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Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 8: Metabolic Syndrome and Diabetes

External Review Draft

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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

ADA	American Diabetes Association
AMI	acute myocardial infarction
AQCD	Air Quality Criteria Document
avg	average
β	beta
BC	black carbon
BMI	body mass index
BRP	body fat percent
CI	confidence interval
CHF	congestive heart failure
CO	Carbon monoxide
COPD	chronic obstructive pulmonary disease
d	day(s)
DLM	distributed lag non-linear models
DM	Diabetes mellitus
EC	elemental carbon
EE	effect estimate
EEM	effect measure modification
e.g.	exempli gratia (for example)
ELF	epithelial lining fluid
etc.	et cetera
EPA	U.S. Environmental Protection Agency
F	female(s)
FBG	fasting blood glucose
g	gram(s)
GDM	gestational diabetes mellitus
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hr	hour(s)
HR	hazard ratio
i.e.	id est (that is)
IQR	interquartile range
ISA	Integrated Science Assessment
L	liter(s)
LDL	low-density lipoproteins
LETO	Long-Evans Tokushima
LUR	land use regression
M	male
Max	maximum
m	milligram
MetS	Metabolic syndrome
Min	minimum
m	meter(s)
µg	microgram
µg/m^3	micrograms per cubic meter
µm	micrometer
min	minute(s)
mL	milliliter
mo	month(s)
n	sample size
N	population size
NA	not applicable
NO_2	nitrogen dioxide
NO_X	NO_2 + NO
NO	nitric oxide
NR	not reported
O_3	ozone
OLETF	Otsuka Long-Evans Tokushima Fatty
OR	odds ratio
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
P5	5th percentile
P10	10th percentile
P25	25th percentile
P75	75th percentile
P95	95th percentile
PM	particulate matter
PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 µm
$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm
ppb	parts per billion
ppm	parts per million
ρ	rho
RR	relative risk or risk ratio
SD	standard deviation
SE	standard error
SES	socioeconomic status
SO_2	sulfur dioxide
STET	space-time extremely randomized trees
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TG	triglycerides
UFP	ultra fine particles
U.K.	United Kingdom
U.S.	United States
VFI	visceral fat index
vs.	versus
wk	week(s)
WC	waist circumference
WHR	waist-to-hip ratio
WHtR	waist-to-height ratio
yr	year(s)

CHAPTER 8 Metabolic Syndrome and Diabetes

Summary of Causality Determinations for Long-term Oxides of Nitrogen Exposure and Metabolic Syndrome and Diabetes

This chapter characterizes the scientific evidence that supports causality determinations for long- and short-term oxides of nitrogen exposure and metabolic syndrome and diabetes. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA 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 (see Section 14.4.3.2). 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 ISAs (U.S. EPA, 2015a). The evidence presented throughout this chapter supports the following causality conclusion(s):

Outcome	Causality Determination
Metabolic Syndrome and Diabetes – Long-term Exposure	Suggestive of, but not sufficient to infer, a causal relationship
Metabolic Syndrome and Diabetes – Short-term Exposure	Inadequate 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.

8.1 Introduction

8.1.1 Summary of the 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) did not include a chapter focused on Metabolic Syndrome and Diabetes. Instead, studies related to diabetes were discussed within the long-term exposure and Cardiovascular and Diabetes Section [see Chapter 6, Section 6.3 in U.S. EPA (2016)]. The available evidence was determined to be suggestive of, but not sufficient to infer, a causal relationship between long-term oxides of nitrogen exposure and cardiovascular effects and

diabetes. The key evidence for effects related to diabetes in the 2016 Oxides of Nitrogen ISA is summarized below.

Epidemiologic evidence reviewed in the previous Oxides of Nitrogen ISA generally supported an association between long-term exposure to oxides of nitrogen and diabetes mellitus. Large prospective cohort studies in women, which evaluated exposure to oxides of nitrogen, primarily nitrogen dioxide (NO_2) and the sum of nitric oxide (NO) and NO_2 (NO_X), using well-validated land use regression (LUR models), found positive associations with incidence of diabetes (Coogan et al., 2012; Kramer et al., 2010). NO_2 exposure has also been associated with prevalent diabetes in cohorts including men and women (Eze et al., 2014; Brook et al., 2008), although one study detected this association only in confirmed diabetes cases and not in the overall analysis (Andersen et al., 2012). NO_2 exposure was additionally associated with factors underlying diabetes, including impaired glucose metabolism in a cohort of adult women and impaired insulin tolerance in children (Teichert et al., 2013; Thiering et al., 2013). Some studies found that associations with NO_2 exposure were robust to adjustment for noise, $PM_{2.5}$, or PM_{10}, but overall, the evidence was limited and no studies adjusted for other traffic-related copollutants [e.g., black carbon (BC), elemental carbon (EC), carbon monoxide (CO)]. There was limited toxicological evidence available to provide coherence with the effects seen in humans. Takano et al. (2004) found evidence of dyslipidemia (i.e., increased triglycerides and decreased high-density lipoprotein (HDL) in an obese rat model.

There were no epidemiologic or toxicological studies examining short-term exposure to oxides of nitrogen and metabolic syndrome or diabetes in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). A single controlled human exposure study, Huang et al. (2012), reported that a 2-hour 500 ppb NO_2 exposure with intermittent exercise increased total and HDL cholesterol 18 hours after exposure.

8.1.2 Chapter Organization and Conventions

This Chapter evaluates recent evidence examining the relationship between oxides of nitrogen exposure and metabolic effects. Its conclusions are drawn from the integration of the full body of evidence available in the 2016 Oxides of Nitrogen ISA and the evidence that has become available since the 2016 Oxides of Nitrogen ISA. The following sections provide an overview of study inclusion criteria for this chapter (see Section 8.2), summaries of the health effects evidence from past ISAs and from recent studies (see Sections 8.3 to 8.9), a discussion of biological plausibility (see Section 8.10), a summary of the evidence for lifestages and populations (see Section 8.11, Table 8-1), and a discussion of the causality determination for long-term (see Section 8.12.1, Table 8-2) and short-term (see Section 8.12.2, Table 8-3) oxides of nitrogen exposure and metabolic effects. Only the sections that have multiple lines of evidence include a "Synthesis Across Lines of Evidence" subsection. 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. Additional information on the organization and conventions for this chapter are discussed below for epidemiologic studies and animal toxicological studies.

Since the 2016 Oxides of Nitrogen ISA, several studies have examined the effects of long- and/or short-term oxides of nitrogen exposure on metabolic-related endpoints. This chapter evaluates the evidence for effects of oxides of nitrogen exposure on diabetes mellitus, metabolic syndrome and its components, metabolic disease mortality, and other metabolic indicators. Metabolic syndrome (MetS) describes a collection of factors, such as hypertension, dyslipidemia, hyperglycemia, and central obesity, which predispose individuals to Type 2 diabetes (reviewed in Section 8.3) and cardiovascular disease (reviewed in Chapters 5 and 6). MetS is described in more detail in Section 8.4 and specific components of MetS are discussed in Sections 8.5 to 8.7, except hypertension which is discussed in Chapter 5, Section 5.7 and Chapter 6, Section 6.5. The bulk of the epidemiologic evidence for this chapter falls within long-term exposure with the strongest evidence for positive associations between long-term oxides of nitrogen and diabetes mellitus and cause-specific mortality.

8.1.2.1 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 Oxides of Nitrogen ISA. When relevant 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., $\rho<0.4$). 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.

This chapter includes both short-term exposures (e.g., less than 30 days) and long-term exposures (e.g., more than 30 days) to oxides of nitrogen. 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 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 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.[1] The increments for standardization for short-term exposure vary by averaging time (e.g., 24-hour avg, 8-hour max, 1-hour max) and oxide of nitrogen. For 24-hour average, effect estimates were scaled to a 20-parts per billion (ppb) increase for NO_2 or NO and a 30-ppb increase for NO_X. For a 1-hour maximum, effect estimates were scaled to a 25-ppb increase for NO_2, a 60-ppb increase for NO, and an 80-ppb increase for NO_X. For an 8-hour maximum, the increments for standardization are 25-ppb increase for NO_2, 40-ppb increase for NO, and 55-ppb increase for NO_X. These increments were derived by calculating the U.S.-wide percentile distributions for a given averaging time and then calculating the approximate difference between the median (a typical pollution day) and the 95th percentile (a more polluted day) for a given averaging time (U.S. EPA, 2015b). There were common exceptions to this standardization method. Averaging times other than 24-hour average or 1-hour maximum were examined, for example, 2- to 15-hour averages. Effect estimates based on these averaging times were not standardized but are presented in this ISA as reported in their respective studies.

For long-term exposure metrics, effect estimates are scaled to a 10-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 U.S. 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, 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 epidemiologic 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

[1]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.

$\mu g/m^3$ at a national scale for the United States or other countries. Therefore, this ISA presents effect estimates based on $\mu g/m^3$ of NO_X as they are reported in their respective studies.

8.1.2.2 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 older or more recent animal toxicological studies, these sections additionally include targeted discussions of analyses examining dose-response relationships, relevance of toxicological responses to human responses, and multipollutant exposures. For apical endpoints with no or limited evidence on these topics, subsections addressing them are not included.

8.2 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.[2] 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 metabolic syndrome and diabetes, recent studies were only included if they met all components of the discipline-specific PECOS statements (see below) and satisfied discipline-specific study quality criteria (see Chapter 14).

[2]The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review 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).

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[3].

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 metabolic syndrome and diabetes 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.

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).[4]

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

Outcome: Outcomes of interest are metabolic effects that relate to human health.

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

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[3]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 Chapter 14.

[4]Five ppm is approximately two orders of magnitude higher than peak NO2 concentrations in the ambient air in the United States. As discussed in the 2015 Preamble to the ISAs (U.S. EPA, 2015a) 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.

8.3 Diabetes Mellitus and Complications from Diabetes

This section summarizes key evidence from the 2016 Oxides of Nitrogen ISA and recent PECOS-relevant epidemiologic evidence examining the relationship between exposure to oxides of nitrogen and diabetes mellitus and corresponding complications from diabetes. Diabetes mellitus (DM) is a chronic condition characterized by an inability to regulate glucose in the blood due to deficits in insulin signaling, insulin secretion, or both, resulting in hyperglycemia (i.e., elevated blood glucose). Several types of DM have been classified by the American Diabetes Association (ADA) (ADA, 2014). The focus of this chapter is on Type 2 diabetes (T2D), which is characterized by defects in insulin secretion in an insulin-resistant environment (see Section 8.3.1). Type 1 diabetes (T1D), which is caused by β-cell dysfunction or destruction that leads to insulin deficiency, is not emphasized in this chapter because evidence for a potential pathway linking oxides of nitrogen exposure with T1D is lacking (see Chapter 13, Section 13.3). In addition, gestational diabetes mellitus (GDM), which is generally diagnosed during the second or third trimester of pregnancy, is discussed in Section 7.3.1 of the Reproductive and Developmental Effects Chapter (Chapter 7).

Recent PECOS-relevant epidemiologic studies examining associations with T2D and related complications have evaluated long-term (30 days or more) exposures to NO_2 and other oxides of nitrogen (see Section 8.3.1). No PECOS-relevant studies examining short-term (less than 30 days) exposures were identified. Animal toxicological studies examining endpoints that underlie DM (i.e., glucose and insulin homeostasis) are discussed in Section 8.5.2.

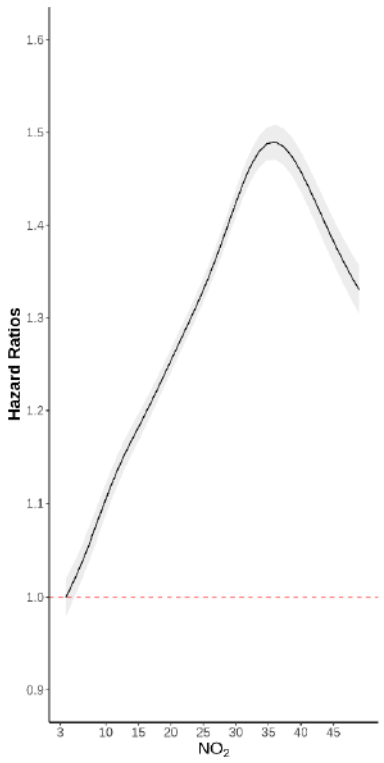
8.3.1 Epidemiologic Studies of Diabetes and Complications from Diabetes

Several recent epidemiologic studies have investigated the relationship between oxides of nitrogen exposure and diabetes mellitus. Evidence from recent studies is summarized below, followed by additional discussion of concentration-response relationships in these studies (see Section 8.3.1.1), the lifestages and populations evaluated (see Section 8.3.1.2), and the potential impacts of copollutant confounding (see Section 8.3.1.3). Section 8.3.1.4 discusses conclusions from these studies and summarizes remaining uncertainties. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and summarized in Appendix A – Appendix Table 8-1.

Most recent studies have evaluated long-term NO_2 exposure and have been conducted among adults and reported positive associations, regardless of study geography. There have been several recent studies conducted in North America that varied in location, exposure assessment methods, and outcome ascertainment, although predominantly observed positive associations between oxides of nitrogen and diabetes.

- Yitshak Sade et al. (2023) constructed a cohort using U.S. Medicare data from 2000 to 2016 for adults 65 years of age and over. They observed a non-linear positive association between

single-pollutant NO_2 and diabetes (see Figure 8-1, corresponding quantitative values not reported).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: Concentration-response curve for the associations with NO_2, from 0.5th percentile to the 99.5th percentile of pollutants, i.e., with 1% poorly constrained extreme values excluded. Results are obtained from a single-pollutant model, adjusted for age, race, sex, Medicaid insurance, annual ZIP code means of summer and winter temperature, and annual ZIP code level sociodemographic variables. The model also includes a random intercept for each ZIP code and a spline function of year.
Source: Adapted from Yitshak Sade et al. (2023). Copyright permission pending.

Figure 8-1 Single-pollutant associations between NO_2 and diabetes.

- In a prospective cohort within the United States, National Social Life, Health, and Aging Project (NSHAP), Honda et al. (2017) investigated the association between 1- to 5-year moving averages of NO_2 and prevalent DM. Honda et al. (2017) observed positive associations for all exposure windows (e.g., 1-year exposure window OR: 1.32 [95% CI: 1.11, 1.57]).
- Howell et al. (2019) conducted a cross-sectional study of the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) data, which includes adults 49 to 74 years old living in large urban centers of Ontario, Canada, to evaluate associations between long-term NO_2 exposure and diabetes prevalence. Authors reported a positive association between NO_2 and diabetes prevalence (OR: 1.11 [95% CI: 1.10, 1.13]).
- Bai et al. (2018) examined the association between a 3-year moving average NO_2 estimated with LUR and incident diabetes among a subset of participants in the Ontario Population Health and Environment Cohort (ONPHEC). The HR for the association in fully adjusted model was 1.06 (95% CI: 1.05, 1.07 per 4 ppb). In another Canadian population, also from the ONPHEC study, Paul et al. (2020b) reported positive associations between 3-year moving

average NO_2 concentrations derived from LUR models and incident diabetes (HR: 1.04 [95% CI: 1.03, 1.05] per IQR, 13.8 ppb).

- Cervantes-Martinez et al. (2022) evaluated the association between monthly NO_2 and T2D within a subsample of the Mexican Teachers' Cohort (MTC), a cohort of female public school teachers. Cervantes-Martinez et al. (2022) reported a positive association (HR: 1.52 [95% CI: 1.37, 1.68] per 10 ppb NO_2).
- The Community of Mine study was a small observational study (n = 552) completed between 2014 and 2017 in San Diego County, U.S. Letellier et al. (2022) assigned long-term NO_2 exposures using two methods: 1) a traditional static approach that linked NO_2 concentrations from the EPA's Air Quality System (AQS) to the participant's home via inverse distance weighting (IDW); and 2) 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. This dynamic exposure assignment is unitless. Letellier et al. (2022) observed a negative association between long-term NO_2 exposure and diabetes for the static exposure method although the 95% CIs included the null (RR: 0.86 [95% CI: 0.67, 1.11] per 0.5 ppb). In contrast, for the dynamic exposure method, Letellier et al. (2022) observed a positive association between long-term NO_2 exposure and diabetes although the 95% CIs crossed the null (RR: 1.05 [95% CI: 0.83, 1.31]).
- In a large cohort of African American women in the United States from 2000 to 2010 (Black Women's Health Study, BWHS), Coogan et al. (2016) evaluated the association between annual NO_2 concentrations and incident T2D using two different exposure metrics: LUR across 56 metropolitan cities and a dispersion model across a subset of 27 metropolitan cities. The HRs were similar and null using either the LUR or dispersion exposure metrics (LUR HR: 0.96 [95% CI: 0.87, 1.06] and dispersion HR: 0.94 [95% CI: 0.80, 1.11]).
- Clark et al. (2017) formed an administrative cohort of adult residents in Vancouver, Canada to investigate associations between 5-year exposures to NO_2 or NO and incident diabetes. Clark et al. (2017) observed a null association with long-term NO_2 exposure (OR: 1.00 [95% CI: 0.98, 1.02] per 4.5 ppb) and a positive association with long-term NO exposure (OR: 1.04 [95% CI: 1.01, 1.05] per 10.7 ppb).
- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (Sacramento Area Latino Study on Aging (SALSA)), Paul et al. (2020a) used the CALINE4 line dispersion model to assign long-term exposure of NO_X concentrations to participants to evaluate associations with prevalent T2D. Authors reported that higher traffic-related NO_X exposure was positively associated with prevalent T2D (OR: 1.24 [95% CI: 1.11, 1.38] per 2.31 ppb).

Studies conducted in Asian countries generally reported positive associations between NO_2 and diabetes regardless of location, length of exposure, or specification of the outcome.

- Zhang et al. (2021b) conducted a cross-sectional study of the China Health and Retirement Longitudinal Study (CHARLS) participants from Wave 3 conducted in 2015. Zhang et al. (2021b) reported positive associations between 1-year average NO_2 exposures (derived from hybrid LUR, satellite, and kriging models) and diabetes prevalence (OR: 1.27 [95% CI: 1.14, 1.42]).
- Using the Henan Rural Cohort Study, Kang et al. (2022) observed a positive association between 3-year average exposure to NO_2 and T2D among adults (OR: 1.06 [95% CI: 1.05, 1.07] per 0.5 ppb).

- Shin and Kim (2023) evaluated the association between long-term NO_2 exposure and incident diabetes from the Cardiovascular Disease Association Study (CAVAS), a prospective cohort of adults aged 40 to 69 years living in Korea. Shin and Kim (2023) reported a positive association (HR: 1.29 [95% CI: 1.12, 1.49] per 10 ppb NO_2).

Studies conducted in European countries generally reported positive associations between oxides of nitrogen and diabetes, although this was inconsistent depending on location, oxides of nitrogen, length of exposure, or specification of the outcome.

- In a pan-European, multi-center, prospective cohort based on the Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS), Nagrani et al. (2023) observed near-null associations between annual NO_2 exposures estimated using ELAPSE and prediabetes (see Figure 8-2, quantitative values not provided).

List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: Parsimonious models were adjusted for age and sex. Fully adjusted models were additionally adjusted for the study region, lifetime alcohol status, membership in a sports club, screen time/week, parental education status, parental smoking and family history of diabetes. Mean of annual average ambient air pollutants (NO_2) are calculated for the entire study period that each participant was followed. Associations represent per IQR increase in ambient NO_2. The IQR for the exposures are study region specific.
Source: Adapted from Nagrani et al. (2023). Copyright permission pending.

Figure 8-2 Association of ambient NO_2 with Prediabetes in children and adolescents of the IDEFICS/I. Family cohort

- A few studies in the Netherlands used national surveys to investigate the association between long-term NO_2 and prevalent diabetes, and all reported positive associations. In a national health survey (the Public Health Monitor) in the Netherlands, Strak et al. (2017) observed that NO_2 was positively associated with prevalent diabetes (OR: 1.07 [95% CI: 1.05, 1.09] per $\mu g/m^3$ NO_2). Similarly, in a cross-sectional study from a national survey in the Netherlands, Klompmaker et al. (2019) observed that NO_2 was positively associated with prevalent diabetes (OR: 1.15 [95% CI: 1.09, 1.22]).
- A few studies in Denmark evaluated a 5-year exposure to oxides to nitrogen and T2D, with all reporting positive associations. Using the Danish National Health Survey from 2010 to 2013, Sørensen et al. (2022a) observed a positive association between a 5-year NO_2 exposure average and incident T2D (HR: 1.14 [95% CI: 1.06, 1.23) per 5.3 ppb NO_2). Sørensen et al. (2022b) created an administrative cohort of all persons aged >50 years living in Denmark from 2005 to 2017, and similarly observed a positive association between a 5-year NO_2 exposure average and incident T2D (HR: 1.06 [95% CI: 1.05, 1.07] per 3.8 ppb NO_2). Sørensen et al. (2022b) additionally observed a positive association between specifically the traffic contribution (estimated using comprehensive emissions inventory for Denmark and spatial modelling) of the 5-year NO_2 exposure average and incident T2D (HR: 1.043 [95% CI: 1.035, 1.052] per 2.7 ppb NO_2). Using the Danish National Diabetes Register (NDR),

Hansen et al. (2016) investigated the association between 5-year mean of NO_2 or NO_X and incident diabetes. Hansen et al. (2016) reported positive associations although the 95% CI crossed the null for both NO_2 and NO_X (HR: 1.13 [95% CI: 0.97, 1.32] per 10 ppb NO_2 and 1.01 [95% CI: 0.98, 1.05] per 5.4 ppb NO_X, respectively).

- In a population-based study, the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), Eze et al. (2017) investigated the association between annual NO_2 and incident diabetes. Eze et al. (2017) observed an inverse association although the 95% CI was imprecise and crossed the null (RR: 0.90 [95% CI: 0.61, 1.34]).
- In a nationwide, population-based administrative cohort study of 35+ year-old adults in Italy, Gandini et al. (2018) reported a negative association between annual or multi-year (1999, 2003, 2005, 2007) NO_2 concentrations and incident diabetes (HR: 0.96 [95% CI: 0.92, 1.01]), although when restricted to Northern and Central Italy, the reported association was positive (HR: 1.02 [95% CI: 0.95, 1.10]).

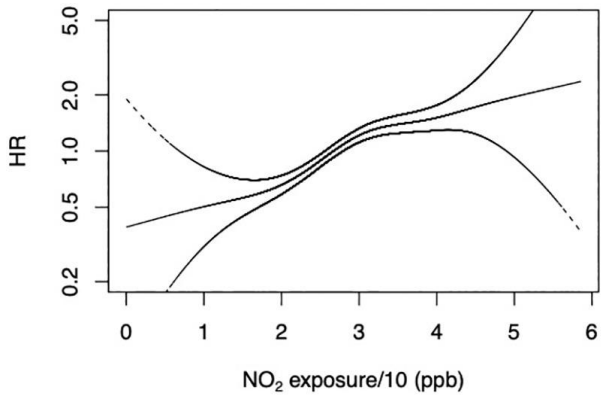
Several recent epidemiologic studies used the UK Biobank, a prospective large-scale biomedical database including >500,000 adult participants, to evaluate long-term exposure to oxides of nitrogen and diabetes. These studies consistently reported positive associations.

- Hu et al. (2023) utilized the UK Biobank, selecting participants aged 40 to 69 years who were recruited between 2006 and 2010, to evaluate the association between annual NO_2 exposure (via LUR) and incident T2D. Hu et al. (2023) reported a positive association per IQR increase in NO_2 (HR: 1.14 [95% CI: 1.05, 1.24]).
- Li et al. (2021) utilized the UK Biobank and observed positive associations between long-term NO_2 and NO exposures and incident T2D (HR: 1.05 [95% CI: 1.02, 1.07] and HR: 1.04 [95% CI: 1.02, 1.05] per standard deviation (SD), respectively).
- Li et al. (2022) utilized the UK Biobank and observed a positive association between long-term NO_2 exposure and incident T2D (HR: 1.16 [95% CI: 1.12, 1.20).
- Luo et al. (2022) utilized the UK Biobank of adult (mean age of 56.1 years) participants to evaluate the association between long-term NO_2 exposure and T2D. Luo et al. (2022) observed a positive association (HR: 1.04 [95% CI: 1.02, 1.06] per 5.3 ppb NO_2).
- Wu et al. (2022b) derived multi-state models to estimate the association between oxides of nitrogen and the dynamic progressions trajectories of T2D from health to incident T2D then to complication and ultimately to death. Wu et al. (2022b) reported positive associations with annual average NO_2 or NO_X for transitions from healthy status to incident T2D (HR: 2.89 [95% CI: 2.76, 3.02] per 10 ppb NO_2 and HR: 1.39 [95% CI: 1.37, 1.42] per 6.6 ppb NO_X, respectively) as well as for transitions from participants with T2D to complications from T2D (HR: 1.45 [95% CI: 1.31, 1.61] per 10 ppb NO_2 and HR: 1.10 [95% CI: 1.06, 1.15] per 6.6 ppb NO_X, respectively).
- Similar to Wu et al. (2022b), 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 or NO_X for transitions from healthy status to incident diabetes (HR: 1.156 [95% CI: 1.080, 1.238] per 10.2 $\mu g/m^3$ NO_2 or HR: 1.107 [95% CI: 1.057, 1.159] per 16.96 $\mu g/m^3$ NO_X, respectively).

8.3.1.1 Concentration-Response

Several studies investigating the association between oxides of nitrogen and diabetes also evaluated the shapes of concentration-response relationships across the distribution of estimated oxides of nitrogen exposures, primarily NO_2. Overall, for the association between NO_2 and diabetes, there was a general indication of an approximately linear, linear plateau/threshold, or supralinear concentration-response relationships reported.

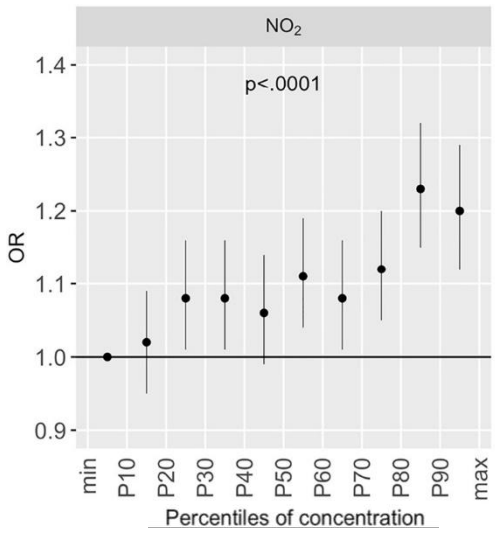
- Yitshak Sade et al. (2023) observed a non-linear, parabolic positive concentration-response curve for the association between NO_2 and diabetes (see Figure 8-1 above).
- Bai et al. (2018) reported that the estimated associations of incident diabetes increased monotonically across the quintiles of NO_2 exposures.
- Cervantes-Martinez et al. (2022) reported a non-linear concentration-response curve for the association between monthly NO_2 and T2D (see Figure 8-3). However, when evaluating the association between NO_2 and T2D categorically (quartiles), the concentration-response appears to increase monotonically (see Table 8-4).



List of abbreviations in alphabetical order: CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide; ppb = parts per billion.
Source: Adapted from Cervantes-Martinez et al. (2022). Copyright permission pending.

Figure 8-3 Spline analysis of nonlinear associations (HR with 95% CI) between exposure to monthly NO_2 (ppb) and incident diabetes.

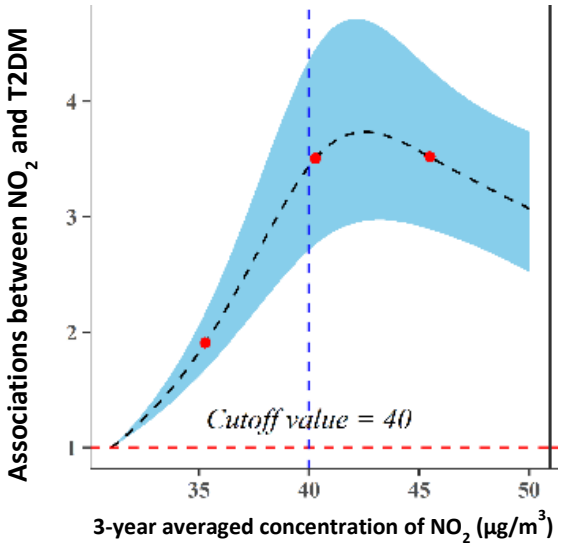
- In a national health survey in the Netherlands, Strak et al. (2017) evaluated associations between deciles of NO_2 concentrations and prevalent diabetes, and they reported no major deviation from a linear association (see Figure 8-4).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; OR = odds ratio.
Notes: Based on percentiles of pollutants (in brackets).
Source: Adapted from Strak et al. (2017). Copyright permission pending.

Figure 8-4 Assessment of linearity of the association between NO_2 and diabetes.

- Kang et al. (2022) reported that the concentration-response curve for the association between 3-year average exposure to NO_2 and T2D among adults was steeply linear at lower concentrations with a threshold at approximately 21.3 ppb (40 µg/m^3) (see Figure 8-5). Additionally, Kang et al. (2022) evaluated the association between 3-year average exposure to NO_2 defined categorically and T2D. The observed association was magnified compared to the continuous exposure (OR: 1.61 [95% CI: 1.50, 1.74] for ≥21.3 ppb (≥40 µg/m^3) vs. <21.3 ppb (<40 µg/m^3)).

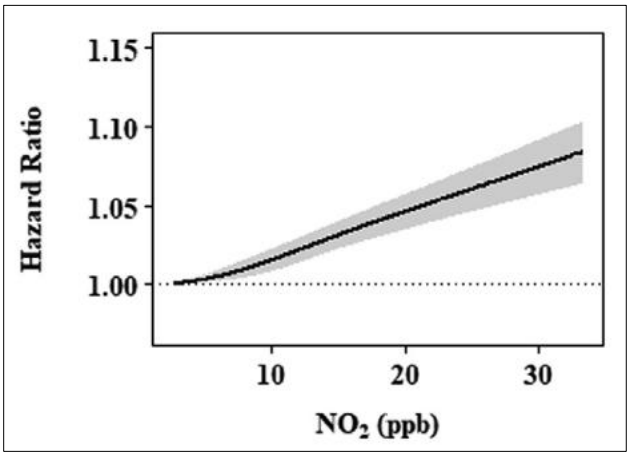


List of abbreviations in alphabetical order: m = meter; NO_2 = nitrogen dioxide; T2DM = Type 2 Diabetes Mellitus; µg=microgram.

Note: Adjusted by Age, Sex, Education Level, Marital Status, Average Monthly Income, Smoking, Drinking Status Activity, High-Fat Diet, Fruits and Vegetables Intake, and History of T2DM
Source: Adapted from Kang et al. (2022). Copyright permission pending.

Figure 8-5 Concentration-response curve for 3-year average NO_2 and T2D.

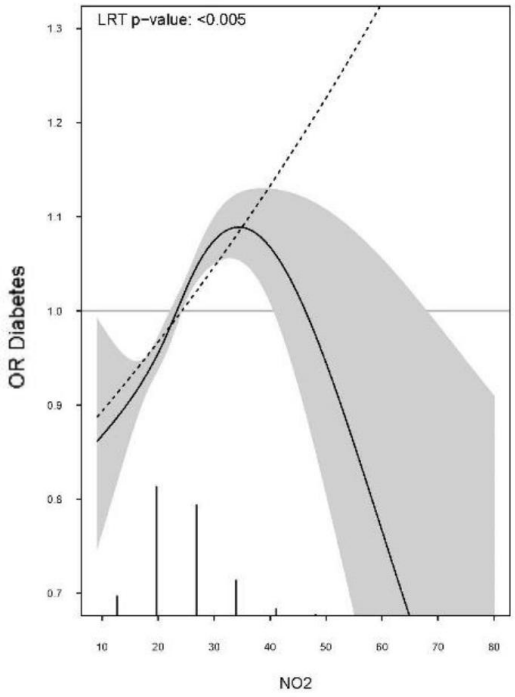
- Paul et al. (2020b) also observed an approximately linear concentration-response curve for the association between NO_2 and incident diabetes (see Figure 8-6; see Table 8-4Table 8- for categorical concentration-response for the 3-year exposure quartiles).



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

Figure 8-6 Concentration-response function of ensemble model for the association between NO_2 and the risk of incident diabetes in Ontario, Canada, during the study period (2001 to 2015).

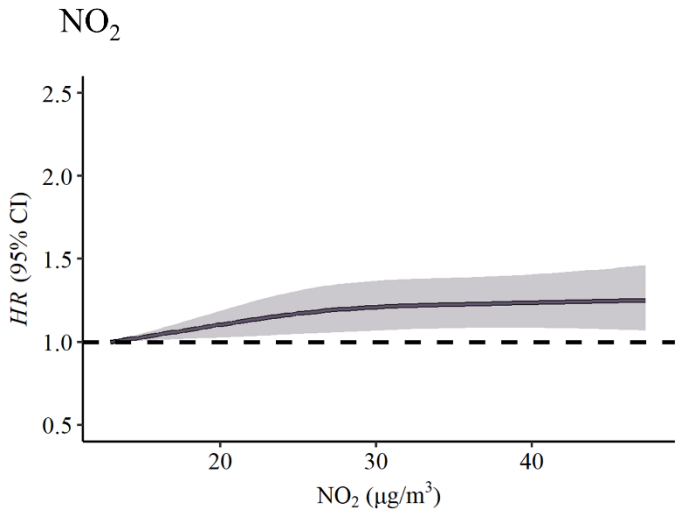
- In SALSA, a cohort of older Mexican Americans, Paul et al. (2020a) evaluated associations between categorical (binary) traffic-related NO_X exposure and prevalent T2D (>2.68 ppb vs. ≤2.68 ppb OR: 1.62 [95% CI: 1.27, 2.05]).
- For the association between NO_2 and prevalent diabetes, Klompmaker et al. (2019) observed a non-linear, parabolic concentration-response curve when using three degrees of freedom and a linear concentration-response curve when using one degree of freedom (see Figure 8-7). When evaluating associations using categorical quintiles for NO_2 with Q1 used as the referent, Klompmaker et al. (2019) observed a higher OR for Q5 vs Q1 compared to Q2 vs Q1 (OR for Q5 vs Q1: 1.20 [95 % CI: 1.14, 1.27] and OR for Q2 vs Q1: 1.08 [95 % CI: 1.02, 1.13], respectively).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Notes: Solid line shows 3 degrees of freedom with grey area showing the 95% CIs Dashed line is the estimated concentration-response curve with 1 degree of freedom. Density bars are shown on the y-axis. Models were adjusted for sex, age, marital status, region of origin, education, work, standardized household income, smoking habits, number of cigarettes per day, alcohol consumption, number of alcohol glasses per week, physical activity, BMI, and neighborhood SES.
Source: Adapted from Klompmaker et al. (2019). Copyright permission pending.

Figure 8-7 Concentration-response curve for the association between NO_2 and prevalent diabetes.

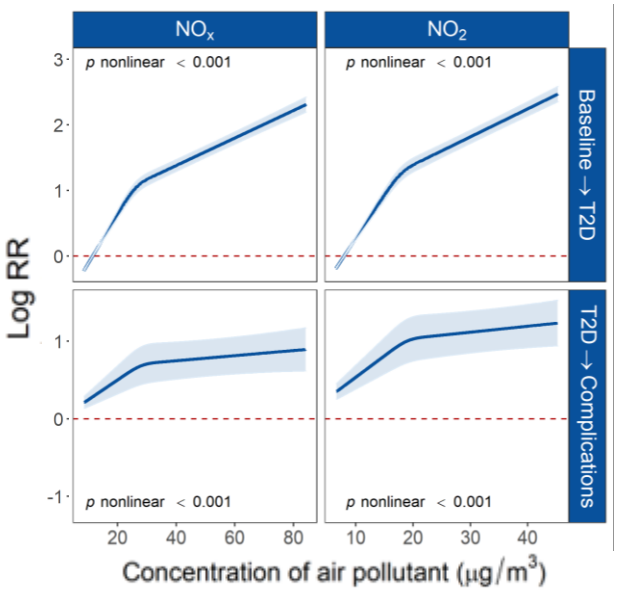
- A few of the UK Biobank studies reported some evidence of concentration-response with differing categorical cut points. Li et al. (2021) observed minimal evidence of concentration-response (i.e., minimal-to-no increase in the effect estimates as well as confidence interval overlap across the distribution) when evaluating long-term NO_2 and NO exposure categorically (quintiles) and incident T2D (see Table 8-). Similarly, Luo et al. (2022) reported no evidence of a concentration-response when evaluating the association between NO_2 categorically by quartile (with Q1 as the referent) and T2D (see Table 8-). Li et al. (2022) observed evidence of concentration-response when evaluating long-term NO_2 exposure categorically (polytomously defined as low, medium, high as well as dichotomously defined using the WHO air quality guideline of 5.3 ppb (10 μg/m^3) at the cut point) and incident T2D (see Table 8-4).
- For the association between NO_2 and incident T2D within the UK Biobank, Hu et al. (2023) observed a linear plateau concentration-response curve with a threshold at approximately 15.9 ppb (30 μg/m^3; see Figure 8-8).



List of abbreviations in alphabetical order: CI = confidence interval; HR = Hazard ratio; NO_2 = nitrogen dioxide; µg=microgram.
Note: Stratified by age group and sex plus adjustment for ethnicity, education, economic status, Townsend deprivation index, assessment center, length of time at residence, smoking status, alcohol intake frequency, sedentary time, sleep duration, physical activity, and healthy diet score, polygenic risk score for T2D.
Source: Adapted from Hu et al. (2023). Copyright permission pending.

Figure 8-8 Concentration-response curve for NO_2 and incident T2D in UK Biobank.

- Also, within the UK Biobank, Wu et al. (2022b) derived multi-state models to estimate the association between oxides of nitrogen and the dynamic progression of T2D and subsequent complications. Concentration-response relationships were estimated using restricted cubic splines; the study observed a supralinear relationships for NO_2 and NO_X with the risk of T2D and linear plateau relationships for NO_2 and NO_X with risk of complications (see Figure 8-9).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; RR = relative risk; T2D: = type 2 diabetes; µg=microgram.
Note: Associations were modelled by restricted cubic splines with 3 knots. Nonlinear associations were tested using likelihood ratio tests. Model adjusted for age, sex, ethnicity, residential area, smoking status, healthy diet, physical activity, and family history of diabetes.
Source: Adapted from Wu et al. (2022b). Copyright permission pending.

Figure 8-9 Concentration-response associations between air pollution exposure (NO_X and NO_2) and different transitions of T2D in UK Biobank.

Table 8-4 Epidemiologic studies evaluating concentration-response between long-term exposure to oxides of nitrogen and diabetes mellitus and complications from diabetes mellitus

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
Exposure to NO				
†Li et al. (2021)	UK Biobank Enrollment: 2006–2010 Follow-up: median 11 years	Quartile 1 Mean = 9.4±2.8 µg/m^3 Quartile 2 Mean = 13.4±3.6 µg/m^3 Quartile 3 Mean = 16±3.7 µg/m^3 Quartile 4 Mean = 18.9±3.9 µg/m^3 Quartile 5 Mean = 29.1±11.9 µg/m^3	Categorical (quartiles)	
Exposure to NO_2				
†Bai et al. (2018)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment: April 1, 1996 Follow-up: through December 31, 2012	Diabetes Cohort Median = 21.1 ppb (IQR 4) Mean = 21.4±3.5 ppb Min-Max = 9.9–50.1 ppb Hypertension Cohort Median = 21.1 ppb (IQR 4.1) Mean = 21.5±3.6 ppb Min-Max = 9.9–50.1 ppb	Categorical (quintiles)	Monotonic
†Cervantes-Martinez et al. (2022)	Mexican Teachers Cohort Enrollment: 2006–2008	Analytical subsample Mean = 34.6±7.3 ppb Monthly mean across study	Penalized splines	Non-linear

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
	Follow-up: 2011–2013 and 2014–2020	period Incident Diabetes Mean = 29.8±5.3 ppb No Diabetes Mean = 28.6±5.4 ppb Total Mean = 28.7±5.4 ppb Monthly mean at baseline Incident Diabetes Mean = 35.3±7.5 ppb No Diabetes Mean = 34.5±7.3 ppb Total Mean = 34.6±7.3 ppb Quartile 1 Median = 22.9 ppb (IQR 3.5) Quartile 2 Median = 34.3 ppb (IQR 2.9) Quartile 3 Median = 25.8 ppb (IQR 3.1) Quartile 4 Median = 43.3 ppb (IQR 3.5) Total population in study area Mean = 34.5±7.4 ppb	Categorical (quartiles)	Monotonic
†Hu et al. (2023)	UK Biobank Enrollment: 2006–2010 Follow-up: through February 20, 2020	Cases (with incident type 2 diabetes) Median = 27.1 µg/m^3 (IQR 9.4) Min-Max = 12.9-105.9 µg/m^3 Non-cases (without incident type 2 diabetes) Median = 25.8 µg/m^3 (IQR 9.8) Min-Max = 12.9-108.5 µg/m^3	Restricted cubic spline analyses with three knots	Linear plateau
†Kang et al. (2022)	Henan Rural Cohort Study 2015–2017	Overall Mean = 39.87±3.6 µg/m^3 Participants with T2DM Mean = 40.63±3.53 µg/m^3 Participants without T2DM Mean = 39.79±3.6 µg/m^3	Categorical (binary)	
†Klompmaker et al. (2019)	Dutch Public Health Monitor 2012 (Dutch PHM 2012)	Median = 23.4 µg/m^3 (IQR 7.85)	1 df	Approximately linear
			3 df	Inverse j-shaped

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
	2012		Categorical (quintiles)	
†Li et al. (2021)	UK Biobank Enrollment: 2006–2010 Follow-up: median 11 years	Quartile 1 Mean = 17.3±2.8 µg/m^3 Quartile 2 Mean = 22.8±2.7 µg/m^3 Quartile 3 Mean = 26.3±2.3 µg/m^3 Quartile 4 Mean = 29.8±2.9 µg/m^3 Quartile 5 Mean = 37±6.4 µg/m^3	Categorical (quartile)	
†Li et al. (2022)	UK Biobank Enrollment: 2007–2010	Physical Activity High Mean = 28.8±9.15 µg/m^3 Low Mean = 29.21±8.99 µg/m^3 Moderate Mean = 29.32±9.49 µg/m^3 Total Mean = 29.14±9.3 µg/m^3	Categorical	
†Luo et al. (2022)	UK Biobank Enrollment: 2006–2010 Follow-up: through May 2021	CMD Free Median = 26 µg/m^3 P25-P75 = 21.2–31.1 µg/m^3 CMM Survivor Median = 27.3 µg/m^3 P25-P75 = 22.5–32.1 µg/m^3 Death with CMM Median = 27.4 µg/m^3 P25-P75 = 22.8–32.5 µg/m^3 Death with FCMD Median = 26.8 µg/m^3 P25-P75 = 22.1–31.8 µg/m^3 Death without CMD Median = 26.2 µg/m^3 P25-P75 = 21.5–31.3 µg/m^3 FCMD Survivor Median = 26.5 µg/m^3 P25-P75 = 21.8–31.4 µg/m^3 Total	Categorical (quartiles)	

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
		Median = 26.1 µg/m^3 P25-P75 = 21.3-31.2 µg/m^3		
†Paul et al. (2020b)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment: January 2001 Follow-up: through December 2015	Cardiovascular Deaths Min-Max = 2.3–54.3 ppb Cohort with Prevalent Diabetes Min-Max = 2.3–58.3 ppb Cohort without Diabetes Min-Max = 2.7–71.4 ppb Diabetes Deaths Min-Max = 2.3–52.4 ppb Incident Diabetes Cases Min-Max = 2.7–71.4 ppb	Categorical	

List of abbreviations in alphabetical order: CMD = cardiometabolic disease; CMM = cardiometabolic multimorbidity; df = degrees of freedom; FCMD = first cardiometabolic disease; IQR = inter-quartile range; Max = maximum; Min = minimum; NO = nitric oxide; NO_2 = nitrogen dioxide; ppb = parts per billion; P25 = 25th percentile; P75 = 75th percentile; T2DM = type 2 diabetes mellitus
[a]For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses
[b]The visual representations of the shape of the curve in the corresponding text.
†Studies published since the 2016 Oxides of Nitrogen ISA.

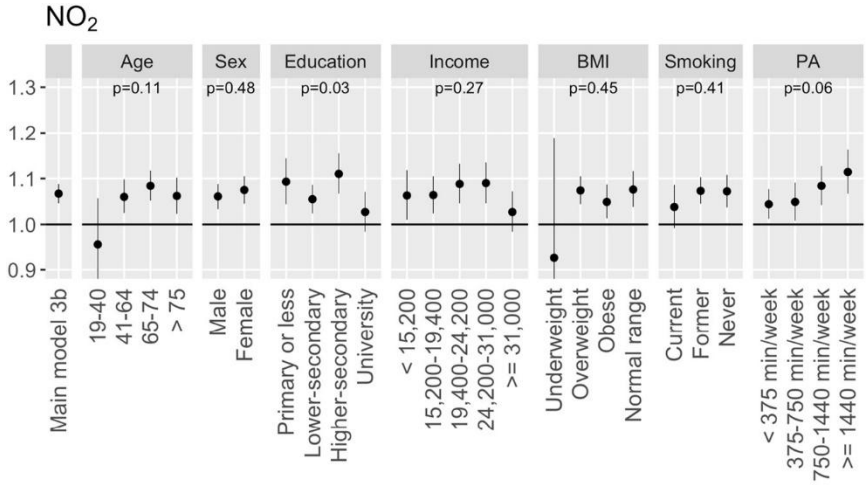
8.3.1.2 Lifestages and Populations

Numerous potential modifiers were evaluated within studies investigating the association between oxides of nitrogen and diabetes, such as age, sex, comorbidities (e.g., obesity), behavior/ lifestyle factors (e.g., diet, physical activity, smoking status, alcohol consumption status), and characteristics of residence (e.g., walkability, urbanicity, proximity to roadways). However, no clear patterns emerged for modifying factors.

- For the LUR exposure metric, when investigating the association between long-term NO_2 and T2D in a large cohort of African American women, Coogan et al. (2016) observed minimal-to-no evidence of modification by neighborhood socioeconomic status (SES), body mass index (BMI), age, education, hypertension, exercise, smoking status, or meat/fried food diet. The HR in the lowest category of BMI (<25) was elevated, although imprecise, compared to the overall HR and the other categories of BMI HR (BMI <25 HR: 1.23 [95% CI: 0.83, 1.82] and overall HR: 0.96 [95% CI: 0.87, 1.06]).
- Howell et al. (2019) reported that when walkability was included in the model as a joint exposure, the association between NO_2 and diabetes prevalence was similar, although slightly magnified (OR: 1.16 [95% CI: 1.15, 1.18]), meaning that the independent benefits of a walkable neighborhood design did not reduce the odds of diabetes when jointly modeled with NO_2 exposure.
- For the association between a 3-year moving average NO_2 exposure and incident diabetes, Bai et al. (2018) evaluated effect measure modification by age, sex, and comorbidities (i.e.,

chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure (CHF), hypertension, acute myocardial infarction (AMI), cancer). Bai et al. (2018) reported elevated HRs among participants <60 years, with no COPD, with no hypertension, and with no AMI; no effect measure modification (EMM) was observed for sex, asthma, CHF, or cancer (see Table 8-5 for details).

- Paul et al. (2020a) reported that higher traffic-related NO_X exposure was positively associated with prevalent T2D among a cohort of older (greater than 60 years; mean of 70.2 years) Mexican American participants in California, and this result was stable upon restriction to participants living within urban locations.
- For the association between NO_2 and prediabetes, Nagrani et al. (2023) reported weak evidence of modification by sex (boys OR: 1.03 [95% CI: 0.87, 1.22]; girls OR: 0.91 [95% CI: 0.76, 1.10] per IQR), obesity status (normal weight OR: 1.00 [95% CI: 0.85, 1.17]; overweight/obese OR: 0.89 [95% CI: 0.69, 1.13] per IQR), and proximity to roadways (residential distance <250 meters to major road OR: 1.10 [95% CI: 0.93, 1.29]; residential distance ≥250 meters to major road OR: 0.80 [95% CI: 0.65, 0 99] per IQR). The weak evidence of modification by sex and proximity to roadways was also observed for the association between NO_2 and MetS (see Section 8.4.1.2), but the modification was observed in the opposite direction.
- In a national health survey in the Netherlands, Strak et al. (2017) evaluated effect measure modification by age, sex, education income, BMI, smoking, and physical activity. Strak et al. (2017) reported some evidence of effect measure modification for participants reporting higher levels of physical activity (see Figure 8-10).



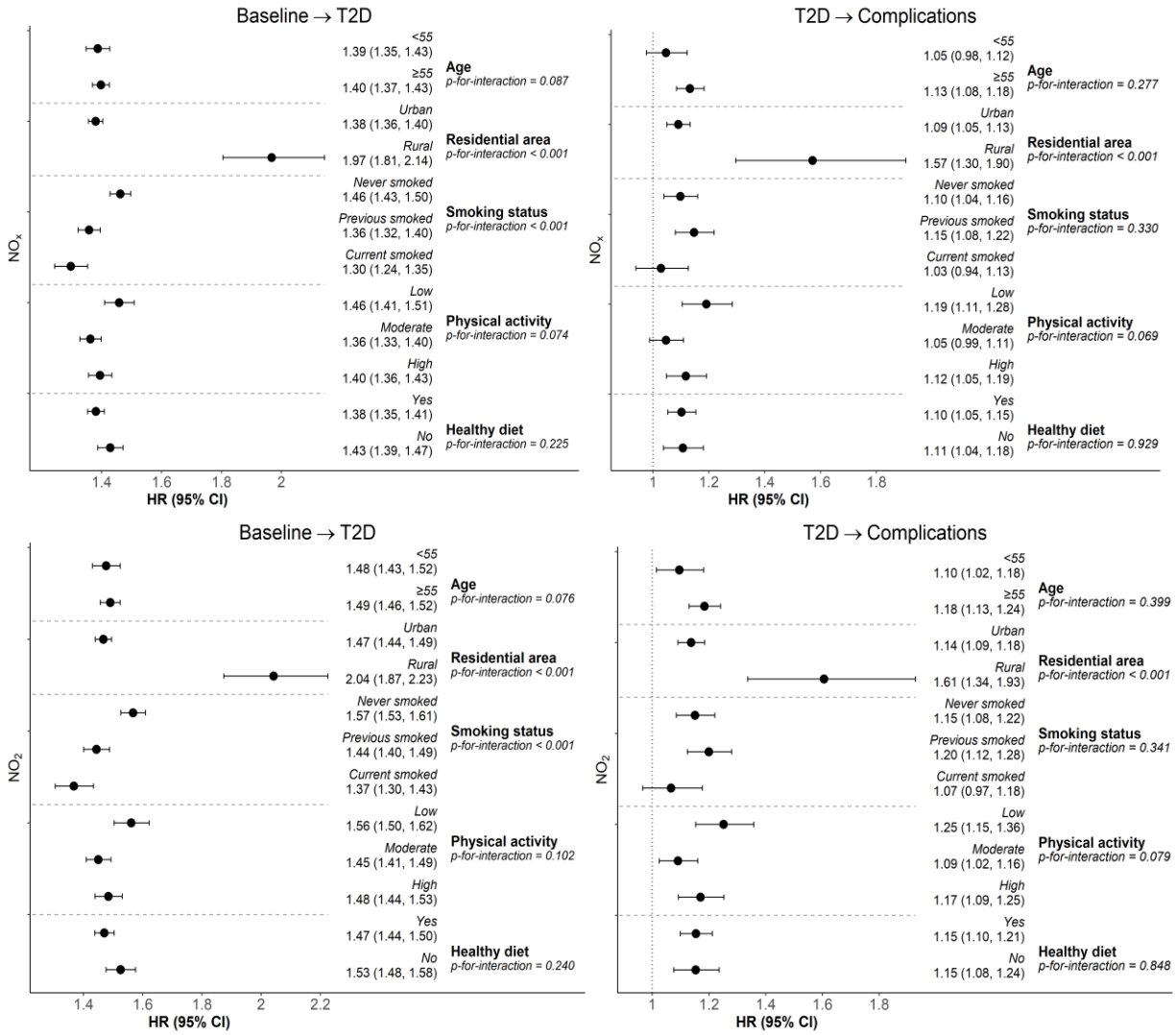
List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; OR = odds ratio.
Source: Adapted from Strak et al. (2017). Copyright permission pending.

Figure 8-10 Stratified analyses for the association between NO_2 and diabetes.

- Shin and Kim (2023) did not observe evidence of modification by sex; however, Shin and Kim (2023) did observe evidence of modification by BMI with participants <23 kg/m^2 had a higher HR of incident diabetes than those ≥23 kg/m^2 (HR: 2.04 [95% CI: 1.42, 2.91] and HR: 1.13 [95% CI: 0.98, 1.30] per 10 ppb NO_2, respectively). Additionally, associations between NO_2 concentrations and incident diabetes were stronger among participants with a lower

dietary intake (quartile 1) of retinol, vitamin A, and cholesterol nutrients compared to those with a higher intake (quartile 4).

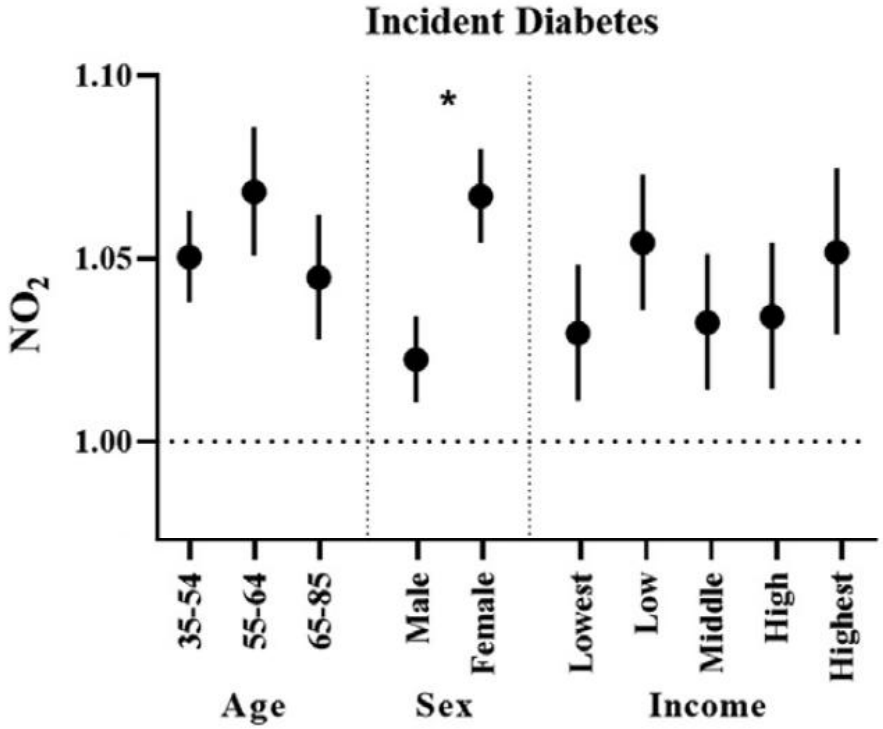
- For the association between NO_2 and incident diabetes, Gandini et al. (2018) observed no evidence of effect modification by urbanicity and sex.
- Hu et al. (2023) observed no evidence of effect measure modification for age or sex for the association between annual NO_2 exposure and incident T2D. Weak evidence of effect measure modification was observed for a healthy diet– with those without a healthy diet having a higher HR than those with a healthy diet; however, the HR for a healthy diet was imprecise.
- Kang et al. (2022) evaluated the association between 3-year average exposure to NO_2 and T2D among adults stratified by obesity status [defined by BMI, waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), body fat percent (BRP), and visceral fat index (VFI)]; there was no evidence of modification by any metric of obesity investigated (refer to Table 8- for details).
- Li et al. (2022) did not observe evidence of modification by physical activity when evaluating continuous long-term NO_2 exposure and incident T2D (see Table 8-5).
- Wu et al. (2022b) derived multi-state models to estimate the association between NO_2 or NO_X and the dynamic progressions trajectories of T2D from health to incident T2D then to complications. Wu et al. (2022b) evaluated effect measure modification for residential area urbanicity, age, smoking status, physical activity, and healthy diet (see Figure 8-11). Effect measure modification was reported for residential area urbanicity for associations between oxides of nitrogen and T2D or complications, with participants within rural residential areas having higher HRs than those within urban residential areas. Some evidence of effect measure modification was also observed physical activity for associations between oxides of nitrogen and T2D or complications, with participants with low physical activity having higher HRs than those with moderate or high physical activity. For the associations between NO_2 or NO_X and T2D, Wu et al. (2022b) observed some evidence of effect measure modification for smoking status with never smokers having the highest HRs compared to those that previously smoked or currently smoked. No effect measure modification was observed for age or healthy diet for oxides of nitrogen and T2D or complications.



List of abbreviations in alphabetical order: HR = hazard ratio; NO_2 = nitrogen dioxide; T2D = type 2 diabetes.
Note: HRs (95% CI) are results for per IQR increase from multi-state models.
Source: Adapted from Wu et al. (2022b). Copyright permission pending.

Figure 8-11 Effect measure modification of the association between NO_2 or NO_X and two transitions of T2D in the UK Biobank.

- Paul et al. (2020b) observed evidence of effect measure modification by sex, with females having a higher risk of NO_2-associated incident diabetes (see Figure 8-12; numeric values not presented). No modification was observed by age or income.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: All models adjusted for age, sex, SES, region, and healthcare access, and stratified by Greater Toronto Area residence. Hazard ratios are expressed per interquartile range (IQR) increase (13.8 ppb). Cochran's Q was used to test for heterogeneity across strata. Significant heterogeneity (P <0.05) is indicated by asterisks.
Source: Adapted from Paul et al. (2020b). Copyright permission pending.

Figure 8-12 Hazard ratios and 95% CIs for the association between NO_2 and incident diabetes stratified by selected characteristics in Ontario during the study period (2001–2015).

Table 8-5 Epidemiologic studies evaluating lifestages and population differences between long-term exposure to oxides of nitrogen and diabetes mellitus and complications from diabetes mellitus

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Behavioral Factors					
Exposure to NO_2					
†Coogan et al. (2016)	Black Women's Health Study (BWHS) Enrollment: 1995	HR (95% CI)[b] Incident T2D LUR model for 56 cities Main Effect: 0.96 (0.87, 1.06)	HR (95% CI)[b] Incident T2D: LUR model BMI: <25: 1.23 (0.83, 1.82)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Follow-up: 1997–2011		BMI: 25–29: 1.04 (0.86, 1.26)	≈	
			BMI: ≥30: 0.97 (0.86, 1.09)	≈	
			Vigorous exercise: <5 hr/wk: 0.97 (0.88, 1.07)	≈	
			Vigorous exercise: ≥5 hr/wk: 0.68 (0.36, 1.29)	≈	
			Smoking: Never: 0.93 (0.81, 1.06)	≈	
			Smoking: Past or current: 1.04 (0.89, 1.21)	≈	
			Meat/fried food diet pattern score: Quintile 1: 0.90 (0.68, 1.18)	≈	
			Meat/fried food diet pattern score: Quintile 2: 0.76 (0.59, 0.99)	≈	
			Meat/fried food diet pattern score: Quintile 3: 1.10 (0.85, 1.44)	≈	
			Meat/fried food diet pattern score: Quintile 4: 0.98 (0.77, 1.25)	≈	
			Meat/fried food diet pattern score: Quintile 5: 1.00 (0.79, 1.26)	≈	
†Hu et al. (2023)	UK Biobank Enrollment: 2006–2010	HR (95% CI)[b] Incident T2D Main Effect: 1.14 (1.05, 1.24)	HR (95% CI)[b] Incident T2D Healthy diet: No: 1.12 (1.02, 1.22)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Follow-up: through February 20, 2020		Healthy diet: Yes: 0.59 (0.20, 1.76)	↓	
†Kang et al. (2022)	Henan Rural Cohort Study 2015–2017	OR (95% CI)[c] T2D Main Effect: 1.06 (1.05, 1.07)	OR (95% CI)[c] T2D BMI: No obesity: 1.53 (1.40, 1.67)	≈	Individual
			BMI: Obesity: 1.53 (1.32, 1.78)	≈	
			WC: No obesity: 1.57 (1.37, 1.80)	≈	
			WC: Obesity: 1.37 (1.25, 1.50)	≈	
			WHR: No obesity: 1.62 (1.35, 1.95)	≈	
			WHR: Obesity: 1.47 (1.35, 1.60)	≈	
			WHtR: No obesity: 1.61 (1.33, 1.96)	≈	
			WHtR: Obesity: 1.44 (1.33, 1.56)	≈	
			BRP: No obesity: 1.71 (1.43, 2.04)	≈	
			BRP: Obesity: 1.52 (1.40, 1.65)	≈	
			VFI: No obesity: 1.49 (1.32, 1.67)	≈	
			VFI: Obesity: 1.53 (1.38, 1.68)	≈	
†Li et al. (2022)	UK Biobank Enrollment: 2007–2010	HR (95% CI)[b] Incident T2D Main Effect: 1.16 (1.12, 1.20)	HR (95% CI)[b] Incident T2D Low physical activity: 1.16 (1.07, 1.25)	≈	Individual
			Medium physical activity: 1.18 (1.11, 1.25)	≈	
			High physical activity: 1.14 (1.08, 1.20)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Nagrani et al. (2023)	Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS),I.Family Study Enrollment: 2009-2010 Follow-up: 2013–2014	OR (95% CI)[c] Prediabetes Main Effect: See Figure 8-2	OR (95% CI)[c] Prediabetes Weight: Normal weight: 1.00 (0.85, 1.17)	≈	Individual
			Weight: Overweight/obese: 0.89 (0.69, 1.13)	↓	
†Shin and Kim (2023)	Cardiovascular Disease Association Study Enrollment: 2005–2011 Follow-up: 2016	HR (95% CI)[c] Incident DM Main Effect: 1.29 (1.12, 1.49)	HR (95% CI)[c] Incident DM BMI: <23 kg/m^2: 2.04 (1.42, 2.91)	↑	Individual
			BMI: ≥23 kg/m^2: 1.13 (0.98, 1.30)	↓	
			MDA index score: <median (24): 1.46 (1.14, 1.88)	≈	
			MDA index score: ≥median (24): 1.18 (1.00, 1.40)	≈	
			Daily milk intake: <median (6.7 g): 1.39 (1.15, 1.67)	≈	
			Daily milk intake: ≥median (6.7 g): 1.20 (0.94, 1.52)	≈	
			Daily dairy product intake: <median (26.7 g): 1.36 (1.13, 1.64)	≈	
			Daily dairy product intake: ≥ median (26.7 g): 1.23 (0.98, 1.54)	≈	
			Daily egg intake: <median (2.5 g): 1.29 (1.07, 1.55)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Daily egg intake: ≥median (2.5 g): 1.22 (1.02, 1.45)	≈	
			Daily vegetable intake: <median (211.7 g): 1.34 (1.11, 1.63)	≈	
			Daily vegetable intake: ≥median (211.7 g): 1.20 (1.01, 1.42)	≈	
			Daily fruit intake: <median (122.1 g): 1.20 (1.00, 1.43)	≈	
			Daily fruit intake: ≥median (122.1 g): 1.36 (1.12, 1.64)	≈	
			Vitamin A: Q1: 1.76 (1.33, 2.33)	↑	
			Vitamin A: Q2: 1.10 (0.81, 1.49)	≈	
			Vitamin A: Q3: 1.21 (0.95, 1.56)	≈	
			Vitamin A: Q4: 1.21 (0.94, 1.56)	≈	
			Retinol: Q1: 1.65 (1.32, 2.07)	↑	
			Retinol: Q2: 0.88 (0.67, 1.17)	≈	
			Retinol: Q3: 1.31 (0.99, 1.73)	≈	
			Retinol: Q4: 1.21 (0.89, 1.64)	≈	
			β-carotene: Q1: 1.53 (1.16, 2.01)	≈	
			β-carotene: Q2: 1.26 (0.95, 1.67)	≈	
			β-carotene: Q3: 1.10 (0.87, 1.42)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			β-carotene: Q4: 1.32 (0.98, 1.77)	≈	
			Vitamin B1: Q1: 1.47 (1.12, 1.93)	≈	
			Vitamin B1: Q2: 1.49 (1.07, 2.08)	≈	
			Vitamin B1: Q3: 1.34 (1.05, 1.73)	≈	
			Vitamin B1: Q4: 1.10 (0.83, 1.46)	≈	
			Vitamin B2: Q1: 1.73 (1.31, 2.27)	≈	
			Vitamin B2: Q2: 1.01 (0.74, 1.39)	≈	
			Vitamin B2: Q3: 1.25 (0.96, 1.62)	≈	
			Vitamin B2: Q4: 1.24 (0.93, 1.67)	≈	
			Niacin: Q1: 1.34 (1.02, 1.77)	≈	
			Niacin: Q2: 1.14 (0.88, 1.49)	≈	
			Niacin: Q3: 1.79 (1.28, 2.51)	≈	
			Niacin: Q4: 1.17 (0.91, 1.49)	≈	
			Vitamin B6: Q1: 1.52 (1.16, 1.98)	≈	
			Vitamin B6: Q2: 1.20 (0.92, 1.55)	≈	
			Vitamin B6: Q3: 1.11 (0.87, 1.42)	≈	
			Vitamin B6: Q4: 1.39 (1.02, 1.90)	≈	
			Folate: Q1: 1.62 (1.24, 2.11)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Folate: Q2: 1.18 (0.92, 1.51)	≈	
			Folate: Q3: 1.07 (0.82, 1.39)	≈	
			Folate: Q4: 1.29 (1.00, 1.67)	≈	
			Vitamin C: Q1: 1.41 (1.08, 1.83)	≈	
			Vitamin C: Q2: 1.14 (0.88, 1.47)	≈	
			Vitamin C: Q3: 1.38 (1.02, 1.88)	≈	
			Vitamin C: Q4: 1.23 (0.95, 1.59)	≈	
			Vitamin E: Q1: 1.37 (1.05, 1.78)	≈	
			Vitamin E: Q2: 1.36 (0.99, 1.87)	≈	
			Vitamin E: Q3: 1.07 (0.82, 1.38)	≈	
			Vitamin E: Q4: 1.29 (1.00, 1.66)	≈	
			Calcium: Q1: 1.72 (1.26, 2.35)	≈	
			Calcium: Q2: 1.06 (0.70, 1.59)	≈	
			Calcium: Q3: 1.37 (1.05, 1.80)	≈	
			Calcium: Q4: 1.10 (0.85, 1.44)	≈	
			Phosphate: Q1: 1.47 (1.13, 1.92)	≈	
			Phosphate: Q2: 1.24 (0.94, 1.63)	≈	
			Phosphate: Q3: 1.23 (0.94, 1.59)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Phosphate: Q4: 1.19 (0.92, 1.54)	≈	
			Iron: Q1: 1.55 (1.19, 2.03)	≈	
			Iron: Q2: 1.17 (0.91, 1.51)	≈	
			Iron: Q3: 1.20 (0.94, 1.52)	≈	
			Iron: Q4: 1.19 (0.88, 1.61)	≈	
			Protein: Q1: 1.38 (1.06, 1.79)	≈	
			Protein: Q2: 1.34 (1.04, 1.73)	≈	
			Protein: Q3: 1.20 (0.90, 1.59)	≈	
			Protein: Q4: 1.21 (0.92, 1.60)	≈	
			Fat: Q1: 1.55 (1.21, 1.99)	≈	
			Fat: Q2: 1.18 (0.92, 1.51)	≈	
			Fat: Q3: 1.08 (0.83, 1.41)	≈	
			Fat: Q4: 1.38 (1.00, 1.91)	≈	
			Carbohydrate: Q1: 1.51 (1.11, 2.06)	≈	
			Carbohydrate: Q2: 1.00 (0.76, 1.32)	≈	
			Carbohydrate: Q3: 1.16 (0.90, 1.50)	≈	
			Carbohydrate: Q4: 1.49 (1.16, 1.91)	≈	
			Sodium: Q1: 1.58 (1.12, 2.22)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Sodium: Q2: 1.42 (1.07, 1.87)	≈	
			Sodium: Q3: 1.19 (0.92, 1.53)	≈	
			Sodium: Q4: 1.14 (0.88, 1.47)	≈	
			Potassium: Q1: 1.68 (1.25, 2.24)	≈	
			Potassium: Q2: 1.22 (0.94, 1.57)	≈	
			Potassium: Q3: 1.01 (0.78, 1.29)	≈	
			Potassium: Q4: 1.29 (1.00, 1.65)	≈	
			Zinc: Q1: 1.47 (1.12, 1.93)	≈	
			Zinc: Q2: 1.15 (0.90, 1.47)	≈	
			Zinc: Q3: 1.21 (0.93, 1.56)	≈	
			Zinc: Q4: 1.52 (1.10, 2.10)	≈	
			Fiber: Q1: 1.29 (0.97, 1.72)	≈	
			Fiber: Q2: 1.52 (1.19, 1.94)	≈	
			Fiber: Q3: 1.07 (0.83, 1.37)	≈	
			Fiber: Q4: 1.19 (0.93, 1.53)	≈	
			Ash: Q1: 1.77 (1.27, 2.47)	≈	
			Ash: Q2: 1.15 (0.87, 1.51)	≈	
			Ash: Q3: 1.34 (1.01, 1.78)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Ash: Q4: 1.21 (0.94, 1.56)	≈	
			Cholesterol: Q1: 1.55 (1.21, 1.98)	↑	
			Cholesterol: Q2: 1.27 (0.91, 1.77)	≈	
			Cholesterol: Q3: 1.25 (0.97, 1.62)	≈	
			Cholesterol: Q4: 1.13 (0.84, 1.53)	≈	
Pre-existing comorbidities					
Exposure to NO_2					
†Bai et al. (2018)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment: April 1, 1996 Follow-up: through December 31, 2012	HR (95% CI)[c] Incident diabetes Main Effect: 1.06 (1.05, 1.07)	HR (95% CI)[c] Incident diabetes COPD: Yes: 1.02 (0.98, 1.06)	↓	Individual
			COPD: No: 1.06 (1.05, 1.07)	≈	
			Asthma: Yes: 1.04 (1.02, 1.07)	≈	
			Asthma: No: 1.06 (1.05, 1.07)	≈	
			CHF: Yes: 1.05 (1.00, 1.10)	≈	
			CHF: No: 1.06 (1.05, 1.07)	≈	
			Hypertension: Yes: 1.04 (1.02, 1.06)	↓	
			Hypertension: No: 1.07 (1.05, 1.08)	↑	
			AMI: Yes: 0.98 (0.92, 1.05)	↓	
			AMI: No: 1.06 (1.05, 1.07)	≈	
			Cancer: Yes: 1.03 (0.99, 1.06)	↓	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Cancer: No: 1.06 (1.05, 1.07)	≈	
†Coogan et al. (2016)	Black Women's Health Study (BWHS) Enrollment: 1995 Follow-up: 1997–2011	HR (95% CI)[b] Incident T2D LUR model for 56 cities Main Effect: 0.96 (0.87, 1.06)	HR (95% CI)[b] Incident T2D LUR model Hypertension: No: 1.05 (0.91, 1.22)	↑	Individual
			Hypertension: Yes: 0.91 (0.79, 1.04)	≈	
Sociodemographic factors					
Exposure to NO					
†Paul et al. (2020a)	Sacramento Area Latino Study on Aging (SALSA) Enrollment: 1998–1999 Follow-up: through 2008	OR (95% CI)[c] T2D Main Effect: 1.24 (1.11, 1.38)	OR (95% CI)[c] T2D Urban only: 1.23 (1.10, 1.37)	≈	Area-level
			Urban only (≤2.68 ppb vs. ≤2.68 ppb): REF 1.00 (1.00, 1.00)		
			Urban only (>2.68 ppb vs. ≤2.68 ppb): 1.63 (1.27, 2.09)	↑	
Exposure to NO_2					
†Bai et al. (2018)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment: April 1, 1996 Follow-up: through December 31, 2012	HR (95% CI)[c] Incident diabetes Main Effect: 1.06 (1.05, 1.07)	HR (95% CI)[c] Incident diabetes Age: <60 yr: 1.07 (1.05, 1.08)	≈	Individual
			Age: 60–74 yr: 1.04 (1.03, 1.06)	≈	
			Age: ≥75 yr: 1.03 (1.00, 1.06)	↓	
			Sex: Males: 1.05 (1.03, 1.06)	≈	
			Sex: Females: 1.07 (1.05, 1.08)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Coogan et al. (2016)	Black Women's Health Study (BWHS) Enrollment: 1995 Follow-up: 1997–2011	HR (95% CI)[b] Incident T2D LUR model for 56 cities Main Effect: 0.96 (0.87, 1.06)	HR (95% CI)[b] Incident T2D LUR model Age: <40 yr: 0.94 (0.74, 1.19)	≈	Individual
			Age: 40–54 yr: 0.97 (0.85, 1.10)	≈	
			Age: ≥55 yr: 1.04 (0.89, 1.21)	↑	
			Education: ≤HS: 0.98 (0.77, 1.24)	≈	
			Education: Some college: 0.97 (0.81, 1.17)	≈	
			Education: College graduate: 0.98 (0.85, 1.13)	≈	
			Neighborhood SES: Quintile 1: 0.89 (0.66, 1.19)	≈	Area-level (U.S. Census data at the block group level)
			Neighborhood SES: Quintile 2: 0.99 (0.75, 1.31)	≈	
			Neighborhood SES: Quintile 3: 0.95 (0.74, 1.22)	≈	
			Neighborhood SES: Quintile 4: 0.78 (0.62, 1.00)	≈	
			Neighborhood SES: Quintile 5: 0.84 (0.65, 1.07)	≈	
†Gandini et al. (2018)	Italian Longitudinal Study (ILS) Enrollment: 1999–2000 Follow-up: 1999–	HR (95% CI)[b] Incident T2D Main Effect: 0.96 (0.92, 1.01)	HR (95% CI)[b] Incident T2D Urbanicity: Rural areas: 0.87 (0.79, 0.97)	≈	Area-level (municipality of residence)

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	2002, 2003–2004, 2005–2006, 2007–2008		Urbanicity: Urban areas: 0.91 (0.81, 1.01)	≈	
			Urbanicity: Metropolitan areas: 0.89 (0.72, 1.11)	≈	
†Gandini et al. (2018)	Italian Longitudinal Study (ILS) Enrollment: 1999–2000 Follow-up: 1999–2002, 2003–2004, 2005–2006, 2007–2008	HR (95% CI)[b] Incident T2D Main Effect: 0.96 (0.92, 1.01)	HR (95% CI)[b] Incident T2D Sex: Female: 0.96 (0.89, 1.04)	≈	Individual
			Sex: Male: 0.98 (0.91, 1.06)	≈	
†Howell et al. (2019)	Cardiovascular Health in Ambulatory Care Research Team (CANHEART) Enrollment: 1991–2007 Follow-up: 2008	OR (95% CI)[b] Prevalent DM Main Effect: 1.11 (1.10, 1.13)	OR (95% CI)[b] Prevalent DM Walkability (Joint effect with NO_2): 1.16 (1.15, 1.18)	↑	Area-level (dissemination area of residence)
†Hu et al. (2023)	UK Biobank Enrollment: 2006–2010 Follow-up: through February 20, 2020	HR (95% CI)[b] Incident T2D Main Effect: 1.14 (1.05, 1.24)	HR (95% CI)[b] Incident T2D Townsend deprivation index: <median: 1.31 (1.16, 1.47)	≈	Area-level
			Townsend deprivation index: ≥median: 1.16 (1.06, 1.27)	≈	
			Age: <65 yr: 1.06 (0.97, 1.15)	≈	Individual
			Age: ≥65 yr: 1.10 (0.94, 1.28)	≈	
			Sex: Female: 1.10 (0.97, 1.25)	≈	
			Sex: Male: 1.16 (1.03, 1.30)	≈	
†Nagrani et al. (2023)	Identifications and prevention of dietary and	OR (95% CI)[c] Prediabetes	OR (95% CI)[c] Prediabetes:	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Main Effect or Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study Enrollment: 2009–2010 Follow-up: 2013–2014	Main Effect: See Figure 8-2	Sex: Males: 1.03 (0.87, 1.22)		
			Sex: Females: 0.91 (0.76, 1.1)	≈	
			Residential distance: >250 m to major road: 1.10 (0.93, 1.29)	↑	
			Residential distance: ≤250 m to major road: 0.80 (0.65, 0 99)	≈	
†Shin and Kim (2023)	Cardiovascular Disease Association Study Enrollment: 2005–2011 Follow-up: 2016	HR (95% CI)[c] Incident DM Main Effect: 1.29 (1.12, 1.49)	HR (95% CI)[c] Incident DM Sex: Male: 1.22 (1.00, 1.48)	≈	Individual
			Sex: Female: 1.32 (1.09, 1.59)	≈	

List of abbreviations in alphabetical order: AMI = acute myocardial infarction; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HR = hazard ratio; LUR = land use regression; m = meter; MDA = mini dietary assessment; NO = nitric oxide; NO2 = nitrogen dioxide; OR = odds ratio; ppb = parts per billion; Q1 = quartile 1; Q2 = quartile2; Q3 = quartile 3; Q4 = quartile 4; SES = socioeconomic status; T2D = type 2 diabetes; VFI = visceral fat index; WC = waist circumference; WHtR = waist-to-height ratio; WHR = waist-to-hip ratio; yr = year.

[a]Up facing arrow (and yellow shading) indicate that the effect of NO2 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 NO2 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 NO2 is comparable between groups.

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

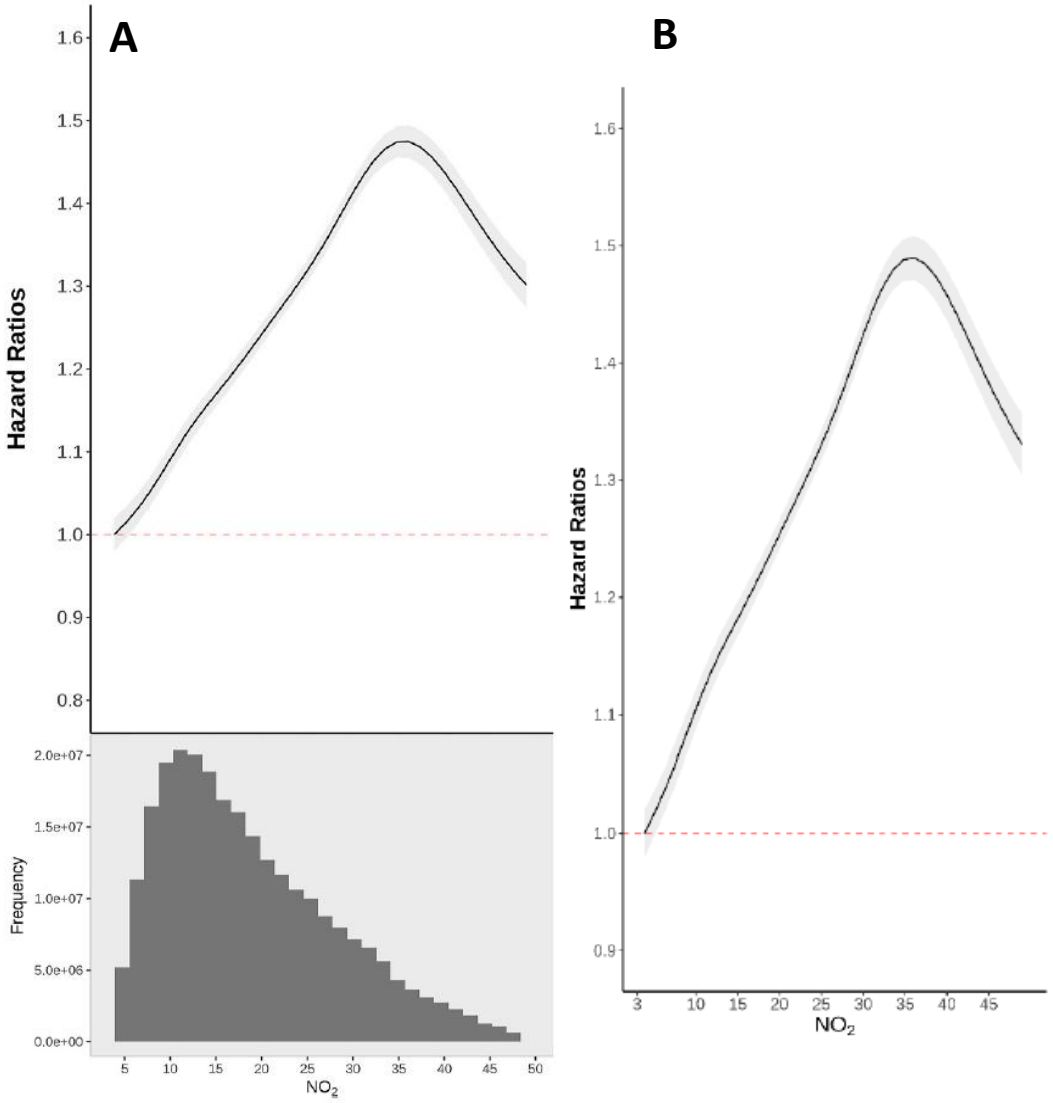
[c]Estimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

8.3.1.3 Copollutants

Several studies evaluated copollutant confounding. There was not complete consistency across studies, but there is some indication that associations are robust after adjustment for ozone (O_3) and $PM_{2.5}$.

- The positive association Honda et al. (2017) observed between a 1-year NO_2 exposure and prevalent DM (OR: 1.32 [95% CI: 1.11, 1.57]) remained positive, but was attenuated after copollutant adjustment for $PM_{2.5}$ (OR: 1.20 [95% CI: 1.00, 1.44]).
- The positive association Cervantes-Martinez et al. (2022) observed between monthly NO_2 exposure and T2D (HR: 1.52 [95% CI: 1.37, 1.68] per 10 ppb NO_2) was attenuated although remained positive after copollutant adjustment for $PM_{2.5}$ (HR: 1.26 [95% CI: 1.12, 1.42] per 10 ppb NO_2).
- The positive association Klompmaker et al. (2019) reported between long-term NO_2 exposure and prevalent diabetes (OR: 1.15 [95% CI: 1.09, 1.22]) was robust after copollutant adjustment for road-traffic noise (OR: 1.15 [95% CI: 1.09, 1.22]), but attenuated after copollutant adjustment for greenness (NDVI 300 meters OR: 1.07 [95% CI: 1.01, 1.14]).
- Hansen et al. (2016) reported a positive association between single-pollutant NO_2 and incident diabetes (HR: 1.13 [95% CI: 0.97, 1.32]). When further copollutant adjusted for PM_{10}, the association was attenuated although remained positive (HR: 1.08 [95% CI: 0.88, 1.32]). However, when copollutant adjusted for $PM_{2.5}$, the association was attenuated to the null (HR: 0.98 [95% CI: 0.78, 1.23]).
- Sørensen et al. (2022b) reported a positive association between a 5-year NO_2 exposure average and incident T2D (HR: 1.06 [95% CI: 1.05, 1.07] per 3.8 ppb NO_2) as well as a positive association between specifically the traffic contribution of the 5-year NO_2 exposure average and incident T2D (HR: 1.043 [95% CI: 1.035, 1.052] per 2.7 ppb NO_2). The total NO_2 association was robust to copollutant or multipollutant adjustment for $PM_{2.5}$, UFP, EC, $PM_{2.5}$ + UFP, $PM_{2.5}$ + EC, and $PM_{2.5}$ + UFP + EC (see Table 8-6). The traffic contribution NO_2 association was robust to copollutant adjustment for traffic-related $PM_{2.5}$, but attenuated to the null for traffic-related UFP, EC, $PM_{2.5}$ + UFP, $PM_{2.5}$ + EC, and $PM_{2.5}$ + UFP + EC (see Table 8-6).
- Bai et al. (2018) reported that the positive association observed between NO_2 and incident diabetes was robust after adjustment for UFP, $PM_{2.5}$, or UFP+$PM_{2.5}$ (see Table 8-6).
- After copollutant adjustment for road noise, aircraft noise, and railway noise, the association between NO_2 and incident diabetes remained similar to the NO_2 single-pollutant model (i.e., inverse association although the 95% CI was imprecise and crossed the null; RR: 0.83 [95% CI: 0.54, 1.28] and RR: 0.90 [95% CI: 0.61, 1.34], respectively) (Eze et al., 2017).
- Yitshak Sade et al. (2023) constructed a cohort using U.S. Medicare data from 2000 to 2016 for adults 65 years of age and over. They reported robust associations between NO_2 and diabetes when copollutant adjusted for $PM_{2.5}$ and warm-months O_3 (see Figure 8-13, corresponding quantitative values not reported).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: A) Concentration-response curve for the association between NO_2 and diabetes occurrence in multipollutant model copollutant adjusted for $PM_{2.5}$ and warm-months O_3. Concentration-response curve for the associations with NO_2, from 0.5th percentile-99.5th percentile of pollutants, i.e., with 1% poorly constrained extreme values excluded. Results are obtained from three single-pollutant models, adjusted for age, race, sex, Medicaid insurance, annual ZIP code means of summer and winter temperature, and annual ZIP code level sociodemographic variables. The model also includes a random intercept for each ZIP code and a spline function of year.
Source: Adapted from Yitshak Sade et al. (2023). Copyright permission pending.

Figure 8-13 Multipollutant (A) and single-pollutant (B) associations between NO_2 and diabetes.

- Zhang et al. (2021b) reported that the positive associations between 1-year average NO_2 exposures and diabetes prevalence (single-pollutant NO_2 OR: 1.27 [95% CI: 1.14, 1.42]) remained robust after copollutant adjustment for O_3 (OR: 1.27 [95% CI: 1.10, 1.47]) and were slightly attenuated after copollutant adjustment for $PM_{2.5}$ (OR: 1.19 [95% CI: 1.01, 1.40]) or $PM_{2.5}$ + O_3 (OR: 1.20 [95% CI: 1.02, 1.42]).

- In an administrative cohort of adult residents in Vancouver, Canada, Clark et al. (2017) reported an attenuation of a positive association (single-pollutant NO OR: 1.04 [95% CI: 1.01, 1.05] per 10.7 ppb) between 5-year exposure to NO and incident diabetes after copollutant adjustment for noise (OR: 1.01 [95% CI: 1.00, 1.04] per 10.7 ppb).
- Shin and Kim (2023) reported a positive association between long-term NO_2 exposure and incident diabetes from a prospective cohort of adults living in Korea HR: 1.29 [95% CI: 1.12, 1.49] per 10 ppb NO_2) and that association remained robust after copollutant adjustment for $PM_{2.5}$ (HR: 1.28 [95% CI: 1.07, 1.54] per 10 ppb NO_2).
- In a national health survey in the Netherlands, Strak et al. (2017) reported a positive association between NO_2 and prevalent diabetes (1.07 [95% CI: 1.05, 1.09] per $\mu g/m^3$ NO_2) and that associations remained robust after copollutant adjustment for PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, or oxidative potential of PM (see Table 8-6).
- The positive association between NO_2 and incident diabetes observed by Paul et al. (2020b) for the single-pollutant model (HR: 1.042 [95% CI: 1.033, 1.051] per IQR, 13.8 ppb) was essentially unchanged after copollutant adjustment for $PM_{2.5}$ or O_3 as well as multipollutant adjustment for $PM_{2.5}$ and O_3 (see Table 8-6).
- Wu et al. (2022b) reported positive associations derived from multi-state models to estimate the association between NO_2 or NO_X and the dynamic progressions trajectories of T2D from health to incident T2D then to complication. For transitions from healthy status to incident T2D, the associations between NO_2 and T2D remained positive for copollutant adjustment for PM_{10} or $PM_{2.5}$ although attenuated. The associations between NO_X and T2D remained positive although attenuated for copollutant adjustment for $PM_{2.5}$; however, for copollutant adjustment for PM_{10}, the association between NO_X and T2D was attenuated to no association. For transitions from incident T2D to complications, the associations between NO_2 and complications were robust, if not strengthened, for copollutant adjustment for PM_{10} or $PM_{2.5}$. The associations between NO_X and complications were also robust for copollutant adjustment for $PM_{2.5}$; however, the association was attenuated, although remained positive for copollutant adjustment for PM_{10} (see Table 8-6).

A limited number of studies also evaluated oxides of nitrogen as a mixture with the results from the mixture being similar to the results from oxides of nitrogen alone.

- Li et al. (2021) created an air pollution score (including NO_2, NO, $PM_{2.5}$, and $PM_{2.5–10}$). Similar to the results observed for NO_2 and NO alone (HR: 1.05 [95% CI: 1.02, 1.07] and HR: 1.04 [95% CI: 1.02, 1.05] per SD, respectively), Li et al. (2021) reported a similar positive association between long-term exposure to the air pollution mixture and T2D (HR: 1.04 [95% CI: 1.02, 1.06] per SD). NO and $PM_{2.5}$ were highly correlated with NO_2 (see Table 8-6Table 8-).
- Hu et al. (2023) additionally evaluated NO_2 as part of a mixture in a multipollutant analysis that included traffic-related noise, $PM_{2.5}$, and NO_2; the HR for incident T2D was 1.06 [95% CI: 1.02, 1.09] per IQR, which was similar to the unstandardized results for NO_2 alone (HR: 1.07 [95% CI: 1.02, 1.11] per 5.2 ppb).

Table 8-6 Epidemiologic studies evaluating copollutants on the associations between exposure to NO_2 and diabetes mellitus and complications from diabetes mellitus

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
Copollutant(s) Adjustment						
Exposure to NO						
†Clark et al. (2017)	Follow-up: January 1999–December 2002	Noise	Noise: 0.42	Logistic		OR (95% CI)[c] Incident diabetes Main Effect: 1.04 (1.01, 1.05)
					↓	Copollutant (with noise): 1.01 (1.00, 1.04)
Exposure to NO_2						
†Bai et al. 2018)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment: April 1, 1996 Follow-up: through December 31, 2012	UFP; $PM_{2.5}$; UFP and $PM_{2.5}$	UFP: 0.17 $PM_{2.5}$: 0.04	Random-effects Cox proportional hazards models		HR (95% CI)[c] Incident diabetes Main Effect: 1.06 (1.05, 1.07)
					≈	Copollutant (with UFP): 1.05 (1.04, 1.06)
					≈	Copollutant (with $PM_{2.5}$): 1.06 (1.05, 1.07)
					≈	Copollutant (with UFP and $PM_{2.5}$): 1.05 (1.04, 1.06)
†Cervantes-Martinez et al. (2022)	Mexican Teachers Cohort Enrollment: 2006–2008 Follow-up: 2011–2013 and 2014–2020	$PM_{2.5}$	$PM_{2.5}$: NR	Time-varying Cox models		HR (95% CI)[c] Incident T2D Main Effect: 1.52 (1.37, 1.68)
					↓	Copollutant (with $PM_{2.5}$): 1.26 (1.12, 1.42)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
†Eze et al. (2017)	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) Enrollment: 1991–2002 Follow-up: 2011	Road noise, aircraft noise, railway noise	Road noise: 0.43; Aircraft noise: 0.13; Railway noise: 0.04	Mixed Poisson regression model with random intercepts		RR (relative risk) (95% CI)[b] Incident T2D Main Effect: 0.90 (0.61, 1.34)
					≈	Copollutant (with road noise, aircraft noise, and railway noise): 0.83 (0.54, 1.28)
†Hansen et al. (2016)	Danish Nurse Cohort (DNC) Enrollment: 1993–1999 Follow-up: through December 31, 2013	$PM_{2.5}$; PM_{10}	$PM_{2.5}$: 0.73 PM_{10}: 0.58	Cox proportional hazard model		HR (95% CI)[b] Incident T2D Main Effect: 1.13 (0.97, 1.32)
					↓	Copollutant (with $PM_{2.5}$): 0.98 (0.78, 1.23)
					≈	Copollutant (with PM_{10}): 1.08 (0.88, 1.32)
†Honda et al. (2017)	National Social Life, Health, and Aging Project (NSHAP) Enrollment: 2005–2006 and 2010–2011	$PM_{2.5}$	$PM_{2.5}$: 0.3	Logistic regression		POR (95% CI)[b] Prevalent DM: 1-yr moving average exposure Main Effect: 1.32 (1.11, 1.57)
					↓	Copollutant (with $PM_{2.5}$): 1.20 (1.00, 1.44)
†Klompmaker et al. (2019)	Dutch Public Health Monitor 2012 (Dutch PHM 2012) 2012	NDVI 300m; NDVI 1000m; road-traffic noise (Lden)	NDVI 300m: -0.49 NDVI 1000m: -0.59 road-traffic noise (Lden): 0.41	Logistic regression		OR (95% CI)[b] Prevalent DM Main Effect: 1.15 (1.09, 1.22)
					↓	Copollutant (with NDVI 300m): 1.07 (1.01, 1.14)
					↓	Copollutant (with NDVI 1000m): 1.07 (1.01, 1.14)
					≈	Copollutant (with road-traffic noise

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						(Lden): 1.15 (1.09, 1.22)
†Paul et al. (2020b)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment: January 2001 Follow-up: through December 2015	$PM_{2.5}$; O_3; $PM_{2.5}$ and O_3	$PM_{2.5}$: 0.652 O_3: -0.133	Cox proportional hazard models		HR (95% CI)[c] Incident diabetes (3 yr exposure) Main Effect: 1.04 (1.03, 1.05)
					≈	Copollutant (with $PM_{2.5}$): 1.05 (1.04, 1.06)
					≈	Copollutant (with O3): 1.04 (1.03, 1.05)
					≈	Copollutant (with $PM_{2.5}$ and O3): 1.05 (1.04, 1.06)
†Shin and Kim (2023)	Cardiovascular Disease Association Study Enrollment: 2005–2011 Follow-up: 2016	$PM_{2.5}$	$PM_{2.5}$: NR	Cox proportional hazard model		HR (95% CI)[c] Incident DM Main Effect: 1.29 (1.12, 1.49)
					≈	Copollutant (with $PM_{2.5}$): 1.28 (1.07, 1.54)
†Strak et al. (2017)	Public Health Monitor 2012	PM_{10}; $PM_{2.5}$; $PM_{10-2.5}$; absorbance; OP^{DTT}; OP^{ESR}	PM_{10}: 0.78 $PM_{2.5}$: 0.25 $PM_{10-2.5}$: 0.79 absorbance: 0.79 OP^{DTT}: 0.55 OP^{ESR}: 0.6	Logistic regression		OR (95% CI)[c] Prevalent DM Main Effect: 1.07 (1.05, 1.09)
					≈	Copollutant (and PM_{10}): 1.07 (1.04, 1.10)
					≈	Copollutant (and $PM_{2.5}$): 1.07 (1.05, 1.09)
					≈	Copollutant (and $PM_{10-2.5}$): 1.07 (1.04, 1.10)
					≈	Copollutant (and absorbance): 1.08 (1.05, 1.11)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
					≈	Copollutant (and OP^{DTT}): 1.04 (1.02, 1.07)
					≈	Copollutant (and OP^{ESR}): 1.07 (1.05, 1.10)
†Sørensen et al. (2022b)	Danish Civil Registration System Enrollment: January 1, 2005 Follow-up: 11.2 yrs	$PM_{2.5}$; UFP; EC; $PM_{2.5}$ + UFP; $PM_{2.5}$ + EC; UFP + EC; $PM_{2.5}$ + UFP + EC; Traffic $PM_{2.5}$; Traffic UFP; Traffic EC; Traffic $PM_{2.5}$ + traffic UFP; Traffic $PM_{2.5}$ + traffic EC; Traffic UFP + traffic EC; Traffic $PM_{2.5}$ + traffic UFP + traffic EC	Correlations with NO_2: $PM_{2.5}$: 0.76 UFP: 0.92 EC: 0.93 Correlations with traffic NO_2: Traffic $PM_{2.5}$: 0.99 Traffic UFP: 0.99 Traffic EC: 0.99	Cox proportional hazards model		HR (95% CI)[c] Incident T2D Main Effect: 1.06 (1.05, 1.07)
					≈	Copollutant (with $PM_{2.5}$): 1.07 (1.06, 1.09)
					≈	Copollutant (with UFP): 1.05 (1.04, 1.07)
					≈	Copollutant (with EC): 1.07 (1.05, 1.08)
					≈	Copollutant (with $PM_{2.5}$ and UFP): 1.06 (1.05, 1.08)
					≈	Copollutant (with $PM_{2.5}$ and EC): 1.08 (1.06, 1.09)
					≈	Copollutant (with UFP and EC): 1.06 (1.04, 1.07)
					≈	Copollutant (with $PM_{2.5}$, UFP, and EC): 1.07 (1.05, 1.08)
						NO_2 traffic: Main Effect: 1.04 (1.04, 1.05)
					≈	NO_2 traffic Copollutant (with $PM_{2.5}$): 1.05 (1.02, 1.07)
					↓	NO_2 traffic: Copollutant (with

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						UFP): 0.98 (0.95, 1.01)
					↓	NO_2 traffic: Copollutant (with EC): 0.98 (0.95, 1.01)
					↓	NO_2 traffic: Copollutant (with $PM_{2.5}$ and UFP): 0.98 (0.94, 1.02)
					↓	NO_2 traffic: Copollutant (with $PM_{2.5}$ and EC): 1.01 (0.98, 1.04)
					↓	NO_2 traffic: Copollutant (with UFP and EC): 0.98 (0.94, 1.01)
					↓	NO_2 traffic: Copollutant (with $PM_{2.5}$, UFP, and EC): 1.00 (0.84, 1.19)
†Wu et al. (2022b)	UK Biobank Enrollment: 2006–2010 Follow-up: through March 31, 2021	PM_{10}; $PM_{2.5}$; traffic noise	Incident T2D (and PM_{10}): 0.798 Incident T2D (and $PM_{2.5}$): 0.798 Among those with T2D, complications from diabetes (and PM_{10}): 0.81 Among those with T2D, complications from diabetes (and $PM_{2.5}$): 0.812 Traffic noise: NR	Multi-state regression model		HR (95% CI)[b] Incident T2D Main Effect: 2.89 (2.76, 3.02)
					↓	Copollutant (with PM_{10}): 1.23 (1.13, 1.34)
					↓	Copollutant (with $PM_{2.5}$): 1.52 (1.39, 1.66)
					≈	Copollutant (with traffic noise): 2.95 (2.80, 3.11)
						Among those with T2D, complications from diabetes Main Effect: 1.45 (1.31, 1.61)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
					≈	Among those with T2D, complications from diabetes Copollutant (with PM_{10}): 1.55 (1.28, 1.88)
					↑	Among those with T2D, complications from diabetes Copollutant (with $PM_{2.5}$): 2.01 (1.67, 2.41)
					≈	Among those with T2D, complications from diabetes Copollutant (with traffic noise): 1.56 (1.39, 1.74)
†Yitshak Sade et al. (2023)	Medicare Enrollment: 2000–2016 Follow-up: Annually until the first recorded diabetes diagnosis, end of enrollment, or death	$PM_{2.5}$ and Warm-months O_3	$PM_{2.5}$: 0.44; Warm-months O_3: 0.18	Cox-equivalent re-parameterized Poisson survival approach		HR (95% CI)[c] Incident DM Main Effect: 1.06 (1.05, 1.06)
					≈	Copollutant (with $PM_{2.5}$ and warm-months O_3): See Figure 8-13
†Zhang et al. (2021b)	China Health and Retirement Longitudinal Study (CHARLS) Enrollment: 2011–2012 Follow-up: 2015	O_3; $PM_{2.5}$; O_3 and $PM_{2.5}$	O_3: 0.56 $PM_{2.5}$: 0.72	Logistic regression		OR (95% CI)[b] Prevalent Diabetes Main Effect: 1.27 (1.14, 1.42)
					≈	Copollutant (with O_3): 1.27 (1.10, 1.47)
					↓	Copollutant (with $PM_{2.5}$): 1.19 (1.01, 1.40)
					↓	Copollutant (with O3 and $PM_{2.5}$): 1.20 (1.02, 1.42)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						Self-report: Main Effect: 1.51 (1.31, 1.73)
					≈	Self-report: Copollutant (with O3): 1.42 (1.21, 1.67)
					↓	Self-report: Copollutant (with $PM_{2.5}$): 1.22 (1.00, 1.49)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
Exposure to NO_X						
†Wu et al. (2022b)	UK Biobank Enrollment: 2006–2010 Follow-up: through March 31, 2021	PM_{10}; $PM_{2.5}$; Traffic noise	PM_{10}: 0.801 $PM_{2.5}$: 0.799 Among those with T2D, complications from diabetes/; PM_{10}: 0.814 $PM_{2.5}$: 0.814 Traffic noise: NR	Multi-state regression model		HR (95% CI)[c] Incident T2D Main Effect: 1.39 (1.37, 1.42)
					↓	Copollutant (with PM_{10}): 0.99 (0.96, 1.02)
					↓	Copollutant (with $PM_{2.5}$): 1.06 (1.03, 1.10)
					≈	Copollutant (with traffic noise): 1.41 (1.38, 1.43)
						Among those with T2D, complications from diabetes Main Effect: 1.10 (1.06, 1.15)
					↓	Among those with T2D, complications from diabetes Copollutant (with PM_{10}): 1.05 (0.99, 1.13)
					≈	Among those with T2D, complications from diabetes Copollutant (with $PM_{2.5}$): 1.15 (1.08, 1.22)
					≈	Among those with T2D, complications from diabetes Copollutant (with traffic noise): 1.12 (1.08, 1.17)
Mixtures						
Exposure to NO_2						

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
†Hu et al. (2023)	UK Biobank Enrollment: 2006–2010 Follow-up: through February 20, 2020	"Cumulative risk index" ($PM_{2.5}$, NO_2, and noise)	"Cumulative risk index" ($PM_{2.5}$, NO_2, and noise): $PM_{2.5}/NO_2$: 0.87; noise/NO_2: 0.35; $PM_{2.5}$/noise: 0.30	Cox proportional hazard model	d	HR (95% CI)[c] Incident T2D Main Effect: 1.07 (1.02, 1.11)
					d	"Cumulative risk index" ($PM_{2.5}$, NO_2, and noise): 1.06 (1.02, 1.09)
†Li et al. (2021))	UK Biobank Enrollment: 2006–2010 Follow-up: median 11 yr	Air pollution score (NO_2, NO, $PM_{2.5}$, $PM_{2.5–10}$)	Air pollution score (NO_2, NO, $PM_{2.5}$, $PM_{2.5–10}$): NO/NO_2: 0.75; $PM_{2.5–10}/NO_2$: 0.20; $PM_{2.5}/NO_2$: 0.86 NO/$PM_{2.5–10}$: 0.24 NO/$PM_{2.5}$: 0.73 $PM_{2.5}/PM_{2.5–10}$: 0.22	Cox proportional hazard models	d	HR (95% CI)[c] Incident T2DM (SD increment) Main Effect: 1.05 (1.02, 1.07) Air pollution score (NO_2, NO, $PM_{2.5}$, $PM_{2.5}$-10): 1.04 (1.02, 1.06)
					d	Main: Q1 vs Q1 (REF): 1.00 (1.00, 1.00) Air pollution score: Q1 vs Q1 (REF): 1.00 (1.00, 1.00)
					d	Main: Q2 vs Q1: 1.04 (0.99, 1.10) Air pollution score: Q2 vs Q1: 1.05 (0.99, 1.10)
					d	Main: Q3 vs Q1: 1.07 (1.01, 1.13) Air pollution score: Q3 vs Q1: 1.06 (1.00, 1.11)
					d	Main: Q4 vs Q1: 1.11 (1.05, 1.17) Air pollution score: Q4 vs Q1: 1.09 (1.03, 1.15)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
					d	Main: Q5 vs Q1: 1.11 (1.04, 1.18) Air pollution score: Q5 vs Q1: 1.12 (1.06, 1.19)

List of abbreviations in alphabetical order: BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; EC = elemental carbon; HR = hazard ratio; NDVI = normalized difference vegetation index; NO = nitric oxide; NO_2 = nitrogen dioxide; NO_X = nitrogen oxides; NR = not reported; O_3 = ozone; OP^{DDT} = oxidative potential of particulate matter via electron spin resonance metric; OP^{ESR} = oxidative potential via dithiothreitol metric; OR = odds ratio; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 µm; PM_{10} = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 µm; ppb = parts per billion; Q1 = quintile 1; Q2 = quintile 2; Q3 = quintile 3; Q4 = quintile 4; Q5 = quintile 5; RR = rate ratio; T2D = type 2 diabetes; T2DM = type 2 diabetes mellitus; UFP = ultrafine particles; yr = year.

[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.

[d]Not a direct comparison.

†Studies published since the 2016 Oxides of Nitrogen ISA.

8.3.1.4 Conclusions and Remaining Uncertainties

Epidemiologic evidence reviewed in the 2016 Oxides of Nitrogen ISA generally supported an association between long-term exposure to oxides of nitrogen and diabetes mellitus. Recent PECOS-relevant epidemiologic evidence continues to suggest a positive association, especially for NO_2 [e.g., Yitshak Sade et al. (2023); Cervantes-Martinez et al. (2022); Paul et al. (2020b); Howell et al. (2019); Bai et al. (2018); Honda et al. (2017); Howell et al. (2019)]. There have been several recent studies conducted in North America that predominantly observed positive associations between NO_2 and diabetes even though the studies varied in location, exposure assessment methods, and outcome ascertainment. Studies conducted in Asian countries (e.g., China, Korea) also generally reported positive associations between NO_2 and diabetes regardless of location, length of exposure, or specification of the outcome. Studies conducted in European countries (e.g., Denmark, Italy, Netherlands, Switzerland, United Kingdom) generally reported positive associations between oxides of nitrogen and diabetes, although this was inconsistent depending on location, oxides of nitrogen, length of exposure, or specification of the outcome.

Several studies investigating the association between oxides of nitrogen and diabetes also evaluated the shapes of concentration-response relationships across the distribution of estimated oxides of nitrogen exposures, primarily NO_2. Overall, for the association between NO_2 and diabetes, there was a general indication of an approximately linear, linear plateau/threshold, or supralinear concentration-response relationships reported. Several studies reported steeply linear concentration-responses at lower concentrations with a threshold at approximately 20–40 $\mu g/m^3$ [e.g., Hu et al. (2023); Wu et al. (2023); Yitshak Sade et al. (2023); Kang et al. (2022); Paul et al. (2020b)]. A few studies also observed monotonic increases in associations when evaluating the association between categorically defined NO_2 concentrations and diabetes [e.g., Cervantes-Martinez et al. (2022); Bai et al. (2018); Strak et al. (2017); Li et al. (2022)].

Additionally, there is some evidence that associations between long-term exposure to NO_2 and diabetes is robust after copollutant adjustment (or associations that were attenuated remained positive), specifically when adjusting for O_3 [e.g., Zhang et al. (2021b); Paul et al. (2020b)] or $PM_{2.5}$ [e.g., Shin and Kim (2023); Yitshak Sade et al. (2023); Cervantes-Martinez et al. (2022); Sørensen et al. (2022b); Zhang et al. (2021b); Bai et al. (2018); Honda et al. (2017); Sørensen et al. (2022); Wu et al. (2022b); Paul et al. (2020b); Strak et al. (2017)]. However, NO_2 tended to be highly correlated with $PM_{2.5}$ so inference is limited when including this copollutant in the model. The evaluation of traffic-related copollutants were not widely evaluated and results were inconsistent when evaluated.

While numerous potential modifiers were evaluated within studies investigating the association between oxides of nitrogen and diabetes, such as age, sex, comorbidities (e.g., obesity), behavior/ lifestyle factors (e.g., diet, physical activity, smoking status, alcohol consumption status), and characteristics of

residence (e.g., walkability, urbanicity, proximity to roadways), no clear patterns emerged for modifying factors.

8.4 Metabolic Syndrome

Metabolic syndrome (MetS) describes a set of cardiometabolic conditions that increase a person's risk for cardiovascular diseases or T2D. A MetS diagnosis commonly includes some combination of: (1) elevated blood pressure, (2) low HDL cholesterol, (3) elevated serum triglycerides, (4) elevated fasting blood glucose, and (5) abdominal obesity. As described in Figure 8-14, four well-established definitions of MetS include those by the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), and the International Diabetes Foundation (IDF). For the IDF MetS definition, the obesity requirement is met by population-specific cut points (Alberti et al., 2009; Huang, 2009).

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia‡ (plasma insulin >75th percentile)	Central obesity (waist circumference§): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m^2	Waist circumference: ≥94 cm (M), ≥80cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria†		

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
†Urinary albumin excretion of ≥20 µg/min or albumin-to-creatinine ratio of ≥30 mg/g.
‡Reliable only in patients without T2D.
§Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

List of abbreviations in alphabetical order: BMI = body mass index; F = female; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; IR = insulin resistance; M = male; NO_2 = nitrogen dioxide; Rx = pharmacologic treatment; T2D = type 2 diabetes; TG = triglyceride.
Source: Huang (2009). Copyright permission pending.

Figure 8-14 Common definitions of metabolic syndrome

This section focuses on epidemiologic studies evaluating associations between long-term oxides of nitrogen exposure and MetS. No PECOS-relevant epidemiologic studies examining short-term exposure or PECOS-relevant animal toxicological studies were identified. Studies examining the individual components of MetS are detailed in the following sections: Glucose and Insulin Homeostasis (see Section 8.5), Blood Lipids (see Section 8.6) and Adiposity and Weight Gain (see Section 8.7). Blood

pressure is discussed in the Cardiovascular Effects chapters (see Chapter 5, Sections 5.7 and Chapter 6, Sections 6.5 and 6.7.1.2).

8.4.1 Epidemiologic Studies of Metabolic Syndrome

There were no epidemiologic studies evaluating oxides of nitrogen exposure and MetS in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). Several recent observational studies have evaluated long-term exposure to NO_2 and MetS, with most studies conducted in adult populations in North America, China, or Europe. Findings from these recent epidemiologic studies are inconsistent (null to positive associations) across lifestage and geography. Evidence from recent studies is summarized below, followed by additional discussions of the lifestages and populations evaluated (see Section 8.4.1.1) and the potential impacts of copollutants (see Section 8.4.1.2). Section 8.4.1.3 discusses conclusions based on these studies and summarizes remaining uncertainties. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-2.

Adults

The recent studies within North America utilized small-to-medium sized cohorts in California, U.S., and defined MetS using the NCEP ATP III.

- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA), Yu et al. (2020) used the CALINE4 line dispersion model to assign long-term NO_X exposures to participants and evaluate associations with MetS. Authors reported that higher traffic-related NO_X exposure was positively associated with MetS, although the 95% CIs were imprecise and crossed the null (HR: 1.41 [95% CI: 0.49, 4.02]).
- The Community of Mine study was a small observational study (n = 552) completed between 2014 and 2017 in San Diego County. Letellier et al. (2022) assigned long-term NO_2 exposures using two methods: 1) a traditional static approach that linked NO_2 concentrations from the EPA's AQS to the participant's home via IDW; and 2) 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. This dynamic exposure assignment is unitless. Letellier et al. (2022) observed a positive association between long-term NO_2 exposure and MetS for both the static and dynamic exposure methods, although the static method had 95% CIs that crossed the null (static RR: 1.07 [95% CI: 0.98, 1.18]; dynamic RR: 1.21 [95% CI: 1.12, 1.30]).

There have been several recent studies conducted in populations outside of North America that have evaluated associations between long-term exposure to NO_2 and MetS. A number of these studies utilized the CHARLS cohort to investigate this association with all reporting positive associations, regardless of variations in exposure assignment methods as well as outcome definitions (Liu et al., 2023; Guo et al., 2022; Han et al., 2022).

- In Wave 3 of the CHARLS conducted in 2015, Guo et al. (2022) estimated 1-year, 2-year, and 3-year exposures to NO_2 using machine learning (deep forest models) and Han et al. (2022) estimated 3-year and 2-year exposures to NO_2 using a different machine learning model (space-time extremely randomized trees (STET) model). Guo et al. (2022) reported that a per IQR increase in 1 year average NO_2 concentration was associated with a 44.0% (OR: 1.44 [95% CI: 1.22, 1.71] per IQR:7.81 ppb) increase in odds of MetS (defined using Joint Interim Societies' definition of MetS, using their categorizations of waist circumference for Chinese people (Alberti et al., 2009). Similarly, Han et al. (2022) reported that a per IQR increase in 3-year average NO_2 concentration was associated with a 30.0% (OR: 1.303 [95% CI: 1.211, 1.403], IQR:11.28 $\mu g/m^3$) increase in odds of MetS using the same outcome definition as Guo et al. (2022).
- Liu et al. (2023) conducted a cross-sectional study of the CHARLS participants from Waves 1 and 2 (2011–2015) and used guidelines of the IDF for the Asian population to define MetS. The 3-year and 2-year average NO_2 exposures were derived from spatiotemporal random forest models. They observed a positive association (OR: 4.70 [95% CI: 4.21, 5.24]) when using the 3-year average NO_2 exposure. Similar results were observed when using the 2-year average NO_2 exposure as well as when using NCEP-ATP III MetS definition.

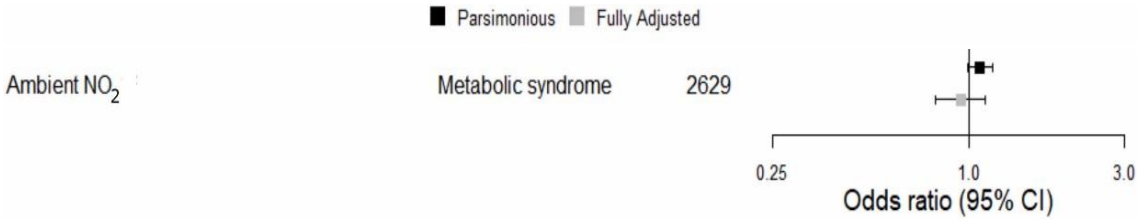
Unlike the studies conducted within Chinese populations, studies in Europe and Australia reported inconsistent evidence.

- Eze et al. (2015) conducted a cross-sectional study with participants from the SAPALDIA to investigate the association between 10-year NO_2 concentrations (estimated via hybrid dispersion and LUR models) and MetS. They evaluated three different MetS definitions – the WHO (MetS-W), the IDF (MetS-I), and the NCEP ATP III (MetS-A). Eze et al. (2015) observed positive associations for all three definitions (MetS-W OR: 1.22 [95% CI: 1.02, 1.46]; MetS-I OR: 1.17 [95% CI: 1.04, 1.31]; MetS-A OR: 1.05 [95% CI: 0.95, 1.17] per 5.3 ppb NO_2).

Children and Adolescents

Few epidemiologic studies have evaluated MetS in children and reported results are inconsistent although geographies differed.

- In a pan-European, multi-center, prospective cohort based on the IDEFICS, Nagrani et al. (2023) observed near-null associations between annual NO_2 exposures estimated using ELAPSE and MetS, defined using a fusion of IDF and NCEP ATP III modified for children (see Figure 8-15, quantitative values not provided).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: Parsimonious models were adjusted for age and sex. Fully adjusted models were additionally adjusted for the study region, lifetime alcohol status, membership in a sports club, screen time/week, parental education status, parental smoking and family history of diabetes. Mean of annual average ambient air pollutants (NO_2) are calculated for the entire study period that each participant was followed. Associations represent per IQR increase in ambient NO_2. The IQR for the exposures are study region specific.
Source: Adapted from Nagrani et al. (2023). Copyright permission pending.

Figure 8-15 Association of ambient NO_2 with MetS in children and adolescents of the IDEFICS/I. Family cohort

- Zhang et al. (2021a) conducted a cross-sectional study of Chinese 10 to 18 year olds to evaluate the association between 2-year mean NO_2 concentrations and MetS (defined according to the IDF with cut-off points for Chinese children) and observed a positive association (OR: 1.71 [95 % CI: 1.06, 2.77]).

8.4.1.1 Lifestages and Populations

Several studies evaluated effect measure modification by sex, age, comorbidities (i.e., diabetes status, weight status, health status), as well as behavioral/lifestyle factors (i.e., smoking status, drinking status, physical activity time, outdoor time, sugar-sweet intake). When modification was observed, older adults consistently had a higher risk of MetS; however, this is based on a limited set of studies (Liu et al., 2023; Guo et al., 2022). While modification by sex was also observed by a few studies (Nagrani et al., 2023; Guo et al., 2022; Zhang et al., 2021a), there was no consistency for which sub-population was at higher risk of MetS. No clear pattern emerged for any of the other modifiers evaluated (see Table 8-7 for details).

- Among 10 to 18 year olds, Zhang et al. (2021a) evaluated effect modification by sex, weight status, outdoor physical activity time, and sugar-sweet beverages intake for NO_2 exposure and MetS. Only modification by sex was observed with an increased odds among boys (boys OR: 2.12 [95% CI: 1.17, 3.82]; girl OR: 1.26 [95% CI: 0.65, 2.43]).
- Among children and adolescents, Nagrani et al. (2023) observed near-null associations between annual NO_2 exposures and MetS. Additionally, there was no evidence of modification by obesity. In contrast, there was weak evidence of modification by sex (boys OR: 0.82 [95% CI: 0.64, 1.06]; girls OR: 1.09 [95% CI: 0.84, 1.41] per IQR) and proximity to roadways (residential distance <250 meters to major road OR: 0.88 [95% CI: 0.71, 1.10]; residential distance ≥250 meters to major road OR: 1.06 [95% CI: 0.77, 1.47] per IQR); though associations were imprecise and these results were in the opposite direction of modification observed for prediabetes.

- For the association between NO_2 and MetS, Liu et al. (2023) evaluated modification by sex, age, health status, and drinking status via both analytical strategies of interaction terms and model restriction, which produced similar results. Authors only observed evidence of modification by age with older participants having higher odds of NO_2-associated MetS (45 to 60 years old OR: 1.43 [95% CI: 1.14, 1.78]; ≥60 years old OR: 5.77 [95% CI: 4.87, 6.84]).
- Guo et al. (2022) evaluated effect modification by physical activity, sex, and age with some evidence of modification for all three factors. There were stronger positive associations between one year NO_2 exposure and MetS among participants that were physically inactive (physically active OR: 1.22 [95% CI: 0.97, 1.55]; physically inactive OR: 1.52 [95% CI: 1.29, 1.81]), men (men OR: 1.64 [95% CI: 1.21, 2.22]; women OR: 1.33 [95% CI: 1.07, 1.65]), and participants aged ≥60 years (≥60 years OR: 1.54 [95% CI: 1.23, 1.93]; <60 years: 1.32 [95% CI: 1.01, 1.72]).
- Eze et al. (2015) observed positive associations for all three definitions (MetS-W, MetS-I, MetS-A), but modification by sex, age, diabetes status, and smoking status were sensitive to the selected MetS definition with no clear patterns.
- Letellier et al. (2022) assigned long-term NO_2 exposures using two methods and observed a positive association between long-term NO_2 exposure and MetS for both the static and dynamic exposure methods although the static method had 95% CIs that crossed the null. Letellier et al. (2022) further evaluated the association modified by Hispanic status. The association with MetS was similar among Hispanic participants for both the dynamic and static exposure (RR: 1.10 [95% CI: 0.92, 1.32] and RR: 1.13 [95% CI: 1.01, 1.27], respectively). Whereas the dynamic exposure method association with MetS for non-Hispanic participants was similar to the overall estimate (RR: 1.23 [95% CI: 1.13, 1.33]), while the static exposure method association with MetS for non-Hispanic participants was attenuated to null (RR: 0.99 [95% CI: 0.86, 1.15]). This may inform important differences of exposure error among sub-populations.

Table 8-7 Epidemiologic studies evaluating effect measure modification between long-term oxides of nitrogen exposure and MetS

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Behavioral Factors					
Exposure to NO_2					
†Eze et al. (2015)	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) Enrollment: 1991 Follow-up: 2001–2002	OR (95% CI)[c] MetS-W Main Effect: 1.22 (1.02, 1.46)	OR (95% CI)[c] MetS-W Vigorous physical activity ≥0.5 hr/wk: Yes: 1.27 (1.08, 1.49)	≈	Individual
			Vigorous physical activity ≥0.5 hr/wk: No: 1.22 (0.93, 1.62)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Never-smoker: Yes: 1.17 (0.94, 1.46)	≈	
			Never-smoker: No: 1.26 (0.97, 1.62)	≈	
		MetS-I Main Effect: 1.17 (1.04, 1.31)	MetS-I Vigorous physical activity ≥0.5 hr/wk: Yes: 1.26 (1.06, 1.48)	≈	
			Vigorous physical activity ≥0.5 hr/wk: No: 1.04 (0.90, 1.20)	↓	
			Never-smoker: Yes: 1.19 (0.98, 1.46)	≈	
			Never-smoker: No: 1.20 (1.03, 1.36)	≈	
		MetS-A Main Effect: 1.05 (0.95, 1.17)	MetS-A Vigorous physical activity ≥0.5 hr/wk: Yes: 1.08 (0.95, 1.23)	≈	
			Vigorous physical activity ≥0.5 hr/wk: No: 1.02 (0.87, 1.18)	≈	
			Never-smoker: Yes: 1.11 (0.98, 1.27)	↑	
			Never-smoker: No: 1.00 (0.85, 1.16)	↓	
†Guo et al. (2022)	China Health and Retirement Longitudinal Study (CHARLS)	OR (95% CI)[b] MetS	OR (95% CI)[b] MetS Physical activity:	↓	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	2015	Main Effect: 1.44 (1.22, 1.71)	Active group: 1.22 (0.97, 1.55)		
			Physical activity: Inactive group: 1.52 (1.29, 1.81)	↑	
†Liu et al. (2023)	China Health and Retirement Longitudinal Study (CHARLS) First survey: 2011–2012 Third survey: 2015	OR (95% CI)[b] MetS Main Effect: 4.70 (4.21, 5.24)	OR (95% CI)[b] MetS Drinking status: >1 time/mo: 1.28 (0.77, 2.14)	↓	Individual
			Drinking status: <1 time/mo: 4.92 (3.19, 7.59)	≈	
			Drinking status: 0 time/mo: 4.87 (4.31, 5.50)	≈	
			Health status: Good/very good: 1.06 (0.81, 1.39)	↓	
			Health status: Fair: 4.60 (3.97, 5.33)	≈	
			Health status: Poor/very poor: 5.32 (4.24, 6.68)	≈	
			Drinking status: >1 time/mo (Stratified models): 3.66 (2.75, 4.87)	≈	
			Drinking status: <1 time/mo (Stratified models): 5.71 (3.60, 9.04)	≈	
			Drinking status: 0 time/mo (Stratified models): 4.93 (4.32, 5.62)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Health status: Good/very good (Stratified models): 4.38 (3.48, 5.51)	≈	
			Health status: Fair (Stratified models): 4.60 (3.96, 5.33)	≈	
			Health status: Poor/very poor (Stratified models): 5.42 (4.31, 6.81)	≈	
†Nagrani et al. (2023)	Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study Enrollment: 2009–2010 Follow-up: 2013–2014	OR (95% CI)[c] MetS Main Effect: See Figure 8-15	OR (95% CI)[c] MetS Weight: Normal weight: 0.91 (0.59, 1.4)	≈	Individual
			Weight: Overweight/obese 0.90 (0.72, 1.14)	≈	
Pre-existing comorbidities					
Exposure to NO_2					
†Eze et al. (2015)	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) Enrollment: 1991 Follow-up: 2001–2002	OR (95% CI)[c] MetS-W Main Effect: 1.22 (1.02, 1.46)	OR (95% CI)[c] MetS-W Diabetes: Yes: 0.84 (0.58, 1.23)	↓	Individual
			Diabetes: No: 1.22 (1.00, 1.50)	≈	
		MetS-I Main Effect: 1.17 (1.04, 1.31)	MetS-I Diabetes: Yes: 0.49 (0.12, 2.03)	↑	
			Diabetes: No: 1.17 (1.05, 1.32)	≈	
		MetS-A	MetS-A	↑	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
		Main Effect: 1.05 (0.95, 1.17)	Diabetes: Yes: 1.56 (0.76, 3.22)		
			Diabetes: No: 1.04 (0.94, 1.16)	≈	
Sociodemographic Factors					
Exposure to NO_2					
†Eze et al. (2015)	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) Enrollment: 1991 Followup: 2001–2002	OR (95% CI)[c] MetS-W Main Effect: 1.22 (1.02, 1.46)	OR (95% CI)[c] MetS-W Age: ≤50 yr: 1.24 (1.04, 1.49)	≈	Individual
			Age: >50 yr: 1.34 (0.91, 1.97)	≈	
			Sex: Males: 1.27 (1.01, 1.61)	≈	
			Sex: Females: 1.22 (1.01, 1.48)	≈	
		MetS-I Main Effect: 1.17 (1.04, 1.31)	MetS-I Age: ≤50 yr: 1.05 (0.81, 1.36)	↓	
			Age: >50 yr: 1.20 (1.07, 1.34)	≈	
			Sex: Males: 1.27 (1.08, 1.48)	↑	
			Sex: Females: 1.08 (0.94, 1.25)	↓	
		MetS-A Main Effect: 1.05 (0.95, 1.17)	MetS-A Age: ≤50 yr: 0.83 (0.65, 1.08)	↓	
			Age: >50 yr: 1.12 (1.01, 1.23)	≈	
			Sex: Males: 1.10 (0.96, 1.25)	≈	
			Sex: Females: 1.02 (0.89, 1.16)	≈	
†Guo et al. (2022)	China Health and Retirement	OR (95% CI)[b] MetS	OR (95% CI)[b] MetS	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Longitudinal Study (CHARLS) 2015	Main Effect: 1.44 (1.22, 1.71)	Men: 1.64 (1.21, 2.22)		
			Women: 1.33 (1.07, 1.65)	↓	
			Age group: <60y: 1.32 (1.01, 1.72)	↓	
			Age group: ≥60y: 1.54 (1.23, 1.93)	↑	
†Letellier et al. (2022)	Community of Mine Study 2014–2017	RR (95% CI)[c] MetS static exposure (1,600m buffer) Main Effect: 1.07 (0.98, 1.18)	RR (95% CI)[c] MetS Static exposure (1,600 m buffer): Hispanic: 1.13 (1.01, 1.27)	≈	Individual
			Static exposure (1,600 m buffer): non-Hispanic: 0.99 (0.86, 1.15)	↓	
		MetS, dynamic exposure (KDE) Main Effect: 1.21 (1.12, 1.30)	MetS Dynamic exposure (KDE): Hispanic: 1.10 (0.92, 1.32)	↓	
			Dynamic exposure (KDE): non-Hispanic: 1.23 (1.13, 1.33)	≈	
†Liu et al. (2023)	China Health and Retirement Longitudinal Study (CHARLS) First survey: 2011–	OR (95% CI)[b] MetS Main Effect: 4.70 (4.21, 5.24)	OR (95% CI)[b] MetS Males: 1.02 (0.88, 1.17)	↓	Individual
			Females: 4.72 (4.13, 5.39)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	2012 Third survey: 2015		Age 45–60 yr: 1.43 (1.14, 1.78)	↓	
			Age ≥60 yr: 5.77 (4.87, 6.84)	↑	
			Males (Stratified models): 4.27 (3.50, 5.21)	≈	
			Females (Stratified models): 4.80 (4.21, 5.47)	≈	
			Age 45–60 yr (Stratified models): 4.09 (3.55, 4.71)	≈	
			Age ≥60 yr (Stratified models): 5.77 (4.86, 6.86)	↑	
†Nagrani et al. (2023)	Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS), I.Family Study Enrollment: 2009–2010 Follow-up: 2013–2014	OR (95% CI)[c] MetS Main Effect: See Figure 8-15	OR (95% CI)[c] MetS Sex: Males: 0.82 (0.64, 1.06)	≈	Individual
			Sex: Females: 1.09 (0.84, 1.41)	↑	
			Residential distance: >250 m to major road: 0.88 (0.71, 1.1)	≈	
			Residential distance: ≤250 m to major road: 1.06 (0.77, 1.47)	↑	

List of abbreviations in alphabetical order: CI = confidence interval; hr = hour; KDE = kernel density estimation; LUR = land use regression; MetS = metabolic syndrome; m = meters; mo = month; NO = nitric oxide; NO_2 = nitrogen dioxide; OR = odds ratio; ppb = parts per billion; RR = rate ratio; yr = years.

[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.

8.4.1.2 Copollutants

A few studies evaluating the association between oxides of nitrogen and MetS additionally investigated the robustness of the results to copollutant or multipollutant adjustment. Overall, most studies observed attenuation to the null upon further adjustment for copollutants (i.e., PM_1, $PM_{2.5}$, PM_{10}, traffic-related noise) (Zhang et al., 2021a; Yu et al., 2020; Eze et al., 2015). A single study observed robust positive associations after copollutant adjustment for O_3 (Han et al., 2022).

- Han et al. (2022) reported that a per IQR increase in 3-year average NO_2 concentration was positively associated MetS, and this association was robust to copollutant adjustment for O_3 (OR: 1.293 [95% CI: 1.192, 1.192]).
- Eze et al. (2015) observed positive associations for all three definitions of MetS (MetS-W, MetS-I, MetS-A), but in copollutant models adjusted for PM_{10}, all of the observed associations were attenuated to near-null (MetS-W OR: 0.94 [95% CI: 0.78, 1.13]; MetS-I OR: 1.04 [95% CI: 0.88, 1.23]; MetS-A OR: 0.93 [95% CI: 0.81, 1.08] per 5.3 ppb NO_2).
- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA), Yu et al. (2020) observed that the positive association (although the 95% CIs were imprecise and crossed the null) in the single-pollutant model was attenuated upon further adjustment for traffic-related noise (HR: 0.84 [95% CI: 0.26, 2.66]).
- Zhang et al. (2021a) observed a positive association between 2-year mean NO_2 concentrations and MetS among 10 to 18 year olds in China. However, in mixture multipollutant models that included different two- and three-pollutant combinations of PM_1, $PM_{2.5}$, PM_{10}, and NO_2, the joint ORs were attenuated toward the null and imprecise.

8.4.1.3 Conclusions and Remaining Uncertainties

While there were no epidemiologic studies evaluating oxides of nitrogen exposure and MetS in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), there have been several recent PECOS-relevant epidemiologic studies, specifically for long-term exposure. However, this recent epidemiologic evidence is inconsistent (null to positive associations) across lifestage and geography. A potentially large reason for the inconsistency is the variability in the outcome assessment for the studies (i.e., applied definition of MetS in the analyses). There was no evaluation of concentration-response. Several potentially modifying factors were evaluated; however, limited patterns emerged with the strongest evidence for older adults consistently having a higher risk of NO_2-associated MetS. Additionally, a few studies investigated the robustness of the results to copollutant or multipollutant adjustment. However, most studies observed attenuation to the null upon further adjustment for copollutants.

8.5 Glucose and Insulin Homeostasis

Insulin regulates glucose homeostasis. Insulin is secreted by β cells within the pancreas in response to glucose levels in the blood. When blood glucose levels rise, depolarization of the pancreatic β cells, or modulation by other hormones, stimulates insulin secretion. Thus, when eating, blood insulin levels rise, stimulating glucose uptake and replenishment of body fuel reserves in the form of triglycerides and glycogen. When insulin levels decrease (e.g., during fasting), fuels such as lipids from adipose tissue and amino acids from muscle are mobilized to the bloodstream where they are used by the liver to synthesize glucose. Several recent epidemiologic and toxicological studies on this topic add to the overall evidence. Endpoints examined in these studies include fasting blood glucose (FBG), hemoglobin A1c (HbA1c), and insulin resistance (e.g., the Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]). Recent epidemiologic and toxicological studies provide generally inconsistent evidence to support the effect of oxides of nitrogen exposure on glucose and insulin homeostasis.

8.5.1 Epidemiologic Studies of Glucose and Insulin Homeostasis

The recent epidemiologic evidence for long-term exposure to oxides of nitrogen was inconsistent, although predominately no associations were observed with indicators of glucose and insulin homeostasis. In North America, several studies were conducted in the United States, especially in California, and predominantly among adults. Evidence from recent studies is summarized below, followed by an additional discussion of concentration-response relationships in these studies (see Section 8.5.1.1), the lifestages and populations evaluated (see Section 8.5.1.2), and the impacts of copollutants (see Section 8.5.1.3). Section 8.5.1.4 discusses conclusions based on these studies and summarizes remaining uncertainties. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-3.

Adults

- In a sub-cohort of the Women's Health Initiative clinical trials in the United States among nondiabetic, postmenopausal women with and without impaired fasting glucose, Holliday et al. (2019) observed near-null (generally negative leaning) associations between long-term exposures to NO_X (365-day means; per 20.3 ppb increase) and fasting glucose, fasting insulin, HOMA-IR, and TyG.
- In a prospective cohort within the United States, NSHAP, Honda et al. (2017) investigated the association between 1- to 5-year moving averages of NO_2 and HbA1c. Honda et al. (2017) observed positive associations for all exposure windows (e.g., 1-year exposure window % change (SE): 2.0%±0.3% per 8.6 ppb).
- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA), Yu et al. (2020) used the CALINE4 line dispersion model to assign long-term exposure of NO_X concentrations to participants to evaluate associations with hyperglycemia. Authors reported imprecise, near-null associations (HR: 1.09 [95% CI: 0.36, 3.34]).

- The Community of Mine study was a small observational study (n = 552) completed between 2014 and 2017 in San Diego County. Letellier et al. (2022) assigned long-term NO_2 exposures using two methods: 1) a traditional static approach that linked NO_2 concentrations from the EPA's AQS to the participant's home via IDW; and 2) 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. This dynamic exposure assignment is unitless. Letellier et al. (2022) observed a near-null association between long-term NO_2 exposure and HOMA-IR for the static exposure method, but a positive association for the dynamic exposure method (β: 0.08 [95% CI: 0.03, 0.13]). For both static and dynamic exposure methods, associations were near-null for fasting glucose and null for HbA1c.

Children and Adolescents

- A small cross-sectional study (n = 218) of six to eight year old children in the Fresno, California, U.S., area reported generally inverse associations, although imprecise, between long-term (i.e., 3-month, 6-month, 1-year) NO_2 and NO_X concentrations and HbA1c (Zhang et al., 2022).
- Mann et al. (2021) evaluated children residing in the Fresno, California area who were enrolled in the Children's Health and Air Pollution Study (CHAPS). Mann et al. (2021) modeled NO_2 using a combination of regulatory and spatially intensive monitoring data at the child's residence to derive 1-month, 3-month, 6-month, and 1-year averages before the outcome assessment. Mann et al. (2021) reported positive associations between 3-month and 6-month NO_2 and HbA1c (β: 0.05 [95% CI: 0.00, 0.11] per 6.20 ppb and β: 0.04 [95% CI: 0.00, 0.09] per 3.42 ppb, respectively), while 1-year NO_2 was not associated with HbA1c (0.00 [95% CI: -0.05, 0.04] per 1.74 ppb).

Studies conducted in China observed positive associations between long-term oxide of nitrogen exposure and glucose and insulin homeostatic endpoints, while studies conducted in European countries reported inconsistent results.

Adults

- Liu et al. (2023) conducted a cross-sectional study of the CHARLS participants from waves 1 and 2 (2011–2015). The 3-year and 2-year average NO_2 exposures were derived from spatiotemporal random forest models. They observed a positive association between the 3-year average NO_2 exposure and elevated fasting glucose (OR: 3.01 [95% CI: 2.75, 3.30]). Similar results were observed when using the 2-year average NO_2 exposure.
- Zhang et al. (2021b) conducted a cross-sectional study of the CHARLS participants from wave 3 (2015). Zhang et al. (2021b) reported a positive association between 1-year average NO_2 exposures (derived from hybrid LUR, satellite, and kriging models) and fasting glucose (% change: 3.42 [95% CI: 2.42, 4.42]) as well as HbA1c (% change: 1.29 [95% CI: 0.73, 1.85]).
- Using the Henan Rural Cohort Study, Kang et al. (2022) observed a positive association between 3-year average exposure to NO_2 and FBG among adults (β: 0.04 [95% CI: 0.03, 0.04] per 0.5 ppb).
- In a pan-European, multi-center, prospective cohort based on IDEFICS, Nagrani et al. (2023) observed a null association between annual NO_2 exposure estimated using ELAPSE and HbA1c (β: 0.00 [95% CI: -0.05, 0.05] per IQR). The associations with HOMA-IR and fasting

glucose were near-null (β: 0.03 [95% CI: -0.04, 0.09] and β: -0.03 [95% CI: -0.08, 0.02] per IQR, respectively).

- Eze et al. (2015) conducted a cross-sectional study with participants from the SAPALDIA cohort to investigate the association between 10-year NO_2 concentrations (estimated via hybrid dispersion and LUR models) and impaired fasting glycemia using two definitions (WHO versus IDF/ATP-III). Eze et al. (2015) observed positive to near-null associations (WHO OR: 1.15 [95% CI: 0.98, 1.34]; IDF/ATP-III OR: 1.06 [95% CI: 0.93, 1.21] per 5.3 ppb NO_2).

Children and Adolescents

- Zhang et al. (2021a) conducted a cross-sectional study of Chinese 10 to 18 year olds to evaluate the association between 2-year mean NO_2 concentrations and elevated fasting glucose (defined according to the International Diabetes Federation with cut-off points for Chinese children) and observed a positive association (OR: 2.31 [95% CI: 1.16, 4.61]).

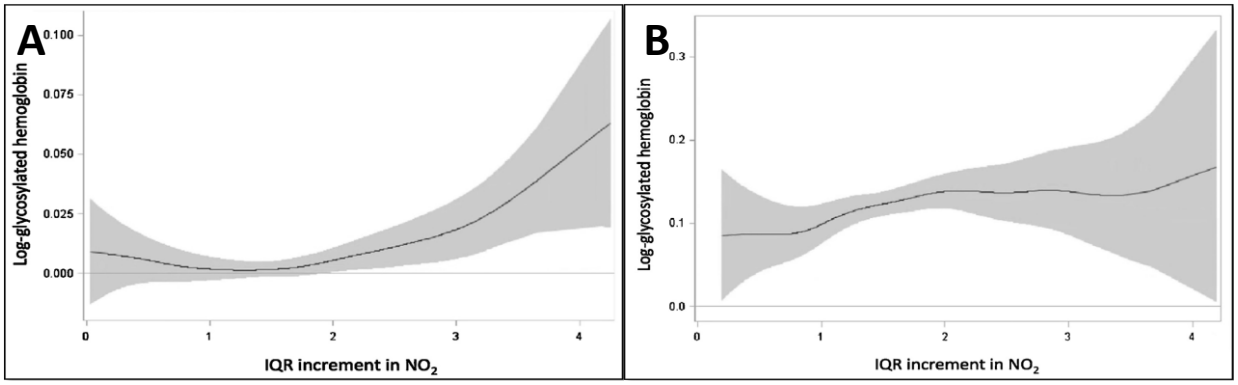
A few recent studies based within the United States evaluated associations between short-term exposures to oxides of nitrogen and markers of glucose metabolism (e.g., fasting glucose, fasting insulin, insulin AUC, HOMA-IR, Matsuda index, TyG, HbA1c). The reported results are generally null across the studies, with some indication of inverse associations. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-3.

- In a sub-cohort of the Women's Health Initiative in the United States among nondiabetic, postmenopausal women with and without impaired fasting glucose (n = 3,915), Holliday et al. (2019) observed near-null (generally negative leaning) associations between short-term exposures to NO_X (2 day means; per 28.4 ppb increase) and fasting glucose, fasting insulin, HOMA-IR, and TyG regardless of fasting glucose status.
- A small cross-sectional study (n = 218) of six to eight year old children in the Fresno, California, U.S., area reported generally inverse associations, although imprecise, between short-term (i.e., one day, one week, one month) NO_2 and NO_X concentrations and HbA1c (Zhang et al., 2022).

8.5.1.1 Concentration-Response

There was limited evaluation of the shapes of concentration-response relationships among epidemiologic studies evaluating the association between oxides of nitrogen and measures of glucose and insulin homeostasis, with inconsistent results across studies.

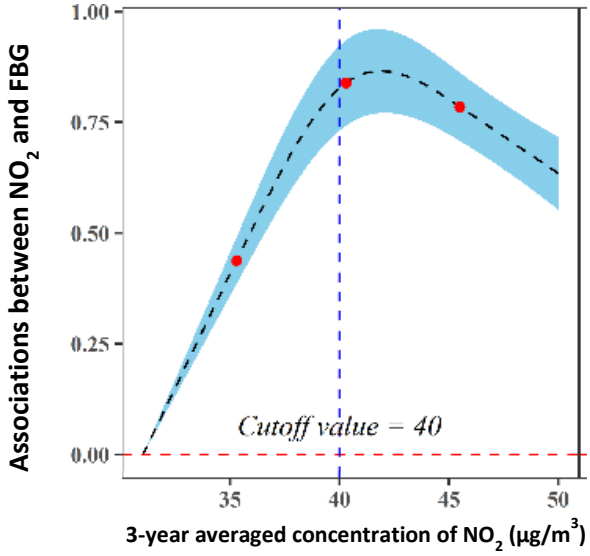
- Honda et al. (2017) investigated the association between 1- to 5-year moving averages of NO_2 and HbA1c. Honda et al. (2017) reported that some evidence of concentration-response for diabetic and non-diabetic participants, with the magnitude of the associations between NO_2 and HbA1c being consistently larger for diabetic participants compared to non-diabetic participants (see Figure 8-16).



List of abbreviations in alphabetical order: HbA1c = glycosylated hemoglobin; IQR = interquartile range; NO_2 = nitrogen dioxide.
Note: Scales between A and B are not equivalent. Adjusted by BMI, age, sex, race, education, diabetic medication use tobacco use, physical activity, region, urbanicity, census track data on median household income, and percent of households living below the poverty line.
Source: Honda et al. (2017). Copyright permission pending.

Figure 8-16 Smoothing dose-response curve for association of an IQR increment of NO_2 with log-HbA1c in A) non-diabetic participants and B) diabetic participants.

- For HOMA-IR, HbA1c, and fasting glucose, there was no evidence of concentration-response when evaluating the exposure categorically by quartiles (Nagrani et al., 2023).
- Kang et al. (2022) reported that the concentration-response curve for the association between 3-year average exposure to NO_2 and FBG among adults was approximately linear at lower concentrations with a threshold at approximately 40 µg/m^3 (see Figure 8-17). Additionally, Kang et al. (2022) evaluated the association between 3-year average exposure to NO_2 defined categorically and FBG. The observed association was magnified compared to the continuous exposure (β: 0.32 [95% CI: 0.29, 0.35] for ≥40 µg/m^3 vs. <40 µg/m^3).



List of abbreviations in alphabetical order: FBG = fasting blood glucose; NO_2 = nitrogen dioxide.

Note: Adjusted by age, sex, education level, marital status, average monthly income, smoking, drinking status activity, high-fat diet, fruits and vegetables intake, and history of T2DM.
Source: Kang et al. (2022). Copyright permission pending.

Figure 8-17 Concentration-response curve between NO_2 and FBG

8.5.1.2 Lifestages and Populations

Several studies evaluated effect measure modification by sex, age, ethnicity, comorbidities (i.e., diabetic status, impaired fasting glucose, health status), as well as behavioral/lifestyle factors (i.e., smoking status, drinking status). Some evidence of modification was observed by ethnicity for HOMA-IR levels (Letellier et al., 2022), self-reporting health for fasting glucose (Liu et al., 2023), diabetes status and HbA1c, and smoking status for fasting glucose and HbA1c; however, this evidence is based on a limited set of studies. No clear pattern emerged for any of the other modifiers evaluated.

- Honda et al. (2017) investigated the association between 1- to 5-year moving averages of NO_2 and HbA1c. Honda et al. (2017) observed the magnitude of the associations with HbA1c was larger for diabetic participants compared to non-diabetic participants (e.g., 1-year exposure window % change (SE) for diabetic participants: 2.0%±0.7% per 8.6 ppb; 1-year exposure window % change (SE) for non-diabetic participants: 0.8%±0.2% per 8.6 ppb).
- For the association between NO_X and indicators of glucose and insulin homeostasis (i.e., fasting glucose, fasting insulin, HOMA-IR, and TyG), Holliday et al. (2019) observed no clear evidence of effect modification among participants with normal versus impaired fasting glucose.
- For the dynamic NO_2 exposure, Letellier et al. (2022) observed that the association with HOMA-IR levels was stronger among Hispanic participants than non-Hispanic participants although the 95% CIs overlapped (β: 0.13 [95% CI: 0.03, 0.24] and β: 0.06 [95% CI: 0.00, 0.11], respectively).
- Liu et al. (2023) evaluated modification by sex, age, health status, and drinking status via both analytical strategies of interaction terms and model restriction, which produced similar results. Authors observed evidence of modification by health status with participants self-reporting fair or poor/very poor health having stronger associations between long-term NO_2 exposure and fasting glucose (good/very good OR: 1.01 [95% CI: 0.81, 1.25]; fair OR: 2.84 [95% CI: 2.52, 3.21]; poor/very poor OR: 3.67 [95% CI: 3.05, 4.42]).

8.5.1.3 Copollutants

There was limited evaluation of copollutant adjustment for the association between oxides of nitrogen and measures of glucose and insulin homeostasis.

- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA), Yu et al. (2020) reported near-null and imprecise associations between NO_X and hyperglycemia were attenuated although remained near-null and imprecise after further adjustment for traffic-related noise (HR: 0.92 [95% CI: 0.27, 3.14]).

- The positive associations observed by Zhang et al. (2021b) between 1-year average NO_2 exposure and fasting glucose as well as HbA1c remained robust after copollutant adjustment for O_3 but were attenuated after copollutant adjustment for $PM_{2.5}$ and $PM_{2.5}$ + O_3.

8.5.1.4 Conclusions and Remaining Uncertainties

The recent epidemiologic evidence for exposure to oxides of nitrogen was inconsistent although predominately no associations were observed with indicators of glucose and insulin homeostasis, regardless of exposure length. There was limited evaluation of concentration-response among epidemiologic studies evaluating the association between oxides of nitrogen and measures of glucose and insulin homeostasis. A single study observed an approximately linear curve at lower concentrations with a threshold at approximately 40 $\mu g/m^3$ (Kang et al., 2022). Several studies evaluated effect measure modification by sex, age, ethnicity, comorbidities (i.e., impaired fasting glucose, health status), as well as behavioral/lifestyle factors (i.e., smoking status, drinking status). However, there was inconsistent evidence for a clear pattern of the modifying factors evaluated. There was limited evaluation of copollutant adjustment for the association between oxides of nitrogen and measures of glucose and insulin homeostasis. A single study observed that the positive associations between long-term exposure to NO_2 and fasting glucose and HbA1c remained robust after adjustment for O_3 but attenuated after adjustment for $PM_{2.5}$ as well as $PM_{2.5}$ + O_3.

8.5.2 Animal Toxicological Studies of Glucose and Insulin Homeostasis

The 2016 Oxides of Nitrogen ISA included a single toxicological study examining glucose levels following NO_2 exposures. Takano et al. (2004) exposed two adult rat strains, Otsuka Long-Evans Tokushima Fatty (OLETF) and Long-Evans Tokushima (LETO), to a range of NO_2 concentrations (0.16 to 4.0 ppm, 24 hours/day) for 32 weeks. No significant changes to non-fasting blood glucose were reported in either the phenotypically normal LETO rats or the OLETF rats, which spontaneously develop hyperglycemia and obesity. A small number of recent studies have further investigated the effect of NO_2 exposure on glucose and insulin homeostasis. These recent studies are summarized below followed by additional discussion of the relevance of the animal models used for humans (see Section 8.5.2.1). Section 8.5.2.2 discusses conclusions based on these animal studies and summarizes remaining uncertainties. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 8-4.

- The HOMA-IR, which is calculated using fasting glucose and fasting insulin levels, was significantly increased in female C57BL/6 mice exposed to 2.5 ppm NO_2 5 hours/day for four weeks (Guo et al., 2023). The same study reported no effects on HOMA-IR or its components in male mice exposed to NO_2. However, another study using only male C57BL/6J mice reported significantly increased fasting serum insulin following a similar NO_2 exposure paradigm (i.e., 2.66 ppm NO_2 5 hours/day for 27 days) (Yan et al., 2016).

- In an intraperitoneal glucose tolerance test, female C57BL/6 mice exposed to NO_2 had a significantly elevated blood glucose response (i.e., increased AUC) compared to controls. In contrast, the AUC of blood glucose following an insulin tolerance test was unaffected by NO_2. NO_2 exposure did not significantly affect the response to either challenge in male mice (Guo et al., 2023).
- Hepatic glycogen content, determined by periodic-acid Schiff (PAS) staining, was significantly decreased in female C57BL/6 mice exposed to 2.5 ppm NO_2 (Guo et al., 2023).

8.5.2.1 Relevance of Animal Responses to Human Responses

Rodents are useful models for understanding the impact of environmental pollutants on glucose and insulin homeostasis. Fasting glucose and insulin are considered first-line tests of metabolic function, followed by glucose and insulin tolerance tests. The surrogate measure of insulin resistance, HOMA-IR, was derived using human clinical data, but has been subsequently validated in mice (Mather, 2009). In humans, the glucose tolerance test is typically conducted using oral glucose consumption, while Guo et al. (2023) used the intraperitoneal injection route. Both administration methods are commonly utilized in rodents, however intraperitoneal injection alters absorption dynamics and bypasses the incretin response (Andrikopoulos et al., 2008), which is a relevant consideration when interpreting glucose homeostasis. Underlying differences between rodent and human metabolism and energy utilization are also key factors to consider when interpreting rodent data (Kowalski and Bruce, 2014).

8.5.2.2 Conclusions and Remaining Uncertainties

Overall, limited evidence suggests that NO_2 exposure may cause insulin resistance and impaired glucose tolerance, particularly in female mice. Future studies should build on these findings, examining alternative exposure paradigms, delineating a potential dose-response relationship, and further evaluating potential sex-based differences in sensitivity to NO_2 exposure. Furthermore, while glucose and insulin tolerance tests are useful screening modalities, euglycemic and hyperglycemic clamp techniques are generally considered the gold standard for measuring insulin secretion and action, thus would be useful in evaluating the effects of NO_2 exposure (Ayala et al., 2010). No data is available on the effects of multipollutant exposure on this endpoint.

8.5.3 Synthesis Across Lines of Evidence

Recent epidemiologic studies of NO_2 and NO_X exposure on glucose and insulin homeostasis have yielded inconsistent results, with many reporting null associations. These studies had limited consideration for confounding by copollutants (i.e., $PM_{2.5}$, O_3) or traffic-related noise. Likewise, evaluation of effect measure modification (e.g., sex, age, metabolic status, lifestyle factors) was limited

and no clear patterns of association emerged. While a single study reported a roughly linear concentration-response relationship between NO_2 and FBG up to 40 μg/m^3, this remains an isolated finding. In contrast, the limited toxicological evidence provides some support that NO_2 exposures at high concentrations (≥2.5 ppm) cause insulin resistance and impaired glucose tolerance, particularly in female mice. The toxicological studies have not adequately assessed the effects of lower, environmentally relevant exposures to NO_2 and have not attempted to delineate a dose-response relationship. Overall, there is limited consistency and coherence across epidemiologic and toxicological studies of glucose and insulin homeostasis, and uncertainties remain regarding concentration-response relationships, effect measure modification, and confounding by traffic-related copollutants.

8.6 Blood Lipids

Blood lipids, including cholesterol and triglycerides, are essential components of human metabolism and serve as biomarkers of metabolic and cardiovascular health. Cholesterol is carried in the bloodstream by lipoproteins, primarily high-density lipoprotein (HDL) and low-density lipoproteins (LDL), which play distinct roles in lipid metabolism. While HDL is responsible for carrying excess cholesterol to the liver for excretion, LDL carries cholesterol to cells and is associated with atherosclerosis when present in excess. Dyslipidemia, a key component of metabolic syndrome, is characterized by elevated triglycerides and low levels of HDL cholesterol. Section 8.6.1 summarizes recent PEOCS-relevant epidemiologic evidence examining the effects of both long-term and short-term oxides of nitrogen exposure on these key lipid parameters. PECOS-relevant controlled human exposure and animal toxicological studies are discussed in Sections 8.6.2 and 8.6.3, respectively.

8.6.1 Epidemiologic Studies of Blood Lipids

Several recent studies evaluated the association between oxides of nitrogen and blood lipid conditions (e.g., dyslipidemia) and blood lipid biomarkers (e.g., triglycerides (TG), total cholesterol, LDL, HDL). The available evidence is inconsistent with a mixture of negative, null, and positive associations. Across the studies there were differences in the exposure estimation approaches, species of oxides of nitrogen evaluated, study geographies, and specific endpoint evaluated. There were several recent studies from North America, with the majority of studies conducted in the United States, especially in California populations. Evidence from recent studies is summarized below, followed by additional discussion of the concentration-response relationships from these studies (see Section 8.6.1.1), the lifestages and populations evaluated (see Section 8.6.1.2), and the impacts of copollutants (see Section 8.6.1.3). Section 8.6.1.4 discusses conclusions based on these studies and summarizes remaining uncertainties in the evidence. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-5.

Long-Term Exposure

- In a sub-cohort of the Women's Health Initiative clinical trials in the United States among nondiabetic, postmenopausal women with and without impaired fasting glucose, Holliday et al. (2019) observed near-null and imprecise associations between long-term exposures to NO_X (365-day means; per 20.3 ppb increase) and triglycerides/HDL cholesterol ratio (TG:HDL-C) (all participants: -0.59 [95% CI: -3.15, 1.97]).
- A small cross-sectional study (n = 218) of six to eight year old children in the Fresno, California, U.S. area generally reported inverse associations between NO_2 exposures (i.e., three months, six months, one year) and HDL (Zhang et al., 2022).
- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA cohort), Yu et al. (2020) used the CALINE4 line dispersion model to assign long-term NOx exposure concentrations to participants to evaluate associations with hypertriglyceridemia. The authors reported a near-null association (HR: 1.29 [95% CI: 0.40, 4.22]). In contrast, the adjusted HR for incident low HDL-cholesterol level was 3.39 [95% CI: 1.37, 8.39] with each 20 ppb increase in traffic-related NO_X.
- The Community of Mine study was a small observational study (n = 552) completed between 2014 and 2017 in San Diego County, U.S. Letellier et al. (2022) assigned long-term NO_2 exposures using two methods: 1) a traditional static approach that linked NO_2 concentrations from the EPA's AQS to the participant's home via IDW; and 2) 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. This dynamic exposure assignment is unitless. Letellier et al. (2022) observed a near-null association between long-term NO_2 exposure and dyslipidemia for the static exposure method and a positive association for the dynamic exposure method (RR: 1.28 [95% CI:1.12, 1.46]). Letellier et al. (2022) additionally evaluated cholesterol, LDL cholesterol, and triglycerides. Cholesterol and LDL cholesterol had similar results to each other with the static exposure method resulting in positive associations although the 95% CI crossed the null, and the dynamic exposure method resulting in positive associations (cholesterol RR: 9.67 [95% CI: 3.71, 15.64]; LDL cholesterol RR: 9.03 [95% CI: 3.63, 14.43]). The observed associations with triglycerides were positive for both static and dynamic exposure methods (β: 0.09 [95% CI: 0.03, 0.16] and β: 0.13 [95% CI: 0.05, 0.22], respectively).

The few studies conducted in Europe generally observed near-null associations with blood lipid biomarkers.

- In a pan-European, multi-center, prospective cohort based on the IDEFICS, Nagrani et al. (2023) observed a null association between annual NO_2 exposure estimated using ELAPSE and HDL (β: 0.00 [95% CI: -0.05, 0.05] per IQR), as well as a near-null association for triglycerides (β: -0.02 [95% CI: -0.07, 0.03] per IQR).
- Eze et al. (2015) conducted a cross-sectional study with participants from the SAPALDIA cohort to investigate the association between 10-year NO_2 concentrations (estimated via hybrid dispersion and LUR models) and blood lipids. Eze et al. (2015) observed near-null associations for high triglycerides (OR: 0.94 [95% CI: 0.85, 1.03] per 5.3 ppb NO_2) as well as low high-density lipoproteins as defined by the WHO (OR: 0.88 [95% CI: 0.76, 1.01]) and low high-density lipoproteins as defined by IDF/ATP-III (OR: 0.95 [95% CI: 0.87, 1.05] per 5.3 ppb NO_2).

- Among preschoolers (age four) in the Spanish Infancia y Medio Ambiente (INMA) birth cohort, Fossati et al. (2020) reported a near-null association between first trimester exposure to NO_2 (estimated for a temporally adjusted LUR model) and lipids score (β: -0.03 [95% CI: -0.14, 0.07]), defined as mean z-scores of triglycerides and HDL. Comparable results were reported in sensitivity analyses using second trimester, third trimester, entire pregnancy, or first year of life exposure to NO_2.

In contrast to the recent European studies, a number of recent studies conducted in China reported positive associations with blood lipid conditions and biomarkers.

- Liu et al. (2023) conducted a cross-sectional study of the CHARLS participants from Waves 1 and 2 (2011 to 2015). The 3-year and 2-year average NO_2 exposures were derived from spatiotemporal random forest models. They observed a positive association between the 3-year average NO_2 exposure and low HDL-C (OR: 3.20 [95% CI: 2.91, 3.52]) as well as high TG (OR: 2.45 [95% CI: 2.23, 2.69]). Similar results were observed when using the 2-year average NO_2 exposure as well as when using NCEP-ATP III MetS component definition.
- Zhang et al. (2021b) conducted a cross-sectional study of the CHARLS participants from wave 3 (2015). The 1-year average NO_2 exposures were derived from hybrid LUR, satellite, and kriging models. Zhang et al. (2021b) reported positive association between NO_2 and prevalent dyslipidemia (OR: 1.22 [95% CI: 1.09, 1.37]), negative association between NO_2 and HDL, LDL, and cholesterol (% change: -3.91 [95% CI: -4.76, -3.05], % change: -2.83 [95% CI: -3.99, -1.66], % change: -2.75 [95% CI: -3.53, -1.98], respectively) as well as a near-null association between NO_2 and triglyceride (% change: 0.74 [95% CI: -1.36, 2.85]).
- In a cross-sectional study of Chinese 10 to 18 year olds, Zhang et al. (2021a) observed positive associations between 2-year mean NO_2 concentrations and high TG (OR: 1.18 [95% CI: 0.76, 1.82]) as well as low HDL (OR: 1.12 [95% CI: 0.71, 1.74]) although effect estimates crossed the null.
- In a national cross-sectional survey of children aged seven to 18 years old in China, Gui et al. (2020) evaluated associations between 3-year mean NO_2 concentrations (estimated via random forest model) and blood lipids as well as dyslipidemias. Gui et al. (2020) observed a positive association for total cholesterol (% change: 5.25 [95% CI: 1.56, 9.07]), near-null for HDL-C (% change: 0.75 [95% CI: -0.58, 2.09]), and negative for LDL and TG though the 95% CIs crossed the null (% change: -1.88 [95% CI: -4.53, 0.84] and % change: -1.70 [95% CI: -3.85, 0.49], respectively). Gui et al. (2020) observed a positive association for hypercholesterolemia (OR: 1.43 [95% CI: 1.05, 1.93]), but negative associations for hypertriglyceridemia (OR: 0.79 [95% CI: 0.60, 1.05]), hypoalphalipoproteinemia (OR: 0.87 [95% CI: 0.71, 1.08]), and hyperbetalipoproteinemia (OR: 0.77 [95% CI: 0.47, 1.27]).

Short-Term Exposure

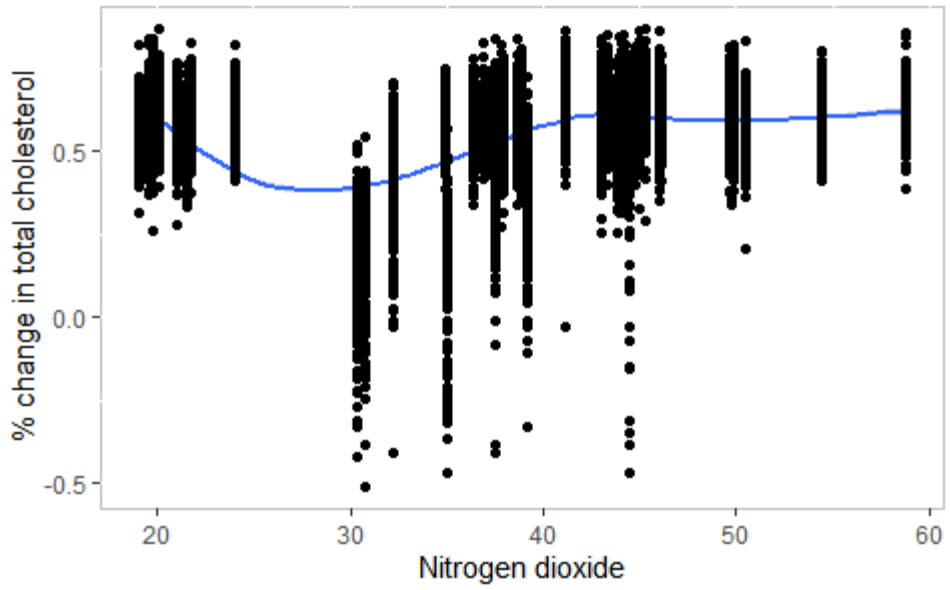
A few recent studies based within the United States evaluated associations between short-term exposures to oxides of nitrogen and blood lipids (e.g., triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, TG:HDL-C). The reported results are generally null across the studies with minimal evidence of associations. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-5.

- In a sub-cohort of the Women's Health Initiative in the United States among nondiabetic, postmenopausal women with and without impaired fasting glucose, Holliday et al. (2019) observed near-null associations between short-term exposures to NO_X (2 day means) and TG:HDL-C (all participants: -0.21 [95% CI: -1.43, 1.00]).
- In a panel study of healthy younger adults (25 to 55 years old) in Chapel Hill, North Carolina, U.S., with high omega-3 intake, short-term NO_2 exposures were associated with reductions in total cholesterol at lag 2 (-2.6% [95% CI: -4.4%, -0.9%]), LDL at lag 2 (-3.1% [95% CI: -5.5%, -0.7%]), and HDL at lag 1 (-2.4% [95% CI: -4.4%, -0.3%]), lag2 (-2.0% [95% CI: -3.8%, -0.1%]), and 5-day moving average (-3.1% [95% CI: -6.1%, -0.01%]) (Chen et al., 2021).
- A small cross-sectional study (n = 218) of six to eight year old children in the Fresno, California, U.S., area reported generally inverse associations between short-term (i.e., one day, one week, one month) NO_2 and NO_X concentrations and HDL levels (Zhang et al., 2022).

8.6.1.1 Concentration-Response

There was limited evaluation of the shapes of concentration-response relationships among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids, with inconsistent results across studies.

- Nagrani et al. (2023) reported no evidence of concentration-response when evaluating the association between annual NO_2 exposure categorically by quartiles and HDL or triglycerides.
- Gui et al. (2020) observed a nonlinear positive association between 3-year mean NO_2 concentrations and total cholesterol (see Figure 8-18). Additionally, when categorizing the exposure into quartiles, Gui et al. (2020) reported similar effect estimates for the second, third, and fourth quartiles compared to the first (second quartile % change: 0.14 [95% CI: 0.05, 0.23], third quartile % change: 0.14 [95% CI: 0.05, 0.23], and fourth quartile % change: 0.17 [95% CI: 0.08, 0.26], respectively).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide
Source: Gui et al. (2020). Copyright permission pending.

Figure 8-18 The dose-response relationships between 3-year average concentration of NO_2 and total cholesterol level

8.6.1.2 Lifestages and Populations

Several studies evaluated effect measure modification by sex, age, ethnicity, comorbidities (i.e., fasting glucose status, BMI, health status), as well as behavioral/lifestyle factors (i.e., dietary intake of omega-3, drinking status). Limited evidence of effect measure modification was observed by sex for low HDL-C with female participants having a higher odds than males as well as effect measure modification by age for high TG with older participants having higher odds (Liu et al., 2023). However, this evidence is based on a single study. No clear or consistent pattern emerged for any of the modifiers evaluated.

Long-Term Exposure

- In the Community of Mine study, the analyses stratified by ethnicity (i.e., Hispanic versus non-Hispanic) did not show evidence of effect measure modification for dyslipidemia for either the static or dynamic exposure approaches (Letellier et al., 2022).
- In a cross-sectional study of the CHARLS participants, Liu et al. (2023) evaluated effect measure modification by sex, age, health status, and drinking status for the association between 3-year or 2-year average NO_2 exposures and blood lipid indicators (i.e., HDL-C and TG). Liu et al. (2023) evaluated effect measure modification using both analytical strategies of interaction terms and model restriction, which produced similar results. Authors reported evidence of modification by sex for low HDL-C with female participants having a higher odds than males (male OR: 0.80 [95% CI: 0.66, 0.98]; females OR: 2.98 [95% CI: 2.66, 3.34]). Effect measure modification by age was also observed for high TG (45–60 years old OR: 1.43 [95% CI: 1.19, 1.72]; ≥60 years old OR: 3.01 [95% CI: 2.61, 3.48]) as well as low

HDL-C (45–60 years old OR: 1.37 [95% CI: 1.14, 1.66]; ≥60 years old OR: 3.84 [95% CI: 3.32, 4.45]) with older participants having higher odds.

- In a national cross-sectional survey of children aged seven to 18 years old in China, Gui et al. (2020) did not observe effect measure modification by sex, age, or BMI for the associations between 3-year mean NO_2 concentrations and blood lipids or dyslipidemias.
- In a sub-cohort of the Women's Health Initiative clinical trials in the United States among nondiabetic, postmenopausal women with and without impaired fasting glucose, Holliday et al. (2019) observed near-null and imprecise associations between long-term exposures to NO_X (365-day means; per 20.3 ppb increase) and TG:HDL-C regardless of fasting glucose status (all participants: -0.59 [95% CI: -3.15, 1.97]; participants with normal fasting glucose: -0.79 [95% CI: -3.55, 1.97]; participants with impaired fasting glucose: 0.00 [95% CI: -3.99, 3.99]).

Short-Term Exposure

- In a sub-cohort of the Women's Health Initiative in the United States among nondiabetic, postmenopausal women with and without impaired fasting glucose, Holliday et al. (2019) observed near-null associations between short-term exposures to NO_X (two day means) and TG:HDL-C regardless of fasting glucose status (all participants: -0.21 [95% CI: -1.43,1.00]; participants with normal fasting glucose: -0.42 [95% CI: -2.01, 1.16]; participants with impaired fasting glucose: -0.11 [95% CI: -2.54, 2.32]).
- In a panel study of healthy younger adults (25 to 55 years old) in Chapel Hill, North Carolina, U.S., Chen et al. (2021) did not observe statistically significant (p interaction <0.1) effect measure modification by diets high versus low in omega-3 intake for the association between short-term NO_2 concentrations and total cholesterol.

8.6.1.3 Copollutants

There was limited evaluation of copollutant confounding among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids.

Long-Term Exposure

- Yu et al. (2020) used the CALINE4 line dispersion model to assign long-term NO_X exposure concentrations to participants to evaluate associations with hypertriglyceridemia. Authors reported a near-null association (HR: 1.29 [95% CI: 0.40, 4.22]) that was attenuated and remained near-null after further adjustment for traffic-related noise (HR: 0.84 [95% CI: 0.23, 3.06]). However, the adjusted HR for incident low HDL-cholesterol level was 3.39 [95% CI: 1.37, 8.39] with each 20 ppb increase in traffic-related NOx, which was also robust to further adjustment for traffic-related noise (HR: 3.14 [95% CI: 1.15, 8.54]).
- For 1-year average NO_2, the associations for triglyceride were strengthened in magnitude after copollutant adjustment for O_3, $PM_{2.5}$, or $PM_{2.5}$ + O_3, while associations with prevalent dyslipidemia and HDL remained robust, and associations with LDL and cholesterol were attenuated to near-null (Zhang et al., 2021b).

Short-Term Exposure

- For the association between short-term NO_2 exposure and total cholesterol, the observed negative associations were generally robust in copollutant models that adjusted for $PM_{2.5}$ or O_3, though they were slightly attenuated (Chen et al., 2021).

8.6.1.4 Conclusions and Remaining Uncertainties

Several recent studies evaluated the association between long-term exposure to oxides of nitrogen and blood lipid conditions (e.g., dyslipidemia) and blood lipid biomarkers (e.g., TG, total cholesterol, LDL, HDL). The available evidence is inconsistent with a mixture of negative, null, and positive associations. Across the studies there were differences in the exposure estimation approaches, species of oxides of nitrogen evaluated, study geographies, and specific endpoint evaluated. There were several recent studies from North America, with the majority of studies conducted in the United States, especially in California-based populations. The few studies conducted in Europe generally observed near-null associations with blood lipid biomarkers. In contrast to the recent European studies, a number of recent studies conducted in China reported positive associations with blood lipid conditions and biomarkers. A few recent studies based within the United States evaluated associations between short-term exposures to oxides of nitrogen and blood lipids (e.g., triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, TG:HDL-C). The reported results are generally null across the studies with minimal evidence of associations.

Regardless of exposure duration, there was limited evaluation of the shapes of concentration-response relationships among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids, with inconsistent results across studies. Additionally, there was limited evaluation of copollutant confounding among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids. While several of the studies evaluated effect measure modification by sex, age, ethnicity, comorbidities (i.e., fasting glucose status, BMI, health status), as well as behavioral/lifestyle factors (i.e., dietary intake of omega-3, drinking status), no clear or consistent pattern emerged for any of the modifiers evaluated.

8.6.2 Controlled Human Exposure Studies of Blood Lipids

There was limited controlled human exposure evidence available to support the effects on blood lipids in the 2016 Oxides of Nitrogen ISA. In a study of healthy adults, exposure to 500 ppb NO_2 for two hours with intermittent exercise increased blood total cholesterol by 4.1% ($p = 0.059$) and increased HDL cholesterol by 5.9% ($p = 0.036$) 18 hours after exposure (Huang et al., 2012). No additional controlled human exposure studies have investigated the effect of oxides of nitrogen exposure on blood lipids.

8.6.3 Animal Toxicological Studies of Blood Lipids

The effect of NO_2 exposure on blood lipids was investigated by one study reviewed in the 2016 Oxides of Nitrogen ISA. Takano et al. (2004) exposed two adult rat strains, OLETF and LETO, to a range of NO_2 concentrations (0.16 to 4.0 ppm, 24 hours/day) for 32 weeks. Only HDL cholesterol was decreased in the phenotypically normal rats (LETO), but additional changes were found in OLETF rats, a model which spontaneously develops hyperglycemia and obesity. Compared to OLETF controls, NO_2 exposure increased triglyceride levels (0.16 ppm group), decreased HDL cholesterol (0.16 and 0.8 ppm groups) and decreased the ratio of HDL to total cholesterol (0.16 ppm group). A small number of recent studies investigated the effect of NO_2 exposure on lipids and cholesterol. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below, followed by an additional discussion of multipollutant exposures evaluated in these studies (see Section 8.6.3.1), information on dose-response relationships (see Section 8.6.3.2), and relevance of the animal responses to humans (see Section 8.6.3.3). Section 8.6.3.4 discusses conclusions based on available animal studies and summarizes remaining uncertainties. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 8-6.

- Triglycerides, total cholesterol, and VLDL were significantly elevated in the serum of female, but not male, C57BL/6 mice following a four-week 2.5 ppm NO_2 (four hours/day) exposure (Guo et al., 2023). Triglycerides, free fatty acids, total cholesterol, and lipid content in the liver of female mice were also increased.
- In a study of spontaneously hypertensive male rats exposed to 0.5 ppm NO_2 for three hours, serum HDL cholesterol was significantly decreased 24-hours after exposure compared to controls; however, this exposure did not significantly affect serum LDL cholesterol or serum triglycerides (Farraj et al., 2016).

8.6.3.1 Multipollutant Exposure

In addition to the NO_2-only exposure group, Farraj et al. (2016) evaluated the effects of sequential exposure to NO_2 and O_3, wherein rats were given a three-hour O_3 exposure two hours after the NO_2 exposure. Serum LDL cholesterol was significantly increased in the sequential exposure group, but not in the NO_2-only or O_3-only exposure groups. Interestingly, while HDL cholesterol was significantly decreased in the NO_2-only exposure group, it was not affected in the O_3-only exposure group or the sequential exposure group. Similarly, serum triglycerides were significantly increased in the O_3-only exposure group but were unaffected in the NO_2-only exposure group and the sequential exposure group.

8.6.3.2 Dose Response

The presence of a dose-response relationship informs and may strengthen causality determinations. Of the available studies, only Takano et al. (2004) investigated multiple NO_2 dosing

groups (0.16, 0.8, and 4.0 ppm). In LETO rats, HDL cholesterol was significantly decreased in all exposure groups, but there was no clear indication of a dose-response gradient. Interestingly, in OLETF rats, no significant effects were detected in the high-exposure group. Rather, effects were observed only in the low-dose group (triglycerides, HDL-to-total cholesterol ratio) or in the low- and medium-dose groups (HDL cholesterol). This finding may be indicative of a non-linear dose-response curve (e.g., U-shaped), but additional studies are needed to elucidate this relationship.

8.6.3.3 Relevance of Animal Responses to Human Responses

Rodents are useful for investigating the impact of environmental pollutants on lipids and lipoproteins. To better emulate human physiology, researchers have developed various genetic, chemical, and diet-induced animal models. OLETF rats, utilized in Takano et al. (2004), are a genetic model that lacks the cholecystokinin-1 receptor. These rats exhibit increased food intake and mimic many aspects of human MetS and T2D (Moran and Bi, 2006; Kawano et al., 1992). Despite their utility, no single model can address all interspecies variances. Comparative studies have shown distinct variations in plasma lipid and cholesterol composition between humans and rodents (Kaabia et al., 2018; Yin et al., 2012) and these species-specific differences should be considered when interpreting these findings.

8.6.3.4 Conclusions and Remaining Uncertainties

Limited evidence suggests that NO_2 exposure may alter lipid and cholesterol profiles in rodents. Among the studied endpoints, findings on HDL cholesterol were the most consistent, with significant reductions reported across varied exposure paradigms (160 ppb for 32 weeks or 500 ppb NO_2 for three hours). NO_2-induced effects on total cholesterol and triglycerides varied between studies. Additionally, there is limited evidence that obese rats and female rats may be more sensitive to these effects; however, these findings are based on single studies and require further replication. Future research should build on these findings by exploring alternative exposure paradigms, further delineating the dose-response relationship, evaluating potential sex-based differences in sensitivity to NO_2 exposure, and investigating additional animal models that mimic aspects of metabolic syndrome.

8.6.4 Synthesis Across Lines of Evidence

Several recent PECOS-relevant epidemiologic studies evaluated the association between long-term exposure to oxides of nitrogen and blood lipid conditions (e.g., dyslipidemia) and blood lipid biomarkers (e.g., TG, total cholesterol, LDL, HDL). The available evidence is inconsistent with a mixture of negative, null, and positive associations. Across the studies there were differences in the exposure estimation approaches, species of oxides of nitrogen evaluated, study geographies, and specific endpoint

evaluated. A few recent studies based within the United States evaluated associations between short-term exposures to oxides of nitrogen and blood lipids (e.g., triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, TG:HDL-C). However, the reported results are generally null across the studies with minimal evidence of associations. Regardless of exposure duration, there was limited evaluation of the shapes of concentration-response relationships among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids, with inconsistent results across studies. Additionally, there was limited evaluation of copollutant confounding among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids. While several of the studies evaluated effect measure modification by sex, age, ethnicity, comorbidities (i.e., fasting glucose status, BMI, health status), as well as behavioral/lifestyle factors (i.e., dietary intake of omega-3, drinking status), no clear or consistent pattern emerged for any of the modifiers evaluated. Limited controlled human exposure evidence suggests that NO_2 may increase blood lipids in healthy adults. Similarly, for toxicological studies, limited evidence suggests that NO_2 exposure increases lipids and cholesterol in the blood and liver of mice and rats.

8.7 Adiposity and Weight Gain

Because obesity is a multifactorial disease that will not occur following an individual's exposure to oxides of nitrogen for <1 month, there are no included studies evaluating the association between short-term exposure to oxides of nitrogen and obesity. Section 8.7.1 summarizes recent PEOCS-relevant epidemiologic evidence examining the effects of long-term oxides of nitrogen exposure on adiposity and weight gain parameters. No PECOS-relevant epidemiologic studies examining short-term exposure, PECOS-relevant controlled human exposure studies, or PECOS-relevant animal toxicological studies were identified.

8.7.1 Epidemiologic Studies of Adiposity and Weight Gain

Several recent studies evaluated associations between long-term exposures to oxides of nitrogen and adiposity and weight gain. A subset of these recent studies were conducted in California, U.S., and had inconsistent results across studies. Evidence from recent studies is summarized below, followed by an additional discussion of concentration-response relationships in these studies (see Section 8.7.1.1), lifestages and populations evaluated (see Section 8.7.1.2), and the potential impacts of copollutants (see Section 8.7.1.3). Section 8.7.1.4 discusses conclusions based on these studies and summarizes remaining uncertainties. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-7.

- The Community of Mine study was a small observational study (n = 552) completed between 2014 and 2017 in San Diego County, U.S. Letellier et al. (2022) assigned long-term NO_2

exposures using two methods: 1) a traditional static approach that linked NO_2 concentrations from the EPA's AQS to the participant's home via IDW; and 2) 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. This dynamic exposure assignment is unitless. Letellier et al. (2022) observed a negative association between long-term NO_2 exposure and obesity using the static exposure method although the 95% CIs crossed the null (RR: 0.90 [95% CI: 0.79, 1.02]). In contrast, for the dynamic exposure method, Letellier et al. (2022) observed a positive association between long-term NO_2 exposure and obesity (RR: 1.21 [95% CI: 1.10, 1.33]). Letellier et al. (2022) additionally evaluated continuous BMI and reported similar associations as categorical obesity with the static exposure method resulting in a negative association although the 95% CIs included the null (β: 0.90 [95% CI: 0.79, 1.02]) while the dynamic exposure approach resulted in a positive association (β: 0.65 [95% CI: 0.18, 1.12]) between long-term NO_2 exposure and BMI.

- In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA cohort), Yu et al. (2020) used the CALINE4 line dispersion model to assign long-term exposure of NO_X concentrations to participants to evaluate associations with abdominal obesity, as defined by NCEP ATP III criteria. Authors reported that higher traffic-related NO_X exposure was negatively associated with abdominal obesity although the 95% CIs crossed the null (HR: 0.30 [95% CI: 0.07, 1.26]).
- Mann et al. (2021) evaluated children residing in the Fresno, California, U.S., area who were enrolled in CHAPS. Mann et al. (2021) modelled NO_2 using a combination of regulatory and spatially intensive monitoring data at the child's residence to derive 1-month, 3-month, 6month, and 1-year averages before the outcome assessment. Mann et al. (2021) reported mostly near-null or positive, although imprecise, associations between 3-month, 6-month, and 1-year NO_2 and indicators of adiposity. For example, the associations between 6-month NO_2 percent body fat, BMI relative to the 95th percentile, and waist-height ratio were β: 0.59 [95% CI: -1.46, 2.64; per 3.42 ppb], β: 4.00 [95% CI: -0.19, 8.36; per 3.42 ppb], and β: 0.01 [95% CI: -0.01, 0.02; per 3.42 ppb], respectively.

The few recent studies conducted in Europe observed near-null associations between oxides of nitrogen and indicators of adiposity and weight gain; whereas the recent studies conducted in China observed positive associations.

- In a pan-European, multi-center, prospective cohort based on the IDEFICS, Nagrani et al. (2023) observed a near-null association between annual NO_2 exposure estimated using ELAPSE and waist circumference (WC) (β: -0.02 [95% CI: -0.08, 0.03] per IQR).
- Among preschoolers (age four) in the Spanish INMA birth cohort, Fossati et al. (2020) reported a near-null association between first trimester exposure to NO_2 (estimated for a temporally adjusted LUR model) and standardized waist circumference (zWC) (β: 0.02 [95% CI: -0.11, 0.15]). Comparable results were reported in sensitivity analyses using second trimester, third trimester, entire pregnancy, or first year of life exposure to NO_2.
- Eze et al. (2015) conducted a cross-sectional study with participants from the SAPALDIA cohort to investigate the association between 10 year NO_2 concentrations (estimated via hybrid dispersion and LUR models) and central obesity using two definitions (BMI>30 kg/m^2 versus predicted waist circumference and European cut-offs (≥94 cm for males and ≥80 cm for females). Eze et al. (2015) observed near-null associations for both (OR: 1.01 [95% CI: 0.89, 1.14] and OR: 1.06 [95% CI: 0.90, 1.26] per 5.3 ppb NO_2, respectively).

- Liu et al. (2023) conducted a cross-sectional study of the CHARLS participants from Waves 1 and 2 (2011 to 2015). The 3-year and 2-year average NO_2 exposures were derived from spatiotemporal random forest models. They observed a positive association between the 3-year average NO_2 exposure and central obesity (OR: 2.65 [95% CI: 2.33, 3.01]). Similar results were observed when using the 2-year average NO_2 exposure as well as when using NCEP-ATP III MetS component definition.
- Zhang et al. (2021a) conducted a cross-sectional study of Chinese 10 to 18 year olds to evaluate the association between 2-year mean NO_2 concentrations and abdominal obesity (defined according to the International Diabetes Federation with cut-off points for Chinese children) and observed a positive association (OR: 1.99 [95% CI: 1.45, 2.73]).

8.7.1.1 Concentration-Response

A single study included an evaluation of concentration-response for the association between NO_2 and WC. In a pan-European, multi-center, prospective cohort based on the IDEFICS, Nagrani et al. (2023) observed near-null associations between annual NO_2 exposure WC when evaluating the exposure categorically by quartiles with no evidence of concentration-response.

8.7.1.2 Lifestages and Populations

Few PECOS-relevant epidemiologic studies included evaluation of effect measure modification. Those that did investigated effect measure modification by sex, age, ethnicity, comorbidities (i.e., health status), as well as behavioral/lifestyle factors (i.e., drinking status). However, no evidence of effect measure modification was observed for associations between long-term NO_2 exposure and obesity or central obesity.

- In the Community of Mine study, Letellier et al. (2022) evaluated the association between long-term NO_2 exposure and obesity. The stratified analyses by ethnicity (i.e., Hispanic versus non-Hispanic) did not show evidence of modification for obesity using either the static or dynamic exposure approaches.
- Liu et al. (2023) conducted a cross-sectional study of the CHARLS participants from waves 1 and 2 (2011 to 2015) to evaluate the association between3-year and 2-year average NO_2 exposures and central obesity Liu et al. (2023) additionally investigated effect measure modification by sex, age, health status, and drinking status using both analytical strategies of interaction terms and model restriction, which produced similar results; however, no evidence of effect measure modification was observed for central obesity.

8.7.1.3 Copollutants

A single study included an evaluation of adjustment for copollutants. In a cohort of older (greater than 60 years; mean of 70.2 years) Mexican Americans (SALSA cohort), Yu et al. (2020) evaluated the

association between long-term exposure to NO_X concentrations to participants to evaluate associations with and abdominal obesity. Authors reported that higher traffic-related NO_X exposure was negatively associated with abdominal obesity although the 95% CIs crossed the null (HR: 0.30 [95% CI: 0.07, 1.26]). This association was robust to further adjustment for traffic-related noise (HR: 0.30 [95% CI: 0.06, 1.45]).

8.7.1.4 Conclusions and Remaining Uncertainties

Several recent PECOS-relevant epidemiologic studies evaluated associations between long-term exposures to oxides of nitrogen and adiposity and weight gain. A subset of these recent studies were conducted in California and had inconsistent results across studies. The few recent studies conducted in Europe observed near-null associations between oxides of nitrogen and indicators of adiposity and weight gain; whereas the recent studies conducted in China observed positive associations. There was limited evaluation of the shapes of concentration-response relationships as well as evaluation of copollutant confounding among PECOS-relevant epidemiologic studies evaluating the association between oxides of nitrogen and measures of adiposity and weight gain. Few PECOS-relevant epidemiologic studies included evaluation of effect measure modification, and those that did, reported no evidence of effect measure modification by sex, age, ethnicity, comorbidities (i.e., health status), or behavioral/lifestyle factors (i.e., drinking status).

8.8 Cause-specific Mortality

This section summarizes recent PECOS-relevant epidemiologic evidence examining the relationship between exposure to oxides of nitrogen and mortality from metabolic diseases (i.e., diabetes mortality (see Section 8.8.1), metabolic mortality (see Section 8.8.2), and cardiometabolic mortality (see Section 8.8.3). No PECOS-relevant animal toxicological studies were identified.

8.8.1 Epidemiologic Studies of Diabetes Mortality

There were no epidemiologic studies evaluating oxides of nitrogen exposure and diabetes mortality in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). Several recent observational studies have evaluated long-term exposure to NO_2 and diabetes mortality across many different geographies (e.g., multi-country study in Europe, South Korea, Canada, United States) and have consistently reported positive associations, although sometimes the 95% CI crossed the null. One recent study evaluated short-term exposures. Below is a bulleted summary of the recent evidence, followed by additional discussion of concentration-response relationships in these studies (see Section 8.8.1.1), the lifestages and populations evaluated (see Section 8.8.1.2), and the potential impacts of copollutants (see Section 8.8.1.3). Section

8.8.1.4 discusses conclusions based on available studies and summarizes remaining uncertainties. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-8.

- To date, the most extensive evaluation of long-term NO_2 exposure and diabetes mortality is the recent multicenter Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (Brunekreef et al., 2021; Strak et al., 2021). This two-pronged study includes analyses of two sets of cohorts: a pooled analysis of data from eight well-established ESCAPE cohorts and an analysis of seven large administrative cohorts in Europe. This study provides strength of inference from a large, pooled dataset of over 325,000 participants with individual-level data and analyses of nationally representative administrative data on over 28 million adults. The authors reported positive associations between long-term NO_2 concentrations and risk of diabetes mortality in the pooled analysis (HR: 1.49 [95% CI: 1.22, 1.83]) and positive but imprecise associations for the meta-analysis of the administrative cohorts (HR: 1.02 [95% CI: 0.92, 1.14]).
- Other recent European studies examined individual ELAPSE cohorts, and in some cases expanded upon those cohorts. Consistent with ELAPSE, these studies of the individual cohorts indicated positive associations of varying magnitude between long-term NO_2 exposure and diabetes mortality. So et al. (2020) observed positive, although imprecise, associations between long-term exposure to NO_2 and diabetes mortality in the Danish Nurse Cohort (n = 24,541; HR: 1.43 [95% CI: 0.87, 2.35]). In a nationwide administrative cohort in Denmark that included two additional years of follow-up from the original ELAPSE project, So et al. (2022) observed a positive association between long-term exposure to NO_2 and diabetes mortality (HR: 1.04 [95% CI: 0.99, 1.09]).
- Among those who have chronic obstructive pulmonary disease in a South Korean cohort, Kang et al. (2023) reported positive associations between 1-year, 3-year, and 5-year exposures to NO_2 and diabetes mortality although the 95% CIs crossed the null (HR: 1.06 [95% CI: 0.94, 1.20], HR: 1.13 [95% CI: 0.99, 1.28], HR: 1.12 [95% CI: 0.94, 1.32], respectively).

Large observational studies in the United States and Canada reported positive associations between long-term exposure to NO_2 and diabetes mortality.

- In a large nationwide study among adults included in the 1991 to 2006 wave of the Canadian Census Health and Environment Cohort (CanCHEC), Crouse et al. (2015) observed a positive association between NO_2 exposure and diabetes mortality (HR: 1.05 [95% CI: 1.00, 1.10]).
- In another Canadian population, among people with prevalent diabetes within the ONPHEC study, Paul et al. (2020b) reported positive associations between 3-year moving average NO_2 concentrations derived from LUR models and diabetes mortality (HR: 1.076 [95% CI: 1.024, 1.130] per IQR, 14.2 ppb).
- Positive associations between long-term exposure to NO_2 and diabetes mortality (HR: 1.09 [95% CI: 1.01, 1.18]) were also observed in a large cohort across the contiguous United States (NIH-AARP Diet and Health Study) (Lim et al., 2018).

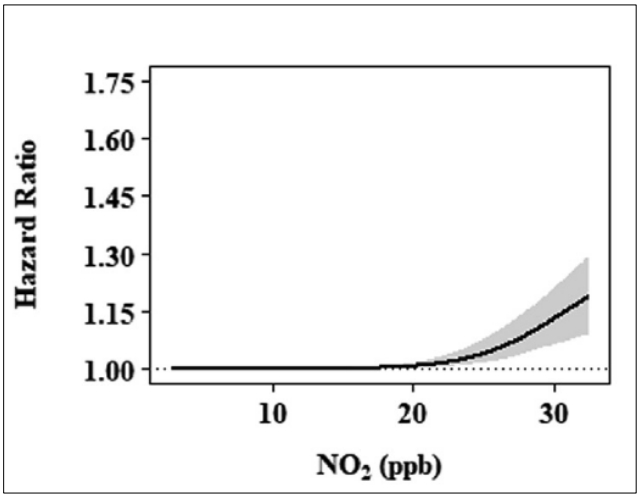
A single recent study evaluated associations between short-term exposure to NO_2 and diabetes mortality. The study investigated associations between daily NO_2, modeled using chemical transport and machine learning, and diabetes mortality in a nationwide analysis of over 15,000 diabetes mortalities in

Italy (Gariazzo et al., 2023). Gariazzo et al. (2023) observed imprecise associations for diabetes mortality for all lags evaluated (e.g., lag 0–5 IR: 1.14 [95% CI: 0.65, 1.99]).

8.8.1.1 Concentration-Response

Several studies investigating the association between oxides of nitrogen and diabetes also evaluated the shapes of concentration-response relationships across the distribution of estimated oxides of nitrogen exposures, primarily NO_2. Overall, for the association between NO_2 and diabetes, there was a general indication of an approximately linear, linear plateau/threshold, or supralinear concentration-response relationships reported.

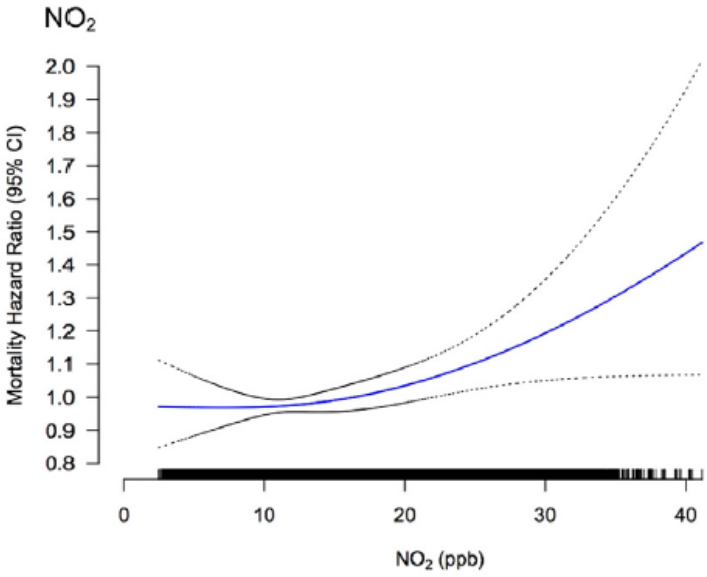
Paul et al. (2020b) observed an approximately linear threshold concentration-response curve (see Figure 8-19; see Appendix A – Appendix Table 8-8 for categorical concentration-response for the 3-year exposure quartiles).



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

Figure 8-19 Concentration-response function of ensemble model for the association between NO_2 and the risk of diabetes mortality in Ontario, Canada, during the study period (2001 to 2015).

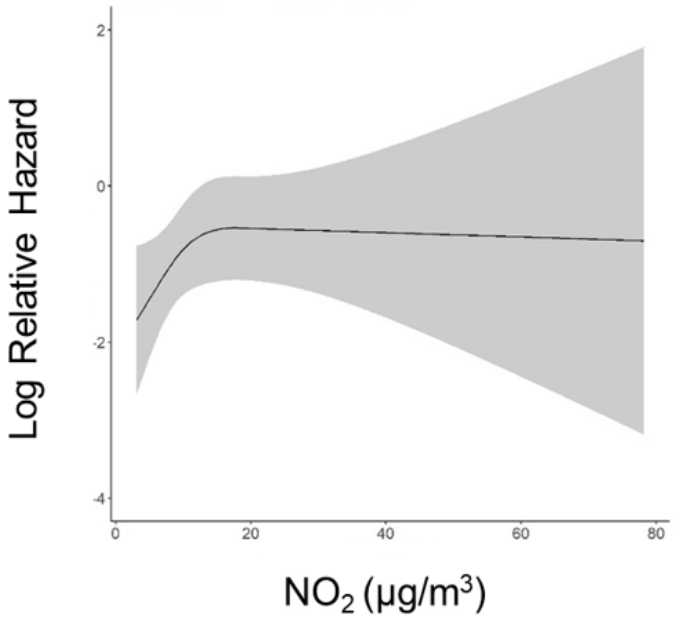
- Lim et al. (2018) also observed an approximately linear threshold concentration-response curve (see Figure 8-20).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Notes: The concentration-response curve is based on natural spline models with 2 degrees of freedom, for standard Cox models adjusted for individual level and contextual covariates. The tick marks on the x-axis identify the distribution of observations according to air pollutant concentrations.
Source: Adapted from Lim et al. (2018). Copyright permission pending.

Figure 8-20 Concentration-response curve (solid line) and 95% CI (dashed lines) relative to the effect at mean concentration, for the association between NO_2 and diabetes mortality.

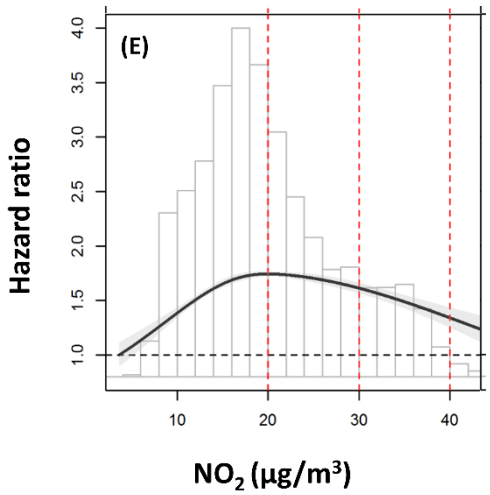
- So et al. (2020) also observed an approximately linear threshold concentration-response curve (see Figure 8-21).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Notes: The concentration-response curve is based Restricted spline curves for the association between NO2 (3 year-running mean with 1-year lag) and diabetes mortality. adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy
Source: Adapted from So et al. (2020). Copyright permission pending.

Figure 8-21 Concentration-response curve for the association between NO_2 and diabetes mortality.

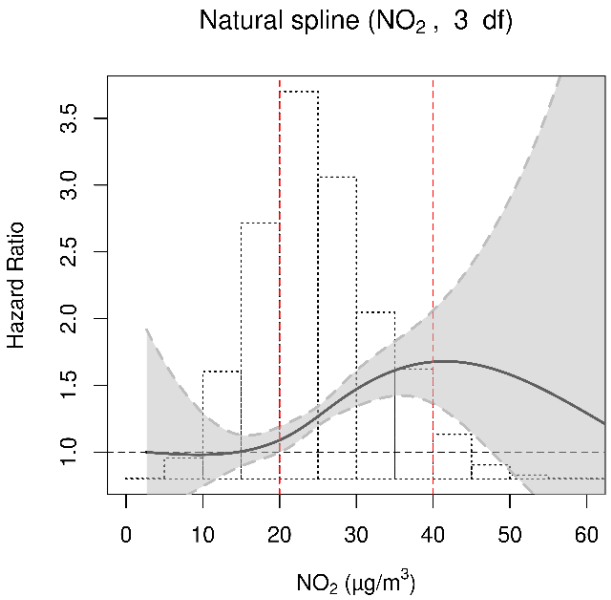
- So et al. (2022) also observed an approximately linear threshold concentration-response curve (see Figure 8-22).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Notes: Red vertical dashed lines show values used for subset analyses: 40 (the EU standard), 30, and 20 µg/m^3. The upper limit of the x-axis was truncated at 99.5 percentile of the distribution of NO_2. Model adjusted for age (underlying time scale), sex (strata), household income in decile, occupational status, immigrant status, marital status, and highest completed education level, regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region. N = 3,083,227.
Source: Adapted from So et al. (2022). Copyright permission pending.

Figure 8-22 Concentration-response curve for the association between long-term exposure to NO_2 and mortality from diabetes in the Danish administrative cohort.

- Brunekreef et al. (2021) evaluated the concentration-response curve for the association between long-term NO_2 exposure and diabetes mortality. Brunekreef et al. (2021) reported an inverted U-shaped concentration-response curve, with positive associations for NO_2 concentrations not starting until about 15 µg/m^3 then peaking at about 40 µg/m^3 (see Figure 8-23).



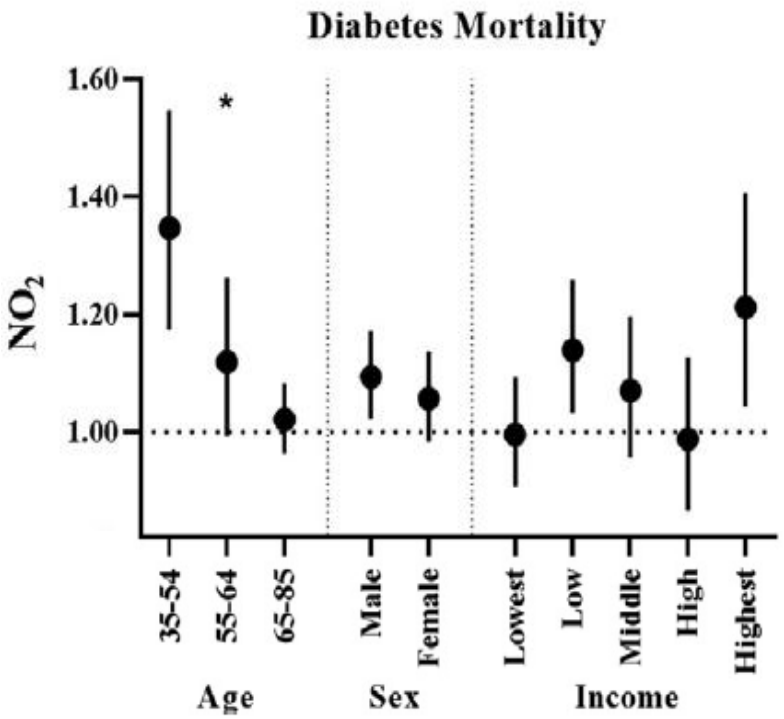
List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: Hazard ratios expressed relative to minimum exposure.
Source: Brunekreef et al. (2021). Copyright permission pending.

Figure 8-23 Natural cubic splines (3 degrees of freedom) for associations between NO_2 exposure and diabetes mortality

8.8.1.2 Lifestages and Populations

While a few studies evaluated factors that may place populations at increased risk, there was little consistency across studies.

- As described above, among those who have chronic obstructive pulmonary disease in a South Korean cohort, Kang et al. (2023) reported positive associations between 1-year, 3-year, and 5-year exposures to NO_2 and diabetes mortality although the 95% CIs crossed the null.
- Lim et al. (2018) also conducted stratified analyses for potential effect modifier subgroups (age, sex, race, smoking history, pre-diagnosed health status (heart disease and diabetes), BMI, and diet). The strength of the NO_2-diabetes mortality association was greater in participants who consumed less than two and a half servings of fruits per day (HR: 1.17 [95% CI: 1.08, 1.27]), compared to those who consumed greater amounts (HR: 0.93 [95% CI: 0.79, 1.09]). There was some evidence of effect modification by sex, with positive associations observed for males (HR: 1.17 [95% CI: 1.06, 1.29]), but not females (HR: 0.96 [95% CI: 0.84, 1.10]).
- Paul et al. (2020b) reported evidence of modification by age, with 35 to 54 year old adults indicating a higher risk for NO_2-associated diabetes mortality than older adult populations (see Figure 8-24).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: All models adjusted for age, sex, SES, region, and healthcare access, and stratified by Greater Toronto Area residence. Hazard ratios are expressed per interquartile range (IQR) increase (14.2 ppb). Cochran's Q was used to test for heterogeneity across strata. Significant heterogeneity (P <0.05) is indicated by asterisks.
Source: Adapted from Paul et al. (2020b). Copyright permission pending.

Figure 8-24 Hazard ratios and 95% CIs for the association between NO_2 and diabetes mortality stratified by selected characteristics in Ontario during the study period (2001-2015).

8.8.1.3 Copollutants

Most positive associations observed for single-pollutant models evaluating the association between long-term exposure to NO_2 and diabetes were attenuated to near-null after adjustment for copollutants.

- So et al. (2020) observed attenuated HRs to near-null with additional adjustment for copollutants (i.e., adjustment for road-traffic noise HR: 1.19 [95% CI: 0.63, 2.26]; adjustment for $PM_{2.5}$ HR: 0.92 [95% CI: 0.49, 1.76]; adjustment for PM_{10} HR: 1.03 [95% CI: 0.57, 1.84]).
- So et al. (2022) reported associations attenuated to null after copollutant adjustment for $PM_{2.5}$ (HR: 0.98 [95% CI: 0.93, 1.04]), but strengthened after copollutant adjustment for BC or O_3 (HR: 1.22 [95% CI: 1.10, 1.35], HR: 1.22 [95% CI: 1.12, 1.32], respectively).
- Crouse et al. (2015) observed associations attenuated to null after multipollutant adjustment for $PM_{2.5}$ and O_3 (HR: 1.00 [95% CI: 0.95, 1.06]).

- The positive association observed by Paul et al. (2020b) for the single-pollutant model was essentially unchanged after copollutant adjustment for $PM_{2.5}$ or O_3 and strengthened after multipollutant adjustment for $PM_{2.5}$ and O_3.

8.8.1.4 Conclusions and Remaining Uncertainties

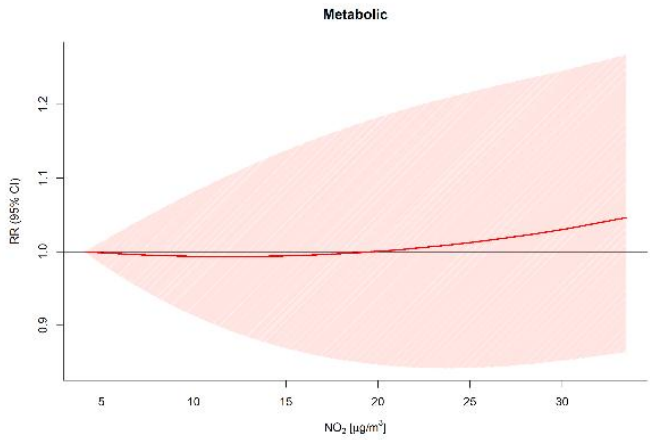
While there were no epidemiologic studies evaluating oxides of nitrogen exposure and diabetes mortality in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), there were several recent studies that evaluated associations between long-term exposure to NO_2 and diabetes mortality and a single recent study evaluating short-term exposure. Overall, these studies consistently reported positive associations, although sometimes the 95% CI crossed the null. In the few studies that evaluated copollutant confounding, no consistent pattern emerged, with effect estimates often attenuated after copollutant adjustment.

8.8.2 Epidemiologic Studies of Metabolic Mortality

There were no epidemiologic studies evaluating oxides of nitrogen exposure and metabolic mortality in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). Additionally, there were no recent epidemiologic studies that evaluated associations between long-term oxides of nitrogen exposure and metabolic mortality. However, there was a single recent study that evaluated associations between short-term exposure to NO_2 and metabolic mortality. Gariazzo et al. (2023) evaluated associations between daily NO_2 concentrations, modeled using chemical transport and machine learning, and metabolic mortality in a nationwide analysis of over 81,000 metabolic mortalities in Italy (Gariazzo et al., 2023). Gariazzo et al. (2023) observed an increased risk of metabolic mortality (lag 0–5 IR: 1.30 [95% CI: 1.04, 1.63]). Additional discussion of the lifestages and populations evaluated in this study and the concentration-response relationship are discussed in Sections 8.8.2.1and 8.8.2.2, respectively. Section 8.8.2.3 discusses conclusions and remaining uncertainties. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-8.

8.8.2.1 Concentration-Response

Gariazzo et al. (2023) also generated concentration-response functions by fitting distributed lag non-linear models (DLMN) in place of the linear term for NO_2; the curve went above the null after about 10.6 ppb (20 $\mu g/m^3$) although had wide 95% confidence intervals (see Figure 8-25).



List of abbreviations in alphabetical order: CI = confidence interval; NO_2 = nitrogen dioxide; RR = relative risk.
Note: Overall curve is reported in red with relative 95% CI as red band.
Source: Gariazzo et al. (2023). Copyright permission pending.

Figure 8-25 Concentration-response function derived by province-specific curves for NO_2 for metabolic mortality in Italy

8.8.2.2 Lifestages and Populations

Gariazzo et al. (2023), evaluated effect modification by sex, age, and urbanicity for metabolic mortality. There was evidence of effect modification by sex, with strong associations in male but not female participants (lag 0–5 among females IR: 0.98 [95% CI: 0.75, 1.28]; lag 0–5 among males IR: 2.04 [95% CI: 1.28, 3.26]).

8.8.2.3 Conclusions and Remaining Uncertainties

There was no epidemiologic evidence reviewed in the previous ISA and a single recent PECOS-relevant epidemiologic study investigating an association between short-term exposure to oxides of nitrogen and metabolic mortality. The single study did report a positive association with evidence of higher risk among males compared to females, though additional studies examining this relationship are needed to draw conclusions.

8.8.3 Epidemiologic Studies of Cardiometabolic Mortality

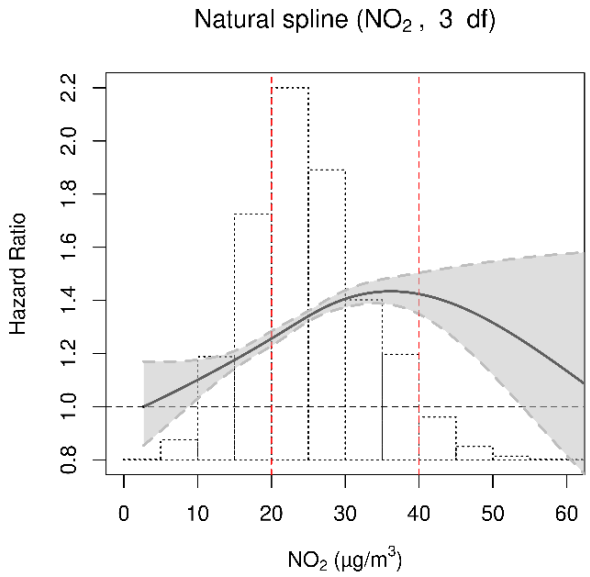
There were no epidemiologic studies evaluating oxides of nitrogen exposure and cardiometabolic mortality in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). Recent studies have defined cardiometabolic mortality generally as cardiovascular disease-related mortality plus diabetes mortality. A short summary of the recent evidence is provided below, followed by additional discussion of the

concentration-response relationships from these studies (see Section 8.8.3.1), the lifestages and populations evaluated (see Section 8.8.3.2), and the potential impacts of copollutants (see Section 8.8.3.3). Section 8.8.3.4 discusses conclusions based on these studies and summarizes remaining uncertainties. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-8.

- To date, the most extensive evaluation of long-term NO_2 exposure and cardiometabolic mortality is the recent multicenter Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (Brunekreef et al., 2021; Strak et al., 2021). This two-pronged study includes analyses of two sets of cohorts: a pooled analysis of data from eight well-established ESCAPE cohorts and analysis of seven large administrative cohorts in Europe. This study provides strength of inference from a large, pooled dataset of over 325,000 participants with individual-level data and analyses of nationally representative administrative data on over 28 million adults. Cardiometabolic mortality was defined as death from all cardiovascular diseases and diabetes combined. The authors reported positive associations between long-term NO_2 concentrations and risk of cardiometabolic mortality in the pooled analysis (HR: 1.19 [1.13, 1.25]) as well as the meta-analysis of the administrative cohorts (HR: 1.05 [95% CI: 1.01, 1.09]).
- In a large nationwide study among adults included in the 1991 to 2006 wave of the CanCHEC, Crouse et al. (2015) observed a positive association between NO_2 exposure and cardiometabolic mortality (HR: 1.05 [95% CI: 1.04, 1.06]), defined as death from circulatory diseases plus diabetes.

8.8.3.1 Concentration-Response

A single study evaluated the concentration-response curve for the association between long-term NO_2 exposure and cardiometabolic mortality. Brunekreef et al. (2021) reported an inverted U-shaped concentration-response curve, with positive associations for NO_2 concentrations peaking at about 35 mg/m^3 (18.6 ppb) (see Figure 8-26). When evaluating threshold cut-points of 21.3 ppb (<40 $\mu g/m^3$), 15.9 ppb (<30 $\mu g/m^3$), and 10.6 ppb (<20 $\mu g/m^3$), they observed similar results across categories (HR: 1.11 [95% CI: 1.08, 1.15], HR: 1.13 [95% CI: 1.08, 1.17], and HR: 1.18 [95% CI: 1.07, 1.31], respectively).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.
Note: Hazard ratios expressed relative to minimum exposure..
Source: Brunekreef et al. (2021). Copyright permission pending.

Figure 8-26 Natural cubic splines (3 degrees of freedom) for associations between NO_2 exposure and cardiometabolic mortality

8.8.3.2 Lifestages and Populations

A single study evaluated lifestages and populations for the association between long-term NO_2 exposure and cardiometabolic mortality. Crouse et al. (2015) evaluated effect modification by sex, sex and age, income, and immigrant status. Evidence of effect modification was observed for income, with a stronger association among the bottom quintile (HR: 1.13 [95% CI: 1.11, 1.16]) and attenuated to near-null among the top quintile (HR: 0.96 [95% CI: 0.93, 1.00]). There was also some evidence of effect modification for immigrant status, with immigrants having a stronger positive association (HR: 1.08 [95% CI: 1.05, 1.11]), whereas non-immigrants had a similar association to the overall effect estimate (HR: 1.04 [95% CI: 1.03, 1.06]).

8.8.3.3 Copollutants

A single study evaluated copollutant confounding for the association between long-term NO_2 exposure and cardiometabolic mortality. The positive association Crouse et al. (2015) observed for the single-pollutant model (HR: 1.05 [95% CI: 1.04, 1.06]) remained robust after multipollutant adjustment for $PM_{2.5}$ and O_3 (HR: 1.04 [95% CI: 1.03, 1.05]).

8.8.3.4 Conclusions and Remaining Uncertainties

Overall, the recent literature suggests positive associations between long-term NO_2 exposure and cardiometabolic mortality. A single study showed stronger associations at lower NO_2 concentrations, suggesting potential nonlinear concentration-response relationship. Copollutant confounding remains a key uncertainty, as only a single study evaluated multipollutant adjustment for $PM_{2.5}$ and O_3. There is also limited research assessing populations potentially at increased risk.

8.9 Other Indicators of Metabolic Function

This section summarizes recent PECOS-relevant epidemiologic evidence (see Section 8.9.1) examining the relationship between long-term exposure to oxides of nitrogen and other proteins/hormones related to metabolic function as well as a cardiometabolic risk score, which included similar components as MetS but lacks inclusion of fasting blood glucose. No PECOS-relevant epidemiologic studies of short-term exposure were identified. Additionally, no PECOS-relevant animal toxicological studies were identified. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 8-9. For non-alcoholic fatty liver disease (NAFLD), see Chapter 13, Section 13.5.

8.9.1 Epidemiologic Studies of Other Indicators of Metabolic Function

Other proteins/hormones

Mann et al. (2021) evaluated children residing in the Fresno, California, U.S., area who were enrolled in CHAPS. Mann et al. (2021) modelled NO_2 using a combination of regulatory and spatially intensive monitoring data at the child's residence to derive 1-month, 3-month, 6-month, and 1-year averages before the outcome assessment. Mann et al. (2021) reported mostly positive, although very imprecise, associations between 3-month, 6-month, and 1-year NO_2 concentrations and adiponectin and leptin. For example, the association between 6-month NO_2 concentration and adiponectin was β: 5.34 (95% CI: -12.58, 26.94) per 3.42 ppb.

Cardiometabolic risk score

A single study evaluated the association between NO_2 and a cardiometabolic risk score defined by summing the z-score for waist circumference, the mean of DBP and SBP z-scores, and the mean of triglyceride and HDL z-scores. Among preschoolers (age four) in the Spanish INMA birth cohort, Fossati et al. (2020) reported a near-null association between first trimester exposure to NO_2 (estimated for a temporally adjusted LUR model) and a cardiometabolic risk score (β: 0.06 [95% CI: -0.15, 0.26]). Comparable results were reported in sensitivity analyses using second trimester, third trimester, entire pregnancy, or first year of life exposure to NO_2.

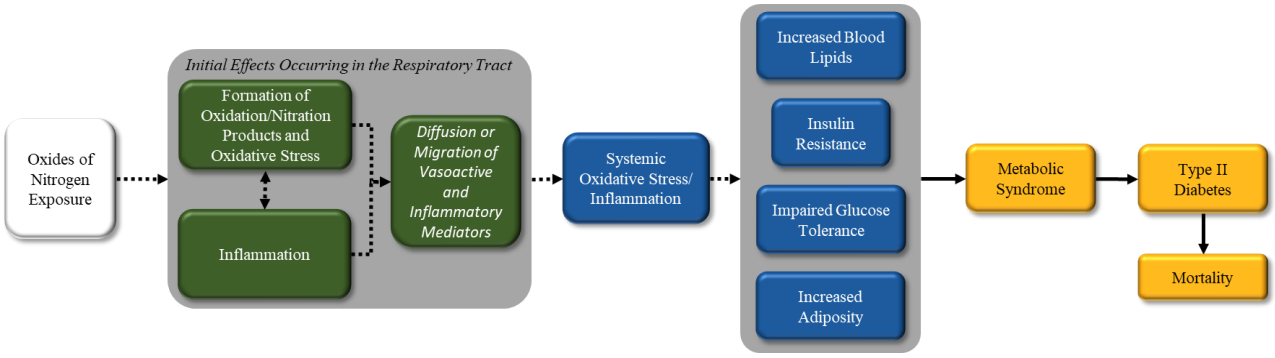
Wu et al. (2022a) examined the association between 3-year average NO_2 exposure and metabolic risk score among adults in the Henan Rural Health Cohort. The authors derived a cardiometabolic risk score by summing the sex and age specific standardized scores for BMI, waist circumference, SBP, DBP, fasting plasma glucose, HOMA2-IR, triglycerides, and HDL cholesterol. An increase in cardiometabolic risk with increasing NO_2 exposure was observed (β: 2.15 [95% CI: 1.90, 2.40]).

8.9.1.1 Conclusions and Remaining Uncertainties

The evidence linking oxides of nitrogen exposure to adiponectin or leptin is limited, with a single epidemiologic study reporting imprecise estimates. Additionally, the evidence linking oxides of nitrogen to a cardiometabolic risk score is limited, with a single epidemiologic study reporting a near-null association.

8.10 Biological Plausibility

This section describes biological pathways that potentially underlie effects on metabolic syndrome and diabetes resulting from exposure to oxides of nitrogen. Figure 8-27 depicts the proposed pathways as a continuum of upstream events connected by arrows that may lead to downstream events observed in epidemiologic studies. Evidence supporting these potential pathways was derived from Sections 8.3 to 8.9 of this ISA, evidence reviewed in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), and recent evidence collected from studies that may not meet the current PECOS criteria but contain mechanistic information supporting these pathways. Discussion of how long-term exposure to oxides of nitrogen may lead to metabolic syndrome and diabetes contributes to an understanding of the biological plausibility of epidemiologic results. The structure of the biological plausibility section and the role of biological plausibility in contributing to the weight-of-evidence analysis are discussed in the Integrated Synthesis (see Section IS.4.2).



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 below. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in this ISA are discussed in the Integrated Synthesis (see Section IS.4.2).

Figure 8-27 Potential biological plausibility pathways for metabolic syndrome and diabetes effects associated with exposure to oxides of nitrogen

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. In rats exposed to 1 ppm NO_2 for four weeks, de Burbure et al. (2007) reported increased plasma lipid peroxidation markers alongside decreased antioxidant enzymes (glutathione peroxidase and superoxide dismutase). (Seilkop et al., 2012) similarly found that NO_2 exposure strongly predicted plasma lipid peroxidation markers. Furthermore, in children aged 6 to 10, higher ambient NO_2 has been associated with elevated levels of urinary 8-isoprostane, a marker of systemic oxidative stress (Zhang et al., 2022; Mann et al., 2021). Oxidative stress and inflammation are tightly linked, and chronic inflammation is a well-established driver of metabolic disturbances, including altered insulin signaling, glucose intolerance and hyperglycemia, dysregulated blood lipids, and obesity (van Beek et al., 2014; O'Rourke, 2009; Arkan et al., 2005; Wellen and Hotamisligil, 2005).

At the molecular level, evidence suggests that NO_2 may interfere with the IRS-1/PI3K/AKT insulin signaling pathway. Under standard physiological conditions, insulin binds to the insulin receptor, activating IRS-1 and promoting the formation of the IRS-1/PI3K complex, which then activates AKT to promote glucose uptake. In mouse liver and skeletal muscle, four weeks of 2.5 ppm NO_2 exposure was shown to reduce IRS-1 and AKT phosphorylation (i.e., reduce activation) (Guo et al., 2023; Yan et al., 2016). AKT has many downstream effects related to cell proliferation, survival, and metabolism. One of

these downstream effectors, GSK-3β, was also affected by NO_2 exposure, which may alter glycogen synthesis (Yan et al., 2016).

Both epidemiologic and animal toxicological evidence indicate that NO_2 exposure may alter glucose and insulin homeostasis, blood lipids, and adiposity, which are discussed in Sections 8.5, 8.6, and 8.7, respectively. Collectively, these perturbations constitute the core features of MetS, which is a known risk factor for T2D. T2D, in turn, can lead to many health complications, including death. The association of oxides of nitrogen exposure with MetS, T2D, and diabetes-related mortality is discussed in Sections 8.4, 8.3, and 8.8.1. Together, the proposed pathway supports the biological plausibility of the epidemiologic associations of metabolic effects and are used to inform causality determinations in this chapter.

8.11 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,[5] extrinsic,[6] 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, 2015a) 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 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 the 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 oxides of nitrogen exposure. Additionally, studies examining whether factors may result in differential exposure to oxides of nitrogen are included. Due to the limited amount of evidence available for short-term exposure to oxides

[5]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.
[6]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.

of nitrogen and metabolic effects, this discussion focused on long-term exposure studies only (see Table 8-1).

8.11.1 Long-term Exposure

8.11.1.1 Pre-existing Comorbidities

In the 2016 Oxides of Nitrogen ISA, a single toxicological study reported that obese OLETF rats were more sensitive to the effects of NO_2 exposure than normal weight controls, as evidenced by more pronounced changes in blood lipid levels (Takano et al., 2004). There were also a few epidemiologic studies that evaluated the potential for pre-existing comorbidities to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. There was no evidence of EMM by asthma, COPD, hypertension, or obesity for association between exposure to oxides of nitrogen and diabetes (Eze et al., 2014; Andersen et al., 2012). However, Andersen et al. (2012) did report elevated effects among participants with a high waist-to-hip ratio for the associations between NO_2 and diabetes. Among the recent epidemiologic evidence (as described in more detail below), pre-existing comorbidities (i.e., AMI, asthma, cancer, CHF, COPD, fasting glucose status, health status, hypertension, and obesity) were evaluated as potential modifiers for the associations between oxides of nitrogen and metabolic-related outcomes; however, the evidence is limited overall and inconsistent across studies. Overall, the collective evidence is inadequate to determine whether pre-existing comorbidities result in modification for the associations between exposure to oxides of nitrogen and metabolic-related effects.

AMI

In the 2016 Oxides of Nitrogen ISA, there were no studies that evaluated the potential for AMI to modify associations between exposure to oxides of nitrogen and metabolic-related effects. A single recent epidemiologic study reported elevated HRs among participants with no AMI for associations between oxides of nitrogen and diabetes (Bai et al., 2018).

Asthma

In the 2016 Oxides of Nitrogen ISA, a single epidemiologic study reported no evidence of EMM after evaluating the potential for asthma to modify the association between exposure to oxides of nitrogen and metabolic-related effects, specifically diabetes (Andersen et al., 2012). A single recent epidemiologic study reported no evidence of EMM by asthma for associations between oxides of nitrogen and diabetes (Bai et al., 2018).

Cancer

In the 2016 Oxides of Nitrogen ISA, there were no studies that evaluated the potential for cancer to modify associations between exposure to oxides of nitrogen and metabolic-related effects. A single

recent epidemiologic study reported no evidence of EMM by cancer for associations between oxides of nitrogen and diabetes (Bai et al., 2018).

CHF

In the 2016 Oxides of Nitrogen ISA, there were no studies that evaluated the potential for CHF to modify associations between exposure to oxides of nitrogen and metabolic-related effects. A single recent epidemiologic study reported no evidence of EMM by CHF for associations between oxides of nitrogen and diabetes (Bai et al., 2018).

COPD

In the 2016 Oxides of Nitrogen ISA, few epidemiologic studies reported no evidence of EMM after evaluating the potential for COPD to modify the association between exposure to oxides of nitrogen and metabolic-related effects, specifically diabetes (Eze et al., 2014; Andersen et al., 2012). A single recent epidemiologic study reported elevated HRs among participants with no COPD for the association between oxides of nitrogen and diabetes (Bai et al., 2018).

Fasting glucose status

In the 2016 Oxides of Nitrogen ISA, there were no studies that evaluated the potential for fasting glucose status to modify associations between exposure to oxides of nitrogen and metabolic-related effects. In a recent epidemiologic study among nondiabetic, postmenopausal women with and without impaired fasting glucose, Holliday et al. (2019) reported near-null associations between long-term exposures to NO_X and TG:HDL-C regardless of fasting glucose status.

Health Status

In the 2016 Oxides of Nitrogen ISA, there were no studies that evaluated the potential for health status to modify associations between exposure to oxides of nitrogen and metabolic-related effects. A single recent epidemiologic study reported evidence of modification by health status with participants self-reporting fair or poor/very poor health having stronger associations between long-term NO_2 exposure and fasting glucose (Liu et al., 2023). However, no evidence of EMM by health status was reported for associations between NO_2 exposure and Mets (Liu et al., 2023), blood lipid indicators (HDL-C and TG) (Liu et al., 2023), adiposity (central obesity) (Liu et al., 2023), or diabetes-related mortality (Lim et al., 2018).

Hypertension

In the 2016 Oxides of Nitrogen ISA, a single epidemiologic study reported no evidence of EMM after evaluating the potential for hypertension to modify the association between exposure to oxides of nitrogen and metabolic-related effects, specifically diabetes (Eze et al., 2014). A single recent epidemiologic study reported elevated HRs among participants with no hypertension for the association between oxides of nitrogen and diabetes (Bai et al., 2018). However, another recent epidemiological study reported minimal-

to-no evidence of EMM by hypertension for the association between oxides of nitrogen and diabetes (Coogan et al., 2016).

Obesity

In the 2016 Oxides of Nitrogen ISA, a single toxicological study in OLETF rats provided evidence that long-term NO_2 exposure had larger effects on dyslipidemia in obsess rats compared to nonobese rats (Takano et al., 2004). However, differences between obese and nonobese strains were limited to 160 ppb NO_2 and not observed at higher NO_2 exposures. There were also a few epidemiologic studies in the 2016 Oxides of Nitrogen ISA that evaluated the potential for metrics of obesity to modify associations between oxides of nitrogen and metabolic-related outcomes. Eze et al. (2014) and Andersen et al. (2012) reported no EMM by obesity for the associations between NO_2 and diabetes. However, Andersen et al. (2012) did report elevated effects among participants with a high waist-to-hip ratio for the associations between NO_2 and diabetes. In recent epidemiological studies, several studies evaluated EMM by obesity/BMI for associations between NO_2 and diabetes, MetS, blood lipids, or diabetes-related mortality (Nagrani et al., 2023; Shin and Kim, 2023; Kang et al., 2022; Zhang et al., 2021a; Gui et al., 2020; Strak et al., 2017; Coogan et al., 2016). Shin and Kim (2023) reported evidence of EMM by BMI with participants <23 kg/m^2 having elevated HRs of incident diabetes compared to participants with BMI ≥23 kg/m^2. However, no-to-minimal evidence of EMM by metrics of obesity (e.g., BMI, WC, WHR, WHtR, BRP, VFI) was reported for a few other studies with inconsistency for the direction of the weak modification across studies for associations between NO_2 and diabetes (i.e., Kang et al. (2022) no EMM, Coogan et al. (2016) elevated effects for lowest category of BMI, Strak et al. (2017) highest category of weight status had elevated effects) or prediabetes (i.e., Nagrani et al. (2023) lowest category of weight status had elevated effects). For metabolic-related outcomes other than diabetes, there was no evidence of EMM by weight status/BMI reported for associations between NO_2 exposure and MetS (Nagrani et al., 2023; Zhang et al., 2021a), blood lipids/dyslipidemia (Gui et al., 2020), or diabetes-related mortality (Lim et al., 2018).

8.11.1.2 Sociodemographic Factors

Education

In the 2016 Oxides of Nitrogen ISA, few epidemiologic studies evaluated the potential for education to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. Eze et al. (2014) and Andersen et al. (2012) reported no evidence of EMM by education for NO_2 exposure and diabetes. In recent epidemiological studies, minimal-to-no evidence of EMM by education for the association between NO_2 and diabetes was reported (Strak et al., 2017; Coogan et al., 2016).

Income

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for income to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. A single epidemiological study reported EMM by income for associations between NO_2 and cardiometabolic-related mortality, with elevated HR for participants within the bottom income quintile compared to the top income quintile (Crouse et al., 2015). However, other epidemiological studies reported minimal-to-no evidence of EMM by income for the associations between NO_2 and diabetes or diabetes-related mortality (Paul et al., 2020b; Strak et al., 2017).

Race/ethnicity

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for race/ethnicity to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. A few epidemiological studies evaluated EMM by race, ethnicity, or immigration status with inconsistent results. A single study reported some evidence of EMM by immigration status for the association between NO_2 and cardiometabolic mortality, with immigrants having elevated associations compared to non-immigrants or overall (Crouse et al., 2015). A single epidemiological study evaluated EMM by ethnicity for the association between NO_2 and MetS and insulin homeostasis using two metrics for the exposure (Letellier et al., 2022). However, there was no consistency for the pattern of EMM across exposure metric and outcome being evaluated. For example, elevated effects were reported for Hispanic participants for the dynamic NO_2 exposure and HOMA-IR, whereas attenuated effects were reported for Hispanic participants for the dynamic NO_2 exposure and MetS. However, the same pattern was not reported for the static NO_2 exposure and HOMA-IR or MetS. Other epidemiologic studies reported no evidence of EMM by race or ethnicity for the associations between NO_2 and adiposity (obesity), blood lipids (dyslipidemia), or diabetes-related mortality (Letellier et al., 2022; Lim et al., 2018).

SES

SES is a composite measure that usually consists of economic status measured by income, social status measured by education, and work status measured by occupation. In the 2016 Oxides of Nitrogen ISA, there were no studies available that evaluated the potential for SES to modify associations between exposure to oxides of nitrogen and metabolic-related effects. A single recent epidemiologic study investigated EMM by SES for the association between long-term NO2 exposure and T2D in a large cohort of African American women, authors reported minimal-to-no evidence of modification by neighborhood SES (Coogan et al., 2016).

Urbanicity

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for urbanicity to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. A single epidemiological study reported EMM by residential area urbanicity for associations between oxides of nitrogen and T2D, with participants within rural residential areas having higher HRs

than those within urban residential areas (Wu et al., 2022b). However, other epidemiological studies reported no evidence of EMM by urbanicity for the associations between NO_2 and diabetes or metabolic-related mortality (Gariazzo et al., 2023; Gandini et al., 2018).

Proximity to roadways

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for proximity to roadways to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. In recent epidemiological studies, a single study reported weak evidence of EMM by proximity to roadways for associations between NO_2 and prediabetes and MetS (Nagrani et al., 2023). The ORs were elevated for residential distance <250 meters to major road compared to ≥250 meters to major road for prediabetes; however, the opposite pattern was observed for MetS with the ORs elevated for ≥250 meters to major road.

8.11.1.3 Behavioral Factors

Behavioral and other factors, such as physical activity and smoking, may modify the association between exposure to oxides of nitrogen and metabolic-related effects. Overall, the collective evidence is inadequate to determine whether behavioral factors result in modification for the associations between exposure to oxides of nitrogen and metabolic-related effects.

Diet

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for diet to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. In recent epidemiological studies, serval evaluated EMM by indicators of diet (Hu et al., 2023; Shin and Kim, 2023; Wu et al., 2022b; Zhang et al., 2021a; Lim et al., 2018; Coogan et al., 2016). Few of these recent epidemiological studies reported evidence of EMM by indications of diet. For the association between annual NO_2 exposure and incident T2D, Hu et al. (2023) reported weak evidence of EMM for a healthy diet – with those without a healthy diet having a higher HR than those with a healthy diet; however, the HR for a healthy diet was imprecise. Shin and Kim (2023) reported associations between NO_2 concentrations and incident diabetes were stronger among participants with a lower dietary intake (quartile 1) of retinol, vitamin A, and cholesterol nutrients compared to those with a higher intake (quartile 4). Lim et al. (2018) reported that the strength of the NO_2-diabetes mortality association was greater in participants who consumed less than two and a half servings of fruits per day (HR: 1.17 [95% CI: 1.08, 1.27]), compared to those who consumed greater amounts (HR: 0.93 [95% CI: 0.79, 1.09]). However, several studies reported no-to-limited minimal EMM by indicators of diet for associations between oxides of nitrogen and metabolic-related outcomes. No EMM by healthy diet was reported for the association between oxides of nitrogen and T2D or complications from T2D (Wu et al., 2022b) as well as minimal-to-no EMM by a meat/fried food diet was reported for the association between NO_2 and T2D in a large cohort of African American women (Coogan et al., 2016). No EMM by sugar-sweet intake

was reported for the association between NO_2 exposure and MetS (Zhang et al., 2021a). The limited consistency across the indicators of diet and definitions of those indicators make it challenging to draw inference regarding EMM by diet.

Drinking Status

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for drinking alcohol to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. A single recent epidemiological study evaluated, but did not observe, EMM by drinking status for the associations between long-term NO_2 exposure and MetS, elevated fasting glucose, blood lipid indicators (HDL-C and TG), and central obesity (Liu et al., 2023).

Physical activity

In the 2016 Oxides of Nitrogen ISA, no epidemiologic studies evaluated the potential for physical activity to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. In recent epidemiological studies, several evaluated EMM by physical activity although results were inconsistent (Guo et al., 2022; Li et al., 2022 2016, 3359571; Wu et al., 2022b; Zhang et al., 2021a; Strak et al., 2017). A recent epidemiologic study reported evidence of EMM by physical activity for the association between NO_2 exposure and diabetes with participants that had higher levels of physical activity having elevated effects compared to those with lower levels of physical activity (Strak et al., 2017). In contrast, Wu et al. (2022b) reported EMM by physical activity for the association between NO_2 exposure and diabetes with participants that had low physical activity having elevated HRs compared to participants that had moderate or high physical activity. Guo et al. (2022) similarly reported elevated positive associations between NO_2 exposure and MetS among participants that were physically inactive. However, other recent epidemiological studies reported minimal-to-no evidence of EMM by physical activity for associations between NO_2 and T2D (Li et al., 2022; Coogan et al., 2016) as well as no evidence of EMM by outdoor physical activity time for associations between NO_2 and MetS (Zhang et al., 2021a).

Smoking Status

In the 2016 Oxides of Nitrogen ISA, few epidemiologic studies evaluated the potential for smoking to modify associations between exposure to oxides of nitrogen and metabolic-related outcomes. The effect of NO_2 was smaller among current or former smoking participants than never smoking participants for diabetes Andersen et al. (2012). Several recent epidemiological studies evaluated EMM by smoking status for the association between long-term NO_2 exposure and diabetes with inconsistent observations (Wu et al., 2022b; Strak et al., 2017; Coogan et al., 2016). Wu et al. (2022b) reported some evidence of EMM for smoking status with never smokers having the highest HRs compared to those that previously smoked or currently smoked. Whereas Strak et al. (2017) and Coogan et al. (2016) reported minimal-to-no evidence of EMM with smoking status. A single study reported no evidence of EMM by smoking history when evaluating the association between NO_2 exposure and diabetes-related mortality (Lim et al., 2018). For the association between NO_2 exposure and MetS, a single study investigated EMM

by smoking status; however, authors reported that evidence of EMM was sensitive to the selected MetS definition with no clear patterns (Eze et al., 2015).

Table 8-1 Summary of evidence for populations at increased risk of metabolic syndrome and diabetes from oxides of nitrogen exposure

	Key Evidence		Key References
Inadequate evidence			
Preexisting comorbidities	Diabetes: Limited evidence with elevated effect estimates reported for participants with no AMI	AMI	†Bai et al. (2018)
	Limited evidence with no reported EMM	Asthma	Andersen et al. (2012); †Bai et al. (2018)
	Limited evidence with no reported EMM	Cancer, CHF	†Bai et al. (2018)
	Limited evidence with inconsistent EMM (either no reported EMM or elevated effect estimates for participants with no COPD)	COPD	Eze et al. (2014); Andersen et al. (2012); †Bai et al. (2018); †Coogan et al. (2016)
	Limited evidence with inconsistent EMM (either no-to-minimal reported EMM or elevated effect estimates for participants with no hypertension)	Hypertension	Eze et al. (2014); Andersen et al. (2012); †Shin and Kim (2023); †Kang et al. (2022); †Coogan et al. (2016); †Strak et al. (2017); †Nagrani et al. (2023)
	Limited evidence with inconsistent EMM (either no-to-minimal reported EMM or EMM reported in opposite directions for strata of weight status)	Obesity/ weight status	
	MetS: Limited evidence with no reported EMM	Health status	†Liu et al. (2023); †Nagrani et al. (2023):
		Obesity/ weight status	†Zhang et al. (2021a)
	Glucose and Insulin Homeostasis: Limited evidence with participants self-reported worse health having elevated effects	Health status	†Liu et al. (2023)

	Key Evidence		Key References
	Blood lipids: Limited evidence with no reported EMM	Fasting glucose status Health status Obesity/ weight status	†Holliday et al. (2019) †Liu et al. (2023) †Gui et al. (2020)
	Adiposity and Weight Gain: Limited evidence with no reported EMM	Health status	†Liu et al. (2023) Takano et al. (2004)
	Limited toxicological support for stronger effects in an obese rat model.	---	
	Diabetes-related mortality: Limited evidence with no reported EMM	Health status, Obesity/ weight status	†Lim et al. (2018)
Sociodemographic factors	Diabetes: Limited evidence with minimal-to-no reported EMM	Education Income SES	Eze et al. (2014); Andersen et al. (2012); †Coogan et al. (2016); †Strak et al. (2017) †Strak et al. (2017) †Coogan et al. (2016) †Wu et al. (2022b); †Gandini et al. (2018) †Nagrani et al. (2023)
	Limited evidence with inconsistent EMM reported (no EMM or rural participants having elevated effects)	Urbanicity	
	Limited evidence with minimal reported EMM (elevated effects for participants residing closer to major roads)	Proximity to roadways	
	MetS: Limited evidence with inconsistently reported EMM (dependent on exposure metric)	Ethnicity	†Letellier et al. (2022) †Nagrani et al. (2023)
	Limited evidence with minimal reported EMM (elevated effects for participants residing further from major roads)	Proximity to roadways	

	Key Evidence		Key References
	Glucose and Insulin Homeostasis: Limited evidence with inconsistently reported EMM (dependent on exposure metric)	Ethnicity	†Letellier et al. (2022)
	Blood Lipids: Limited evidence with no reported EMM	Race/ethnicity	†Letellier et al. (2022)
	Adiposity and Weight Gain: Limited evidence with no reported EMM	Race/ethnicity	†Letellier et al. (2022)
	Diabetes-related Mortality: Limited evidence with no reported EMM	Income	†Paul et al. (2020b)
		Race/ethnicity	†Lim et al. (2018)
	Metabolic-related Mortality: Limited evidence with no reported EMM	Urbanicity	†Gariazzo et al. (2023)
	Cardiometabolic Mortality: Limited evidence with EMM reported (elevated effects for lowest quintile of income or immigrants)	Income, Race/ethnicity (Immigration status)	†Crouse et al. (2015)
Behavioral factors	Diabetes: Limited evidence with inconsistent EMM (either no-to-minimal reported EMM or stronger effect estimates for participants with less healthy diets/ reduced nutrient intake compared to participants overall)	Diet	†Hu et al. (2023); †Shin and Kim (2023); †Wu et al. (2022b); †Coogan et al. (2016)
			†Li et al. (2022); †Coogan et al. (2016); †Wu et al. (2022b); †Strak et al. (2017)
	Limited evidence with inconsistent EMM (minimal-to-no EMM reported, elevated effects among physically inactive participants, or elevated effects among the most physically active participants)	Physical activity	Andersen et al. (2012); †Wu et al. (2022b); †Coogan et al. (2016); †Strak et al. (2017)
	Limited evidence with inconsistent EMM (either no reported EMM or smaller effect estimates for current/former smoking participants than never smoking participants)	Smoking	

	Key Evidence		Key References
	MetS:		
	Limited evidence with no reported EMM	Diet	†Zhang et al. (2021a) †Liu et al. (2023)
	Limited evidence with no reported EMM	Drinking	†Zhang et al. (2021a); †Guo et al. (2022)
	Limited evidence with inconsistent EMM (either no EMM reported or elevated effects among physically inactive participants)	Physical activity	†Eze et al. (2015)
	Limited evidence sensitive to selected definition with no clear pattern	Smoking	
	Glucose and insulin homeostasis: Limited evidence with no reported EMM	Drinking	†Liu et al. (2023)
	Blood Lipids: Limited evidence with no reported EMM	Drinking	†Liu et al. (2023)
	Adiposity and weight gain: Limited evidence with no reported EMM	Drinking	†Liu et al. (2023)
	Diabetes-related mortality: Limited evidence of EMM reported (with elevated effects in participants who consumed less than two and a half servings of fruits per day)	Diet	†Lim et al. (2018)
	Limited evidence with no observed EMM	Smoking	†Lim et al. (2018)

List of abbreviations in alphabetical order: EMM = effect measure modification; GDM = gestational diabetes mellitus; T1D = Type 1 Diabetes.
†Studies published since the 2016 Oxides of Nitrogen ISA.

8.12 Summary and Causality Determination

8.12.1 Long-term Exposure

The 2016 Oxides of Nitrogen ISA did not include a chapter focused on Metabolic Syndrome and Diabetes. Instead, studies related to diabetes were discussed within the long-term exposure and Cardiovascular and Diabetes Section [see Section 6.3 in U.S. EPA (2016)]. The available evidence was determined to be suggestive of, but not sufficient to infer, a causal relationship between long-term oxides of nitrogen exposure and cardiovascular effects and diabetes. Epidemiologic evidence reviewed in the

previous ISA generally supported a positive association between long-term exposure to oxides of nitrogen (primarily NO_2 or NO_X) and diabetes mellitus. NO_2 exposure was additionally associated with factors underlying diabetes, including impaired glucose metabolism. Some studies found that associations with NO_2 exposure were robust to adjustment for noise and particulate matter ($PM_{2.5}$, PM_{10}), but overall, the evidence was limited and no studies adjusted for other traffic-related copollutants. There was limited toxicological evidence available to provide coherence with the effects seen in humans. Takano et al. (2004) found evidence of dyslipidemia (i.e., increased triglycerides and decreased HDL) in an obese rat model.

Given the expansion of PECOS-relevant epidemiologic studies since the 2016 Oxides of Nitrogen ISA, this chapter focused on metabolic-related effects, organized by health endpoints including diabetes, MetS, glucose and insulin homeostasis, blood lipids, adiposity and weight gain, other indicators of metabolic function, and cause-specific mortality. There continued to be limited PECOS-relevant controlled human exposure studies or PECOS-relevant toxicological studies, which were discussed within the glucose and insulin homeostasis or blood lipids sections.

Recent PECOS-relevant epidemiologic evidence continues to suggest a positive association, especially for NO_2. There have been several recent studies conducted in North America that predominantly observed positive associations between NO_2 and diabetes even though the studies varied in location, exposure assessment methods, and outcome ascertainment. Studies conducted in Asian countries also generally reported positive associations between NO_2 and diabetes regardless of location or specification of the outcome. Studies conducted in European countries generally reported positive associations between oxides of nitrogen and diabetes, although this was inconsistent depending on location, oxides of nitrogen, or specification of the outcome. Several studies investigating the association between oxides of nitrogen and diabetes also evaluated the shapes of concentration-response relationships across the distribution of estimated oxides of nitrogen exposures, primarily NO_2. Overall, for the association between NO_2 and diabetes, there was a general indication of an approximately linear, linear plateau/threshold, or supralinear concentration-response relationships reported. Several studies reported steeply linear concentration-responses at lower concentrations with a threshold at approximately 20 to 40 $\mu g/m^3$. A few studies also observed monotonic increases in associations when evaluating the association between categorically defined NO_2 concentrations and diabetes. Additionally, there is some evidence that associations between long-term exposure to NO_2 and diabetes is robust after copollutant adjustment (or associations that were attenuated remained positive), specifically when adjusting for O_3 or $PM_{2.5}$. However, NO_2 tended to be highly correlated with $PM_{2.5}$ so inference is limited when including this copollutant in the model. The evaluation of traffic-related copollutants were not widely investigated and results were inconsistent when evaluated.

While there were no epidemiologic studies evaluating oxides of nitrogen exposure and metabolic-related mortality (i.e., diabetes mortality, metabolic mortality, cardiometabolic mortality) in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), there were several recent studies that evaluated associations

between long-term exposure to NO_2 and metabolic-related mortality, primarily diabetes mortality. Overall, these studies consistently reported positive associations, although sometimes the 95% CI included the null. In the few studies that evaluated copollutant confounding, no consistent pattern emerged, with effect estimates often attenuated after copollutant adjustment. No PECOS-relevant animal toxicological studies were identified.

While there were no epidemiologic studies evaluating oxides of nitrogen exposure and MetS in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), there have been several recent PECOS-relevant epidemiologic studies, specifically for long-term exposure. However, this recent epidemiologic evidence is inconsistent (null to positive associations) across lifestage and geography (e.g., United States, China, Australia, Switzerland). A potentially large reason for the inconsistency is the variability in the outcome assessment for the studies (i.e., applied definition of MetS in the analyses). There was limited evaluation of concentration-response with a single study reporting no evidence of a concentration-response. Additionally, a few studies investigated the robustness of the results to copollutant or multipollutant adjustment. However, most studies observed attenuation to the null upon further adjustment for copollutants. No PECOS-relevant animal toxicological studies were identified.

Recent epidemiologic studies of NO_2 and NO_X exposure on glucose and insulin homeostasis have yielded inconsistent results, with many reporting no associations. These studies had limited consideration for confounding by copollutants (i.e., $PM_{2.5}$, O_3) or traffic-related noise. Additionally, there was limited evaluation of concentration-response or copollutant adjustment among epidemiologic studies evaluating the association between oxides of nitrogen and measures of glucose and insulin homeostasis. In contrast, the limited toxicological evidence provides some support that NO_2 exposures at high concentrations (≥2.5 ppm) cause insulin resistance and impaired glucose tolerance, particularly in female mice. The toxicological studies have not adequately assessed the effects of lower, environmentally relevant exposures to NO_2 and have not attempted to delineate a dose-response relationship. Overall, there is limited consistency and coherence across epidemiologic and toxicological studies of glucose and insulin homeostasis, and uncertainties remain regarding concentration-response relationships, effect measure modification, and confounding by traffic-related copollutants.

Several recent PECOS-relevant epidemiologic studies evaluated the association between long-term exposure to oxides of nitrogen and blood lipid conditions (e.g., dyslipidemia) and blood lipid biomarkers (e.g., TG, total cholesterol, LDL, HDL). The available evidence is inconsistent with a mixture of negative, null, and positive associations. Across the studies there were differences in the exposure estimation approaches, species of oxides of nitrogen evaluated, study geographies, and specific endpoint evaluated. There was limited evaluation of the shapes of concentration-response relationships among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids, with inconsistent results across studies. Additionally, there was limited evaluation of copollutant confounding among epidemiologic studies evaluating the association between oxides of nitrogen and measures of blood lipids. Limited controlled human exposure evidence suggests that NO_2 may increase

blood lipids in healthy adults. Similarly, for toxicological studies, limited evidence suggests that NO_2 exposure increases lipids and cholesterol in the blood and liver of mice and rats.

Several recent PECOS-relevant epidemiologic studies evaluated associations between long-term exposures to oxides of nitrogen and adiposity and weight gain. However, this recent epidemiologic evidence is inconsistent (inverse, null, or positive associations) across geography (e.g., United States, China, Europe). Additionally, there was limited evaluation of concentration-response relationships as well as evaluation of copollutant confounding among PECOS-relevant epidemiologic studies. No recent PECOS-relevant animal toxicological studies were identified for adiposity and weight gain.

Overall, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between long-term oxides of nitrogen exposure and metabolic effects and diabetes. The strongest evidence comes from epidemiologic studies within the United States reporting a generally consistent pattern of positive associations between exposure to NO_2 and diabetes (see Table 8-2). Among the epidemiologic studies, there remains uncertainty regarding the concentration-response relationship, potential differences across lifestages and populations, and the potential for copollutant confounding. However, for epidemiologic studies evaluating the association between long-term exposure to NO_2 and diabetes, a generally pattern of concentration-response was observed (i.e., steeply linear at lower concentrations with a threshold at approximately 20 to 40 $\mu g/m^3$ or monotonic increases in associations NO_2 concentrations were categorically defined). Additionally, associations between long-term exposures to NO_2 and diabetes were generally robust, or attenuated but remained positive, after copollutant adjustment for O_3 or $PM_{2.5}$. Animal toxicological studies provided some support for observations in epidemiologic studies, but coherence was limited overall. A small number of studies reported that NO_2 alters glucose and insulin homeostasis, increases triglycerides, and increases cholesterol.

Table 8-2 Summary of evidence contributing to causality determinations for long-term oxides of nitrogen exposure and metabolic syndrome and diabetes

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Generally consistent findings in epidemiologic studies of diabetes.	Positive associations within the U.S. studies, especially for NO_2.	†Yitshak Sade et al. (2023) †Honda et al. (2017) †Howell et al. (2019) †Bai et al. (2018) †Paul et al. (2020b) †Cervantes-Martinez et al. (2022) Section 8.3.1	Mean NO_2: 5.53 – 34.6 ppb

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
	Steeply linear concentration-responses at lower concentrations with a threshold at approximately 20-40 μg/m^3, or monotonic increases in associations NO_2 concentrations were categorically defined	†Yitshak Sade et al. (2023) †Kang et al. (2022) †Paul et al. (2020b) †Hu et al. (2023) †Wu et al. (2023) †Strak et al. (2017) †Cervantes-Martinez et al. (2022) †Bai et al. (2018) †Li et al. (2022) Section 8.3.1.1	Mean NO_2: 9.9 – 34.6 ppb Median NO_2: 8.0 – 21.1 ppb
	Associations were generally robust (or associations that were attenuated remained positive) after copollutant adjustment, specifically when adjusting for O_3 or $PM_{2.5}$	†Paul et al. (2020b) †Honda et al. (2017) †Cervantes-Martinez et al. (2022) †Sørensen et al. (2022b) †Bai et al. (2018) †Yitshak Sade et al. (2023) †Zhang et al. (2021b) †Shin and Kim (2023) †Strak et al. (2017) †Wu et al. (2022b) Section 8.3.1.3	Mean NO_2: 5.5 – 27.9 ppb Median NO_2: 8.0 – 34.6 ppb
Generally, consistent findings in epidemiologic studies of diabetes-related mortality.	Positive associations for NO_2	Section 8.8.1–8.8.3	Mean NO_2: 7.1 – 13.0 ppb Median NO_2: 10.4 – 20.5 ppb
Inconsistent findings from epidemiologic studies for MetS, glucose and insulin homeostasis, blood lipids, and adiposity and weight gain.	Lacking consistency across studies.	Section 8.4.1, Section 8.5.1, Section 8.6.1, Section 8.7.1	Mean NO_2: 5.53 – 34.6 ppb Median NO_2: 8.0 – 34.6 ppb
Animal toxicological studies provide some support for observations in epidemiologic studies, but coherence is limited overall	A small number of studies report that NO_2 alters glucose and insulin homeostasis, increases triglycerides, and increases cholesterol.	†Guo et al. (2023) †Yan et al. (2016) †Takano et al. (2004)	160 – 4,000 ppb NO_2
Biological plausibility derived from multiple lines of evidence		Section 8.10	

List of abbreviations in alphabetical order: MetS = metabolic syndrome; NO_2 = nitrogen dioxide; O_3 = ozone; ppb = parts per billion; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; μg/m^3 = micrograms per cubic meter.
[a]Based on application of the causality framework described in section 3.3.4 of volume 2 of the Integrated Review Plan for the Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (U.S. EPA, 2024).

[b]Describes the key evidence and provides references contributing to the causality determination. References to earlier sections indicate where the full body of evidence is described.
†Studies published since the 2016 Oxides of Nitrogen ISA.

8.12.2 Short-term Exposure

There were no epidemiologic or toxicological studies examining short-term exposure to oxides of nitrogen and metabolic syndrome or diabetes in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). Studies of short-term exposure to oxides of nitrogen and metabolic effects and diabetes remain limited. While there are limited controlled human exposure studies and animal toxicological studies, the existing evidence lacks coherence across these disciplines. The single controlled human exposure study results conflicts with the single toxicological study. The controlled human exposure study reported that a 2-hour 500 ppb NO_2 exposure with intermittent exercise increased total and HDL cholesterol 18 hours after exposure (Huang et al., 2012). In contrast, the single toxicological study in rodents reported decreased HDL cholesterol 24 hours after a 3-hour NO_2 exposure (Farraj et al., 2016). Numerous uncertainties persist regarding concentration-response relationships, copollutant confounding, and biological plausibility.

The majority of the limited short-term exposure evidence comes from epidemiologic studies (see Table 8-3). There were no PECOS-relevant epidemiologic studies examining short-term exposure to oxides of nitrogen and diabetes or MetS. However, there were limited PECOS-relevant epidemiologic studies examining short-term exposure to oxides of nitrogen glucose and insulin homeostasis, blood lipids, and cause-specific mortality. The evidence for markers of glucose metabolism were generally null with some indication of inverse associations. A few recent studies evaluated associations between short-term exposures to oxides of nitrogen and blood lipids; however, the reported results were generally null across the studies with minimal evidence of associations. A single epidemiologic study reported an increased risk of metabolic mortality following short-term exposure to NO_2. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between short-term oxides of nitrogen exposure and metabolic effects and diabetes.**

Table 8-3 Summary of evidence contributing to causality determinations for short-term oxides of nitrogen exposure and metabolic syndrome and diabetes

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Inconsistent findings in epidemiologic studies for glucose and insulin homeostasis, blood lipids, adiposity and weight gain, and cause-specific mortality.	The evidence for markers of glucose metabolism were generally null with some indication of inverse associations.	Section 8.5.1	Median NO_2: 7.3 – 7.9 ppb Mean NO_X: 40.5 ppb Median NO_X: 14.6 – 31.5 ppb
	The evidence for blood lipids was generally null with minimal evidence of associations.	Section 8.6.1	Mean NO_2: 5.3 ppb Median NO_2: 7.3 – 7.9 ppb Mean NO_X: 40.5 ppb Median NO_X: 14.6 – 17.1 ppb
	Evidence is limited for diabetes or metabolic-related mortality. A single study reported an increased risk of metabolic mortality.	†Gariazzo et al. (2023) Section 8.8.1, 8.8.2	Means across studies: 6.3 – 15.8 ppb NO_2
Limited evidence from a controlled human exposure study.	A single study reported increased total and HDL cholesterol following a 2-hour NO_2 exposure.	Huang et al. (2012)	500 ppb NO_2
Limited coherence from toxicological evidence.	A single study in rodents reported decreased HDL cholesterol following a 3-hour NO_2 exposure.	Farraj et al. (2016)	500 ppb NO_2

List of abbreviations in alphabetical order: HDL = high-density lipoprotein; NO_2 = nitrogen dioxide; ppb = parts per billion.
[a]Based on application of the causality framework described in section 3.3.4 of volume 2 of the Integrated Review Plan for the Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (U.S. EPA, 2024).
[b]Describes the key evidence and provides references contributing to the causality determination. References to earlier sections indicate where the full body of evidence is described.

8.13 References

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