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Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 6: Cardiovascular Effects – Long-Term Exposure

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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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Acronyms and Abbreviation

AARP	American Association of Retired People
ABI	Ankle Brachial Index
ADONIX	Adult-Onset asthma and exhaled Nitric Oxide
AIC	Akaike Information Criterion
AQS	Air Quality System
ATP	adenosine triphosphate
AVC	aortic valve calcium
avg	average
β	beta
baPWV	brachial-ankle pulse wave velocity
BC	Black Carbon
BiB	Born in Bradford
BIC	Bayesian information criteria
BL	bronchial lavage
BLPM	Blood Pressure Lowering Medications
BMI	coronary heart disease
BP	Blood Pressure
CAC	coronary artery calcium
CAD	coronary artery disease
CanCHEC	Canadian Census Health and Environment Cohort
CANDLE	Conditions Affecting Neurocognitive Development and Learning in Early Childhood
CAVI	cardio-ankle vascular index
CBVD	cerebrovascular disease
CCHS	Canadian Community Health Survey
CEANS	Cardiovascular Effects of Air Pollution and Noise in Stockholm
CFPS	China Family Panel Studies
CHAPS	Children's Health and Air Pollution Study
CHARLS	China Health and Retirement Longitudinal Study
CHD	Congenital heart disease
CHF	congestive heart failure
CHRLS	China Health and Retirement Longitudinal Study
CHS	Children's Health Study
CI	confidence interval
cIMT	carotid intima-media thickness
CKD	Chronic Kidney Disease
CLHLS	Chinese Longitudinal Healthy Longevity Survey
Cm^3	cubic centimeters
CMD	cardiometabolic disease
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CPD	cardiopulmonary disease
CPS- II	Cancer Prevention Study-II cohort
CRP	high-sensitivity C-reactive protein
CTM	chemical transport modeling
CTS	California Teachers' Study
C-V	cross-validation
CVD	cardiovascular disease
C-R	concentration-response
d	square distance
DBP	diastolic blood pressure
DCH	Danish Diet, Cancer and Health
DEHM	Danish Eulerian Hemispheric Model
df	degrees of freedom
DHC	Danish Nurse Cohort
DID	difference-in-difference
DNA	Deoxyribonucleic acid
DNBC	Danish National Birth Cohort
DNC	Danish Nurses' Cohort
Dutch PHM	Dutch Public Health Monitor
Dx	diagnosis
E3N	Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale
ED	emergency department
EDEN	´Etude des D´eterminants pr´e-et postnatals du d´eveloppement et de la sant´e de l'Enfant
EDV	end-diastolic volume
EE	effect estimate
EC	elemental carbon
EF	ejection fraction
e.g.	exempli gratia (for example)
EGAT	Electricity Generating Authority of Thailand
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ELF	epithelial lining fluid
EMM	effect measure modification
ENVIRONAGE	ENVIRonmental influence ON AGEing
EPA	Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer and Nutrition

EPIC-MORGEN	European Prospective Investigation into Cancer and Nutrition- Monitoring Project on Risk Factors and Chronic Diseases in Netherlands;
EPIC-NL	European Prospective Investigation into Cancer and Nutrition in the Netherlands
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
etc.	et cetera
ETS	environmental tobacco smoke
F	female(s)
Fe	iron
FCMD	First Cardiometabolic Disease
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
g	gram(s)
GDM	Gestational Diabetes Mellitus
GDP	Gross Domestic Product
GEE	generalized estimating equation
GINIplus	German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy
GMC	Good Movement Corridor
GRAD	Greek administrative cohort
h	hour
Hb	Hemoglobin
HDL	high density lipid
HEI	Health Effects Institute
HELIX	Human Early-life Exposome project
HF	heart failure
HNR	Heinz Nixdorf Recall
HR	hazard ratio
hr	hour(s)
HRS	Health and Retirement Study
HRV	heart rate variability
HS	Hemorrhagic Stroke
HSC	Harvard Six Cities study
HUBRO	Oslo Health Study
HUNT	Helseundersøkelsen i Nord-Trøndelag
HYENA	Hypertension and Environmental Noise near Airports
ICAM-1	intercellular adhesion molecule 1
ICC	immunocytochemistry
ICD	International Classification of Diseases
ICD-(10)	International Classification of Diseases-(Clinical Modification)
IDW	Inverse distance weighting
IHD	ischemic heart disease
IL-6	interleukin 6
IL-8	interleukin 8
ILS	Italian Longitudinal Study
INMA	INfancia y Medio Ambiente
INTERGENE	Interplay between Genetic susceptibility and environmental factors for the risk of chronic diseases in West Sweden
IPW	inverse probability weighted
IQR	interquartile range
IRR	incidence rate ratio
IS	Ischemic Stroke
ISA	Integrated Science Assessment
JOR	joint odds ratios
KANC	Kaunas Cohort
KED	Kriging with external drift
KORA	Cooperative Health Research in the Region of Augsburg
KPNC	Kaiser Permanente Northern California
L	liter(s)
LA	left atrial
LA EF	Left Atrial Ejection Fraction
LAVI	left atrial volume index
LDL	low density lipid
LETO	Long-Evans Tokushima
LISA	Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Childhood
LOOCV	leave-one-out cross-validation
LRT	likelihood-ratio test.
LSOAs	Lower Super Output Areas
LTA	lifetime average
LTL	leukocyte telomere length
LUR	Land use regression
LV	Left Ventricular
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

LVEF	Left Ventricular Ejection Fraction
LVESD	left ventricle end-systolic diameter
LVESV	Left Ventricular end-systolic volume
LV mass	Left Ventricular mass
LVMVR	Left Ventricular mass to end-diastolic volume ratio
LVPWd	left ventricular end-diastolic posterior wall thickness
LVPWs	left ventricular end-systolic posterior wall thickness
m^3	Meters cubed
M	male
m	milligram
M/F	male/female
m/s	meter per second
m	meter(s)
M-CHAT	Multicultural Community Health Assessment Trial
MA	moving average
MAC	mitral annular calcium
MAP	Mean Arterial Pressure
Max	Maximum
MDA	malondialdehyde
MEDPAR	Medicare Provider Analysis and Review
MESA	Multi-Ethnic Study of Atherosclerosis
MET	Metabolic Syndrome
mg/dL	milligrams per deciliter
MI	myocardial infarction
min	minute(s)
mL	milliliter
mmHg	millimeters of mercury
mo	month(s)
MoBa	Norwegian Mother and Child Cohort Study
MORGEN	Monitoring Project on Risk Factors and Chronic Diseases in Netherlands
MPP	Mean Pulse Pressure
MR	means ratios
MRI	magnetic resonance imaging
ms	milliseconds
MS	multiple sclerosis
MSE	mean square error
N	Population size
NAPS	National Air Pollution Surveillance
NDIT	Nicotine Dependence in Teens Study
NDVI	Normalized Difference Vegetation Index
NEPSY	Neuropsychological Assessment
NHIRD	National Health Insurance Database
NHID	National Health Information Database
NHIS	National Health Insurance Survey
NHS	Nurses' Health Study
NIH	National Institutes of Health
NLCS	Netherlands Cohort Study on Diet and Cancer
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO	nitric oxide
NO_2	nitrogen dioxide
NO_X	NO_2 + NO
NOMAS	Northern Manhattan Study
NR	Not reported
NSHAP	National Social Life Health, and Aging Project
nSES	neighborhood socioeconomic status
O_2	oxygen
O_3	ozone
OHS	Ontario Health Study
OLETF	Otsuka Long-Evans Tokushima fatty
ONPHEC	Ontario Population Health and Environment Cohort
OP DTT	oxidative potential dithiothreitol
OP ESR	oxidative potential electron spin resonance
OR	odds ratio
OSA	obstructive sleep apnea
OSPM	Operational Street Pollution Model
OXPHOS	mitochondrial oxidative phosphorylation capacity
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PHM	Public Health Monitor
PM	particulate matter
$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm
PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 µm
POR	Prevalence Odds Ratio
ppb	parts per billion
ppm	parts per million
PSG	polysomnography
PWV	pulse wave velocity
Q	quantile (could be quartile or quintile)
R	Organic radical
r^2	quality assurance
RA	Right Atrial
RA EF	Right Atrial Ejection Fraction
RD	Risk Difference
Ref	Reference

REIN	Renal Epidemiology and Information Network
RERI	relative excess risk due to interaction
RHEA	Mother and Child Cohort in Crete
RHINE	Respiratory Health in Northern Europe
RMSE	root mean square error
RoLS	Rome Longitudinal Study
ROS	Reactive Oxygen Species
RR	relative risk or risk ratio
RVEDV	Right Ventricular end-diastolic volume
RVEF	Right Ventricular Ejection Fraction
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 Aging
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
SBI	subclinical brain infarct
SBP	systolic blood pressure
SCAPIS	Swedish Cardio Pulmonary bioImage Study
SCHIF	Shape Constrained Health Impact Function
SD	standard deviation
SDPP	Stockholm Diabetes Prevention Program
SE	standard error
SES	socioeconomic status
SIDRIA-Turin	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
SNP	single-nucleotide polymorphisms
SO_2	sulfur dioxide
SPARC	Stroke Prevention and Atherosclerosis Research Centre
SPB	Systolic Blood Pressure
T	tertile
t	time
TAC	thoracic aortic calcification
TBARS	thiobarbituric acid reactive substances
TCBV	total cerebral brain volume
TDI	Townsend Deprivation Index
TI	tortuosity index
TPVV	Total Pulmonary Vascular Volume
$TPVV_{CT}$	total pulmonary vascular volume using noncontrast chest computed tomography
UBM	Urban Background Model
UFP	Ultrafine particle
µg	microgram
U.K.	United Kingdom
µm	Micrometer
U.S.	United States
VCMS	Veterans' Cohort Mortality Study
VHM&PP	Vorarlberg Health Monitoring and Prevention Programme
vs.	versus
WHI	Women's Health Initiative
WHO	World Health Organization
WMHV	log-white matter hyperintensity volume
wk	week(s)
yr	year(s)
33 CCHS	33 Communities Chinese Health Study

CHAPTER 6 Cardiovascular Effects – Long-Term Exposure

Summary of Causality Determinations for Long-Term Oxides of Nitrogen Exposure and Cardiovascular Effects

This chapter characterizes the scientific evidence that supports causality determinations for long-term oxides of nitrogen exposure and cardiovascular effects. The types of studies evaluated within this chapter are consistent with the overall scope of the Integrated Science Assessment as detailed in Chapter 14 (see Section 14.4.3.2). In assessing the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in Table 14-5 of Chapter 14. More details on the approach used to make causality determinations is included in Appendix A of Volume 2 of the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (U.S. EPA, 2024), which builds on the approach described in the 2015 Preamble to the Integrated Science Assessments (U.S. EPA, 2015). The evidence presented throughout this chapter supports the following causality conclusion(s):

Outcome	Causality Determination
Cardiovascular Effects	Suggestive of, but not sufficient to infer, a causal relationship

The Executive Summary, Integrated Synthesis, and all other appendices of this ISA can be found at https://www.epa.gov/isa/integrated-science-assessment-isa-oxides-nitrogen-health-criteria.

6.1 Introduction

6.1.1 Summary of Previous ISA

The U.S. Environmental Protection Agency's (EPA) 2016 Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (hereafter referred to as the 2016 Oxides of Nitrogen ISA) reviewed evidence of long-term oxides of nitrogen exposure and cardiovascular effects together with endpoints related to metabolism and diabetes (U.S. EPA, 2016) and determined the evidence to be suggestive of, but not sufficient to infer, a causal relationship. In this ISA, evidence for effects of oxides of nitrogen exposure on metabolism and diabetes is discussed in Chapter 8. The key evidence related to long-term nitrogen dioxide (NO_2) exposure and cardiovascular effects in the 2016 Oxides of Nitrogen ISA is briefly summarized below.

Several large and well-conducted prospective epidemiologic studies reported positive associations between long-term NO_2 exposure and both heart disease. Indications that findings were likely to be biased by selective participation or missing data were not evident, and studies generally considered potential confounding by a wide array of cardiovascular risk factors. Annual average or multi-year average residential exposures were typically considered surrogates for long-term exposure in these studies and studies were generally not designed to distinguish the effect of long- from short-term exposures. Exposure assessment methods varied across studies; however, several studies used well-validated methods that captured fine-scale variability in NO_2 concentrations. Confounding by correlated traffic-related pollutants and noise, however, remained an uncertainty because these co-occurring environmental exposures may be independently associated with cardiovascular effects. Further, experimental studies did not clearly support the biological plausibility of associations observed in the epidemiologic studies. Further, most studies did not distinguish the effects of long- from short-term exposure. These limitations introduced uncertainty regarding the independent effect of long-term NO_2 exposure. **Overall, the evidence from epidemiologic and experimental studies in the 2016 Oxides of Nitrogen ISA was determined to be *suggestive of, but not sufficient to infer, a causal relationship* between long-term NO_2 exposure and cardiovascular effects.**

6.1.2 Chapter Organization and Conventions

This chapter evaluates recent evidence examining the relationship between long-term oxides of nitrogen exposure and cardiovascular effects.[1] The following sections provide an overview of study inclusion criteria for this chapter (see Section 6.2), summaries of recent health effects evidence (see Sections 6.3 to 6.8), a discussion of biological plausibility (see Section 6.9), a summary of lifestages and population differences (see Section 6.10, Table 6-1), and a discussion of the causality determination for long-term oxides of nitrogen exposure and cardiovascular effects (see Section 6.11, Table 6-2). Evidence inventories include study-specific details for the epidemiologic and toxicological studies including, for example, study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are located in Appendix A – Appendix Tables. For outcomes supported by evidence from multiple disciplines, subsections titled "Synthesis Across Lines of Evidence" are included.

6.1.2.1 Epidemiologic Studies

In sections assessing the epidemiologic evidence, this chapter summarizes the evidence from previous ISAs and from recent studies that have become available since the last ISA. When relevant

[1]Evidence related to metabolic effects, including diabetes, and exposure to oxides of nitrogen is discussed separately in Chapter 8.

information is available from older or more recent epidemiologic studies, these sections additionally include targeted discussion of available analyses examining concentration-response relationships, effects in particular lifestages and populations, and the potential for confounding by copollutants. For apical endpoints with no or limited evidence on these topics, the subsections addressing them are not included.

In the assessment of the recent epidemiologic evidence, the "Lifestages and Populations" sections, as well as "Summary of Lifestage and Populations" section, discuss analyses of effect measure modification. Effect measure modification occurs when the effect of a pollutant exposure on a health outcome of interest differs between subgroups or strata of risk factors (Rothman and Greenland, 1998). When a risk factor is an effect measure modifier, it changes the magnitude of the association between the pollutant exposure and the health outcome in stratified analyses. For risk factors that modify the association, effect estimates for each stratum will differ from one another and from the overall estimate, indicating there to be different quantitative relationships between exposure metric and outcome for populations represented by these variables.

In the assessment of recent epidemiologic evidence, the "Copollutant" section discussed examination of potential confounding by copollutants. Copollutant modeling, sometimes referred to as two-pollutant models or co-adjusted models, can reduce concern for confounding by copollutants when correlations between the copollutants are relatively low (e.g., correlation coefficient, rho (ρ) <0.4). However, when correlations are high (e.g., ρ>0.7), collinearity between pollutants makes copollutant modeling less informative, leading to greater uncertainty in the degree to which reported associations reflect health effects of exposure to oxides of nitrogen independently.

Throughout this chapter, long-term exposure to oxides of nitrogen is assumed to be approximately 30 days or greater. Additionally, in the summaries of the recent epidemiologic evidence, the abbreviation "NO_X" is widely used in the epidemiologic literature and is assumed to be the sum of nitric oxide (NO) and NO_2, which are the dominant forms of oxides of nitrogen emitted from major sources (see Chapter 1, Section 1.3.1 and Chapter 2, Section 2.2).

To increase the comparability of results across epidemiologic studies, this Oxides of Nitrogen ISA presents effect estimates for associations with health outcomes scaled to the same increment of oxide of nitrogen concentration.[2]

For long-term exposure metrics, effect estimates are scaled to a 10 parts per billion (ppb) increase in NO_2, a 15-ppb increase in NO, and a 20-ppb increase in NO_X. These increments were derived by calculating the United States nationwide percentile distributions for annual average concentrations and then calculating the approximate difference between the median (a typical pollution year) and the 95th percentile (a more polluted year) concentrations among monitors in the State and Local Air Monitoring Stations network. Long-term averages of oxides of nitrogen in ambient air are less variable across time,

[2]This is in contrast with reported effect estimates that are scaled to various changes in concentration, such as interquartile range for the study period or an arbitrary unit such as 10 ppb.

and do not differ widely among multi-month averages, annual averages, or multi-year averages. Thus, all long-term exposure metrics were scaled to the same increment. Some studies reported effect estimates in terms of $\mu g/m^3$ increases in oxides of nitrogen, which could be converted to ppb and standardized for NO_2 and NO but not NO_X. This conversion could not be made for NO_X because the proportions of NO_2 and NO are unknown for the various NO_X metrics. Also, data are not available to calculate the percentiles of NO_X concentrations in micrograms per cubic meter ($\mu g/m^3$) at a national scale for the United States or other countries. Therefore, the ISA presents effect estimates based on $\mu g/m^3$ of NO_X as they are reported in their respective studies.

6.1.2.2 Animal Toxicological Studies

In sections assessing the animal toxicological evidence, this chapter summarizes the evidence from previous ISAs and from recent studies that have become available since the last ISA. When relevant information is available from recent animal toxicological studies, targeted discussions of analyses examining dose-response relationships, relevance of toxicological responses to human responses, and multipollutant exposures are included. For apical endpoints with no or limited evidence on these topics, the subsections addressing them are not included.

6.2 Scope

The evidence that has become available since the 2016 Oxides of Nitrogen ISA has been evaluated for relevance using scoping criteria defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statements help to define the scope of the assessment and establish study inclusion criteria, thereby facilitating identification of the relevant literature for this Oxides of Nitrogen ISA.[3] In order to identify the most relevant literature, the body of evidence from the 2016 Oxides of Nitrogen ISA was considered in the development of the PECOS statements for this chapter. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2016 Oxides of Nitrogen ISA inform the scope of this chapter. Studies that were included in the 2016 Oxides of Nitrogen ISA, including studies that do not meet the current PECOS criteria, are discussed in this chapter to establish the state of the evidence prior to this assessment. Except for supporting evidence used to examine the biological plausibility of oxides of nitrogen-associated cardiovascular effects, recent studies

[3]The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review (narrative, scoping, systematic, and meta-analyses of systematic reviews) articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases), and health impact assessments (an assessment tool used to designed to investigate how a proposed program, project, policy, or plan may impact health and well-being and inform decision-makers of these potential outcomes before the decision is made).

were only included if they meet all components of the discipline-specific PECOS statements (see below) and satisfy discipline-specific study quality criteria (Chapter 14).

Epidemiologic Studies:

Population: Any human population, including populations or lifestages that might be at increased risk.

Exposure: Exposure to oxides of nitrogen concentrations relevant to ambient air in the United States.[4]

Comparison: Per unit increase (in ppb) or humans exposed to lower concentrations of oxides of nitrogen compared to higher concentrations (e.g., categorical comparisons between different exposure metric quantiles).

Outcome: Change or difference in risk (incidence/prevalence) of cardiovascular health effects.

Study Design: Epidemiologic studies, such as panel, case-crossover, time-series, case-control studies, cohort, cross-sectional studies, and quasi-experimental, with appropriate timing of exposure for the health outcome of interest.

Study Design: Studies that perform controlled human exposures meeting the above criteria or that analyze data from previously conducted controlled human exposures (e.g., reanalysis, meta-analysis).

Animal Toxicological Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., nonhuman primate, mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage including models of increased susceptibility.

Exposure: Inhalation exposure to relevant oxides of nitrogen concentrations (i.e., 5 ppm or below).[5]

[4]Epidemiologic studies examining associations with NO_2 that report an overall average of NO_2 exposures (i.e., averaged across study populations/locations and over study periods) above 22 ppb were flagged for additional study quality evaluation. This concentration cutoff reflects the 98th percentile of annual average NO_2 concentrations measured at ambient monitors in the United States during the most recent 15-years of available data (i.e., 2008 to 2022) (U.S. EPA, 2023). Studies reporting average NO_2 exposures greater than 22 ppb are considered for inclusion in the ISA if they meet additional study quality criteria described in the Process chapter (See Chapter 14).

[5]Five ppm is approximately two orders of magnitude higher than peak NO_2 concentrations in the ambient air in the United States. As discussed in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and in the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen Volume 2 (U.S. EPA, 2024), animal exposures within one to two orders of magnitude of recent ambient air concentrations are considered relevant to ambient air exposures. This concentration cutoff is also consistent with that used in the 2016 ISA for Oxides of Nitrogen – Health Criteria (U.S. EPA, 2016). Experimental studies investigating the effects of concentrations greater than 5 ppm may be considered for inclusion in the ISA if they provide insight into biological plausibility.

Comparison: An appropriate control group exposed to clean air (e.g., room air, filtered air).

Outcome: Cardiovascular effects.

Study Design: Controlled exposure studies of animals in vivo meeting the above criteria.

6.3 Heart Disease

Several epidemiologic studies of the association between long-term exposure to oxides of nitrogen and cardiovascular disease (CVD) were assessed in previous Oxides of Nitrogen ISAs (U.S. EPA, 2016, 2008). Some epidemiologic studies reported positive associations of NO_2 and NO_X exposure with heart disease, stroke, and hypertension. The body of evidence in the 2016 Oxides of Nitrogen ISA was generally consistent for heart disease and included several large, longitudinal studies with consideration of multiple potential confounding factors including age, sex, body mass index (BMI), smoking, and pre-existing conditions. The evidence comprised analyses of large U.S. cohorts of women including the Women's Health Initiative (WHI) (Miller et al., 2007), the Nurses' Health Study (NHS) (Lipsett et al., 2011), and California Teachers' Study (CTS) (Hart et al., 2013) as well as several Canadian (Beckerman et al., 2012; Gan et al., 2011) and European studies (Cesaroni et al., 2014; Atkinson et al., 2013). Some studies were notable for their use of land use regression (LUR) models that underwent rigorous stepwise regression to obtain best fit (Cesaroni et al., 2014; Beckerman et al., 2012). Beckerman et al. (2012) and de Kluizenaar et al. (2013) reported that their results persisted after adjustment for particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) and noise, respectively. Overall, most epidemiologic studies, however, were not designed to distinguish the independent effect of NO_2 from other traffic-related pollutants [i.e., $PM_{2.5}$, carbon monoxide (CO), black carbon (BC), elemental carbon (EC), ultrafine particles (UFP), other particulate matter (PM) constituents, and volatile organic compounds (VOCs)], traffic noise, or stress (U.S. EPA, 2016).

6.3.1 Epidemiologic Studies of Myocardial Infarction and Coronary Heart Disease

Recent studies add to the evidence base pertaining to heart diseases including myocardial infarction (MI) and coronary heart disease (CHD). Study-specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 6-1. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in greater detail in Sections 6.3.1.1, 6.3.1.2, and 6.3.1.3, respectively. Section 6.3.1.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for MI and CHD.

Among the recent studies are several analyses of U.S. Medicare data that comprises men and women 65-years or older. These studies typically rely on national hospital admission data collected over multiple years for millions of beneficiaries.

- (Schwartz et al., 2023) analyzed data from more than four million hospital admissions among U.S. Medicare recipients 65-years or older. Annual average NO_2 concentration was estimated at the zip code level using a high-resolution spatiotemporal model (1 x 1 km grid) that combined estimates from several machine learning algorithms with LUR, chemical transport model predictions, satellite data, and meteorologic variables. The R^2 value for the accuracy of the model predictions, which was assessed using 10-fold C-V against held out monitoring site measurements, was 0.84 for NO_2. Grid cell concentrations were averaged, and exposure was assigned based on the zip code of the residence. The change in MI rate associated with NO_2 exposure was estimated using several methods, each subject to different potential biases, including regression adjustment with propensity scores, negative controls, and a difference in differences (DID) approach with a separate spline for time varying factors, which was designed to control both measured and unmeasured confounders but may be subject to bias resulting from misclassification or exclusion of time intervals (Sheridan et al., 2023). The change in MI rate per 10,000 persons was inconsistent in direction and magnitude across methods (see Table 6-3).

Table 6-3 Results of the Schwartz et al. (2023) study comparing epidemiologic methods

Epidemiologic Method	Change in MI Rate Per 10,000 Person-Years for Each 10 ppb Increase in NO_2 Exposure	Description and Assumptions
Regression adjustment	0.13 (-0.735, 0.995)	Models are fit within categories of exposure that predict the outcome based on all the covariates, including other air pollutants, to obtain category specific coefficients of the effect of the covariates on the outcome, conditional on being exposed in that category. Results can be used to directly estimate the counterfactual.
Regression adjustment + Inverse Probability Weighting	0.93 (-0.52, 2.38)	Propensity scores that rely on the assumption that inverse probability weights make exposure independent of all covariates were used to serve as a valid substitute for the counterfactual, assuming no unmeasured confounding. Although this assumption cannot be tested, the method offers an approach to high-dimensional confounding and complex functional forms and allows for the possibility of checking covariate balance after weighting and matching.
Negative Controls	0.66 (0.785, 0.535)	A quasi-Poisson model was used to estimate the exposure effect, adjusting for covariates including the copollutants, and negative exposure and outcome controls to control for unmeasured confounding.
Two-way fixed effect model (referred to as "Difference in Differences" by the authors)	-0.80 (-0.005, -1.595)	This method relies on the assumption that time trends due to unmeasured confounders are the same in each exposure group (i.e., parallel trends assumption).

List of abbreviations in alphabetical order: MI = myocardial infarction; NO_2 = nitrogen dioxide; ppb = parts per billion.

- Several other Medicare analyses using the exposure assessment method described by Schwartz et al. (2023) report inverse associations of long-term NO_2 exposure and MI hospitalizations. Danesh Yazdi et al. (2021) employed a doubly robust method (i.e., inverse probability weighting and adjustment in the outcome model) to estimate a Risk Difference (RD) of -0.0084% (95% CI: -0.0102, -0.0066) and Danesh Yazdi et al. (2022) employed a DID approach to obtain a RD of -8.3 (95% CI: -15.55, -1.05) per 100,000 person years. The main models from these studies were adjusted for $PM_{2.5}$ and ozone (O_3).
- In another analysis of U.S. Medicare data, Klompmaker et al. (2021a) used Cox proportional hazard regression in combination with the previously mentioned exposure assessment approach (Schwartz et al., 2023). This study reported associations between annual average NO_2 exposure and CHD hospitalization (HR: 1.027 [95% CI: 1.023, 1.031]) in the full cohort. The association persisted in the fully adjusted model that was simultaneously adjusted for NO_2, O_3 and $PM_{2.5}$ (HR: 1.016 [95% CI: 1.012, 1.021]). A larger association was observed among those whose long-term exposure were always below 20 ppb (HR: 1.146 [95% CI: 1.133, 1.16]).

A recent study of Ohio, U.S., residents and several Canadian studies also add to the evidence that has become available since the 2016 Oxides of Nitrogen ISA.

- Hartiala et al. (2016) examined the association of long-term (36-months) NO_2 exposure with coronary artery disease (CAD) severity at baseline and risk of MI during a three-year follow-up period. Among Ohio residents in the study, no associations were observed. The odds ratio comparing the highest severity (>3 vessels) to the lowest severity (0 vessels) was inverse with CIs that overlapped with the null value, i.e., OR: 0.74 (95% CI: 0.31, 1.77). An imprecise inverse association with incident MI was observed (HR: 0.82 [95% CI: 0.4, 1.67]).
- Olaniyan et al. (2022) examined the association of NO_2 with incident hospitalization for MI among approximately 2.7 million participants in the Canadian Census Health and Environment Cohort (CanCHEC) who were followed from 2006 to 2016. The 10-year moving average NO_2 concentration was estimated using a national LUR model that explained 75% of the variance in NO_2 concentrations at monitoring sites. The hazard ratio was 1.036 (95% CI: 1.001, 1.073) in the fully adjusted model. In two-pollutant models, adjusted for $PM_{2.5}$ and O_3, the associations were attenuated (HR: 1.017 [95% CI: 0.977, 1.06] and 1.01 [95% CI: 0.18, 5.56], respectively). Stratified analyses indicated that the single pollutant associations were stronger in the lower income quintiles and at higher O_3 concentrations (see Section 6.3.1.3).
- Recent analyses of the Canadian Ontario Population Health and Environment Cohort (ONPHEC) were also conducted. Bai et al. (2019b) used a Cox proportional hazards model approach to evaluate the association of long-term NO_2 exposure with physician-diagnosed MI. NO_2 concentration was estimated using a LUR model that explained 70% of the variance and 3-year moving averages, and exposures were assigned at the postal code level in this study. In age- and sex-stratified models that were adjusted for neighborhood level covariates the HR was 1.05 (95% CI: 1.0, 1.10). Associations were attenuated toward the null after adjustment for UFPs and $PM_{2.5}$ (HR: 0.98 [95% CI: 0.93, 1.03] and HR: 1.03 [95% CI: 0.98, 1.08]). In another analysis Bai et al. (2019a) conducted a concentration-response analysis (see Section 6.3.1.1) and presented results that are stratified by age, sex, income, and comorbid conditions (see Section 6.3.1.2).
- Also analyzing the ONPHEC data, Zhang et al. (2020) used LUR to estimate non-tailpipe emissions [i.e., iron (Fe) and Copper (Cu) in $PM_{2.5}$]. Annual average NO_2 was estimated

using a validated LUR model (r^2 = 0.69) to conduct analyses designed to distinguish the effects of non-tailpipe from tailpipe emissions. In addition, LUR models were used to estimate mass concentrations of $PM_{2.5}$, Cu and Fe and their impact on Reactive Oxygen Species (ROS) concentration in lung epithelial lining fluid. This study reported that associations between NO_2 and MI were attenuated after adjustment for ROS. The HR for the association between 3-year moving average NO_2 and MI was 1.067 [95% CI: 1.016, 1.12]. After adjustment for ROS, the association was attenuated (1.012 [95% CI: 0.958, 1.069]).

Many recent studies were conducted in Europe, including multi-country analyses and analyses of national datasets in Denmark, United Kingdom, Netherlands, Italy, and Sweden.

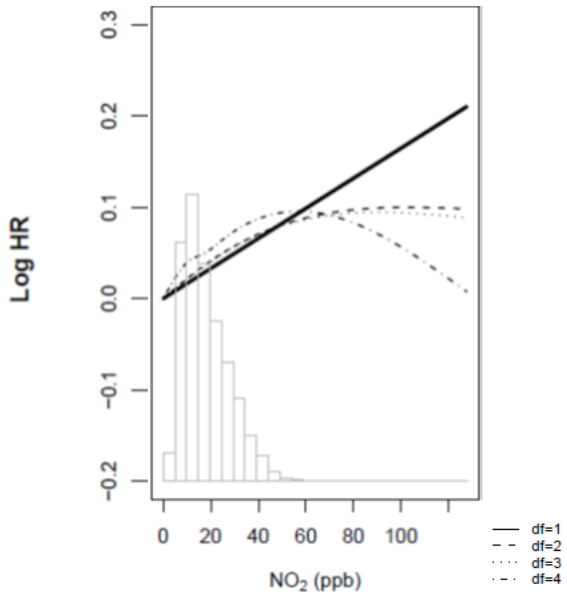
- Extensive analyses including comparisons of various methodological approaches were conducted and compiled in a Health Effects Institute (HEI) report focusing on the health effects of low-level pollution (i.e., concentrations below current international guidelines). In this study Brunekreef et al. (2021) used data from multiple European countries and developed an LUR model to estimate exposure that achieved a high spatial resolution for NO_2 (R^2: 0.58). The association (HR) of annual average NO_2 exposure assigned at baseline with CHD incidence was 1.08 (95% CI: 1.02, 1.14). The HR increased after adjustment for $PM_{2.5}$ (HR: 1.12 [95% CI: 1.04, 1.2]) and BC (HR: 1.18 [95% CI: 1.03, 1.34]) but was attenuated after adjustment for O_3 (HR: 1.04 [95% CI: 0.96, 1.12]). Select results from Brunekreef et al. (2021) were also reported by Wolf et al. (2021).
- Several studies were conducted using national datasets from Denmark. Poulsen et al. (2023c) examined the association between long-term NO_2 exposure (5-year running average) and MI among Danes aged 50 to 85 years. An integrated modeling approach (r = 0.60 to 0.80) for NO_2 that incorporated estimates from the Danish Eulerian Hemispheric Model (DEHM) for long-range transported regional background air pollution, the Urban Background Model (UBM) and the Operational Street Pollution Model (OSPM) was used. The association (HR) of NO_2 exposure with MI was 1.08 (95% CI: 1.05, 1.11). There was no evidence of effect modification by sociodemographic factors including sex, education, occupation, or income (see Section 6.3.1.2).
- Also in Denmark, Cramer et al. (2020) studied the association between residential NO_2 and NO_X exposure (1-, 3- and 23-year running means) and MI incidence (and fatal MI) among women enrolled in the Danish Nurses' Cohort (1993 to 1999; followed until 2014). The associations (HRs) of 1-, 3- and 23-year mean NO_2 exposure and MI were 1.10 (0.86, 1.40), 1.12 (95% CI: 0.88, 1.43) and 1.25 (95% CI: 0.98, 1.59), respectively. The HRs were not attenuated after adjustment for traffic noise across averaging times (e.g., HR for the association with 23 years mean NO_2 exposure: 1.12 (95% CI: 0.87, 1.44]). Associations with NO_X were generally weaker than associations with NO_2.
- Klompmaker et al. (2019) analyzed data from a national survey in the Netherlands to determine the relationship between green space, air pollution and road traffic noise with heart attack. Kriging with external drift (KED) was applied to the observed data and used in combination with a chemical transport model to estimate annual average exposure. NO_2 was inversely associated (OR included the null value) with self-reported heart attack (OR: 0.95 [95% CI: 0.87, 1.04]). In an analysis of National Health Interview Survey (NHIS) data from Italy and hospitalizations during follow-up, Gandini et al. (2018) observed positive associations between NO_2 and cardiac disease hospitalization (HR: 1.06 [95% CI: 1.02, 1.10]) and atherosclerosis disease hospitalization (HR: 1.20 [95% CI: 1.06, 1.35]).

- Cai et al. (2018) used data from three cohorts in Norway and the United Kingdom in combination with European LUR models to estimate the associations of annual average (2007) NO_2 and noise with incident CVD outcomes. An inverse association between long-term NO_2 exposure and ischemic heart disease (IHD) that was close to the null value was observed in the fully adjusted model (HR: 0.968 [95% CI: 0.865, 1.082]). Similarly, the association for acute coronary events was inverse and inclusive of the null (HR: 0.91 [95% CI: 0.76, 1.09]) and remained essentially unchanged after adjustment for noise (HR: 0.97 [95% CI: 0.87, 1.08]) as did the association with IHD (HR: 0.91 [95% CI: 0.76, 1.09]).
- Levinsson et al. (2014) used data from the 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) study to examine whether the risk of MI and hypertension differed depending on genotype strata for variants in the GSTP1, GSTT1 and GSTCD genes. The association (OR) between annual mean NO_2 and MI was 2.96 (95% CI: 1.08, 8.09). The effect of NO_2 exposure on the risk of acute MI varied by genotype strata; however, confidence intervals were overlapping (see Section 6.3.1.2).
- An analysis of the UK Biobank data reported that leukocyte telomere length (LTL) did not mediate the association between annual or multiyear average NO_2 exposure and CHD Kuo et al. (2023).

6.3.1.1 Concentration-Response

No studies examining the shape of the C-R curve were evaluated in the 2016 Oxides of Nitrogen ISA. Table 6-4 and Figure 6-1 to Figure 6-4 as well as the accompanying text summarize analyses of concentration-response relationships from recent studies of CHD. Overall, the limited evidence comprising studies of different populations and representing only a subset of those available, indicates a linear or supralinear relationship, with one study showing no association at concentrations below approximately 10.6 ppb (20 $\mu g/m^3$).

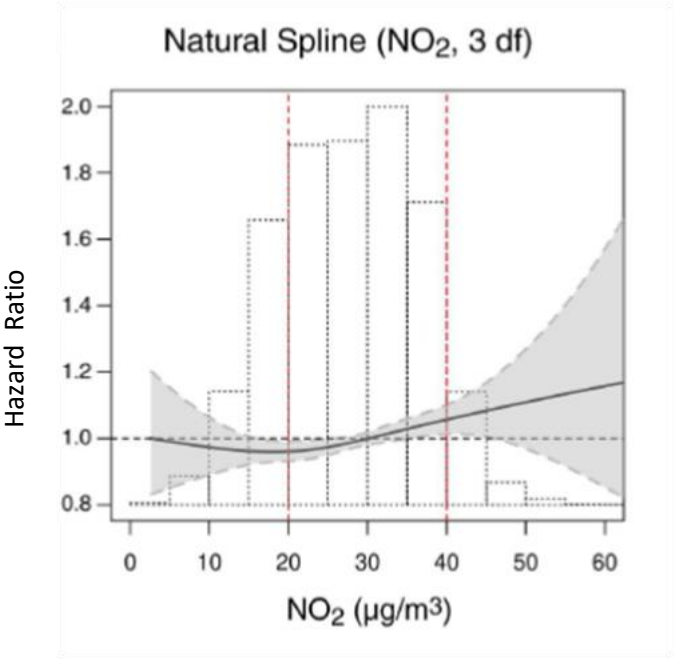
- Klompmaker et al. (2021a) examined the concentration-response relationship among Medicare recipients 65-years or older (see Figure 6-1). Natural splines with two, three, or four degrees of freedom were used. The concentration-response (C-R) function was linear or supralinear depending on the degrees of freedom. For the supralinear curves, the flattening occurred above approximately 60 ppb where data were sparse. Associations were larger in magnitude for the group with annual average exposures always below 20 ppb. There was no evidence of a threshold indicated by the analyses that were conducted.



List of abbreviations in alphabetical order: CHD = coronary heart disease; df = degrees of freedom; HR = hazard ratio; ppb = parts per billion.
Source: Klompmaker et al. (2021a). Copyright permission pending.

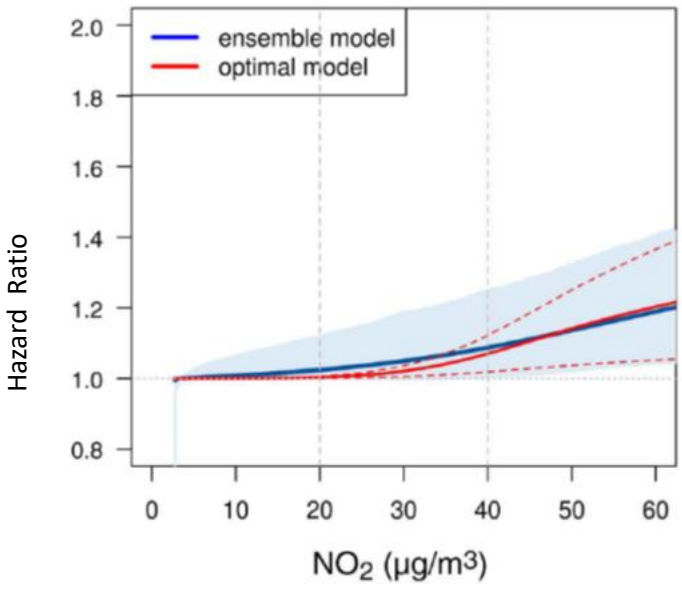
Figure 6-1 Concentration-response curve from fully adjusted models with natural splines (1, 2, 3, and 4 degrees of freedom) of NO_2 CHD hospitalization. Histograms of the exposure are shown on the x-axis.

- Brunekreef et al. (2021) conducted extensive C-R and threshold analyses in the European Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) cohort. The shape of the C-R relationship was examined using multiple methods including natural splines with 2–4 degrees of freedom and Shape Constrained Health Impact Function (SCHIF) using the fully adjusted model that included area-level socioeconomic status (SES) variables (see Figure 6-2 and Figure 6-3). The SCHIF model specifies a range of model shapes and the most optimal is selected. The ensemble model combines different sigmoidal models weighted by their likelihood. Penalized splines with degrees of freedom (df) determined by the algorithm were also modeled and showed similar patterns (not shown). There was little indication of an association between annual average NO_2 and CHD at concentrations below 20 µg/m^3 regardless of the method used to examine the shape of the function (i.e., the shape was sublinear). The subset analysis for CHD indicated pattern of imprecise associations that fluctuated in magnitude (i.e., 1.01 to 1.05 depending on the cut point [i.e., <40 µg/m^3 (21.3 ppb), <30 µg/m^3 (15.9 ppb), <20 µg/m^3 (10.6 ppb)]). In addition, the C-R model performance was slightly worse for CHD in the subset of data with concentrations <10.6 ppb.



List of abbreviations in alphabetical order: CHD = coronary heart disease; df = degrees of freedom; NO_2 = nitrogen dioxide.
Note: Red dotted lines are air quality limits and guideline values. Hazard ratios are relative to the minimum exposure. Histograms reflect the exposure distributions.
Source: Brunekreef et al. (2021). Copyright permission pending.

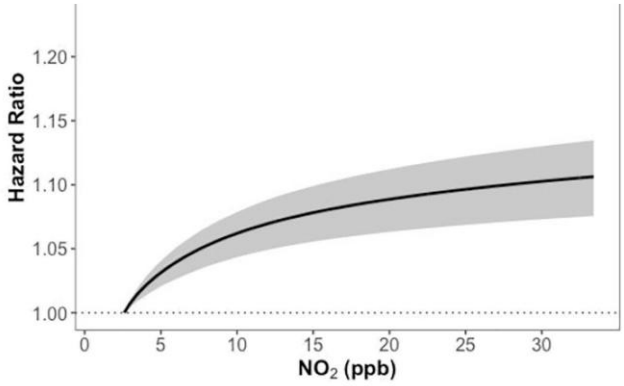
Figure 6-2 Concentration-response relationship for association between NO_2 exposure and CHD incidence with a natural cubic spline, 3 degrees of freedom



List of abbreviations in alphabetical order: CHD = coronary heart disease; NO_2 = nitrogen dioxide; SCHIF = Shape Constrained Health Impact Function.
Note: Vertical dotted lines are air quality limit and guideline values. Hazard ratios are expressed relative to minimum exposure.
Source: Brunekreef et al. (2021). Copyright permission pending.

Figure 6-3 Concentration-response relationship for the associations between annual average NO_2 concentrations and CHD incidence with shape constrained health impact functions.

- In an analysis of ONPHEC, Bai et al. (2019a) examined the C-R relationship of long-term NO_2 exposure with MI (see Figure 6-4). This study characterized the shape of the function using SCHIFs in combination with fully adjusted proportional hazards models.



List of abbreviations in alphabetical order: MI = myocardial infarction; NO_2 = nitrogen dioxide; SCHIF = Shape Constrained Health Impact Function.
Note: The grey area represents the 95% confidence interval.
Source: Bai et al. (2019a). Copyright permission pending.

Figure 6-4 Concentration-response relationship for the association of myocardial infarction with NO_2 exposure.

Table 6-4 Epidemiologic studies evaluating concentration-response relationship between long-term exposure to oxides of nitrogen and myocardial infarction and coronary heart disease

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
Exposure to NO_2				
†Bai et al. (2019b)	ONPHEC Enrollment: April 1, 1996 Follow-up: December 31, 2012	2.7–71.4 ppb	SCHIF	Supralinear
†Brunekreef et al. (2021)	ELAPSE Project (CEANS, DCH, E3N, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC Varese) Recruitment: 1992–2011 Follow-up: 2011–2017	Distribution depicted in Figure 6-2. Min-Max = 1.42–43.6 ppb, depending on the cohort: CEANS-SIXTY Cohort Min-Max = 1.42–25.45 ppb (2.68-47.88 µg/m^3) E3N Cohort Min-Max = 1.84-43.06 ppb (3.46–81.02 µg/m^3)	(1) Natural splines with 2–4 degrees of freedom, (2) penalized splines with df determined by the algorithm, and (3) SCHIF	Linear, no association observed below 10.6 ppb (20 µg/m^3)
†Klompmaker et al. (2021a)	Medicare denominator and Medicare Provider Analysis and Review (MEDPAR) Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	See Figure 6-1	Natural Spline, 2–4 df	Linear/supralinear depending on df

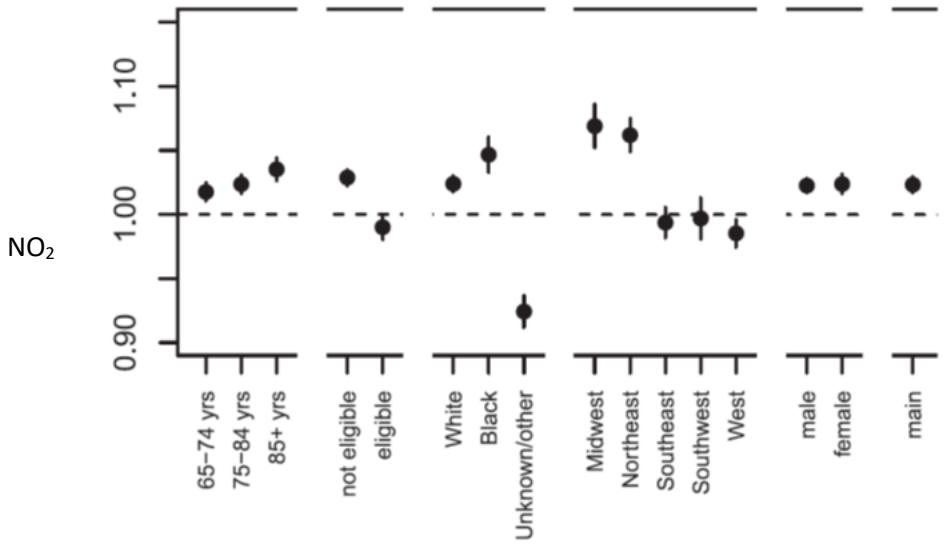
List of abbreviations in alphabetical order: CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CHD = Coronary Heart Disease; DCH = Danish Diet, Cancer and Health; df = degrees of freedom; E3N = Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; DNC = Danish Nurses' Cohort; EPIC = European Prospective Investigation into Cancer and Nutrition; ; 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-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 = Heinz Nixdorf Recall Study; ONPHEC = Ontario Population Health and Environment Cohort; MI = myocardial infarction; SCHIF = Shape Constrained Health Impact Functions; VHM&PP = Vorarlberg Health Monitoring and Prevention Programme.
[a]For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.
[b]There visual representations of the shape of the curve in the corresponding text.
†Studies published since the 2016 Oxides of Nitrogen ISA.

6.3.1.2 Lifestages and Populations

The 2016 Oxides of Nitrogen ISA assessed small number of studies that examined modification of the association between NO_2 exposure and MI by lifestyle factors (BMI, diet, smoking, physical activity) (Hart et al., 2013), TNF-α gene expression (Panasevich et al., 2013), education, sex and age

(Rosenlund et al., 2009) and reported no difference across levels of these factors. Recent studies add to the evidence. Results from these studies are summarized in Table 6-5.

- In an analysis of U.S. Medicare data, Klompmaker et al. (2021a) use Cox proportional hazard regression to analyze the association of NO_2 exposure with coronary heart disease. Stratified analyses indicate that the associations with NO_2 exposure were somewhat larger in older populations, positive only among individuals not eligible for Medicare, and larger in Black compared to white individuals (see Figure 6-5). Associations did not differ between males and females.



List of abbreviations in alphabetical order: CHD = coronary heart disease. Eligible and not eligible refers to Medicare eligibility.
Source: Klompmaker et al. (2021a). Copyright permission pending.

Figure 6-5 Associations of NO_2 with CVD, HD and CBVD hospitalization stratified by age, Medicaid eligibility, race, United States region, and sex.

- Bai et al. (2019a) conducted stratified analyses of the ONPHEC study data and reported that the association of NO_2 with MI were stronger in the lower income category and among those with diabetes. In another Canadian study, Olaniyan et al. (2022) examined the association of NO_2 with incident hospitalization for MI among approximately 2.7 million participants in CanCHEC (2006 to 2016). The HR, which was 1.04 (95% CI: 1.00, 1.07) in the fully adjusted model, was stronger in the lowest income quintile e.g., (HR: 1.091 [95% CI: 1.016, 1.171]) and at the highest O_3 tertile (HR: 1.06 [95% CI: 1.00, 1.12]).
- Several studies were conducted using national datasets from Denmark. Poulsen et al. (2023c) examined the association between long-term NO_2 exposure (5-year running average) and MI among Danes aged 50 to 85-years. The association (HR) of NO_2 concentration with MI was 1.08 [95% CI: 1.05, 1.11]. There was little evidence of effect modification by sociodemographic factors including sex, education, occupation, or income.
- Levinsson et al. (2014) used data from the INTERGENE/ADONIX study to examine whether the risk of acute MI differed depending on genotype strata for variants in the GSTP1, GSTT1 and GSTCD genes. The association (OR) between NO_2 and MI was 2.96 (95% CI: 1.08,

8.09). The effect of NO_2 exposure on risk of acute MI varied by genotype strata; however, confidence intervals were overlapping.

The studies that investigated the association of long-term oxides of nitrogen exposure with MI or CHD did not indicate a pattern of consistently positive associations. Further, single pollutant associations did not generally persist after adjustment for copollutants in most studies. A limited number of studies of MI or CHD examined effect measure modification by factors that may result in increased risk including age, sex, comorbid conditions, SES, and genetic factors. Single studies examined factors such as smoking or overweight. For factors evaluated in more than one study (i.e., age, sex and proxies for SES), no clear patterns emerged pointing to specific factors that appeared to consistently confer an increase in risk. Table 6-6-5 below includes basic information on each study cohort in addition to a qualitative summary of the direction of effect measure modification for a given subgroup (e.g., males) relative to a reference subgroup (e.g., males), as well as the corresponding quantitative effect estimates for each subgroup if available. The direction listed in the table does not necessarily indicate a statistically significant between-group difference in NO_2-related health risk. Instead, the table is meant to highlight the pattern of results across studies.

Table 6-5 Epidemiologic studies evaluating effect measure modification between long-term oxide of nitrogen exposure and coronary heart disease and myocardial infarction

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Lifestage					
Exposure to NO_2					
†Bai et al. (2019a)	ONPHEC Enrollment: April 1, 2001 Follow-up: December 31, 2015	HR (95% CI)[b] MI, 34-44: 1.06 (1.03, 1.10)	HR (95% CI)[b] MI, 45-54: 1.01 (0.99, 1.04) MI, 55-64: 0.99 (0.97, 1.02) MI, 65-74: 1.01 (0.99, 1.04) MI, 75-85: 1.02 (1.00, 1.05)	↓	Individual
†Brunekreef et al. (2021)	CEANS, DCH, DNC, E3N cohort, EPIC-MORGEN, EPIC-Prospect, EPIC-Varese, ESCAPE, HNR study, KORA, VHM&PP Recruitment: 1992–2011 Follow-up: 2011–2017	HR (95% CI)[b] CHD <65 yrs: Figure P56 from Brunekreef et al. (2021)	HR (95% CI)[b] CHD, ≥65 yrs: Figure P56 from Brunekreef et al. (2021)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Olaniyan et al. (2022)	CanCHEC Enrollment: 1981 Follow-up: through December 31, 2016	HR (95% CI)[b] MI, 25-44: 1.10 (0.92, 1.31)	HR (95% CI)[b] MI, 45–64: 1.07 (1.01, 1.14) MI, 65+: 1.03 (0.99, 1.08)	↓	Individual
Sex					
Exposure to NO_2					
†Bai et al. (2019a)	ONPHEC Enrollment: April 1, 2001 Follow-up: December 31, 2015	HR (95% CI)[b] MI, male: 0.99 (0.98, 1.01)	HR (95% CI)[b] MI, female: 1.01 (0.99, 1.04)	≈	Individual
†Olaniyan et al. (2022)	CanCHEC Enrollment: 1981 Follow-up: through December 31, 2016	HR (95% CI)[b] MI, male: 1.07 (1.01, 1.13)	HR (95% CI)[b] MI, female: 1.02 (0.97, 1.06)	↓	Individual
†Poulsen et al. (2023c)	Danish Death Registry, Danish Patient Register Enrollment: 1979–2005 Follow-up: 2005–2017	HR (95% CI)[b] MI, male: 1.08 (1.04, 1.12)	HR (95% CI)[b] MI, female: 1.06 (1.01, 1.11)	≈	Individual
Pre-existing Conditions/Comorbidities					
Exposure to NO_2					
†Bai et al. (2019a)	ONPHEC Enrollment: April 1, 2001 Follow-up: December 31, 2015	HR (95% CI)[b] MI, no diabetes: 1.01 (0.99, 1.02)	HR (95% CI)[b] MI, diabetes: 1.04 (1.01, 1.07)	↑	Individual
		MI, no hypertension: 1.01 (1.00, 1.03)	MI, hypertension: 1.03 (1.01, 1.05)	↑	
†Brunekreef et al. (2021)	CEANS, DCH, DNC, E3N cohort, EPIC-MORGEN, EPIC-Prospect, EPIC-Varese, ESCAPE, HNR study, KORA, VHM&PP Recruitment: 1992–2011 Follow-up: 2011–2017	HR (95% CI)[b] CHD, normal BMI: Figure P56 from Brunekreef et al. (2021)	HR (95% CI)[b] CHD, low BMI: Figure P56 from Brunekreef et al. (2021) CHD, high BMI: Figure P56 from Brunekreef et al. (2021)	≈	Individual
Exposure to NO_2					
†Olaniyan et al. (2022)	CanCHEC Enrollment: 1981 Follow-up: through December 31, 2016	HR (95% CI)[b] MI, Low frailty (Charleson Index): 0.98 (0.93, 1.03)	HR (95% CI)[b] MI, High frailty (Charleson Index): 1.00 (0.86, 1.15)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Socioeconomic Status					
Exposure to NO_2					
†Bai et al. (2019a)	ONPHEC Enrollment: April 1, 2001 Follow-up: December 31, 2015	HR (95% CI)[b] MI, lower income: 1.01 (0.99, 1.04)	HR (95% CI)[b] MI, higher income: 0.96 (0.93, 0.99)	↓	Individual
†Brunekreef et al. (2021)	CEANS, DCH, DNC, E3N cohort, EPIC-MORGEN, EPIC-Prospect, EPIC-Varese, ESCAPE, HNR study, KORA, VHM&PP Recruitment: 1992–2011 Follow-up: 2011–2017	HR (95% CI)[b] CHD, high education: Figure P56 from Brunekreef et al. (2021)	HR (95% CI)[b] CHD, medium education: Figure only CHD, low education: Figure P56 from Brunekreef et al. (2021)	↑	Individual
†Olaniyan et al. (2022)	CanCHEC Enrollment: 1981 Follow-up: through December 31, 2016	HR (95% CI)[b] MI, lower income (5th quintile): 1.09 (1.02, 1.17)	HR (95% CI)[b] MI, higher income (1st quintile): 1.02 (0.93, 1.13)	↓	Individual
†Poulsen et al. (2023c)	Danish Death Registry, Danish Patient Register Enrollment: 1979–2005 Follow-up: 2005–2017	HR (95% CI)[b] MI, low personal income: 1.04 (0.99, 1.09)	HR (95% CI)[b] MI, Med personal income: 1.10 (1.06, 1.14)	↑	Individual
			MI, High personal income: 1.00 (0.91, 1.10)	↓	
		MI, low household income: 1.06 (1.02, 1.10)	MI, Med household income: 1.08 (1.04, 1.12)	≈	
			MI, High household income: 1.10 (1.01, 1.19)	≈	
		MI, Mandatory education: 1.08 (1.03, 1.13)	MI, Secondary/ Vocational education: 1.06 (1.02, 1.10)	≈	

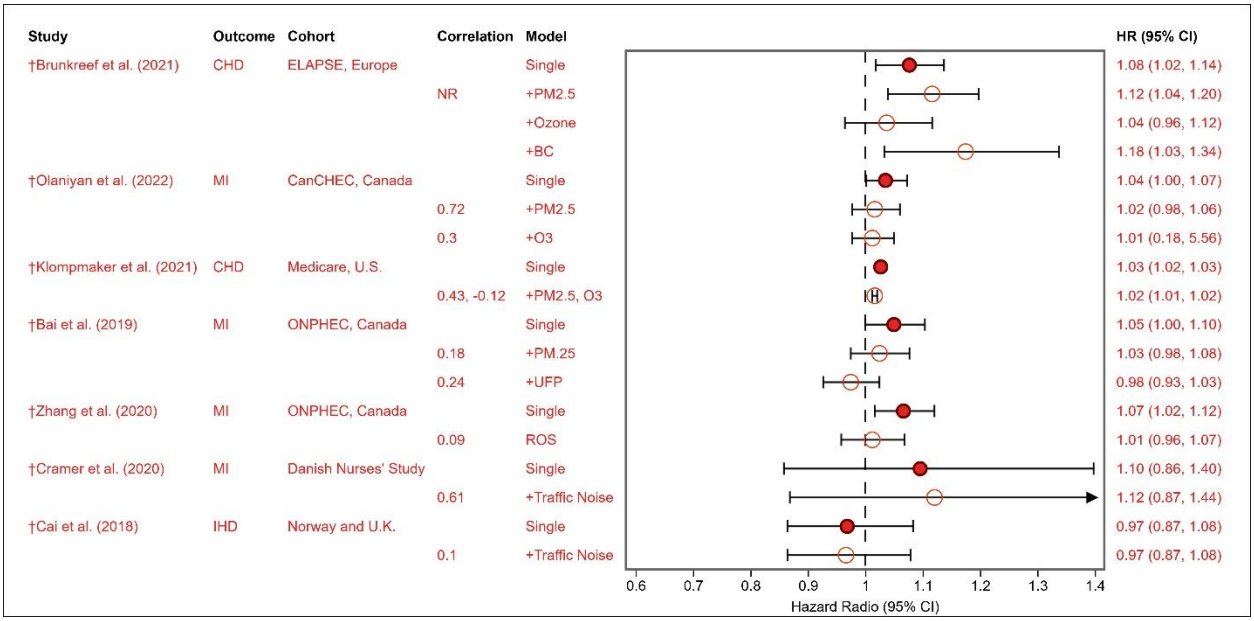
Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			MI, Higher education: 1.06 (0.98, 1.14)	≈	
Genetics					
Exposure to NO_2					
Levinsson et al. (2014)	INTERGENE/ ADONIX Recruitment: April 2001–January 2004	OR (95% CI)[b] MI/GSTP1: rs596603 GG: 1.88 (0.55, 6.40)	OR (95% CI)[b] MI/ GSTP1: rs596603 TT+GT: 4.11 (1.18, 14.30)	↑	Individual
		MI/ GSTT1: rs2266637 Non-null: 3.75 (1.26, 11.17)	MI/ GSTT1: rs2266637 Null: 1.88 (0.12, 28.66)	↓	
		MI/GSTCD: rs10516526 AA: 1.02 (0.09, 11.64)	MI/GSTCD: rs10516526 GG+AG: 4.60 (1.52, 13.93)	↑	

List of abbreviations in alphabetical order: BMI = body mass index; CanCHEC = Canadian Census Health and Environment Cohort; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI = confidence interval; DCH = Danish Diet, Cancer and Health; DHC = Danish Nurse Cohort; EMM = effect-measure modification;E3N = Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EPIC = European Prospective Investigation into Cancer and Nutrition; ESCAPE = European Study of Cohorts for Air Pollution Effects; HNR = Heinz Nixdorf Recall; HR = hazard ratio; NO_2 = nitrogen dioxide; 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; MORGEN = Monitoring Project on Risk Factors and Chronic Diseases in Netherlands; ONPHEC = Ontario Population Health and Environment Cohort; OR = odds ratio; Ref = reference; VHM&PP = Vorarlberg Health Monitoring and Prevention Programme;
[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of [insert outcome]) in the group with the factor evaluated than in the reference group. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller in the group with the factor evaluated than in the reference group An almost equal sign (and grey shading) indicate that the effect of NO_2 is comparable between groups.
[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.

6.3.1.3 Copollutants

A single study evaluated in the 2016 Oxides of Nitrogen ISA examined confounding by traffic-related noise, and no studies examined confounding by traffic-related copollutants. Recent studies add to the evidence on this topic. These studies generally relied on mutual adjustment (i.e., NO_2 or NO_X were modelled simultaneously with a copollutant or with noise). Most single pollutant associations were attenuated to the null after adjustment for O_3, $PM_{2.5}$, ROS or UFP. A notable exception was the ELAPSE analysis by Brunekreef et al. (2021) in which the single pollutant association persisted after adjustment for BC but was attenuated after adjustment for O_3. Some recent studies adjusted for traffic-related noise. Moderate correlations between noise and traffic pollutants including BC were observed in multiple studies in Europe and the United States (see Chapter 2, Section 2.4.3.1), suggesting that controlling for traffic noise may also control, in part, for other traffic related pollutants. In addition, noise may be

independently associated with CVD. Cramer et al. (2020) reported a larger association after adjustment for traffic noise while null associations were observed in the analysis by Cai et al. (2018). Overall, the results from the multipollutant models were limited and, collectively, did not indicate an independent effect of NO_2 exposure on MI or CHD (see Figure 6-6).



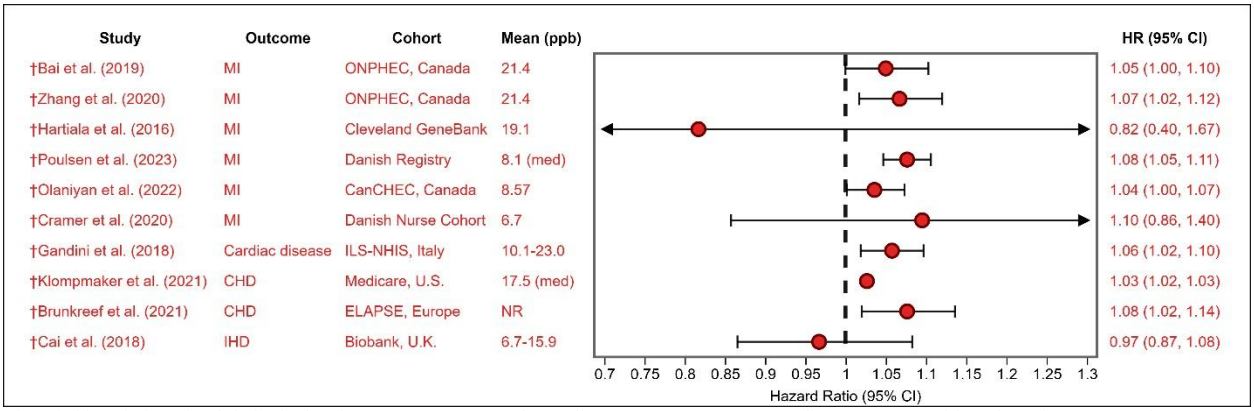
List of abbreviations in alphabetical order: CHD = coronary heart disease; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-6 Single pollutant associations of long-term exposure to NO_2 with myocardial infarction and ischemic heart disease or coronary heart disease and associations that are adjusted for copollutants or traffic related noise.

6.3.1.4 Conclusions and Remaining Uncertainties

The literature on long-term exposure has expanded since the 2016 Oxides of Nitrogen ISA was published. Recent studies do not substantially reduce the uncertainties identified in the previous ISA. Overall, the studies that have investigated the association of long-term NO_2 and NO_X exposure with MI and CHD are not entirely consistent (see Figure 6-7). In addition, several analyses of hospital admissions among Medicare recipients (not pictured because they do not present HRs) reported inconsistent results across the various epidemiologic methods used to determine the association between long term NO_2 exposure and MI/CHD (Schwartz et al., 2023; Danesh Yazdi et al., 2022; Danesh Yazdi et al., 2021; Klompmaker et al., 2021a). In a Canadian study of hospitalization for MI, the small association observed by Olaniyan et al. (2022) was attenuated after adjustment for $PM_{2.5}$ and O_3. In an analysis of the European

cohorts in the ELAPSE project reported that the association between NO_2 exposure and CHD incidence was larger after adjustment for $PM_{2.5}$ and BC but was attenuated with confidence intervals that no longer excluded the null value after adjustment for O_3. The small positive associations of long term NO_2 with physician diagnosed MI observed in the ONPHEC study did not persist after adjustment for $PM_{2.5}$, UFP (Bai et al., 2019b) or ROS (Zhang et al., 2020). Further, single pollutant associations between long-term NO_2 exposure in Denmark, the Netherlands, the United Kingdom, Norway and Sweden were not consistently positive. A limited number of studies of MI or CHD examined effect measure modification by a various factors including age, sex, comorbid conditions, SES, and genetic factors; no clear pattern of modification emerged from these analyses, however. Overall, it is not clear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, confounding by traffic-related copollutants (i.e., $PM_{2.5}$, CO, BC/EC, UFP, other PM constituents, and VOCs) or other environmental determinants, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health care access, health behaviors). Most studies used validated exposure assessment models with moderate to high performance and the variable methods did not appear to explain inconsistences in the findings.



List of abbreviations in alphabetical order: CHD = coronary heart disease; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; ILS-NHIS: Italian Longitudinal Study, National Health Interview Survey; MI = myocardial infarction; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-7 Epidemiologic studies of the association of long-term NO_2 exposure with ischemic heart disease (or coronary heart disease) and myocardial infarction.

6.3.2 Epidemiologic Studies of Heart Failure

Heart failure is a condition that occurs when the heart is weakened and cannot pump sufficiently to deliver oxygenated blood to the body. Symptoms include fatigue, shortness of breath and/or coughing. There were no studies of long-term exposure to oxides of nitrogen and heart failure assessed in the 2016 Oxides of Nitrogen ISA. Recent studies have evaluated associations with heart failure. Study specific details including study population characteristics, exposure assessment metrics, potential confounders,

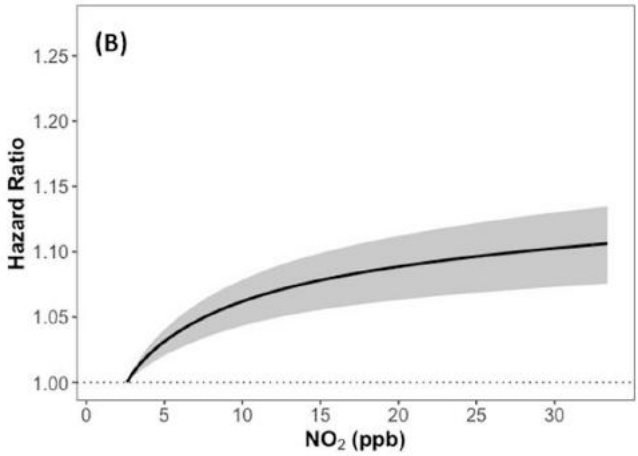
and select results are in Appendix A – Appendix Table 6-2. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on observed associations are discussed in greater detail in Sections 6.3.2.1, 6.3.2.2, and 6.3.2.3, respectively. Section 6.3.2.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for heart failure.

- Jin et al. (2022) conducted an analysis of Medicare data to investigate the association between long-term NO_2 exposure and CHF in U.S. adults enrolled in Medicare. Annual average NO_2 exposure was estimated at the zip code level using spatiotemporal ensemble models that have been described previously. A positive association was observed (HR: 1.12 [95% CI: 1.11, 1.12]). The HR was stronger at lower (<10 ppb) exposure concentrations [HR: 1.31 [95% CI: 1.28, 1.34]).
- Bai et al. (2019b) analyzed data from ONPHEC, which included residents of Ontario, Canada aged 30 to 100-years who were enrolled between 1996 and 2012. In age and sex stratified models that were also adjusted for neighborhood level covariates, the HR was 1.04 (95% CI: 1.03, 1.04). Associations with heart failure remained after adjustment for UFPs and $PM_{2.5}$ (HR: 1.03 [95% CI: 1.02, 1.04] and HR: 1.04 [95% CI: 1.03, 1.04]). Bai et al. (2019a) additionally conducted a concentration-response analysis (see Section 6.6.1.1) and presents results that are stratified by age, sex, income, and comorbid conditions (see Section 6.6.1.2). In another analysis of the ONPHEC data, Zhang et al. (2020) used LUR to estimate the non-tailpipe emissions (i.e., Fe and Cu in $PM_{2.5}$) in order to examine their combined impact on reactive oxygen species (ROS) concentration in lung epithelial lining fluid. NO_2 was estimated using a validated LUR model ($r^2 = 0.69$) to conduct analyses designed to distinguish non-tailpipe from tailpipe emissions. This study reported that associations between NO_2 and CHF were slightly attenuated after adjustment for ROS. The HR for the association between 3-year moving average NO_2 and CHF was 1.10 (95% CI: 1.07, 1.14). After adjustment for ROS, the association persisted (HR: 1.08 [95% CI: 1.04, 1.11]).
- Lim et al. (2021) examined the association of 3-year mean NO_2 exposure and heart failure among participants in the Danish Nurse cohort. A positive association was observed in the fully adjusted model though the CI included the null value (HR: 1.23 [95% CI: 0.98, 1.55]). The association was attenuated but remained positive after adjustment for $PM_{2.5}$ (HR: 1.09 [95% CI: 0.81, 1.46] and noise (HR: 1.14 [95% CI: 0.86, 1.50]). In a model that simultaneously adjusted for $PM_{2.5}$ and noise, no association was observed (HR: 1.00 [95% CI: 0.71, 1.42]).
- Wang et al. (2021) investigated the relationship between air pollution and heart failure among participants in the UK Biobank study. The associations for an increase in annual average NO_2 and NO_X with heart failure were 1.20 (95% CI: 1.09, 1.32) and 1.04 (95% CI: 1.02, 1.06), respectively. The estimate for NO_X is not standardized (i.e., presented per 10 $\mu g/m^3$).

6.3.2.1 Concentration-Response

There were no studies of heart failure assessed in the 2016 Oxides of Nitrogen ISA. Recent studies of the association between long-term NO_2 exposure and heart failure are limited in general and studies that investigate the shape of the C-R function were even more sparse. Bai et al. (2019a) analyzed data from the Canadian ONPHEC study (see Figure 6-8). The shape of the C-R function was

characterized using SCHIF in combination with fully adjusted proportional hazards models. A supralinear relationship was observed, with attenuation at concentrations greater than approximately 10 ppb. In a second study, Jin et al. (2022) reported that the HR for CHF hospital admissions among older adults was somewhat larger at lower (i.e., <18 ppb) NO_2 concentrations (HR: 1.12 [95% CI: 1.11, 1.12]) versus higher concentrations (≥18 ppb) (HR: 1.31 [95% CI: 1.28, 1.34]).



List of abbreviations in alphabetical order: CHF = congestive heart failure; MI = myocardial infarction; NO_2 = nitrogen dioxide; SCHIF = Shape Constrained Health Impact Function.
Note: The grey area represents the 95% Confidence Interval.
Source: Bai et al. (2019a). Copyright permission pending.

Figure 6-8 Concentration-response relationship for the association of CHF with NO_2 exposure.

6.3.2.2 Lifestages and Populations

There were no studies of heart failure assessed in the 2016 Oxides of Nitrogen ISA. A small number of studies within the recent but limited evidence base for heart failure examined factors that modified the associations with oxides of nitrogen. The factors examined included race/ethnicity, age, sex, comorbid conditions and genetic factors. Overall, the literature was too sparse to allow comparison across studies.

- Jin et al. (2022) examined the pattern of associations between NO_2 exposure and first Medicare claim for congestive heart failure in older adults in the U.S. population. The study reported that associations were strongest in magnitude among Black Medicaid enrollees compared to white Medicaid enrollees. HRs for other racial/ethnic groups (i.e., Asian, Hispanic, Native American, and other) were smaller in magnitude relative to the HR for white enrollees. The study also reported larger HRs among people with diabetes compared to people without diabetes, but confidence intervals for the CHF HRs overlapped substantially comparing people with and without hypertension and with and without hyperlipidemia.
- In the Canadian ONPHEC study described previously, Bai et al. (2019a) conducted analyses that stratified by age, sex, income, and comorbid conditions. This study reported that the HR

in older age groups were progressively smaller in magnitude than the HRs in the youngest age group (e.g., for people between 35 to 44-years old the HR was 1.17 [95% CI: 1.12, 1.22] and for the 65 to 74-years old age group the HR was 1.01 [95% CI: 1.00, 1.03]). The HR for females (HR: 1.02 [95% CI: 1.01, 1.04]) was approximately the same as that for males (HR: 1.01 [95% CI: 1.00, 1.03]). The authors also observed a somewhat larger magnitude HR in the lower income groups and among individuals without diabetes or hypertension.

- Wang et al. (2021) examined the pattern of association between long-term NO_2 exposure and incident heart failure across genetic risk groups. The authors created a genetic risk score for HF using 12 single-nucleotide polymorphisms (SNPs) that were hypothesized to confer susceptibility. The association between annual average NO_2 exposure and heart failure increased with increasing genetic risk (medium genetic risk HR: 1.15 [95% CI: 1.05, 1.25] versus low genetic risk and high genetic risk HR: 1.30 [95% CI: 1.19, 1.42]).

6.3.2.3 Copollutants

A few studies evaluated copollutant confounding in models that mutually adjusted for NO_2, UFP, $PM_{2.5}$, estimated ROS in lung epithelial fluid and noise (Lim et al., 2021; Zhang et al., 2020; Bai et al., 2019b). The studies reported that associations between NO_2 and heart failure were slightly attenuated but remained positive after adjustment for these co-exposures providing limited evidence for an independent effect of NO_2 on heart failure.

6.3.2.4 Conclusions and Remaining Uncertainties

A small number of recent studies consistently reported positive associations between long-term exposure to NO_2 and heart failure. A single study indicated that the C-R function may be supralinear. Overall, the literature was too sparse to allow comparison across studies of factors such as race/ethnicity, age, sex, comorbid conditions and genetic factors that may confer increased risk. Although the uncertainties remain regarding the independent effect of NO_2 exposure, several studies reported that the association between NO_2 and heart failure was only slightly attenuated and remained positive after adjustment UFP, $PM_{2.5}$, ROS in epithelial fluid and traffic related noise. Most studies used validated exposure assessment models reporting moderate to high model performance.

6.3.3 Epidemiologic Studies of Atrial Fibrillation

The 2016 Oxides of Nitrogen ISA did not include any studies that specifically examined long-term exposure to oxides of nitrogen and atrial fibrillation, which is an irregular heart rhythm in the upper chamber of the heart that can increase the risk for stroke. A single study in the 2016 Oxides of Nitrogen ISA reported no association with arrhythmia defined by International Classification of Diseases 10 (ICD10) codes I46–49, which includes atrial fibrillation (Atkinson et al., 2013). Analyses from these

studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in greater detail in Sections 6.3.3.1, 6.3.3.2, and 6.3.3.3, respectively. Section 6.3.3.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for atrial fibrillation.

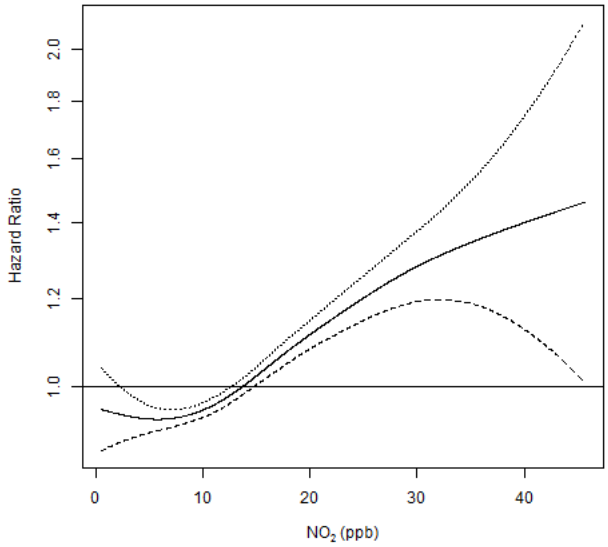
Atrial fibrillation was examined in relation to long-term NO_2 exposure in recent studies that analyzed data from U.S. Medicare and cohorts in Canada and Europe. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-3.

- Jin et al. (2022) conducted an analysis of Medicare hospitalization data to investigate the association of atrial fibrillation with long-term NO_2 exposure in U.S. adults. NO_2 was estimated at the zip code level using spatiotemporal ensemble models that have been described previously, and annual average exposure was estimated. A positive association between annual average NO_2 exposure and atrial fibrillation was observed (HR: 1.059 [95% CI: 1.054, 1.062]). The HR was larger at lower (<18 ppb) exposure concentrations (HR: 1.26 [95% CI: 1.24, 1.28]). Associations were strongest in magnitude among Black Medicaid enrollees (see Section 6.3.3.2). In another analysis of hospital admissions using Medicare data, Danesh Yazdi et al. (2021) employed a doubly robust method (i.e., inverse probability weighting and adjustment in the outcome model) to estimate a risk difference (RD) of 0.0129% [95% CI: 0.0112, 0.0146]). The largest magnitude association with hospital admissions for atrial fibrillation was observed at lower NO_2 concentrations.
- In a study of U.S. women enrolled in the Women's Health Initiative (WHI), NO_2 was associated with atrial fibrillation (HR: 1.18 [95% CI: 1.13, 1.24] comparing Q4 [16.1–45.6 ppb] to Q1 [<7.52 ppb]) (Hart et al., 2021). This study estimated NO_2 using WHI methods (regionalized national universal Kriging). Postmenopausal women enrolled in the WHI study (50–79-years old) were linked to Medicare records (i.e., inpatient, outpatient or physician diagnosis) for this analysis. The associations persisted in sensitivity analysis that adjusted for comorbid conditions. Additional analyses provided some evidence that HRs were largest in the west of the United States, but little consistent support for effect measure modification by age, educational attainment, smoking status or self-reported comorbidities (see Section 6.3.3.2).
- Shin et al. (2019) used data from ONPHEC (Ontario residents aged 35 to 85 at enrollment) to examine the association of 5-year running average NO_2 with atrial fibrillation (hospitalization, emergency department (ED) visit, or physician billings), observing a positive association (HR: 1.02 [95% CI: 1.01, 1.03] per IQR) in the fully adjusted model (see Section 6.3.3.2).
- Andersen et al. (2021) examined the association of 1-, 3-, and 23-year average NO_2 exposures among women (aged >44 years at baseline) enrolled in the Danish Nurses' Cohort. No associations with NO_2 were observed regardless of averaging time (e.g., HR: 1.0 [95% CI: 0.87, 1.15]). Inverse associations were observed for 1- and 3-year mean NO_2 concentration and atrial fibrillation after adjustment for $PM_{2.5}$ (e.g., HR: 0.78 [95% CI: 0.63, 0.96]). A previous analysis of the Danish Diet, Cancer and Health Cohort, which enrolled males and females (age 50 to 64 at enrollment between 1993 and 1997) living in Copenhagen or Aahus reported an association between 10-year mean exposure to NO_2 preceding diagnosis and atrial fibrillation (incidence rate ratio [IRR]: 1.16 [95% CI: 1.03, 1.3]) (Monrad et al., 2016) in adjusted models. NO_X was not modelled as a linear term; however, a 10-year time-

weighted mean exposure to more than 16.9 μg/m^3 NO_X (versus <13.8 μg/m^3) was associated with an increased risk of atrial fibrillation (IRR: 1.16 [95% CI: 1.02, 1.32]). The association was similar in men and women. A stronger association was observed among those with hypertension (see Section 6.6.1.2).

6.3.3.1 Concentration-Response

A single study, Hart et al. (2021), examined the relationship between annual average NO_2 exposure and incident atrial fibrillation using penalized splines (with 3 knots) among post-menopausal women in the WHI study (see Figure 6-9). A positive linear relationship was observed above approximately 12 ppb while the association appeared to be inverse below that concentration. In another study, Jin et al. (2022) reported the HR was somewhat larger at lower (<18 ppb) exposure concentrations.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Note: Models were adjusted for baseline information on BMI, educational attainment, physical activity, alcohol consumption, and overall diet quality, and time-varying information on hormone replacement therapy use, smoking status and pack-years, and neighborhood SES.
Source: Hart et al. (2021). Copyright permission pending.

Figure 6-9 Penalized splines with three knots for the C-R relationship between annual average NO_2 exposure and incident atrial fibrillation.

6.3.3.2 Lifestages and Populations

A small number of epidemiologic studies investigated modification of the association between oxides of nitrogen and atrial fibrillation by factors including age, sex, race, comorbid conditions and region.

- Jin et al. (2022) observed a positive association between annual average NO_2 exposure and atrial fibrillation among those enrolled in Medicare (HR: 1.0585 [95% CI: 1.0548, 1.0622]). Associations were strongest in magnitude among Black Medicaid enrollees.
- The Hart et al. (2021) analysis of post-menopausal women enrolled in WHI provided little consistent support for effect measure modification by age, educational attainment, smoking status or self-reported comorbidities. The interaction analyses indicated differences in the magnitude of the HRs by region, with the largest magnitude HRs (comparing the highest quartile of NO_2 to the lowest) were in the northeast (HR: 1.18 [95% CI: 1.07, 1.30]) and the west (HR: 1.21 [95% CI: 1.09, 1.35]) of the United States compared to the south and the midwest (HR: 1.06 [95% CI: 0.95, 1.18]).
- Shin et al. (2019) reported a positive association of 5-year running average NO_2 with atrial fibrillation (HR: 1.02 [95% CI: 1.01, 1.02]) in the fully adjusted model. The observed association with atrial fibrillation was somewhat stronger among women and those with comorbid conditions.
- Monrad et al. (2016) reported an association between 10-year mean exposure to NO_2 preceding diagnosis and atrial fibrillation (IRR: 1.16 [95% CI: 1.03, 1.3]) (Monrad et al., 2016) in the DDCHC. The association was similar in men and women. A stronger association was observed among those with hypertension.

6.3.3.3 Copollutants

A single study examined the impact of copollutant confounding on the association between long-term oxides of nitrogen exposure and AF (Andersen et al., 2021). This study reported no association between 1-, 3-, or 23-year average NO_2 exposures in the Danish Nurses' Cohort (e.g., 1-year mean HR: 1.0 [95% CI: 0.87, 1.15]). Inverse associations were observed for 1- and 3-year mean NO_2 concentration and atrial fibrillation after adjustment for $PM_{2.5}$ (e.g., 1-year mean HR: 0.78 [95% CI: 0.63, 0.96]).

6.3.3.4 Conclusions and Remaining Uncertainties

Overall, findings from the limited body of evidence investigating the association between long-term exposure to oxides of nitrogen and atrial fibrillation are inconsistent. Most studies did not examine confounding by traffic related pollutants ($PM_{2.5}$, CO, BC/EC, UFP, other PM constituents, and VOCs), while one study reported an inverse association after adjustment for $PM_{2.5}$. In addition, a study reported a positive linear relationship between annual average NO_2 concentration above approximately 12 ppb, and an inverse relationship below that concentration. Although regional differences and stronger associations in individuals with comorbid conditions were observed, considering the collective body of evidence, patterns across studies could not be evaluated due to the small number of available analyses. Overall, it is not clear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, confounding by traffic-related copollutants or other environmental determinants, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health

care access, health behaviors). Most studies assessed exposure to NO_2 using validated exposure models with moderate to good performance.

6.4 Cerebrovascular Disease and Stroke

6.4.1 Epidemiologic Studies of Cerebrovascular Disease and Stroke

Several epidemiologic studies of the association between long-term exposure to oxides of nitrogen and cerebrovascular disease were assessed in the 2016 Oxides of Nitrogen ISA [Table 6-7, (U.S. EPA, 2016)]. Lipsett et al. (2011) reported no association with stroke in an analysis of the California Teachers Study (CTS) that used inverse distance weighting (IDW) to estimate ambient exposure to NO_2 at the residence (HR: 1.02 [95% CI: 0.90, 1.16]) and NO_X (HR: 1.01 [95% CI: 0.98, 1.05]). In a Canadian study, Johnson et al. (2013) observed positive imprecise associations with ischemic and hemorrhagic stroke (HR: 1.06 [95% CI: 0.88, 1.28] and HR: 1.14 [95% CI: 0.85, 1.54], respectively). Several national studies conducted in European countries reported mixed results (Sørensen et al., 2014; Atkinson et al., 2013; Andersen et al., 2012). Overall, evidence from epidemiologic studies was not consistent, and there was uncertainty in the extent to which the findings could be explained by traffic-related noise or exposures to traffic-related copollutants.

Recent studies of stroke using U.S. Medicare data have been published since the 2016 Oxides of Nitrogen ISA. Study-specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-4. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in greater detail in Sections 6.4.1.1, 6.4.1.2, and 6.4.1.3, respectively. Section 6.4.1.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for cerebrovascular disease and stroke.

- In an analysis of U.S. Medicare data (i.e., first hospitalization), Klompmaker et al. (2021a) used Cox proportional hazard regression in combination with the previously mentioned exposure assessment approach. This study observed a positive association between annual average NO_2 exposure and cerebrovascular disease hospitalization (HR: 1.05 [95% CI: 1.03, 1.04]) in the single pollutant model. In models that were simultaneously adjusted for NO_2, $PM_{2.5}$ and O_3, the association was attenuated but remained (HR: 1.018 [95% CI: 1.014, 1.022]). A larger association was observed among those whose exposure concentrations were always below 20 ppb (HR: 1.165 [95% CI: 1.151, 1.18]). The ways in which the pattern of associations between NO_2 and cerebrovascular disease differed by temperature, relative humidity, and greenness was not clear from sensitivity analyses. The study observed modification of the association between NO_2 exposure and cerebrovascular disease by region (see Section 6.4.1.2).

- Danesh Yazdi et al. (2021) employed a doubly robust method (i.e., inverse probability weighting and adjustment in the outcome model) to estimate a stroke risk difference (RD) for a 10 ppm increase in NO_2 exposure of 0.0059% (95% CI: 0.0039, 0.0075) per 100,000 person-years and Danesh Yazdi et al. (2022) employed a DID approach to obtain a RD of 4.9 (95% CI: -1.25, 11.05) per 100,000 person years. Analyses of the pattern of associations indicated that for NO_2-associated stroke, the risk was higher among those who were not Medicaid eligible than among those who were Medicaid-eligible. NO_2 associated stroke risk was also higher among Black individuals compared to white individuals (see Section 6.4.1.2).
- Ma et al. (2022) reported a positive association of annual average NO_2 exposure with stroke incidence in the Medicare population (HR: 1.058 [95% CI: 1.054, 1.063]). These associations remained after adjustment for $PM_{2.5}$ and O_3. This study also examined the concentration-response relationship (see Section 6.6.1.1), and it observed that the HRs were larger in magnitude among Black, Medicaid eligible, lower income and lower education categories (see Section 6.4.1.2). In another analysis using similar methods, Jin et al. (2022) reported that a 10 ppb increase in annual NO_2 was associated (HR) with a 1.10 (95% CI: 1.09, 1.11) increase in stroke hospitalization in the Medicare population.

Other recent U.S. studies have been conducted among post-menopausal women in WHI and Ohio residents seeking elective cardiac evaluation.

- Kulick et al. (2023) examined the association of long-term NO_2 exposure with stroke among women enrolled in the WHI, a multicenter U.S. study. NO_2 concentrations were derived using kriging methods combined with geographic covariates. Annual average concentration was estimated at each participant's residential address. If the address was updated, the annual average was calculated as the average of the predicted concentrations for the current and previous year. Annual average NO_2 was associated with an increased risk of stroke hospitalization (HR: 1.06 [95% CI: 1.02, 1.11]). Associations with ischemic stroke and CBVD hospitalization were similar in magnitude.
- Hartiala et al. (2016) examined the association of long-term (36- months) NO_2 exposure with the risk of stroke during a three-year follow-up period among Ohio residents undergoing elective cardiac evaluation. A positive but imprecise association with incident stroke was observed (HR: 3.11 [95% CI: 0.85, 11.35]). Not included in Figure 6-15 due to wide confidence intervals.

Several studies of the association between long-term exposure to NO_2 and cerebrovascular disease were conducted in Canada.

- Olaniyan et al. (2022) examined the association between NO_2 and incident hospitalization for stroke among approximately 2.7 million participants of CanCHEC (2006 to 2016). The 10-year moving average NO_2 concentration was estimated using a national LUR model that explained 75% of the variance in NO_2 concentration. The HR for stroke was 0.993 with CIs that included the null value (95% CI: 0.947, 1.041) in the fully adjusted model. In a two-pollutant model that was adjusted for $PM_{2.5}$, the inverse association remained (HR: 0.903 [95% CI: 0.857, 0.951]). In the two-pollutant model that adjusted for O_3 the inverse association also remained, although the HR was closer to null (HR: 0.971 [95% CI: 0.928, 1.017]). Stratified analyses did not indicate a factor that conferred increased risk of NO_2-related stroke (see Section 6.4.1.2).
- Shin et al. (2019) used data from ONPHEC (Ontario residents aged 35 to 85 at enrollment) to examine the association of 5-year running average NO_2 with stroke, observing a positive

association (HR: 1.02 [95% CI: 1.00, 1.03]). The association with stroke was somewhat higher among women and among individuals in lower income quartiles (see Section 6.4.1.2).

Recent studies conducted in Europe and Asia examining the association of long-term NO_2 exposure and cerebrovascular disease were also conducted.

- Tian et al. (2022) investigated the association of annual average NO_2 and NO_X (ESCAPE LUR) with stroke and post-stroke cardiovascular events in the UK Biobank cohort using a multistate regression model that is an extension of classical survival analysis that was applied to explore the different stages of disease progression. The study observed an association between annual average NO_2 and incident stroke (HR: 1.08 [95% CI: 1.02, 1.14]), and between annual average NO_2 and post-stroke CVD (HR: 1.16 [95% CI: 1.08, 1.25]). Associations with NO_X were similar in magnitude.
- Stafoggia et al. (2014) examined the association of long-term NO_2 and NO_X exposure estimated using measured concentrations in conjunction with LUR models to predict residential annual concentrations for each study participant. No association between NO_2 (HR: 0.98 [9% CI: 0.8, 1.21]) or NO_X exposure (HR: 0.98 [95% CI: 0.89, 1.07] per 20 $\mu g/m^3$) and stroke incidence was reported in this study. Effects at relatively low exposures in ESCAPE study were examined by Brunekreef et al. (2021). These extensive analyses were compiled in a Health Effects Institute (HEI) report focusing on the health effects of low-level pollution (i.e., concentrations below current international guidelines). In this cohort, i.e., ELAPSE, Brunekreef et al. (2021) developed a LUR to estimate exposure that achieved a spatial resolution of 100 by 100 meters for NO_2. A positive association between NO_2 exposure and stroke incidence was observed (HR: 1.16 ([95% CI: 1.08, 1.24]). Results were also reported by (Wolf et al., 2021).
- In a study of individuals aged 50 or greater living in Denmark, Poulsen et al. (2023a) reported a positive association between long-term NO_2 exposure and the incidence of stroke. The HR for 5-year running mean residential NO_2 concentration was 1.075 (95% CI: 1.044, 1.107), while the HR for the association with the traffic-related NO_2 was 1.077 (95% CI: 1.065, 1.089) per 1.4 ppb) and the HR for the association with non-traffic related NO_2 was essentially null 1.001 (95% CI: 0.991, 1.01 per 2.7 ppb). This study reported similar magnitude HRs across age strata (see Section 6.4.1.2). In an analysis of the same dataset Poulsen et al. (2023b) reported that the association of NO_2 with stroke did not persist in models adjusted for $PM_{2.5}$ (HR: 0.943 [95% CI: 0.906, 0.982] or UFP (1.016 [95% CI: 0.047, 21.948]) but remained after adjustment for BC (1.109 [95% CI: 1.058, 1.162]). (Poulsen et al., 2023d) examined effect modification by sociodemographic factors finding stronger associations with increasing noise, greenspace, and lower population density (see Section 6.4.1.2).
- Gandini et al. (2018) observed a positive association between NO_2 and cerebrovascular disease hospitalizations, though CIs included the null value (HR: 1.04 [95% CI: 0.97, 1.11]), using Italian NHIS data. The HRs were overlapping and close to the null value across strata defined by residence in urban, rural and metropolitan areas.
- Cai et al. (2018) used data from three cohorts in Norway and the United Kingdom in combination with European LUR models to estimate the associations of annual mean NO_2 and noise with incident CBVD outcomes. The positive but imprecise HRs (CIs included the null value) for CBVD (1.05 [95% CI: 0.90, 1.24]), ischemic stroke (1.07 [95% CI: 0.83, 1.38]) and the essentially null association for hemorrhagic stroke (0.97 [95% CI: 0.72, 1.32])

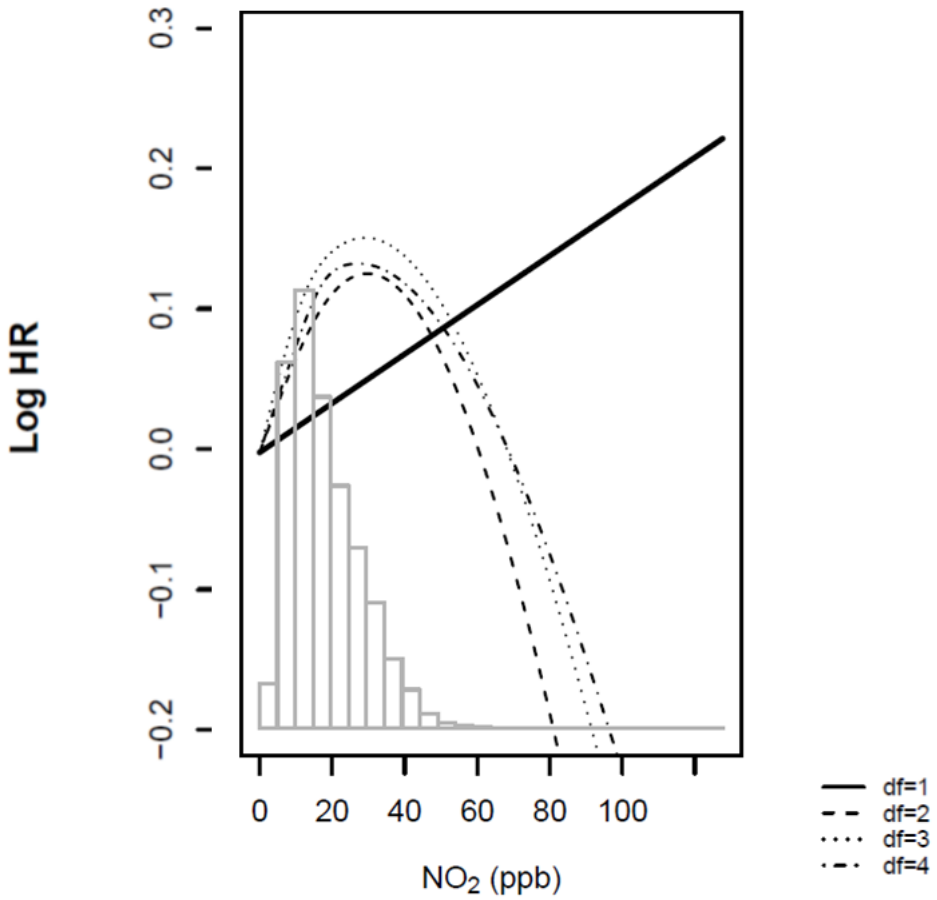
did not change after adjustment for noise (HR: 1.05 [95% CI: 0.89, 1.24], HR: 1.067 [95% CI: 0.83, 1.38] and HR: 0.98 [95% CI: 0.79, 1.22], respectively).

- Amini et al. (2020) conducted an analysis of the Danish Nurse Cohort to estimate the association of long-term exposure to NO_2 and NO_X and the incidence of stroke (overall, ischemic, hemorrhagic), adjusting for road traffic noise. This study used the validated high-resolution Danish air pollution modeling system to estimate NO_2 concentration and derived 1-, 3-, and 23-year averages. In general, positive HRs were attenuated but persisted with longer averaging times. A positive association was observed between 1-year average exposure to NO_2 and overall stroke (HR: 1.12 [95% CI: 0.94, 1.34]) that remained after adjustment for noise (HR: 1.12 [95% CI: 0.92, 1.37]). A similar magnitude association was observed for ischemic stroke (HR: 1.15 [95% CI: 0.96, 1.37]) but an imprecise inverse association with hemorrhagic stroke was observed (HR: 0.93 [95% CI: 0.54, 1.6]). The associations with stroke subtypes were similar in magnitude after adjustment for noise.
- Wang et al. (2023) conducted a nationwide study of adults in China (2010 to 2018) to examine the association of the annual average NO_2 exposure, estimated using a spatiotemporal model, and the risk of stroke considering death as a competing event given that premature death may mask the association with the morbidity outcomes studied. The HR was 2.61 (95% CI: 2.29, 2.97).
- A study in Korea of the National Health Insurance Service-Health Screening Cohort (Kim et al., 2022) reported inverse associations between 7-day (OR: 0.50 [95% CI: 0.42, 0.59] per 0.1 ppm) and 30-day (OR: 0.44 [95% CI: 0.36, 0.54] per 0.1 ppm) NO_2 concentration and ischemic and hemorrhagic stroke. In addition, 90- and 365-day exposures were inversely associated with stroke.

6.4.1.1 Concentration-Response

None of the studies assessed in the 2016 Oxides of Nitrogen ISA examined the shape of the C-R function for cerebrovascular disease or stroke. Some recent studies expand the evidence on this topic. Table 6-6, Figure 6-10, Figure 6-11, Figure 6-12, Figure 6-13, Figure 6-14 and accompanying text summarize analyses of concentration-response relationships from recent studies of cerebrovascular disease. Overall, the limited evidence comprising studies of different populations, and representing only a subset of available studies, indicates a linear or supralinear relationship, with one study showing a widening of CIs and flattening above 5.3 ppb for NO_2, and 30 $\mu g/m^3$ for NO_X.

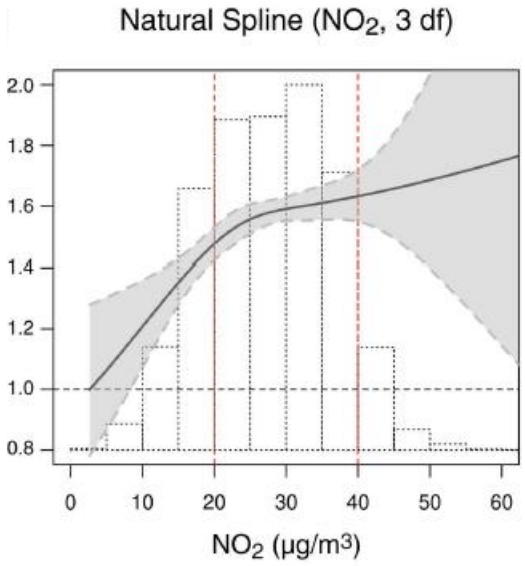
- Klompmaker et al. (2021a) examined the concentration-response among Medicare recipients 65-years or older (see Figure 6-10). Natural splines with two, three, or four degrees of freedom were used, and associations were separately estimated for exposures below 20 ppb NO_2. Depending on the degrees of freedom, the C-R function increased linearly with increasing concentration or increased until approximately 30 ppb and then decreased with further increases in concentration. Associations were generally larger in magnitude for those whose annual exposures were always below 20 ppb (Klompmaker et al., 2021a).



List of abbreviations in alphabetical order: df = degrees of freedom; HR = hazard ratio; NO_2: nitrogen dioxide; ppb = parts per billion.
Note: The histogram reflects the exposure distribution.
Source: Klompmaker et al. (2021a), Copyright permission pending.

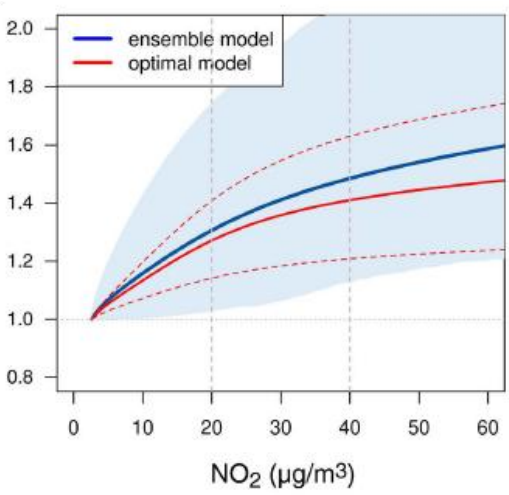
Figure 6-10 Concentration-response curves from fully adjusted models with natural splines (one, two, three, and four degrees of freedom) of NO_2 with cerebrovascular disease hospitalization among older adults enrolled in Medicare.

- Brunekreef et al. (2021) conducted extensive C-R and threshold analyses in the European ELAPSE cohort. The shape of the C-R relationship was examined using natural splines with 2-4 degrees of freedom, penalized splines with df determined by the algorithm and SCHIF using the fully adjusted model that included area-level SES variables (see Figure 6-11 and Figure 6-12). The SCHIF model specifies a range of model shapes and the most optimal is selected. The ensemble model combines different sigmoidal models weighted by their likelihood. The association with stroke incidence at the lowest concentrations (i.e., <20 $\mu g/m^3$ or 10.6 ppb) was less precise but larger in magnitude (HR: 1.16 [95% CI: 0.97, 1.40]) than the association in the full dataset (HR: 1.16 [95% CI: 1.08, 1.24]). Overall, the curves were supralinear with attenuation above approximately 25 $\mu g/m^3$ (13.3 ppb) regardless of method.



List of abbreviations in alphabetical order: df = degrees of freedom; µg/m^3 = micrograms per cubic meter; NO_2 = nitrogen dioxide.
Note: Hazard ratios are relative to the minimum exposure. The histogram reflects the exposure distribution.
Source: Brunekreef et al. (2021). Copyright permission pending.

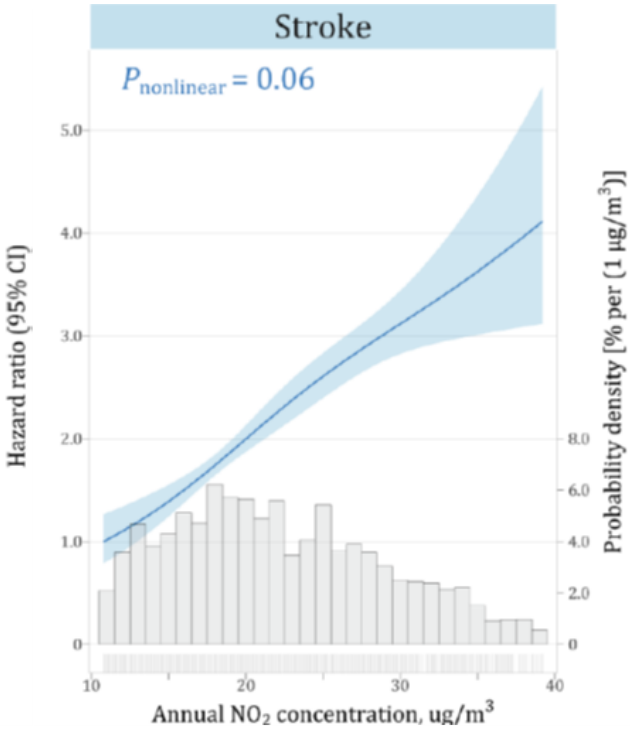
Figure 6-11 Concentration-response relationship for the association between NO_2 exposure and stroke incidence, with natural cubic spline, three degrees of freedom.



List of abbreviations in alphabetical order: µg/m^3 = micrograms per cubic meter; NO_2 = nitrogen dioxide; NO_2 = nitrogen dioxide; SCHIF = Shape Constrained Health Impact Function.
Note: Hazard ratios are expressed relative to minimum exposure.
Source: Brunekreef et al. (2021). Copyright permission pending.

Figure 6-12 Concentration-response relationship for the association between NO_2 exposure and stroke incidence, with SCHIF.

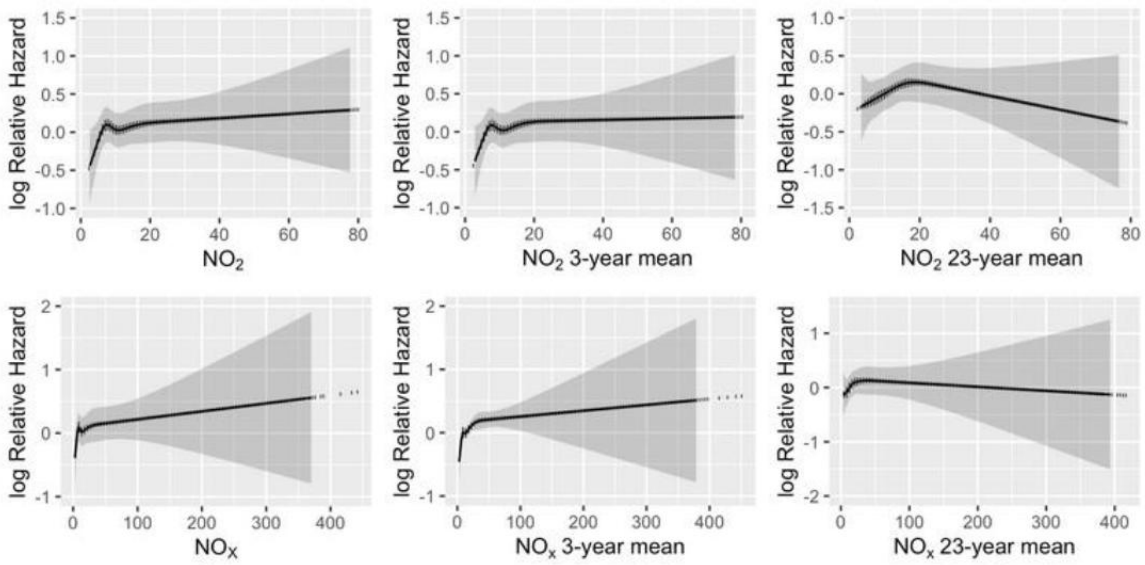
- Wang et al. (2023) conducted a nationwide study of adults in China (2010 to 2018) to examine the association of NO_2 exposure with stroke. Restricted cubic splines were used to examine the shaper of the C-R function. The shape was approximately linear with no evidence of a threshold (see Figure 6-13).



List of abbreviations in alphabetical order: CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide; µg/m³ = micrograms per cubic meter.
Source: Wang et al. (2023). Copyright permission pending.

Figure 6-13 Concentration-response association for incident stroke per 10 µg/m³ rise across the NO_2 exposure range of 2.5th to 97.5th percentile.

- Ma et al. (2022) examined the shape of the C-R relationship between annual NO_2 exposure and stroke incidence in the Medicare population using penalized splines and adjusting for all covariates in multipollutant models. The C-R relationship was linear with no evidence of a threshold.
- Amini et al. (2020) analyzed data from the Danish Nurse Cohort to examine the association of long-term exposure to NO_2 and NO_X and the incidence of stroke. This study also conducted a C-R analysis using restricted cubic splines for the association of 1-, 3-, and 23-year NO_2 and NO_X concentrations with overall stroke. If the plots indicated a flattening of the relationship, exposure values were truncated corresponding to a piecewise linear relationship with two segments. Except for the association with 3-year mean NO_X concentration, no deviations from linearity at lower concentrations were observed. The study observed an indication of a threshold above which the effect was not observed of 10 µg/m³ (5.3 ppb) for NO_2, and 30 µg/m³ for NO_X (for overall stroke); data were sparse, and confidence intervals were wide at higher concentrations (see Figure 6-14).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen.
Note: units for concentration in µg/m^3.
Source: Amini et al. (2020). Copyright permission pending.

Figure 6-14 Plots of restricted cubic spline concentration-response curves for the association of 1-, 3- and 23-year NO_2 and NO_X concentrations with overall stroke.

Table 6-6 Epidemiologic studies evaluating the concentration-response relationship or conducting threshold analyses for long-term exposure to oxides of nitrogen and cerebrovascular morbidity

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
Exposure to NO_2				
†Amini et al. (2020)	DNC Enrollment: 1993 and 1999 Follow-up: December 31, 2014	Mean = 12.6 (SD = 8.0)	Cubic spline	Linear, no threshold observed
†Brunekreef et al. (2021)	ELAPSE Project (CEANS, DCH, E3N, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC Varese) Recruitment: 1992–2011 Follow-up: 2011–2017	Distribution depicted in Figure 6-2 (Brunekreef et al., 2021). Min-Max = 1.42–43.6 ppb, depending on the cohort: CEANS-SIXTY Cohort Min-Max = 1.42–25.45 ppb (2.68–47.88 µg/m^3)	(1) natural spline with 2–4 df, (2) penalized spline with df determined by algorithm, (3) SCHIF	Supralinear

		E3N Cohort Min-Max = 1.84–43.06 ppb (3.46–81.02 µg/m^3)		
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	See Figure 6-8 in Klompmaker et al. (2021a)	Natural splines with 1–4 df	Linear (data sparse above approximately 40 ppb where log HR decreases with increasing NO_2 concentration)
†Ma et al. (2022)	MEDPAR 2000–2017	Mean = 17.5 (SD = 12.4)	Penalized splines	Linear, no threshold observed
†Wang et al. (2023)	China Family Panel Studies (CFPS) Enrollment waves: 2010, 2014, 2016, 2018 Follow-up: through 2018	Min-Max = 3.7–30.5 ppm (6.9–57.4 µg/m^3)	Restricted cubic spline with 3 knots at 10th, 50th and 90th percentiles (outliers excluded)	Approximately linear, no threshold observed

List of abbreviations in alphabetical order: CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CFPS = China Family Panel Studies; DCH = Danish Diet, Cancer and Health; df = degrees of freedom; 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-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; KORA = Cooperative Health Research in the Region of Augsburg; Max = Maximum; MEDPAR = Medicare denominator and Medicare Provider Analysis and Review; Min = Minimum; SCHIF = Shape Constrained Health Impact Function; VHM&PP = Vorarlberg Health Monitoring and Prevention Programme.
[a]For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.
[b]There visual representations of the shape of the curve in the corresponding text.
†Studies published since the 2016 Oxides of Nitrogen ISA.

6.4.1.2 Lifestages and Population

A single study that examined whether the association of NO_2 exposure with stroke was modified by pre-existing disease, BMI, age, sex or education, reported a larger magnitude association among individual with asthma but no differences across the other factors that were examined (Andersen et al., 2012). An additional study reported no sex-related differences in the magnitude of the associations between NO_2 and stroke (Johnson et al., 2013). Recent studies of long-term NO_2 exposures and cerebrovascular disease examine effect measure modification by a range of factors including sex, race, smoking, overweight, and SES. In addition, potential modification by greenspace, population density and rural versus urban communities was examined. Results from these studies are summarized in Table 6-7.

- In an analysis of U.S. Medicare data (i.e., first hospitalization), Klompmaker et al. (2021a) reported associations between annual average NO_2 exposure and cerebrovascular disease hospitalization (HR: 1.036 [95% CI: 1.032, 1.04]). The way in which the pattern of associations between NO_2 and cerebrovascular disease differed by temperature, relative

humidity, and greenness was not clear from sensitivity analyses. The study observed modification of the association between NO_2 exposure and cerebrovascular disease by region.

- Danesh Yazdi et al. (2022) reported a rate difference of 4.9 (95% CI: -1.25, 11.05) per 100,000 person years) for stroke. Analyses of the pattern of associations indicated that for NO_2-associated stroke, the risk was higher among those who were not Medicaid eligible than among those who were Medicaid-eligible. NO_2-associated stroke risk was also higher among Black individuals compared to white individuals.
- Ma et al. (2022) reported a positive association between annual average NO_2 exposure and stroke incidence in the Medicare population (HR: 1.073 [95% CI: 1.068, 1.079] per 12.4 ppb). The study observed that the HRs were larger in magnitude among Black, Medicaid eligible, lower income and lower education categories.
- Olaniyan et al. (2022) examined the association between NO_2 and incident hospitalization for stroke in CanCHEC. The HR for the association of 10-year moving average NO_2 exposure with stroke was 0.99 (95% CI: 0.95, 1.04) in the fully adjusted model. Stratified analyses did not indicate a factor (i.e., income, SES, region, urbanicity) that conferred increased risk of NO_2-related stroke.
- Shin et al. (2019) reported a positive association of 5-year running average NO_2 with stroke in the ONPHEC study (HR: 1.02 [95% CI: 1.00, 1.03]). The association with stroke was somewhat larger among women and among individuals in lower income quartiles.
- (Poulsen et al., 2023d) examined effect modification by sociodemographic factors finding stronger associations between long-term NO_2 exposure and the incidence of stroke with increasing noise, greenspace, and lower population density among individuals living in Denmark. Poulsen et al. (2023a) reported positive associations that were similar in magnitude across age strata.
- Wang et al. (2023) reported a positive association between annual average NO_2 exposure and stroke (HR: 2.61 [95% CI: 2.287, 2.97]) in a nationwide study of Chinese adults. Factors including SES, sex and smoking did not modify the association while the association was larger among those living in urban areas compared to rural areas and among obese people compared to underweight people.

The collective evidence did not indicate consistently positive associations between long-term exposure to oxides of nitrogen and cerebrovascular disease. A subset of the available studies examined modification by a variety of factors; however, many factors were only examined in single studies (i.e., smoking, and overweight). Several studies that examined effect modification by SES and sex allow results to be compared across studies; however, no consistent pattern was observed and most studies reported similar magnitude associations across strata, though a single study reported a large association in females while others found approximately similar differences by sex. Although no studies examined EMM by comorbid conditions, two studies in different populations reported that the association between long-term exposure to NO_2 and stroke was larger among those with a higher frailty index (i.e., Charleston Index). Finally, although factors are not directly comparable, a study from China reported larger associations with stroke in urban areas, while a national study of Danes reported larger associations in areas with more greenspace and smaller associations in areas with greater population density.

Table 6-7 Epidemiologic studies evaluating effect measure modification between long-term oxides of nitrogen exposure and cerebrovascular disease

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Lifestage					
Exposure to NO_2					
†Brunekreef et al. (2021)	ELAPSE Project (CEANS, DCH, E3N, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC Varese) Recruitment: 1992–2011 Follow-up: 2011–2017	HR (95% CI)[b] Stroke <65 yrs: Figure P57 from Brunekreef et al. (2021)	HR (95% CI)[b] Stroke ≥65 yrs: Figure P57 from Brunekreef et al. (2021)	↑	Individual
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CBVD, 65-74 y: 0.00 Figure 3 from Klompmaker et al. (2021a)	HR (95% CI)[b] CBVD, 75–84 y: Figure 3 from Klompmaker et al. (2021a)	≈	Individual
			CBVD, 85+ y: Figure 3 from Klompmaker et al. (2021a)	≈	
†Ma et al. (2022)	MEDPAR 2000–2017	HR (95% CI)[b] Stroke/ age <75: Figure 4 from Ma et al. (2022)	HR (95% CI)[b] Stroke/ age ≥ 75: Figure 4 from Ma et al. (2022)	↓	Individual
†Olaniyan et al. (2022)	CanCHEC Enrollment: 2006 Follow-up: 2006–2016	HR (95% CI)[b] Stroke/ age 25–44: 0.95 (0.75, 1.22)	HR (95% CI)[b] Stroke/ age 45–64: 0.94 (0.86, 1.04)	≈	Individual
			Stroke/ age 65+: 1.03 (0.98, 1.09)	↑	
†Poulsen et al. (2023a)	Danish Civil Registration System Enrollment: 2005–2017 Follow-up: Through 2017	HR (95% CI)[b] Stroke (total NO_2)/50–70 yrs: 1.06 (1.02, 1.11)	HR (95% CI)[b] Stroke (total NO_2)/70–80 yrs: 1.11 (1.06, 1.15)	↑	Individual
			Stroke (total NO_2)/80+ yrs: 1.06 (1.02, 1.10)	≈	
†Shin et al. (2019)	ONPHEC Enrollment: April 1, 1996 Follow-up: through March 31, 2015	HR (95% CI)[b] Stroke, age 35–44: 1.06 (1.00, 1.11)	HR (95% CI)[b] Stroke, age 45-54: 1.06 (0.99, 1.12)	≈	Individual
			Stroke, age 55-64: 1.03 (0.99, 1.07)	↓	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Stroke, age 65-74: 1.01 (0.98, 1.04)	↓	
			Stroke, age 75-85: 1.02 (1.00, 1.05)	↓	
†Danesh Yazdi et al. (2021)	Medicare 2000–2016	RD (95% CI)[b] Stroke, age 64–75: Figure 3 from Danesh Yazdi et al. (2021)	RD (95% CI)[b] Stroke, age 74–85: Figure 3 from Danesh Yazdi et al. (2021)	≈	Individual
			Stroke, 85+: Figure 3 from Danesh Yazdi et al. (2021)	≈	
Pre-existing Disease/Comorbidities					
Exposure to NO_2					
†Brunekreef et al. (2021)	ELAPSE Project (CEANS, DCH, E3N, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC Varese) Recruitment: 1992–2011 Follow-up: 2011–2017	HR (95% CI)[b] Stroke/ normal BMI: Figure P57 from Brunekreef et al. (2021)	HR (95% CI)[b] Stroke/ BMI = 25.0–29.9 Figure P57 from Brunekreef et al. (2021)	≈	Individual
			Stroke/ BMI≥30: Figure P57 from Brunekreef et al. (2021)	≈	
†Olaniyan et al. (2022)	CanCHEC Enrollment: 2006 Follow-up: 2006–2016	HR (95% CI)[b] Stroke/ Charleston Index 1-2: 0.975 (0.918, 1.036)	HR (95% CI)[b] Stroke/ Charleston Index 3–4: 0.941 (0.875, 1.013)	≈	Individual
			Stroke/ Charleston Index 5+: 1.073 (0.953, 1.208)	↑	
†Shin et al. (2019)	ONPHEC Enrollment: April 1, 1996 Follow-up: through March 31, 2015	HR (95% CI)[b] Stroke/ no hypertension: 1.03 (1.00, 1.06)	HR (95% CI)[b] Stroke/ hypertension: 1.03 (1.01, 1.05)	≈	Individual
		Stroke/ no diabetes: 1.02 (1.00, 1.05)	Stroke/ diabetes: 1.03 (1.00, 1.06)	≈	
		Stroke/ no CHD: 1.03 (1.01, 1.05)	Stroke/ CHD: 1.02 (0.97, 1.06)	≈	
Race/Ethnicity					
Exposure to NO_2					

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CBVD/white: Figure 3 from Klompmaker et al. (2021a)	HR (95% CI)[b] CBVD/Black: Figure 3 from Klompmaker et al. (2021a)	↑	Individual
†Danesh Yazdi et al. (2021)	Medicare 2000–2016	RD (95% CI)[b] Stroke, white: Figure 3 from Danesh Yazdi et al. (2021)	RD (95% CI)[b] Stroke, Black Figure 3 from Danesh Yazdi et al. (2021)	↑	Individual
†Ma et al. (2022)	MEDPAR 2000–2017	HR (95% CI)[b] Stroke/white: Figure Only	HR (95% CI)[b] Stroke/Black: Figure Only	↑	Individual
Region of the U.S.					
Exposure to NO_2					
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CBVD/West: Figure 3 from Klompmaker et al. (2021a)	HR (95% CI)[b] CBVD/Midwest: Figure 3 from Klompmaker et al. (2021a)	↑	Individual
			CBVD/Northeast: Figure 3 from Klompmaker et al. (2021a)	↑	
			CBVD/Southeast: Figure 3 from Klompmaker et al. (2021a)	≈	
			CBVD/Southwest: Figure 3 from Klompmaker et al. (2021a)	↑	
Sex					
Exposure to NO_2					
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CBVD/male: Figure 3 from Klompmaker et al. (2021a)	HR (95% CI)[b] CBVD/female: Figure 3 from Klompmaker et al. (2021a)	↑	Individual
†Ma et al. (2022)	MEDPAR 2000–2017	HR (95% CI)[b] Stroke/male: Figure Only	HR (95% CI)[b] Stroke/female: Figure Only	↓	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Shin et al. (2019)	ONPHEC Enrollment: April 1, 1996 Follow-up: through March 31, 2015	HR (95% CI)[b] Stroke, males: 1.02 (1.00, 1.05)	HR (95% CI)[b] Stroke, females: 1.04 (1.02, 1.06)	↑	Individual
†Danesh Yazdi et al. (2021)	Medicare 2000–2016	RD (95% CI)[b] Stroke, male: Figure 3 from Danesh Yazdi et al. (2021)	RD (95% CI)[b] Stroke, female: Figure 3 from Danesh Yazdi et al. (2021)	≈	Individual
Socioeconomic Status					
Exposure to NO_2					
†Brunekreef et al. (2021)	ELAPSE Project (CEANS, DCH, E3N, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC Varese) Recruitment: 1992–2011 Follow-up: 2011–2017	HR (95% CI)b Stroke/ high education: Figure P57 from Brunekreef et al. (2021)	HR (95% CI)b Stroke/ medium education: Figure P57 from Brunekreef et al. (2021)	↑	Individual
			Stroke/low education: Figure P57 from Brunekreef et al. (2021)	↑	
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CBVD/Medicaid Eligible: Figure 3 from Klompmaker et al. (2021a)	HR (95% CI)[b] CBVD/not Medicaid eligible: Figure 3 from Klompmaker et al. (2021a)	↑	Individual
†Ma et al. (2022)	MEDPAR 2000–2017	HR (95% CI)[b] Stroke/ Medicaid eligible: Figure 4 from Ma et al. (2022)	HR (95% CI)[b] Stroke/ not Medicaid eligible: Figure 4 from Ma et al. (2022)	↓	Individual
		Stroke/ high household income: Figure 4 from Ma et al. (2022)	Stroke/ low household income: Figure 4 from Ma et al. (2022)	↑	
		Stroke/high education: Figure 4 from Ma et al. (2022)	Stroke/low education: Figure 4 from Ma et al. (2022)	↑	
†Olaniyan et al. (2022)	CanCHEC Enrollment: 1981 Follow-up: through December 31, 2016	HR (95% CI)[b] Stroke, highest income (1st quintile): 1.012 (0.881, 1.161)	HR (95% CI)[b] Stroke, lowest income (5th Quintile): 0.964 (0.885, 1.051)	↓	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Shin et al. (2019)	ONPHEC Enrollment: April 1, 1996 Follow-up: through March 31, 2015	HR (95% CI)[b] Stroke, highest income (Q5): 1.01 (0.97, 1.04)	HR (95% CI)[b] Stroke, lowest income (Q1): 1.06 (1.04, 1.09)	↑	Individual
†Danesh Yazdi et al. (2021)	Medicare 2000-2016	RD (95% CI)[b] Stroke, not Medicaid eligible: Figure 3 from Danesh Yazdi et al. (2021)	RD (95% CI)[b] Stroke, Medicaid eligible: Figure 3 from Danesh Yazdi et al. (2021)	↓	Individual
Urbanicity					
Exposure to NO_2					
†Gandini et al. (2018)	ILS Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008	HR (95% CI)[b] CBVD/ Rural: 0.98 (0.88, 1.10)	HR (95% CI)[b] CBVD/ Urban: 0.96 (0.83, 1.11)	≈	Individual
			CBVD/ Metropolitan: 1.02 (0.76, 1.36)	≈	

List of abbreviations in alphabetical order: BMI = body mass index; CanCHEC = Canadian Census Health and Environment Cohort; CBVD = Cerebrovascular Disease; CI = confidence interval; 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-MORGEN = European Prospective Investigation into Cancer and Nutrition-Monitoring Project on Risk Factors and Chronic Diseases in Netherlands; 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; MEDPAR = Medicare denominator and Medicare Provider Analysis and Review; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort; RD = Risk Difference; VHM&PP = Vorarlberg Health Monitoring and Prevention Programme.

[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of cerebrovascular disease and stroke) in the group with the factor evaluated than in the reference group. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller in the group with the factor evaluated than in the reference group. An almost equal sign (and grey shading) indicate that the effect of NO_2 is comparable between groups.

[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.

6.4.1.3 Copollutants

None of the studies assessed in the 2016 Oxides of Nitrogen ISA examined confounding by traffic related copollutants; however, and a single study (de Kluizenaar et al., 2013) reported that the positive association that was observed between annual average NO_2 exposure and stroke remained after adjustment for noise. In recent studies, mutually adjusted models were used to evaluate the potential for other pollutants and stressors such as noise to confound risk estimates of long-term exposure to oxides of

nitrogen and cerebrovascular effects. The subset of studies that examine confounding by copollutants and noise are summarized in Table 6-8 and below.

- Klompmaker et al. (2021a) reported a positive association between annual average NO_2 exposure and cerebrovascular disease hospitalization among Medicare recipients (HR: 1.036 [95% CI: 1.032, 1.04]) in the single pollutant model. In models that were simultaneously adjusted for NO_2, $PM_{2.5}$ and O_3, the association was attenuated but remained positive (HR: 1.018 [95% CI: 1.014, 1.022]).
- Ma et al. (2022) reported a positive association of annual average NO_2 exposure with stroke incidence also in in the Medicare population (HR: 1.058 95% CI: 1.054, 1.063]). These associations remained robust after adjustment of $PM_{2.5}$ and O_3.
- Olaniyan et al. (2022) examined the association between NO_2 and incident hospitalization for stroke in CanCHEC (2006 to 2016). The HR for stroke associated with 10-year moving average NO_2 exposure was 0.993 (95% CI: 0.947, 1.041) in the fully adjusted model. In a two-pollutant model that was adjusted for $PM_{2.5}$, the inverse association remained (HR: 0.903 [95% CI: 0.857, 0.951]). In the two-pollutant model that adjusted for O_3 the HR did not substantially change (HR: 0.971 [95% CI: 0.928, 1.017]).
- In European studies, Poulsen et al. (2023b) reported that the association of NO_2 with stroke was robust to adjustment for EC (1.109 [95% CI: 1.058, 1.162]) but did not persist in models adjusted for $PM_{2.5}$ (HR: 0.943 [95% CI: 0.906, 0.982]) and UFP (HR: 1.016 (95% CI: 0.047, 21.95]). Cai et al. (2018) reported that the positive HRs for CBVD, ischemic stroke and the null association for hemorrhagic stroke did not change after adjustment for noise (HR: 1.052 [95% CI: 0.894, 1.237], HR: 1.067 [95% CI: 0.826, 1.378] and HR: 0.978 [95% CI: 0.786, 1.217], respectively). A positive association was observed between 1-year average exposure to NO_2 and overall stroke (HR: 1.05 [95% CI: 0.97, 1.13] per IQR) that remained after adjustment for noise (HR: 1.05 [95% CI: 0.97, 1.15] per IQR) (Amini et al., 2020). In ELAPSE, Brunekreef et al. (2021) reported that the positive association between annual average NO_2 exposure and stroke (HR: 1.16 [95% CI: 1.08, 1.24]) observed in single pollutant models persisted positive after adjustment for $PM_{2.5}$ (HR: 1.18 [95% CI: 1.07, 1.29]), BC (1.22 [95% CI: 1.04, 1.42]) and O_3 (HR: 1.18 [95% CI: 1.08, 1.28]).

The evaluation of copollutant confounding was limited in studies examining long-term exposure to oxides of nitrogen and cerebrovascular disease. The copollutants that were examined include $PM_{2.5}$, and O_3. Confounding by traffic noise exposure was also examined in several studies. Moderate correlations between noise and traffic pollutants including BC were observed in multiple studies in Europe and the United States (see Chapter 2, Section 2.4.3.1), suggesting that controlling for traffic noise may also control, in part, for other traffic related pollutants. Single pollutant associations of long-term NO_2 exposure with cerebrovascular disease or stroke were attenuated but remained positive in some (Ma et al., 2022; Klompmaker et al., 2021a), but not all (Poulsen et al., 2023b; Shin et al., 2019), studies in which models were adjusted for $PM_{2.5}$ or O_3. In studies that observed inverse associations between long-term exposure to NO_2 and cerebrovascular disease, copollutant adjustment did not change the direction of those associations (Olaniyan et al., 2022). Single pollutant associations from two European studies remained positive after adjustment for noise (Amini et al., 2020; Cai et al., 2018). A limited number of the available cerebrovascular studies that examined confounding by O_3, traffic-related copollutants

($PM_{2.5}$, CO, BC/EC, UFP) or noise. The association with NO_2 in models that adjusted for $PM_{2.5}$ or O_3 were mixed, while the positive associations observed in studies that adjusted for noise remained positive.

Table 6-8 Epidemiologic studies evaluating copollutant associations between long-term exposure to oxides of nitrogen and cerebrovascular disease and stroke

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of Association[a]	Effect Estimate (95% CI)
Exposure to NO_2						
†Amini et al. (2020)	DNC Enrollment: 1993 and 1999 Follow-up: December 31, 2014	Noise	0.6	Simultaneous inclusion of NO_2 and noise in Cox Proportional Hazard model	≈	HR (95% CI)[b] All Stroke, 1-yr (Main Effect): 1.12 (0.94, 1.34) All Stroke, 1-yr+ noise: 1.12 (0.92, 1.37)
					≈	IS, 1-yr (Main Effect): 1.15 (0.96, 1.37) IS, 1-yr+ noise: 1.17 (0.95, 1.44)
					↓	HS, 1-yr (Main Effect): 0.93 (0.54, 1.60) HS, 1-yr+ noise: 0.84 (0.45, 1.59)
†Brunekreef et al. (2021)	ELAPSE Project (CEANS, DCH, E3N, ESCAPE, VHM&PP, HNR study, KORA, DNC, EPIC-MORGEN, EPIC-Prospect, EPIC Varese) Recruitment: 1992–2011 Follow-up: 2011–2017	$PM_{2.5}$ BC O_3	0.49 0.65 -0.76	Simultaneous inclusion of NO_2 and a second pollutant in Cox Proportional Hazard model		HR (95% CI)[b] Stroke (Main Effect): 1.16 (1.08, 1.24)
					≈	+O3: 1.18 (1.08, 1.28)
					≈	+$PM_{2.5}$: 1.18 (1.07, 1.29)
					≈	+BC: 1.22 (1.04, 1.42)
†Cai et al. (2018)		Noise	0.1	Simultaneous inclusion of NO_2 and noise in Cox Proportional Hazard model	≈	HR (95% CI)[b] CBVD (Main Effect): 1.05 (0.89, 1.24) CBVD + noise: 1.05 (0.89, 1.24)
					≈	IS (Main Effect): 1.07 (0.83, 1.38) IS+noise: 1.07 (0.83, 1.38)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of Association[a]	Effect Estimate (95% CI)
	UK Biobank, EPIC-Oxford, HUNT Enrollment: - UK Biobank: 2006–2010 - HUNT: 1995–1997 - EPIC-Oxford: 1993–1999 Follow-up: - UK Biobank: 1.3 mean years - HUNT: 14.1 mean years - EPIC-Oxford: 10.8 mean years				≈	HS (Main Effect): 0.97 (0.72, 1.32) HS+noise: 0.98 (0.79, 1.22)
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	$PM_{2.5}$ O_3	0.43 -0.12	Simultaneous inclusion of NO_2, $PM_{2.5}$ and Ozone in Cox Proportional Hazard model	↓	HR (95% CI)[b] CBVD (Main Effect): 1.04 (1.03, 1.04) +$PM_{2.5}$, Ozone: 1.02 (1.01, 1.02)
†Olaniyan et al. (2022)	CanCHEC Enrollment: May 16, 2006 Follow-up: December 31, 2016	$PM_{2.5}$ O_3	0.72 0.3	Simultaneous inclusion of NO_2 and a second pollutant in Cox Proportional Hazard model		HR (95% CI)[b] Stroke (Main Effect): 0.99 (0.95, 1.04)
					↓	Stroke - $PM_{2.5}$: 0.90 (0.86, 0.95)
					≈	Stroke - Ozone: 0.97 (0.93, 1.02)
†Poulsen et al. (2023b)	Danish Civil Registration System Enrollment: 1979 Follow-up: 2005–2017	$PM_{2.5}$ UFP EC	0.76 0.92 0.93	Simultaneous inclusion of NO_2 and a second pollutant in Cox Proportional Hazard model		HR (95% CI)[b] Stroke (total NO_2) (Main Effect): 1.08 (1.04, 1.11)
					↓	+$PM_{2.5}$: 0.94 (0.91, 0.98)
					↓	+UFP: 1.02 (0.05, 21.95)
					↑	+EC: 1.11 (1.06, 1.16)

List of abbreviations in alphabetical order: CanCHEC = Canadian Census Health and Environment Cohort; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI = confidence interval; 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-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-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; HS = Hemorrhagic Stroke; HUNT = Helseundersøkelsen i Nord-Trøndelag; IS = Ischemic Stroke; KORA = Cooperative Health Research in the Region of Augsburg; MEDPAR = Medicare denominator and Medicare Provider Analysis and Review; NO_2 = nitrogen dioxide; O_3 = Ozone; ONPHEC = Ontario Population Health and Environment Cohort; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 μm; ppb = parts per billion; UFP = Ultrafine Particulate; VHM&PP = Vorarlberg Health Monitoring and Prevention Programme.

[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of cerebrovascular disease and stroke) with the copollutant evaluated than in the single pollutant model. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller with the copollutant evaluated than in the single pollutant model. An almost equal sign (and grey shading) indicates that the effect of NO_2 is comparable between the single pollutant analysis and copollutant analysis.

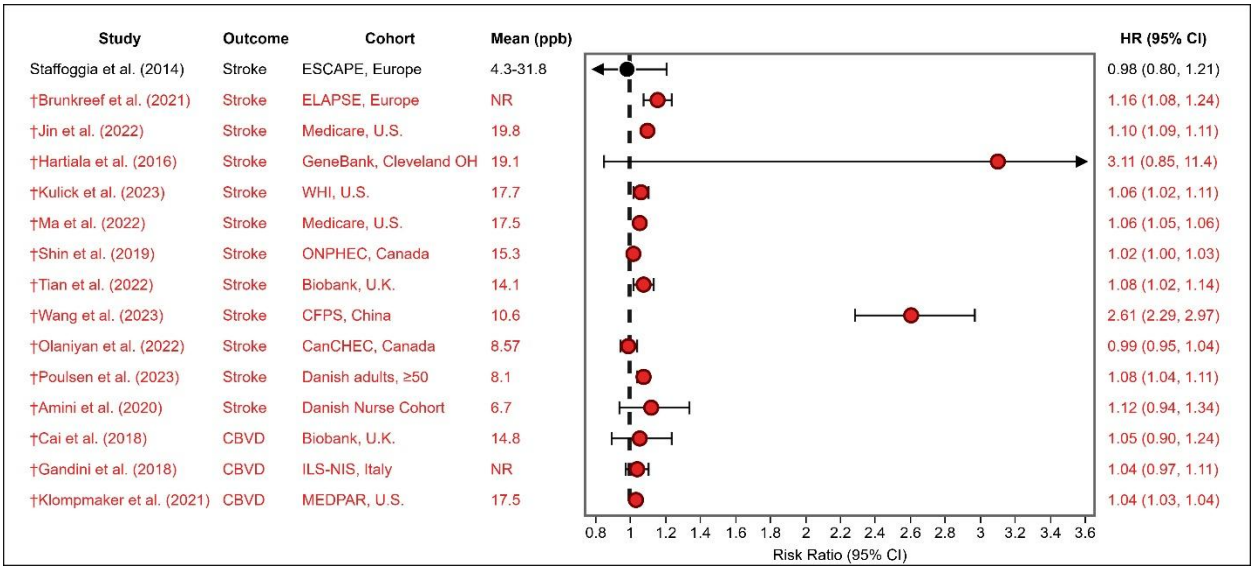
[b]Effect estimates are standardized and are presented as a 20 ppb change in NO_2 for 24-hour average averaging time; 20 ppb change in NO for 24-hour average averaging time; 30 ppb change in NO_X for 24-hour averaging time; 25 ppb change in NO_2 for 1-hour maximum averaging time; 60 ppb change in NO 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.

6.4.1.4 Conclusions and Remaining Uncertainties

The evidence regarding long-term exposure to NO_2 and NO_X and cerebrovascular disease has expanded substantially since the 2016 Oxides of Nitrogen ISA. Overall, the lack of consistency that was observed in the 2016 Oxides of Nitrogen ISA continues (see Figure 6-15). Results from recent studies varied in both direction and magnitude. A limited number of cerebrovascular studies examined confounding by copollutants and noise. The results from models that simultaneously adjusted for $PM_{2.5}$ or O_3 were mixed, while the positive associations observed in two studies that adjusted for noise remained positive. Overall, uncertainty remains regarding the independent effect of oxides of nitrogen exposure on cerebrovascular disease. The small subset of studies that examined the shape of the C-R function indicated linear or supralinear relationships, with one study showing a widening of CIs and flattening above 10 $\mu g/m^3$ for NO_2, and 30 $\mu g/m^3$ for NO_X where no association was observed. Several at-risk factors were examined in single studies and the factors that were examined in multiple studies did not reveal a consistent pattern of effect measure modification. Overall, it is not clear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, confounding by traffic-related copollutants or other environmental determinants, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health care access, health behaviors). Most studies assessed exposure to NO_2 using validated exposure models with moderate to high model performance.



List of abbreviations in alphabetical order: CHD = coronary heart disease; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; CPFS: China Family Panel Studies; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; ILS-NHIS: Italian Longitudinal Study, National Health Interview Survey; MEDPAR: Medicare denominator and Medicare Provider Analysis and Review; MI = myocardial infarction; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-15 Epidemiologic studies of the association of long-term NO_2 exposure with cerebrovascular disease and stroke.

6.5 Hypertension

High blood pressure is generally defined as a systolic blood pressure above 140 millimeters of mercury (mm Hg) or a diastolic blood pressure above 90 mm Hg. Hypertension, which is the clinically relevant consequence of chronically high blood pressure, typically develops over years.

6.5.1 Epidemiologic Studies of Hypertension

The 2016 Oxides of Nitrogen ISA assessed several studies that examined the association of NO_2 or NO_X with hypertension or increases in blood pressure (U.S. EPA, 2016). Overall, findings from studies of adults and children report weak, inconsistent results for the association between NO_2 and hypertension (Dong et al., 2013; Coogan et al., 2012; Sørensen et al., 2012) and increased blood pressure (see Section 6.7.1). One prospective study using LUR to estimate exposure and adjusting for CVD risk factors reported a positive association between NO_X and hypertension (Coogan et al., 2012). Uncertainties remained regarding the independent effect of NO_2 on hypertension and blood pressure, specifically whether confounding by correlated traffic-related pollutants or noise can explain the positive associations observed.

Recent studies expand the evidence pertaining to oxides of nitrogen and hypertension, including several analyses of established North American cohorts (i.e., an updated analysis of the BWHS, and analyses of Multi-Ethnic Study of Atherosclerosis [MESA], ONPHEC, CANHEART). Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-5. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in greater detail in Sections 6.5.1.1, 6.5.1.2, and 6.5.1.3, respectively. Section 6.5.1.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for hypertension.

- Coogan et al. (2017) extended the analysis of (Coogan et al., 2012), who examined the association of NO_X with hypertension in a subset of the BWHS participants who resided in Los Angeles, California, U.S. (Coogan et al., 2012) reported an association (IRR) of 1.31 (95% CI: 1.07, 1.61) in models adjusted for noise and other important covariates. Slight attenuation of the association was observed after adjustment for $PM_{2.5}$. Coogan et al. (2017) examined the association in the full cohort that includes Black women from 56 U.S. metropolitan areas including the women residing Los Angeles who participated in the earlier study. Multi-year average NO_2 exposure (1995 to the end of follow-up) was estimated using a spatiotemporal model (R^2: 0.80). The HR for the association of long-term NO_2 exposure and incident hypertension indicated an inverse association in fully adjusted models (HR: 0.92 [95% CI: 0.86, 0.98]). The association between SES, a potential confounding factor, and hypertension differed between the Los Angeles and the full cohort, possibly explaining the discrepant results. The inverse association persisted after adjustment for O_3 (HR: 0.93 [95% CI: 0.86, 1.00]) and $PM_{2.5}$ (HR: 0.90 [95% CI: 0.82, 0.98]).
- In an analysis by Adar et al. (2018), 1-year average NO_2 exposure was associated with incident hypertension among MESA participants in models that adjusted for time-varying age; however, when calendar time was included in the model to account for population-wide period effects (e.g., changes in efficacy of antihypertension medications or prescribing practices) the associations were substantially attenuated (HR: 1.29 [95% CI: 1.11, 1.50]) without adjustment for calendar time versus (HR: 1.08 [95% CI: 0.92, 1.27]) after adjustment. Analyses of subclinical blood pressure changes in the MESA cohort, showed a similar pattern, and are discussed in Section 6.7.1.
- Bai et al. (2018) examined the association of 3-year moving average NO_2 estimated with LUR (R^2: 0.70) with hypertension among participants in the ONPHEC study. The HR for the association in fully adjusted models was (1.02 [95% CI: 1.00, 1.05]). After adjustment for UFP the association was null (HR: 1.00 [95% CI: 0.98, 1.02]). The association was unchanged after adjustment for $PM_{2.5}$ (HR: 1.02 [95% CI: 1.00, 1.05]).
- Howell et al. (2019) conducted a cross-sectional analysis of CANHEART data, including adults 49–74-years old who live in large urban centers in Ontario Canada. The CANHEART dataset combines administrative health care data with exposure and sociodemographic data. LUR models were used to predict annual average NO_2 concentration at the neighborhood of residence ($r^2 = 0.73$). The OR for the association of annual average NO_2 exposure with hypertension was 1.02 (95% CI: 1.01, 1.03). When NO_2 exposure and neighborhood walkability were modelled jointly (i.e., simultaneously), the association between NO_2 exposure and hypertension increased (OR: 1.09 [95% CI: 1.08, 1.10]). In addition, an interaction between NO_2 exposure and walkability was observed indicating that the benefits of living in a neighborhood with high walkability decreased with increasing NO_2 exposure.

- Letellier et al. (2022) investigated the association of NO_2 with hypertension (and metabolic disorders, see Chapter 8) in participants enrolled in Community of Mine study in San Diego County, California, U.S. Multi-year average (2014 to 2017) NO_2 exposures were estimated using two approaches. A traditional static approach was used to link NO_2 concentrations from EPA's Air Quality System (AQS) to the participant's home via IDW, and a novel dynamic approach that used a personal GPS device worn by the participant for two weeks to create a long-term time-weighted activity space using the Kernal Density Equation model in ArcGIS that reflected the participants mobility. The time-weighted activity space was then multiplied by each pollution layer to derive a total exposure that accounted for time and locations visited. The authors observed an inverse association between long-term NO_2 exposure and hypertension for the static exposure method that was close to the null value (RR: 0.94 [95% CI: 0.68, 1.31]). In contrast, for the dynamic exposure method, Letellier et al. (2022) observed a positive association, although the 95% CIs included the null value (RR: 1.10 [95% CI: 0.82, 1.46]).

Recent studies of hypertension were also conducted in Europe and Asia. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-5.

- Fuks et al. (2014) examined the cross-sectional association of NO_2 and NO_X exposure with blood pressure and prevalent hypertension (i.e., systolic ≥140 mm Hg and diastolic ≥90 or use of blood pressure lowering medication [BPLM]) among participants enrolled in 15 ESCAPE cohorts. The standard ESCAPE LUR protocol was used to estimate annual average NO_2 and NO_X exposure. The ORs for the associations of NO_2 with measured hypertension and BPLM were (0.96 [95% CI: 0.86, 1.08]) and (1.02 [95% CI: 0.95, 1.10]), respectively. Fuks et al. (2017) added to their previous analysis by examining the association annual average NO_2 and NO_X exposure at baseline and incident hypertension (self-reported hypertension, measured hypertension and BPLM use). Small inverse relative risks that included the null value were observed for measured hypertension (e.g., RR (NO_2): 0.94 [95% CI: 0.84, 1.06] and RR (NO_X): 0.96 [95% CI: 0.92, 1.01]). The associations did not change after adjustment for noise.
- Klompmaker et al. (2019) analyzed data from a national survey in the Netherlands to determine the relationship between green space, air pollution and road traffic noise with hypertension. Annual average NO_2 exposure was associated with a OR for hypertension of 1.05 (95% CI: 1.01, 1.09). The joint effects of NO_2, noise and decreasing greenspace are discussed in Section 6.5.1.3. Jendrossek et al. (2017) also investigated associations between residential air pollution, traffic load on major roads within 100 meters of the home residence, greenness, and hypertension. This study used data from mothers enrolled in two German birth cohorts. The cohorts were the German Infant Study on the Influence of Nutrition Intervention plus Air pollution and Genetics on Allergy Development (GINIplus) and the Influence of Life-style factors on Development of the Immune System and Allergies in East and West Germany plus Air Pollution and Genetics on Allergy Development (LISAplus). Data for the analysis was restricted to those who lived in and around Munich and Wesel. Annual average NO_2 and NO_X exposure was estimated using the ESCAPE methodology and linked with information on doctor diagnosed hypertension in mothers that was collected every 15-years. Long-term NO_2 concentration was estimated using ESCAPE methods (i.e., validated LUR models) and categorized into tertiles for the analysis. An inverse, imprecise association between NO_2 exposure and self-reported maternal hypertension was observed in the urban area of Munich (OR: 0.83 [95% CI: 0.53, 1.29] tertile 3 vs. tertile 1) and a positive, imprecise association was observed in the rural area of Wesel (OR: 1.52 [95% CI: 0.93, 2.51] tertile 3

vs. tertile 1). A similar pattern indicating little evidence of an association was observed for NO_x and estimates were not substantially changed in models that also included adjustment for traffic related noise.

- Levinsson et al. (2014) reported an inverse association between NO_2 and hypertension (OR: 0.82 [95% CI: 0.57, 1.19]) among participants in the INTERGENE/ADONIX. The risk of NO_2-associated MI and hypertension did not differ depending on genotype strata for variants in the GSTP1, GSTT1 and GSTCD genes, which are implicated in oxidative stress and may confer susceptibility to heart disease (see Section 6.5.1.2).
- In an analysis of UK Biobank data, Weng et al. (2022) reported cross-sectional associations of annual average NO_2 and NO_X with hypertension in the whole population (HR: 1.02 [95% CI: 1.00, 1.04] and 1.01 [95% CI: 1.01, 1.02 per 10 $\mu g/m^3$]), respectively). Additionally, the authors reported that participants with a high genetic risk (i.e., highest tertile of polygenetic risk score based on SNPs associated with hypertension) and high NO_X exposure (above the median exposure) had a higher risk of hypertension than the reference group with a low genetic risk (lowest tertile) and low NO_X exposure (below the median) (HR: 1.65 [95% CI: 1.60, 1.70] per 10 $\mu g/m^3$). Compared to the same reference group, the association of low NO_X exposure with hypertension in the high genetic risk group was approximately the same (HR: 1.63 [95% CI: 1.53, 1.68] per 10 $\mu g/m^3$). The association of high NO_X exposure with hypertension in the low genetic risk group was substantially lower (HR: 1.06 [95% CI: 1.03, 1.09 per 10 $\mu g/m^3$]). The relative excess risk due to the interaction (RERI) was 0.12 (95% CI: 0.08, 0.16) among those in the highest tertile of risk score.
- Wang et al. (2023) conducted a nationwide study of adults in China (2010 to 2018) to examine the association of annual average NO_2 exposure for the county of residence. NO_2 exposure was estimated using a spatiotemporal model and risk of hypertension considering death as a competing event because premature death may mask the association with hypertension. The HR was 2.20 (95% CI: 1.93, 2.51).
- Yang et al. (2017) reported a positive association of 3-year average NO_2 with prehypertension, i.e., systolic blood pressure (SBP) 120 to 139 mm Hg and diastolic blood pressure (DBP) 80 to 89 mm Hg and not taking hypertensive medication, (OR: 1.18 [95% CI: 1.05, 1.32] per IQR). These associations were stronger than associations with hypertension. Yang et al. (2018) examined whether overweight modified the association between long-term exposure to NO_2 and prehypertension in Chinese adults (18 to 74 years) in three Chinese cities. The prevalence OR for the association among those with normal weight (OR: 1.09 [95% CI: 0.96, 1.22] was smaller than the association among those who were overweight (PRR: 1.32 [95% CI: 1.13, 1.54]). The RERI was more than additive (0.41 [95% CI: 0.13, 0.69]). The 3-year average NO_2 exposure metric was derived from daily measurements of the existing monitors, which reflect the background NO_2 concentrations.
- (Hou et al., 2021) studied the interactive effects of different obesity indices and air pollutants on BP and prevalent hypertension among Chinese adults enrolled in the Henan Rural Health cohort. Higher NO_2 (≥21.6 ppb [40 $\mu g/m^3$] v. <21.6 ppb [40 $\mu g/m^3$]) was associated with higher blood pressure (β (SPB): 6.11 [95% CI: 5.72, 6.49], β (DPB): 4.55 [95% CI: 4.31, 4.79], β (PP): 1.56 [95% CI: 1.32, 1.8], β (MAP): 5.07 [95% CI: 4.79, 5.34]) and increased odds of hypertension (OR: 1.83 (95% CI: 1.74, 1.93]). This study also reported that obesity increased the effect of NO_2 exposure on BP and hypertension.
- Zhang et al. (2023) investigated the association of 3-year average NO_2 exposure estimated using a validated spatiotemporal model (C-V R^2: 0.84) with blood pressure and hypertension among adults from the China Health and Retirement Longitudinal Study. The OR for the association with prevalent hypertension was 1.32 (95% CI: 1.20, 1.46).

Two studies investigated the association of oxides of nitrogen exposure with pulmonary hypertension (or prognosis among pulmonary hypertension patients), which is a condition that occurs when the blood pressure in the arteries of the lung is elevated, causing possible damage to the heart because it makes it more difficult to pump blood into the lungs. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-5.

- Sofianopoulou et al. (2019) investigated the association of NO_2 with transplant-free survival and pulmonary hemodynamic severity at baseline among patients with pulmonary arterial hypertension. Annual average NO_2 concentrations for the year 2010 were linked to participant residential address. No associations were reported between NO_2 exposure and transplant-free survival or pulmonary hemodynamics at baseline. This study may be vulnerable to selection bias because the study was restricted to transplant free survival.
- Shi et al. (2023) investigated the association of NO_2 and NO_X with pulmonary hypertension among participants in the UK Biobank study. After adjustment for covariates including noise, the HRs for pulmonary hypertension incidence were 1.42 (95% CI: 1.37, 1.48 per IQR) for NO_2, and 1.35 (95% CI: 1.31, 1.40 per IQR) for NO_X. The IQRs were not reported.

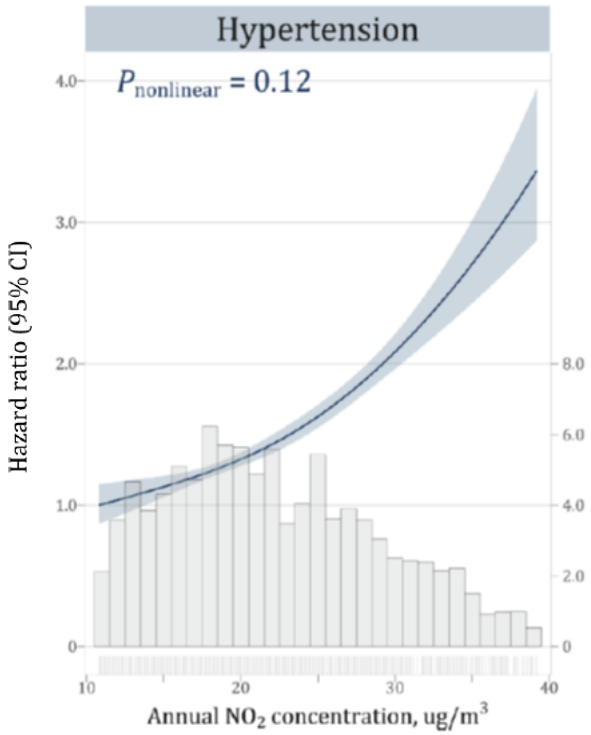
Recent studies, including two analyses of U.S. children enrolled in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort, as well as European studies were conducted.

- Ni et al. (2021) examined the association of pre- and post-natal NO_2 exposure with blood pressure at four to six years, among children enrolled in the CANDLE cohort. Annual average NO_2 exposure was estimated using LUR with kriging components and then assigned at the participant's residential address for the pre- and postnatal exposure periods. Although associations with increases in SBP and DBP and risk of high blood pressure (i.e., SBP and/or DBP at ≥90th percentile) were observed, none of the confidence intervals excluded the null value. For example, the ORs for the associations of pre-natal NO_2 exposure and post-natal NO_2 exposure with high blood pressure were 1.16 (95% CI: 0.61, 2.22) and 2.01 (95% CI: 0.83, 4.89), respectively. The study also examined effect measure modification by maternal Healthy Eating Index, child sex, folate concentrations and race (see Section 6.5.1.2).

6.5.1.1 Concentration-Response

There were no studies that examined the shape of the C-R function for the relationship between NO_2 or NO_X exposure and hypertension assessed in the 2016 Oxides of Nitrogen ISA. A single study examined the shape of the C-R function (see Figure 6-16).

- Wang et al. (2023) conducted a nationwide study of adults in China (2010 to 2018) to examine the association of NO_2 exposure with hypertension. Restricted cubic splines were used to examine the shape of the C-R function. The shape was approximately linear with no evidence of a threshold (see Figure 6-16).



List of abbreviations in alphabetical order: CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide, µg/m^3 = micrograms per cubic meter.
Source: Wang et al. (2023). Copyright permission pending.

Figure 6-16 Concentration-response relationship of incident hypertension per 10 µg/m^3 increase in NO_2 concentration.

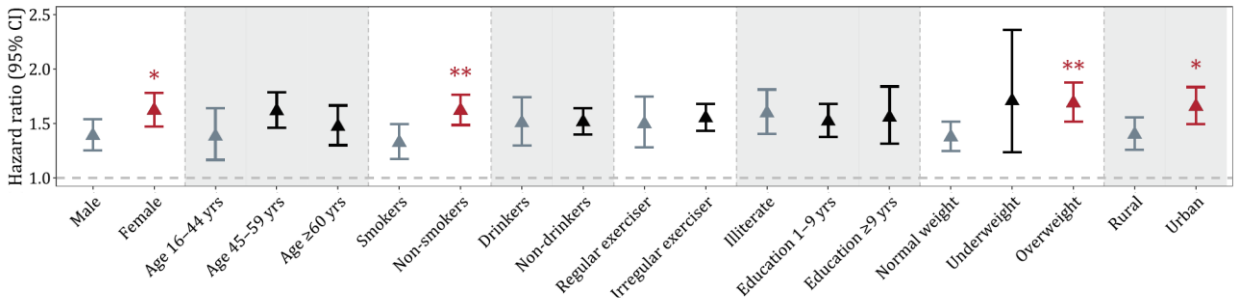
6.5.1.2 Lifestages and Populations

A single study investigated whether the association between NO_2 exposure and hypertension varied depending on age but reported no difference. The evidence from the recent studies that examined the difference in effect estimates between subgroups or strata, remains limited. Results from these studies are summarized in Table 6-9.

- Ni et al. (2021) examined the association of pre- and post-natal NO_2 exposure with blood pressure at four to six years, among children enrolled in the CANDLE cohort. The study also examined effect measure modification by maternal Healthy Eating Index, child sex, folate concentrations and race. Confidence intervals were generally overlapping across these strata; however, a larger magnitude association between postnatal NO_2 exposure and high blood pressure was observed in male children compared to female children. The association with postnatal NO_2 exposure was also larger in magnitude in Black compared to non-Black children. Ni et al. (2022) investigated the association of NO_2 with blood pressure and hypertension in high (2 high risk alleles) and low (0 or 1 risk allele) risk APOL1 groups in this population. An increase in NO_2 exposure was positively, but imprecisely, associated with hypertension in mothers in the APOL1 high-risk group (RR = 2.93 [95% CI: 0.29, 30.1]). In

the low risk APOL1 group the association was imprecise and negative (RR: 0.73 [95% CI: 0.41, 1.31]). There was no discernable pattern across child genotype risk groups.

- Wang et al. (2023) conducted a nationwide study of adults in China (2010 to 2018) to examine the association of NO_2 exposure with hypertension. The association with hypertension was larger among females, non-smokers, overweight individuals, and those who lived in urban environments (see Figure 6-17).



List of abbreviations in alphabetical order: CI = confidence interval; yrs = years.
Source: Wang et al. (2023). Copyright permission pending.

Figure 6-17 Subgroup analyses of HR with 95% CI for incident hypertension with a 10 µg/m^3 rise in exposure to NO_2

- In an analysis of the Chinese Health Study, Yang et al. (2017) reported a positive association of NO_2 with prehypertension, i.e., SBP 120 to 139 mm Hg and DBP 80 to 89 mm Hg and not taking hypertensive medication, (OR: 1.18 [95% CI: 1.05,1.32] per IQR). The association was somewhat larger in women (OR: 1.21 [95% CI: 1.07, 1.37]) than in men (OR: 1.13 [95% CI: 0.99, 1.29]) and in those ≥55 years old (OR: 1.27 [95% CI: 1.19, 1.35]) compared to those 35 to 55-years old (OR: 1.17 [95% CI: 1.10, 1.23]). Yang et al. (2018) examined whether being overweight modified the association between long-term exposure to NO_2 and prehypertension in Chinese adults (18 to 74-years) in three Chinese cities. The prevalence OR for the association among those with normal weight [POR: 1.09 [95% CI: 0.96, 1.22])] was smaller than the association among those who were overweight (POR: 1.32 [95% CI: 1.13, 1.54]). The RERI was 0.41 (95% CI: 0.13, 0.69).
- In an analysis of UK Biobank data, Weng et al. (2022) reported that participants' with a high genetic risk (i.e., highest tertile of polygenetic risk score based on SNPs associated with hypertension) and high NO_X exposure (above the median) had a higher risk of hypertension than participants in the reference group with a low (lowest tertile) genetic risk and low (below the median) NO_X exposure (HR: 1.65 [95% CI: 1.60, 1.70] per 10 µg/m^3). The RERI was 0.12 (95% CI: 1.42, 1.63).
- Levinsson et al. (2014) used data from the INTERGENE/ADONIX study to examine whether the risk of MI and hypertension differed depending on genotype strata for variants in the GSTP1, GSTT1 and GSTCD genes. The OR for the association between NO_2 and hypertension was (0.69 [95% CI: 0.34, 1.38]). This study reported no interaction between genetic variants in the GST genes and NO_2 exposure for hypertension.

Only a small subset of the hypertension studies evaluated modification of the association with long-term oxides of nitrogen exposure. Two studies conducted in China reported that associations with NO_2 were larger in females while reporting mixed results for effect measure modification by age. Two

additional studies reported results indicating that genetic factors may increase the risk of NO_2-related hypertension. Single studies evaluated modification by smoking, being overweight, educational attainment, and rural versus urban.

Table 6-9 Epidemiologic studies evaluating effect measure modification between long-term oxides of nitrogen exposure and hypertension

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Lifestage					
Exposure to NO_2					
†Yang et al. (2017)	33 CCHS NR	PRR (95% CI)[b] Prehypertension/ < age 35: 1.12 (1.09, 1.23)	PRR (95% CI)[b] Prehypertension/ age 35-55: 1.12 (1.10, 1.23)	≈	Individual
			Prehypertension/≥ age 55: 1.27 (1.19, 1.53)	↑	
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ age 45–59, Figure 6-17	HR (95% CI)[b] Hypertension/ age ≥60, Figure 6-17	≈	Individual
Sex					
Exposure to NO_2					
†Ni et al. (2021)	CANDLE Enrollment 1: December 2006-August 2008 Enrollment 2: September 2007-July 2011 Follow-up: 8-9-yrs	IRR (95% CI)[b] Prenatal Male: 1.40 (0.70, 2.82)	IRR (95% CI)[b] Prenatal Female: 0.90 (0.35, 2.36)	↓	Individual
		Postnatal Male: 2.59 (0.99, 6.80)	Postnatal Female: 1.34 (0.4, 4.52)	↓	
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ Male, Figure 6-17	HR (95% CI)[b] Hypertension/ Female, Figure 6-17	≈	Individual
†Yang et al. (2017)	33 CCHS 2009	OR (95% CI)[b] prehypertension/ male: 1.13 (0.99, 1.29)	OR (95% CI)[b] Prehypertension/ female: 1.21 (1.07, 1.37)	↑	Individual
Race/Ethnicity					
Exposure to NO_2					
†Letellier et al. (2022)	Community of Mine Study 2014-2017	RR (95% CI)[b] non-Hispanic: 1.32 (0.76, 2.30)	RR (95% CI)[b] Hispanic: 1.04 (0.75, 1.43)	↓	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Ni et al. (2021)	CANDLE cohort Enrollment 1: December 2006-August 2008 Enrollment 2: September 2007-July 2011 Follow-up: 8-9-yrs	IRR (95% CI)[b] Prenatal non-Black: 1.16 (0.33, 4.13)	IRR (95% CI)[b]) Prenatal Black: 1.16 (0.58, 2.33)	≈	Individual
		Postnatal non-Black: 0.66 (0.16, 2.80)	Postnatal Black: 2.93 (1.10, 7.82)	↑	
Socioeconomic Status					
Exposure to NO_2					
†Yang et al. (2018)	33 CCHS NR	PRR (95% CI)[b] Low GDP , normal weight: 1.00 (0.80, 1.26)	PRR (95% CI)[b] Low GDP, overweight: 1.59 (1.33, 1.91)	↑	Individual
		High GDP, normal wt: 1.29 (0.99, 1.69)	High GDP, overweight: 0.77 (0.56, 1.05)	↓	
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ 1-9 yr education, Figure 6-17	HR (95% CI)[b] Hypertension/ >9 yr education, Figure 6-17	≈	Individual
Pre-existing Diseases/Comorbidities					
Exposure to NO_2					
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ Normal weight, Figure 6-17	HR (95% CI)[b] Hypertension/ Overweight, Figure 6-17	↑	Individual
†Yang et al. (2018)	33 Communities Chinese Health Study (33CCHS) NR	PRR (95% CI)[b] Normal Weight: 1.09 (0.96, 1.22)	PRR (95% CI)[b] Overweight: 1.32 (1.13, 1.54)	↑	Individual
†Yang et al. (2018)	33 CCHS 2009	PRR (95% CI)[b] <60 yrs, normal wt: 1.09 (0.95, 1.24)	PRR (95% CI)[b] <60 yrs, overweight: 1.29 (1.09, 1.52)	↑	Individual
		≥60 yrs, normal: 1.00 (0.68, 1.47)	≥60 yrs, overweight: 1.34 (0.84, 2.14)	↓	
†Yang et al. (2018)	33 CCHS NR	PRR (95% CI)[b] Men, normal weight: 1.11 (0.93, 1.31)	PRR (95% CI)[b] Men, overweight: 1.15 (0.94, 1.41)	≈	Individual
		Women, normal weight: 1.04 (0.83, 1.31)	Women, overweight: 1.49 (1.14, 1.94)	↑	
†Yang et al. (2018)	33 Communities Chinese Health Study (33CCHS) NR	PRR (95% CI)[b] Low Population Density, normal wt: 1.15 (0.90, 1.47)	PRR (95% CI)[b] Low Population Density, overweight: 1.44 (1.05, 1.97)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
		High Population Density, normal weight: 1.04 (0.86, 1.27)	High Population Density, overweight: 1.24 (0.99, 1.56)	↑	
Lifestyle Factors					
Exposure to NO_2					
†Ni et al. (2021)	CANDLE cohort Enrollment 1: December 2006-August 2008 Enrollment 2: September 2007-July 2011 Follow-up: 8 yrs	IRR (95% CI)[b] Prenatal Low Healthy Eating Index: 1.05 (0.44, 2.49)	IRR (95% CI)[b] Prenatal High Healthy Eating Index: 1.47 (0.56, 3.86)	≈	Individual
		Postnatal/ Low Healthy Eating Index: 2.01 (0.57, 7.05)	Postnatal High Healthy Eating Index: 2.10 (0.64, 6.89)	≈	
		Prenatal/ Low Folate: 0.95 (0.37, 2.46)	Prenatal High/ Folate: 1.28 (0.60, 2.73)	≈	
		Postnatal Low Folate: 1.84 (0.48, 7.04)	Postnatal / High Folate 2.10 (0.75, 5.89)	≈	
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ Non-drinkers, Figure 6-17	HR (95% CI)[b] Hypertension/ Drinkers, Figure 6-17	≈	Individual
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ Non-smokers, Figure 6-17	HR (95% CI)[b] Hypertension/ Smokers, Figure 6-17	↓	Individual
†Wang et al. (2023)	Chinese adults 2006-2009	HR (95% CI)[b] Hypertension/ Regular exerciser, Figure 6-17	HR (95% CI)[b] Hypertension/ Irregular exerciser, Figure 6-17	≈	Individual
†Zhang et al. (2023)	China Health and Retirement Longitudinal Study (CHARLS) 2013-2015	OR (95% CI)[b] Sufficient Physical Activity: 1.91 (1.69, 2.16)	OR (95% CI)[b] Insufficient Physical Activity: 1.40 (1.21, 1.62)	≈	Individual
Genetics					
Exposure to NO_2					
†Levinsson et al. (2014)	INTERGENE/ ADONIX) April 2001 - January 2004 (case recruitment)	OR (95% CI)b Hypertension/ GSTP1: rs1871042 CC: 0.64 (0.27, 1.51)	OR (95% CI)b Hypertension/ GSTP1: rs1871042 TT+TC: 0.80 (0.35, 1.86)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
		Hypertension/ GSTP1: rs762803 CC: 0.60 (0.23, 1.53)	Hypertension/ GSTP1: rs762803 AA+CA: 0.93 (0.42, 2.03)	≈	
		Hypertension/ GSTT1: rs2266637 Non-null: 0.80 (0.39, 1.67)	Hypertension/ GSTT1: rs2266637 null: 0.72 (0.16, 3.19)	≈	
		Hypertension/ GSTCD: rs10516526 AA: 0.77 (0.18, 3.30)	Hypertension/ GSTCD: rs10516526 GG+AG: 0.82 (0.40, 1.70)	≈	
†Ni et al. (2022)	CANDLE NR	RR (95% CI)[b] Hypertension/low risk APOL1 variant: 0.73 (0.41, 1.31)	RR (95% CI)[b] Hypertension/ high risk APOL1 variant: 2.93 (0.29, 30.1)	↑	Individual
Exposure to NOx					
†Weng et al. (2022)	UK Biobank Enrollment: 2006-2010 Follow-up: median 8.7 yrs	HR (95% CI)[c] Low genetic risk/ Low air pollution: 1.00 (reference)	HR (95% CI)[c] High genetic risk/ high air pollution: 1.65 (1.60, 1.70) RERI (95% CI)[c] Interaction: 0.12 (0.08, 0.16)	↑	Individual

List of abbreviations in alphabetical order: 33 CCHS = 33 Communities Chinese Health Study; BMI = body mass index; CI = confidence interval; CANDLE = Conditions Affecting Neurocognitive Development in Early Childhood; GDP = Gross Domestic Product; HR = Hazard Ratio; 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; IRR = Incidence Rate Ratio; NO = nitric oxide; NO_2 = nitrogen dioxide; NOx = nitrogen oxides; OR = Odds Ratio; PRR = Prevalence Rate Ratio; RERI = Relative Excess Risk due to Interaction.

[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of [insert outcome]) in the group with the factor evaluated than in the reference group. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller in the group with the factor evaluated than in the reference group An almost equal sign (and grey shading) indicate that the effect of NO_2 is comparable between groups.

[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.

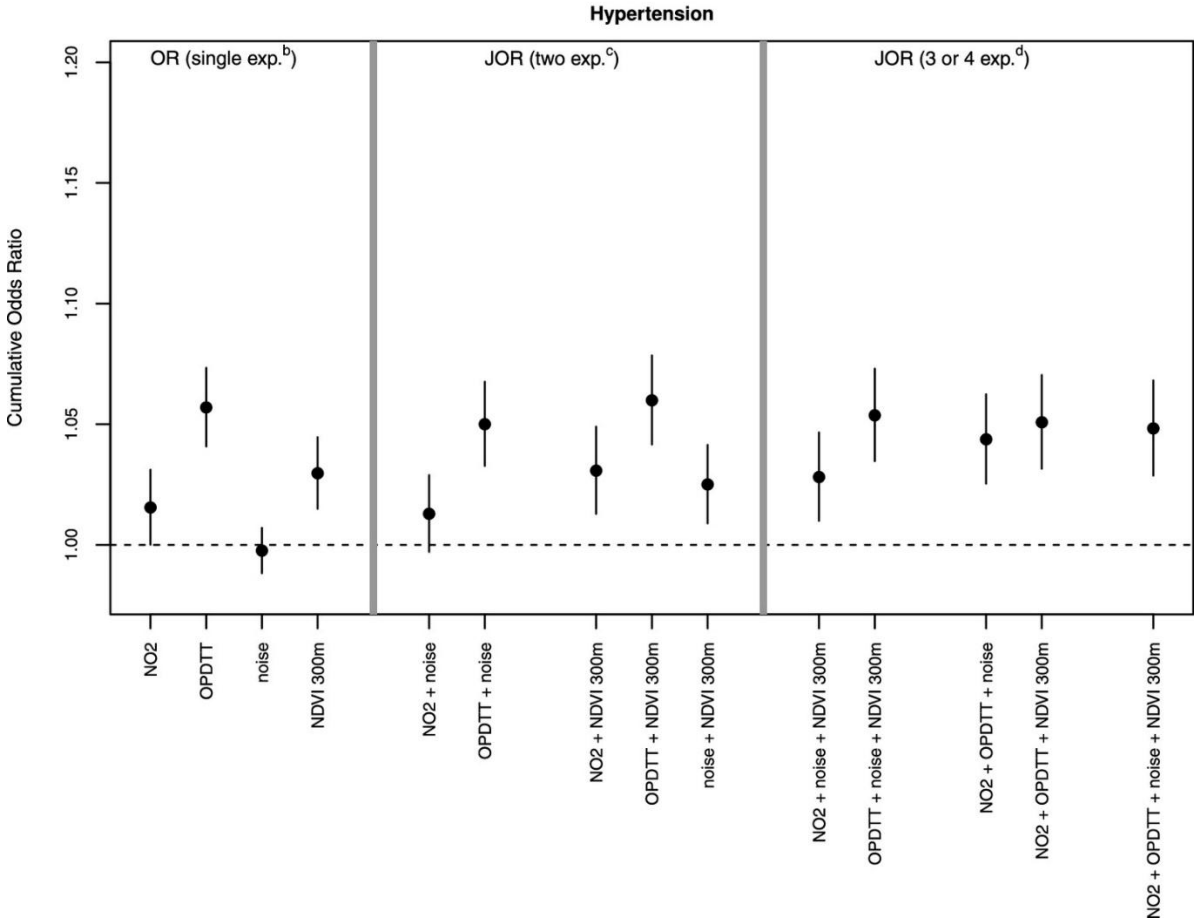
†Studies published since the 2016 Oxides of Nitrogen ISA.

6.5.1.3 Copollutants

None of the studies assessed in the 2016 Oxides of Nitrogen ISA examined confounding by copollutants using mutually adjusted models or by estimating the joint effects of several pollutants including NO_2 or NO_X. A limited number of recent studies conduct such analyses. A large U.S. cohort study reported inverse associations that persisted after adjustment for O_3 and $PM_{2.5}$, while a study in Canada reported that a positive association was attenuated toward the null after adjustment for UFP. A

European study calculated the joint odds ratios (JORs) for the combined effect of NO_2, noise, and green space (i.e., based on a vegetation index or the density of green vegetation) on hypertension.

- Coogan et al. (2017) examined the association reported that multi-year average NO_2 exposure (1995 to the end of follow-up) was inversely associated with hypertension (HR: 0.92 [95% CI: 0.86, 0.98] per 9.7 ppb). The inverse association persisted after adjustment for O_3 (HR: 0.93 [95% CI: 0.87, 1.01]) and $PM_{2.5}$ (HR: 0.90 [95% CI: 0.83, 0.98]).
- Bai et al. (2018) reported positive association of 3-year moving average NO_2 with hypertension among participants in the ONPHEC study. The HR for the association in fully adjusted models was 1.02 (95% CI: 1.00, 1.05). After adjustment for UFP the association was null (HR: 1.00 [95% CI: 0.98, 1.02]). The association was unchanged after adjustment for $PM_{2.5}$ (HR: 1.02 [95% CI: 1.00, 1.05]).
- Klompmaker et al. (2019) analyzed data from a national survey in the Netherlands to determine the relationship between green space, air pollution and traffic-related noise with hypertension. Annual average NO_2 was associated with an OR for hypertension of 1.05 (95% CI: 1.01, 1.09). This study also calculated JORs for NO_2 plus noise and NO_2 plus noise and green space with hypertension. JORs represent the odds for an IQR increase in NO_2, noise, and IQR decrease in green space relative to the odds of no increase (or no decrease in the case of green space). The joint exposure analysis indicated that single exposure models may overestimate the combined effects on hypertension because the JOR is smaller than adding the estimates from the single stressor models (see Figure 6-18).

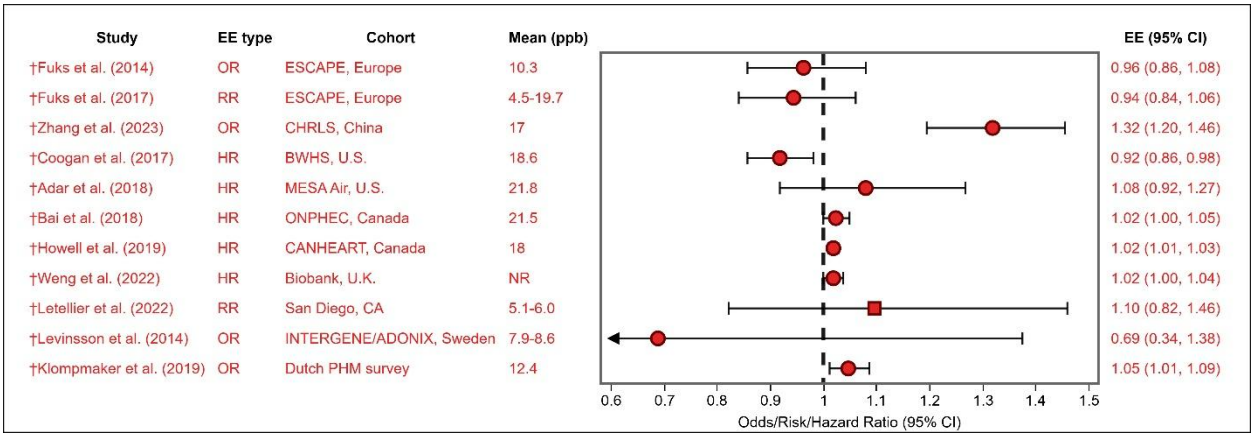


List of abbreviations in alphabetical order: JOR = joint odds ratio; m = meter; NDVI = Normalized Difference Vegetation Index; NO_2 = nitrogen dioxide; OP DTT = oxidative potential dithiothreitol; OP ESR = oxidative potential electron spin resonance.
Source: Klompmaker et al. (2019). Copyright permission pending.

Figure 6-18 Joint odds ratios for the associations of air pollution, road traffic noise, and decreased surrounding green with hypertension.

6.5.1.4 Conclusions and Remaining Uncertainties

Results from studies of long-term exposure to oxides of nitrogen and hypertension lack consistency in both magnitude and direction (see Figure 6-19). An inverse association was observed in an analysis of the BWHS that persisted after adjustment for $PM_{2.5}$ and O_3. Only a small subset of the hypertension studies evaluated modification of the association with long-term NO_2 exposure, and results from those studies were inconclusive. It is unclear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, confounding by traffic-related copollutants or other environmental determinants, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health care access, health behaviors). Most studies assessed exposure to NO_2 using validated exposure models with R^2 values indicating moderate to high model performance.



List of abbreviations in alphabetical order: BWHS: Black Women's Health Study; CHD = coronary heart disease; CANHEART: Cardiovascular Health in Ambulatory Care Research Team; CI = confidence interval; CHRLS: China Health and Retirement Longitudinal Study; Dutch PHM: Dutch Public Health Monitor; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; INTERGENE/ADONIX: INTERplay between GENEetic susceptibility and environmental factors for the risk of chronic diseases in West Sweden/ADult-Onset asthma and exhaled Nitric oXide; MESA: Multi-Ethnic Study of Atherosclerosis; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-19 Epidemiologic studies of the association of long-term NO_2 exposure with hypertension.

6.6 Combinations of Cardiovascular Related Outcomes

In addition to analyses of individual CVDs such as MI, stroke, and HF, several epidemiologic studies examined CVDs in aggregate (i.e., specific combination of CVDs). Several studies defined outcome categories that aggregated across specific types of CVDs and CBVDs such as MI, stroke, CHD, and HF. Associations of long-term exposure to oxides of nitrogen with such combinations of clinical outcomes are presented here with an emphasis on studies that leverage large sample sizes and numbers of events within aggregated outcome groupings to conduct analyses.

6.6.1 Epidemiologic Studies of Cardiovascular-Related Outcomes

Several studies define outcome categories that aggregate across specific types of cardiovascular and cerebrovascular diseases. Associations of long-term exposure to oxides of nitrogen with such combinations of clinical outcomes are presented here with an emphasis on studies that leverage large sample sizes and numbers of events within aggregated outcome groupings to conduct analyses. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-6. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in

greater detail in Sections 6.6.1.1, 6.6.1.2, and 6.6.1.3, respectively. Section 6.6.1.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for hypertension.

- In an analysis of U.S. Medicare data, Klompmaker et al. (2021a) use Cox proportional hazard regression in combination with the previously mentioned exposure assessment approach. This study reported associations between long-term NO_2 exposure and CVD hospitalization (HR: 1.016 [95% CI: 1.014, 1.019]) in multipollutant models that were adjusted for $PM_{2.5}$ and O_3. A larger association was observed among those whose exposure concentrations were always below 20 ppb (HR: 1.107 [95% CI: 1.100, 1.114]).
- Meng et al. (2021) studied a cohort of adult beneficiaries of California's Medicaid program for low-income individuals to evaluate whether a policy to reduce traffic-related pollution, i.e., the Goods Movement Plan, resulted in improvements air pollution and health care utilization. Changes in mean air pollutant exposure concentrations among those living in the three zones were compared between the pre-policy period (2004 to 2007) and the post-policy period (2008–2010) using difference-in-differences regression. Meng et al. (2021) reported reductions in NO_2 concentrations in the 1-year post-policy period (−2.35 ppb reduction [95% CI: −2.40, −2.30] Good Movement Corridor [GMC] and controls); post policy reductions in health care utilization (i.e., ER visits) for heart diseases including atherosclerosis, CAD, and CHF were not observed.
- Cai et al. (2018) used data from 3 cohorts in Norway and the United Kingdom in combination with European LUR models to estimate the associations of NO_2 and noise with incident CVD outcomes. The fully adjusted HR per IQR for all CVD (1.047 [95% CI: 0.922, 1.189]) did not change after adjustment for noise (HR: 1.047 [95% CI: 0.922, 1.189]).
- Wang et al. (2023) conducted a nationwide study of adults in China (2010–2018) to examine the association of annual average NO_2 exposure estimated using a spatiotemporal model and the risk of CVD considering death as a competing event as premature death may mask the association with the morbidity outcomes studied. The HR was 2.30 (95% CI: 2.09, 2.55).
- Alexeeff et al. (2018) investigated the association of oxides of nitrogen estimated using street-level mobile monitoring on 30-meter road segments and linked to residential addresses, among a cohort of adults living in Oakland, California. NO_2 and NO were associated with imprecise increases in risk of a cardiovascular event of 1.08 (95% CI: 0.86, 1.36) and 1.09 (95% CI: 0.85, 1.41), respectively. A larger magnitude increased risk of 1.35 for NO_2 (95% CI: 1.04, 1.74) and 1.56 for NO (95% CI: 1.12, 2.18) was observed among those older than 65-years.
- In an analysis of NHIS data from Italy and hospitalizations during follow-up, Gandini et al. (2018) observed positive associations between NO_2 and circulatory system diseases (HR: 1.10 [95% CI: 1.06, 1.14]). The association in women was somewhat smaller than in men but CIs overlapped (HR: 1.08 [95% CI: 1.04, 1.06] and HR: 1.12 [95% CI: 1.07, 1.17], respectively). Regional differences were also reported.
- Su et al. (2020) analyzed Taiwan's national level health claim data to estimate the association between cardiovascular effects among diabetic patients. Associations were reported for three different epidemiologic models. A 1 ppb increase in monthly NO_2 concentration was not associated with CVD effects in multivariable Bayesian survival spatial, Cox, or Weibull models (HR: 0. 0.72 [95% CI: 0.48, 1.10], HR: 1.05 [95% CI: 0.88, 1.26], and HR: 1.05 [95% CI: 0.87, 1.26], respectively).
- Analyses of the UK Biobank were conducted. Wu et al. (2023) derived multi-state models to estimate the association between oxides of nitrogen and the dynamic progression of

hypertension, diabetes, and CKD. This study reported associations with annual average NO_2 for different transitions from healthy status to incident hypertension, diabetes, or CKD (HR: 1.123 [95% CI: 1.071, 1.178]), to multimorbidity status, i.e., two or more diseases (HR: 1.054 [95% CI: 0.923, 1.204]), and to death (HR: 1.064 [95% CI: 0.969, 1.168]). Similar results were observed for NO_X. In another analysis of the Biobank data, Luo et al. (2022) reported the risk of transition from baseline to first cardiometobolic disease (CMD) and from first CMD to CMD multimorbidity and death were also increased with increasing annual average NO_2 exposures. The study observed statistical evidence that the NO_2 association was modified by age and physical activity (Wu et al., 2023).

- In a study that aimed to elucidate the association between noise and heart disease in the Hypertension and Environmental Noise near Airports (HYENA) study, Floud et al. (2013) reported the cross-sectional association between NO_2 exposure and self-reported heart disease and stroke for the United Kingdom and the Netherlands combined (OR: 3.18 [95% CI: 1.26, 8.02]) and Sweden (OR: 1.86 [95% CI: 0.41, 8.45]). After adjustment for noise the estimates lost precisions but were essentially unchanged (OR: 3.51 [95% CI: 1.05, 11.7] and OR: 1.88 [95% CI: 0.36, 9.89]).

- Li et al. (2022) examined the association of NO and NO_X with microvascular disease (see Section 11.6.3.1 for retinopathy and peripheral neuropathy) using data from the UK Biobank. Annual average NO_2 and NO_X concentrations were estimated using the ESCAPE LUR model (C-V R^2: 87% and 88%, respectively). The adjusted HRs for the association of NO_2 with the composite microvascular disease outcome was 1.04 (95% CI: 1.03, 1.06) and the HR for NO_X was 1.04 (95% CI: 1.02, 1.07 per 41.8 $\mu g/m^3$).

6.6.1.1 Concentration-Response

An important consideration in characterizing the association between long-term NO_2 exposure and CVDs is whether the concentration-response relationships are linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. Table 6-10 and Figure 6-20, Figure 6-21, Figure 6-22, and Figure 6-23 below summarize analyses of concentration-response relationships from recent studies.

- Klompmaker et al. (2021a) examined the concentration-response among Medicare recipients 65-years or older (Figure 6-20). Natural splines with 2, 3 or 4 degrees of freedom were used, and associations were separately estimated for exposures below 20 ppb NO_2. The C-R function was linear or supralinear depending on the degrees of freedom. Associations were larger in magnitude for the group with annual exposures always below 20 ppb (HR: 1.02 [95% CI: 1.01, 1.02] versus HR: 1.11 [95% CI: 1.10, 1.11]).
- Wang et al. (2023) conducted a nationwide study of adults in China (2010–2018) to examine the association of NO_2 exposure with all CVD. Restricted cubic splines were used to examine the shape of the C-R function. The shape was approximately linear with no evidence of a threshold (see Figure 6-21).
- Analyses of the UK Biobank were conducted. Wu et al. (2023) derived multi-state models to estimate the association between oxides of nitrogen and the dynamic progression of hypertension, diabetes, and/or CKD. C-R relationships were estimated using restricted cubic

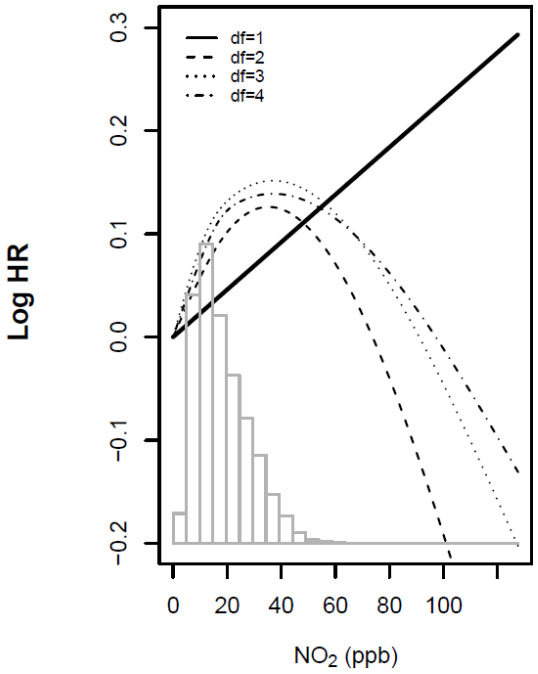
splines; the study observed a supralinear relationship of NO_2 and NO_X with the risk of incident disease (see Figure 6-22).

- Alexeeff et al. (2018) investigated the association of oxides of nitrogen estimated using street-level mobile monitoring on 30-meter road segments, and linked to residential addresses, among a cohort of adults living in Oakland, California. Restricted cubic splines were used to model the C-R relationship and no statistical evidence of deviation from linearity was observed using the Wald test for the spline terms (see Figure 6-23).

Table 6-10 Epidemiologic studies evaluating concentration-response relationship or conducting threshold analyses between long-term exposure to oxides of nitrogen and cardiovascular related outcomes

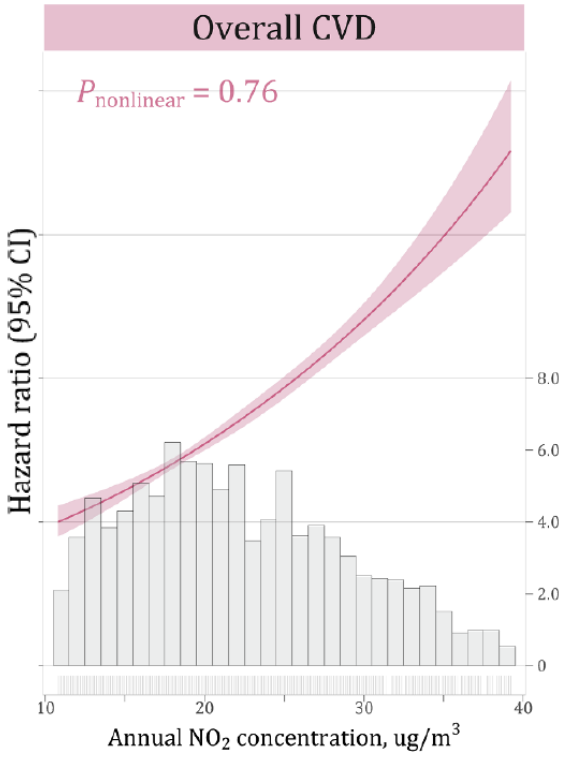
Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
Exposure to NO_2				
†Alexeeff et al. (2018) CVD Events	KPNC Enrollment: 2010–2015 Follow-up: through December 31, 2015	Mean: 9.9 ppb (SD 3.8)	Restricted cubic spline	No deviation from linearity observed
†Klompmaker et al. (2021a) CVD Events	MEDPAR Enrollment: January 2000–December 2016 Follow-up: January 2000 or January of the year following entry	See Figure 6-20	Natural splines with 1-4 df	Linear or supralinear depending on the df
†Wang et al. (2023) CVD Events	CFPS Enrollment waves: 2010, 2014, 2016, 2018 Follow-up: through 2018	Min-Max: 3.7-30.5 ppb (6.9–57.4 µg/m^3)	Restricted cubic splines	Linear no threshold
†Wu et al. (2023) Hypertension, diabetes, and CKD	UK Biobank 2006–2010	Mean: 14.2 (SD: 4.1) ppm (Mean 26.7 [SD: 7.7] µg/m^3)	Restricted cubic spline	Supralinear, flattening at concentrations above the mean

List of abbreviations in alphabetical order:: CFPS = China Family Panel Studies; CKD = Chronic Kidney Disease; CVD = Cardiovascular Disease; df = degrees of freedom; KPNC = Kaiser Permanente Northern California; MEDPAR = Medicare denominator and Medicare Provider Analysis and Review; Max = Maximum; Min = Minimum; NO_2 = nitrogen dioxide; ppb = parts per billion; SD = standard deviation.
[a]For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses
[b]There visual representations of the shape of the curve in the corresponding text.
†Studies published since the 2016 Oxides of Nitrogen ISA.



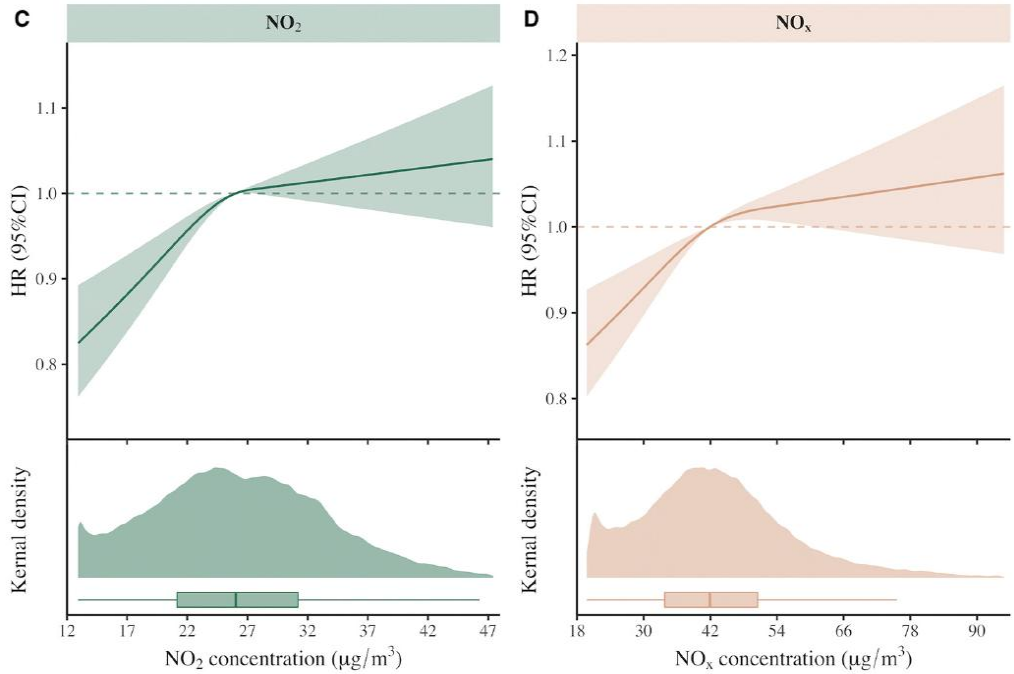
List of abbreviations in alphabetical order: df = degrees of freedom; HR = hazard ratio; ppb = parts per billion.
Source: Klompmaker et al. (2021a). Copyright permission pending.

Figure 6-20 Concentration-response curves from fully adjusted models with natural splines (1, 2, 3, and 4 degrees of freedom) of NO_2 with all cardiovascular disease hospitalization.



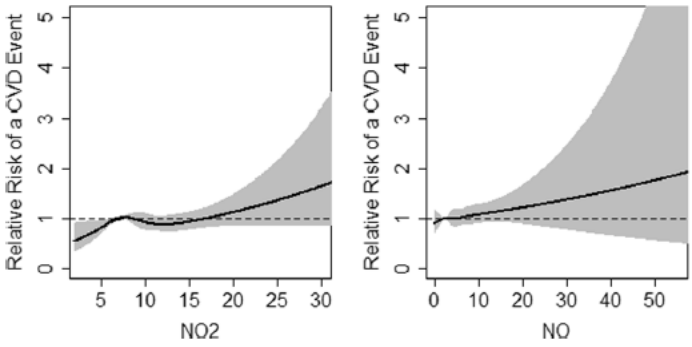
List of abbreviations in alphabetical order: CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; NO_2 = nitrogen dioxide.
Source: Wang et al. (2023). Copyright permission pending.

Figure 6-21 Concentration-response relationship of incident overall cardiovascular disease per 10 µg/m³.



List of abbreviations in alphabetical order: CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide.
Source: Wu et al. (2023). Copyright permission pending.

Figure 6-22 Concentration-response relationship for NO_2 and NO_X and incident disease combination that included hypertension, diabetes, and/or chronic kidney disease.



List of abbreviations in alphabetical order: CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide.
Source: Alexeeff et al. (2018). Copyright permission pending.

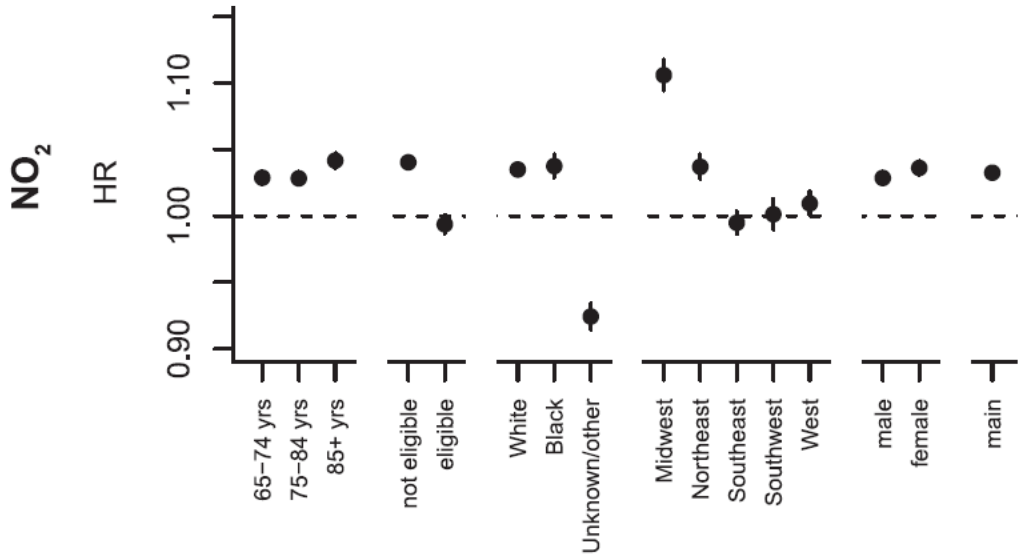
Figure 6-23 Estimated concentration-response relationship for NO_2 and NO exposure with the relative risk of a cardiovascular disease event using cubic splines.

6.6.1.2 Lifestages and Populations

The evidence for long-term NO_2 exposures and cardiovascular morbidity includes studies that examine EMM by a range of factors modifying association factors. Results from these studies are summarized in Table 6-11.

Recent studies examine the modification of the association between long-term oxides of nitrogen exposure and CVDs.

- In an analysis of U.S. Medicare data, Klompmaker et al. (2021a) use Cox proportional hazard regression to analyze the association of NO_2 exposure with CVD hospitalization. Stratified analyses indicate that the associations with NO_2 exposure were generally similar across age groups, between men and women and Black and white individuals. Associations were consistently larger in populations not eligible for Medicaid, when compared to eligible populations, and they varied substantially by region (see Figure 6-24).



List of abbreviations in alphabetical order: CBVD = cerebrovascular disease; CVD = cardiovascular disease; HD = heart disease.
Source: Klompmaker et al. (2021a). Copyright permission pending.

Figure 6-24 Associations of NO_2 with cardiovascular hospitalization stratified by age, Medicaid eligibility, race, U.S. region and sex.

- Gandini et al. (2018) observed positive associations between NO_2 and diseases of the circulatory system (HR: 1.10 [95% CI: 1.06, 1.14]). Stratified analyses comparing the HRs in rural (HR: 1.02 [0.99, 1.05]), urban (HR: 1.04 [95% CI: 1.01, 1.07]), and metropolitan areas indicated that the associations were positive in rural and urban areas and null in metropolitan areas (HR: 1.00 [95% CI: 0.90, 1.11]), possibly due to the small number of study participants residing in metropolitan areas and the potential for exposure misclassification as the exposure assessment method may not have captured the within city variability in NO_2 concentration.
- Wang et al. (2023) conducted a nationwide study of adults in China (2010-2018) to examine the association of NO_2 exposure estimated using a spatiotemporal model and risk of CVD.

The association with CVD was larger among overweight individuals and those residing in urban areas.

A small number of studies of cardiovascular morbidity examine at-risk factors including sex, SES, and urbanicity. Single studies examined other factors such as race, smoking or overweight/obesity (≥24 kg/m^2). Patterns indicating that a specific factor may confer an increased risk in the population studied were not discernable from the limited epidemiologic evidence (see Table 6-11).

Table 6-11 Epidemiologic studies evaluating effect measure modification between long-term oxides of nitrogen exposure and cardiovascular related outcomes

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Lifestage					
Exposure to NO					
†Alexeeff et al. (2018)	KPNC Enrollment: 2010-2015 Follow-up: through December 31, 2015	HR (95% CI)[b] CVD/ <65 yrs: 0.78 (0.50, 1.22)	HR (95% CI)[b] CVD/ 65+: 1.56 (1.12, 2.18)	↑	Individual
Exposure to NO_2					
†Alexeeff et al. (2018)	KPNC Enrollment: 2010-2015 Follow-up: through December 31, 2015	HR (95% CI)[b] CVD/ <65 yrs: 0.83 (0.62, 1.10)	HR (95% CI)[b] CVD/ 65+: 1.35 (1.04, 1.74)	↑	Individual
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CVD/ 65-74 y: Figure 6-24	HR (95% CI)[b] CVD/ 75-84 y: Figure 6-24	≈	Individual
			CVD/ 85+ y: Figure 6-24	↑	
†Luo et al. (2022)	UK Biobank Enrollment: 2006-2010 Follow-up: through May 2021	HR (95% CI)[b] Baseline to FCMD/age <60: 0.98 (0.94, 1.02)	HR (95% CI)[b] Baseline to FCMD/ age 60+: 1.10 (1.06, 1.14)	↑	Individual
		FCMD to CMM/ age <60: 1.08 (0.97, 1.19)	FCMD to CMM/ age 60+: 1.14 (1.06, 1.22)	↑	
Sex					
Exposure to NO_2					

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Gandini et al. (2018)	ILS Enrollment: 1999-2000 Follow-up: 1999-2002, 2003-2004, 2005-2006, 2007-2008	HR (95% CI)[b] Circulatory/ men: 1.12 (1.07, 1.17)	HR (95% CI)[b] Circulatory/ women: 1.08 (1.04, 1.12)	≈	Individual
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CVD/male: see Figure 6-24	HR (95% CI)[b] CVD/female: see Figure 6-24	≈	Individual
†Luo et al. (2022)	UK Biobank Enrollment: 2006-2010 Follow-up: through May 2021	HR (95% CI)[b] Baseline to FCMD/ male: 1.06 (1.02, 1.10)	HR (95% CI)[b] Baseline to FCMD/ female: 1.08 (1.04, 1.12)	≈	Individual
		FCMD to CMM/ male: 1.16 (1.08, 1.24)	FCMD to CMM/ female: 1.06 (0.95, 1.18)	↓	
Race/Ethnicity					
Exposure to NO_2					
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CVD/ White: see Figure 6-24	HR (95% CI)[b] CVD/ Black: see Figure 6-24	≈	Individual
Socioeconomic Status					
Exposure to NO_2					
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry	HR (95% CI)[b] CVD/ Medicaid Eligible: see Figure 6-24	HR (95% CI)[b] CVD/ not Medicaid Eligible: see Figure 6-24	↑	Individual
†Luo et al. (2022)		HR (95% CI)[b] Baseline to FCMD/ high Townsend Deprivation Index: 1.18 (1.13, 1.23)	HR (95% CI)[b] Baseline to FCMD/ low Townsend Deprivation Index: 1.14 (1.11, 1.17)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	UK Biobank Enrollment: 2006-2010 Follow-up: through May 2021	FCMD to CMM/ high Townsend Deprivation Index: 1.22 (1.09, 1.36)	FCMD to CMM/ low Townsend Deprivation Index: 1.18 (1.11, 1.25)	≈	
Pre-existing Conditions/Comorbidity					
Exposure to NO_2					
†Luo et al. (2022)	UK Biobank Enrollment: 2006-2010 Follow-up: through May 2021	HR (95% CI)[b] Baseline to FCMD/ BMI <25 kg/m2: 1.08 (1.02, 1.14)	HR (95% CI)[b] Baseline to FCMD/ BMI≥25 kg/m2: 1.06 (1.03, 1.09)	≈	Individual
		FCMD to CMM/ BMI <25 kg/m2: 1.10 (0.94, 1.28)	FCMD to CMM/ BMI≥25 kg/m2: 1.12 (1.05, 1.19)	≈	
Lifestyle Characteristics					
Exposure to NO_2					
†Luo et al. (2022)	UK Biobank Enrollment: 2006-2010 Follow-up: through May 2021	HR (95% CI)[b] Baseline to FCMD/ drinking less: 1.02 (0.97, 1.07)	HR (95% CI)[b] Baseline to FCMD/ drinking more: 1.08 (1.02, 1.14)	↑	Individual
		FCMD to CMM/ Drinking less: 1.08 (0.97, 1.20)	FCMD to CMM/ drinking more: 1.14 (1.06, 1.22)	↑	
		HR (95% CI)[b] Baseline to FCMD/ active: 1.08 (1.03, 1.13)	HR (95% CI)[b] Baseline to FCMD/ inactive: 1.10 (1.05, 1.15)	≈	
		FCMD to CMM/ active: 1.16 (1.05, 1.28)	FCMD to CMM/ inactive: 1.02 (0.93, 1.12)	↓	
		HR (95% CI)[b] Baseline to FCMD/ non smoker: 1.08 (1.04, 1.12)	HR (95% CI)[b] Baseline to FCMD/ ever smoker: 1.04 (1.00, 1.08)	↓	
		FCMD to CMM/ non-smoker: 1.10 (1.00, 1.20)	FCMD to CMM/ ever smoker: 1.12 (1.03, 1.21)	≈	
Region of U.S.					
Exposure to NO_2					
†Klompmaker et al. (2021a)		HR (95% CI)[b] CVD/ West: see Figure 6-24	HR (95% CI)[b] CVD/ Midwest: see Figure 6-24	↑	Individual
			CVD/Northeast: see Figure 6-24	↑	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	MEDPAR Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry		CVD/ Southeast: see Figure 6-24	↓	
			CVD/ Southwest: see Figure 6-24	≈	
Urbanicity					
Exposure to NO_2					
†Gandini et al. (2018)	ILS Enrollment: 1999-2000 Follow-up: 1999-2002, 2003-2004, 2005-2006, 2007-2008	HR (95% CI)[b] Circulatory/ rural: 1.04 (0.98, 1.10)	HR (95% CI)[b] Circulatory/urban: 1.08 (1.02, 1.14)	↑	Individual
			Circulatory/ metro: 1.00 (0.90, 1.11)	↓	

List of abbreviations in alphabetical order: BMI = Body Mass Index; CMM = Cardiometabolic Multimorbidity; FCMD = First Cardiometabolic Disease; HR = Hazard Ratio; ILS = Italian Longitudinal Study; Kg/m2 = kilogram per meter squared; KPNC = Kaiser Permanente Northern California; MEDPAR = Medicare denominator and Medicare Provider Analysis and Review; NO = nitric oxide; NO_2 = nitrogen dioxide; SES = Socioeconomic Status.

[a] Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of [insert outcome]) in the group with the factor evaluated than in the reference group. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller in the group with the factor evaluated than in the reference group An almost equal sign (and grey shading) indicate that the effect of NO_2 is comparable between groups.

[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.

6.6.1.3 Copollutants

Copollutant models are used to evaluate the potential for other pollutants and other stressors such as noise to confound risk estimates of long-term exposure to oxides of nitrogen and cardiovascular effects. Recent studies that examine confounding by copollutants and noise are summarized in Table 6-12.

- Klompmaker et al. (2021a) reported an association between long-term NO_2 exposure and CVD hospitalization that persisted after adjustment for $PM_{2.5}$ and O_3.
- Floud et al. (2013) reported a cross-sectional association between NO_2 exposure and self-reported heart disease and stroke for the United Kingdom and the Netherlands combined (OR: 3.18 [95% CI: 1.26, 8.02]) and Sweden (OR: 1.86 [95% CI: 0.41, 8.45]). After adjustment for noise the estimates lost precisions but were essentially unchanged (OR: 3.51 [95% CI: 1.05, 11.7] and OR: 1.88 [95% CI: 0.36, 9.89]).

Overall, the evaluation of copollutants confounding in recent studies was limited. Co-exposures that were examined included $PM_{2.5}$ and noise. Uncertainty regarding the independent effect of oxides of nitrogen remains.

Table 6-12 Epidemiologic studies evaluating copollutant associations between long-term exposure to oxides of nitrogen and cardiovascular related outcomes

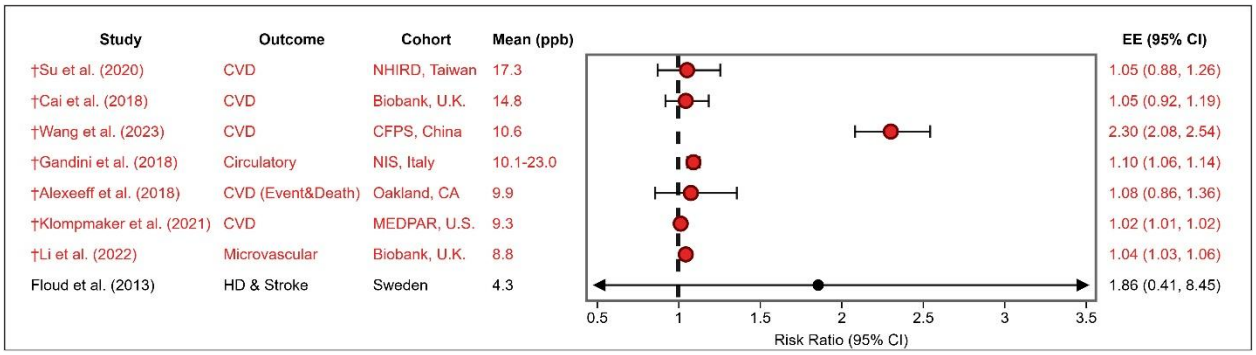
Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of Association[a]	Effect Estimate (95% CI)
Exposure to NO_2						
Floud et al. (2013)	HYENA 3 yr period (2004-2006)	Noise	UK and Netherlands: 0.51 Sweden: 0.35	Simultaneous inclusion of NO_2 and noise in logistic regression model	≈	OR (95% CI)[b] HD and Stroke/UK and Netherlands (Main Effect): 3.18 (1.26, 8.02) +noise: 3.51 (1.05, 11.70)
					≈	HD and Stroke/Sweden (Main Effect): 1.86 (0.41, 8.45) +noise: 1.88 (0.36, 9.89)
†Klompmaker et al. (2021a)	MEDPAR Enrollment: January 2000 to December 2016 Follow-up: January 2000 or January of the year following entry	$PM_{2.5}$ O_3	0.43 -0.12	Simultaneous inclusion of NO_2, $PM_{2.5}$ and Ozone in Cox Proportional Hazard model	≈	HR (95% CI)[b] CVD (Main Effect): 1.02 (1.02, 1.03) +$PM_{2.5}$ and O_3: 1.02 (1.01, 1.02)

List of abbreviations in alphabetical order:: CI = confidence interval; HYENA = Hypertension and Environmental Noise near Airports; MEDPAR = Medicare denominator and Medicare Provider Analysis and Review; NO_2 = nitrogen dioxide; ppb = parts per billion; O_3 = ozone; OR = odds ratio; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 μm; HR = hazard ratio;
[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of [insert outcome]) with the copollutant evaluated than in the single pollutant model. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller with the copollutant evaluated than in the single pollutant model. An almost equal sign (and grey shading) indicates that the effect of NO_2 is comparable between the single pollutant analysis and copollutant analysis.
[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.

6.6.1.4 Conclusions and Remaining Uncertainties

The epidemiologic evidence pertaining to the long-term cardiovascular effects of NO_2 and NO_X exposure has expanded since the 2016 Oxides of Nitrogen ISA was finalized. The body of evidence includes large prospective studies with adjustment for a wide array of potential confounding factors.

Some studies report positive associations while others report imprecise associations with confidence intervals that substantially overlap with the null value (see Figure 6-25). The results from a small number of studies that examined the shape of the C-R relationship varied considerably, with studies reporting linear and supralinear relationships as well as a steep decline at upper levels and no relationship at lower levels. The evaluation of copollutant confounding in recent studies was limited. Although a small number of studies of cardiovascular morbidity examine factors that may put some groups at higher risk (i.e., sex, SES, and urbanicity, race, smoking and overweight), patterns indicating that a specific factor may confer an increased risk were not discernable from the limited epidemiologic evidence. Again, it is not clear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, confounding by traffic-related copollutants or other environmental determinants, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health care access, health behaviors). Most studies used validated exposure assessment models with moderate to high model performance and did not appear to explain inconsistences in the findings.



List of abbreviations in alphabetical order: CVD = cardiovascular disease; CI = confidence interval; CFPS: China Family Panel Studies; HR = hazard ratio; MEDPAR: Medicare Provider Analysis and Review; NHIRD: National Health Insurance Research Database; NO_2 = nitrogen dioxide.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-25 Epidemiologic studies of the association of long-term NO_2 exposure with cardiovascular related outcomes.

6.7 Subclinical Effects Underlying Cardiovascular Disease

CVD is often multifactorial and occurs progressively over time. Subclinical markers, such as arterial stiffness, circulating lipids, subclinical atherosclerosis, and heart rate variability (HRV), can be used as markers of disease and mortality risk. Changes in these markers over time can help to measure disease progression. The following sections describe the available epidemiology (see Section 6.7.1) and animal toxicology (see Section 6.7.2) evidence investigating the relationship between long-term exposure to NO_2 (or other oxides of nitrogen) and subclinical markers of heart disease and mortality.

6.7.1 Epidemiologic Studies of Subclinical Effects Underlying Cardiovascular Disease

Atherosclerosis involves the buildup of plaque in the arteries and can lead to arterial stiffness, which can interfere in the vessel's ability to expand and contract increasing one's risk for cardiovascular events and mortality. Two epidemiologic studies assessed in the 2016 Oxides of Nitrogen ISA examined the association of long-term NO_2 exposure with subclinical atherosclerosis or arterial stiffness (Breton et al., 2012; Lenters et al., 2010). NO_2 exposure was not associated with carotid intima-media thickness (cIMT) in these studies, while association with measures of arterial stiffness (pulse wave velocity [PWV] and augmentation index) were observed. In addition, Felber Dietrich et al. (2008) provided some evidence that long-term exposure to NO_2 may be associated with reduced HRV, which may indicate autonomic dysfunction, among women and in subjects with pre-existing CVDs. This section summarizes information from epidemiologic studies examining associations with atherosclerosis, blood pressure, and other subclinical cardiovascular markers. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in greater detail in Sections 6.7.1.1, 6.7.1.2, and 6.7.1.3, respectively. Section 6.7.1.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for subclinical markers of cardiovascular effects.

Atherosclerosis

Recent studies of the association between long-term oxides of nitrogen and measures of atherosclerosis have become available since the 2016 Oxides of Nitrogen ISA. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-7.

The recent evidence comprises analyses of MESA participants with no history of CVD. MESA enrolled participants from four ethnic groups (Hispanic, Black, white, and Chinese) between the years 2000 and 2002 who were from 45- to 84-years old at enrollment and resided in six areas of the U.S. Community-specific spatiotemporal models were developed to predict NO_2 and NO_X concentrations for each participant's residential address history (overall model fit r^2: 90–97%). Model predictions from area specific model varied by site (median [range] C-V r^2: 0.78 [0.45, 0.90] for NO_2 and 0.72 [0.50, 0.92] for NO_X). Most MESA participants received CT scans to measure coronary artery calcium (CAC) and assessment of cIMT using ultrasound during 2002 through 2005, and a subset of participants received a second measurement between 2010 and 2012 (zielska et al., 2016).

- zielska et al. (2016) reported that NO_X exposure averaged over the years 2000-2010 was associated with a 2.4 Agatston units per year (95% CI: 0.5, 4.4) increase in the rate of CAC progression. NO_2 exposure was associated with 2.7 Agatston units per year (95% CI: –0.3, 5.7) increase in the rate of CAC progression. No associations were observed for NO_2 or NO_X with cIMT. The positive association between NO_X and CAC was attenuated after adjustment for copollutants (see Section 6.7.1.3) and there was some evidence of effect measure modification by race and obesity (see Section 6.7.1.2). In another MESA analysis, Tibuakuu et al. (2017) examined the association of NO_X exposure over a shorter follow-up than zielska

et al. (2016), i.e., 2.5-years, with aortic valve calcium (AVC) and mitral annular calcium (MAC) and reported no associations with these measures of valvular calcification (β AVC: −1.0 [95% CI: −3.1, 1.2] and β MAC: −1.29 [95% CI: −3.17, 0.59] Agatston units per year). The study used multiplicative interaction terms to assess effect measure modification by race/ethnicity, age, sex or by $PM_{2.5}$ (see Section 6.7.1.2).

- Jones et al. (2015) estimated the direct and indirect associations of exposure to NO_X with cIMT, hypothesizing that accounting for air pollution would result in smaller associations with cIMT in African American, Hispanic and Chinese individuals compared to Caucasian individuals in the MESA cohort. The analysis did not find evidence that NO_X influenced observed racial differences in cIMT.

Several other studies of atherosclerosis were conducted in North American populations. This recent evidence included a study of individuals undergoing elective angiography, a study of healthy volunteers who were followed to determine annual change in markers of atherosclerosis and a cross-sectional analysis that examined the association of NO_2 with total plaque area in a patient population.

- Hartiala et al. (2016) analyzed data from a cohort study of Ohio residents undergoing elective diagnostic coronary angiography. Multinomial regression was used to assess the relationship between 36-month exposure to NO_2 and CAD severity at baseline. These authors also followed the participants to examine the association of air pollution with MI (see Section 6.3.1), stroke (see Section 6.4.1) and mortality. NO_2 was not positively associated with CAD severity. The ORs for the associations of NO_2 with atherosclerosis in 1–2 vessels and in ≥ 3 vessels were close to the null value (OR: 1.00 [95% CI: 0.43, 2.33] and OR: 0.74 [95% CI: 0.31, 1.77], respectively).
- Gan et al. (2014) studied healthy volunteers in Vancouver, Canada (age 30–65) and followed them for approximately five-years. Baseline assessment of atherosclerosis included measures of cIMT, plaque area, number and total area. A LUR model with a 10 m spatial resolution was used to estimate NO_2 (COV R^2: 0.56) and NO (COV R^2: 0.62). Residential exposure to community noise was also assessed in the study. Associations with the annual change in measures of atherosclerosis after adjustment for covariates including noise were close to the null value for all measures (e.g., cIMT β: −0.28 [95% CI: −6.26, 5.71]), Plaque Area β: 0.32 (95% CI: −0.79, 1.43) and Plaque Number β: 0.046 [95% CI: −0.046, 0.139]). Associations with NO were similar in their magnitude.
- Johnson et al. (2020) conducted a cross-sectional analysis of data from the Stroke Prevention and Atherosclerosis Research Centre (SPARC) study of a patient population in London, Ontario, Canada with the objective of examining the association of NO_2 with markers of atherosclerosis (i.e., total plaque area, which is a stronger indicator of atherosclerosis than cIMT). An LUR model that explained 78% of the variance was used to estimate NO_2. Annual average NO_2 was associated with an increase in total carotid plaque area (β: 12.2 mm^2 [95% CI: 2.90, 21.5]) in the study. NO_2 was also positively associated with triglycerides, total cholesterol, and the ratio of low- to high-density lipoprotein cholesterol. Diabetes was reported to mediate the association of NO_2 and total plaque area.
- Recent studies were conducted in established cohorts in Europe (i.e., SAPALDIA, SCAPIS Gothenburg, HNR) and in a cohort in Thailand. Atherosclerosis was assessed using measures of arterial stiffness (PWV and cardio-ankle vascular index [CAVI]) and CAC.
- Endes et al. (2017) investigated whether physical activity modifies the association between annual average NO_2 exposure and arterial stiffness (brachial-ankle pulse wave velocity

(baPWV) ≥14.4 m/s) among participants in the Swiss SAPALDIA study. Annual average NO_2 was estimated using a hybrid approach (LUR with dispersion models based on emissions inventories). Self-reported physical activity was assessed using a questionnaire and dichotomized as active or inactive. An inverse association (CIs inclusive of the null value) with annual average NO_2 exposure was observed in the fully adjusted model (OR: 0.95 [95% CI: 0.81, 1.12] per IQR [NR]). Although the association in the whole population did not indicate an increased risk in arterial stiffness with increasing NO_2 exposure, an interaction between physical activity and NO_2 was observed (see Section 6.7.1.2).

- Edlund et al. (2022) examined the association of NO_X exposure with indices of atherosclerosis (CAC and carotid artery plaques) in the Swedish SCAPIS Gothenburg study. CAC was dichotomized to indicate a positive score (CAC score ≥10 vs. CAC score <10) or a high score (≥100 vs. CAC score <100) and plaques were indicated as any carotid plaque or the presence of bilateral carotid plaque. Multi-year average (1990–2015) NO_X exposure was estimated using a validated dispersion model. NO_X exposure was positively associated with high (≥ 100) CAC score (PR: 1.05 [95% CI: 0.99, 1.1] per 10 $\mu g/m^3$) and the presence of bilateral plaque (PR: 1.03 [95% CI: 1, 1.06] per 10 $\mu g/m^3$) in the cohort. The associations with CAC were somewhat stronger among females (see Section 6.7.1.2) and remained after adjustment for traffic noise (see Section 6.7.1.3).
- Hennig et al. (2020) investigated the association of NO_2 exposure with several measures of atherosclerosis progression (i.e., CAC, cIMT and thoracic aortic calcification [TAC]) among adults enrolled (45–75-years) in the HNR cohort. Multi-year average NO_2 exposure (2000–2003 and 2006–2008) was estimated using two approaches: (1) LUR (R^2: 0.88) and (2) the EURAD chemical transport model. NO_2 exposure was positively associated with incident CAC (ORCTM: 1.39 [95% CI: 0.96, 2.03] and ORLUR: 1.78 [95% CI: 0.99, 3.2]) and incident TAC using Chemical Transport Modeling (CTM) (ORCTM: 1.31 [95% CI: 0.72, 2.37]). The association with incident TAC using LUR was close to the null (ORLUR:1.03 [95% CI: 0.59, 1.79]). Progression of atherosclerosis, which was determined as the change in left cIMT and right cIMT and the growth rate of CAC and TAC, over a 5-year follow-up, was generally positively associated with NO_2 exposure; however, the CIs included the null value and results appeared to be sensitive to exposure assessment method (see Appendix A – Appendix Table 6-7). In subgroup analyses with participants with no or minor atherosclerosis and participants with advanced atherosclerosis, the pattern of associations differed depending on exposure assessment approach. The most consistently positive associations were for NO_2 modeled by CTM and increase in left cIMT and growth rate of CAC/TAC, among participants with no or minor atherosclerosis at baseline.
- Paoin et al. (2021) investigated the association between NO_2 exposure, estimated using validated kriging models, and indicators of atherosclerosis (i.e., Ankle Brachial Index [ABI] and CAVI) among participants in the Electricity Generating Authority of Thailand (EGAT) study. Annual average NO_2 exposure was inversely associated (CIs included the null value) with ABI (−0.34% [95% CI: −1.22, 0.54]) and positively associated with CAVI (13.2% [95% CI: 0.71, 25.77]). Higher CAVI indicates greater arterial stiffness.

Several additional studies focus on the association of NO_2 exposure with lipid concentrations. High concentrations of some lipids, e.g., low density lipid (LDL) cholesterol, is a risk factor known to contribute to the progression of atherosclerosis. Dyslipidemia refers to a pattern of abnormal levels of lipids in the blood involving increased LDL cholesterol and triglycerides and decreased high density lipid (HDL) cholesterol.

- Letellier et al. (2022) investigated the association of NO_2 with dyslipidemia (and metabolic disorders, see Chapter 8) in participants enrolled in Community of Mine study in San Diego County. Multi-year average (2014–2017) NO_2 exposures were estimated using a traditional static approach that linked NO_2 concentrations from the EPA's AQS to the participant's home via IDW and a novel dynamic approach that used a personal GPS device worn by the participant for two weeks to create a long-term time-weighted activity space that reflected the participants mobility using the Kernal Density Equation model in ArcGIS. The time-weighted activity space was then multiplied by pollution layers to derive a total exposure that accounted for time and locations visited. The authors observed a positive association between long-term NO_2 exposure and dyslipidemia for the static exposure method that was close to the null value (RR: 1.02 [95% CI: 0.85, 1.22]). In contrast, for the dynamic exposure method, Letellier et al. (2022) observed a more robustly positive association (RR: 1.28 [95% CI: 1.12, 1.46]). NO_2 estimated by the dynamic method was associated with higher total (β: 9.67 [95% CI: 3.71, 15.64]) and LDL (β: 9.03 [95% CI: 3.63, 14.43]) cholesterol, as well as triglycerides (β: 0.13 [95% CI: 0.05, 0.22]). Dyslipidemia was defined as the presence of one of more of the following conditions: total cholesterol (TC) ≥200 mg/dL, triglycerides ≥150 mg/dL, LDL-C ≥130 mg/dL or HDL-C <40 mg/dL.
- Zhang et al. (2021a) examined the association of NO_2 with diabetes (see Section 8.3.1) and dyslipidemia and biomarkers that indicate these conditions (i.e., HDL, LDL cholesterol and triglyceride are covered in this section) among participants in the China Health and Retirement Longitudinal Study (CHRLS). The study reported that annual average NO_2 exposure was associated with an increase in the prevalence of dyslipidemia, which was defined as the ratio of cholesterol to HDL ≥5.0 (1.22 [95% CI: 1.09, 1.37]), a decrease in HDL (−3.91% [95% CI: −4.76, −3.05]), LDL (−2.83% [95% CI: −3.99, −1.66]) and cholesterol (−2.75% [95% CI: −3.69, −1.82]), and an association with triglycerides that was close to the null value (0.75% [95% CI: −1.36, 2.85]). A pattern of association that was more consistent with dyslipidemia (i.e., inverse association with HDL cholesterol, a positive association with LDL cholesterol and triglycerides) emerged after adjustment for O_3 and $PM_{2.5}$ (see Section 6.7.1.3) and there was little evidence of effect measure modification by age, sex, BMI, smoking status, or drinking status (see Section 6.7.1.2).
- Wu et al. (2022) examined the association between 3-year average NO_2 exposure and metabolic risk score among adults in the Henan Rural Health Cohort. The authors derived a CMD risk score by summing the sex and age specific standardized scores for BMI, waist circumference, SBP, DBP, fasting plasma glucose, HOMA2-IR, triglycerides, and HDL cholesterol. An increase in CMD risk with increasing NO_2 exposure was observed (β: 2.15 [95% CI: 1.90, 2.40]).

Recent analyses are available that examine the associations of markers of CMD risk including atherosclerosis with long-term exposure to NO_2 or NO_X in children. The evidence comprises analyses of the Children's Health and Air Pollution Study (CHAPS) and the Southern California Children's Health Study (CHS). The CHAPS study enrolled children living in the San Joaquin Valley where there is a large Hispanic population, high rates of poverty and high air pollution concentrations relative to other areas in the United States. The Southern California CHS includes children living in areas with a range of concentrations and mixtures of regional ambient air pollutants, including NO_2. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-7.

- Farzan et al. (2021) conducted a pilot study of a subset of children (n = 70) within the Southern California CHS to examine the association of air pollution with atherosclerosis progression (indicated by changes in cIMT) from age 10–11 through age 21–22. Average residential NO_2 (i.e., birth to time of measurement at 10–11-years) was assigned by interpolating air monitoring data, and NO_X was modelled using the CALINE4 line source dispersion model. Traffic-related total NO_X exposure and freeway NO_X monthly average exposures were associated with a greater yearly rate of change in cIMT from childhood to adulthood (β: 1.94 μm/yr [95% CI: 0.7, 3.18] and β: 2.14 μm/yr [95% CI: 0.81, 3.48]). The association of cIMT change with NO_2 was essentially null (β: 1.7 [95% CI: −4.55, 8.02]). The pattern of association was similar for the progression of atherosclerosis during the adult period but the magnitude of the change in cIMT was larger.
- The association of NO_2 with markers of metabolic dysfunction that are linked to CVD were investigated in children residing in the Fresno California area who were enrolled in CHAPS (Zhang et al., 2022). Among the markers these studies examined were glucose concentrations and hemoglobin A1c (HbA1c), which are discussed in more detail in Chapter 10, oxidative stress markers and cholesterol and which is discussed here. Zhang et al. (2022) reported an inverse association of HDL cholesterol with NO_2 and NO_X, e.g., there was a –15.4 mg/dL change (95% CI: –27.4, –3.4) per 9.3 ppb (i.e., an IQR) increase in 3-month NO_2. HDL cholesterol protects against atherosclerosis by eliminating excess cholesterol in arterial walls and reducing inflammation. The marker of oxidative stress, indicated as a change in natural log transformed 8-isoprostane to creatinine ratio (ng/mg), was consistently increased in association with short-term (1-day and 1-week) exposures, and more weakly associated with 6-month (β: 0.6 [95% CI: 0.3, 0.9] per 6 ppb) and 1-year (β: 0.8, [95% CI: 0.7, 1.1] per 2.2 ppb) exposures. The pattern of associations observed with NO_X exposure were similar.
- Peralta et al. (2022) investigated the association of annual average NO_2 at the birth residence through the residence at age 14 (ESCAPE LUR) with cIMT at age 16 among adolescents in the Dutch PIAMA birth cohort. The authors applied quantile regression to understand whether the association varied across deciles of cIMT. The associations were positive and larger in magnitude at lower cIMT quantiles and were attenuated toward the null or negative in the upper quantiles (see Appendix A – Appendix Table 6-7); all CIs were wide and included the null value, however, providing little evidence to support an association. Fossati et al. (2020) examined the association of first trimester and pregnancy NO_2 exposure (ESCAPE LUR) with blood pressure (see Section that follows) and lipids among children in the INfancia y Medio Ambiente (INMA) birth cohort at age 4-years. The authors calculated z scores for lipids as the regression outcome. The associations were close to the null for the change in lipid z-score (β: −0.03 [95% CI: −0.15, 0.26], per 10.7 ppb increase in first trimester NO_2 exposure).

Blood Pressure

The 2016 Oxides of Nitrogen ISA assessed several studies that examined the association of NO_2 or NO_X with hypertension or increases in blood pressure (U.S. EPA, 2016). Overall, findings from studies of adults and studies of children report small, inconsistent results for the association between NO_2 and hypertension (see Section 6.5.1) and increased blood pressure (Bilenko et al., 2015; Foraster et al., 2014; Liu et al., 2014; Clark et al., 2012). Uncertainties remained regarding the independent effect of NO_2 on hypertension and blood pressure, specifically whether confounding by correlated traffic-related pollutants or noise can explain the positive associations observed. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A

– Appendix Table 6-7. Many epidemiologic studies that examined changes blood pressure also examined hypertension, which are discussed in Section 6.5.1.

Recent analyses of adults in the MESA cohort and in the Community of Mine study in San Diego County add to the evidence for the association of oxides of nitrogen and changes in blood pressure.

- In an analysis by Adar et al. (2018), 1-year average NO_2 concentration was associated with incident hypertension among MESA participants in models that adjusted for time-varying age; however, when calendar time was included in the model to account for a potential period effect, the associations were substantially attenuated (see Section 6.5.1). Similarly, no associations were reported with increases in blood pressure after adjustment for calendar time (e.g., the 1.7 mmHg increase in SBP [95% CI: 0.9, 2.5 and 0.6 mmHg increase in DBP [95% CI: 0.2, 1.0] without adjustment for calendar time were essentially null after adjustment for calendar time). Interactions of NO_2 exposure with race/ethnicity, age, diabetes, and obesity were not observed (data NR).
- African American and Chinese race/ethnicity is associated with hypertension compared to whites among participants enrolled in the MESA study. Song et al. (2020) evaluated the mediating effects of ambient air pollution on the association between race and or ethnicity and blood pressure levels. The authors observed that racial disparities in blood pressure were increased after accounting for NO_X exposure, but findings lost precision after adjustment for site.

Recent studies of the association between oxides of nitrogen and blood pressure in children residing in the United States and Canada were also conducted.

- Ni et al. (2021) examined the association of pre- and post-natal NO_2 exposure with blood pressure at 4- to 6-years, among children enrolled in the CANDLE cohort. Annual average NO_2 exposure was estimated using LUR with kriging components and then assigned at the participant's residential address for the pre- and postnatal exposure periods. Pre- and post-natal (birth to 4–6-years) NO_2 exposures were associated with small, imprecise increases in SBP and DBP that were close to the null values, providing little evidence for an association.
- Mann et al. (2021) examined the association of NO_2 exposure with increased blood pressure (ages 6–8-years) among children residing in the Fresno California area who were enrolled in CHAPS. The study modelled NO_2 using a combination of regulatory and spatially intensive monitoring data at the child's residence to derive 1-day lag, and 1-week, 1-month, 3-month, 6-month, and 1-year averages before the outcome assessment. This study reported associations between NO_2 and increased SBP for 1-month, 3-month, 6-month and 1-year average exposures. For example, 3-month average NO_2 concentration was associated with a 9.4 mmHg increase in SBP (95% CI: 2.8, 15.9) per 6.2 ppb. Positive associations that included the null value were observed for longer term NO_2 average exposure (3-month, 6-month and 1-year) and DBP and 8-isoprostane, which is a marker of oxidative stress. A positive association between 1-month average NO_2 exposure and 8-isoprostane that did not include the null value was also reported.
- In a study conducted in Canada, Marrone et al. (2023) investigated the association of NO_2 with SBP among adolescents in Montréal, Canada using data from the Nicotine Dependence Teens study. This study estimated NO_2 concentration using a LUR (model r^2: 73%). Elevated SBP was defined as SBP ≥90th percentile (adjusted for age, sex and height). The study reported an increase in annual average NO_2 exposure was positively associated with elevated

SBP (OR: 1.17 [95% CI: 0.5, 2.75]), although the association was imprecise, and the CI included the null value.

- Pedersen et al. (2019) used data from the Danish National Birth Cohort to investigate the association of pre- (pregnancy period) and post-natal (birth to age 7) NO_2 exposure, estimated using a validated dispersion model, and noise from road traffic with insulin resistance (see Chapter 8, Section 8.5.1) and increased blood pressure in children 10–15- years old. The authors reported small increases in DBP that were close to the null value (β: 0.31 mmHg [95% CI: −0.87, 1.48] per 10 $\mu g/m^3$) while NO_2 associated decreases in SBP were observed. In models that mutually adjusted for NO_2 and noise, NO_2 was associated with small increases in SBP and DBP that were close to the null value (CIs included the null value).

- de Prado-Bert et al. (2022) examined association between short-term (see Chapter 5, Section 5.7.1) and annual average NO_2 exposure estimated using the ESCAPE LUR approach, with blood pressure among children 6–11 enrolled in Human Early-life Exposome (HELIX) project, which is based on six longitudinal population-based cohorts (i.e., Born in Bradford [BiB], Etude de cohorte généraliste menée en France sur les Déterminants pré et post natals précoces du développement psychomoteur et de la santé de l'Enfant [EDEN], INMA, the Kaunas Cohort [KANC], the Norwegian Mother, Father and Child Cohort Study, and the Mother-Child Cohort in Crete. Increases in SBP and DBP were observed in association with annual average NO_2 exposure, but confidence intervals included the null value.

- Fossati et al. (2020) examined the association of first trimester and pregnancy NO_2 exposure (ESCAPE LUR) with CMD risk factors including blood pressure and lipids among children in the INMA birth cohort at age 4-years. The authors calculated z scores for blood pressure (mean of DPB and SPB z-scores) as the regression outcome. The associations were close to the null for the change in BP (β: 0.07 [95% CI: −0.04, 0.19], per 10.7 ppb increase in first trimester NO_2 exposure, respectively).

Other Subclinical Markers

Recent studies including analyses of the UK Biobank and the German Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) cohorts expand the evidence for reduced cardiac function in relation to exposure to oxides of nitrogen. Cardiac remodeling and subsequent changes in heart function typically precede the development of heart failure. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-7.

- Aung et al. (2018) examined the cross-sectional association of long-term NO_2 and NO_X exposure with an array of cardiac parameters (left ventricular [LV] end-diastolic volume (EDV), LV end-systolic volume (LV ESV), LV ejection fraction (EF), LV mass, RVEDV, RVESV, RVEF, left atrial [LA] maximal volume, LA EF, right atrial maximal volume, right atrial EF, and LV geometric remodeling patterns). Higher NO_2 concentration was associated with larger LVEDV (1.5% [95% CI: 0.20, 2.81%] and RVEDV (1.4% [95% CI: 0.09, 2.72%]), but not the other outcomes examined.

- Ohlwein et al. (2016) investigated the cross-sectional association between annual average NO_2 and NO_X exposure (ESCAPE LUR r^2: 0.88 and 0.89, respectively) with diastolic function (i.e., ratio of peak early diastolic filling velocity and peak early diastolic mitral annulus velocity [E/E'] and left atrial volume index [LAVI]) among older women (69–79-years) in the German SALIA cohort. Beta coefficients from linear regression models were

transformed to means ratios (MR), which is the ratio of estimated levels of outcome at the 3rd quartile of the exposure in relation to the estimated levels of outcome at the 1st quartile of the exposure. In the fully adjusted models, LAVI was positively but imprecisely associated with NO_X (β: 4.0% [95% CI: 0.0; 9.0] per 20.6 μg/m^3) and NO_2 (β: 8.6% [-2.1, 19.2]) at follow-up and at baseline (NO_X and NO_2 β: 5.0% [95% CI: 0.0, 11.0] per 20.6 μg/m^3 and 10.7% [95% CI: -1.07, 22.5]). Imprecise associations with E/E' that were close to the null for both NO_X and NO_2 at follow-up (and baseline) were observed (e.g., β: -1.0% [95% CI: -6.0, 4.0 per 20.6 μg/m^3 NO_X and -2.1 (-12.8, 8.6) per 10 ppb NO_2]). The association of NO_2 with LAVI was modified by BMI, hypertension status, alcohol consumption, TNF-α and use of hypertensive medication (see Section 6.7.1.2).

Several studies examined circulating markers of inflammation. These studies were conducted across a range of populations in Canada, Germany, and China.

- In Canada, Laratta et al. (2020) examined the association of NO_2 with markers of inflammation in a cohort with suspected obstructive sleep apnea (OSA), which is associated with inflammation and CVD. No associations were observed in models with or without an interaction term between NO_2 and OSA severity.
- Pilz et al. (2018) conducted a cross-sectional study to examine the relationship of NO_2 and NO_X with hs-CRP, which is a marker of systemic inflammation, among German Cooperative Health Research in the Region of Augsburg (KORA) participants. Annual average pollutant exposure was assigned at the participant's residence using the ESCAPE LUR methodology. The authors reported imprecise increases in hs-CRP with increasing annual average NO_2 (3.29 [95% CI: −14.5, 21.1]) and NO_X (3.45 [95% CI: −1.48, 8.61] per 8.7 μg/m^3) exposure. Population and lifestage differences are discussed in Section 6.7.1.2.
- In a study of Chinese participants in the World Health Organization (WHO) study on global aging and adult health (SAGE), which is a longitudinal study evaluating in detail the health and wellbeing of adult populations in middle-income countries, Elbarbary et al. (2021) reported an association between 3-year moving average NO_2 and a higher serum hs-CRP (β: 22.2% [95% CI: 16.7, 27.8]). The authors also present analyses to indicate that the association may be modified by smoking status (see Section 6.7.1.2).

Other recent United States and Canadian Studies have investigated an array of endpoints including subclinical indicators of stroke, DNA methylation, pulmonary vascular volume, telomere length and hemoglobin. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 6-7.

- Aaron et al. (2019) examined total pulmonary vascular volume using noncontrast chest computed tomography ($TPVV_{CT}$) and peripheral $TPVV_{CT}$ (i.e., vascular volume in the outer portion of the lung) among MESA participants between 2010 and 2012. The authors hypothesized air pollution-related changes in $TPVV_{CT}$, because increases in the measure were observed in current and ex-smokers enrolled in MESA. After adjustment for city, NO_2 was associated with increased $TPVV_{CT}$ (β (mean difference): 1.08 [95% CI: -1.04, 3.19]) and peripheral $TPVV_{CT}$ (β (mean difference): 1.00 (-0.19, 2.19). The associations of NO_X with these endpoints were smaller in magnitude and closer to the null value.
- Chi et al. (2016) reported that annual average NO_X exposure (MESA spatiotemporal model) was not associated with DNA methylation patterns that are associated with CVD. In another analysis of MESA, C. Chi et al. (2022) studied DNA methylation in CD14+ monocytes and

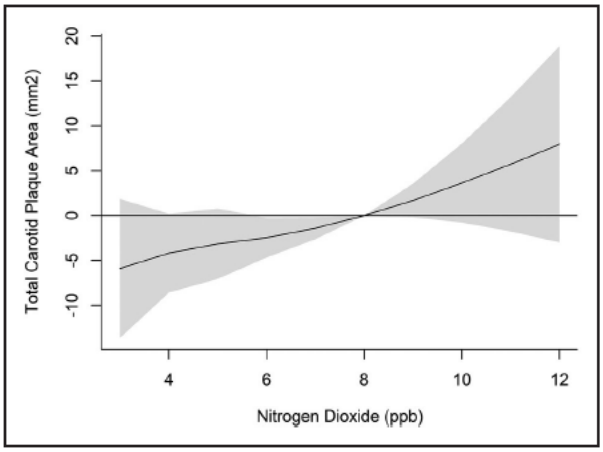
annual average NO_X exposure. The authors reported differential DNA methylation (i.e., cg11756214 within ZNF347) in monocytes associated with long-term NO_X exposure.

- In a study of stroke-free individuals (≥50-years) participating in the Northern Manhattan Study (NOMAS), Kulick et al. (2017) examined the cross-sectional association of NO_2 with subclinical indicators of stroke (see Section 6.4.1) ascertained using magnetic resonance imaging (MRI) (i.e., white matter hyperintensity volume [WMHV], total cerebral brain volume [TCBV] and subclinical brain infarcts [SBI]). MESA methods were employed to estimate long-term NO_2 concentration. There was no evidence of associations of 1-year average NO_2 concentration with log-WMHV (−0.015 [95% CI: −0.061, 0.030]), TCBV (−0.003 [95% CI: −0.184,0.178]), or SBI (0.026 [95% CI: −0.161, 0.214]). A similar pattern of lack of association was observed with NO_X.
- Honda et al. (2017) conducted an analysis of the association of NO_2 exposure with hemoglobin concentrations and prevalence of anemia in older Americans enrolled in the National Social Life, Health, and Aging Project. NO_2 exposure was estimated using the nearest monitor. NO_2 was associated with anemia prevalence (POR: 1.43 [95% CI: 1.26, 1.67] and with a decrease in average hemoglobin of 0.81 g/dL ($p<0.001$). This association persisted but was somewhat attenuated after adjustment for $PM_{2.5}$ (see Section 6.5.1.3). Honda et al. (2017) used natural cubic spline regression to investigate the shape of the concentration-response function. This analysis indicated no evidence of a threshold and the largest decrements in hemoglobin were observed at the highest concentrations (see Section 6.7.1.2).

6.7.1.1 Concentration-Response

Studies of preclinical atherosclerosis and anemia examined the shapes of the C-R functions (see Figure 6-26 and Figure 6-27).

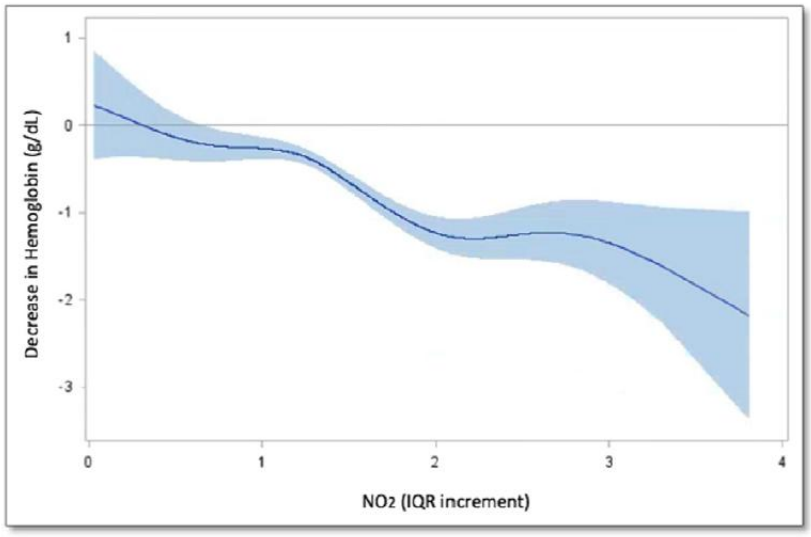
- Johnson et al. (2020) conducted a cross-sectional analysis of data from the SPARC study in the city of London in Ontario, Canada with the objective of examining the association of NO_2 exposures with markers of atherosclerosis (i.e., total plaque area, which is a stronger indicator of atherosclerosis than cIMT). Johnson et al. (2020) also conducted a dose-response analysis using a natural cubic spline function that indicates a linear relationship between NO_2 concentration and total plaque area (see Figure 6-26). In this analysis a 1.2 mm^2 increase in cube root transformed total plaque area per 1 ppb increase in NO_2 was observed.



List of abbreviations in alphabetical order: mm^2 = millimeters squared, ppb = parts per billion.
Source: Johnson et al. (2020). Copyright permission pending.

Figure 6-26 Concentration-response relationship for NO_2 and total plaque area in adjusted models.

- Honda et al. (2017) conducted an analysis of the association of NO_2 exposure with hemoglobin concentrations and prevalence of anemia in older Americans enrolled in the National Social Life, Health, and Aging Project. The study used natural cubic spline regression to investigate the shape of the concentration-response function. This analysis indicated no evidence of a threshold, and the largest decrements in hemoglobin were observed at the highest concentrations (see Figure 6-27).



List of abbreviations in alphabetical order: IQR = Interquartile Range; NO_2 = nitrogen dioxide.
Note: The model is adjusted for age, sex, tobacco use, physical activity, education, race, region, census track 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. The shaded region indicates 95% CIs.
Source: Honda et al. (2017). Copyright permission pending.

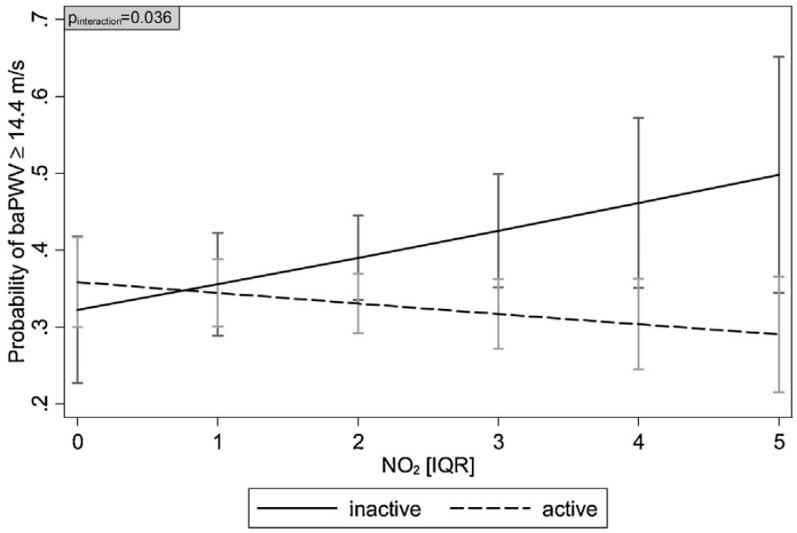
Figure 6-27 Spline regression for the association between an IQR increment of NO_2 and decrements in hemoglobin (g/dL).

6.7.1.2 Lifestages and Populations

To identify factors that potentially lead some portions of the population to be at increased risk of NO_2-related health effects, epidemiologic studies often evaluate effect-measure modification (EMM), which occurs when the estimated effect of NO_2 differs between subgroups or strata (e.g., effect estimates that vary by age group or other potential risk factor). Results from studies that examine modification of the association between long-term oxides of nitrogen exposure and subclinical markers underlying CVD are summarized below.

- zielska et al. (2016) reported that NO_X exposure averaged over the years 2000-2010 was associated with a 2.4 Agatston units per year (95% CI: 0.5, 4.4) increase in the rate of CAC progression. There was some evidence of effect measure modification by race indicating that the increase in CAC is larger in white and Black individuals compared to Chines and Hispanic individuals. In another MESA analysis, Tibuakuu et al. (2017) reported no associations between NO_X exposure and measures of valvular calcification (β AVC: −1 [95% CI: −3.1, 1.2] and β MAC: −1.29 [95% CI: −3.17, 0.59] Agatston units per year). The study used multiplicative interaction terms to assess effect measure modification by race/ethnicity, age, sex or by $PM_{2.5}$ and reported no statistical evidence that the associations with NO_X were modified by these factors (quantitative results were not reported).
- Endes et al. (2017) investigated whether physical activity modified the association between annual average NO_2 exposure and arterial stiffness (baPWV ≥14.4 m/s) among participants in the Swiss SAPALDIA study. Although an inverse association (CIs inclusive of the null

value) with annual average NO_2 exposure was observed (OR: 0.95 [95% CI: 0.81, 1.12 per IQR, which was not reported]), an interaction between physical activity and NO_2 was observed such that the effect of NO_2 was observed only among the inactive participants (see Figure 6-28).



List of abbreviations in alphabetical order: IQR = Interquartile Range; NO_2 = nitrogen dioxide.
Note: Models adjusted for age, sex, education socioeconomic position, pack-years of smoking, BMI, heart rate and mean arterial pressure. The scale of the x-axis extends from the lower to the upper quartile of NO_2 concentration.
Source: Endes et al. (2017). Copyright permission pending.

Figure 6-28 Association between the probability of increased branchial-ankle pulse wave velocity and NO_2 per IQR among physically active and inactive subjects.

- Edlund et al. (2022) reported that NO_X exposure was positively associated with high CAC score (PR: 1.05 [95% CI: 0.99, 1.1] per 10 µg/m^3) and the presence of bilateral plaque (PR: 1.03 [95% CI: 1, 1.06] per 10 µg/m^3) in the Swedish SCAPIS study. The associations with CAC were somewhat stronger among females.
- Zhang et al. (2021a) reported that annual average NO_2 exposure was associated with an increase in the prevalence of dyslipidemia and changes in lipid concentrations. There was little evidence of effect measure modification by age, sex, BMI, smoking status, or drinking status.
- Ni et al. (2022) investigated the association of NO_2 with blood pressure in high and low risk APOL1 groups of children and their mothers. A two-ppb increase in NO_2 exposure was associated with increases in SBP and DBP in mothers with the APOL1 high-risk group (β: 1.81 mmHg [95% CI: −2.64, 6.26] and β: 1.83 mmHg [95% CI: 1.11, 4.78], respectively). In the low risk APOL1 group the associations were closer to the null value and confidence levels overlapped between groups (β: −0.2 [95% CI: −1.3, 0.91] and β: 0.18 [95% CI: −0.84, 1.2 for SBP and DBP, respectively). There was no discernable pattern across child genotype risk groups.
- Ohlwein et al. (2016) investigated the cross-sectional association between annual average NO_2 and NO_X exposure with LAVI in the German SALIA cohort. In the fully adjusted

models, LAVI was positively associated with NO_X at follow-up (MR: 1.04 [95% CI: 1.00; 1.09]) and NO_2 (MR: 1.04 [95% CI: 0.99, 1.09]) and at baseline for both (1.05 [95% CI: 1.00, 1.11]). The association of NO_2 with LAVI was modified by BMI, hypertension status, alcohol consumption, TNF-α and use of hypertensive medication (see Appendix A – Appendix Table 6-7).

- Pilz et al. (2018) conducted a cross-sectional study to examine the relationship of NO_2 and NO_X with hs-CRP, which is a marker of systemic inflammation, among German Cooperative Health Research in the Region of Augsburg (KORA) participants. The authors examined interactions between NO_2 and sex, obesity smoking status, diabetes and CVD status. Positive associations with hs-CRP were observed among females (25.8 [95% CI: 0.86, 52.54]) while a negative association was observed in males (-19.4 [95% CI: -43.9, 4.87). Positive associations with hs-CRP were observed among females (25.8 [95% CI: -0.86, 52.54]) while a negative association was observed in males (-19.4 [95% CI: -43.9, 4.87). Both estimates were imprecise. Associations changed from positive to inverse among obese individuals and those with prediabetes, diabetes or CVD.
- Elbarbary et al. (2021) reported an association between 3-year moving average NO_2 and a higher serum hs-CRP (β: 22.2% [95% CI: 16.7, 27.8]) among Chinese participants of the SAGE study. The authors also present analyses to indicate that the association may be modified by income (larger increase in hs-CRP among those with higher incomes).

The evidence for modification of the associations between long-term exposure to oxides of nitrogen and subclinical markers underlying CVD is limited. Single studies covered a diverse array of endpoints. Some studies reported little evidence effect T function and inflammation precluding evaluation of the patterns of effect measure modification within outcome categories.

6.7.1.3 Copollutants

A limited number of studies examined confounding of the association between long-term NO_2 exposure and subclinical markers underlying cardiovascular effects by copollutant exposures. Recent studies that adjusted associations of long-term NO_2 exposure with indicators of atherosclerosis and hemoglobin concentration are summarized below.

- In an analysis of the MESA cohort, zielska et al. (2016) reported that NO_X concentration was associated with a 4.8 Agatston units per year (95% CI: 0.9, 8.7) increased rate of CAC progression (per 40 ppb), and NO_2 concentration was associated with an increase of 2.7 Agatston units per year (95% CI: –0.3, 5.7) increased rate of CAC progression (per 10 ppb). Associations with NO_X and NO_2 were substantially attenuated with CIs including the null value after adjustment for $PM_{2.5}$.
- Edlund et al. (2022) examined the association of NO_X exposure with indices of atherosclerosis (CAC and carotid artery plaques) in the Swedish SCAPIS Gothenburg study. NO_X exposure was positively associated with high CAC score (PR: 1.05 [95% CI: 0.99, 1.1] per 10 $\mu g/m^3$) and the presence of bilateral plaque (PR: 1.03 [95% CI: 1, 1.06] per 10 $\mu g/m^3$) in the whole cohort. These associations with CAC remained after adjustment for traffic noise.
- Honda et al. (2017) conducted an analysis of the association of NO_2 exposure with hemoglobin concentrations and prevalence of anemia in older Americans enrolled in the

National Social Life, Health, and Aging Project. 1-year moving average NO_2 was positively associated with anemia prevalence (POR 1.43 [95% CI: 1.25, 1.63]) per IQR and a decrease in average hemoglobin of 0.81 g/dL (p-value <0.001). This association with decreased hemoglobin persisted but was somewhat attenuated after adjustment for $PM_{2.5}$ (−0.57 p-value <0.001).

6.7.1.4 Conclusions and Remaining Uncertainties

The evidence indicates a lack of consistency across studies of markers of atherosclerosis and blood pressure. Some studies (Edlund et al., 2022; Paoin et al., 2021; Hennig et al., 2020), but not all (Endes et al., 2017; Hartiala et al., 2016; Gan et al., 2014), reported positive single-pollutant associations between long-term exposure to oxides of nitrogen and measures of atherosclerosis (e.g., CAC, plaque area and arterial stiffness). Several studies additionally observed a pattern of single-pollutant associations with lipid concentrations that indicate an increased risk for atherosclerosis (Letellier et al., 2022; Wu et al., 2022; Zhang et al., 2021a). However, in a MESA analysis, the association of NO_2 and NO_X with CAC was substantially attenuated after adjustment for $PM_{2.5}$ (zielska et al., 2016). For blood pressure, no association with NO_2 was observed after adjustment for calendar time in the MESA cohort (Adar et al., 2018), and a relatively large body of recent prospective studies reported mixed results for associations with pre- and postnatal changes (through age 7) in blood pressure in children (4- to 15-years of age). The positive associations that were observed with blood pressure were generally close to the null value (Marrone et al., 2023; de Prado-Bert et al., 2022; Ni et al., 2021; Fossati et al., 2020; Pedersen et al., 2019), though one study reported relatively strong associations of shorter-term NO_2 exposures (i.e., <1-month) with SBP, DPB and 8-isoprostane, while still observing positive associations with longer-term exposures of 3-months to 1-year.

Regarding other subclinical endpoints, recent studies report associations between long-term exposure to oxides of nitrogen and cardiac parameters indicating reduced functioning, including LV EDV and LAVI (Aung et al., 2018; Ohlwein et al., 2016) and markers of inflammation (Pilz et al., 2018). Single studies reported associations of oxides of nitrogen exposure with patterns of DNA methylation linked to CVD risk and with increased prevalence of anemia, but not with reduced pulmonary vascular volume or subclinical indicators of stroke. The evidence examining concentrations response relationships, and the modification of the associations observed in the studies of subclinical markers was limited. Some study findings were sensitive to exposure assessment method. For example, Hennig et al. (2020) reported multi-year average NO_2 exposure modelled using CTM and LUR was associated with incident CAC, while in subgroup analyses comparing participants with no or minor atherosclerosis and participants with advanced atherosclerosis, the pattern of associations differed depending on exposure assessment approach. In addition, Letellier et al. (2022) compared results from two exposure models reporting that the approach that considered time activity patterns to better capture spatial variability in NO_2 concentrations (as opposed to IDW of monitoring concentrations) appeared to increase the sensitivity to detect the associations of interest, confirming findings from the 2016 Oxides of Nitrogen ISA. Overall, it

is not clear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, confounding by traffic-related copollutants or other environmental determinants, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health care access, health behaviors). Most studies used validated exposure assessment models; however, findings from one study indicated results were sensitive to the choice of LUR versus CTM to estimate long term exposure to oxides of nitrogen.

6.7.2 Animal Toxicological Studies of Subclinical Effects Underlying Cardiovascular Disease

The 2016 Oxides of Nitrogen ISA described a limited number of animal studies that looked at the effects of long-term exposure to NO_2 on subclinical markers related to CVD. The endpoints reported in these studies were either general markers of systemic inflammation and oxidative stress or related to changes in more general markers of cardiovascular health including heart rate, blood lipid profile, hemoglobin, and hematocrit markers [see Table 6-9 in U.S. EPA (2016)]. Given the overlap between cardiovascular and metabolic markers of disease, some of these studies are also described in the context of metabolic disease (see Chapter 8). A summary of the evidence presented in the 2016 Oxides of Nitrogen ISA is below.

- Studies of monkeys exposed for 14- or 16-months to 1–2 ppm NO_2 showed no statistically significant changes in hematocrit or hemoglobin levels compared to filtered air exposure (Fenters et al., 1973; Furiosi et al., 1973). Furiosi et al. (1973) did report an NO_2-induced increase in RBC concentration but a lack of change in mean corpuscular hemoglobin or hematocrit suggested a reduced mean corpuscular volume. In the same study, similar findings were seen in rats exposed to the same concentration of NO_2 for 3 or 9 months.
- Exposure of dogs and rats to NO_2 ranging from 0.4 ppm to 5 ppm for 1 month to 18 months resulted in no significant changes in hematocrit or hemoglobin measures compared to control (Suzuki et al., 1981; Furiosi et al., 1973; Wagner et al., 1965).
- Decreased heart rate (compared to control exposure) in rats was reported following exposure to NO_2 in the range of 1.2–4 ppm after one month of exposure which returned to normal with longer exposure durations (Suzuki et al., 1981). In another study, the heart rate of rats was not changed with exposure to 400 ppb NO_2 for 4 weeks (Tsubone and Suzuki, 1984).
- One study of rats fed selenium-enriched and selenium-deficient diets for 14 weeks prior to 4 weeks of NO_2 exposure (1 and 10 ppm) and investigated the impact on blood antioxidant enzymes and markers of oxidative damage (thiobarbituric acid-reactive substances) (de Burbure et al., 2007). The authors reported increases in the plasma thiobarbituric acid-reactive substances immediately following exposure to 1 ppm but not 10 ppm NO_2, regardless of selenium diet. These markers were either no longer statistically different or statistically decreased compared to controls after 48 hours. Activity of antioxidant enzymes in the blood and associated with RBC was variable and did not show clear dose, time, or selenium-dependent trends.
- Takano et al. (2004) reported that rats that were genetically predisposed for weight gain had elevated concentrations of triglycerides and decreased HDL and HDL/total cholesterol

concentrations after long-term exposure to 160 ppb NO_2 for 24 weeks compared to control rats breathing clean air. Decreased HDL was also seen with exposure to 800 ppb NO_2 for 24 weeks in obese rats but not with 4,000 ppb NO_2 exposure. In control rats, exposure at any NO_2 concentration (160–4,000 ppb) resulted in decreased HDL but no change to HDL/total cholesterol. This suggested that obese individuals may be more prone to dyslipidemia in response to long-term NO_2 exposure.

- A study of mixtures containing various concentrations of NO_2 in mice for 50 days showed that NO_2 concentration was a strong predictor of thiobarbituric acid-reactive substances but not heme oxygenase response (Seilkop et al., 2012).

Recent animal studies have investigated the impact of long-term NO_2 exposure on subclinical markers relevant to CVD. The results of these recent studies are summarized below with study details in Appendix A – Appendix Table 6-8.

- Exposure of mice to 2.5 ppm NO_2 for 5 hours/day over 28 days resulted in increased markers of left ventricular dilation specifically in male mice that corresponded to signs of decreased cardiac output (Ji et al., 2022). The hearts of the male mice exposed to NO_2 also had increased markers of cardiac cell injury and apoptosis.
- Exposure of rats to 5 ppm NO_2 for 4 hours/ day for 30 days did not alter the number of inflammatory cells in the blood unless sensitized and challenged with OVA (Lu et al., 2023b). Exposure of mice during gestation led to small but not statistically significant increases in blood immune cell numbers in the offspring that became significant with OVA challenge (Lu et al., 2023b; Lu et al., 2023a).
- Rats exposed to 5 ppm NO_2 for 3 hours/day for 3 weeks showed increased mitochondrial ROS production that corresponded to reduced endothelial mediated vasorelaxation and reduced cardiac output (Karoui et al., 2020). The authors also reported signs of left ventricular dilation including increased left ventricular diastolic and systolic diameters and reduced left ventricular fractional shortening. Of note, in this model, short-term exposure (i.e. a single 3-hour exposure) to NO_2 resulted in transient mitochondrial ROS production and reversible left ventricular dysfunction. Repeated 3-hour exposures over 3 weeks resulted in heightened mitochondrial effects and more prolonged left ventricular dysfunction.

6.7.2.1 Dose-Response

The animal toxicology database for subclinical endpoints to cardiovascular effects is limited in number. Evidence of dose-dependent relationships varies by endpoint. Effects of NO_2 on triglycerides and HDL levels were seen in rats genetically predisposed to obesity following 0.160 ppm NO_2 but were generally unchanged following exposures to 0.8 or 4 ppm (Takano et al., 2004). As discussed above, no changes in hematocrit were reported in multiple animal models of NO_2 exposure ranging from 0.4 to 5 ppm and exposure durations ranging from 1 to 18 months (Suzuki et al., 1981; Fenters et al., 1973; Furiosi et al., 1973; Wagner et al., 1965). Dose or time-dependent effects on changes to plasma of RBC-related antioxidant status were not clearly seen in rats exposed to 1 – 50 ppb NO_2 from 30 minutes to 28 days (de Burbure et al., 2007). However, a recent study showed that repeated exposure to NO_2 for 3 hours a day for 5 days a week for 3 weeks resulted in greater and more prolonged mitochondrial impairment and

worsened left ventricular dysfunction compared to exposure for 3 hours on one day (Karoui et al., 2020). NO_2 exposure showed dose-dependent decreases in heart rate after 1 month of exposure in the range of 0.4 to 4 ppm but was not seen after 2 or 3 months of exposure (Suzuki et al., 1981). Another study showed greater decreases in heart rate following longer exposure times (1 to 24 hours) to 10 or 20 ppm NO_2 compared to shorter durations. Effects on heart rate were not seen after longer exposures (1 to 4 weeks) to lower concentrations of NO_2 (0.4 ppm or 4 ppm). Overall, there is considerable variability in the dose-response relationships across endpoints, and NO_2 exposure ranges.

6.7.2.2 Conclusions and Remaining Uncertainties

Recent findings expand the animal toxicology evidence base for long-term NO_2-induced cardiovascular changes. While the database is still limited in size and lacks consistency in reported endpoints, recently identified endpoints suggest exaggeration of ROS production and increased markers of cardiac cell injury that are supported by changes in left ventricular function and decreased cardiac output. Changes in these endpoints over an extended period of time could plausibly contribute to the development of CVD. The primary limitations of the existing literature base are the limited number of studies available and the inconsistency in measured endpoints which limit the comparison of results among studies.

6.7.3 Synthesis Across Lines of Evidence

The 2016 Oxides of Nitrogen ISA noted that the evidence base for subclinical cardiovascular effects was limited and results were often inconsistent. Recent studies have expanded this evidence base, examining the potential for long-term NO_2 exposure to impart subclinical changes in CVD-related endpoints including progression of subclinical markers of atherosclerotic plaque development, blood pressure changes, induction of inflammation and oxidative stress, and changes in indicators of cardiac function.

Recent evidence of associations between long-term NO_2 exposure and common measures of atherosclerosis, such as artery calcification, plaque area, and cIMT values, are mixed. Recent studies of cIMT report generally null associations, although positive associations between NO_X exposure, but not NO_2 exposure, and cIMT progression were reported in children. Positive associations between long-term NO_2 exposures and arterial calcification values or plaque area were reported, but the associations were often lost when controlling for confounding factors. There is limited epidemiology evidence of inverse associations for long-term NO_2 or NO_X exposures and levels of protective HDL. These associations are supported by a small body of animal toxicology evidence showing reduced HDL following NO_2 exposures from 160 ppb–4,000 ppb.

Recent epidemiology studies in adult populations continued to show inconsistent associations between long-term NO_2 exposures and blood pressure changes, although multiple recent studies have shown positive associations with NO_2 and SBP in studies of children. The evaluation of confounding factors on these associations is limited and in the few studies that control for factors like calendar-time, observed associations are lost. There is a lack of animal toxicology studies that investigate blood pressure changes to support the epidemiology results.

The result of long-term NO_2 exposures on other potentially relevant cardiovascular endpoints is limited and is inconsistent. Evidence for inflammation and oxidative stress continue to be mixed and include a wide variety of endpoints and markers making comparison difficult. Animal toxicology data is limited in the number of studies but has shown heart structural changes (increased LVEDD and LVEDV) and increased evidence of induction of cardiac ROS production following long periods of NO_2 exposure.

6.8 Cardiovascular Mortality

Positive associations with deaths due to CVD were observed in several cohort studies conducted in the United States and Europe that were assessed in the 2016 Oxides of Nitrogen ISA. The strongest evidence came from studies that observed positive associations between exposure to NO_2 and NO_X and IHD mortality (Cesaroni et al., 2013; Chen et al., 2013; Lipsett et al., 2011; Yorifuji et al., 2010), CHD mortality (Gan et al., 2011; Rosenlund et al., 2008), and circulatory disease mortality (Yorifuji et al., 2010; Jerrett et al., 2009). Some coherence for the effect of long-term exposure to oxides of nitrogen and cardiovascular endpoints was provided by the evidence from studies of short-term exposure and cardiovascular mortality and morbidity.

6.8.1 Epidemiologic Studies of Cardiovascular Mortality

Krewski et al. (2000) reported a positive association between annual average NO_2 exposure and cardiopulmonary disease (CPD) mortality in the Harvard Six Cities cohort. However, associations were null in the American Cancer Society Cancer Prevention Study-II cohort (CPS-II) cohort in stratified analyses by season. Jerrett et al. (2013) also evaluated the CPS-II cohort and observed positive associations between NO_2 exposure averaged over 1988-2002 and mortality from CVD, IHD, and stroke with one additional year of follow-up compared to Krewski et al. (2000). Gan et al. (2011) observed increased risk for CHD mortality associated with annual averages of NO (RR: 1.08 [95% CI: 1.03, 1.14]) and NO_2 (RR: 1.09 [95% CI: 1.01, 1.18]) in a cohort of Vancouver residents. In an Ontario cohort, Chen et al. (2013) reported positive associations between annual averages of NO_2 exposure and IHD mortality (RR: 1.19 [95% CI: 1.08, 1.30]) and CVD mortality (RR: 1.17 [95% CI: 1.10, 1.23]). The authors reported a null association for CBVD mortality.

Cesaroni et al. (2013) reported increased risks for NO_2-related CVD mortality (HR: 1.06 [95% CI: 1.04, 1.08]) and IHD mortality (HR: 1.10 [95% CI: 1.07, 1.13]) in a cohort of noninstitutionalized adults in Rome. Hoek et al. (2002) observed positive imprecise associations between NO_2 exposure and CPD mortality in a Dutch cohort. Updated analyses of the same cohort with two additional years of follow-up likewise reported a positive imprecise increase in risk for CVD mortality associated with 10-year average NO_2 exposure (Brunekreef et al., 2009; Beelen et al., 2008). Exposure assessment in the later analyses used more precise estimates by involving a longer exposure assessment period, use of kriging in addition to inverse distance squared weighting for interpolation of pollutant estimates, more complete road network and traffic intensity data, and use of exact residential addresses and circular buffers instead of postal codes for geocoding. Carey et al. (2013) conducted a cohort study of English primary care patients and reported a positive imprecise association between NO_2 exposure estimated with dispersion models for the year 2002 and circulatory disease mortality. Beelen et al. (2014) evaluated associations of NO_2 and NO_X with nonaccidental mortality in 22 cohorts from the European Study of Cohorts for Air Pollution Effects (ESCAPE). The authors reported null results for the associations between exposure to NO_2 or NO_X and CVD, IHD, MI, and CBVD mortality.

This section summarizes information from epidemiologic studies examining associations with cardiovascular mortality. Study-specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 6-9. Analyses from these studies examining the shapes of concentration-response relationships, the lifestages and populations that may be at increased risk, and the potential impacts of copollutants on reported associations are discussed in greater detail in Sections 6.8.1.1 to 6.8.1.3. Section 6.8.1.4 presents conclusions and summarizes remaining uncertainties in the epidemiologic evidence for cardiovascular mortality.

Recent North American cohort studies present generally positive associations between long-term NO_2 and NO_X exposure and mortality due to CVD (see Figure 6-29).

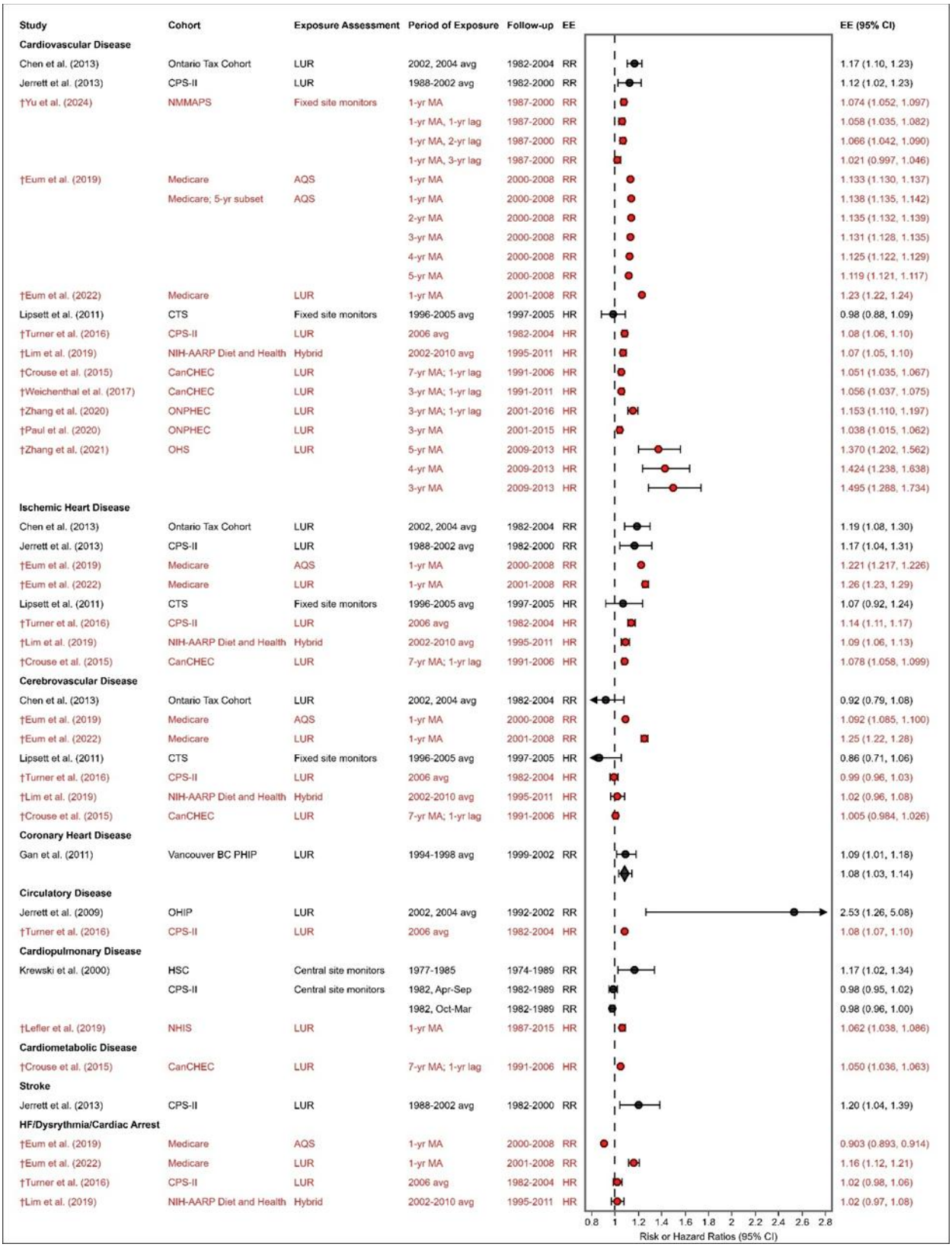
- (Yu et al., 2024) evaluated 14-years of data from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) using a difference-in-differences design to compare year-to-year changes in annual concentrations of air pollutants with changes in the number of deaths per year in 108 municipalities. In a conditional Poisson regression model including spatial and temporal factors, seasonal variation, and population-level characteristics, the relative risk for CVD mortality per 10-ppb increase in concurrent NO_2 exposure was 1.074 (95% CI: 1.052, 1.097). In sensitivity analyses using various lag times (1-3-years), the relative risk for nonaccidental mortality was strongest for a lag of 2-years (RR: 1.066 [95% CI: 1.042, 1.090]), and weakest for a lag of 3-years (RR: 1.021 [95% CI: 0.997, 1.046]).
- Eum et al. (2019) and Eum et al. (2022) examined associations between NO_2 exposures and deaths from CVD, IHD, cerebrovascular disease (CBVD), and congestive heart failure (CHF) among Medicare enrollees in December 2000-2008 aged 65–120-years. Eum et al. (2019) reported positive associations for CVD, IHD, and CBVD mortality, and negative associations for CHF mortality, in the entire United States and by regions, associated with 12 month moving averages of NO_2 concentrations from EPA AQS monitors. Eum et al. (2019) also

reported positive associations for moving averages ranging from 1- to 5-years, and the strongest associations were identified using the shortest moving averages. Eum et al. (2022) included more than 3.5 times the number of Medicare enrollees that were in the previous study and reported positive associations for all cardiovascular mortality outcomes in association with 12 month moving average NO_2 concentrations estimated using an LUR model with a 100 m x 100 m grid. Adjustment for $PM_{2.5}$ or BC in the two-pollutant models slightly increased the strength of associations in this study. Compared to Eum et al. (2019), the Eum et al. (2022) study included a greater proportion of rural participants (10.9% vs. 4.0%), better reflecting the general population in the U.S. Rural zip codes had greater exposure error than urban zip codes in the validation of the LUR model (rural: $r^{2 =}$ 0.69; urban: $r^{2 =}$ 0.80).

- A single study using data from the American Cancer Society Cancer Prevention Study-II (ACS CPS-II) cohort observed increased risk of death from diseases of the circulatory system (including diabetes) (HR: 1.08 [95% CI: 1.06, 1.09]), CVD (HR: 1.08 [95% CI: 1.06, 1.10]), and IHD (HR: 1.14 [95% CI: 1.11, 1.17]) associated with a 10-ppb increase in annual average NO_2 exposure estimated for the year 2006 with an LUR model at 10 km x 10 km spatial resolution (r^2 = 0.78) (Turner et al., 2016). In contrast, the authors reported null findings for deaths from dysrhythmias/heart failure/cardiac arrest (HR: 1.02 [95% CI: 0.98, 1.06]) and CBVD disease (HR: 0.99 [95% CI: 0.95, 1.02]).
- In the NIH-AARP Diet and Health Study (1995–1996), Lim et al. (2019) reported positive associations between annual averages of NO_2, estimated with a hybrid model combining kriging models and LUR methods, and mortality from CVD (HR: 1.07 [95% CI: 1.04, 1.09] per 10-ppb increase in NO_2) and IHD (HR: 1.09 [95% CI: 1.05, 1.12]). Association of NO_2 exposure with mortality from CBVD (HR: 1.02 [95% CI: 0.97, 1.09]) and cardiac arrest/heart failure (HR: 1.02 [95% CI: 0.97, 1.08]) were somewhat smaller in magnitude and less precise.
- Lefler et al. (2019) observed a positive association (HR: 1.062 [95% CI: 1.038, 1.086] per 10-ppb increase in NO_2) between annual average NO_2 and CPD mortality in a study among U.S. NHIS participants (1987 to 2014) using an LUR model to estimate NO_2 exposure.
- A few studies examined data from the Canadian Census Health and Environment Cohort (CanCHEC), which is a large national population-based cohort of non-institutionalized Canadian residents ≥ 25-years of age at baseline (Weichenthal et al., 2017; Crouse et al., 2015). These studies estimated NO_2 concentrations with LUR models (100 m x 100 m) developed from National Air Pollution Surveillance (NAPS) monitoring data. Crouse et al. (2015) evaluated data of CanCHEC participants enrolled in 1991 and reported positive associations between 7-year moving averages of NO_2 exposure with a 1-year lag and mortality from CMD (HR: 1.050 [95% CI: 1.036, 1.063] per 10-ppb increase in NO_2), CVD (HR: 1.051 [95% CI: 1.035, 1.067]), and IHD (HR: 1.078 [95% CI: 1.058, 1.099]). The association for CBVD mortality was positive but close to null and imprecise (HR: 1.005 [95% CI: 0.984, 1.026]). The authors reported effect modification of the relationship between NO_2 exposure and CMD mortality by age and sex categories, income, and immigrant status (see Section 6.8.1.2). A later study of CanCHEC participants enrolled in 2001 reported a positive association between 3-year moving averages of NO_2 exposure with 1-year lag and CVD mortality (HR: 1.056 [95% CI: 1.037, 1.075] per 10-ppb increase in NO_2) (Weichenthal et al., 2017). No apparent pattern of associations was identified in analyses stratifying by tertiles of exposure.
- In an analysis using ONPHEC data, Zhang et al. (2020) used LUR models to estimate non-tailpipe emissions (i.e., Fe and Cu in $PM_{2.5}$). ROS concentration in lung epithelial lining fluid

to account for $PM_{2.5}$ oxidative potential was calculated using Fe and Cu concentrations. 3-year moving average NO_2 concentrations were estimated using a validated LUR model (R^2 = 0.69) to conduct analyses designed to distinguish non-tailpipe from tailpipe emissions. This study observed that association between NO_2 and CVD mortality was attenuated, but remained positive, after adjustment for ROS. The HR for the association between NO_2 and CVD mortality was (1.153 [95% CI: 1.110, 1.197] per 10-ppb increase in NO_2). After adjustment for ROS, the association was (HR: 1.047 [95% CI: 1.002, 1.094]). Another ONPHEC study used NAPS LUR models and reported positive associations with CVD mortality among people with prevalent diabetes (HR: 1.038 [95% CI: 1.015, 1.062] per 10-ppb increase in NO_2) (Paul et al., 2020).

- A study using data from the Ontario Health Study (2009–2013) observed a positive association between 5-year moving averages of NO_2 and cardiovascular mortality (HR: 1.370 [95% CI: 1.202, 1.562] per 10-ppb increase in NO_2) (Zhang et al., 2021b). NO_2 exposure was estimated with an LUR model based on the NAPS (r^2 = 0.73). This result was robust in sensitivity analyses using 3- and 4-year moving averages, limiting to subcohorts of participants exposed to concentrations of NO_2 below 19.5 ppb and 17.0 ppb, adjusting for $PM_{2.5}$, and stratifying by age, sex, fruit and veggie intake, physical activity, smoking, and income.


Study
Cohort
Exposure Assessment
Period of Exposure
Follow-up
EE
EE (95% CI)
Cardiovascular Disease
Chen et al. (2013) Ontario Tax Cohort LUR 2002, 2004 avg 1982-2004 RR 1.17 (1.10, 1.23)
Jerrett et al. (2013) CPS-II LUR 1988-2002 avg 1982-2000 RR 1.12 (1.02, 1.23)
†Yu et al. (2024) NMMAPS Fixed site monitors 1-yr MA 1987-2000 RR 1.074 (1.052, 1.097)
1-yr MA, 1-yr lag 1987-2000 RR 1.058 (1.035, 1.082)
1-yr MA, 2-yr lag 1987-2000 RR 1.066 (1.042, 1.090)
1-yr MA, 3-yr lag 1987-2000 RR 1.021 (0.997, 1.046)
†Eum et al. (2019) Medicare AQS 1-yr MA 2000-2008 RR 1.133 (1.130, 1.137)
Medicare; 5-yr subset AQS 1-yr MA 2000-2008 RR 1.138 (1.135, 1.142)
2-yr MA 2000-2008 RR 1.135 (1.132, 1.139)
3-yr MA 2000-2008 RR 1.131 (1.128, 1.135)
4-yr MA 2000-2008 RR 1.125 (1.122, 1.129)
5-yr MA 2000-2008 RR 1.119 (1.121, 1.117)
†Eum et al. (2022) Medicare LUR 1-yr MA 2001-2008 RR 1.23 (1.22, 1.24)
Lipsett et al. (2011) CTS Fixed site monitors 1996-2005 avg 1997-2005 HR 0.98 (0.88, 1.09)
†Turner et al. (2016) CPS-II LUR 2006 avg 1982-2004 HR 1.08 (1.06, 1.10)
†Lim et al. (2019) NIH-AARP Diet and Health Hybrid 2002-2010 avg 1995-2011 HR 1.07 (1.05, 1.10)
†Crouse et al. (2015) CanCHEC LUR 7-yr MA; 1-yr lag 1991-2006 HR 1.051 (1.035, 1.067)
†Weichenthal et al. (2017) CanCHEC LUR 3-yr MA; 1-yr lag 1991-2011 HR 1.056 (1.037, 1.075)
†Zhang et al. (2020) ONPHEC LUR 3-yr MA; 1-yr lag 2001-2016 HR 1.153 (1.110, 1.197)
†Paul et al. (2020) ONPHEC LUR 3-yr MA 2001-2015 HR 1.038 (1.015, 1.062)
†Zhang et al. (2021) OHS LUR 5-yr MA 2009-2013 HR 1.370 (1.202, 1.562)
4-yr MA 2009-2013 HR 1.424 (1.238, 1.638)
3-yr MA 2009-2013 HR 1.495 (1.288, 1.734)
Ischemic Heart Disease
Chen et al. (2013) Ontario Tax Cohort LUR 2002, 2004 avg 1982-2004 RR 1.19 (1.08, 1.30)
Jerrett et al. (2013) CPS-II LUR 1988-2002 avg 1982-2000 RR 1.17 (1.04, 1.31)
†Eum et al. (2019) Medicare AQS 1-yr MA 2000-2008 RR 1.221 (1.217, 1.226)
†Eum et al. (2022) Medicare LUR 1-yr MA 2001-2008 RR 1.26 (1.23, 1.29)
Lipsett et al. (2011) CTS Fixed site monitors 1996-2005 avg 1997-2005 HR 1.07 (0.92, 1.24)
†Turner et al. (2016) CPS-II LUR 2006 avg 1982-2004 HR 1.14 (1.11, 1.17)
†Lim et al. (2019) NIH-AARP Diet and Health Hybrid 2002-2010 avg 1995-2011 HR 1.09 (1.06, 1.13)
†Crouse et al. (2015) CanCHEC LUR 7-yr MA; 1-yr lag 1991-2006 HR 1.078 (1.058, 1.099)
Cerebrovascular Disease
Chen et al. (2013) Ontario Tax Cohort LUR 2002, 2004 avg 1982-2004 RR 0.92 (0.79, 1.08)
†Eum et al. (2019) Medicare AQS 1-yr MA 2000-2008 RR 1.092 (1.085, 1.100)
†Eum et al. (2022) Medicare LUR 1-yr MA 2001-2008 RR 1.25 (1.22, 1.28)
Lipsett et al. (2011) CTS Fixed site monitors 1996-2005 avg 1997-2005 HR 0.86 (0.71, 1.06)
†Turner et al. (2016) CPS-II LUR 2006 avg 1982-2004 HR 0.99 (0.96, 1.03)
†Lim et al. (2019) NIH-AARP Diet and Health Hybrid 2002-2010 avg 1995-2011 HR 1.02 (0.96, 1.08)
†Crouse et al. (2015) CanCHEC LUR 7-yr MA; 1-yr lag 1991-2006 HR 1.005 (0.984, 1.026)
Coronary Heart Disease
Gan et al. (2011) Vancouver BC PHIP LUR 1994-1998 avg 1999-2002 RR 1.09 (1.01, 1.18)
1.08 (1.03, 1.14)
Circulatory Disease
Jerrett et al. (2009) OHIP LUR 2002, 2004 avg 1992-2002 RR 2.53 (1.26, 5.08)
†Turner et al. (2016) CPS-II LUR 2006 avg 1982-2004 HR 1.08 (1.07, 1.10)
Cardiopulmonary Disease
Krewski et al. (2000) HSC Central site monitors 1977-1985 1974-1989 RR 1.17 (1.02, 1.34)
CPS-II Central site monitors 1982, Apr-Sep 1982-1989 RR 0.98 (0.95, 1.02)
1982, Oct-Mar 1982-1989 RR 0.98 (0.96, 1.00)
†Lefler et al. (2019) NHIS LUR 1-yr MA 1987-2015 HR 1.062 (1.038, 1.086)
Cardiometabolic Disease
†Crouse et al. (2015) CanCHEC LUR 7-yr MA; 1-yr lag 1991-2006 HR 1.050 (1.036, 1.063)
Stroke
Jerrett et al. (2013) CPS-II LUR 1988-2002 avg 1982-2000 RR 1.20 (1.04, 1.39)
HF/Dysrythmia/Cardiac Arrest
†Eum et al. (2019) Medicare AQS 1-yr MA 2000-2008 RR 0.903 (0.893, 0.914)
†Eum et al. (2022) Medicare LUR 1-yr MA 2001-2008 RR 1.16 (1.12, 1.21)
†Turner et al. (2016) CPS-II LUR 2006 avg 1982-2004 HR 1.02 (0.98, 1.06)
†Lim et al. (2019) NIH-AARP Diet and Health Hybrid 2002-2010 avg 1995-2011 HR 1.02 (0.97, 1.08)
0.8 1 1.2 1.4 1.6 1.8 2 2.2 2.4 2.6 2.8
Risk or Hazard Ratios (95% CI)

List of abbreviations in alphabetical order: AQS = Air Quality System; avg = average; BC PHIP = British Columbia Provincial Health Insurance Plan; CI = confidence interval; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CPS-II = American Cancer Society Cancer Prevention Study-II; CTS = California Teachers Study; EE = effect estimate; HR = hazard ratio; HSC = Harvard Six Cities study; LUR = land use regression; MA = moving average; NHIS = National Health Interview Survey; NIH-AARP = National Institutes of Health American Association of Retired Persons; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; OHIP = Ontario Health Insurance Plan; OHS = Ontario Health Study; ONPHEC = Ontario Population Health and Environment Cohort; RR = risk ratio; VCMS = Veterans' Cohort Mortality Study; yr= year.
Notes: Results are standardized to a 10-ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-29 Associations between long-term exposure to NO_2 and cardiovascular mortality in North American cohorts.

Several studies of European cohorts likewise presented mostly positive risk estimates for the relationship between NO_2 and NO_X exposure and cardiovascular mortality (see Figure 6-30). A majority of these studies evaluated cohorts from the ESCAPE or ELAPSE projects.

- A few recent studies conducted extensive analyses of cohorts in the ELAPSE project. A report focusing on the health effects of low-level pollution (i.e., concentrations below current international guidelines) (Brunekreef et al., 2021) analyzed two sets of data from 11 countries, including eight traditional cohorts with over 28 million adults and seven large administrative cohorts with over 325,000 participants total. Strak et al. (2021) evaluated only the eight traditionally established cohorts while Stafoggia et al. (2022) evaluated only the seven administrative cohorts. These studies assessed exposure to NO_2 using hybrid models for 2010 at a 100 meter x 100 meter spatial resolution. Within the traditional cohorts, the HRs per 10-ppb increase in NO_2 for CVD mortality, IHD mortality, CBVD, and CMD mortality were 1.174 (95% CI: 1.115, 1.236), 1.192 (95% CI: 1.102, 1.290), 1.132 (95% CI: 1.020, 1.256), and 1.192 (95% CI: 1.134, 1.254), respectively. The association of long-term NO_2 exposure with CVD mortality also persisted after adjustment for noise, which was available for approximately 30% of the full population (i.e., Stockholm, two Danish, and two German cohorts). The association for CVD mortality in this subset of the data was 1.116 (95% CI: 1.024, 1.216) in the single-pollutant model and 1.102 (95% CI: 0.999, 1.216) after adjustment for noise. Within the administrative cohorts, the HR for the association between NO_2 exposure and CVD mortality was 1.048 (95% CI: 1.012, 1.085) per 10-ppb increase in NO_2. This estimate remained positive when analysis was restricted to concentrations below 40 $\mu g/m^3$ (21.3 ppb) of NO_2 (based on the WHO 2005 air quality guideline for NO_2) (HR: 1.057 [95% CI: 1.020, 1.096]) and below 20 $\mu g/m^3$ (10.6 ppb) (HR: 1.075 [95% CI: 0.961, 1.201]).
- A study in a Danish national administrative cohort examined cardiovascular mortality risk associated with annual average NO_2 concentrations estimated for the year 2010 using the ESCAPE LUR model and a back-and-forward extrapolation method based on the chemical transport Danish Eulerian Hemispheric Model (DEHM) (So et al., 2022). The risk of cardiovascular mortality was slightly attenuated in the analysis using back-extrapolated time-varying exposure compared to the estimate using the LUR model (HR: 1.02 [95% CI: 1.00, 1.04] vs. 1.08 [95% CI: 1.06, 1.10] per 10-ppb increase in NO_2). For IHD and stroke mortality, estimates were positive (HR IHD: 1.08 [95% CI: 1.05, 1.11]; HR stroke: 1.04 [95% CI: 1.00, 1.08]) and attenuated to the null (HR IHD: 0.98 [95% CI: 0.96, 1.00]; HR stroke: 0.98 [95% CI: 0.96, 1.00]) using back-extrapolated exposure. In low exposure analyses, estimates were strongest when exposure was restricted to the lowest category (<20 $\mu g/m^3$, or

approximately 10.6 ppb) for mortality from CVD (HR: 1.34 [95% CI: 1.29, 1.40]), IHD (HR: 1.43 [95% CI: 1.35, 1.52]), and stroke (HR: 1.39 [95% CI: 1.30, 1.48]).

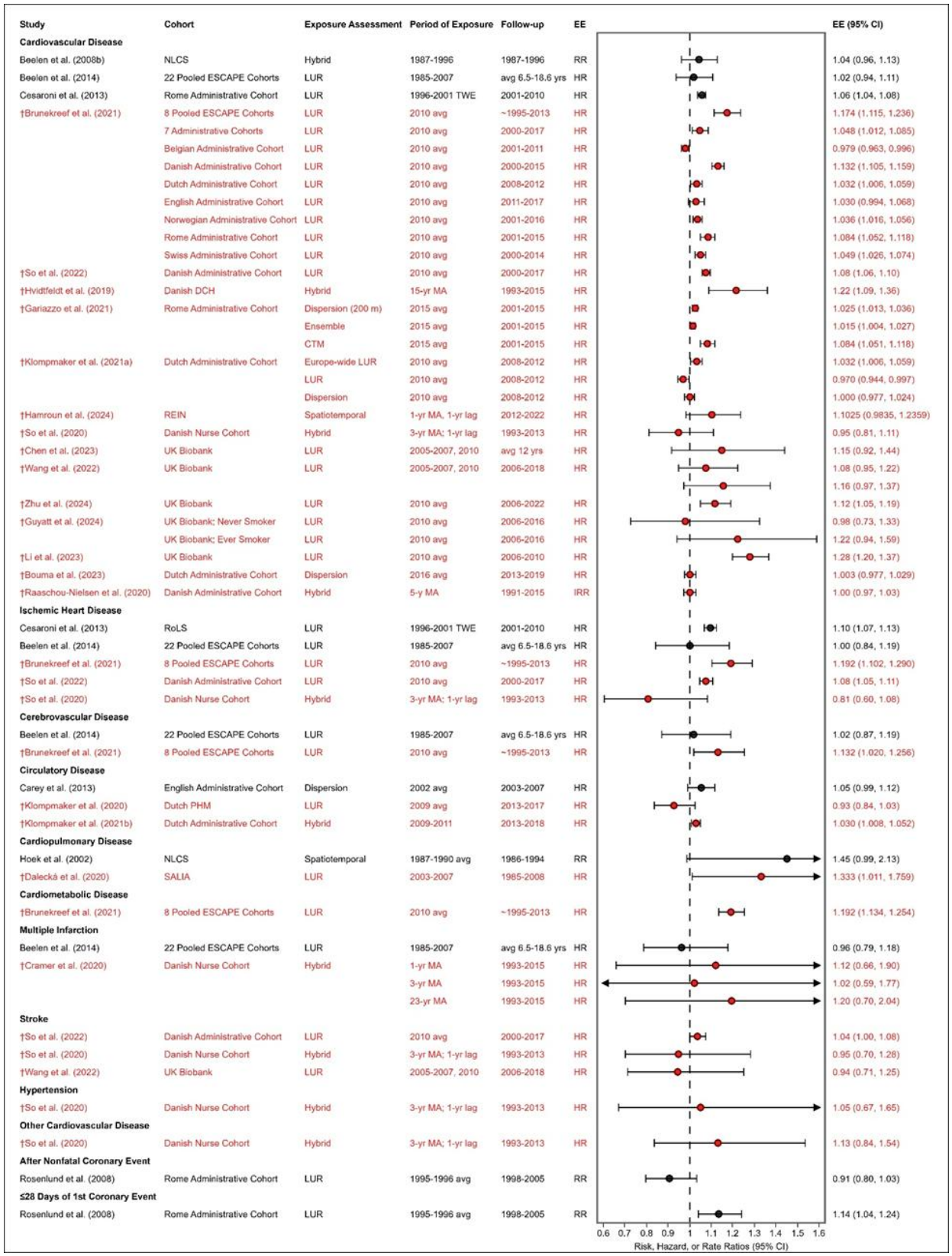
- Hvidtfeldt et al. (2019) reported positive associations among participants in the Danish Diet, Cancer and Health (DCH) study between 15-year moving averages of NO_2 and CVD mortality in single (HR: 1.22 [95% CI: 1.09, 1.36] per 10-ppb increase in NO_2) and two-pollutant analyses with noise (HR: 1.22 [95% CI: 0.98, 1.52]). NO_2 exposure was estimated with a hybrid model combining the DEHM, UBM, OSPM, and GIS. Stronger associations were observed in men and among current smokers (see Section 6.8.1.2). Positive associations remained robust using exposure at baseline and at different moving averages of NO_2 exposure (1-, 5-, and 10-years).
- A study using data from the Rome Longitudinal Study (RoLS) reported consistently increased risks for CVD mortality in association with NO_2 annual means estimated with a chemical transport model (HR: 1.084 [95% CI: 1.051, 1.118] per 10-ppb increase in NO_2), machine learning model (HR: 1.015 [95% CI: 1.004, 1.027]), and dispersion model (HR: 1.025 [95% CI: 1.013, 1.036]) with 1 km, 200 m, and 200 m spatial resolutions, respectively (Gariazzo et al., 2021).
- Recent studies of Dutch national administrative cohorts (derived from Statistics Netherlands in 2008 and 2013) compared results across three exposure assessment methods: 1) a national LUR model (5 m x 5 m) and 2) a Europe-wide LUR model that combined satellite measurements and chemical transport model predictions with a classical LUR (100 m x 100 m), both developed using the ESCAPE protocol, and 3) a national dispersion model that combined long-distance transport and local scale road traffic emissions (25 m x 25 m) (Klompmaker et al., 2021b; Klompmaker et al., 2021c). Klompmaker et al. (2021b) reported a positive association between annual averages of NO_2 and cardiovascular mortality using the Europe-wide LUR model (HR: 1.03 [95% CI: 1.01, 1.06] per 10-ppb increase in NO_2) while results were null using either the national LUR model (HR: 0.97 [95% CI: 0.94, 1.00]) or the dispersion model (HR: 1.00 [95% CI: 0.98, 1.02]). Differences in spatial resolution and measurement error between the models may help explain some of the discrepancies in associations based on the three models. For example, the Europe-wide LUR model had a coarser resolution compared to the national LUR and dispersion models. However, the two LUR models were validated with different methods and used different numbers of measurement sites, making model performance comparisons difficult. Klompmaker et al. (2021c) furthermore reported a positive association between NO_2 annual averages based on the average of the three exposure models and circulatory disease mortality (HR: 1.03 [95% CI: 1.01, 1.05] per 10-ppb increase in NO_2).
- Dalecká et al. (2021) evaluated lung function-mediated associations between CPD mortality and annual average NO_2 and NO_X estimated with the ESCAPE LUR model among women aged 51-66-years at baseline in the large multi-city SALIA cohort in Germany. In particular, the authors mediated the association by reduced forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC combined as metrics of reduced lung function. The authors reported positive associations for the direct (HR NO_2: 1.333 [95% CI: 1.011, 1.759] per 10 ppb NO_2; HR NO_X: 1.306 [95% CI: 0.977, 1.589] per 46 $\mu g/m^3$ NO_X), indirect (HR NO_2: 1.040 [95% CI: 1.002, 1.079]; HR NO_X: 1.027, [95% CI: 1.006, 1.055]), and total (HR NO_2: 1.386 [95% CI: 1.051, 1.828]; HR NO_X: 1.340 [95% CI: 1.017, 1.636]) effects of NO_2 and NO_X on CPD mortality, suggesting that lung function may mediate this relationship.
- Hamroun et al. (2024) reported a positive imprecise association (HR: 1.1025 [95% CI: 0.9835, 1.2359] per 10-ppb NO_2) between annual moving averages of NO_2 exposure with 1-

year lag and CVD mortality within a national registry of end-stage renal disease patients receiving maintenance dialysis in France. Estimates were similar using lags of 2- or 3-years.

- A handful of UK Biobank cohort studies examined associations with NO_2 and NO_X estimated with the ESCAPE hybrid model (Tao et al., 2024; Zhu et al., 2024; Chen et al., 2023; Li et al., 2023; Wang et al., 2022) or LUR models using AirBase monitoring data. Li et al. (2023) reported an HR of 1.28 (95% CI: 1.20, 1.37) for CVD mortality per 10-ppb increase in annual average NO_2 exposure and an HR of 1.05 (95% CI: 1.04, 1.07 per 10 $\mu g/m^3$) for the association between annual average NO_X and CVD mortality. There was little statistical evidence that sex, age, ethnicity and obesity modified these associations. Wang et al. (2022) reported imprecise positive associations with mortality from CVD (HR: 1.08 [95% CI: 0.95, 1.22]) and CHD (HR: 1.16 [95% CI: 0.97, 1.37]), but not with stroke (HR: 0.94 [95% CI: 0.71, 1.25]), per 10-ppb increase in NO_2. This study had a shorter follow-up period compared to Li et al. (2023) (median 8.1 versus 12-years) and accrued fewer CVD deaths. The associations with NO_X were somewhat smaller but exhibited the same pattern. Chen et al. (2023) examined the association of CVD mortality among those with inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC). The authors reported HRs of 1.15 (95% CI: 0.92, 1.44), 0.98 (95% CI: 0.71, 1.35), and 1.17 (95% CI: 0.79, 1.72) per 10-ppb increase in NO_2, and HRs of 1.22 (95% CI: 1.02, 1.47), 1.03 (95% CI: 0.74, 1.43), and 1.31 (95% CI: 1.04, 1.64) per 15.6 $\mu g/m^3$ increase in NO_X, for CVD mortality among those with IBD, CD, and UC, respectively. Zhu et al. (2024) likewise reported increased risk of total mortality from NO_2 (HR: 1.12 [95% CI: 1.05, 1.19] per 10-ppb) and NO_X (HR: 1.06 [95% CI: 1.03, 1.05] per 16.55 $\mu g/m^3$). Tao et al. (2024) reported a positive imprecise association between annual average NO_2 and CVD mortality among English participants of the UK Biobank (HR: 1.026 [95% CI: 0.994, 1.059] per 1 SD [NR] increase in NO_2). Guyatt et al. (2024) observed a null association between NO_2 and CVD mortality in never smokers (HR: 0.98 [95% CI: 0.73, 1.33] per 10-ppb increase in NO_2) and a positive association in ever smokers (HR: 1.22 [95% CI: 0.94, 1.59]). $PM_{2.5}$, NO_2, NO_X and PM_{10} were highly correlated with each other in these studies (Pearson $\rho = 0.50–0.87$), making it challenging to disentangle the individual effects of NO_2 or NO_X on CVD mortality.
- In an analysis of the Danish Nurse Cohort (DNC) (enrolled in 1993 and 1999), Cramer et al. (2020) examined the association between residential NO_2 and NO_X concentrations (1-, 3-, and 23-year running averages) and fatal MI. The HRs per 10-ppb increase in 1-, 3-, and 23-year mean NO_2 and fatal MI were 1.12 (95% CI: 0.66, 1.90), 1.02 (95% CI: 0.59, 1.77) and 1.20 (95% CI: 0.70, 2.04), respectively. Associations with NO_X were generally weaker. The HRs were stronger after adjustment for noise for all averaging times (HR: 1.20 [95% CI: 0.68, 2.10], 1.12 [95% CI: 0.62, 2.01], and 1.30 [95% CI: 0.73, 2.32] for 1-, 3-, and 23-year running averages, respectively).
- Raaschou-Nielsen et al. (2020) evaluated long-term NO_2 exposure and mortality in an administrative cohort (born 1921-1985) of all persons who lived in Denmark sometime since April 1968 and were followed up for mortality outcomes in 1991-2015. Exposure was estimated using a dispersion model combining predictions from regional background (DEHM) and local (UBM) emissions at a 1 km x 1 km spatial resolution. Model predictions for NO_2 showed good agreement with measured concentrations at monitoring stations in Denmark ($r^2 = 0.87$). Raaschou-Nielsen et al. (2020) reported an HR of 1.00 (95% CI: 0.97, 1.03) for the association between 5-year moving average NO_2 exposure and CVD mortality, taking changes in residence into account with time-weighted averages of exposure.
- In an analysis of the DNC, So et al. (2020) applied spatiotemporal inputs from the AirGIS air pollution model to the DEHM/UBM model to create a hybrid model with correlation coefficients ranging from 0.80 to 0.84 for annual average NO_2, regionally. The authors

reported an imprecise HR of 0.95 (95% CI: 0.81, 1.11) per 10-ppb increase in NO_2 for the association between 3-year moving averages of NO_2 with 1-year lag and CVD mortality. Associations remained imprecise in analyses stratified by subtype of CVD (HR IHD: 0.81 [95% CI: 0.60, 1.08]; HR stroke: 0.95 [95% CI: 0.70, 1.28]; HR hypertension: 1.05 [95% CI: 0.67, 1.65]; HR other CVD: 1.13 [95% CI: 0.84, 1.54]).

- Klompmaker et al. (2020) and Bouma et al. (2023) used an ESCAPE LUR model with 100 m^2 spatial resolution and a dispersion model with 10 m^2 spatial resolution, respectively, in small national cohorts in the Netherlands. In the Klompmaker et al. (2020) study, the association of NO_2 with death from diseases of the circulatory system was null. Likewise, Bouma et al. (2023) reported a null association with CVD mortality.


Study
Cohort
Exposure Assessment
Period of Exposure
Follow-up
EE
EE (95% CI)
Cardiovascular Disease
Beelen et al. (2008b) NLCS Hybrid 1987-1996 1987-1996 RR 1.04 (0.96, 1.13)
Beelen et al. (2014) 22 Pooled ESCAPE Cohorts LUR 1985-2007 avg 6.5-18.6 yrs HR 1.02 (0.94, 1.11)
Cesaroni et al. (2013) Rome Administrative Cohort LUR 1996-2001 TWE 2001-2010 HR 1.06 (1.04, 1.08)
†Brunekreef et al. (2021) 8 Pooled ESCAPE Cohorts LUR 2010 avg ~1995-2013 HR 1.174 (1.115, 1.236)
7 Administrative Cohorts LUR 2010 avg 2000-2017 HR 1.048 (1.012, 1.085)
Belgian Administrative Cohort LUR 2010 avg 2001-2011 HR 0.979 (0.963, 0.996)
Danish Administrative Cohort LUR 2010 avg 2000-2015 HR 1.132 (1.105, 1.159)
Dutch Administrative Cohort LUR 2010 avg 2008-2012 HR 1.032 (1.006, 1.059)
English Administrative Cohort LUR 2010 avg 2011-2017 HR 1.030 (0.994, 1.068)
Norwegian Administrative Cohort LUR 2010 avg 2001-2016 HR 1.036 (1.016, 1.056)
Rome Administrative Cohort LUR 2010 avg 2001-2015 HR 1.084 (1.052, 1.118)
Swiss Administrative Cohort LUR 2010 avg 2000-2014 HR 1.049 (1.026, 1.074)
†So et al. (2022) Danish Administrative Cohort LUR 2010 avg 2000-2017 HR 1.08 (1.06, 1.10)
†Hvidtfeldt et al. (2019) Danish DCH Hybrid 15-yr MA 1993-2015 HR 1.22 (1.09, 1.36)
†Gariazzo et al. (2021) Rome Administrative Cohort Dispersion (200 m) 2015 avg 2001-2015 HR 1.025 (1.013, 1.036)
Ensemble 2015 avg 2001-2015 HR 1.015 (1.004, 1.027)
CTM 2015 avg 2001-2015 HR 1.084 (1.051, 1.118)
†Klompmaker et al. (2021a) Dutch Administrative Cohort Europe-wide LUR 2010 avg 2008-2012 HR 1.032 (1.006, 1.059)
LUR 2010 avg 2008-2012 HR 0.970 (0.944, 0.997)
Dispersion 2010 avg 2008-2012 HR 1.000 (0.977, 1.024)
†Hamroun et al. (2024) REIN Spatiotemporal 1-yr MA, 1-yr lag 2012-2022 HR 1.1025 (0.9835, 1.2359)
†So et al. (2020) Danish Nurse Cohort Hybrid 3-yr MA; 1-yr lag 1993-2013 HR 0.95 (0.81, 1.11)
†Chen et al. (2023) UK Biobank LUR 2005-2007, 2010 avg 12 yrs HR 1.15 (0.92, 1.44)
†Wang et al. (2022) UK Biobank LUR 2005-2007, 2010 2006-2018 HR 1.08 (0.95, 1.22)
1.16 (0.97, 1.37)
†Zhu et al. (2024) UK Biobank LUR 2010 avg 2006-2022 HR 1.12 (1.05, 1.19)
†Guyatt et al. (2024) UK Biobank; Never Smoker LUR 2010 avg 2006-2016 HR 0.98 (0.73, 1.33)
UK Biobank; Ever Smoker LUR 2010 avg 2006-2016 HR 1.22 (0.94, 1.59)
†Li et al. (2023) UK Biobank LUR 2010 avg 2006-2010 HR 1.28 (1.20, 1.37)
†Bouma et al. (2023) Dutch Administrative Cohort Dispersion 2016 avg 2013-2019 HR 1.003 (0.977, 1.029)
†Raaschou-Nielsen et al. (2020) Danish Administrative Cohort Hybrid 5-y MA 1991-2015 IRR 1.00 (0.97, 1.03)
Ischemic Heart Disease
Cesaroni et al. (2013) RoLS LUR 1996-2001 TWE 2001-2010 HR 1.10 (1.07, 1.13)
Beelen et al. (2014) 22 Pooled ESCAPE Cohorts LUR 1985-2007 avg 6.5-18.6 yrs HR 1.00 (0.84, 1.19)
†Brunekreef et al. (2021) 8 Pooled ESCAPE Cohorts LUR 2010 avg ~1995-2013 HR 1.192 (1.102, 1.290)
†So et al. (2022) Danish Administrative Cohort LUR 2010 avg 2000-2017 HR 1.08 (1.05, 1.11)
†So et al. (2020) Danish Nurse Cohort Hybrid 3-yr MA; 1-yr lag 1993-2013 HR 0.81 (0.60, 1.08)
Cerebrovascular Disease
Beelen et al. (2014) 22 Pooled ESCAPE Cohorts LUR 1985-2007 avg 6.5-18.6 yrs HR 1.02 (0.87, 1.19)
†Brunekreef et al. (2021) 8 Pooled ESCAPE Cohorts LUR 2010 avg ~1995-2013 HR 1.132 (1.020, 1.256)
Circulatory Disease
Carey et al. (2013) English Administrative Cohort Dispersion 2002 avg 2003-2007 HR 1.05 (0.99, 1.12)
†Klompmaker et al. (2020) Dutch PHM LUR 2009 avg 2013-2017 HR 0.93 (0.84, 1.03)
†Klompmaker et al. (2021b) Dutch Administrative Cohort Hybrid 2009-2011 2013-2018 HR 1.030 (1.008, 1.052)
Cardiopulmonary Disease
Hoek et al. (2002) NLCS Spatiotemporal 1987-1990 avg 1986-1994 RR 1.45 (0.99, 2.13)
†Dalecká et al. (2020) SALIA LUR 2003-2007 1985-2008 HR 1.333 (1.011, 1.759)
Cardiometabolic Disease
†Brunekreef et al. (2021) 8 Pooled ESCAPE Cohorts LUR 2010 avg ~1995-2013 HR 1.192 (1.134, 1.254)
Multiple Infarction
Beelen et al. (2014) 22 Pooled ESCAPE Cohorts LUR 1985-2007 avg 6.5-18.6 yrs HR 0.96 (0.79, 1.18)
†Cramer et al. (2020) Danish Nurse Cohort Hybrid 1-yr MA 1993-2015 HR 1.12 (0.66, 1.90)
3-yr MA 1993-2015 HR 1.02 (0.59, 1.77)
23-yr MA 1993-2015 HR 1.20 (0.70, 2.04)
Stroke
†So et al. (2022) Danish Administrative Cohort LUR 2010 avg 2000-2017 HR 1.04 (1.00, 1.08)
†So et al. (2020) Danish Nurse Cohort Hybrid 3-yr MA; 1-yr lag 1993-2013 HR 0.95 (0.70, 1.28)
†Wang et al. (2022) UK Biobank LUR 2005-2007, 2010 2006-2018 HR 0.94 (0.71, 1.25)
Hypertension
†So et al. (2020) Danish Nurse Cohort Hybrid 3-yr MA; 1-yr lag 1993-2013 HR 1.05 (0.67, 1.65)
Other Cardiovascular Disease
†So et al. (2020) Danish Nurse Cohort Hybrid 3-yr MA; 1-yr lag 1993-2013 HR 1.13 (0.84, 1.54)
After Nonfatal Coronary Event
Rosenlund et al. (2008) Rome Administrative Cohort LUR 1995-1996 avg 1998-2005 RR 0.91 (0.80, 1.03)
≤28 Days of 1st Coronary Event
Rosenlund et al. (2008) Rome Administrative Cohort LUR 1995-1996 avg 1998-2005 RR 1.14 (1.04, 1.24)
0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5 1.6
Risk, Hazard, or Rate Ratios (95% CI)

List of abbreviations in alphabetical order: avg = average; CI = confidence interval; DCH = Diet, Cancer, and Health; EE = effect estimate; EPIC-NL = European Prospective Investigation into Cancer and Nutrition in the Netherlands; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ratio; IRR = incidence rate ratio; LUR = land use regression; m = meter; MA = moving average; NLCS = Netherlands Cohort Study on Diet and Cancer; PHM = Public Health Monitor; REIN = Renal Epidemiology and Information Network; RHINE = Respiratory Health in Northern Europe; RoLS = Rome Longitudinal Study; RR = risk ratio; SALIA = Study on the influence of Air pollution on Lung function, Inflammation and Ageing; TWE = time-weighted exposure; yr= year.
Notes: Results are standardized to a 10-ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-30 Associations between long-term exposure to NO_2 and cardiovascular mortality in European cohorts.

A single recent Chinese study provided evidence supporting a positive association between long-term NO_2 exposure and CVD mortality while a single study in South Korea observed mostly null associations for the relationship between 1-year, 3-year, and 5-year average NO_2 and mortality from CVD, CBVD, and hypertension.

- A recent study conducted in 4 cities in Northern China reported a positive association between CVD mortality and annual averages of NO_2 exposure assessed by a machine learning ensemble model (cross-validation r^2 = 0.80–0.93) combining ground measurements, satellite retrievals, emissions, chemical transport model simulations, and other sources (10 km x 10 km) (HR: 1.54 [95% CI: 1.44, 1.65]) (Huang et al., 2023). Associations were stronger for male participants. Correlations of NO_2 with PM_{10}, $PM_{2.5}$, and SO_2 were very low in this cohort (Spearman ρ = 0.06, 0.03, and 0.36, respectively). Associations were similar after adjustment for O_3, applying inverse probability weighted (IPW), and using exposures across different lag years (lag 0–1 to 0–5-year).
- Kang et al. (2023) used a geospatial kriging model at 0.01° × 0.01° (approximately 10 km^2) to estimate exposure for participants in the South Korean National Health Interview Survey. Associations with annual averages of NO_2 were null for CVD mortality, CBVD mortality, and hypertension-related morality. The authors repeated analyses using longer averaging times (3- and 5-year moving averages) and reported an inverse association for CBVD mortality per 10-ppb increase in 5-year moving average NO_2 exposure (HR: 0.883 [95% CI: 0.793, 0.983]).

6.8.1.1 Concentration-Response

An important consideration in characterizing the association between long-term NO_2 exposure and cardiovascular mortality is whether the concentration-response relationships are linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. A few recent studies have employed spline models, SCHIFs, and subset analyses to explore the nature of the relationship between NO_2 and cardiovascular mortality across the NO_2 concentration distribution. SCHIF models allow for a variety of monotonically non-decreasing shapes and minimizes unrealistic wiggling of the curve, which makes it well-suited for health impact assessments. Table 6-13 and Figure 6-31 through Figure 6-37 below summarize analyses of concentration-response relationships from recent studies.

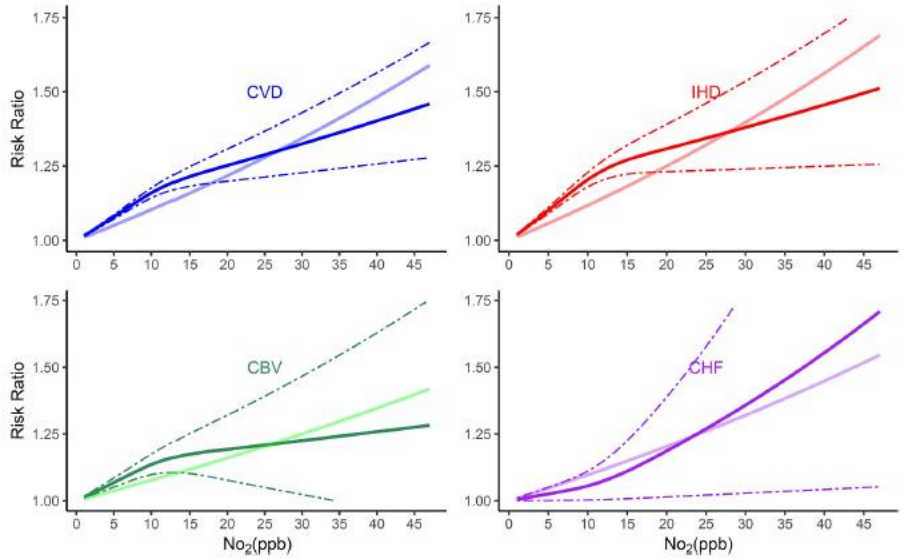
Table 6-13 Summary of epidemiologic studies examining the concentration-response relationship or conducting threshold analyses for long-term exposure to oxides of nitrogen and cardiovascular mortality: North American studies and Effects of Low-Level Air Pollution: A Study in Europe Project

Study Location-Cohort	Outcome(s)	Exposure Mean (Range)	Statistical Analysis Summary
†Eum et al. (2022) Medicare, U.S.	CVD IHD CBVD CHF	10.90 (1.03–47.04)	Restricted cubic splines with 3 knots, performance evaluated by BIC criteria
†Zhang et al. (2021b) Ontario Health Study Canada	CVD	10.9 (IQR: 6.5–14.4)	SCHIF to derive an ensemble model using weighted average of all shapes (weights defined by likelihood function).
†Paul et al. (2020) ONPHEC Canada	CVD (among those with prevalent diabetes)	18.2 (IQR: 13.8)	SCHIF to derive an ensemble model using weighted average of all shapes (weights defined by likelihood function).
†Brunekreef et al. (2021) & †Strak et al. (2021) Pooled Cohort Analysis	CVD	13.0 (1.4–43.1)	Multiple methods: natural cubic splines with 4 knots using AIC/BIC to evaluate goodness of fit. Penalized splines using AIC for optimal smoothing. SCHIF optimal and ensemble models to evaluate range of functions with plausible shapes, ensemble model weighted by likelihood function.
†Brunekreef et al. (2021) Belgian national administrative cohort	CVD	16.2 (3.9–49.8)	Natural cubic splines with 4 knots.
†Brunekreef et al. (2021) Danish national administrative cohort	CVD	10.8 (IQR: 7.8–13.2)	Natural cubic splines with 4 knots.
†Brunekreef et al. (2021) Dutch national administrative cohort	CVD	16.7 (IQR: 14.2–19.1)	Natural cubic splines with 4 knots.
†Brunekreef et al. (2021) English national administrative cohort	CVD	16.2 (1.6–38.6)	Natural cubic splines with 4 knots.
†Brunekreef et al. (2021) Norwegian national administrative cohort	CVD	8.1 (0.1–31.7)	Natural cubic splines with 4 knots.
†Brunekreef et al. (2021) Swiss national administrative cohort	CVD	12.6 (0.9–44.1)	Natural cubic splines with 4 knots.
†Brunekreef et al. (2021) Roman administrative cohort	CVD	17.5 (5.4–35.0)	Natural cubic splines with 4 knots.

List of abbreviations in alphabetical order: AIC = Akaike information criterion; BIC = Bayesian information criteria; CHF = congestive heart failure; CVD = cardiovascular disease; ELAPSE = Effects of Low-Level Air Pollution = A Study in Europe; IHD = ischemic heart disease; SCHIF = Shape Constrained Health Impact Function.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Several United States and Canadian studies examined the concentration-response relationship between NO_2 exposure and cardiovascular mortality outcomes.

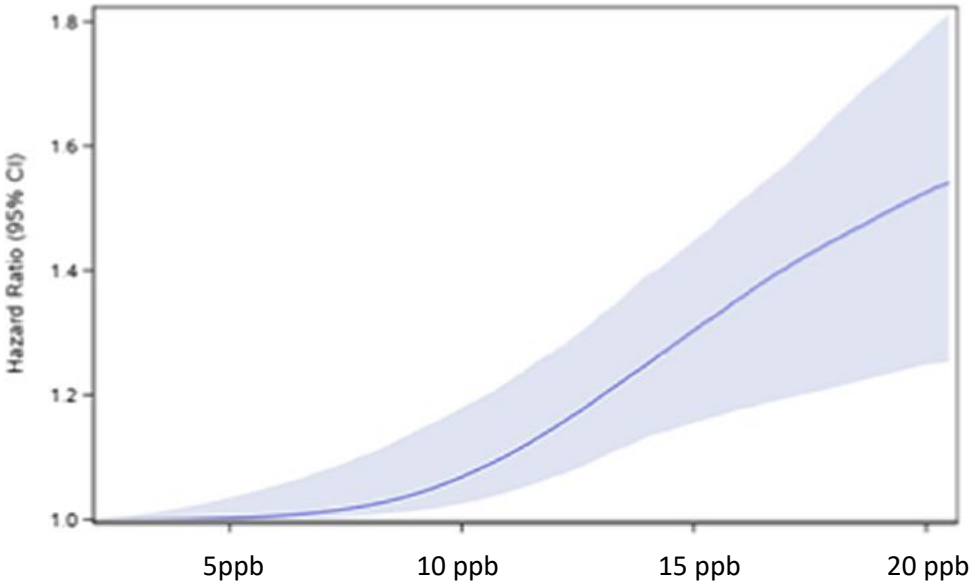
- Using the U.S. NMMAPS database, Yu et al. (2024) observed a sublinear curve for CVD mortality with a much flatter positive slope below the 75th percentile (approximately 25 ppb) of NO_2 concentrations in a natural cubic spline model with 3 degrees of freedom.
- In a study of Medicare enrollees, 65-years or older, Eum et al. (2022) examined the C-R relationship between 12-month moving average NO_2 exposure and cardiovascular mortality (see Figure 6-31). Analyses were modelled with strata for sex, race, age and zip code, with zip code- and state-level SES as covariates included. The C-R relationships were supra-linear for CVD, IHD, and CVB with greater increases in HRs at lower NO_2 concentrations (i.e., <approximately 12 ppb). The C-R relationship for CHF was approximately linear or sublinear.



List of abbreviations in alphabetical order: CBV = cerebral blood volume; CHF = congestive heart failure; CVD = cardiovascular disease; IHD = ischemic heart disease; NO_2 = nitrogen dioxide; ppb = parts per billion.
Note: The solid bold line represents the non-linear relationship estimated using restricted cubic spline, the dotted line represents the 95% confidence interval for the non-linear association, and the muted solid line represents the linear association.
Source: Eum et al. (2022). Copyright permission pending.

Figure 6-31 Concentration-response relationship between 12-month moving average NO_2 exposure and cardiovascular cause-specific mortality.

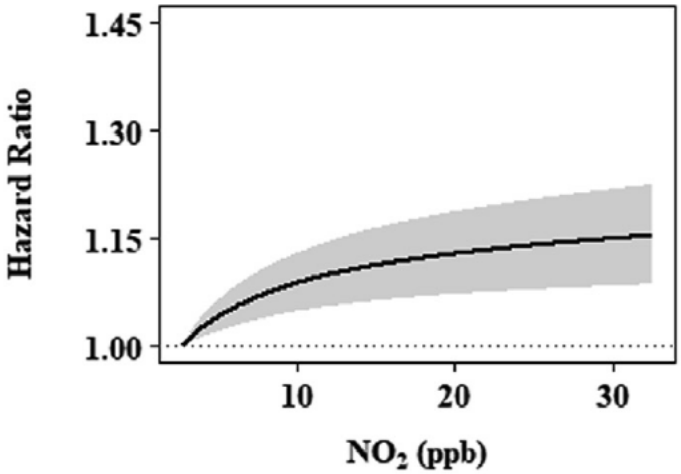
- In a Canadian study, Zhang et al. (2021b) used a SCHIF to model nonlinearity in the relationship between 5-year moving averages of NO_2 and cardiovascular mortality. The shape of the C-R function was sublinear, i.e., the curve was steeper at mid-range concentrations and a flatter slope below 10 ppb NO_2 concentration (see Figure 6-32).



List of abbreviations in alphabetical order: CI = confidence interval; ppb = parts per billion.
Source: Adapted from Zhang et al. (2021b). Copyright permission pending.

Figure 6-32 Concentration-response relationships between NO_2 5-year moving averages and cardiovascular mortality estimated using SCHIF. The concentration-response curves are presented as solid lines with 95% uncertainty bounds (shaded area).

- In another Canadian study, Paul et al. (2020) examined associations between 3-year moving average NO_2 exposure and CVD mortality among people with prevalent diabetes who were enrolled in ONPHEC. The C-R relationship was supralinear, with steeper increases in HRs at lower concentrations (see Figure 6-33).

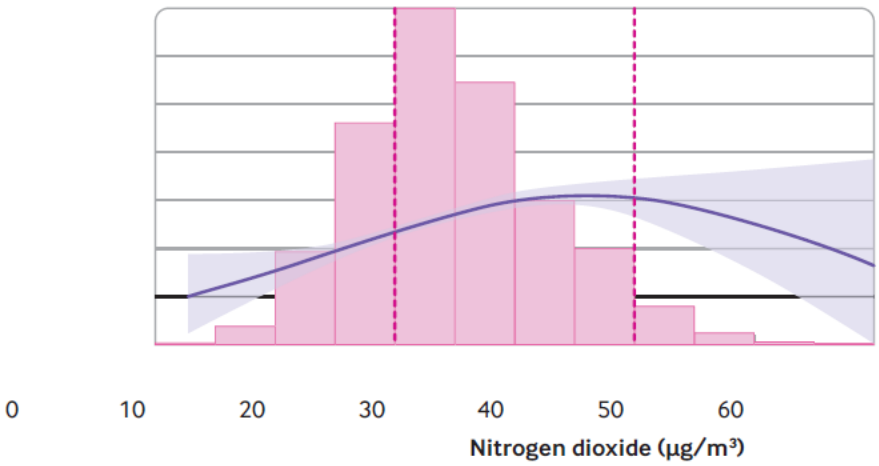


List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Source: Paul et al. (2020). Copyright permission pending.

Figure 6-33 Concentration-response relationship for the SCHIF derived ensemble models for the association between 3-year moving average NO_2 exposure and cardiovascular mortality among those with prevalent diabetes.

Extensive analyses of effects of long-term exposure to low-level pollution (i.e., concentrations below current international guidelines) on cardiovascular mortality, including comparisons of various methodological approaches were conducted for the ELAPSE project. These analyses were compiled in an HEI report (Brunekreef et al., 2021). Cohorts from seven countries with individual level data including lifestyle characteristics that could be pooled for the analysis were selected. In addition, the authors analyzed data from national administrative databases representing more than 28 million participants across Europe. Because the individual level covariates collected in these databases varied each individual cohort was analyzed separately. Findings related to the C-R relationship between NO_2 exposure and cardiovascular mortality are summarized below:

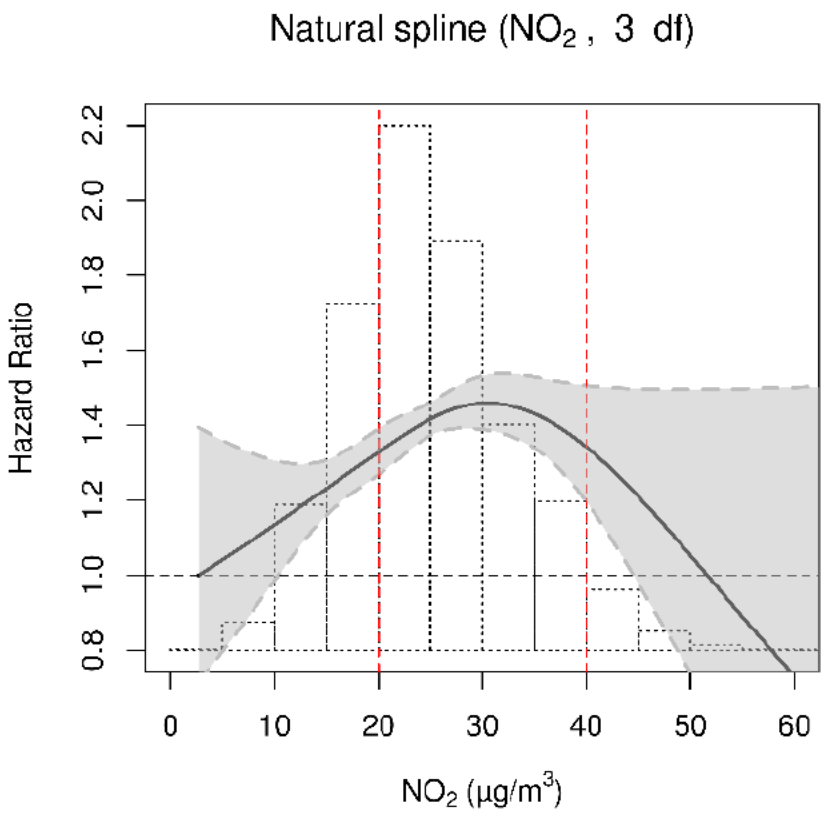
- Brunekreef et al. (2021) and Strak et al. (2021) summarized selected results for cause-specific mortality for the pooled cohorts. The C-R function using natural cubic splines with 3 degrees of freedom for associations between exposure to NO_2 and CVD mortality is in Figure 6-34. The SCHIF function indicated a similar relationship, i.e., steeper curve at lower concentrations and attenuation/decline at higher concentrations where the data are sparse.



Note: Purple shaded areas represent 95% confidence intervals. The histogram depicts the exposure distribution. The red lines indicate the WHO suggested limit for burden of disease quantification (20 µg/m^3; 10.63 ppb) and the EU limit value and WHO air quality guidelines (40 µg/m^3; 21.26 ppb).
Source: Strak et al. (2021). Copyright permission pending.

Figure 6-34 Concentration-response relationship for the association between NO_2 exposure, and deaths from cardiovascular disease.

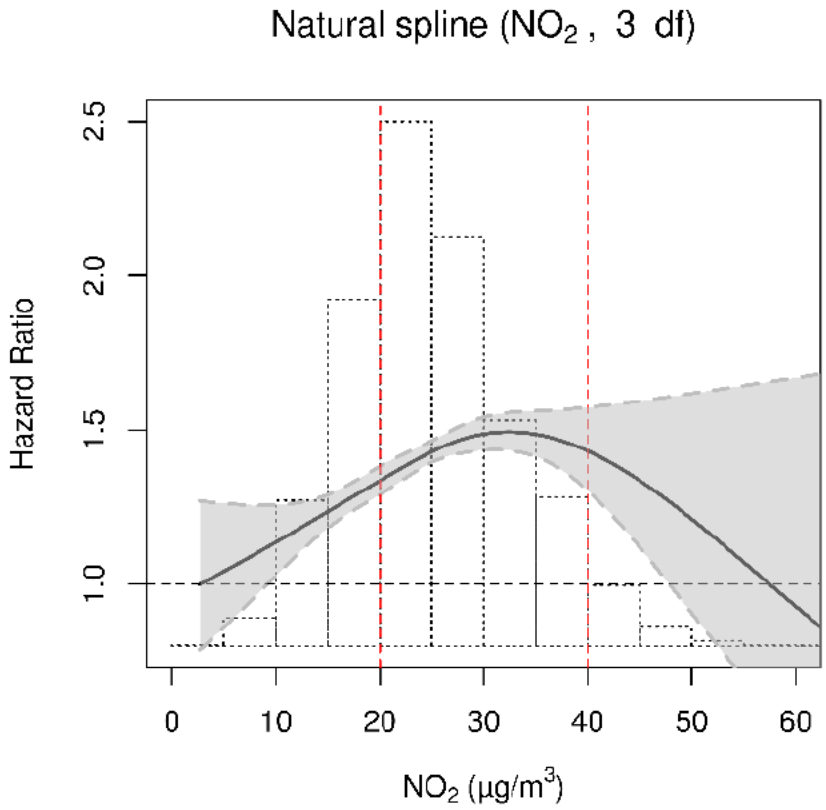
- The C-R relationship for the association between NO_2 exposure and CBVD mortality using natural cubic splines with 3 degrees of freedom is shown in Figure 6-35 (Brunekreef et al., 2021; Strak et al., 2021). The curve is relatively steep at low exposures and decreases above approximately 30 µg/m^3 (15.95 ppb) where the data begins to become sparse. The SCHIF function for cerebrovascular disease indicates attenuation above 30 µg/m^3 but little evidence of a decrease.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: The shaded areas represent 95% confidence intervals. The histogram depicts areas of sparse data. The red lines indicate the WHO suggested limit for burden of disease quantification (20 µg/m^3; 10.63 ppb) and the EU limit value and WHO air quality guidelines (40 µg/m^3; 21.26 ppb).
Source: Brunekreef et al. (2021). Copyright permission pending.

Figure 6-35 Concentration-response relationship for the association between NO_2 exposure and deaths from cerebrovascular disease.

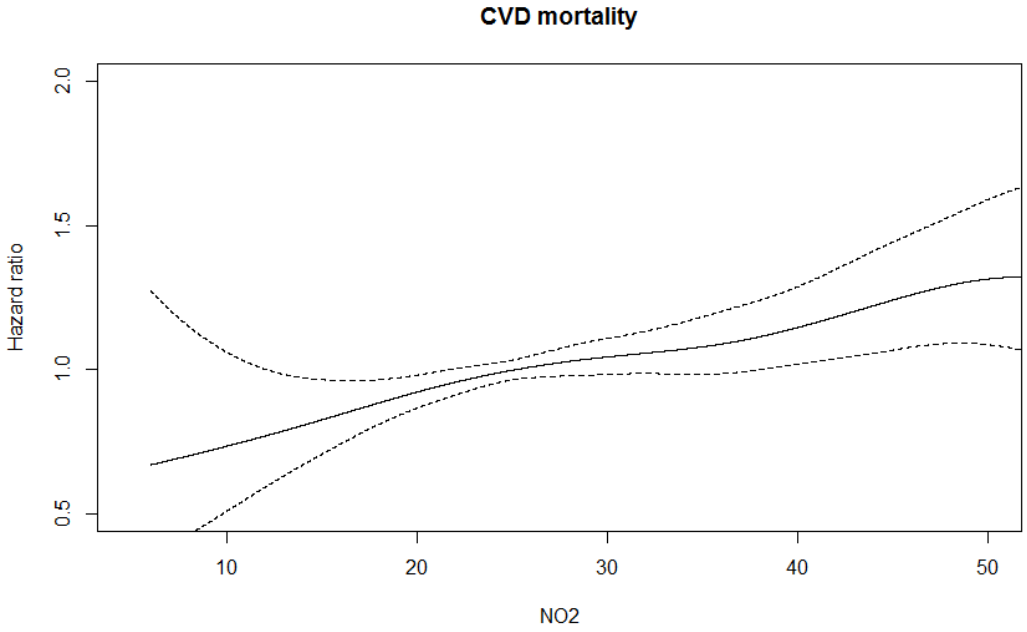
- The shape of the relationship between NO_2 exposure and IHD mortality obtained with natural cubic splines and SCHIF methods is similar to that of cerebrovascular mortality curves, i.e., steeper through 30 µg/m^3 (15.95 ppb) and then decreases (see Figure 6-36) (Brunekreef et al., 2021; Strak et al., 2021).



List of abbreviations in alphabetical order: df = degrees of freedom; NO_2 = nitrogen dioxide
Note: The shaded areas represent 95% confidence intervals. The histogram depicts areas of sparse data. The red lines indicate the WHO suggested limit for burden of disease quantification (20 µg/m^3; 10.63 ppb) and the EU limit value and WHO air quality guidelines (40 µg/m^3; 21.26 ppb)
Source: Brunekreef et al. (2021). Copyright permission pending.

Figure 6-36 Concentration-response relationship for the association between NO_2 exposure and deaths from ischemic heart disease.

- Other C-R analyses of the same administrative cohorts as Brunekreef et al. (2021), often with different lengths of follow-up, also provide evidence of an approximately linear relationship between NO_2 exposure and total mortality, though with some indication of a plateau or inverse relationship at higher concentrations (So et al., 2022; Klompmaker et al., 2021b; Raaschou-Nielsen et al., 2020).
- In an analysis of the Danish DCH cohort from the ESCAPE study, Hvidtfeldt et al. (2019) observed an approximately linear relationship between NO_2 exposure and CVD mortality in a penalized spline model (see Figure 6-37). So et al. (2022) reported a linear curve using a natural cubic spline with 4 knots.



List of abbreviations in alphabetical order: CVD = cardiovascular disease; IHD = ischemic heart disease; NO_2 = nitrogen dioxide.
Note: the dotted lines represent 95% confidence intervals. The solid line represents the hazard ratios.
Source: Hvidtfeldt et al. (2019). Copyright permission pending.

Figure 6-37 Concentration-response relationship for the association between NO_2 exposure and deaths from cardiovascular disease.

6.8.1.2 Lifestages and Populations

To identify factors that potentially lead some portions of the population to be at increased risk of NO_2-related health effects, epidemiologic studies often evaluate EMM, which occurs when the estimated effect of NO_2 exposure differs between subgroups or strata (e.g., effect estimates that vary by age group or other potential risk factor). The available evidence for long-term NO_2 exposures and cardiovascular mortality includes studies that examine EMM by a range of factors. Results from these studies are summarized in Table 6-14. Summary tables include basic information on each study cohort in addition to a qualitative summary of the direction of EMM for a given subgroup (e.g., males) relative to a reference subgroup (e.g., females), as well as the corresponding quantitative effect estimates for each subgroup. The direction of EMM listed in the table does not necessarily indicate a statistically significant between-group difference in NO_2-related health risk. Instead, the table is meant to highlight the pattern of results across studies. In many cases, authors evaluate binary subgroups (e.g., males and females or history of CVD and no history of CVD), in which case the table is organized such that the same subgroups are consistently listed as the reference group across studies to make it easier to discern patterns in the evidence. A similar approach is used for subgroups with more than two categories. For example, because many studies evaluated models stratified by nonuniform age categories that are not directly comparable across studies,

the youngest age group from each study is listed as the reference group to ensure that the direction of EMM in the table reflects NO_2-related risk in an older versus younger age group.

Several United States and Canadian studies examined effect measure modification by factors that may increase the risk of NO_2-related cardiovascular mortality.

- In a study of Medicare enrollees 65-years old or greater, Eum et al. (2022) examined the C-R relationship between 12-month moving average NO_2 exposure and cardiovascular mortality. The associations with mortality from CVD, IHD, and CHF were larger at older ages while the association with CBVD mortality was smaller at older ages. HRs for females were higher in all CVD categories except CHF mortality. The HR was larger among Black Medicare enrollees compared to white enrollees while it was lower among Asian and Hispanic enrollees.
- Crouse et al. (2015) examined effect modification of the relationship between NO_2 exposure and CMD mortality by age and sex categories, income, and immigrant status. HRs were larger in older age groups among men, while HRs were smaller in older age groups among women. Those with lower incomes and immigrants were at higher risk compared to those with higher incomes and non-immigrants. HRs for those residing in micropolitan and rural areas were smaller compared to HRs for those residing in urban areas.
- Zhang et al. (2020) reported that the HRs were smaller in older age groups relative to younger age groups among those enrolled in the Ontario Population Health and Environment Cohort. HRs were larger in females compared to males, current smokers compared to never smokers, and among those who reported moderate physical activity compared to low physical activity.

Table 6-14 Epidemiologic studies evaluating effect measure modification between long-term oxides of nitrogen exposure and cardiovascular mortality

Study	Cohort (Follow-up)	Outcome	Reference Category	Factor Evaluated	Direction of EMM[a]	Effect Estimate (95% CI)	Spatial Scale of Modifier
Age							
†Eum et al. (2022)	Medicare 2000–2008	CVD	<75	≥75	↑	Ref: HR: 1.08 (1.07,1.09) HR: 1.10 (1.09,1.11)	Individual
		IHD	<75	≥75	↑	Ref: HR: 1.05 (1.04,1.07)) HR: 1.12 (1.11,1.14)	
		CBVD	<75	≥75	↓	Ref: HR: 1.09 (1.07,1.12) HR: 1.07 (1.05,1.09)	
		CHF	<75	≥75	↑	Ref: HR: 1.01 (0.97,1.04) HR: 1.08 (1.05,1.12)	
†Crouse et al. (2015)	CanCHEC 1991–2006	CMD	Male <60	Male 60–69	↑	Ref HR: 1.045 (0.981, 1.112) HR: 1.082 (1.030, 1.137)	Individual

Study	Cohort (Follow-up)	Outcome	Reference Category	Factor Evaluated	Direction of EMM[a]	Effect Estimate (95% CI)	Spatial Scale of Modifier
			<60	70–79	↑	HR: 1.070 (1.032, 1.108)	
			<60	80–89	≈	HR: 1.046 (1.009, 1.085)	
†Crouse et al. (2015)	CanCHEC 1991–2006	CMD	Female <60	Female 60–69	↓	Ref HR: 1.286 (1.161, 1.425) HR: 1.058 (0.972, 1.152)	Individual
			<60	70–79	↓	HR: 1.087 (1.034, 1.143)	
			<60	80–89	↓	HR: 1.028 (0.991, 1.068)	
†Yu et al. (2024)	NMMAPS 1987-2000	CVD	<65	65–74	≈	Ref HR: 1.096 (1.065, 1.129) HR: 1.097 (1.068, 1.128)	Individual
			<65	≥75	≈	HR: 1.091 (1.065, 1.118)	
†Zhang et al. (2021b)	Ontario Health Study 2009–2017	CVD	<65	≥65	↓	Figure 1 from Zhang et al. (2021b)	Individual
Sex							
†Eum et al. (2022)	Medicare 2000–2008	CVD	Male	Female	↑	Ref HR: 1.10 (1.09,1.11) HR: 1.11 (1.10,1.12)	Individual
		IHD	Male	Female	↑	Ref HR: 1.05 (1.04,1.07) HR: 1.15 (1.14,1.16)	
		CBVD	Male	Female	↑	Ref HR: 1.07 (1.05,1.09) HR: 1.08 (1.06,1.10)	
		CHF	Male	Female	↓	Ref HR: 1.11 (1.07,1.14) HR: 1.09 (1.06,1.13)	
†Hvidtfeldt et al. (2019)	Danish DCH 1993- 2015	CVD	Male	Female	↓	Ref HR: 1.20 (1.12, 1.28) HR: 1.06 (0.98, 1.14)	
†Zhang et al. (2021b)	Ontario Health Study 2009–2017	CVD	Male	Female	↑	Ref HR: 1.280 (1.095, 1.496) HR: 1.708 (1.329, 2.196)	Individual
Race							
†Eum et al. (2022)	Medicare 2000–2008	CVD	white	Black	↑	Ref HR: 1.13 (1.12,1.14) HR: 1.17 (1.16,1.18)	Individual

Study	Cohort (Follow-up)	Outcome	Reference Category	Factor Evaluated	Direction of EMM[a]	Effect Estimate (95% CI)	Spatial Scale of Modifier
			white	Asian	↓	Ref HR: 1.13 (1.12,1.14) HR: 1.03 (1.01,1.05)	
			white	Hispanic	↓	Ref HR: 1.13 (1.12,1.14) HR: 1.04(1.02,1.06)	
Smoking							
†Guyatt et al. (2024)	UK Biobank 2006-2016	CVD	Never Smoker	Ever smoker	↑	Ref HR: 0.98 (0.73, 1.33) HR: 1.22 (0.94, 1.59)	Individual
†Hvidtfeldt et al. (2019)	DCH 1993- 2015	CVD	Never Smoker	Former Smoker	↑	Ref HR: 1.08 (0.96, 1.21) HR: 1.16 (1.05, 1.27)	Individual
			Never Smoker	Current Smoker	↑	Ref HR: 1.08 (0.96, 1.21) HR: 1.16 (1.09, 1.23)	Individual
†Zhang et al. (2021b)	Ontario Health Study 2009–2017	CVD	Never Smoker	Current Smoker	↑	Figure 1 from Zhang et al. (2021b)	Individual
Physical activity							
†Zhang et al. (2021b)	Ontario Health Study 2009–2017	CVD	Low Physical Activity	Moderate Physical activity	↑	Ref HR: 1.083 (0.862, 1.361) HR: 2.100 (1.657, 2.661)	Individual
			Low Physical Activity	High physical activity	≈	HR: 1.149 (0.903, 1.463)	
Socioeconomic status – income							
Crouse et al. (2015)	CanCHEC 1991–2006	Cardio-metabolic	Top Quintile	Bottom Quintile	↑	Ref HR: 0.964 (0.929, 1.001) HR: 1.134 (1.105, 1.163)	Individual
†Zhang et al. (2021b)	Ontario Health Study 2009–2017	CVD	Top Quintile	Bottom Quintile	≈	Figure 1 from Zhang et al. (2021b)	Individual
Urbanicity							
†Eum et al. (2022)	Medicare 2000–2008	CVD	Urban	Micropolitan	↓	Ref HR: 1.11 (1.10,1.12) HR: 1.08 (1.05,1.11)	Individual
			Urban	Rural	↓	Ref HR: 1.11 (1.10,1.12) HR: 1.09 (1.06,1.12)	
Immigrant status							
Crouse et al. (2015)	CanCHEC	Cardio-metabolic	Non-immigrant	Immigrant	↑	Ref HR: 1.042 (1.026, 1.058)	Individual

Study	Cohort (Follow-up)	Outcome	Reference Category	Factor Evaluated	Direction of EMM[a]	Effect Estimate (95% CI)	Spatial Scale of Modifier
	1991–2006					HR: 1.080 (1.048, 1.112)	

List of abbreviations in alphabetical order: CanCHEC=Canadian Census Health and Environment Cohorts; CBVD=Cerebrovascular Disease; CMD=Cardiometabolic Disease; CVD=Cardiovascular Disease; DCH=Diet Cancer, and Health Cohort; EMM=Effect Measure Modification; HR=Hazard Ratio; IHD=Ischemic Heart Disease; NMMAPS=National Morbidity, Mortality and Air Pollution Study; NO2=Nitrogen Dioxide.
[a] Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of [insert outcome]) in the group with the factor evaluated than in the reference group. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller in the group with the factor evaluated than in the reference group An almost equal sign (and grey shading) indicate that the effect of NO_2 is comparable between groups.
†Studies published since the 2016 Oxides of Nitrogen ISA.

6.8.1.3 Copollutants

Copollutant models are used to evaluate the potential for other pollutants and other stressors such as noise to confound risk estimates of long-term exposure to oxides of nitrogen and cardiovascular effects. Studies that examine confounding by copollutants and noise are summarized in Table 6-15, Figure 6-38, Figure 6-39, Figure 6-40, and below.

Recent United States and Canadian studies that evaluate copollutant confounding have been conducted.

- Eum et al. (2019) and Eum et al. (2022) examined associations between NO_2 exposures and deaths from CVD, IHD, CBVD, and CHF among Medicare enrollees (65-years or older). Eum et al. (2019) used a two-stage model that regressed NO_2 concentration on the $PM_{2.5}$ concentration in the first stage, and the residuals from that regression as the exposure measure in second stage proportional hazards model. Adjustment for $PM_{2.5}$ generally attenuated mortality risk ratios for the entire United States. Associations in the Western region were the most attenuated, while associations in the center region were unchanged or even strengthened for some causes of CVD mortality after controlling for $PM_{2.5}$. Due to the possible collinearity of NO_2 and $PM_{2.5}$ ($\rho = 0.59$) and the potential overcontrol for $PM_{2.5}$ and consequent underestimation of the mortality risk associated with NO_2, Eum et al. (2022) used two approaches to control for copollutant confounding. In the first approach the authors used a typical two-pollutant model that simultaneously included NO_2 and the copollutant. HRs were similar in magnitude to the single pollutant model estimates. As an alternative approach, they used the two-stage model previously used in Eum et al. (2019). HRs were attenuated but remained positive using this approach. Only the two-pollutant model approach was used to adjust for BC ($\rho = 0.54$). Estimates were unchanged by adjustment for BC.
- Turner et al. (2016) conducted a multipollutant analysis including near-source $PM_{2.5}$ (Pearson's $\rho = 0.60$), regional $PM_{2.5}$ ($\rho = 0.21$), and O_3 ($\rho = -0.08$) analyzing data from the ACS CPS-II cohort. HRs for mortality from diseases of the circulatory system (including diabetes), CVD, IHD, dysrhythmias/heart failure/cardiac arrest, and CBVD disease were slightly attenuated but not substantially different.
- Lefler et al. (2019) observed positive associations between annual average NO_2 and CPD mortality that changed direction after adjusting for $PM_{2.5}$ in a study among United States. National Health Interview Survey participants (1987–2014). The association between NO_2 and CVD mortality was attenuated but remained positive after adjustment for $PM_{10-2.5}$, SO_2,

O_3, and CO separately in two-pollutant models. A multipollutant model with all copollutants adjusted simultaneously also showed an inverse association.

- Crouse et al. (2015) reported positive associations between NO_2 exposure and mortality from CMD, CVD, and IHD among CanCHEC participants. These associations were attenuated but remained positive after adjustment for O_3 and $PM_{2.5}$. The association with CBVD mortality was null in single pollutant models and slightly positive after adjustment for O_3 and $PM_{2.5}$. NO_2 concentrations in this cohort were moderately correlated with $PM_{2.5}$ ($\rho = 0.40$) and had little correlation with O_3 ($\rho = 0.19$).
- Zhang et al. (2020) used LUR models to estimate non-tailpipe emissions (i.e., Fe and Cu in $PM_{2.5}$) and ROS concentration in lung epithelial lining fluid to account for $PM_{2.5}$ oxidative potential. The association with CVD mortality was attenuated but still positive after adjustment for ROS. In another Ontario study, Zhang et al. (2021b) observed attenuated but positive associations after adjustment for $PM_{2.5}$ for CVD mortality.

Two-pollutant models were specified for both the recent pooled and administrative analyses of the ELAPSE project, which included multiple countries across Europe.

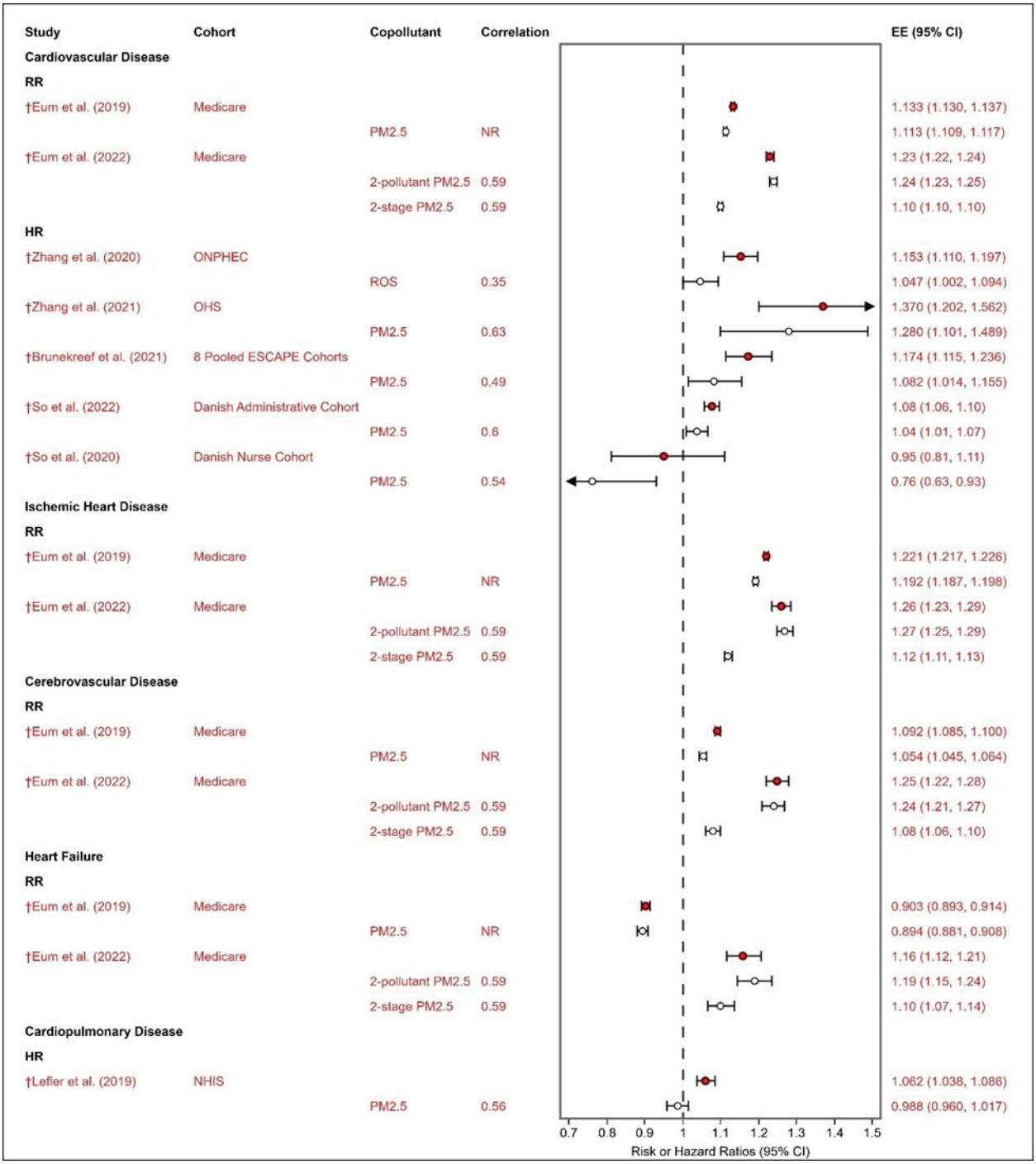
- For the pooled cohort dataset, a positive association was observed in single pollutant models for CVD mortality (HR: 1.089 [95% CI: 1.060, 1.120] per 10 $\mu g/m^3$) (Brunekreef et al., 2021). The associations were attenuated but remained positive after adjustment for $PM_{2.5}$ and O_3. The positive association between NO_2 exposure and CVD mortality among the cohorts where traffic noise was available also persisted in adjusted models. The weaker less precise positive association with CBVD was attenuated but remained positive after adjustment for noise. The null IHD mortality association remained essentially null after adjustment for noise.
- A relatively small HR for the single pollutant association between long-term NO_2 exposure and CVD mortality in the administrative cohorts was observed (Brunekreef et al., 2021). The small positive HRs remained approximately the same after adjustment for $PM_{2.5}$, BC, and O_3. The noise adjusted models for the administrative dataset were presented for each country with traffic noise data separately. The imprecise inverse association observed for the Belgian cohort remained after adjustment for noise. The positive associations in the Dutch cohort, the Norwegian and Roman cohorts also remained. The positive association observed in the Swiss cohort was attenuated to the null after adjustment for noise.
- In a study evaluating a Danish national administrative cohort (enrolled 2000) (So et al., 2022), adjustment for $PM_{2.5}$ slightly attenuated the association between annual average NO_2 exposure in 2010 and CVD mortality between 2000 to 2017 (HR single-pollutant: 1.08 [95% CI: 1.06, 1.10]; HR NO_2+$PM_{2.5}$: 1.04 [95% CI: 1.01, 1.07]). Adjusting for BC or O_3 resulted in slightly stronger positive associations (HR NO_2+BC: 1.12 [95% CI: 1.08, 1.16]; HR NO_2+O_3: 1.14 [95% CI: 1.10, 1.18]).
- So et al. (2020) reported an HR of 0.95 (95% CI: 0.81, 1.11) for CVD mortality, which was similar after adjustment for noise (HR: 0.92 [95% CI: 0.75, 1.14]) and inverse after adjustment for $PM_{2.5}$ (HR: 0.76 [95% CI: 0.63, 0.93]) and PM_{10} (HR: 0.79 [95% CI: 0.65, 0.94]) in the DNC (enrolled 1993 and 1999).

Table 6-15 Epidemiologic studies evaluating copollutant associations between long-term exposure to oxides of nitrogen and cardiovascular mortality that examine confounding by copollutants and noise. North American studies and results from the Effects of Low-Level Air Pollution: A Study in Europe

Study	Exposure	Outcome	Single Pollutant	Copollutant Adjusted
†Eum et al. (2022) Medicare	12-month moving average NO_2 at zip code of residence	CVD	HR: 1.23 (1.22,1.24) **Positive**	Two pollutant +$PM_{2.5}$: HR: 1.24 (1.23,1.25) **Positive** Two stage +$PM_{2.5}$: HR: 1.10 (1.10,1.11) **Attenuated but positive** Two pollutant +BC: 1.24 (1.23,1.26) **Positive**
†Lefler et al. (2019) NHIS	Annual average NO_2 (2000) at census block level	Cardio-pulmonary	**Positive** Figure 2 from Lefler et al. (2019)	+$PM_{2.5}$ **Inverse** +$PM_{2.5-10}$,+SO_2,+ozone, +CO **Inverse**
†Zhang et al. (2020) ONPHEC	Annual average NO_2 at zipcode of residence	CVD	1.060 (1.044,1.077) **Positive**	1.019 (1.001,1.038) **Attenuated but positive**
Crouse et al. (2015) CanCHEC	Annual average NO_2 at zipcode of residence	CVD	HR: 1.041 (1.028, 1.053) **Positive**	HR 1.035 (1.022, 1.048) +Ozone, $PM_{2.5}$ **Attenuated but positive**
		IHD	HR: 1.063 (1.047, 1.079) **Positive**	HR: 1.042 (1.026, 1.058)+ Ozone, $PM_{2.5}$ **Attenuated but positive**
		CBVD	HR: 1.004 (0.977, 1.031) **Null**	HR: 1.020 (0.993, 1.049)+ Ozone, $PM_{2.5}$ **Positive**
†Brunekreef et al. (2021) ELAPSE (Results for pooled analysis)	NO_2 annual average concentration for 100 x 100 m grid	CVD	HR: 1.089 (1.060, 1.120) **Positive**	HR: 1.043 (1.007, 1.079)+ $PM_{2.5}$ HR: 1.077, (1.012, 1.146)+BC HR: 1.051 (1.010, 1.094)+ ozone **Attenuated but positive**
†Brunekreef et al. (2021) (Results for cohorts in the pooled analysis with noise data)			HR: 1.060 (1.013, 1.110) **Positive**	HR: 1.053 (1.000, 1.110)+ noise **Attenuated but positive**
		CBVD	HR: 1.039 (0.951, 1.134) **Positive**	HR: 1.023 (0.927, 1.130)+ noise **Attenuated but positive**

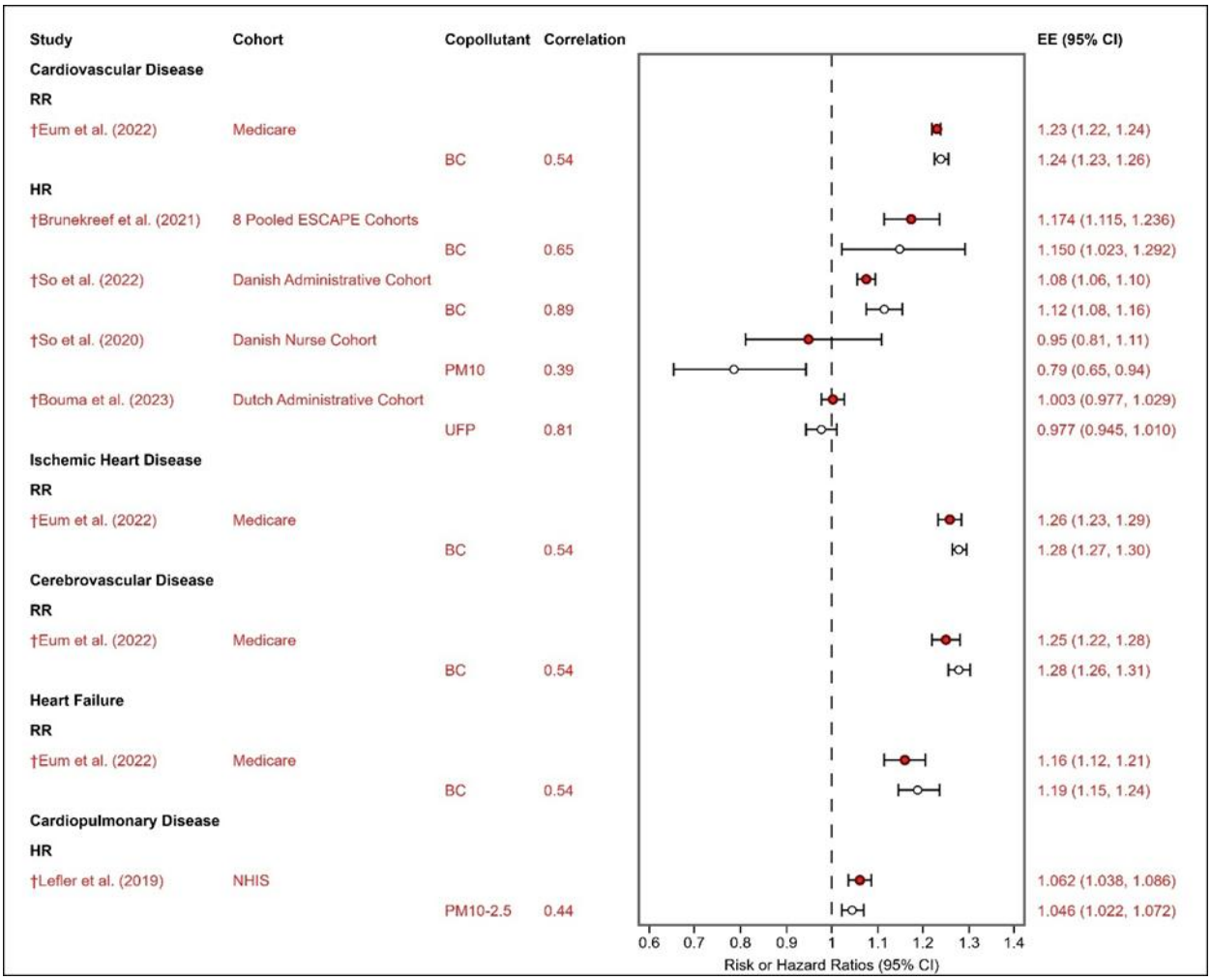
Study	Exposure	Outcome	Single Pollutant	Copollutant Adjusted
		IHD	HR: 1.000 (0.931, 1.075) **Null**	HR: 1.012 (0.933, 1.098)+ noise **Null**
†Brunekreef et al. (2021) ELAPSE (Results for administrative databases)	Annual average NO_2	CVD	1.025 (1.006, 1.044) **Positive**	HR: 1.022 (1.005, 1.040)+ $PM_{2.5}$ HR: 1.023 (0.997, 1.050)+BC **Positive** HR: 1.033 (1.013, 1.053)+ ozone **Increased and positive**
†Brunekreef et al. (2021) (Results for administrative cohorts with noise data)		CVD	Belgium: HR: 0.980 (0.950, 1.010) **Null**	HR: 0.982 (0.952, 1.013)+ noise **Null**
			Dutch: HR: 1.030 (1.019, 1.041) **Positive**	HR: 1.029 (1.014, 1.044)+ noise **Positive**
			Norwegian: HR: 1.036 (1.023, 1.049] **Positive**	HR: 1.030 (1.016, 1.043)+ noise **Positive**
			Roman cohorts (HR: 1.028 (1.018, 1.038) **Positive**	HR: 1.036 (1.018, 1.055)+ noise **Positive**
			Swiss cohort (HR: 1.026 (1.014, 1.039) **Positive**	HR: 1.004 (0.991, 1.017)+ noise **Attenuated to the null**

List of abbreviations in alphabetical order: CanCHEC=Canadian Census Health and Environment Cohorts; CBVD = cerebrovascular disease; CVD = cardiovascular disease; ELAPSE=Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; NHIS= National Health Interview Survey; ONPHEC=Ontario Population Health and Environment Cohort..
†Studies published since the 2016 Oxides of Nitrogen ISA.



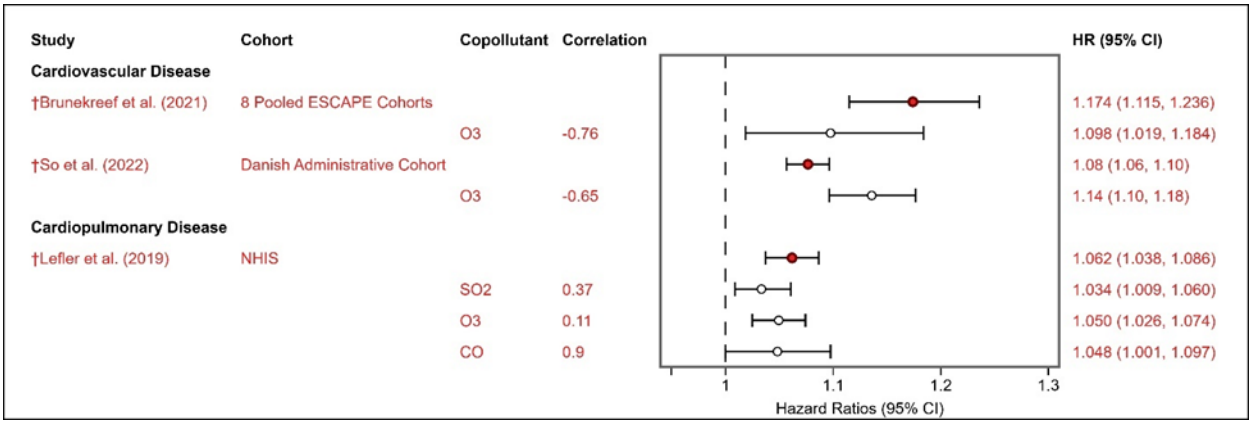
List of abbreviations in alphabetical order: CI = confidence interval; EE = effect estimate; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ratio; NHIS = National Health Interview Survey; OHS = Ontario Health Study; ONPHEC = Ontario Population Health and Environment Cohort; $PM_{2.5}$ = fine particulate matter; ROS = reactive oxygen species; RR = risk ratio.
Notes: Results are standardized to a 10-ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-38 Associations between long-term exposure to NO_2 and cardiovascular mortality in single pollutant models and models adjusted for fine particulate matter or reactive oxygen species.



List of abbreviations in alphabetical order: BC = black carbon; CI = confidence interval; EE = effect estimate; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ratio; NHIS = National Health Interview Survey; OHS = Ontario Health Study; ONPHEC = Ontario Population Health and Environment Cohort; PM10 = particulate matter with a diameter >10 micrometers; PM10-2.5 = particulate matter with a diameter between 2.5 and 10 micrometers; ROS = reactive oxygen species; RR = risk ratio; UFP = ultrafine particle
Notes: Results are standardized to a 10-ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-39 Associations between long-term exposure to NO_2 and cardiovascular mortality in single pollutant models and models adjusted for black carbon, ultrafine particles, or coarse particulate matter.



List of abbreviations in alphabetical order: CI = confidence interval; CO = carbon monoxide; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ratio; NHIS = National Health Interview Survey; O3 = ozone; SO2 = sulfur dioxide.
Notes: Results are standardized to a 10-ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-40 Associations between long-term exposure to NO_2 and cardiovascular mortality in single pollutant models and models adjusted for gaseous pollutants.

6.8.1.4 Conclusions and Remaining Uncertainties

Most studies reported positive associations between long-term exposure to NO_2 and cardiovascular mortality; however, several studies reported null associations. A limited number of studies examining CBVD mortality reported mixed results. There is uncertainty regarding the independent effect of oxides of nitrogen because most studies did not consider confounding by copollutants, particularly those most closely linked with traffic ($PM_{2.5}$, BC, and UFP), or noise. In addition, the extent to which specific regions, populations or lifestages are at increased risk for NO_2-related cardiovascular mortality remains an uncertainty.

6.9 Biological Plausibility

As discussed in the 2016 Oxides of Nitrogen ISA, NO_2 and NO have distinct chemical properties that impact initiating events related to downstream health effects [see Section 4.3 of U.S. EPA (2016)]. Given the lack of recent mechanistic evidence related to the impacts of long-term NO exposure on the cardiovascular system, the following discussion will focus on plausible pathways linking NO_2 exposure to cardiovascular effects. As detailed in Chapter 2, NO_2 is a highly reactive gas that occurs as a radical that, once inhaled, encounters the epithelial lining fluid (ELF) of the respiratory tract. In the ELF, NO_2 chemically interacts with antioxidants, unsaturated lipids, and other compounds generating reactive oxygen and nitrogen species and provoking inflammation. These localized effects can result in diffusion and migration of inflammatory mediators into circulation, potentially affecting other organ systems,

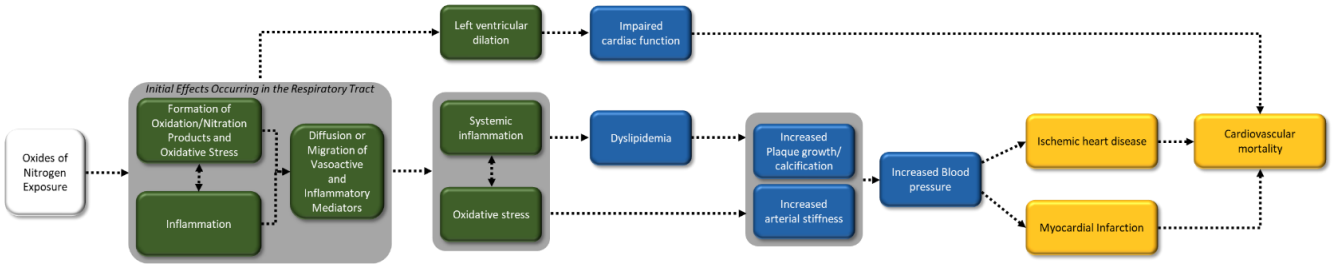
including the cardiovascular system. Experimental evidence supports several plausible pathways by which long-term exposure to NO_2 may result in cardiovascular morbidity and mortality reported in epidemiologic studies (see Figure 6-41). The structure of the biological plausibility figures is described in IS.4.2.

Experimental and epidemiologic data suggest two plausible pathways by which long-term NO_2 exposure could result in cardiovascular morbidity and mortality. It is worth noting that the experimental and epidemiologic evidence supporting some of the steps in these proposed pathways are limited and, in some cases, inconsistent with other studies making the proposed pathways, while plausible, more uncertain.

The first pathway linking long-term exposure to NO_2 with cardiovascular morbidity and mortality is through the induction of systemic inflammation and oxidative stress. de Burbure et al. (2007) reported increased concentrations of thiobarbituric acid-reactive substances (an indicator of oxidative stress) in the plasma of rats following 4 weeks of 1 ppm NO_2 exposure which corresponded with suppression of oxidant defense systems. A separate study observed that NO_2 exposure concentration was a strong predictor of thiobarbituric acid-reactive substance concentration in the plasma (Seilkop et al., 2012), which supports the systemic induction of ROS from NO_2. Rats exposed to 5 ppm NO_2 for 3 weeks had increased ROS production from mitochondria isolated from cardiac tissue (Karoui et al., 2020). Inflammation can affect many downstream responses, including altering lipid metabolism and trafficking that can promote formation of atherosclerotic plaques. Long-term exposure to NO_2 has been reported to change lipid profiles in obese rats including increased triglycerides and reduced HDL cholesterol (Takano et al., 2004). This change in lipid profile could promote the formation or growth of atherosclerotic plaques. An epidemiologic study that showed positive associations between long-term NO_2 exposures and triglycerides, total cholesterol, and LDL/HDL ratio also showed a relationship between NO_2 exposures and plaque area (Johnson et al., 2020). While toxicology data are lacking on the impact of long term NO_2 on arterial plaque growth and formation, there is some indications from epidemiologic studies of a relationship between long-term NO_2 or NO_X exposure and indicators of CVD including increased measures of arterial stiffness (Lenters et al., 2010), plaque calcification (zielska et al., 2016), and cIMT (Farzan et al., 2021), although associations with these outcomes are inconsistent across the broader body of epidemiologic studies. Similarly, while not consistent, epidemiologic evidence exists for associations between long-term NO_2 exposure and increased SBP (Mann et al., 2021), which could potentially result from growth of arterial plaques and subsequent occlusion of blood vessels. In this way, long-term exposure to NO_2 could potentially lead to ischemic heart disease or infarction and subsequent cardiovascular mortality.

An alternative pathway for long-term NO_2 exposure to result in cardiovascular effects is through promoting ventricular dysfunction. Toxicology studies provide evidence for NO_2-induced dilation of the left ventricle at diastole (Ji et al., 2022; Karoui et al., 2020). This is supported by epidemiologic findings of increased left ventricular dilation (Aung et al., 2018). Interestingly, this result seems isolated to male

animals (Ji et al., 2022). Dilation of the left ventricle can lead to impairment of cardiac function that may precede CVD development and subsequent mortality. Two animal studies found increased measures of ventricular dilation following long-term NO_2 exposures were present in conjunction with decreased measures of cardiac function including decreased ventricular contractility, lowered ejection fraction (a measure of efficient blood pumping by the heart), and reduced cardiac output (Ji et al., 2022; Karoui et al., 2020).



Note: The boxes represent the effects for which there is experimental or epidemiologic evidence related to oxides of nitrogen exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway used in an experimental study involving oxides of nitrogen exposure. Dotted arrows denote a possible relationship between effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color coded (white, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text above. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the Oxides of Nitrogen ISA are discussed in Section 6.11.

Figure 6-41 Potential biological plausibility pathways for cardiovascular effects associated with exposure to oxides of nitrogen.

6.10 Summary of Lifestages and Population Differences

Some populations and lifestages may be at greater risk of oxides of nitrogen related health effects than the general population. Higher risks could be due to intrinsic,[6] extrinsic,[7] and/or exposure-related factors. In assessing the recent evidence, these factors are identified, evaluated, and characterized to inform conclusions on the populations and lifestages that may be at increased risk. The systematic approach used to evaluate factors that may increase the risk of a population or specific lifestage to an air pollutant-related health effect is described in more detail in the Preamble to the ISAs (U.S. EPA, 2015) and the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen Volume 2 (U.S. EPA, 2024). The evaluation of these factors focuses on health effect studies that conduct stratified analyses to compare populations or lifestages exposed to similar air pollutant

[6]Intrinsic factors such as genetics, lifestage, or disease status can contribute to larger or more serious responses to a particular pollutant exposure, and physiological differences between groups (e.g., differences in breathing patterns between children and adults) can contribute to higher internal pollutant doses in some populations.
[7]Extrinsic factors (e.g., nutritional status) and exposure-related factors (e.g., working outdoors, living near roadways or other pollution sources) can also contribute to increased risk, and many of the characteristics commonly used to classify populations potentially at increased risk (e.g., race, SES, educational attainment) are surrogates for the combined impact of several intrinsic, extrinsic, and exposure-related factors.

concentrations within the same study design. For the evaluation of these studies, important considerations include whether the stratified analyses were planned a priori or were post hoc analyses, whether the study conducted multiple comparisons, and whether there were small sample sizes in individual strata. These study design issues can increase the probability of finding associations by chance or reduce power to detect associations in subgroup analyses. Experimental studies that examine health effects exclusively in human subjects or animal models with a particular factor, such as pre-existing disease, are also important lines of evidence to evaluate because they inform judgments of the coherence and biological plausibility of effects observed in epidemiologic studies, as well as the independent effect of NO_2 exposure. Additionally, studies examining whether factors may result in differential exposure to NO_2 are included.

Although, there were few studies overall, most epidemiologic studies in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016) that examined lifestages and population differences investigated whether having a preexisting CVD modified the association of NO_2 with other CVDs. For example, a small number of studies examined whether preexisting diabetes, obesity, hypertension or hypercholesteremia modified the association of NO_2 with blood pressure, circulating markers of inflammation, or stroke. Of the small number of studies that conducted these types of analyses, most found no evidence of differences in associations between individuals with or without underlying CVD. Furthermore, no discernable patterns of modification by genetic factors, lifestage, SES, race, urbanicity, distance to roadways, diet, and smoking were evident in the available set of studies.

Recent studies of large cohorts in the United States (older adults enrolled in Medicare), Canada (ONPHEC and CanCHEC), Europe (Danish adults, UK Biobank) and China expand the evidence that is available to evaluate differences in oxides of nitrogen related cardiovascular effects that depend on population or lifestage. There was some evidence to indicate stronger associations between NO_2 and CVD among older adults scoring higher on frailty indices (i.e., Charleston Comorbidity Index) (Poulsen et al., 2023d; Olaniyan et al., 2022). The limited number of studies examining effect modification by specific pre-existing diseases such as diabetes or hypertension did not indicate that those with underlying disease were at increased risk of NO_2 related CVD, however. Studies that evaluated differences across lifestage, age, sex, race, SES, genetic and other factors did not identify consistent patterns of association to indicate that one lifestage or population is at increased risk of oxides of nitrogen related CVD.

Overall, the collective evidence is inadequate to determine whether the factors evaluated result in a population or lifestage being at increased risk of oxides of nitrogen-related cardiovascular effects (see Table 6-1). Experimental studies are lacking, and the available epidemiologic studies are of insufficient quantity and consistency to permit a conclusion to be drawn. Given the uncertainties related to potential confounding by traffic related pollutants and other risk factors for CVD, the evidence pertaining to lifestage, and population differences is further weakened.

Table 6-1 Summary of evidence for populations at increased risk of cardiovascular effects from oxides of nitrogen exposure

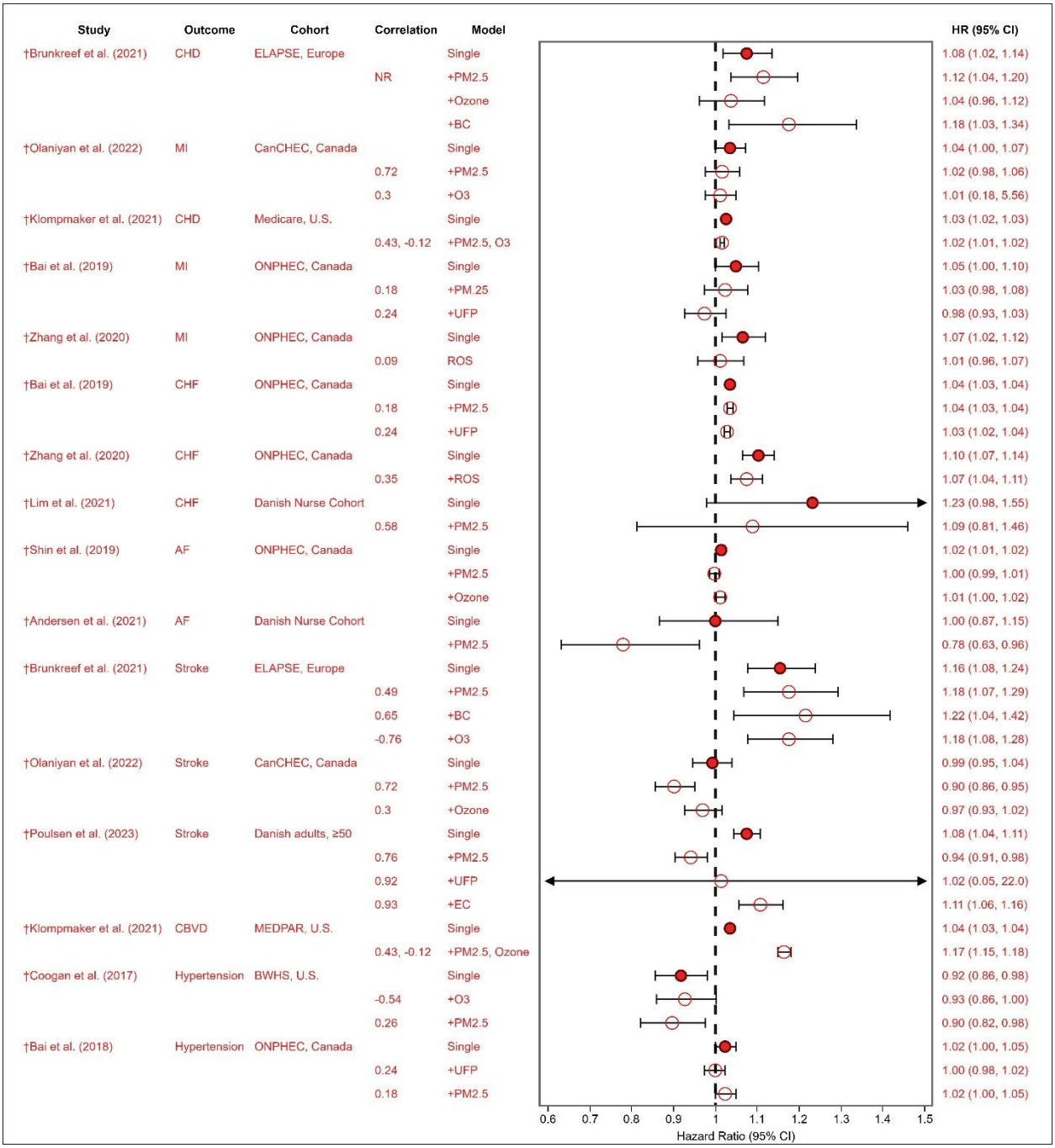
	Key Evidence	Key References
Suggestive Evidence		
Comorbid conditions (frailty)	Single studies in Canada and Denmark indicate the potential for stronger NO_2 related cardiovascular associations among older adults with higher frailty indices.	Olaniyan et al. (2022), Poulsen et al. (2023d)
Inadequate Evidence		
Age	Limited and inconsistent evidence.	Sections 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.4.1.2 , 6.5.1.2, 6.6.1.2, 6.7.1.2
Sex	Limited and inconsistent evidence.	Sections 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.4.1.2, 6.5.1.2, 6.6.1.2, 6.7.1.2
Race	Limited and inconsistent evidence.	Sections 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.4.1.2, 6.5.1.2, 6.6.1.2, 6.7.1.2
Genetic factors	Limited and inconsistent evidence.	Sections 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.4.1.2, 6.5.1.2, 6.6.1.2, 6.7.1.2
Pre-existing conditions (diabetes, hypertension, overweight)	Limited and inconsistent evidence.	Sections 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.4.1.2, 6.5.1.2, 6.6.1.2, 6.7.1.2
Socioeconomic status	Limited and inconsistent evidence.	Sections 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.4.1.2, 6.5.1.2, 6.6.1.2, 6.7.1.2

6.11 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA concluded that the evidence was "suggestive of, but not sufficient to infer," a causal relationship between long-term nitrogen dioxide exposure and cardiovascular effects. This causality determination was primarily based on epidemiologic studies that consistently reported positive associations with long-term increases in NO_2 exposures and cardiovascular mortality. Epidemiologic evidence of associations of long-term NO_2 exposure and heart disease were generally supportive but not entirely consistent. Evidence from controlled human exposure studies and animal toxicological studies provided limited biological plausibility of an underlying mechanism, although inflammation and oxidative stress were implicated. The epidemiologic evidence did not consistently link long-term NO_2 exposures to markers of cardiovascular risk (e.g., ABI, arterial stiffness, cIMT, and markers of inflammation). Uncertainty remained regarding the impact of copollutant confounding on findings from epidemiology studies, the extent to which exposure assessment methods captured the spatial variability and the lack of coherence from animal or controlled human exposure studies to support epidemiologic findings.

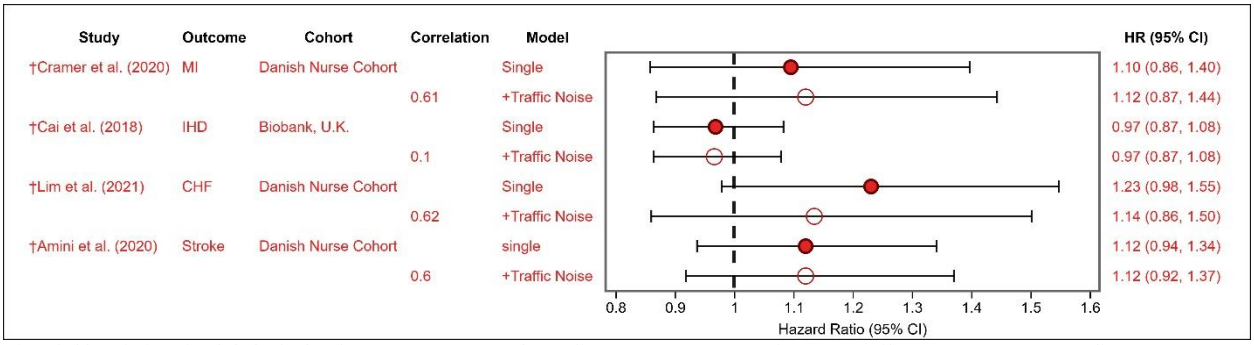
Recent epidemiologic evidence includes large, well conducted cohort studies across North America, Europe, and Asia of cardiovascular morbidity and mortality. These studies generally show increased risk of cardiovascular mortality with increased long-term NO_2 exposure with various averaging times, and exposure assessment methods. Associations were strongest for mortality related to total cardiovascular disease, ischemic heart disease, cardiopulmonary disease-related factors, and circulatory disease/CVD. Positive associations between long-term NO_2 and CVD mortality were reported in multiple cohorts in the United States, Europe, and Canada while data from Asia was more limited and inconsistent. In studies that looked at cardiovascular mortality associations with both NO_2 and NO_X, associations with NO_2 generally showed stronger positive associations. There is uncertainty regarding the independent effect of oxides of nitrogen because most studies did not consider confounding by copollutants, particularly those most closely linked with traffic, such as $PM_{2.5}$, BC, UFP and noise. In addition, the extent to which specific regions, populations or lifestages may be at increased risk for NO_2-related cardiovascular mortality remains an uncertainty.

Epidemiologic studies of cardiovascular morbidity have increased in number since the previous review Recent studies do not substantially reduce the uncertainties identified in the previous ISA, however. Recent studies of MI and CHD (see Figure 6-7) show mixed results (i.e., associations varied in magnitude and direction). Although the body of evidence examining the association of long-term exposure with stroke expanded substantially, the findings do not consistently support NO_2-related cerebrovascular effects and only a small subset of the cerebrovascular studies examined confounding by copollutants and noise. There continues to be a lack of animal or controlled human exposure study information that support plausible pathways through which long-term NO_2 exposure could cause hemodynamic changes that underlie cerebrovascular disease or stroke. Studies of atrial fibrillation, which is risk factor for stroke, and hypertension, which is a risk factor for an array of CVDs, did not provide consistent evidence of positive association with long-term NO_2 exposure. A small number of recent studies consistently reported positive associations between long-term exposure to NO_2 and heart failure but the extent to which these positive associations indicate an independent effect of NO_2 remains uncertain. Single pollutant associations with CVDs, and associations after adjustment for copollutants and noise are summarized in Figure 6-42 and Figure 6-43, respectively. Positive associations were often attenuated after controlling for other pollutants. The more limited body of studies examined confounding by traffic related noise and found that estimates remained generally unchanged after adjustment, although the single pollutant studies were imprecise and inconsistent. Moderate correlations between noise and traffic pollutants including BC were observed in multiple studies in Europe and the United States (see Chapter 2, Section 2.4.3.1), suggesting that controlling for traffic noise may also control, in part, for other traffic related pollutants.



List of abbreviations in alphabetical order: AF = Atrial Fibrillation; BWHS = Black Women's Health Study; CHD = coronary heart disease; CHF = Congestive Heart Failure; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-42 Single pollutant associations between long-term NO_2 exposure and cardiovascular effects, and associations with NO_2 after adjustment for copollutants.



List of abbreviations in alphabetical order: CHD = coronary heart disease; CHF = Congestive Heart Failure; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 6-43 Single pollutant associations between long-term NO_2 exposure and cardiovascular effects, and associations with NO_2 after adjustment for noise.

The epidemiologic evidence for subclinical effects that underlie the development of CVD continues to be limited and often inconsistent. Finding from studies of NO_2 associated changes in markers of atherosclerosis and blood pressure lack consistency and a MESA analysis indicated that the association of NO_2 and NO_X with CAC was substantially attenuated after adjustment for $PM_{2.5}$ (zielska et al., 2016). Further, another MESA analysis found no association of NO_2 with blood pressure adjustment for calendar time (Adar et al., 2018). Regarding other subclinical endpoints, a limited number of recent studies reported associations between long-term exposure to oxides of nitrogen and cardiac parameters indicating reduced functioning, including LVEDV and LAVI (Aung et al., 2018; Ohlwein et al., 2016) and markers of inflammation (Pilz et al., 2018). Recent animal toxicological studies report increased cardiac structural changes in response to NO_2 exposure. Specifically, long-term NO_2 exposure was shown to increase LVEDD following NO_2 exposure providing some coherence for the single epidemiologic study described above (Aung et al., 2018). Repeated exposures resulted in increased LVEDD compared to a single exposure, suggesting that repeat or chronic exposure to NO_2 may cause more severe effects than a single acute exposure. Investigation of changes in blood lipid markers like HDL that can be indicative of future CVD also provide some support for epidemiologic associations but are limited in number. Animal toxicological studies do not report consistent increases in markers of systemic inflammation following long-term NO_2 exposure, however, NO_2 exposure in animals sensitized and challenged with an allergen show more pronounced increases in circulating inflammatory cells (Lu et al., 2023b; Lu et al., 2023a). In addition, controlled human exposures to shorter durations of NO_2 (2–6 hours over 1–4 days) do not provide strong evidence of increased systemic inflammation (see Chapter 5, Section 5.10.4.2). While there is limited availability of toxicological studies to directly support epidemiology associations with CVD or systemic inflammation, one study reported that repeated exposure to NO_2 resulted in greater

cardiac ROS production than a single exposure, again suggesting that repeat or chronic exposure to NO_2 may cause more severe subclinical effects than a single acute exposure (Karoui et al., 2020). Overall, the endpoints investigated in available toxicologic studies are general markers of systemic response while evidence of specific changes to cardiac structure and function are more limited in number. Support for the biological plausibility of NO_2-induced cardiovascular effects remains based on a small number of animal and controlled human exposure studies.

Overall, the evidence is *suggestive of, but not sufficient to infer, a causal relationship between* long-term oxides of nitrogen exposure and cardiovascular effects. The strongest evidence comes from epidemiologic studies associated with long-term NO_2 exposures and increased cardiovascular-related mortality (see Table 6-2). Epidemiologic evidence for cardiovascular morbidity is more mixed. Broad uncertainty remains in recent epidemiologic studies regarding the independent effect of NO_2 on the cardiovascular system due to the potential for confounding by traffic-related copollutants (i.e., $PM_{2.5}$, CO, BC/EC, UFP, other PM constituents, and VOCs) or other environmental determinants. In addition, it is unclear whether the heterogeneity in study findings is due to the variation in epidemiologic methods and confounder control, or differences in the composition of the populations studied (e.g., socio-demographic, co-morbidities, health care access, health behaviors). Animal toxicological and controlled human exposure studies provide some support for biologically plausible NO_2-associated effects on the cardiovascular system, although these studies are limited in number, the results are often inconsistent, and the strongest evidence is for endpoints related to systemic markers (e.g., oxidative stress markers) and evidence of effects on cardiac structure and function are less consistent or are informed by a small number of studies.

Table 6-2 Summary of evidence contributing to causality determinations for long-term oxides of nitrogen exposure and cardiovascular effects

Rationale for Causality Determination	Key Evidence	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Cardiovascular Disease Mortality			
Generally consistent evidence of long-term exposure to NO_2 with CVD mortality	Positive associations in U.S. and Canadian studies for CVD, IHD, CPD, and circulatory disease/CMD mortality.	Section 6.8.1 Eum et al. (2019) Eum et al. (2022) Weichenthal et al. (2017) Crouse et al. (2015)	Median NO_2 annual average: 9.14-14.23 ppb
Confounding and other biases cannot be ruled out in epidemiologic studies.	A limited number of studies examined confounding by copollutants, i.e., $PM_{2.5}$, O_3, BC, CO, or traffic-related noise. NO_2 related effects were attenuated but remained positive in most studies; some estimates became inverse or null.	Sections 6.8.1.3 and 6.8.1.4 Table 6-13	Mean NO_2 annual average:8.1-18.2 ppb

Rationale for Causality Determination	Key Evidence	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Heart Failure			
Generally consistent results in limited number of epidemiologic studies of heart failure	Positive associations in U.S., Canadian and European studies	Section 6.3.2 Jin et al. (2022) Bai et al. (2019b) Zhang et al. (2020)	Mean NO_2 annual average: 7.17-21.4 ppb
Confounding and other biases cannot be entirely ruled out in epidemiologic studies.	A limited number of studies examined confounding by traffic-related noise or copollutants, i.e., UFP, $PM_{2.5}$, or ROS. NO_2-related effects were only slightly attenuated and remained positive after adjustment for these co-exposures.	Bai et al. (2019b) Zhang et al. (2020) Lim et al. (2021)	Mean NO_2 annual average: 7.17-21.4 ppb
Coherence with observations in epidemiologic studies of heart failure provided by limited number of studies of cardiac ventricular dilation both within and across lines of evidence.	Animal toxicological studies demonstrate increase in LVEDD providing some support for an independent effect of NO_2. NO_2-related increases in LVEDV and RVEDV observed in cross-sectional epidemiologic study.	Karoui et al. (2020) Ji et al. (2022) Aung et al. (2018)	Mice: 2.5 ppm for 5 hr/d for 28 d, or 5 ppm for 3hr/d for 5 d/wk for 3 wk Annual median NO_2 15 ppb (28.2 µg/m^3)
Heart Disease: Myocardial Infarction and Coronary Heart Disease			
Inconsistent findings in epidemiologic studies of long-term NO_2 exposure and MI or CHD**.**	Some but not all U.S., Canadian and European studies reported positive associations. Several U.S. studies of Medicare data reported inconsistent findings that depended on the statistical model used in the analysis.	Section 6.3.1, Figure 6-7 Schwartz et al. (2023) Danesh Yazdi et al. (2021) Danesh Yazdi et al. (2022) Klompmaker et al. (2021a)	Mean NO_2 annual average: 6.7-22.1 ppb Median NO_2 annual average: 6.22-21.1 ppb
Limited coherence for observations in epidemiologic studies of MI and CHD both across and within lines of evidence.	Reductions in HDL cholesterol demonstrated in rodents. Inconsistent evidence in epidemiologic studies of atherosclerosis, i.e., CAC, Plaque area, and arterial stiffness. A limited number of epidemiologic studies found associations with lipid profiles indicating dyslipidemia.	Takano et al. (2004) Section 6.7.1 zielska et al. (2016), Tibuakuu et al. (2017), Hartiala et al. (2016), Gan et al. (2014) Letellier et al. (2022) Johnson et al. (2020) Zhang et al. (2022)	Rats: 160 ppb or 800 ppb NO_2 for 32 wk Humans: 3-mo NO_2 IQR 9.3 ppb, 6-mo average NO_2 IQR 6.0 ppb, 3-mo NO_X IQR 12.6 ppb, 6-mo average NO_X IQR 8.7 ppb

Rationale for Causality Determination	Key Evidence	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Confounding and other biases cannot be ruled out in epidemiologic studies.	A limited number of studies of MI and CHD examined confounding by copollutants, i.e., $PM_{2.5}$, O_3, BC, UFP, ROS, or traffic-related noise. NO_2-related effects were generally attenuated or did not persist after adjustment for at least one of these co-exposures, e.g., the association with CAC observed in the MESA cohort was substantially attenuated after adjustment for $PM_{2.5}$.	Sections 6.3.1.3, 6.3.1.4, 6.7.1.3, and 6.7.1.4 Figure 6-6	Mean NO_2 annual average: 6.7-22.1 ppb Median NO_2 annual average: 6.22-21.1 ppb
Atrial Fibrillation			
Inconsistent findings in limited number of epidemiologic studies of atrial fibrillation.	Positive associations that varied substantially in magnitude were found in U.S. and Canadian, but not European studies.	Section 6.3.3 Jin et al. (2022), Danesh Yazdi et al. (2021), Hart et al. (2021), Andersen et al. (2021)	Mean NO_2 annual average: 12.3-19.8 ppb Median NO_2 annual average: 5.42-17.44 ppb
Cerebrovascular Disease and Stroke			
Epidemiologic evidence from studies of cerebrovascular disease or stroke was not entirely consistent.	Some studies report positive associations with stroke and/or cerebrovascular disease with long-term exposure to NO_2.	Section 6.4.1	Mean NO_2 annual average: 4.3-31.9 ppb Median NO_2 annual average: 2.0-23.4 ppb
Lack of supporting data providing coherence and biological plausibility.	Lack of animal or controlled human studies of endpoints directly related to stroke or clotting. Mixed evidence from epidemiologic studies of atrial fibrillation, which is a risk factor for stroke.	Section 6.4.1	Mean NO_2 annual average: 12.3-19.8 ppb Median NO_2 annual average: 5.42-17.44 ppb
Confounding and other biases cannot be ruled out in epidemiologic studies.	Limited investigation of the influence of other traffic-related noise and copollutants (i.e., O_3 and $PM_{2.5}$). Results from copollutants models were mixed while positive association persisted after adjustment for noise.	Sections 6.4.1.3 and 6.4.1.4	Mean NO_2 annual average: 4.3-31.9 ppb Median NO_2 annual average: 2.0 -19.95 ppb
Hypertension			
In consistent epidemiologic evidence.	Results from in the U.S. Canada, Europe and Asia lack consistence in magnitude and direction. Associations are attenuated in MESA analysis after adjustment for calendar time, and in an extended analysis of the BWHS cohort.	Section 6.5.1 Adar et al. (2018) Coogan et al. (2017)	Mean NO_2 annual average:4.5-25.5 ppb

Rationale for Causality Determination	Key Evidence	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Lack of coherence and biological plausibility both within and between lines of evidence.	Little evidence for associations with pulmonary hypertension or clinical effects in those with underlying pulmonary hypertension. Lack of consistency in epidemiologic studies of NO_2-related changes in blood pressure. Experimental animal studies of blood pressure are lacking.	Shi et al. (2023) Sofianopoulou et al. (2019) Section 6.7.1	Mean NO_2 annual average: 3.5-29.9 ppb
Inflammation and Oxidative Stress			
Limited biological plausibility provided by inconsistent evidence pertaining to NO_2 induced inflammation and oxidative stress.	Some, but not entirely consistent evidence of increased oxidative stress in rats (i.e., MDA, TBARS). Multiple exposures resulted in increased ROS compared to single exposures.	de Burbure et al. (2007) Karoui et al. (2020) Section 6.7.2	Rats: 1,000 ppb for 28 d, or 5,000 ppb for 3 wk
	Inconsistent results from animal toxicological studies of inflammation. Increased immune cell populations in the circulation in response to allergen challenge and sensitization.	Section 6.3.9 of U.S. EPA (2016) Lu et al. (2023a) Lu et al. (2023b)	5 ppm NO_2 4 hr/d for 30 d
	Inconsistent epidemiologic evidence for increases in CRP and IL-6 in adults	Section 6.3.8 of U.S. EPA (2016)	
	Limited and inconclusive evidence in controlled human exposure studies (i.e., IL-6, IL-8, ICAM-1).	Chapter 5, Section 5.10.4.2	350 and 500 ppb for 2 h

List of abbreviations in alphabetical order: CBVD = cerebrovascular disease; CHD = congestive heart disease; CHF = congestive heart failure; CMD = cardiometabolic disease; CO = carbon monoxide; CPD = cardiopulmonary disease; CRP = c reactive protein; CVD = CVD; d = day; HDL = high density lipoprotein; hr = hour; ICAM-1 = intercellular adhesion molecule 1; IHD = ischemic heart disease; IL-6 – interleukin 6; IL-8 = interleukin 8; MDA = malondialdehyde; MI = myocardial infarction; mo = month; ppb = parts per billion; ppm = parts per million; ROS = reactive oxygen species; TBARS = thiobarbituric acid reactive substances; week = wk.

6.12 References

Aaron, CP; Hoffman, EA; Kawut, SM; Austin, JHM; Budoff, M; Michos, ED; Hinckley Stukovsky, K; Sack, C; Szpiro, AA; Watson, KD; Kaufman, JD; Barr, RG. (2019). Ambient air pollution and pulmonary vascular volume on computed tomography: The MESA Air Pollution and Lung cohort studies. Eur Respir J 53. http://dx.doi.org/10.1183/13993003.02116-2018

Adar, SD; Chen, YH; D'Souza, JC; O'Neill, MS; Szpiro, AA; Auchincloss, AH; Park, SK; Daviglus, ML; Diez Roux, AV; Kaufman, JD. (2018). Longitudinal Analysis of Long-Term Air Pollution Levels and Blood Pressure: A Cautionary Tale from the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect 126: 107003. http://dx.doi.org/10.1289/EHP2966

Alexeeff, SE; Roy, A; Shan, J; Liu, X; Messier, K; Apte, JS; Portier, C; Sidney, S; Van Den Eeden, SK. (2018). High-resolution mapping of traffic related air pollution with Google street view cars and incidence of cardiovascular events within neighborhoods in Oakland, CA. Environ Health 17: 13. http://dx.doi.org/10.1186/s12940-018-0382-1

Amini, H; Dehlendorff, C; Lim, YH; Mehta, A; Jørgensen, JT; Mortensen, LH; Westendorp, R; Hoffmann, B; Loft, S; Cole-Hunter, T; Bräuner, EV; Ketzel, M; Hertel, O; Brandt, J; Solvang Jensen, S; Christensen, JH; Geels, C; Frohn, LM; Backalarz, C; ... Andersen, ZJ. (2020). Long-term exposure to air pollution and stroke incidence: A Danish nurse cohort study. Environ Int 142: 105891. http://dx.doi.org/10.1016/j.envint.2020.105891

Andersen, ZJ; Cramer, J; Jørgensen, JT; Dehlendorff, C; Amini, H; Mehta, A; Cole-Hunter, T; Mortensen, LH; Westendorp, R; So, R; Li, S; Hoffmann, B; Loft, S; Bräuner, EV; Ketzel, M; Hertel, O; Brandt, J; Jensen, SS; Christensen, JH; Geels, C; Frohn, LM; Backalarz, C; Simonsen, MK; Lim, YH. (2021). Long-term exposure to road traffic noise and air pollution, and incident atrial fibrillation in the Danish nurse cohort. Environ Health Perspect 129: 87002. http://dx.doi.org/10.1289/EHP8090

Andersen, ZJ; Kristiansen, LC; Andersen, KK; Olsen, TS; Hvidberg, M; Jensen, SS; Ketzel, M; Loft, S; Sørensen, M; Tjønneland, A; Overvad, K; Raaschou-Nielsen, O. (2012). Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: A cohort study. Stroke 43: 320-325. http://dx.doi.org/10.1161/STROKEAHA.111.629246

Atkinson, RW; Carey, IM; Kent, AJ; van Staa, TP; Anderson, HR; Cook, DG. (2013). Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24: 44-53. http://dx.doi.org/10.1097/EDE.0b013e318276ccb8

Aung, N; Sanghvi, MM; Zemrak, F; Lee, AM; Cooper, JA; Paiva, JM; Thomson, RJ; Fung, K; Khanji, MY; Lukaschuk, E; Carapella, V; Kim, YJ; Munroe, PB; Piechnik, SK; Neubauer, S; Petersen, SE. (2018). Association between ambient air pollution and cardiac morpho-functional phenotypes: Insights from the UK Biobank population imaging study. Circulation 138: 2175-2186. http://dx.doi.org/10.1161/CIRCULATIONAHA.118.034856

Bai, L; Chen, H; Hatzopoulou, M; Jerrett, M; Kwong, JC; Burnett, RT; van Donkelaar, A; Copes, R; Martin, RV; Van Ryswyk, K; Lu, H; Kopp, A; Weichenthal, S. (2018). Exposure to ambient ultrafine particles and nitrogen dioxide and incident hypertension and diabetes. Epidemiology 29: 323-332. http://dx.doi.org/10.1097/EDE.0000000000000798

Bai, L; Shin, S; Burnett, RT; Kwong, JC; Hystad, P; van Donkelaar, A; Goldberg, MS; Lavigne, E; Copes, R; Martin, RV; Kopp, A; Chen, H. (2019a). Exposure to ambient air pollution and the incidence of congestive heart failure and acute myocardial infarction: A population-based study of 5.1 million Canadian adults living in Ontario. Environ Int 132: 105004. http://dx.doi.org/10.1016/j.envint.2019.105004

Bai, L; Weichenthal, S; Kwong, JC; Burnett, RT; Hatzopoulou, M; Jerrett, M; van Donkelaar, A; Martin, RV; Van Ryswyk, K; Lu, H; Kopp, A; Chen, H. (2019b). Associations of Long-Term Exposure

to Ultrafine Particles and Nitrogen Dioxide With Increased Incidence of Congestive Heart Failure and Acute Myocardial Infarction. Am J Epidemiol 188: 151-159. http://dx.doi.org/10.1093/aje/kwy194

Beckerman, BS; Jerrett, M; Finkelstein, M; Kanaroglou, P; Brook, JR; Arain, MA; Sears, MR; Stieb, D; Balmes, J; Chapman, K. (2012). The association between chronic exposure to traffic-related air pollution and ischemic heart disease. J Toxicol Environ Health A 75: 402-411. http://dx.doi.org/10.1080/15287394.2012.670899

Beelen, R; Hoek, G; van den Brandt, PA; Goldbohm, RA; Fischer, P; Schouten, LJ; Jerrett, M; Hughes, E; Armstrong, B; Brunekreef, B. (2008). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect 116: 196-202. http://dx.doi.org/10.1289/ehp.10767

Beelen, R; Hoek, G; Vienneau, D; Eeftens, M; Dimakopoulou, K; Pedeli, X; Tsai, MY; Künzli, N; Schikowski, T; Marcon, A; Eriksen, KT; Raaschou-Nielsen, O; Stephanou, E; Patelarou, E; Lanki, T; Yli-Toumi, T; Declercq, C; Falq, G; Stempfelet, M; ... de Hoogh, K. (2013). Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe - The ESCAPE project. Atmos Environ 72: 10-23. http://dx.doi.org/10.1016/j.atmosenv.2013.02.037

Beelen, R; Stafoggia, M; Raaschou-Nielsen, O; Andersen, ZJ; Xun, WW; Katsouyanni, K; Dimakopoulou, K; Brunekreef, B; Weinmayr, G; Hoffmann, B; Wolf, K; Samoli, E; Houthuijs, D; Nieuwenhuijsen, M; Oudin, A; Forsberg, B; Olsson, D; Salomaa, V; Lanki, T; Yli-Tuomi, T; Oftedal, B; Aamodt, G; Nafstad, P; De Faire, U; Pedersen, NL; Ostenson, CG; Fratiglioni, L; Penell, J; Korek, M; Pyko, A; Eriksen, KT; Tjønneland, A; Becker, T; Eeftens, M; Bots, M; Meliefste, K; Wang, M; Bueno-De-Mesquita, B; Sugiri, D; Krämer, U; Heinrich, J; de Hoogh, K; Key, T; Peters, A; Cyrys, J; Concin, H; Nagel, G; Ineichen, A; Schaffner, E; Probst-Hensch, N; Dratva, J; Ducret-Stich, R; Vilier, A; Clavel-Chapelon, F; Stempfelet, M; Grioni, S; Krogh, V; Tsai, MY; Marcon, A; Ricceri, F; Sacerdote, C; Galassi, C; Migliore, E; Ranzi, A; Cesaroni, G; Badaloni, C; Forastiere, F; Tamayo, I; Amiano, P; Dorronsoro, M; Katsoulis, M; Trichopoulou, A; Vineis, P; Hoek, G. (2014). Long-term exposure to air pollution and cardiovascular mortality: An analysis of 22 European cohorts. Epidemiology 25: 368-378. http://dx.doi.org/10.1097/EDE.0000000000000076

Bilenko, N; Rossem, LV; Brunekreef, B; Beelen, R; Eeftens, M; Hoek, G; Houthuijs, D; de Jongste, JC; Kempen, EV; Koppelman, GH; Meliefste, K; Oldenwening, M; Smit, HA; Wijga, AH; Gehring, U. (2015). Traffic-related air pollution and noise and children's blood pressure: Results from the PIAMA birth cohort study. Eur J Prev Cardiol 22: 4-12. http://dx.doi.org/10.1177/2047487313505821

Bouma, F; Janssen, NA; Wesseling, J; van Ratingen, S; Strak, M; Kerckhoffs, J; Gehring, U; Hendricx, W; de Hoogh, K; Vermeulen, R; Hoek, G. (2023). Long-term exposure to ultrafine particles and natural and cause-specific mortality. Environ Int 175: 107960. http://dx.doi.org/10.1016/j.envint.2023.107960

Breton, CV; Wang, X; Mack, WJ; Berhane, K; Lopez, M; Islam, TS; Feng, M; Lurmann, F; McConnell, R; Hodis, HN; Künzli, N; Avol, E. (2012). Childhood air pollutant exposure and carotid artery intima-media thickness in young adults. Circulation 126: 1614-1620. http://dx.doi.org/10.1161/CIRCULATIONAHA.112.096164

Brunekreef, B; Beelen, R; Hoek, G; Schouten, L; Bausch-Goldbohm, S; Fischer, P; Armstrong, B; Hughes, E; Jerrett, M; van den Brandt, P. (2009). Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: The NLCS-AIR Study. (139). Boston, MA: Health Effects Institute. http://www.n65.nl/NCLS-AIR-Study-2009.pdf

Brunekreef, B; Strak, M; Chen, J; Andersen, ZJ; Atkinson, R; Bauwelinck, M; Bellander, T; Boutron, MC; Brandt, J; Carey, I; Cesaroni, G; Forastiere, F; Fecht, D; Gulliver, J; Hertel, O; Hoffmann, B; de Hoogh, K; Houthuijs, D; Hvidtfeldt, U; ... Hoek, G. (2021). Mortality and morbidity effects

of long-term exposure to low-level PM2.5, BC, NO2, and O3: An analysis of European cohorts in the ELAPSE Project (pp. 1-127). (ISSN 1041-5505

EISSN 2688-6855

Research Report No. 208). Boston, MA: Health Effects Institute.

C. Chi, G; Liu, Y; Macdonald, JW; M. Reynolds, L; Enquobahrie, DA; L. Fitzpatrick, A; Kerr, KF; J. Budoff, M; Lee, S, i; Siscovick, D; D. Kaufman, J. (2022). Epigenome-wide analysis of long-term air pollution exposure and DNA methylation in monocytes: Results from the Multi-Ethnic Study of Atherosclerosis. Epigenetics 17: 297-313. http://dx.doi.org/10.1080/15592294.2021.1900028

Cai, Y; Hodgson, S; Blangiardo, M; Gulliver, J; Morley, D; Fecht, D; Vienneau, D; de Hoogh, K; Key, T; Hveem, K; Elliott, P; Hansell, AL. (2018). Road traffic noise, air pollution and incident cardiovascular disease: A joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. Environ Int 114: 191-201. http://dx.doi.org/10.1016/j.envint.2018.02.048

Carey, IM; Atkinson, RW; Kent, AJ; van Staa, T; Cook, DG; Anderson, HR. (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187: 1226-1233. http://dx.doi.org/10.1164/rccm.201210-1758OC

Cesaroni, G; Badaloni, C; Gariazzo, C; Stafoggia, M; Sozzi, R; Davoli, M; Forastiere, F. (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect 121: 324-331. http://dx.doi.org/10.1289/ehp.1205862

Cesaroni, G; Forastiere, F; Stafoggia, M; Andersen, ZJ; Badaloni, C; Beelen, R; Caracciolo, B; de Faire, U; Erbel, R; Eriksen, KT; Fratiglioni, L; Galassi, C; Hampel, R; Heier, M; Hennig, F; Hilding, A; Hoffmann, B; Houthuijs, D; Jöckel, KH; Korek, M; Lanki, T; Leander, K; Magnusson, PK; Migliore, E; Ostenson, CG; Overvad, K; Pedersen, NL; J, JP; Penell, J; Pershagen, G; Pyko, A; Raaschou-Nielsen, O; Ranzi, A; Ricceri, F; Sacerdote, C; Salomaa, V; Swart, W; Turunen, AW; Vineis, P; Weinmayr, G; Wolf, K; de Hoogh, K; Hoek, G; Brunekreef, B; Peters, A. (2014). Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. BMJ 348: f7412.

Chen, C; Dan, D; Sun, S; Yuan, Y; Liu, L; Chen, C; Jiang, J; Fu, F; Zhang, Z; Deng, D; Wang, W; Li, L. (2023). Ambient air pollution and risk of enterotomy, gastrointestinal cancer, and all-cause mortality among 4,708 individuals with inflammatory bowel disease: A prospective cohort study. Environ Health Perspect 131: 77010. http://dx.doi.org/10.1289/EHP12215

Chen, H; Goldberg, MS; Burnett, RT; Jerrett, M; Wheeler, AJ; Villeneuve, PJ. (2013). Long-term exposure to traffic-related air pollution and cardiovascular mortality. Epidemiology 24: 35-43. http://dx.doi.org/10.1097/EDE.0b013e318276c005

Chi, GC; Liu, Y; Macdonald, JW; Barr, RG; Donohue, KM; Hensley, MD; Hou, L; Mccall, CE; Reynolds, LM; Siscovick, DS; Kaufman, JD. (2016). Long-term outdoor air pollution and DNA methylation in circulating monocytes: results from the multi-ethnic study of atherosclerosis (MESA). Environ Health 15: 119. http://dx.doi.org/10.1186/s12940-016-0202-4

Clark, C; Crombie, R; Head, J; van Kamp, I; van Kempen, E; Stansfeld, SA. (2012). Does traffic-related air pollution explain associations of aircraft and road traffic noise exposure on children's health and cognition? A secondary analysis of the United Kingdom sample from the RANCH project. Am J Epidemiol 176: 327-337. http://dx.doi.org/10.1093/aje/kws012

Coogan, PF; White, LF; Jerrett, M; Brook, RD; Su, JG; Seto, E; Burnett, R; Palmer, JR; Rosenberg, L. (2012). Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation 125: 767-772. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.052753

Coogan, PF; White, LF; Yu, J; Brook, RD; Burnett, RT; Marshall, JD; Bethea, TN; Rosenberg, L; Jerrett, M. (2017). Long-term exposure to NO2 and ozone and hypertension incidence in the black women's health study. Am J Hypertens 30: 367-372. http://dx.doi.org/10.1093/ajh/hpw168

Cramer, J; Jã Rgensen, JT; Hoffmann, B; Loft, S; Brã¤Uner, EV; Prescott, E; Ketzel, M; Hertel, O; Brandt, J; Jensen, SS; Backalarz, C; Simonsen, MK; Andersen, ZJ. (2020). Long-term exposure to air pollution and incidence of myocardial infarction: A Danish nurse cohort study. Environ Health Perspect 128: 57003. http://dx.doi.org/10.1289/EHP5818

Crouse, DL; Peters, PA; Hystad, P; Brook, JR; van Donkelaar, A; Martin, RV; Villeneuve, PJ; Jerrett, M; Goldberg, MS; Pope, CA; Brauer, M; Brook, RD; Robichaud, A; Menard, R; Burnett, RT. (2015). Ambient PM 2.5, O 3, and NO 2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 123: 1180-1186. http://dx.doi.org/10.1289/ehp.1409276

Dalecká, A; Wigmann, C; Kress, S; Altug, H; Jiřík, V; Heinrich, J; Abramson, MJ; Schikowski, T. (2021). The mediating role of lung function on air pollution-induced cardiopulmonary mortality in elderly women: The SALIA cohort study with 22-year mortality follow-up. Int J Hyg Environ Health 233: 113705. http://dx.doi.org/10.1016/j.ijheh.2021.113705

Danesh Yazdi, M; Wang, Y; Di, Q; Wei, YG; Requia, WJ; Shi, LH; Sabath, MB; Dominici, F; Coull, BA; Evans, JS; Koutrakis, P; Schwartz, JD. (2021). Long-term association of air pollution and hospital admissions among Medicare participants using a doubly robust additive model. Circulation 143: 1584-1596. http://dx.doi.org/10.1161/CIRCULATIONAHA.120.050252

Danesh Yazdi, M; Wei, Y; Di, Q; Requia, WJ; Shi, L; Sabath, MB; Dominici, F; Schwartz, J. (2022). The effect of long-term exposure to air pollution and seasonal temperature on hospital admissions with cardiovascular and respiratory disease in the United States: A difference-in-differences analysis. Sci Total Environ 843: 156855. http://dx.doi.org/10.1016/j.scitotenv.2022.156855

de Burbure, CY; Heilier, JF; Nève, J; Becker, A; Albrecht, C; Borm, PJA; Gromadzinska, J; Wasowicz, W; Rydzynski, K; Bernard, AM. (2007). Lung permeability, antioxidant status, and NO2 inhalation: A selenium supplementation study in rats. J Toxicol Environ Health A 70: 284-294. http://dx.doi.org/10.1080/15287390600884875

de Kluizenaar, Y; van Lenthe, FJ; Visschedijk, AJ; Zandveld, PY; Miedema, HM; Mackenbach, JP. (2013). Road traffic noise, air pollution components and cardiovascular events. Noise Health 15: 388-397. http://dx.doi.org/10.4103/1463-1741.121230

de Prado-Bert, P; Warembourg, C; Dedele, A; Heude, B; Borràs, E; Sabidó, E; Aasvang, GM; Lepeule, J; Wright, J; Urquiza, J; Gützkow, KB; Maitre, L; Chatzi, L; Casas, M; Vafeiadi, M; Nieuwenhuijsen, MJ; de Castro, M; Grazuleviciene, R; Mceachan, RRC; Basagaña, X; Vrijheid, M; Sunyer, J; Bustamante, M. (2022). Short- and medium-term air pollution exposure, plasmatic protein levels and blood pressure in children. Environ Res 211: 113109. http://dx.doi.org/10.1016/j.envres.2022.113109

Dong, GH; Qian, ZM; Xaverius, PK; Trevathan, E; Maalouf, S; Parker, J; Yang, L; Liu, MM; Wang, D; Ren, WH; Ma, W; Wang, J; Zelicoff, A; Fu, Q; Simckes, M. (2013). Association between long-term air pollution and increased blood pressure and hypertension in China. Hypertension 61: 578-584. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.00003

Edlund, K; Sallsten, G; Molnár, P; Andersson, EM; Ögren, M; Segersson, D; Fagman, E; Fagerberg, B; Barregard, L; Bergström, G; Stockfelt, L. (2022). Long-term exposure to air pollution, coronary artery calcification, and carotid artery plaques in the population-based Swedish SCAPIS Gothenburg cohort. Environ Res 214: 113926. http://dx.doi.org/10.1016/j.envres.2022.113926

Elbarbary, M; Oganesyan, A; Honda, T; Morgan, G; Guo, Y; Guo, Y; Negin, J. (2021). Systemic Inflammation (C-Reactive Protein) in Older Chinese Adults Is Associated with Long-Term Exposure to Ambient Air Pollution. Int J Environ Res Public Health 18. http://dx.doi.org/10.3390/ijerph18063258

Endes, S; Schaffner, E; Caviezel, S; Dratva, J; Stolz, D; Schindler, C; Künzli, N; Schmidt-Trucksäss, A; Probst-Hensch, N. (2017). Is physical activity a modifier of the association between air pollution and arterial stiffness in older adults: The SAPALDIA cohort study. Int J Hyg Environ Health 220: 1030-1038. http://dx.doi.org/10.1016/j.ijheh.2017.06.001

Eum, KD; Honda, TJ; Wang, B; Kazemiparkouhi, F; Manjourides, J; Pun, VC; Pavlu, V; Suh, H. (2022). Long-term nitrogen dioxide exposure and cause-specific mortality in the U.S. Medicare population. Environ Res 207: 112154. http://dx.doi.org/10.1016/j.envres.2021.112154

Eum, KD; Kazemiparkouhi, F; Wang, B; Manjourides, J; Pun, V; Pavlu, V; Suh, H. (2019). Long-term NO2 exposures and cause-specific mortality in American older adults. Environ Int 124: 10-15. http://dx.doi.org/10.1016/j.envint.2018.12.060

Farzan, SF; Habre, R; Danza, P; Lurmann, F; Gauderman, WJ; Avol, E; Bastain, T; Hodis, HN; Breton, C. (2021). Childhood traffic-related air pollution and adverse changes in subclinical atherosclerosis measures from childhood to adulthood. Environ Health 20: 44. http://dx.doi.org/10.1186/s12940-021-00726-x

Felber Dietrich, D; Gemperli, A; Gaspoz, JM; Schindler, C; Liu, LJ; Gold, DR; Schwartz, J; Rochat, T; Barthélémy, JC; Pons, M; Roche, F; Probst Hensch, NM; Bridevaux, PO; Gerbase, MW; Neu, U; Ackermann-Liebrich, U. (2008). Differences in heart rate variability associated with long-term exposure to NO2. Environ Health Perspect 116: 1357-1361. http://dx.doi.org/10.1289/ehp.11377

Fenters, JD; Findlay, JC; Port, CD; Ehrlich, R; Coffin, DL. (1973). Chronic exposure to nitrogen dioxide: Immunologic, physiologic, and pathologic effects in virus-challenged squirrel monkeys. Arch Environ Health 27: 85-89. http://dx.doi.org/10.1080/00039896.1973.10666324

Floud, S; Blangiardo, M; Clark, C; de Hoogh, K; Babisch, W; Houthuijs, D; Swart, W; Pershagen, G; Katsouyanni, K; Velonakis, M; Vigna-Taglianti, F; Cadum, E; Hansell, AL. (2013). Exposure to aircraft and road traffic noise and associations with heart disease and stroke in six European countries: A cross-sectional study. Environ Health 12: 89. http://dx.doi.org/10.1186/1476-069X-12-89

Foraster, M; Basagaña, X; Aguilera, I; Rivera, M; Agis, D; Bouso, L; Deltell, A; Marrugat, J; Ramos, R; Sunyer, J; Vila, J; Elosua, R; Künzli, N. (2014). Association of long-term exposure to traffic-related air pollution with blood pressure and hypertension in an adult population-based cohort in Spain (the REGICOR Study). Environ Health Perspect 122: 404-411. http://dx.doi.org/10.1289/ehp.1306497

Fossati, S; Valvi, D; Martinez, D; Cirach, M; Estarlich, M; Fernández-Somoano, A; Guxens, M; Iñiguez, C; Irizar, A; Lertxundi, A; Nieuwenhuijsen, M; Tamayo, I; Vioque, J; Tardón, A; Sunyer, J; Vrijheid, M. (2020). Prenatal air pollution exposure and growth and cardio-metabolic risk in preschoolers. Environ Int 138: 105619. http://dx.doi.org/10.1016/j.envint.2020.105619

Fuks, KB; Weinmayr, G; Basagaña, X; Gruzieva, O; Hampel, R; Oftedal, B; Sørensen, M; Wolf, K; Aamodt, G; Aasvang, GM; Aguilera, I; Becker, T; Beelen, R; Brunekreef, B; Caracciolo, B; Cyrys, J; Elosua, R; Eriksen, KT; Foraster, M; ... Hoffmann, B. (2017). Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). Eur Heart J 38: 983-990. http://dx.doi.org/10.1093/eurheartj/ehw413

Fuks, KB; Weinmayr, G; Foraster, M; Dratva, J; Hampel, R; Houthuijs, D; Oftedal, B; Oudin, A; Panasevich, S; Penell, J; Sommar, JN; Sørensen, M; Tiittanen, P; Wolf, K; Xun, WW; Aguilera, I; Basagaña, X; Beelen, R; Bots, ML; Brunekreef, B; Bueno-De-Mesquita, HB; Caracciolo, B; Cirach, M; de Faire, U; de Nazelle, A; Eeftens, M; Elosua, R; Erbel, R; Forsberg, B; Fratiglioni, L; Gaspoz, JM; Hilding, A; Jula, A; Korek, M; Krämer, U; Künzli, N; Lanki, T; Leander, K; Magnusson, PK; Marrugat, J; Nieuwenhuijsen, MJ; Ostenson, CG; Pedersen, NL; Pershagen, G; Phuleria, HC; Probst-Hensch, NM; Raaschou-Nielsen, O; Schaffner, E; Schikowski, T; Schindler, C; Schwarze, PE; Søgaard, AJ; Sugiri, D; Swart, WJ; Tsai, MY; Turunen, AW; Vineis, P; Peters, A; Hoffmann, B. (2014). Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European study of cohorts for air pollution effects (ESCAPE) [Review]. Environ Health Perspect 122: 896-905. http://dx.doi.org/10.1289/ehp.1307725

Furiosi, NJ; Crane, SC; Freeman, G. (1973). Mixed sodium chloride aerosol and nitrogen dioxide in air: Biological effects on monkeys and rats. Arch Environ Occup Health 27: 405-408. http://dx.doi.org/10.1080/00039896.1973.10666414

Gan, W; Koehoorn, M; Davies, H; Demers, P; Tamburic, L; Brauer, M. (2011). Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. Environ Health Perspect 119: 501-507. http://dx.doi.org/10.1289/ehp.1002511

Gan, WQ; Allen, RW; Brauer, M; Davies, HW; Mancini, GB; Lear, SA. (2014). Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: a prospective cohort study. BMJ Open 4: e004743. http://dx.doi.org/10.1136/bmjopen-2013-004743

Gandini, M; Scarinzi, C; Bande, S; Berti, G; Carnà, P; Ciancarella, L; Costa, G; Demaria, M; Ghigo, S; Piersanti, A; Rowinski, M; Spadea, T; Stroscia; Cadum, E; Group, LMc. (2018). Long term effect of air pollution on incident hospital admissions: Results from the Italian Longitudinal Study within LIFE MED HISS project. Environ Int 121: 1087-1097. http://dx.doi.org/10.1016/j.envint.2018.10.020

Gariazzo, C; Carlino, G; Silibello, C; Tinarelli, G; Renzi, M; Finardi, S; Pepe, N; Barbero, D; Radice, P; Marinaccio, A; Forastiere, F; Michelozzi, P; Viegi, G; Stafoggia, M; Group, BC. (2021). Impact of different exposure models and spatial resolution on the long-term effects of air pollution. Environ Res 192: 110351. http://dx.doi.org/10.1016/j.envres.2020.110351

Guyatt, AL; Cai, YS; Doiron, D; Tobin, MD; Hansell, AL. (2024). Air pollution, lung function and mortality: Survival and mediation analyses in UK Biobank [Editorial]. ERJ Open Res 10. http://dx.doi.org/10.1183/23120541.00141-2024

Hamroun, Ag; Genin, Mi; Glowacki, Fr; Sautenet, Be; Leffondre, Ka; De Courreges, An; Dauchet, Lu; Gauthier, Vi; Bayer, Fl; Lassalle, Ma; Couchoud, Ce; Amouyel, Ph; Occelli, Fl. (2024). Multiple air pollutant exposure is associated with higher risk of all-cause mortality in dialysis patients: a French registry-based nationwide study. Front Public Health 12: 1390999-. http://dx.doi.org/10.3389/fpubh.2024.1390999

Hart, JE; Hohensee, C; Laden, F; Holland, I; Whitsel, EA; Wellenius, GA; Winkelmayer, WC; Sarto, GE; Warsinger Martin, L; Manson, JE; Greenland, P; Kaufman, J; Albert, C; Perez, MV. (2021). Long-term exposures to air pollution and the risk of atrial fibrillation in the Women's Health Initiative cohort. Environ Health Perspect 129: 97007. http://dx.doi.org/10.1289/EHP7683

Hart, JE; Rimm, EB; Rexrode, KM; Laden, F. (2013). Changes in traffic exposure and the risk of incident myocardial infarction and all-cause mortality. Epidemiology 24: 734-742. http://dx.doi.org/10.1097/EDE.0b013e31829d5dae

Hartiala, J; Breton, CV; Tang, WH; Lurmann, F; Hazen, SL; Gilliland, FD; Allayee, H. (2016). Ambient air pollution is associated with the severity of coronary atherosclerosis and incident myocardial infarction in patients undergoing elective cardiac evaluation. J Am Heart Assoc 5. http://dx.doi.org/10.1161/JAHA.116.003947

Hennig, F; Geisel, MH; Kälsch, H; Lucht, S; Mahabadi, AA; Moebus, S; Erbel, R; Lehmann, N; Jöckel, KH; Scherag, A; Hoffmann, B. (2020). Air pollution and progression of atherosclerosis in different vessel beds—Results from a prospective cohort study in the Ruhr area, Germany. Environ Health Perspect 128: 1-9. http://dx.doi.org/10.1289/EHP7077

Hoek, G; Brunekreef, B; Goldbohm, S; Fischer, P; van den Brandt, PA. (2002). Association between mortality and indicators of traffic-related air pollution in the Netherlands: A cohort study. Lancet 360: 1203-1209. http://dx.doi.org/10.1016/s0140-6736(02)11280-3

Honda, T; Pun, VC; Manjourides, J; Suh, H. (2017). Anemia prevalence and hemoglobin levels are associated with long-term exposure to air pollution in an older population. Environ Int 101: 125-132. http://dx.doi.org/10.1016/j.envint.2017.01.017

Hou, J; Gu, J; Liu, X; Tu, R; Dong, X; Li, R; Mao, Z; Huo, W; Chen, G; Pan, M; Guo, Y; Li, S; Wang, C. (2021). Long-term exposure to air pollutants enhanced associations of obesity with blood pressure and hypertension. Clin Nutr 40: 1442-1450. http://dx.doi.org/10.1016/j.clnu.2021.02.029

Howell, NA; Tu, JV; Moineddin, R; Chen, H; Chu, A; Hystad, P; Booth, GL. (2019). Interaction between neighborhood walkability and traffic-related air pollution on hypertension and diabetes: The CANHEART cohort. Environ Int 132: 104799. http://dx.doi.org/10.1016/j.envint.2019.04.070

Huang, W; Zhou, Y; Chen, X; Zeng, X; Knibbs, LD; Zhang, Y; Jalaludin, B; Dharmage, SC; Morawska, L; Guo, Y; Yang, X; Zhang, L; Shan, A; Chen, J; Wang, T; Heinrich, J; Gao, M; Lin, L; Xiao, X; ... Dong, G. (2023). Individual and joint associations of long-term exposure to air pollutants and cardiopulmonary mortality: A 22-year cohort study in Northern China. Lancet Reg Health West Pac 36: 100776. http://dx.doi.org/10.1016/j.lanwpc.2023.100776

Hvidtfeldt, UA; Sørensen, M; Geels, C; Ketzel, M; Khan, J; Tjønneland, A; Overvad, K; Brandt, J; Raaschou-Nielsen, O. (2019). Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. Environ Int 123: 265-272. http://dx.doi.org/10.1016/j.envint.2018.12.010

Jendrossek, M; Standl, M; Koletzko, S; Lehmann, I; Bauer, CP; Schikowski, T; von Berg, A; Berdel, D; Heinrich, J; Markevych, I. (2017). Residential air pollution, road traffic, greenness and maternal hypertension: Results from GINIplus and LISAplus. Int J Occup Environ Med 8: 131-142. http://dx.doi.org/10.15171/ijoem.2017.1073

Jerrett, M; Burnett, RT; Beckerman, BS; Turner, MC; Krewski, D; Thurston, G; Martin, RV; van Donkelaar, A; Hughes, E; Shi, Y; Gapstur, SM; Thun, MJ; Pope, CA, III. (2013). Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 188: 593-599. http://dx.doi.org/10.1164/rccm.201303-0609OC

Jerrett, M; Finkelstein, MM; Brook, JR; Arain, MA; Kanaroglou, P; Stieb, DM; Gilbert, NL; Verma, D; Finkelstein, N; Chapman, KR; Sears, MR. (2009). A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada. Environ Health Perspect 117: 772-777. http://dx.doi.org/10.1289/ehp.11533

Ji, S; Guo, Y; Li, G; Sang, N. (2022). NO2 exposure contributes to cardiac hypertrophy in male mice through apoptosis signaling pathways. Chemosphere 309: 136576. http://dx.doi.org/10.1016/j.chemosphere.2022.136576

Jin, T; Di, Q; Réquia, WJ; Yazdi, MD; Castro, E; Ma, T; Wang, Y; Zhang, H; Shi, L; Schwartz, J. (2022). Associations between long-term air pollution exposure and the incidence of cardiovascular diseases among American older adults. Environ Int 170: 107594. http://dx.doi.org/10.1016/j.envint.2022.107594

Johnson, JYM; Rowe, BH; Allen, RW; Peters, PA; Villeneuve, PJ. (2013). A case-control study of medium-term exposure to ambient nitrogen dioxide pollution and hospitalization for stroke. BMC Public Health 13: 368. http://dx.doi.org/10.1186/1471-2458-13-368

Johnson, M; Brook, JR; Brook, RD; Oiamo, TH; Luginaah, I; Peters, PA; Spence, JD. (2020). Traffic-Related Air Pollution and Carotid Plaque Burden in a Canadian City With Low-Level Ambient Pollution. J Am Heart Assoc 9: e013400. http://dx.doi.org/10.1161/JAHA.119.013400

Jones, MR; Diez-Roux, AV; O'Neill, MS; Guallar, E; Sharrett, AR; Post, W; Kaufman, JD; Navas-Acien, A. (2015). Ambient air pollution and racial/ethnic differences in carotid intima-media thickness in the Multi-Ethnic Study of Atherosclerosis (MESA). J Epidemiol Community Health 69: 1191-1198. http://dx.doi.org/10.1136/jech-2015-205588

Kang, S; Hong, YS; Park, J; Kang, D; Kim, H; Lee, J; Kim, W; Kang, SW; Guallar, E; Cho, J; Park, HY. (2023). Air pollution and mortality in patients with chronic obstructive pulmonary disease: A cohort study in South Korea. Ther Adv Chronic Dis 14: 20406223231176175. http://dx.doi.org/10.1177/20406223231176175

Karoui, A; Crochemore, C; Harouki, N; Corbière, C; Preterre, D; Vendeville, C; Richard, V; Fardel, O; Lecureur, V; Vaugeois, JM; Sichel, F; Mulder, P; Monteil, C. (2020). Nitrogen dioxide inhalation exposures induce cardiac mitochondrial reactive oxygen species production, impair mitochondrial function and promote coronary endothelial dysfunction. Int J Environ Res Public Health 17: 5526. http://dx.doi.org/10.3390/ijerph17155526

Kim, SY; Kim, JH; Kim, YH; Wee, JH; Min, C; Han, SM; Kim, S; Choi, HG. (2022). Short- and long-term exposure to air pollution increases the risk of stroke. Int J Stroke 17: 654-660. http://dx.doi.org/10.1177/17474930211042118

Klompmaker, JO; Hart, JE; James, P; Sabath, MB; Wu, X; Zanobetti, A; Dominici, F; Laden, F. (2021a). Air pollution and cardiovascular disease hospitalization - Are associations modified by greenness, temperature and humidity? Environ Int 156: 106715. http://dx.doi.org/10.1016/j.envint.2021.106715

Klompmaker, JO; Hoek, G; Bloemsma, LD; Marra, M; Wijga, AH; van den Brink, C; Brunekreef, B; Lebret, E; Gehring, U; Janssen, NAH. (2020). Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality. Environ Int 134: 105341. http://dx.doi.org/10.1016/j.envint.2019.105341

Klompmaker, JO; Janssen, N; Andersen, ZJ; Atkinson, R; Bauwelinck, M; Chen, J; de Hoogh, K; Houthuijs, D; Katsouyanni, K; Marra, M; Oftedal, B; Rodopoulou, S; Samoli, E; Stafoggia, M; Strak, M; Swart, W; Wesseling, J; Vienneau, D; Brunekreef, B; Hoek, G. (2021b). Comparison of associations between mortality and air pollution exposure estimated with a hybrid, a land-use regression and a dispersion model. Environ Int 146: 106306. http://dx.doi.org/10.1016/j.envint.2020.106306

Klompmaker, JO; Janssen, NAH; Bloemsma, LD; Gehring, U; Wijga, AH; Van Den Brink, C; Lebret, E; Brunekreef, B; Hoek, G. (2019). Associations of combined exposures to surrounding green, air pollution, and road traffic noise with cardiometabolic diseases. Environ Health Perspect 127: 87003. http://dx.doi.org/10.1289/EHP3857

Klompmaker, JO; Janssen, NAH; Bloemsma, LD; Marra, M; Lebret, E; Gehring, U; Hoek, G. (2021c). Effects of exposure to surrounding green, air pollution and traffic noise with non-accidental and cause-specific mortality in the Dutch national cohort. Environ Health 20: 82. http://dx.doi.org/10.1186/s12940-021-00769-0

Krewski, D; Burnett, RT; Goldberg, MS; Hoover, K; Siemiatycki, J; Jerrett, M; Abrahamowicz, M; White, WH. (2000). Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. Cambridge, MA: Health Effects Institute. https://docs.house.gov/meetings/SY/SY00/20130801/101246/HMTG-113-SY00-20130801-SD026.pdf

Kulick, ER; Eliot, MN; Szpiro, AA; Coull, BA; Tinker, LF; Eaton, CB; Whitsel, EA; Stewart, JD; Kaufman, JD; Wellenius, GA. (2023). Long-term exposure to ambient particulate matter and stroke etiology: Results from the Women's Health Initiative. Environ Res 224: 115519. http://dx.doi.org/10.1016/j.envres.2023.115519

Kulick, ER; Wellenius, GA; Kaufman, JD; Derosa, JT; Kinney, PL; Cheung, YK; Wright, CB; Sacco, RL; Elkind, MS. (2017). Long-Term Exposure to Ambient Air Pollution and Subclinical Cerebrovascular Disease in NOMAS (the Northern Manhattan Study). Stroke 48: 1966-1968. http://dx.doi.org/10.1161/STROKEAHA.117.016672

Kuo, CL; Liu, R; Godoy, LDC; Pilling, LC; Fortinsky, RH; Brugge, D. (2023). Association between Residential Exposure to Air Pollution and Incident Coronary Heart Disease Is Not Mediated by Leukocyte Telomere Length: A UK Biobank Study. Toxics 11: 489. http://dx.doi.org/10.3390/toxics11060489

Laratta, CR; Kendzerska, T; Carlsten, C; Brauer, M; van Eeden, SF; Allen, AJM; Fox, N; Peres, BU; Ayas, NT. (2020). Air pollution and systemic inflammation in patients with suspected OSA living in an urban residential area. Chest 158: 1713-1722. http://dx.doi.org/10.1016/j.chest.2020.05.596

Lefler, JS; Higbee, JD; Burnett, RT; Ezzati, M; Coleman, NC; Mann, DD; Marshall, JD; Bechle, M; Wang, Y; Robinson, AL; Arden Pope, C. (2019). Air pollution and mortality in a large, representative U.S. cohort: multiple-pollutant analyses, and spatial and temporal decompositions. Environ Health 18: 101. http://dx.doi.org/10.1186/s12940-019-0544-9

Lenters, V; Uiterwaal, CS; Beelen, R; Bots, ML; Fischer, P; Brunekreef, B; Hoek, G. (2010). Long-term exposure to air pollution and vascular damage in young adults. Epidemiology 21: 512-520. http://dx.doi.org/10.1097/EDE.0b013e3181dec3a7

Letellier, N; Zamora, S; Spoon, C; Yang, JA; Mortamais, M; Escobar, GC; Sears, DD; Jankowska, MM; Benmarhnia, T. (2022). Air pollution and metabolic disorders: Dynamic versus static measures of

exposure among Hispanics/Latinos and non-Hispanics. Environ Res 209: 112846. http://dx.doi.org/10.1016/j.envres.2022.112846

Levinsson, A; Olin, AC; Modig, L; Dahgam, S; Björck, L; Rosengren, A; Nyberg, F. (2014). Interaction effects of long-term air pollution exposure and variants in the GSTP1, GSTT1 and GSTCD genes on risk of acute myocardial infarction and hypertension: A case-control study. PLoS ONE 9: e99043. http://dx.doi.org/10.1371/journal.pone.0099043

Li, FR; Zhu, B; Liao, J; Cheng, Z; Jin, C; Mo, C; Liang, F. (2022). Ambient air pollutants and incident microvascular disease: A cohort study. Environ Sci Technol 56: 8485-8495. http://dx.doi.org/10.1021/acs.est.2c00898

Li, ZH; Wang, XM; Xiang, JX; Nan, Y; Chen, YJ; Zhang, PD; Liu, D; Shen, D; Zhang, XR; Zhong, WF; Chen, PL; Huang, QM; Song, WQ; Qiu, CS; Liang, F; Li, C; Mao, C. (2023). Associations of long-term joint exposure to various ambient air pollutants with all-cause and cause-specific mortality: Evidence from a large population-based cohort study. Environ Sci Pollut Res Int 30: 84357-84367. http://dx.doi.org/10.1007/s11356-023-28224-2

Lim, CC; Hayes, RB; Ahn, J; Shao, Y; Silverman, DT; Jones, RR; Garcia, C; Bell, ML; Thurston, GD. (2019). Long-term exposure to ozone and cause-specific mortality risk in the United States. Am J Respir Crit Care Med 200: 1022-1031. http://dx.doi.org/10.1164/rccm.201806-1161OC

Lim, YH; Jørgensen, JT; So, R; Cole-Hunter, T; Mehta, AJ; Amini, H; Bräuner, E; Westendorp, RGJ; Liu, S; Mortensen, LH; Hoffmann, B; Loft, S; Ketzel, M; Hertel, O; Brandt, J; Jensen, SS; Backalarz, C; Simonsen, MK; Tasic, N; Andersen, ZJ. (2021). Long-term exposure to air pollution, road traffic noise, and heart failure incidence: The Danish nurse cohort. J Am Heart Assoc 10: e021436. http://dx.doi.org/10.1161/JAHA.121.021436

Lipsett, MJ; Ostro, BD; Reynolds, P; Goldberg, D; Hertz, A; Jerrett, M; Smith, DF; Garcia, C; Chang, ET; Bernstein, L. (2011). Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am J Respir Crit Care Med 184: 828-835. http://dx.doi.org/10.1164/rccm.201012-2082OC

Liu, C; Fuertes, E; Tiesler, CMT; Birk, M; Babisch, W; Bauer, CP; Koletzko, S; von Berg, A; Hoffmann, B; Heinrich, J. (2014). The associations between traffic-related air pollution and noise with blood pressure in children: Results from the GINIplus and LISAplus studies. Int J Hyg Environ Health 217: 499-505. http://dx.doi.org/10.1016/j.ijheh.2013.09.008

Lu, C; Liu, Q; Deng, M; Liao, H; Yang, X; Ma, P. (2023a). Interaction of high temperature and NO2 exposure on asthma risk: In vivo experimental evidence of inflammation and oxidative stress. Sci Total Environ 869: 161760. http://dx.doi.org/10.1016/j.scitotenv.2023.161760

Lu, C; Wang, F; Liu, Q; Deng, M; Yang, X; Ma, P. (2023b). Effect of NO2 exposure on airway inflammation and oxidative stress in asthmatic mice. J Hazard Mater 457: 131787. http://dx.doi.org/10.1016/j.jhazmat.2023.131787

Luo, H; Zhang, Q; Yu, K; Meng, X; Kan, H; Chen, R. (2022). Long-term exposure to ambient air pollution is a risk factor for trajectory of cardiometabolic multimorbidity: A prospective study in the UK Biobank. EBioMedicine 84: 104282. http://dx.doi.org/10.1016/j.ebiom.2022.104282

Luyten, LJ; Dockx, Y; Provost, EB; Madhloum, N; Sleurs, H; Neven, KY; Janssen, BG; Bové, H; Debacq-Chainiaux, F; Gerrits, N; Lefebvre, W; Plusquin, M; Vanpoucke, C; De Boever, P; Nawrot, TS. (2020). Children's microvascular traits and ambient air pollution exposure during pregnancy and early childhood: prospective evidence to elucidate the developmental origin of particle-induced disease. BMC Med 18: 128. http://dx.doi.org/10.1186/s12916-020-01586-x

Ma, T; Yazdi, MD; Schwartz, J; Réquia, WJ; Di, Q; Wei, Y; Chang, HH; Vaccarino, V; Liu, P; Shi, L. (2022). Long-term air pollution exposure and incident stroke in American older adults: A national cohort study. Global Epidemiology 4: 100073. http://dx.doi.org/10.1016/j.gloepi.2022.100073

Mann, JK; Lutzker, L; Holm, SM; Margolis, HG; Neophytou, AM; Eisen, EA; Costello, S; Tyner, T; Holland, N; Tindula, G; Prunicki, M; Nadeau, K; Noth, EM; Lurmann, F; Hammond, SK; Balmes, JR. (2021). Traffic-related air pollution is associated with glucose dysregulation, blood

pressure, and oxidative stress in children. Environ Res 195: 110870. http://dx.doi.org/10.1016/j.envres.2021.110870

Marrone, E; Longo, C; O'Loughlin, J; Villeneuve, PJ; Zappitelli, M; Bartlett-Esquilant, G; Barnett, TA. (2023). Association between annual exposure to air pollution and systolic blood pressure among adolescents in Montréal, Canada. Health Promot Chronic Dis Prev Can 43: 191-198. http://dx.doi.org/10.24095/hpcdp.43.4.04

Meng, YY; Su, JG; Chen, X; Molitor, J; Yue, D; Jerrett, M. (2021). Improvements in Air Quality and Health Outcomes Among California Medicaid Enrollees Due to Goods Movement Actions. Res Rep Health Eff Inst 2021: 1-61.

Miller, KA; Siscovick, DS; Sheppard, L; Shepherd, K; Sullivan, JH; Anderson, GL; Kaufman, JD. (2007). Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356: 447-458. http://dx.doi.org/10.1056/NEJMoa054409

Monrad, M; Sajadieh, A; Christensen, JS; Ketzel, M; Raaschou-Nielsen, O; Tjønneland, A; Overvad, K; Loft, S; Sørensen, M. (2016). Long-term exposure to traffic-related air pollution and risk of incident atrial fibrillation: A cohort study. Environ Health Perspect 125: 422-427. http://dx.doi.org/10.1289/EHP392

Ni, Y; Simpson, CL; Davis, RL; Szpiro, AA; Karr, CJ; Kovesdy, CP; Hjorten, RC; Tylavsky, FA; Bush, NR; LeWinn, KZ; Winkler, CA; Kopp, JB; Obi, Y. (2022). Associations between APOL1 genetic variants and blood pressure in African American mothers and children from a U.S. pregnancy cohort: Modification by air pollution exposures. Environ Res 212: 113186. http://dx.doi.org/10.1016/j.envres.2022.113186

Ni, Y; Szpiro, AA; Young, MT; Loftus, CT; Bush, NR; Lewinn, KZ; Sathyanarayana, S; Enquobahrie, DA; Davis, RL; Kratz, M; Fitzpatrick, AL; Sonney, JT; Tylavsky, FA; Karr, CJ. (2021). Associations of pre- and postnatal air pollution exposures with child blood pressure and modification by maternal nutrition: A prospective study in the CANDLE cohort. Environ Health Perspect 129: 47004. http://dx.doi.org/10.1289/EHP7486

Ohlwein, S; Klümper, C; Vossoughi, M; Sugiri, D; Stolz, S; Vierkötter, A; Schikowski, T; Kara, K; Germing, A; Quass, U; Krämer, U; Hoffmann, B. (2016). Air pollution and diastolic function in elderly women - Results from the SALIA study cohort. Int J Hyg Environ Health 219: 356-363. http://dx.doi.org/10.1016/j.ijheh.2016.02.006

Olaniyan, T; Pinault, L; Li, C; van Donkelaar, A; Meng, J; Martin, R; Hystad, P; Robichaud, A; Ménard, R; Tjepkema, M; Bai, L; Kwong, JC; Lavigne, E; Burnett, RT; Chen, H. (2022). Ambient air pollution and the risk of acute myocardial infarction and stroke: A national cohort study. Environ Res 204: 111975. http://dx.doi.org/10.1016/j.envres.2021.111975

Panasevich, S; Leander, K; Ljungman, P; Bellander, T; de Faire, U; Pershagen, G; Nyberg, F. (2013). Interaction between air pollution exposure and genes in relation to levels of inflammatory markers and risk of myocardial infarction. BMJ Open 3: e003058. http://dx.doi.org/10.1136/bmjopen-2013-003058

Paoin, K; Ueda, K; Vathesatogkit, P; Ingviya, T; Buya, S; Phosri, A; Seposo, XT; Thongmung, N; Yingchoncharoen, T; Honda, A; Takano, H; Sritara, P. (2021). Effects of long-term air pollution exposure on ankle-brachial index and cardio-ankle vascular index: A longitudinal cohort study using data from the Electricity Generating Authority of Thailand study. Int J Hyg Environ Health 236: 113790. http://dx.doi.org/10.1016/j.ijheh.2021.113790

Paul, LA; Burnett, RT; Kwong, JC; Hystad, P; van Donkelaar, A; Bai, L; Goldberg, MS; Lavigne, E; Copes, R; Martin, RV; Kopp, A; Chen, H. (2020). The impact of air pollution on the incidence of diabetes and survival among prevalent diabetes cases. Environ Int 134: 105333. http://dx.doi.org/10.1016/j.envint.2019.105333

Pedersen, M; Halldorsson, TI; Ketzel, M; Grandström, C; Raaschou-Nielsen, O; Jensen, SS; Grunnet, LG; Vaag, A; Sørensen, M; Olsen, SF. (2019). Associations between ambient air pollution and noise from road traffic with blood pressure and insulin resistance in children from Denmark. Environ Epidemiol 3: e069. http://dx.doi.org/10.1097/EE9.0000000000000069

Peralta, AA; Schwartz, J; Gold, DR; Vonk, JM; Vermeulen, R; Gehring, U. (2022). Quantile regression to examine the association of air pollution with subclinical atherosclerosis in an adolescent population. Environ Int 164: 107285. http://dx.doi.org/10.1016/j.envint.2022.107285
Pilz, V; Wolf, K; Breitner, S; Rückerl, R; Koenig, W; Rathmann, W; Cyrys, J; Peters, A; Schneider, A; group, KO-S. (2018). C-reactive protein (CRP) and long-term air pollution with a focus on ultrafine particles. Int J Hyg Environ Health 221: 510-518. http://dx.doi.org/10.1016/j.ijheh.2018.01.016
Poulsen, AH; Sørensen, M; Hvidtfeldt, UA; Brandt, J; Frohn, LM; Ketzel, M; Christensen, JH; Im, U; Raaschou-Nielsen, O. (2023a). 'Source-specific' air pollution and risk of stroke in Denmark. Int J Epidemiol 52: 727-737. http://dx.doi.org/10.1093/ije/dyad030
Poulsen, AH; Sørensen, M; Hvidtfeldt, UA; Christensen, JH; Brandt, J; Frohn, LM; Ketzel, M; Andersen, C; Jensen, SS; Münzel, T; Raaschou-Nielsen, O. (2023b). Concomitant exposure to air pollution, green space, and noise and risk of stroke: A cohort study from Denmark. Lancet Reg Health Eur 31: 100655. http://dx.doi.org/10.1016/j.lanepe.2023.100655
Poulsen, AH; Sørensen, M; Hvidtfeldt, UA; Frohn, LM; Ketzel, M; Christensen, JH; Brandt, J; Massling, A; Khan, J; Lassen, CF; Raaschou-Nielsen, O. (2023c). Air pollution and myocardial infarction; effect modification by sociodemographic and environmental factors. A cohort study from Denmark. Environ Res 229: 115905. http://dx.doi.org/10.1016/j.envres.2023.115905
Poulsen, AH; Sørensen, M; Hvidtfeldt, UA; Ketzel, M; Christensen, JH; Brandt, J; Frohn, LM; Khan, J; Jensen, SS; Lund, T; Raaschou-Nielsen, O. (2023d). Air pollution and stroke; effect modification by sociodemographic and environmental factors. A cohort study from Denmark. Int J Hyg Environ Health 251: 114165. http://dx.doi.org/10.1016/j.ijheh.2023.114165
Raaschou-Nielsen, O; Thorsteinson, E; Antonsen, S; Holst, GJ; Sigsgaard, T; Geels, C; Frohn, LM; Christensen, JH; Brandt, J; Pedersen, CB; Hvidtfeldt, UA. (2020). Long-term exposure to air pollution and mortality in the Danish population a nationwide study. EClinicalMedicine 28: 100605. http://dx.doi.org/10.1016/j.eclinm.2020.100605
Rosenlund, M; Bellander, T; Nordquist, T; Alfredsson, L. (2009). Traffic-generated air pollution and myocardial infarction. Epidemiology 20: 265-271. http://dx.doi.org/10.1097/EDE.0b013e318190ea68
Rosenlund, M; Picciotto, S; Forastiere, F; Stafoggia, M; Perucci, CA. (2008). Traffic-related air pollution in relation to incidence and prognosis of coronary heart disease. Epidemiology 19: 121-128. http://dx.doi.org/10.1097/EDE.0b013e31815c1921
Rothman, KJ; Greenland, S. (1998). Modern Epidemiology (2 ed.). Philadelphia, PA: Lippincott-Raven.
Schwartz, J; Wei, Y; Dominici, F; Yazdi, MD. (2023). Effects of low-level air pollution exposures on hospital admission for myocardial infarction using multiple causal models. Environ Res 232: 116203. http://dx.doi.org/10.1016/j.envres.2023.116203
Seilkop, SK; Campen, MJ; Lund, AK; McDonald, JD; Mauderly, JL. (2012). Identification of chemical components of combustion emissions that affect pro-atherosclerotic vascular responses in mice. Inhal Toxicol 24: 270-287. http://dx.doi.org/10.3109/08958378.2012.667455
Sheridan, P; Chen, C; Thompson, CA; Benmarhnia, T. (2023). Immortal Time Bias With Time-Varying Exposures in Environmental Epidemiology: A Case Study in Lung Cancer Survival. Am J Epidemiol 192: 1754-1762. http://dx.doi.org/10.1093/aje/kwad135
Shi, H; Chen, L; Zhang, S; Li, R; Wu, Y; Zou, H; Wang, C; Cai, M; Lin, H. (2023). Dynamic association of ambient air pollution with incidence and mortality of pulmonary hypertension: A multistate trajectory analysis. Ecotoxicol Environ Saf 262: 115126-115126. http://dx.doi.org/10.1016/j.ecoenv.2023.115126
Shin, S; Burnett, RT; Kwong, JC; Hystad, P; van Donkelaar, A; Brook, J. R.; Goldberg, MS; Tu, K; Copes, R; Martin, R; Lia, Y; Kopp, A; Chen, H. (2019). Ambient Air Pollution and the Risk of Atrial Fibrillation and Stroke: A Population-Based Cohort Study. Environ Health Perspect 127: 87009. http://dx.doi.org/10.1289/EHP4883

So, R; Andersen, ZJ; Chen, J; Stafoggia, M; de Hoogh, K; Katsouyanni, K; Vienneau, D; Rodopoulou, S; Samoli, E; Lim, YH; Jørgensen, JT; Amini, H; Cole-Hunter, T; Mahmood Taghavi Shahri, S; Maric, M; Bergmann, M; Liu, S; Azam, S; Loft, S; ... Mehta, AJ. (2022). Long-term exposure to air pollution and mortality in a Danish nationwide administrative cohort study: Beyond mortality from cardiopulmonary disease and lung cancer. Environ Int 164: 107241. http://dx.doi.org/10.1016/j.envint.2022.107241

So, R; Jørgensen, JT; Lim, YH; Mehta, AJ; Amini, H; Mortensen, LH; Westendorp, R; Ketzel, M; Hertel, O; Brandt, J; Christensen, JH; Geels, C; Frohn, LM; Sisgaard, T; Bräuner, EV; Jensen, SS; Backalarz, C; Simonsen, MK; Loft, S; Cole-Hunter, T; Andersen, ZJ. (2020). Long-term exposure to low levels of air pollution and mortality adjusting for road traffic noise: A Danish Nurse Cohort study. Environ Int 143: 105983. http://dx.doi.org/10.1016/j.envint.2020.105983

Sofianopoulou, E; Kaptoge, S; Gräf, S; Hadinnapola, C; Treacy, CM; Church, C; Coghlan, G; Gibbs, JSR; Haimel, M; Howard, LS; Johnson, M; Kiely, DG; Lawrie, A; Lordan, J; Mackenzie Ross, RV; Martin, JM; Moledina, S; Newnham, M; Peacock, AJ; Price, LC; Rhodes, CJ; Suntharalingam, J; Swietlik, EM; Toshner, MR; Wharton, J; Wilkins, MR; Wort, SJ; Pepke-Zaba, J; Condliffe, R; Corris, PA; Di Angelantonio, E; Provencher, S; Morrell, NW. (2019). Traffic exposures, air pollution and outcomes in pulmonary arterial hypertension: a UK cohort study analysis. Eur Respir J 53. http://dx.doi.org/10.1183/13993003.01429-2018

Song, L; Smith, GS; Adar, SD; Post, WS; Guallar, E; Navas-Acien, A; Kaufman, JD; Jones, MR. (2020). Ambient air pollution as a mediator in the pathway linking race/ethnicity to blood pressure elevation: The multi-ethnic study of atherosclerosis (MESA). Environ Res 180: 108776. http://dx.doi.org/10.1016/j.envres.2019.108776

Sørensen, M; Hoffmann, B; Hvidberg, M; Ketzel, M; Jensen, SS; Andersen, ZJ; Tjønneland, A; Overvad, K; Raaschou-Nielsen, O. (2012). Long-term exposure to traffic-related air pollution associated with blood pressure and self-reported hypertension in a Danish cohort. Environ Health Perspect 120: 418-424. http://dx.doi.org/10.1289/ehp.1103631

Sørensen, M; Lühdorf, P; Ketzel, M; Andersen, ZJ; Tjønneland, A; Overvad, K; Raaschou-Nielsen, O. (2014). Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke? Environ Res 133: 49-55. http://dx.doi.org/10.1016/j.envres.2014.05.011

Stafoggia, M; Cesaroni, G; Peters, A; Andersen, ZJ; Badaloni, C; Beelen, R; Caracciolo, B; Cyrys, J; de Faire, U; de Hoogh, K; Eriksen, KT; Fratiglioni, L; Galassi, C; Gigante, B; Havulinna, AS; Hennig, F; Hilding, A; Hoek, G; Hoffmann, B; Houthuijs, D; Korek, M; Lanki, T; Leander, K; Magnusson, PK; Meisinger, C; Migliore, E; Overvad, K; Ostenson, CG; Pedersen, NL; Pekkanen, J; Penell, J; Pershagen, G; Pundt, N; Pyko, A; Raaschou-Nielsen, O; Ranzi, A; Ricceri, F; Sacerdote, C; Swart, WJ; Turunen, AW; Vineis, P; Weimar, C; Weinmayr, G; Wolf, K; Brunekreef, B; Forastiere, F. (2014). Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. Environ Health Perspect 122: 919-925. http://dx.doi.org/10.1289/ehp.1307301

Stafoggia, M; Oftedal, B; Chen, J; Rodopoulou, S; Renzi, M; Atkinson, RW; Bauwelinck, M; Klompmaker, JO; Mehta, A; Vienneau, D; Andersen, ZJ; Bellander, T; Brandt, J; Cesaroni, G; de Hoogh, K; Fecht, D; Gulliver, J; Hertel, O; Hoffmann, B; ... Janssen, NAH. (2022). Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. The Lancet Planetary Health 6: e9-e18. http://dx.doi.org/10.1016/S2542-5196(21)00277-1

Strak, M; Weinmayr, G; Rodopoulou, S; Chen, J; de Hoogh, K; Andersen, ZJ; Atkinson, R; Bauwelinck, M; Bekkevold, T; Bellander, T; Boutron-Ruault, MC; Brandt, J; Cesaroni, G; Concin, H; Fecht, D; Forastiere, F; Gulliver, J; Hertel, O; Hoffmann, B; ... Samoli, E. (2021). Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: Pooled analysis. BMJ 374: n1904. http://dx.doi.org/10.1136/bmj.n1904

Su, PF; Sie, FC; Yang, CT; Mau, YL; Kuo, S; Ou, HT. (2020). Association of ambient air pollution with cardiovascular disease risks in people with type 2 diabetes: a Bayesian spatial survival analysis. Environ Health 19: 110. http://dx.doi.org/10.1186/s12940-020-00664-0

Suzuki, AK; Tsubone, H; Ichinose, T; Oda, H; Kubota, K. (1981). [Effects of subchronic nitrogen dioxide exposure on arterial blood pHa, PaCO2 and PaO2 in rats]. Nippon Eiseigaku Zasshi 36: 816-823. http://dx.doi.org/10.1265/jjh.36.816

Takano, H; Yanagisawa, R; Inoue, KI; Shimada, A; Ichinose, T; Sadakane, K; Yoshino, S; Yamaki, K; Morita, M; Yoshikawa, T. (2004). Nitrogen dioxide air pollution near ambient levels is an atherogenic risk primarily in obese subjects: A brief communication. Exp Biol Med 229: 361-364.

Tao, C; Liu, Z; Fan, Y; Yuan, Y; Wang, X; Qiao, Z; Li, Z; Xu, Q; Lou, Z; Wang, H; Li, X; Li, R; Lu, C. (2024). Estimating neighborhood-based mortality risk associated with air pollution: A prospective study. J Hazard Mater 475: 134861. http://dx.doi.org/10.1016/j.jhazmat.2024.134861

Tian, F; Cai, M; Li, H; Qian, Z; Chen, L; Zou, H; Zhang, Z; Wang, C; Xian, H; McMillin, SE; Lin, H. (2022). Air pollution associated with incident stroke, poststroke cardiovascular events, and death: A trajectory analysis of a prospective cohort. Neurology 99: E2474-E2484. http://dx.doi.org/10.1212/WNL.0000000000201316

Tibuakuu, M; Jones, MR; Navas-Acien, A; Zhao, D; Guallar, E; Gassett, AJ; Sheppard, L; Budoff, MJ; Kaufman, JD; Michos, ED. (2017). Exposure to ambient air pollution and calcification of the mitral annulus and aortic valve: the multi-ethnic study of atherosclerosis (MESA). Environ Health 16: 133. http://dx.doi.org/10.1186/s12940-017-0346-x

Tsubone, H; Suzuki, AK. (1984). Reflex cardiopulmonary responses by stimulation to type J receptors in rats exposed to NO2. J Toxicol Environ Health 13: 905-917. http://dx.doi.org/10.1080/15287398409530550

Turner, MC; Jerrett, M; Pope, A, III; Krewski, D; Gapstur, SM; Diver, WR; Beckerman, BS; Marshall, JD; Su, J; Crouse, DL; Burnett, RT. (2016). Long-term ozone exposure and mortality in a large prospective study. Am J Respir Crit Care Med 193: 1134-1142. http://dx.doi.org/10.1164/rccm.201508-1633OC

U.S. EPA (U.S. Environmental Protection Agency). (2008). Integrated science assessment for oxides of nitrogen – Health criteria (Final report, 2008) [EPA Report]. (EPA/600/R-08/071). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645

U.S. EPA (U.S. Environmental Protection Agency). (2015). Preamble to the Integrated Science Assessments [EPA Report]. (EPA/600/R-15/067). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, RTP Division. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

U.S. EPA (U.S. Environmental Protection Agency). (2016). Integrated science assessment for oxides of nitrogen: Health criteria (Final report, Jan 2016) [EPA Report]. (EPA/600/R-15/068). Washington, DC. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879

U.S. EPA (U.S. Environmental Protection Agency). (2023). Overview of nitrogen dioxide (NO2) air quality in the United States, Updated: February 07, 2023. Washington, DC. https://www.epa.gov/system/files/documents/2022-08/NO2_2021.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2024). Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen. Volume 2: Planning for the Review and the Integrated Science Assessment [EPA Report]. (EPA-452/R-24-010b). Washington, DC.

Wagner, WD; Duncan, BR; Wright, PG; Stokinger, HE. (1965). Experimental study of threshold limit of NO2. Arch Environ Health 10: 455-466. http://dx.doi.org/10.1080/00039896.1965.10664029

Wang, K; Yuan, Y; Wang, Q; Yang, Z; Zhan, Y; Wang, Y; Wang, F; Zhang, Y. (2023). Incident risk and burden of cardiovascular diseases attributable to long-term NO2 exposure in Chinese adults. Environ Int 178: 108060. http://dx.doi.org/10.1016/j.envint.2023.108060

Wang, M; Zhou, T; Song, Y; Li, X; Ma, H; Hu, Y; Heianza, Y; Qi, L. (2021). Joint exposure to various ambient air pollutants and incident heart failure: a prospective analysis in UK Biobank. Eur Heart J 42: 1582-1591. http://dx.doi.org/10.1093/eurheartj/ehaa1031

Wang, MY; Zhou, T; Song, QY; Ma, H; Hu, YH; Heianza, Y; Qi, L. (2022). Ambient air pollution, healthy diet and vegetable intakes, and mortality: A prospective UK Biobank study. Int J Epidemiol 51: 1243-1253. http://dx.doi.org/10.1093/ije/dyac022

Weichenthal, S; Pinault, LL; Burnett, RT. (2017). Impact of oxidant gases on the relationship between outdoor fine particulate air pollution and nonaccidental, cardiovascular, and respiratory mortality. Sci Rep 7: 16401. http://dx.doi.org/10.1038/s41598-017-16770-y

Weng, Z; Liu, Q; Yan, Q; Liang, J; Zhang, X; Xu, J; Li, W; Xu, C; Gu, A. (2022). Associations of genetic risk factors and air pollution with incident hypertension among participants in the UK Biobank study. Chemosphere 299: 134398. http://dx.doi.org/10.1016/j.chemosphere.2022.134398

Wolf, K; Hoffmann, B; Andersen, ZJ; Atkinson, RW; Bauwelinck, M; Bellander, T; Brandt, J; Brunekreef, B; Cesaroni, G; Chen, J; de Faire, U; de Hoogh, K; Fecht, D; Forastiere, F; Gulliver, J; Hertel, O; Hvidtfeldt, UA; Janssen, NAH; Jørgensen, JT; ... Ljungman, PLS. (2021). Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: A pooled analysis of six European cohorts within the ELAPSE project. The Lancet Planetary Health 5: e620-e632. http://dx.doi.org/10.1016/S2542-5196(21)00195-9

Wu, G; Cai, M; Wang, C; Zou, H; Wang, X; Hua, J; Lin, H. (2023). Ambient air pollution and incidence, progression to multimorbidity and death of hypertension, diabetes, and chronic kidney disease: A national prospective cohort. Sci Total Environ 881: 163406. http://dx.doi.org/10.1016/j.scitotenv.2023.163406

Wu, X; Liu, X; Liao, W; Dong, X; Li, R; Hou, J; Mao, Z; Huo, W; Guo, Y; Li, S; Chen, G; Wang, C. (2022). Healthier lifestyles attenuated association of single or mixture exposure to air pollutants with cardiometabolic risk in rural Chinese adults. Toxics 10. http://dx.doi.org/10.3390/toxics10090541

Yang, BY; Qian, ZM; Vaughn, MG; Nelson, EJ; Dharmage, SC; Heinrich, J; Lin, S; Lawrence, WR; Ma, H; Chen, DH; Hu, LW; Zeng, XW; Xu, SL; Zhang, C; Dong, GH. (2017). Is prehypertension more strongly associated with long-term ambient air pollution exposure than hypertension? Findings from the 33 Communities Chinese Health Study. Environ Pollut 229: 696-704. http://dx.doi.org/10.1016/j.envpol.2017.07.016

Yang, BY; Qian, ZMM; Vaughn, MG; Howard, SW; Pemberton, JP; Ma, HM; Chen, DH; Hu, LW; Zeng, XW; Zhang, C; Tian, YP; Nian, M; Xiao, X; Dong, GH. (2018). Overweight modifies the association between long-term ambient air pollution and prehypertension in Chinese adults: The 33 Communities Chinese Health Study. Environ Health 17: 57. http://dx.doi.org/10.1186/s12940-018-0401-2

Yorifuji, T; Kashima, S; Tsuda, T; Takao, S; Suzuki, E; Doi, H; Sugiyama, M; Ishikawa-Takata, K; Ohta, T. (2010). Long-term exposure to traffic-related air pollution and mortality in Shizuoka, Japan. Occup Environ Med 67: 111-117. http://dx.doi.org/10.1136/oem.2008.045542

Yu, Yo; Tang, Zi; Huang, Yu; Zhang, Ji; Wang, Yi; Zhang, Yu; Wang, Qu. (2024). Assessing long-term effects of gaseous air pollution exposure on mortality in the United States using a variant of difference-in-differences analysis. Sci Rep 14: 16220-. http://dx.doi.org/10.1038/s41598-024-66951-9

Zhang, AL; Balmes, JR; Lutzker, L; Mann, JK; Margolis, HG; Tyner, T; Holland, N; Noth, EM; Lurmann, F; Hammond, SK; Holm, SM. (2022). Traffic-related air pollution, biomarkers of metabolic dysfunction, oxidative stress, and CC16 in children. J Expo Sci Environ Epidemiol 32: 530-537. http://dx.doi.org/10.1038/s41370-021-00378-6

Zhang, JL; Zhang, F; Xin, C; Duan, ZZ; Wei, J; Zhang, X; Han, SC; Niu, ZP. (2023). Associations of long-term exposure to air pollution, physical activity with blood pressure and prevalence of hypertension: The China Health and Retirement Longitudinal Study. Front Public Health 11: 1137118. http://dx.doi.org/10.3389/fpubh.2023.1137118

Zhang, Q; Liu, C; Wang, Y; Gong, J; Wang, G; Ge, W; Chen, R; Meng, X; Zhao, Y; Kan, H. (2021a). Associations of long-term exposure to ambient nitrogen dioxide with indicators of diabetes and dyslipidemia in China: A nationwide analysis. Chemosphere 269: 128724. http://dx.doi.org/10.1016/j.chemosphere.2020.128724

Zhang, Z; Wang, J; Kwong, JC; Burnett, RT; van Donkelaar, A; Hystad, P; Martin, RV; Bai, L; Mclaughlin, J; Chen, H. (2021b). Long-term exposure to air pollution and mortality in a prospective cohort: The Ontario Health Study. Environ Int 154: 106570. http://dx.doi.org/10.1016/j.envint.2021.106570

Zhang, Z; Weichenthal, S; Kwong, JC; Burnett, RT; Hatzopoulou, M; Jerrett, M; van Donkelaar, A; Bai, L; Martin, RV; Copes, R; Lu, H; Lakey, P; Shiraiwa, M; Chen, H. (2020). Long-term exposure to iron and copper in fine particulate air pollution and their combined impact on reactive oxygen species concentration in lung fluid: a population-based cohort study of cardiovascular disease incidence and mortality in Toronto, Canada. Int J Epidemiol 50: 589-601. http://dx.doi.org/10.1093/ije/dyaa230

Zhu, Yi; Wu, Ya; Cheng, Ju; Liang, Hu; Chang, Qi; Lin, Fe; Li, Di; Zhou, Xi; Chen, Xi; Pan, Pi; Liu, Ho; Guo, Yu; Zhang, Ya. (2024). Ambient air pollution, lifestyle, and genetic predisposition on all-cause and cause-specific mortality: A prospective cohort study. Sci Total Environ 933: 173120-. http://dx.doi.org/10.1016/j.scitotenv.2024.173120

zielska, B; Mainka, A; Żak, M; Kaleta, D; Mucha, W; Kaufman, JP; Adar, SD; Barr, RG; Budoff, M; Burke, GL; Curl, CL; Diez Roux, AV; Gassett, AJ; Jacobs, DR, Jr; Kronmal, R; Larson, TV; Navas-Acien, A; Olives, C; Sampson, PD; Sheppard, L; Siscovick, DS; Stein, JH; Szpiro, AA; Watson, KE. (2016). Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet 388: 696-704. http://dx.doi.org/10.1016/S0140-6736(16)00378-0