
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Oslo Health Study (HUBRO), EPIC-Oxford, European Prospective Investigation into Cancer and Nutrition (EPIC)-Umea, Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect, EPIC-Varese, EPIC-Turin, EPIC-San Sebastian, Italian Studies of Respiratory Disorders in Childhood and Environment (SIDRIA-Rome)		The LUR models were validated and previously linked to lung cancer and other cancer sites. Averaging time: NO ₂ - annual average Exposure years: 2008-2011	CEANS Mean = 5.74±2.4 (10.8±4.6 µg/m ³) DCH Mean = 8.72±4 (16.4±7 µg/m ³) EPIC-Netherlands Mean = 13.4±3.3 (25.2±6.2 µg/m ³) EPIC-Oxford Mean = 13±4 (24.5±8 µg/m ³) EPIC-San Sebastian Mean = 12.6±3.5 (23.8±6.6 µg/m ³) EPIC-Turin Mean = 28.3±5.74 (53.2±10.8 µg/m ³) EPIC-Turin-Varese Mean = 25.5±8.34 (47.9±15.7 µg/m ³) EPIC-Umea Mean = 2.8±1.3 (5.2±2.5 µg/m ³) EPIC-Varese Mean = 23.1±9.19 (43.5±17.3 µg/m ³) HUBRO		Adjusted for: Age, Sex, calendar time, smoking status, smoking intensity, smoking duration, occupational exposure, employment status, educational level, area level SES	NO ₂ HR (95% CI) ^b Gastrointestinal Cancer - UADT Cancer Incidence: 0.93 (0.75, 1.14) Gastrointestinal Cancer - Gastric Cancer Incidence: 1.04 (0.84, 1.28) NO _x HR (95% CI) ^b Gastrointestinal Cancer - Gastric Cancer Incidence: 1.04 (0.94, 1.16) Gastrointestinal Cancer - UADT Cancer Incidence: 0.99 (0.90, 1.08)
N = 323,807						
Stockholm, London, Rome, Oslo, Copenhagen, Varese, Italy, Vorarlberg, Oxford, UK, San Sebastian, Spain, Umeå, Turin,						

Sweden, United Kingdom, Denmark, Spain, Italy, Norway, Austria, Netherlands	Mean = 11.1±4 (20.9±8 µg/m ³)
Recruitment: 1990s Follow-up: 2000s–2010s	SIDRIA-Rome Mean = 21±5 (39±9 µg/m ³)
Cohort	VHM&PP Mean = 10.6±2.9 (19.9±5.5 µg/m ³)
	NO _x (µg/m ³)
	CEANS Mean = 19±10.1
	DCH Mean = 26.8±18.4
	EPIC-Netherlands Mean = 37.9±11.3
	EPIC-Oxford Mean = 40.9±15.6
	EPIC-San Sebastian Mean = 47.2±12.5
	EPIC-Turin Mean = 96.4±21
	EPIC-Turin-Varese Mean = 91.2±35.5
	EPIC-Umea Mean = 8.7±5.8
	EPIC-Varese Mean = 86.1±41.8

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			HUBRO Mean = 38.3±15.4			
			SIDRIA-Rome Mean = 82.1±23.7			
			VHM&PP Mean = 39.9±9.5			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
† Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code 150; ICD-10 code C15 ICD-9 code 151; ICD-10 code C16 ICD-9 code 153-154; ICD-10 code C18-C21 ICD-9 code 156; ICD-10 code C23-C24 ICD-9 code 157; ICD-10 code C25	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Gastrointestinal Cancer - Esophageal Cancer Mortality: 1.03 (0.89, 1.20) Gastrointestinal Cancer - Stomach Cancer Mortality: 1.08 (0.94, 1.24) Gastrointestinal Cancer - Colorectal Cancer Mortality: 1.09 (1.03, 1.16) Gastrointestinal Cancer - Gallbladder Cancer Mortality: 1.00 (0.78, 1.28) Gastrointestinal Cancer - Pancreatic Cancer Mortality: 1.06 (0.98, 1.15)
Cancers outside the Lungs: Kidney Cancer						

† Hvidtfeldt et al. (2022)	We included all participants without any previous cancer at baseline (with the exception of non-melanoma skin cancer).	LUR	NR	ICD-9 code 189.0; ICD-10 code C64	Cox proportional hazard model	HR (95% CI) ^b Kidney parenchyma cancer: 1.06 (0.86, 1.30)
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Dutch European Investigation into Cancer and Nutrition (EPIC-NL), Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'éducation Nationale (E3N), Danish Nurse Cohort (DNC), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect		A large fraction of measured spatial variation in the annual average concentration in HOV was explained (59% for NO ₂).			Adjusted for: Age, sex, year of baseline visit, BMI, smoking status, duration, intensity, marital status, employment status	
N = 302,493		Averaging time: NO ₂ - annual average				
Stockholm, Kungsholmen, Vorarlberg, Sweden, France, Denmark, Austria, Netherlands		Exposure years: 2009–2010				
Enrollment: 1985–2005 Follow up: 2011–2015						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cohort						

†Raaschou-Nielsen et al. (2016)	Adults cohort participants from the ESCAPE study with primary cancer, not metastases.	LUR	NO ₂ (ppb)	ICD-10/ICD-O3 code C64	Cox proportional hazard model	NO ₂
European Study of Cohorts for Air Pollution Effects (ESCAPE)		Averaging time: NO ₂ - annual average, NO _x - annual average	CEANS, Stockholm, Sweden Mean = 5.69 (10.7 µg/m ³)		Adjusted for: Age, sex, calendar time, smoking status, smoking intensity, smoking duration, occupation/employment status, educational level, BMI, hypertension, area-level SES	HR (95% CI) ^b Kidney parenchyma cancer incidence, Overall: 1.08 (0.85, 1.37)
n = 289,002						
Sweden, England, Denmark, Spain, Italy, Norway, Austria, Netherlands		Exposure years: October 2008 and April 2011	DCH, Copenhagen, Denmark Mean = 8.72 (16.4 µg/m ³)			NO _x HR (95% CI) ^c Kidney parenchyma cancer incidence, Overall: 1.03 (0.93, 1.14)
Study years NR			EPIC-NL, Netherlands Mean = 13.4 (25.2 µg/m ³)			
Cohort			EPIC-Oxford, London/Oxford, United Kingdom Mean = 13 (24.4 µg/m ³)			
			EPIC-San Sebastian, San Sebastian, Spain Mean = 12.6 (23.8 µg/m ³)			
			EPIC-Turin, Turin, Italy Mean = 28.3 (53.2 µg/m ³)			
			EPIC-Umea , Umea , Sweden Mean = 2.8 (5.2 µg/m ³)			
			EPIC-Varese,			

Varese, Italy
Mean = 23.1 (43.5
 $\mu\text{g}/\text{m}^3$)

HUBRO, Oslo,
Norway
Mean = 11.1 (20.9
 $\mu\text{g}/\text{m}^3$)

VHM&PP,
Vorarlberg, Austria
Mean = 10.6 (19.9
 $\mu\text{g}/\text{m}^3$)

NO_x ($\mu\text{g}/\text{m}^3$)

CEANS, Stockholm,
Sweden
Mean = 18.9

DCH, Copenhagen,
Denmark
Mean = 26.8

EPIC-NL,
Netherlands
Mean = 37.9

EPIC-Oxford,
London/Oxford,
United Kingdom
Mean = 40.8

EPIC-San Sebastian,
San Sebastian, Spain
Mean = 47.2

EPIC-Turin, Turin,
Italy
Mean = 96.4

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			EPIC-Umea , Umea , Sweden Mean = 8.7			
			EPIC-Varese, Varese, Italy Mean = 86.7			
			HUBRO, Oslo, Norway Mean = 38.2			
			VHM&PP, Vorarlberg, Austria Mean = 39.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code 189; ICD-10 code C64-66, C68	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Kidney Cancer Mortality: 0.98 (0.84, 1.16)
Cancers outside the Lungs: Laryngeal Cancer						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
†Turner et al. (2017) Cancer Prevention Study II (CPS-II) N = 623,048 United States, Puerto Rico Enrollment: 1982 Follow up: 1982–2004 Cohort	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code 161; ICD-10 code C32	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Laryngeal Cancer: 1.11 (0.80, 1.54)

†Wang et al. (2023)						
UK Biobank	We excluded participants with laryngeal cancer at baseline or who were missing data on exposure to any air pollutants.	LUR	NO ₂ (ppb)	ICD code C32	Cox proportional hazard model	NO
N = 418,914		Averaging time: NO ₂ - annual average	Quantile 1 Mean = 9.14±1.4 (17.2±2.6 µg/m ³)		Adjusted for: Age, sex, ethnicity, work, education, income, physical activity, drinking status, smoking status, BMI, SBP, hypertension at baseline, diabetes at baseline	HR (95% CI) ^c Laryngeal Cancer - Overall, per SD increase: 1.16 (1.11, 1.21)
England, Scotland, Wales, U.K.		Exposure years: 2010–2011	Quantile 2 Mean = 12±1.1 (22.6±2.1 µg/m ³)			NO ₂
Recruitment: 2006–2010			Quantile 3 Mean = 14±1.2 (26.3±2.2 µg/m ³)			HR (95% CI) ^b Laryngeal Cancer - Overall, per SD increase: 1.18 (1.12, 1.24)
Follow up: median period of 12.5 years			Quantile 4 Mean = 16±1.2 (30±2.3 µg/m ³)			
Cohort			Quantile 5 Mean = 19.9±3.2 (37.4±6.1 µg/m ³)			
			NO (µg/m ³)			
			Quantile 1 Mean = 26.8±4.4			
			Quantile 2 Mean = 36.3±3.7			
			Quantile 3 Mean = 42.4±3.7			
			Quantile 4 Mean = 48.7±4.2			
			Quantile 5 Mean = 66.3±17.2			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Cancers outside the Lungs: Liver Cancer						

†Pedersen et al. (2017)	Excluded participants with a cancer (except non-melanoma skin cancer) before enrollment or for whom information about exposure to air pollution or the most important potential confounders could not be obtained.	LUR	NO ₂ (ppb)	ICD-10 codes or ICD-O code	Cox proportional hazard model	NO ₂
Danish Diet, Cancer and Health (DCH), European Study of Cohorts for Air Pollution Effects (ESCAPE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), EPIC-Varese, EPIC-Turin		NO ₂ and NO _x were measured at 40 sites selected to represent spatial variation of air pollution in the residential areas of the participants in each of the study areas.	DCH Cohort Mean = 8.72±4 (16.4±7 µg/m ³) P5 = 4.4 (8.2 µg/m ³) P95 = 16 (30.1 µg/m ³)	C22.0, C22.1 C22.2, C22.3, C22.4, C22.7 and C22.9	Adjusted for: Age, sex, calendar year, smoking status, alcohol, occupational exposure, employment status, education, area-specific SES	HR (95% CI) ^b Liver Cancer Incidence, DCH Cohort: 1.24 (0.63, 2.45) Liver Cancer Incidence, VHM&PP Cohort: 1.28 (0.78, 2.09) Liver Cancer Incidence, EPIC-Varese, EPIC-Turin: 1.06 (0.61, 1.82) Liver Cancer Incidence, Overall: 1.20 (0.87, 1.64)
N = 174,770			EPIC-Turin Cohort Mean = 28.8±6.22 (54.1±11.7 µg/m ³) P5 = 18.3 (34.4 µg/m ³) P95 = 37 (69.7 µg/m ³)			NO _x
Copenhagen, Turin, Italy, Varese, Italy, Vorarlberg, Denmark, Italy, Austria		Averaging time: NO ₂ - annual average				HR (95% CI) ^c Liver Cancer Incidence, DCH Cohort: 1.02 (0.78, 1.32) Liver Cancer Incidence, Overall: 1.12 (0.96, 1.30) Liver Cancer Incidence, VHM&PP Cohort: 1.33 (1.00, 1.77) Liver Cancer Incidence, EPIC-Varese, EPIC-Turin: 1.07 (0.84, 1.37)
Enrollment: 1985–2005 Follow-up: mean of 17 years		Exposure years: 2008–2011	EPIC-Varese Cohort Mean = 23.1±9.19 (43.5±17.3 µg/m ³) P5 = 7.39 (13.9 µg/m ³) P95 = 31.8 (59.9 µg/m ³)			
Cohort			VHM&PP Cohort Mean = 10.6±2.9 (19.9±5.5 µg/m ³) P5 = 5.74 (10.8 µg/m ³) P95 = 15.5 (29.2 µg/m ³)			
			NO _x (µg/m ³)			
			DCH Cohort Mean = 26.8±18.4 P5 = 7.2 P95 = 66			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
			EPIC-Turin Cohort Mean = 99.5±26.3 P5 = 62.9 P95 = 140.9			
			EPIC-Varese Cohort Mean = 86.1±41.8 P5 = 15.6 P95 = 124.3			
			VHM&PP Cohort Mean = 40±9.6 P5 = 25.8 P95 = 57.6			

†So et al. (2021)						
Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS), Danish Diet, Cancer and Health (DCH), Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'éducation Nationale (E3N), Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Dutch European Investigation into Cancer and Nutrition (EPIC-NL), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE Study (60YO/IMPROVE), Stockholm Diabetes Prevention Program (SDPP), EPIC Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN), EPIC-Prospect	Excluded persons with any cancer diagnosis before cohort baseline. Excluded those with missing information on the date of start or end of follow-up, cancer before enrollment, missing information on prevalent cancer status, with missing air pollution exposure data, missing data on the individual level and area level risk factors.	LUR The model explained spatial variation in the measured concentration well; the R2 for NO ₂ was 0.59. Averaging time: NO ₂ - annual average Exposure years: 1985–2005	NO ₂ (ppb) Air Pollutants for the year 2010 Liver Cancer Mean = 13.2±3.9 (24.8±7.4 µg/m ³) No Liver Cancer Mean = 13.2±4 (24.9±8 µg/m ³) Total Mean = 13.2±4 (24.9±8 µg/m ³)	ICD-9 code 155 or ICD-10 code C22	Cox proportional hazard model Adjusted for: Age, sex, subcohort, calendar year of baseline, smoking status, employment status, and mean income at the neighborhood level in 2001	HR (95% CI) ^b Liver Cancer Incidence, <40 µg/m ³ : 1.41 (1.06, 1.88) Liver Cancer Incidence with O ₃ : 0.91 (0.63, 1.32) Liver Cancer Incidence with BC: 1.45 (0.77, 2.73) Liver Cancer Incidence, <30 µg/m ³ : 1.06 (0.70, 1.59) Liver Cancer Incidence with PM _{2.5} : 1.39 (0.99, 1.94) Liver Cancer Incidence, <20 µg/m ³ : 1.02 (0.35, 2.96) Liver Cancer Incidence: 1.34 (1.03, 1.75)
N = 330,064						
Stockholm, Kungsholmen, Copenhagen, Aarhus, Vorarlberg, Stockholm County, Sweden, France, Denmark, Austria, Netherlands						
Enrollment: 1985–2005						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and confounders	Effect Estimate (95% CI)
Follow-up: 2011–2015						
Cohort						
† Turner et al. (2017)	Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. Participants were excluded from analysis because of missing or invalid residence information (n = 385,422) or selected base-line covariate data (n = 130,119) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment.	LUR A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and about 4 million satellite-based measurements in an approximate 10 km x 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model r ² = 0.78) Averaging time: NO ₂ - annual average Exposure years: 1982–2004	NO ₂ (ppb) Mean = 11.6±5.1 Median = 10.8 Min = 1 Max = 37.6 P5 = 5.1 P25 = 8.1 P75 = 14.1 P95 = 21.2	ICD-9 code 155; ICD-10 code C22	Cox proportional hazard model Adjusted for: Age, race/ethnicity, baseline values of education, marital status, BMI, BMI squared, smoking status, cigarettes per day, cigarettes per day squared, duration of smoking squared, age started smoking, passive smoking, vegetable, fruit, fiber consumption, fat consumption, alcohol consumption, industrial exposures, occupation dirtiness index, 1990 ecological covariates	HR (95% CI) ^b Liver Cancer Mortality: 1.05 (0.89, 1.22)
Cancer Prevention Study II (CPS-II)						
N = 623,048						
United States, Puerto Rico						
Enrollment: 1982						
Follow up: 1982–2004						
Cohort						

List of abbreviations in alphabetical order: BC = black carbon; BMI = body mass index; CI = confidence interval; EC = elemental carbon; HR = hazard ratio; ICD = international classification of diseases; ICCC-3 = International Classification of Childhood Cancer, 3rd Edition; ICDO = International Classification of Diseases for Oncology; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; O₃ = ozone; OR = odds ratio; P5 = 5th percentile; P10 = 10th percentile; P25 = 25th percentile; P75 = 75th percentile; P95 = 95th percentile; ppb = parts per billion; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; RR = rate ratio; SES = socioeconomic status; TWA = time weighted average

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time

^cEstimates are not standardized

[†]Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 12-4 Toxicological studies of oxides of nitrogen exposure and genotoxicity assessed in vivo

Study Details and Population	Exposure Details	Endpoints Examined*
Gooch et al. (1977)	Whole body inhalation with filtered air controls	0 d after exposure Chromosome aberration frequency (NS)
Mouse (C3H) age not reported, males number of animals per group not reported	100 ppb (0.1 ppm) NO ₂ , continuous for 6 hr 1,000 ppb (1 ppm) NO ₂ , continuous for 6 hr 5,000 pbb (5 ppm) NO ₂ , continuous for 6 hr 10,000 ppb (10 ppm) NO ₂ , continuous for 6 hr	7 d after exposure - Chromosome aberration frequency (NS) 14 d after exposure - Chromosome aberration frequency (NS)
Victorin et al. (1990)	Whole body inhalation with unclear control conditions	7 hr after exposure Micronucleus assay (NS)
Mouse (NMRJ) 9–12-wk-old, males n = 3/group	20,000 ppb (20 ppm) NO ₂ , continuous for 23 hr	

List of abbreviations in alphabetical order: d = day; hr = hour; n = sample size; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million

*Simplified results interpreted as: NS = no experimental groups were significantly different from control.

Appendix Table 12-5 Toxicological studies of oxides of nitrogen exposure and genotoxicity assessed in vitro

Study Details	Population and Exposure Details	Endpoints Examined*
Arroyo et al. (1992)	Bacterial cells (<i>S. typhimurium</i> , strain TA1535) with appropriate control conditions Replicates reported as: n = 3 Experiment 1: 0–90,000 ppb (0–90 ppm) NO for 30 min Experiment 2: 0–60,000 ppb (0–60 ppm) NO ₂ for 30 min Experiment 3: 10,000 ppb (10 ppm) NO for 0–140 min	Experiment 1 - Ames Test (reverse mutation) (↑) Experiment 2 - Ames Test (reverse mutation) (↑) Experiment 3 - Ames Test (reverse mutation) (↑)
Gorsdorf et al. (1990)	Hamster cells (Chinese hamster V79) with appropriate control conditions Replicates reported as: n = 2–6 Experiment 1: 0–200,000 ppb (0–200 ppm) NO ₂ for 5–30 min Experiment 2: 0–500,000 ppb (0–500 ppm) NO for 5–30 min	Experiment 1 - DNA single-strand breaks (↑) Experiment 2 - DNA single-strand breaks (NS)
Koehler et al. (2010)	Human cells (primary nasal epithelial) with appropriate control conditions Replicates reported as: n = 10 0–10,000 ppb (0–10 ppm) NO ₂ for 30 min	- Comet assay (DNA fragmentation/migration) (↑) - Micronucleus assay (double nucleated cells) (NS)
Koehler et al. (2011)	Human cells (primary nasal epithelial) with appropriate control conditions Replicates reported as: n = 10 100 ppb (0.1 ppm) NO ₂ for 0.5–3 hr	- Comet assay (DNA fragmentation/migration) (↑) - Micronucleus assay (double nucleated cells) (↑)
Koehler et al. (2013)	Human cells (primary nasal epithelial) with appropriate control conditions Replicates reported as: n = 10 10 ppb (0.01 ppm) NO ₂ for 0.5–3 hr	- Comet assay (DNA fragmentation/migration) (↑) - Micronucleus assay (double nucleated cells) (↑)
Nguyen et al. (1992)	Human cells (TK6 lymphoblasts) with appropriate control conditions Replicates reported as: Not specified, but mean values presented	- DNA single-strand breaks (↑) - TK mutation test (forward mutations) (↑)

Study Details	Population and Exposure Details	Endpoints Examined*
	0–0.375 mL NO gas/mL culture media NO for 1 hr	
Shiraishi and Bandow (1985)	Hamster cells (Chinese hamster V79) with appropriate control conditions Replicates reported as: n = 2 independent experiments 0–8,000 ppb (0–8 ppm) NO ₂ for 2 hr	Sister chromatid exchange (↑)
Victorin et al. (1990)	Fruit fly (<i>D. melanogaster</i>) with appropriate control conditions Replicates reported as: n = 10 50,000 ppb (50 ppm) NO ₂ for 27 hr	Wing spot test (somatic mutation and recombination) (NS)

List of abbreviations in alphabetical order: hr = hour; min = minute; n = sample size; mL = milliliter; NO₂ = nitrogen dioxide; ppb = parts per billion; ppm = parts per million.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ↑ = at least one experimental group had a statistically significant increase.

A.11. Health Effects with Limited Evidence

Appendix Table 13-1 Epidemiologic studies of oxides of nitrogen exposure and health effects with limited evidence

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Immune Effects						
† Burte et al. (2018) European Community Respiratory Health Survey (ECRHS), Epidemiologic Study on the Genetics and Environment of Asthma (EGEA) n = 1,533 Sweden, France, England, Denmark, Spain, Italy, Belgium, Switzerland, Iceland, Norway, Germany, Estonia, Netherlands 2000–2007 Cohort	Young adult participants from two European cohorts	LUR Averaging time: NO ₂ - annual average Exposure years: October 2008 and April 2011	NO ₂ (µg/m ³) Mean = 29.3±15.1	Questionnaire	Poisson regression Adjusted for: age, sex, number of siblings, family history of allergy, smoking status, educational level - as a proxy of socio-economic status - and asthma status	IRR (95% CI) ^c Rhinitis: 1.00 (0.91, 1.09) Rhinitis - PM _{2.5} : 1.01 (0.84, 1.17) Rhinitis in asthmatics: 1.09 (0.84, 1.39) Rhinitis in non-asthmatics: 0.99 (0.90, 1.08) Rhinitis in smokers: 0.96 (0.85, 1.07) Rhinitis in non-smokers: 1.10 (0.99, 1.22) Rhinitis in women: 0.99 (0.88, 1.10) Rhinitis in men: 1.04 (0.92, 1.16)
† Burte et al. (2020) European Community Respiratory Health Survey (ECRHS), Epidemiologic Study on the Genetics and Environment of Asthma (EGEA) n = 1,408	Patients with asthma—adults or children—enrolled from hospital chest clinics, their first-degree relatives, and controls who were recruited from other hospital wards or from electoral lists	LUR Averaging time: NO ₂ - annual average Exposure years: 2009–2010	NO ₂ (µg/m ³) Mean = 29.9±14.6	Questionnaire	Polytomous logistic regression Adjusted for: age, sex, smoking status, asthma, and allergic sensitization	OR (95% CI) ^c Rhinitis, mild: 1.15 (1.02, 1.30) Rhinitis, moderate: 1.17 (1.02, 1.44) Rhinitis, severe: 1.14 (1.00, 1.53) Rhinitis, mild without allergic sensitization: 1.24 (1.06, 1.64) Rhinitis, moderate without allergic sensitization: 1.29 (1.09, 1.29) Rhinitis, severe without allergic sensitization: 1.38 (1.16, 1.64)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
European Region, Sweden, France, England, Denmark, Spain, Italy, Belgium, Switzerland, Norway, Germany, Estonia, Netherlands EGEA: enrolled between 1991 and 1995. The first follow-up was conducted between 2003 and 2007 and the second between 2011 and 2013 ECRHS: recruited 1992–1994, followed up 2000–2002, and 2011–2013. Included in the analysis are those from 2011–2013 Cross-Sectional						Rhinitis, mild without asthma: 1.14 (1.00, 1.29) Rhinitis, moderate without asthma: 1.37 (1.17, 1.59) Rhinitis, severe without asthma: 1.19 (1.03, 1.39)
† Chung et al. (2016) Taiwan National Health Insurance Research Database (NHIRD) n = 9,960 Taiwan 2007–2011 Cross-Sectional	Preschool children aged 0–6 years	Fixed site monitor Averaging time: NO _x - 24-hour average Exposure years: 2007–2011	NO _x (ppb) Mean = 19.6±5.72 Median = 20.5 Min = 2.33 Max = 29.7 P25 = 16.1 P75 = 22.9	ICD codes	Logistic regression Adjusted for: variables that may have been effective in incidence (e.g., age or gender)	OR (95% CI) ^c Allergic rhinitis Level 2: one-week: 1.83 (1.38, 2.53) Allergic rhinitis Level 3: one-week: 1.94 (1.41, 2.71) Allergic rhinitis Level 2: two-week: 1.50 (1.19, 2.03) Allergic rhinitis Level 3: two-week: 1.41 (1.11, 1.89)
† Deng et al. (2019) n = 3,383	children aged 3–6	Central site monitor Averaging time:	NO ₂ (µg/m ³) During entire pregnancy	Doctor diagnosed eczema	Binary logistic regression Adjusted for: age,	OR (95% CI) ^c Eczema-four year olds: 0.92 (0.80, 1.07)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
Hubei Province, China November to December 2017 Cross-Sectional		NO ₂ - annual average Exposure years: 2016–2017	Mean = 38.94±12.25 IQR = 25.28 Min = 25.64 Max = 56.73 P25 = 29.2 P75 = 54.48 First year of life Mean = 38.39±12.48 IQR = 24.46 Min = 25.26 Max = 56.73 P25 = 29.2 P75 = 56.73		gender (male or female), birth weight (<2500 g or ≥2500 g), preterm birth (yes/no), breastfeeding duration (≤6 month or >6 months), eating milk powder (born or after a few months), and exposing to secondhand smoke (yes/no). Parental covariates included education level (junior high school or below, high school, junior college, or bachelor degree or above), overall health status (well, medium, or poor), maternal secondhand smoke exposure (yes/no), and paternal smoking (yes/no). Domestic covariates included self-assessment of family economic situation (well, medium, or poor) and distance of residence from the nearest main traffic road (≤200 m or >200 m)	Eczema-eight year olds: 0.88 (0.74, 1.04)
†Fuertes et al. (2020) Gene and Environment Prospective Study on Infancy in Italy (GASPII), Infancia y Medio Ambiente; Environment	Participants in European birth cohorts	LUR, Dispersion model Averaging time: NO ₂ - annual average, NO _x -	NO ₂ (µg/m ³) BIB Mean = 23.9 Median = 23.5	Questionnaire	Logistic regression Adjusted for: Maternal and paternal asthma and hay fever, maternal and paternal education,	NO ₂ OR (95% CI) ^c Rhinoconjunctivitis- four year olds: 0.91 (0.75, 1.10) Rhinoconjunctivitis- eight year olds: 1.21 (1.07, 1.37)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
and Childhood (INMA), EDEN, Born In Bradford (BIB), Mother-child Greek cohort (RHEA)		annual average	EDEN Mean = 21.7 Median = 19.7		breastfeeding, older siblings, daycare attendance during first year of life, maternal smoking during pregnancy, parental smoking at home during early-life, mould or dampness at home during early-life, furry pets in the home during early-life and use of gas for cooking during early-life	NO _x OR (95% CI) ^c Rhinoconjunctivitis- four year olds: 0.98 (0.63, 1.52) Rhinoconjunctivitis- eight year olds: 1.30 (1.04, 1.64)
n = 6,856		Exposure years: 2002–2011	GASPII Mean = 44.3 Median = 43			
Rome, Italy; Gipuzkoa, Spain; Sabadell, Spain; Valencia, Spain; Nancy, France; Poitiers, France; Bradford, United Kingdom; Heraklion, Greece			INMA - Sab Mean = 37.9 Median = 39.4			
2003–2011			INMA - Val Mean = 27.2 Median = 27.5			
Cohort			INMA - Gip Mean = 15.4 Median = 16.1			
			RHEA Mean = 12.3 Median = 11.2			
			NO _x (µg/m ³)			
			BIB Mean = 39.4 Median = 39.2			
			GASPII Mean = 69.8 Median = 65.5			
			INMA - Gip Mean = 31.5 Median = 32.9			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			INMA - Sab Mean = 65.3 Median = 65.9			
			INMA - Val Mean = 44 Median = 43.9			
			RHEA Mean = 17.6 Median = 16.3			
† Honda et al. (2023) Medicare n = 52,902,921 U.S. 2000–2008 Cohort	Centers for Medicare and Medicaid Services for 53 million Medicare beneficiaries (ages 65–120) living in the conterminous US	LUR Averaging time: NO ₂ - Annual average Exposure years: 2001–2008	NO ₂ (ppb) Mean = 10.9±5.6	ICD-10 code mortality from type 1 diabetes (E10)	Cox proportional hazards model Adjusted for: age, sex, race (white/non-white), and ZIP code, controlling for ZIP code and state SES	OR (95% CI) ^b Type 1 Diabetes Related Mortality: 1.25 (1.09, 1.43) Type 1 Diabetes Related Mortality - co-adjusted for PM _{2.5} : 1.27 (1.09, 1.48)
† Huang et al. (2015) Taiwan Birth Cohort Study n = 16,686 Taiwan 2005 Cohort	A multistage stratified sampling from the Taiwanese national registry data was performed based on different administrative divisions (four strata: district, city, urban township and rural township) and total fertility rate (three	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2006	NO ₂ (ppb) Mean = 17.3±6.6 Median = 17.1 IQR = 9.7 P25 = 12.1 P75 = 21.8	Professional interviewers followed these infants at the age of 6 months, 18 months and 3 years, and each time the structured questionnaires were completed after the	Logistic regression Adjusted for: infant sex, maternal age, birthweight, atopy of parents, birth order, recently immigrated mother, maternal environmental tobacco smoke, maternal education, annual household income,	OR (95% CI) ^b Atopic dermatitis - Trimester 1: 1.47 (0.89, 2.43) Atopic dermatitis - Trimester 2: 1.05 (0.66, 1.66) Atopic dermatitis - Trimester 3: 1.04 (0.62, 1.75) Atopic dermatitis - 3 months after birth: .0.95 (0.57, 1.59) Atopic dermatitis - Whole gestation period: 2.00 (0.97, 4.14) Atopic dermatitis - From conception

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
	strata: low, medium and high).			mother's informed consent.	mouldy walls, nearby factories, postnatal environmental tobacco smoke, birth season and county of residence	to 3 months postnatal: 1.47 (0.62, 3.47)
† Kousha and Castner (2016) n = 4,815 Canada Times series case-crossover	Data on ED visits for OM by children birth to 3 years of age in Windsor, Ontario, Canada were retrieved from the National Ambulatory Care Reporting System.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2004–2010	NO ₂ (ppb) Mean =15.9±6.6 IQR = 8.5	ED visits with ICD-10 codes H65 (nonsuppurative otitis media) and H66 (suppurative and unspecified otitis media) were used to measure visits for conditions related to middle ear inflammation (both acute and chronic).	Distributed lag nonlinear models (DLNMs)	OR (95% CI) ^b Emergency department visits for otitis media - lag 0: 0.93 (0.9, 1.09) Emergency department visits for otitis media - lag 1: 0.98 (0.84, 1.14) Emergency department visits for otitis media - lag 2: 1.02 (0.88, 1.19) Emergency department visits for otitis media - lag 3: 1.12 (0.97, 1.30) Emergency department visits for otitis media - lag 4: 1.05 (0.90, 1.22) Emergency department visits for otitis media - lag 5: 1.07 (0.91, 1.26) Emergency department visits for otitis media - lag 6: 1.00 (0.86, 1.17) Emergency department visits for otitis media - lag 7: 1.00 (0.89, 1.12)
† Marchetti et al. (2023) Gene Environment Interactions in Respiratory Diseases (GEIRD) study, Pisa study n = 4,111 Turin, Verona, Pavia, Terni, Ancona, Sassari, Italy	Two cohorts sampling from the general population	Hybrid model r ² = 0.6 Averaging time: Six-month exposure, April to September Exposure years: 2013–2015	NO ₂ (µg/m ³) Mean = 27.2±9.7	Questionnaire	Mixed logistic regression Adjusted for: sex, age, education level, smoking habits/pack-years, BMI, climatic index	OR (95% CI) ^c Rhinitis: 0.98 (0.76, 1.26) Atopic dermatitis - Trimester 1 Rhinitis - males: 1.46 (1.17, 1.84) Rhinitis - females: 1.17 (0.94, 1.45) Rhinitis - <50 years of age: 1.15 (1.02, 1.30) Rhinitis ≥50 years of age: 1.17 (1.02, 1.34)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
2007–2016						
Case-Control						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Zhao et al. (2020) CARTaGENE cohort n = 5,485 Quebec, Canada 2009–2010 for enrollment Cohort	20,000 randomly selected residents of four census metropolitan areas of Quebec, Canada. All aged between 40 and 69 years at cohort entry	Hybrid model r ² = 0.73 Averaging time: NO ₂ - annual average Exposure years: 2005–2010	NO ₂ (ppb) ANA Negative Mean = 14±5.6 ANA positive Mean = 14±5.4	Serum samples	Logistic regression Adjusted for: Age, French Canadian ancestry, smoking habits, and family income level	OR (95% CI) ^c Anti-nuclear antibodies: 0.99 (0.98, 1.01)
Renal Effects						
† Bi et al. (2021) n = 306,595 Atlanta, GA, United States 2002–2008 Cross-Sectional	Emergency department patients	CMAQ Averaging time: NO ₂ - 1-hour max Exposure years: 2002–2008	NO ₂ (ppb) Mean = 21.58±6.97 IQR = 9.52 Min = 3.18 Max = 45.29 NO _x (ppb) Mean = 45.63±30.48 IQR = 33.51 Min = 4.75 Max = 219.46	ICD codes	Quasi-Poisson log-linear time-series models Adjusted for: cubic terms for daily maximum air temperature and mean dew-point temperature, indicator variables for season (spring, summer, fall, and winter), day of week and holidays, and hospital participation	NO ₂ OR (95% CI) ^c ED visits for renal disease: 1.02 (1.00, 1.04) NO _x OR (95% CI) ^c ED visits for renal disease: 1.02 (1.00, 1.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Cai et al. (2023) n = 101,919 Nationwide, China 2015–2019 Case-crossover	Deaths attributed to kidney disease	Hybrid model Averaging time: NO ₂ - 24-hour average Exposure years: 2015–2019	NO ₂ (µg/m ³) Median = 26.07 P25 = 18.88 P75 = 36.79	ICD codes	Time-stratified case-crossover Adjusted for: Five-day moving averages (lag 0–4) of daily temperature and relative humidity prior to the date of death	β (as relative percent increase) (95% CI) ^c CKD mortality: 1.26% (0.29, 2.24)
† Chu et al. (2023) n = 1,209,934 New York, U.S. 2007–2016 Cross-Sectional	Patients aged ≥18 years from the NYS Department of Health Statewide Planning and Research Cooperative System	Ensemble machine learning model Averaging time: NO ₂ - 1-hour max Exposure years: 2006–2016	NO ₂ (ppb) Mean = 11.2±8 Median = 9.3 P25 = 5.5 P75 = 14.7	ICD codes	Conditional logistic regression Adjusted for: daytime mean outdoor WBGT, daily mean dew point temperature, wind speed, and solar radiation	OR (95% CI) ^c Acute kidney failure: 1.01 (1.01, 1.02) Urolithiasis: 1.01 (1.00, 1.01) Glomerular disease: 1.00 (0.95, 1.04) Renal tubulo-interstitial disease: 1.00 (0.99, 1.01) Chronic kidney disease: 1.00 (0.98, 1.02) Dysnatremia: 1.01 (1.00, 1.02) Volume depletion: 1.01 (1.00, 1.01)
† Groves et al. (2020) n = 46,96 Victoria, New South Wales, Australia January 1, 2008–December 31, 2016 Time-series	Patients in the Adult Patient Database	Fixed site monitor Averaging time: NO ₂ - 24-hour average Exposure years: 2007–2016	NO ₂ (ppb) Mean = 8 P25 = 5 P75 = 12	ICU registry	Case-crossover Adjusted for: temperature, humidity, influenza and public holidays	OR (95% CI) ^c ED visits for acute renal failure: 0.91 (0.79, 1.06)

†So et al. (2022)	Cohort of individuals 30 years or older	LUR	NO ₂ (µg/m ³)	ICD codes	Cox proportional hazards model	OR (95% CI) ^c Incidence of chronic kidney disease: 1.05 (1.00, 1.11)
Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE)		r ² = 0.58	Mean = 20.3±7.94		Adjusted for: Age, sex, individual	
n = 3,083,227		Averaging time: NO ₂ - annual average	IQR = 10.3 Min = 3.7 Max = 72.2 P5 = 9.4 P25 = 14.6 P75 = 24.9 P95 = 35.7		socioeconomic status (SES) including household income in deciles, occupational status (unemployed, employed, or sick/cash support/student/ pension/others), immigrant status (Danish origin, immigrants/ descendants from Western country of origin, immigrants/ descendants from non- Western country of origin), marital status (unmarried, divorced, widowed, married/registered partnership), and highest completed education level (primary, upper secondary, vocation/qualifying, vocation bachelor/ short-cycle higher education, or more than college level), regional mean household income, regional percentage of unemployment, and the difference of mean household income and	
Denmark		Exposure years: 1999–2017				
January 1, 2000–December 31, 2017						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					percentage of unemployment, between parish and region	

†So et al. (2022)	Cohort of individuals 30 years or older	Hybrid model	NO ₂ (µg/m ³)	ICD codes	Cox proportional hazards model	OR (95% CI) ^c Incidence of chronic kidney disease: 1.05 (1.00, 1.11)
Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE)		r ² = 0.58	Mean = 20.3±7.94		Adjusted for: Age, sex, individual	
n = 3,083,227		Averaging time: NO ₂ - annual average	IQR = 10.3 Min = 3.7 Max = 72.2 P5 = 9.4 P25 = 14.6 P75 = 24.9 P95 = 35.7		socioeconomic status (SES) including household income in deciles, occupational status (unemployed, employed, or sick/cash support/student/pension/ others), immigrant status (Danish origin, immigrants/ descendants from Western country of origin, immigrants/ descendants from non- Western country of origin), marital status (unmarried, divorced, widowed, married/registered partnership), and highest completed education level (primary, upper secondary, vocation/qualifying, vocation bachelor/ short-cycle higher education, or more than college level), regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of	
Nationwide, Denmark		Exposure years: 1999–2017				
January 1, 2000–December 31, 2017						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					unemployment, between parish and region	
† Wang et al. (2022)	Participants without a history of CKD and with complete data on air pollutants exposure at baseline in this study	LUR	NO ₂ (ppb)	ICD-10 codes I12.0, I13.1, I13.2, N18, N18.0, N18.1, N18.2, N18.3, N18.4, N18.5, N18.8, N18.9 and ICD-9 codes 585, 5859	Cox proportional hazards model	HR (95% CI) ^c
UK Biobank		Averaging time: NO ₂ - annual average	IQR: 5.85 (11.00 µg/m ³)		Adjusted for: age, sex, ethnicity, education level, average total household income before tax, physical activity, smoking status, drinking status, body mass index, systolic blood pressure, high-density lipoprotein, and hemoglobin A1c	CKD for exposure to NO ₂ : 1.05 (1.03, 1.07)
n = 260,050			NO _x (µg/m ³)			CKD for exposure to NO _x : 1.06 (1.04, 1.08)
U.K.		Averaging time: NO _x - annual average	IQR: 16.55			
2006–2010						
Cohort		Exposure years: NO ₂ : 2006, 2007, 2010 NO _x : 2010				
† Wu et al. (2022)	Patients in the national CKD program	Hybrid model	NO ₂ (ppb)	Biochemistry and physical examination	Cox proportional hazards model	OR (95% CI) ^c
n = 6,480		r ² = 0.88	Mean: NR Median: NR		Adjusted for: Age, gender, baseline eGFR stages, county of residence, education, occupation, smoking status, and sports habits	ESRD middle tertile compared to lower: 1.08 (0.10, 1.19)
Taichung, Taiwan		Averaging time: NO ₂ - annual average				ESRD upper tertile compared to lower: 1.60 (1.46, 1.76)
January 2006–December 2020						
Cohort		Exposure years: 2005–2020				

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Wu et al. (2023)	Sample of half a million U.K. citizens	LUR	NO ₂ (µg/m ³)	CKD ePhenotype	multi-state models	NO ₂ OR (95% CI) ^c
UK Biobank		0.87 for NO ₂ , and 0.88 for NO _x	Mean = 26.65±7.74		Adjusted for: Age, sex, ethnicity, body mass index (BMI), smoking status, physical activity, household income, Townsend deprivation index and green space	CKD: 0.97 (0.89, 1.05)
n = 162,334			NO _x (µg/m ³)			NO _x OR (95% CI) ^c
Nationwide, U.K.		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 43.82±15.61			CKD: 1.00 (0.94, 1.06)
2006–2010						
Cohort		Exposure years: 2010–2011				
Hepatic Effects						
† Hsieh et al. (2017)	Participants in a prospective study on the pathophysiology of type 2 diabetes at the Yale Pediatric Obesity Clinic. Participants needed to have baseline and follow-up measurements two years later on at least one liver outcome were included in the sample. Participants who were taking medications or had medical conditions that could affect lipid metabolism were excluded. Participants were excluded if they did not have a residential address.	Hybrid model	NO ₂ (ppb)	Measured using enzyme-based immunosorbent assay	Linear regression	β (U/L) (SE) ^c
n = 74		Averaging time: NO ₂ - two-year annual averages	Mean = 7±1.7		Adjusted for: baseline measurement, age, and sex	Liver Outcomes - CK-18: 11.40 (5.4)
Connecticut, United States			Median = 7 (IQR 1.91)			Liver Outcomes - ALT: -0.95 (1.8)
2006–2009		Exposure years: 2006–2009	Min = 3.5	Measured using standard automated kinetic enzymatic assays		Liver Outcomes - AST: -0.39 (0.8)
Cohort			Max = 11	Hepatic fat was measured using MRI with the 2-point Dixon Technique as modified by Fishbein		Liver Outcomes - HFF: -0.49 (0.9)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Liu et al. (2023) UK Biobank n = 425,773 United Kingdom 2006–2010 Cross-Sectional	Participants of the UK Biobank study. Participants were 37–73 years at baseline. Participants with liver diseases at baseline, missing data on air pollution or the four liver enzymes were excluded.	LUR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: 2006–2010	NO ₂ (ppb) Mean = 14.13±4.05 (26.58±7.62 µg/m ³) NO _x (µg/m ³) Mean = 43.9±15.61	Measured by enzyme rate method	Linear regression Adjusted for: age, gender, ethnicity, education level, employment status, household income, BMI, smoke status, alcohol drinking, physical activity, triglycerides, vascular problems, diabetes	NO ₂ β (Percent change) (95% CI) ^b Liver enzyme levels - AST: 0.42 (0.32, 0.51) Liver enzyme levels - ALT: 0.14 (0.00, 0.29) Liver enzyme levels - GGT: 0.57 (0.37, 0.76) Liver enzyme levels - ALP: 0.04 (-0.06, 0.13) NO _x β (Percent change) (95% CI) ^c Liver enzyme levels - AST: 0.17 (0.13, 0.22) Liver enzyme levels - ALT: 0.07 (-0.01, 0.15) Liver enzyme levels - GGT: 0.37 (0.27, 0.47) Liver enzyme levels - ALP: 0.04 (-0.01, 0.09)
Ocular Effects						
† Bai et al. (2021) n = 175, 489 Taiwan January 1, 2000–December 31, 2011 Cohort	Participants aged 20 years or older	Spatiotemporal/geospatial model Averaging time: NO _x - 24-hour average, NO - 24-hour average Exposure years: 2000–2011	NO (ppb) Mean = 11±10.1 NO _x (ppm) Mean = 36.3±34.9	ICD code	Cox proportional hazards model Adjusted for: sex, age, urbanization level, and comorbidities	NO HR (95% CI) ^c Uveitis Q1: Reference Uveitis Q2: 1.14 (0.99, 1.30) Uveitis Q3: 1.46 (1.27, 1.67) Uveitis Q4: 2.05 (1.81, 2.32) NO _x HR (95% CI) ^c Uveitis Q1: Reference Uveitis Q2: 1.27 (1.11, 1.44) Uveitis Q3: 1.34 (1.16, 1.53) Uveitis Q4: 1.85 (1.63, 2.09)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Cheng et al. (2016) Taiwan National Health Insurance Research Database (NHIRD) n = 96 Nationwide, Taiwan January 2000–December 2013 (enrollment) Case-crossover	Randomly selected patients in a mandatory national health insurance program in Taiwan who were newly diagnosed with CRAO between 2001 and 2013 who were ≥20 years at diagnosis.	Fixed site monitor Averaging time: NO ₂ - daily 1-hour average Exposure years: 2000–2013		ICD code	Cox proportional hazards model	OR (95% CI) ^c Central Retinal Artery Occlusion: 1.03 (1.01, 1.05)
† Chua et al. (2020) UK Biobank n = 51,710 Nationwide, United Kingdom 2006–2010 Cohort	U.K. residents registered with NHS ages 40–69	LUR Averaging time: NO ₂ - annual average Exposure years: 2005, 2006, 2007, and 2010	NO ₂ (µg/m ³) Median = 32.38 (IQR 12.64) Min = 9.44 Max = 86.65 NO _x (µg/m ³) Median = 44.72 (IQR 14.97) Min = 19.74 Max = 263.96	Ocular assessment	Multivariable linear regression Adjusted for: age, sex, race, Townsend deprivation index, BMI, smoking status, and SER	NO ₂ β (µm) (95% CI) ^c RNFL: -0.70 (-0.14, 0.00) GCIPL: 0.04 (-0.05, 0.12) INL: -0.14 (-0.17, -0.11) NO _x β (µm) (95% CI) ^c RNFL: 0.09 (0.04, 0.14) GCIPL: -0.21 (-0.27, -0.16) INL: -0.05 (-0.07, -0.03)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Chung et al. (2021)	participants aged 30–70 years old with no history of cancers	Hybrid model	NO ₂ (ppb)	Health examination	Multiple logistic regression	PR (95% CI) ^c
Taiwan Biobank		$r^2 = 0.63$	Case Mean = 15.24±2.88		Adjusted for: age, education, hormone supplementation, arthritis, and allergy	Dry eye disease: 1.43 (1.15, 1.78)
n = 6,880		Averaging time: NO ₂ - annual average	Control Mean = 15.1±2.91			
Nationwide, Taiwan		Exposure years: 2007–2016				
2008–2016						
Cross-Sectional						

†Szyszkowicz et al. (2016)	Patients of ED visits	Other	NO ₂ (ppb)	ICD code	Case-crossover	OR (95% CI) ^c
n = 77,439		Averaging time: NO ₂ - 24-hour average	Algoma Mean = 5.1 IQR = 4 Min = 0 Max = 24		Adjusted for: Meteorological factors	Conjunctivitis: 1.04 (1.01, 1.07) Conjunctivitis - male: 1.02 (1.00, 1.05) Conjunctivitis - female: 1.04 (1.02, 1.05)
Algoma, Ontario; Halton, Ontario; Hamilton, Ontario; London, Ontario; Ottawa, Ontario; Peel, Ontario; Toronto, Ontario; Windsor, Ontario; York, Ontario, Canada		Exposure years: 2004–2011	Halton Mean = 12.9 IQR = 7.7 Min = 1 Max = 51.2			Conjunctivitis- ≤17 years of age: 1.06 (1.03, 1.08) Conjunctivitis- ≥18 years of age: 1.04 (1.02, 1.05)
April 2004–December 2011			Hamilton Mean = 13.9 IQR = 9.5 Min = 1.7 Max = 63			Conjunctivitis- male during warm season: 1.04 (1.01, 1.07) Conjunctivitis- female during warm season: 1.04 (1.01, 1.07)
Case-crossover			London Mean = 10.9 IQR = 7 Min = 0 Max = 51			
			Ottawa Mean = 8.7 IQR = 7 Min = 1 Max = 47			
			Peel Mean = 13.2 IQR = 9.5 Min = 2 Max = 54			
			Toronto			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			Mean = 18.5 IQR = 9.4 Min = 4.5 Max = 62.1			
			Windsor Mean = 15.6 IQR = 8.1 Min = 2.4 Max = 55.5			
			York Mean = 8.2 IQR = 7 Min = 0 Max = 47			

† Yang et al. (2021)	Children from primary and secondary schools	Ensemble machine learning model	NO ₂ (µg/m ³) Mean = 14.4	Standardization Administration of China visual acuity chart	Logistic regression	OR (95% CI) ^c decreased eyesight scores in both eyes: 1.28 (1.17, 1.39)
n = 61,995		r ² = 0.72			Adjusted for: children's age (years), children's sex (male vs female), children's ethnicity (Han vs others), children's physical activity (<1 h per day, 1–2 h per day, and ≥2 h per day), children's urbanity (urban vs rural), children's daily time for watching TV (minutes), children's daily time for using computer or playing video games (minutes), children's daily sleeping time (<7 h, 7–9 h, 9–11 h, and ≥11 h), weight control (yes or no), caesarean section (yes or no), low birth weight (yes or no), parental education level (defined as the highest degree of either parent: primary school or illiterate, secondary school, high school, and college or university or above), household income per month (<2,000 Yuan per person, 2001–5000 Yuan per person, and ≥5,000 Yuan per person), parental smoking (yes vs no),	
Shanghai, China; Guangdong Province, China; Tianjin, China; Chongqing, China; Liaoning Province, China; Ningxia, China; Hunan Province, China		Averaging time: NO ₂ - annual average				
2013		Exposure years: 2010–2012				
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
					parental myopia (yes or no), region-level gross domestic product per capita (Yuan), air temperature (°C), and greenness (evaluated by normalized difference vegetation index within a 500 m buffer)	
Gastrointestinal Effects						

† Elten et al. (2020)	All live births occurring in hospitals. Children were excluded if they had invalid health card number, a multiple birth, had an invalid recorded sex, ineligible for provincial health insurance at birth, or were missing their 6-digit postal code for exposure ascertainment.	LUR	NO ₂ (ppb)	ICD 9 Codes 555, 556; ICD-10 Codes K50, K51	Cox proportional hazard model	HR (95% CI) ^c
n = 2,218,789 IBD cases: 2,491		Averaging time: NO ₂ - Weekly average	Childhood Mean = 10.17±5.8 IQR = 7.91		Adjusted for: sex, maternal IBD as identified from the Ontario Crohn's and Colitis Cohort using validated algorithms, rural/urban area of residence at birth using Statistics Canada definition of rurality in the 2006 Census, and median neighborhood household income	Overall Incidence of IBD - Trimester 1: 1.03 (1.00, 1.07) Overall Incidence of IBD - Trimester 2: 0.97 (0.94, 1.00) Overall Incidence of IBD - Trimester 3: 1.00 (0.97, 1.03) Overall Incidence of IBD - Pregnancy: 1.00 (0.96, 1.03) Overall Incidence of IBD - Childhood: 0.96 (0.86, 1.06) Overall Incidence of Crohn's Disease - Trimester 1: 1.03 (0.98, 1.09) Overall Incidence of Crohn's Disease - Trimester 2: 0.94 (0.91, 0.98) Overall Incidence of Crohn's Disease - Trimester 3: 1.03 (0.98, 1.08) Overall Incidence of Crohn's Disease - Pregnancy: 1.00 (0.95, 1.04) Overall Incidence of Crohn's Disease - Childhood: 0.92 (0.80, 1.06) Overall incidence of ulcerative colitis - Trimester 1: 1.04 (0.98, 1.11) Overall incidence of ulcerative colitis - Trimester 2: 1.01 (0.96, 1.06) Overall incidence of ulcerative colitis - Trimester 3: 0.95 (0.90, 1.01) Overall incidence of ulcerative colitis - Pregnancy: 1.00 (0.94, 1.06) Overall incidence of ulcerative colitis - Childhood: 1.01 (0.85, 1.20)
Ontario, Canada		Exposure years: April 1, 1990–December 25, 2016	Pregnancy Mean = 12.73±7.43 IQR = 10.08			
April 1, 1991–March 31, 2014			Trimester 1 Mean = 12.7±7.7 IQR = 10.31			
Cohort			Trimester 2 Mean = 12.6±7.78 IQR = 10.46			
			Trimester 3 Mean = 12.39±7.65 IQR = 10.19			

† Opstelten et al. (2016)	Participants (men and women) recruited from one of five centers participating in the EPIC study.	LUR	NO ₂ (ppb)	The medical reports of all potential cases were reviewed by local gastroenterologists to confirm the diagnoses and to obtain information on diagnostic investigations and disease extent	Logistic regression	NO ₂ OR (95% CI) ^b
European Prospective Investigation into Cancer and Nutrition (EPIC)		Averaging time: NO ₂ - annual average, NO _x - annual average	Denmark Controls Median = 8.02 (15.1 µg/m ³) Min = 3.25 (6.11 µg/m ³) Max = 19 (35.7 µg/m ³) P5 = 4.34 (8.16 µg/m ³) P10 = 4.67 (8.79 µg/m ³) P90 = 15 (28 µg/m ³) P95 = 15.7 (29.5 µg/m ³)		Adjusted for: smoking status (categorized into never smoker, former smoker, and current smoker) and socioeconomic status using educational level (categorized into primary school, technical school, secondary school, and higher education)	Crohn's disease: 1.26 (0.37, 4.27) Ulcerative colitis: 0.98 (0.51, 1.90) Inflammatory bowel disease: 1.10 (0.62, 1.95)
n = 227,620 cases of Crohn's disease: 38 cases of ulcerative colitis: 104		Exposure years: 2008–2011	IBD Cases Median = 8.24 (15.5 µg/m ³) Min = 3.04 (5.72 µg/m ³) Max = 22.4 (42.1 µg/m ³) P5 = 3.21 (6.04 µg/m ³) P10 = 4.59 (8.64 µg/m ³) P90 = 14.8 (27.8 µg/m ³) P95 = 20.4 (38.3 µg/m ³)			NO _x OR (95% CI) ^c Ulcerative colitis: 1.03 (0.76, 1.38) Inflammatory bowel disease: 1.08 (0.83, 1.40) Crohn's disease: 1.17 (0.67, 2.03)
France, United Kingdom, Denmark, Netherlands			France Controls Median = 12.5 (23.5 µg/m ³) Min = 7.17 (13.5 µg/m ³)			
1993–2000						
Case-Control						

Max = 25.6 (48.2
µg/m³)
P10 = 7.65 (14.4
µg/m³)
P90 = 20.7 (38.9
µg/m³)
IBD Cases
Median = 12.6 (23.8
µg/m³)
Min = 7.17 (13.5
µg/m³)
Max = 34.2 (64.3
µg/m³)
P10 = 7.6 (14.3
µg/m³)
P90 = 30.2 (56.8
µg/m³)

Netherlands
Controls
MORGEN cohort
Median = 10.9 (20.5
µg/m³)
Min = 7.33 (13.8
µg/m³)
Max = 22.2 (41.7
µg/m³)
P5 = 8.56 (16.1
µg/m³)
P10 = 9.14 (17.2
µg/m³)
P90 = 15.9 (29.9
µg/m³)
P95 = 18.8 (35.4
µg/m³)
Controls
Prospect Cohort
Median = 18 (33
µg/m³)
Min = 10 (18.9

$\mu\text{g}/\text{m}^3$
Max = 20.2 (38.1
 $\mu\text{g}/\text{m}^3$
P5 = 10.7 (20.1
 $\mu\text{g}/\text{m}^3$
P10 = 11.1 (20.8
 $\mu\text{g}/\text{m}^3$
P90 = 18 (33 $\mu\text{g}/\text{m}^3$)
P95 = 17.9 (33.6
 $\mu\text{g}/\text{m}^3$
IBD Cases
MORGEN cohort
Median = 10.8 (20.3
 $\mu\text{g}/\text{m}^3$
Min = 8.34 (15.7
 $\mu\text{g}/\text{m}^3$
Max = 24 (46
 $\mu\text{g}/\text{m}^3$
P5 = 8.66 (16.3
 $\mu\text{g}/\text{m}^3$
P10 = 9 (17 $\mu\text{g}/\text{m}^3$)
P90 = 19 (36 $\mu\text{g}/\text{m}^3$)
P95 = 21.4 (40.2
 $\mu\text{g}/\text{m}^3$
IBD Cases
Prospect Cohort
Median = 13.1 (24.7
 $\mu\text{g}/\text{m}^3$
Min = 9.25 (17.4
 $\mu\text{g}/\text{m}^3$
Max = 18.4 (34.6
 $\mu\text{g}/\text{m}^3$
P5 = 9.35 (17.6
 $\mu\text{g}/\text{m}^3$
P10 = 10.8 (20.3
 $\mu\text{g}/\text{m}^3$
P90 = 17.5 (32.9
 $\mu\text{g}/\text{m}^3$
P95 = 18.3 (34.5
 $\mu\text{g}/\text{m}^3$)

U.K.
Controls
Median = 12.3 (23.2
 $\mu\text{g}/\text{m}^3$)
Min = 6.86 (12.9
 $\mu\text{g}/\text{m}^3$)
Max = 28.2 (53.1
 $\mu\text{g}/\text{m}^3$)
P5 = 7.02 (13.2
 $\mu\text{g}/\text{m}^3$)
P10 = 8.13 (15.3
 $\mu\text{g}/\text{m}^3$)
P90 = 19.3 (36.4
 $\mu\text{g}/\text{m}^3$)
P95 = 21.9 (41.2
 $\mu\text{g}/\text{m}^3$)
IBD Cases
Median = 13 (24
 $\mu\text{g}/\text{m}^3$)
Min = 6.96 (13.1
 $\mu\text{g}/\text{m}^3$)
Max = 19.7 (37.1
 $\mu\text{g}/\text{m}^3$)
P5 = 7.02 (13.2
 $\mu\text{g}/\text{m}^3$)
P10 = 7.81 (14.7
 $\mu\text{g}/\text{m}^3$)
P90 = 19 (35.7
 $\mu\text{g}/\text{m}^3$)
P95 = 19.7 (37.1
 $\mu\text{g}/\text{m}^3$)

NO_x ($\mu\text{g}/\text{m}^3$)

Denmark
Controls
Median = 21.7
Min = 2.53
Max = 78.2

P5 = 7.03
P10 = 9.23
P90 = 62.2
P95 = 64.1
IBD Cases
Median = 62
Min = 1.78
Max = 91.2
P5 = 2.43
P10 = 8.94
P90 = 62
P95 = 83.5

France
Controls
Median = 38.1
Min = 25.6
Max = 100
P10 = 31.8
P90 = 88.1
IBD Cases
Median = 34.5
Min = 22.7
Max = 127
P10 = 24.2
P90 = 109

Netherlands
Controls
MORGEN cohort
Median = 31.2
Min = 241.7
Max = 77.6
P5 = 24.4
P10 = 25.2
P90 = 48
P95 = 57.4
Controls
Prospect Cohort
Median = 37.7

Min = 25.6
Max = 79.1
P5 = 29.4
P10 = 30.3
P90 = 59
P95 = 70.3
IBD Cases
MORGEN cohort
Median = 30.5
Min = 24.2
Max = 86
P5 = 24.7
P10 = 25.7
P90 = 56.2
P95 = 78.9
IBD Cases
Prospect Cohort
Median = 35.1
Min = 25.8
Max = 71.2
P5 = 26.2
P10 = 30.3
P90 = 48.4
P95 = 68.9

U.K.
Controls
Median = 40.1
Min = 19.8
Max = 116
P5 = 21.2
P10 = 25
P90 = 63.7
P95 = 80.7
IBD Cases
Median = 39.8
Min = 20
Max = 66
P5 = 20.5
P10 = 21.2

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
			P90 = 60.2 P95 = 64.3			
† Szyszkowicz (2015) n = 11,110 Edmonton, Canada April 17, 1998–March 31, 2002 Case-crossover	Emergency department visits due to colitis among patients younger than 15 years of age and served by 5 hospitals in Edmonton.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: April 17, 1998 to March 31, 2002	NO ₂ (ppb) IQR = 12.8	ICD 9 code of 558.9	Cox proportional hazard model Adjusted for: NA	OR (95% CI) ^b Colitis - ED visits for Lag 0: 1.02 (0.95, 1.08) Colitis - ED visits for Lag 1: 1.05 (0.99, 1.11) Colitis - ED visits for Lag 2: 1.06 (1.00, 1.13) Colitis - ED visits for Lag 3: 1.10 (1.03, 1.16) Colitis - ED visits for Lag 4: 1.08 (1.02, 1.14) Colitis - ED visits for Lag 5: 1.05 (0.99, 1.10) Colitis - ED visits for Lag 6: 1.03 (0.97, 1.10) Colitis - ED visits for Lag 7: 1.06 (1.00, 1.13) Colitis - ED visits for Lag 8: 1.05 (0.99, 1.11) Colitis - ED visits for Lag 9: 1.05 (1.00, 1.10)
Musculoskeletal Effects						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Lai et al. (2022)	Participants aged 37–73 years in the United Kingdom. n = 352,265 United Kingdom 2006–2010 Cross-Sectional	LUR	NO ₂ (ppb)	Based on the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) criteria, hand grip strength (average of left and right hands), Appendicular lean mass index (ALMI), and walking pace were used to assess the three components of sarcopenia.	Logistic regression	NO ₂ OR (95% CI) ^b
UK Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Mean = 15.48±4.92 (29.12±9.26 µg/m ³)		Adjusted for: age, sex, BMI, education, income, deprivation index, physical activity, smoking status, and alcohol intake	Sarcopenia: 1.21 (1.18, 1.25)
			NO _x (µg/m ³)			NO _x OR (95% CI) ^c
		Exposure years: NO _x : 2010; NO ₂ : 2005, 2006, 2007, 2010	Mean = 43.71±15.53			Sarcopenia: 1.06 (1.05, 1.08)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Lin et al. (2020)	Community-based volunteers aged 30–70 years with no history of cancer. Participants must have complete air pollution measurements during the enrollment period.	Central site monitor	NO ₂ (ppb)	The BMD (g/cm ²) of the calcaneus in the non-dominant foot was measured using an Achilles InSight ultrasound device.	Linear regression	NO β (95% CI) ^b
Taiwan Biobank			Mean = 15.1±5.7		Adjusted for: age, sex, smoking history, DM, hypertension, BMI, SBP, DBP, fasting glucose, log	Bone mineral density: -0.60 (-0.76, -0.44)
N = 5,000 n = 4,595		Averaging time: NO ₂ - annual average, NO _x - annual average, NO - annual average	NO (ppb)		triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, hemoglobin, eGFR, uric acid, and regular exercise	Bone mineral density - Female: -0.65 (-0.85, -0.44)
Taiwan			Mean = 4.2±4.1			Bone mineral density - Male: -0.38 (-0.62, -0.13)
Enrollment: Study years NR Follow-up: until April 2014		Exposure years: Not reported	NO _x (ppb)			NO ₂ β (95% CI) ^b
Cohort			Mean = 19.3±9			Bone mineral density: -0.23 (-0.31, -0.16)
					Adjusted for: age, smoking history, DM, hypertension, BMI, SBP, DBP, fasting glucose, log triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, hemoglobin, eGFR, uric acid and regular exercise	Bone mineral density - Male: -0.16 (-0.27, -0.05)
						Bone mineral density - Female: -0.26 (-0.36, -0.16)
						NO _x β (95% CI) ^b
						Bone mineral density: -0.34 (-0.44, -0.24)
						Bone mineral density - Male: -0.24 (-0.38, -0.10)
						Bone mineral density - Female: -0.38 (-0.50, -0.26)

† Prada et al. (2023)	Postmenopausal women aged 50–79 years	AQS	NO ₂ (ppb)	Participants underwent dual-energy X-ray absorptiometry scanning using Hologic machines (QDR2000, 2000+, or 4500). When Hologic QDR 2000 machines were upgraded to QDR 4500 machines, in vivo cross calibration was performed, and results were adjusted for correction factors and longitudinal changes in scanner performance. Certified technicians used dual energy X-ray absorptiometry (DXA, QDR 2000, 2000+, or 4500 W; Hologic Inc, Bedford, MA, USA) to measure BMD in g/cm ² following	Linear regression	NO β (g/cm ² /year) (95% CI) ^c Bone mineral density: Whole body: Longitudinal for 1-yr average: -0.006 (-0.010, -0.003) Bone mineral density: Whole body: Longitudinal for 3-yr average: -0.022 (-0.027, -0.017) Bone mineral density: Whole body: Longitudinal for 5-yr average: -0.001 (-0.006, 0.004) NO ₂ β (g/cm ² /year) (95% CI) ^c Bone mineral density: Whole body- Longitudinal for 1-yr average: 0.003 (-0.002, 0.008) Bone mineral density: Whole body - Longitudinal for 3-yr average: -0.004 (-0.010, 0.002) Bone mineral density: Whole body - Longitudinal for 5-yr average: 0.001 (-0.007, 0.008)
Women's Health Initiative Study (WHI)		Averaging time: NO ₂ - 24-hour average, NO - 24-hour average	1-yr average Mean = 17.9±5.27 3-yr average Mean = 18.12±4.74		Adjusted for: demographic characteristics (i.e., age, race/ethnicity, education, income, neighborhood socioeconomic status, and U.S. Census region), clinical characteristics (body mass index), behavioral characteristics (smoking, physical activity), study membership (clinical trials or observational study), hormone therapy randomization arm (hormone treatment or control), dietary modification trial arm, and calcium/vitamin D randomization arm (calcium/vitamin D or control)	
n = 9,041			5-yr average Mean = 18.17±4.74			
United States		Exposure years: NR				
Enrollment: October 1, 1993 and December 21, 1998						
Cross-sectional and Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
				standard protocols at screening and annual visits (1, 3, 6, and 9 years of follow-up).		
[†] Qi et al. (2023)	Participants at baseline were 40–69 years of age in the United Kingdom. Specifically, participants were excluded if withdrew at baseline, lacked residential air pollution exposure data, and self-reported fractures without validated hospital admission records or fracture occurrence date during follow-up.	LUR Averaging time: NO ₂ - annual average, NO _x - annual average Exposure years: NO _x : 2010; NO ₂ : 2005–2007, 2010	NO ₂ (ppb) Fractures Mean = 15.5±4.8 (29.2±9.1 µg/m ³) No fractures Mean = 15.43±4.79 (29.03±9.02 µg/m ³) NO _x (µg/m ³) Fractures Mean = 44.7±16.03 No fractures Mean = 44.01±15.45	ICD 10 codes for all new-onset total clinical fractures, (clinical hip fractures, clinical vertebral fractures, and other clinical fractures)	Cox proportional hazard model Adjusted for: demographic, spatiotemporal, lifestyle, dietary supplements, comorbidities, and physiological conditions (menopause status, self-rated health, diabetes mellitus, cancer, and cardiovascular diseases)	NO ₂ HR (95% CI) ^b Incident fracture risk: 1.16 (1.12, 1.20) NO _x HR (95% CI) ^c Incident fracture risk: 1.04 (1.03, 1.05)

†Xu et al. (2022)	Participants aged 40–69 years in the United Kingdom	LUR	NO ₂ (ppb)	ICD 10 Codes M80–M82 for osteoporosis	Cox proportional hazard model	NO ₂ HR (95% CI) ^b
UK Biobank		NO _x cross-validation r ² = 88%	Median = 13.6 (IQR 5) (25.6 µg/m ³ (IQR 9.5 µg/m ³)		Adjusted for: age, sex, Townsend Deprivation index, alcohol consumption (never, previous, current, missing), smoking status (never, previous, current, missing), body mass index (<25 kg/m ² , 25 to 29.9 kg/m ² , ≥30 kg/m ² , missing), physical activity (MET-min/week), and diabetes (yes, no, missing)	Osteoporosis: 1.12 (1.04, 1.20)
n = 422,955		NO ₂ cross-validation r ² = 87%	Min = 6.86 (12.9 µg/m ³)			NO _x HR (95% CI) ^c
osteoporosis=6,923			Max = 57.29 (107.8 µg/m ³)			Osteoporosis: 1.03 (1.01, 1.04)
non-osteoporosis=416,032			P5 = 7.87 (14.8 µg/m ³)			
United Kingdom		Averaging time: NO ₂ - annual average, NO _x - annual average	P25 = 11 (21 µg/m ³)			
2006–2010			P75 = 16.2 (30.5 µg/m ³)			
Cohort		Exposure years: NO _x : 2010; NO ₂ : 2005–2007, 2010	P95 = 20.5 (38.5 µg/m ³)			
			NO ₂ (µg/m ³)			
			Median = 25.6 (IQR 9.5)			
			Min = 12.9			
			Max = 107.8			
			P5 = 14.8			
			P25 = 21			
			P75 = 30.5			
			P95 = 38.5			
			NO _x (µg/m ³)			
			Median = 33.6 (IQR 16.1)			
			Min = 19.7			
			Max = 265.9			
			P5 = 22.7			
			P25 = 33.6			
			P75 = 49.7			
			P95 = 69.4			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yang et al. (2023)	Participants of the UK Biobank study with bone mineral density information at baseline, had corresponding data for air pollution, physical activity, and covariates	LUR	NO ₂ (ppb)	ICD 10 Codes: M80	Cox proportional hazard model	NO ₂ HR (95% CI) ^b
UK Biobank		NO ₂ r ² = 82% NO _x r ² = 78%	Mean = 15.45±4.92 (29.07±9.26 µg/m ³)	(osteoporosis with	Adjusted for: age at recruitment, sex,	Osteoporosis Incidence: 1.12 (1.07, 1.18)
UK Biobank N = 502,461		Averaging time: NO ₂ - annual average, NO _x - annual average	Median = 14.81 (IQR 5.79) (27.86 µg/m ³) (IQR 10.9 µg/m ³)	pathological fracture), M81 (osteoporosis without	education level, annual household income, ethnicity, Townsend deprivation, smoking status, and physical activity	OR (95% CI) ^b
Overall cohort n = 341,311			P25 = 12.08 (22.73 µg/m ³)	pathological fracture), and M82		Osteoporosis Prevalence: 1.12 (1.07, 1.18)
Follow-up n = 330,998		Exposure years: NO ₂ : 2005–2007, 2010; NO _x : 2010	P75 = 17.9 (33.68 µg/m ³)	(osteoporosis in diseases	Logistic regression	NO _x HR (95% CI) ^c
United Kingdom			NO _x (µg/m ³)	classified elsewhere)	Adjusted for: age at recruitment, sex, education level, annual household income, ethnicity, Townsend deprivation, smoking status, and physical activity	Osteoporosis Incidence: 1.06 (1.03, 1.09) OR (95% CI) ^c
Enrollment: 2006–2010			Mean = 43.56±15.52 Median = 41.89 (IQR 16.6)			Osteoporosis Prevalence: 1.04 (1.01, 1.06)
Follow-up through 2021			P25 = 33.84 P75 = 50.43			
Cross-Sectional						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Yu et al. (2023)	UK adults aged between 40–69 years	LUR	NO ₂ (ppb)	Osteoporosis ICD 10 codes M80, M81, M82	Cox proportional hazard model	NO ₂ HR (95% CI) ^b Osteoporosis: 1.71 (1.18, 2.49) Fracture: 1.51 (1.10, 2.06)
UK Biobank		NO ₂ r ² = 87% NO _x r ² = 88%	Mean = 15.48±4.88 (29.12±9.19 µg/m ³)	Fracture ICD 10 codes: M484, M485, M80, M843, M844, S12, S22, S32, S42, S52, S72, S82, Z8731, Z87310, Z87311	Adjusted for: age, sex, genotyped batch, Townsend deprivation index, height, weight, smoking status	NO _x HR (95% CI) ^c Osteoporosis: 1.03 (1.01, 1.05) Fracture: 1.02 (1.01, 1.04)
N = 430,120 OP cases: 13,291 fracture cases: 19,695		Averaging time: NO ₂ - annual average, NO _x - annual average	NO _x (µg/m ³) Mean = 43.86±15.59			
United Kingdom		Exposure years: NO ₂ : 2005, 2006, 2007, 2010; NO _x : 2010				
Baseline: 2006–2010						
Cohort						
Other Health Effects						
† Adams et al. (2016)	Older adults aged 57 to 85 years.	Monitor data	NO ₂ (ppb)	Olfactory function was assessed with the odor identification portion of the Olfactory Function Field Exam, a validated test for field studies.	Logistic regression	OR (95% CI) ^c Olfactory dysfunction: 1.35 (1.07, 1.72)
National Social Life, Health, and Aging Project (NSHAP)		Averaging time: NO ₂ - 365-day moving average	Mean = 15.6±7 Median = 14.7 (IQR 8.9) P25 = 10.8 P75 = 19.7		Adjusted for: age (decades), sex, race/ethnicity, education, cognition, comorbidity (modified Charlson Index), current smoking, season of home interview	
n = 1,832		Exposure years: 2005–2006				
United States						
2005–2006						
Cohort						

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Honda et al. (2017) National Social Life, Health, and Aging Project (NSHAP) N = 4,121 Anemic n = 1,438 Non-anemic n = 2,683 United States Enrollment period 1: 2005–2006 Enrollment period 2: 2010–2011 Cohort	Older adults born between 1920 and 1947 selected from eligible households identified in the Health and Retirement Study (HRS).	EPA AQS Averaging time: NO ₂ - 1-year moving average NO ₂ - 2-year moving average NO ₂ - 3-year moving average NO ₂ - 4-year moving average NO ₂ - 5-year moving average Exposure years: NA	NO ₂ (ppb) Anemic Mean = 14.5±6.8 Non-anemic Mean = 13.3±6.5 Total Mean = 13.11±7	Hemoglobin was collected via dried blood spots captured and transported on filter paper to centralized laboratories. Colorimetric analysis was conducted using Drabkin's solution, which converts hemoglobin to cyanmethemoglobin. Color development in the sample is directly proportional to hemoglobin concentration and can be read photometrically	Linear regression Adjusted for: age, sex, tobacco use, physical activity, education, race, region, census tract data on median household income, percent of households living below the poverty line, urbanicity, use of: glucocorticoids, anti-neoplastics, anti-rheumatics, diuretics, and recombinant erythropoietin Linear regression - Mediation analysis Adjusted for: age, sex, tobacco use, physical activity, education, race, region, census tract data on median household income, percent of households living below the poverty line, urbanicity, use of: glucocorticoids, anti-neoplastics, anti-rheumatics, diuretics, and recombinant erythropoietin	PR (95% CI) ^c Hemoglobin - 1-year moving average: 1.43 (1.25, 1.63) Hemoglobin - 2-year moving average: 1.39 (1.26, 1.56) Hemoglobin - 3-year moving average: 1.39 (1.25, 1.56) Hemoglobin - 4-year moving average: 1.34 (1.20, 1.49) Hemoglobin - 5-year moving average: 1.33 (1.20, 1.48) Hemoglobin - 1-year moving average: 1.34 (1.17, 1.54) Hemoglobin - 2-year moving average: 1.33 (1.19, 1.49) Hemoglobin - 3-year moving average: 1.35 (1.21, 1.51) Hemoglobin - 4-year moving average: 1.31 (1.18, 1.46) Hemoglobin - 5-year moving average: 1.31 (1.18, 1.45) β (g/dL decrease in hemoglobin) (95% CI) ^c Hemoglobin - Mediation analysis: C-reactive protein as a mediator; Total effect: -0.73 (0.00, 0.00) Hemoglobin - Mediation analysis: C-reactive protein as a mediator; Indirect effect: -0.09 (0.00, 0.00)

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Li et al. (2022)	Participants were aged 37 to 73 between 2006 and 2010. If missing sleep-related variables, participants were excluded (n: 90,132). If missing ambient air pollution or road traffic noise data, participants were excluded (n: 34,134).	LUR	NO ₂ (ppb)	Self-report of sleep behaviors (snoring, chronotype, sleep duration, excessive daytime sleepiness, and insomnia)	Logistic regression	NO ₂ OR (95% CI) ^b
UK Biobank		Averaging time: NO ₂ - annual average, NO _x - annual average	Healthy Sleep Pattern (n: 140,490) Mean = 13.92±4.04 (26.19±7.61 µg/m ³)		Adjusted for: age, gender, ethnicity, professional qualification, smoking, drinking, employment, BMI categories, and physical activity	Sleep pattern - Intermediate vs. Healthy: 1.06 (1.05, 1.07) Sleep pattern - Poor vs. Healthy: 1.12 (1.09, 1.15)
n = 378,223		Exposure years: 2010	Intermediate Sleep Pattern (n: 220,627) Mean = 14.11±4.01 (26.55±7.54 µg/m ³)			NO _x OR (95% CI) ^c
United Kingdom			Poor Sleep Pattern (n: 17,106) Mean = 14.5±4.08 (27.3±7.68 µg/m ³)			Sleep pattern - Intermediate vs. Healthy: 1.05 (1.04, 1.07) Sleep pattern - Poor vs. Healthy: 1.12 (1.08, 1.15)
2006–2010			NO _x (µg/m ³)			
Cohort			Healthy Sleep Pattern (n: 140,490) Mean = 43.12±15.42			
			Intermediate Sleep Pattern (n: 220,627) Mean = 43.86±15.49			
			Poor Sleep Pattern (n: 17,106) Mean = 45.42±16.06			

Study Reference	Participant Description	Exposure Assessment	Concentration Examination ^a	Outcome Assessment	Statistical Model and Confounders	Effect Estimate (95% CI)
† Szyszkowicz et al. (2021) N = 882,918 Toronto, Canada April 2004–December 2015 Cohort	Patients with emergency department visits for genitourinary system.	Central site monitor Averaging time: NO ₂ - 24-hour average Exposure years: April 2004 to December 2015	NO ₂ (ppb) Mean = 16.1 Median = 15 (IQR 8.1) Min = 3.2 Max = 59.8 P25 = 11.1 P75 = 19.9	ICD 10 codes N00 to N99	Poisson regression	RR (95% CI) ^b ED visits for genitourinary system - lag 0: 1.07 (1.05, 1.09) ED visits for genitourinary system - lag 1: 1.03 (1.01, 1.04) ED visits for genitourinary system - lag 2: 1.01 (1.00, 1.03) ED visits for genitourinary system - lag 0 - Females: 1.06 (1.04, 1.08) ED visits for genitourinary system - lag 0 - Males: 1.08 (1.05, 1.10)

List of abbreviations in alphabetical order: AQS = air quality system; BMI = body mass index; CI = confidence interval; CMAQ = community multiscale air quality modeling system; ED: emergency department; HR = hazard ratio; IQR = interquartile range; IRR = incidence rate ratio; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; NO = nitric oxide; OR = odds ratio; O₃ = ozone; ppb = parts per billion; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; RR = rate ratio; SE = standard error.

^aFor studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.

^bEffect estimates are standardized and are presented as a 20 ppb change in NO₂ for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_x for 24-hour averaging time; 25 ppb change in NO₂ for 1-hour maximum averaging time; 60 ppb change in NO for 1-hour maximum averaging time; 80 ppb change in NO_x for 1-hour maximum averaging time; 25 ppb change in NO₂ for 8-hour maximum averaging time; 40 ppb change in NO for 8-hour maximum averaging time; 80 ppb change in NO_x for 8-hour maximum averaging time; a 10 ppb change in NO₂ for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_x for annual average averaging time.

^cEstimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

Appendix Table 13-2 Toxicological studies of oxides of nitrogen exposure and hepatic effects

Study Details and Population	Exposure Details	Endpoints Examined*
† Guo et al. (2023) Mouse (C57BL/6) Age not reported, males and females n = 3–9/group	Whole body inhalation with room air controls 2,500 ppb (2.5 ppm) NO ₂ , 5 hr/d for 28 d	Timing unclear - Hepatic H&E analysis (Inflammasome aggregation and steatosis) - Hepatic collagen fibers (sirius red stain) (NS) - Hepatic lipid content (oil red O stain) (♀↑) - Serum ALT, AST, and ALP activity (♀↑)

List of abbreviations in alphabetical order: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; H&E = hematoxylin and eosin stain; n = sample size; NO₂ = nitrogen dioxide.

*Simplified results interpreted as: NS = no experimental groups were significantly different from control; ♀↑ = results were analyzed by sex and there was a statistically significant increase in at least one female experimental group and non-significant effect in males.

†Studies published since the 2016 Oxides of Nitrogen ISA.