EPA/600/R-25/232
July 2026
www.epa.gov/isa

Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 10: Total Mortality – Short-Term Exposure

External Review Draft

July 2026

U.S. Environmental Protection Agency

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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

AQCD	Air Quality Criteria Document	NO	nitric oxide
avg	average	NO_2	nitrogen dioxide
BC	black carbon	NO_X	NO_2 + NO
CI	confidence interval	NR	not reported
CHD	Congenital Heart Disease	O_3	ozone
CO	carbon monoxide	OR	odds ratio
COPD	chronic obstructive pulmonary disease	P10	10^{th} percentile
		P25	25^{th} percentile
C-R	concentration-response	P5	5^{th} percentile
d	day(s)	P75	75^{th} percentile
e.g.	exempli gratia (for example)	P95	95^{th} percentile
EC	elemental carbon	PECOS	Population, Exposure, Comparison, Outcome, and Study Design
ED	emergency department		
EPA	U.S. Environmental Protection Agency	PM	particulate matter
ERR	excess relative risk	PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm
etc.	et cetera		
F	female(s)		
g	gram(s)	$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm
HDI	high density interval		
hr	hour(s)	ppb	parts per billion
HR	hazard ratio	ppm	parts per million
i.e.	id est (that is)	RR	relative risk or risk ratio
IHD	ischemic heart disease	SD	standard deviation
IQR	interquartile range	SE	standard error
ISA	Integrated Science Assessment	SES	socioeconomic status
L	liter(s)	SO_2	sulfur dioxide
LPM	linear probability model	U.K.	United Kingdom
LUR	land use regression	U.S.	United States
M	male	UFP	ultra fine particles
m	milligram	vs.	versus
m	meter(s)	VOC	volatile organic compounds
Max	maximum	WLS	weighted least squares
MI	myocardial infarction	wk	week(s)
Min	minimum	YLL	years of life lost
min	minute(s)	yr	year(s)
mL	milliliter	μg	microgram
mo	month(s)	β	beta
moonRF	m-out-of-n random forest	$\mu g/m^3$	micrograms per cubic meter
n	sample size	μm	micrometer
N	population size	ρ	rho
NA	not applicable		

CHAPTER 10 Total Mortality – Short-Term Exposure

Summary of Causality Determination for Short-Term Oxides of Nitrogen Exposure and Total Mortality

This chapter characterizes the scientific evidence that supports the causality determination for short-term oxides of nitrogen exposure and total mortality. 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 the Volume 2 of the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (U.S. EPA, 2024), which builds on the approach described in the 2015 Preamble to the Integrated Science Assessments (U.S. EPA, 2015a). The evidence presented throughout this chapter supports the following causality conclusion(s):

Outcome	Causality Determination
Total Mortality	Suggestive of, but not sufficient to infer, a causal relationship

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

10.1 Introduction

10.1.1 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) issued a causality determination for the effects of short-term oxides of nitrogen exposure and mortality (U.S. EPA, 2016). Multicity epidemiologic studies reviewed in the 2016 Oxides of Nitrogen ISA reported consistently positive associations between short-term nitrogen dioxide (NO_2) exposures and mortality. These studies examined the influence of the extent of temporal adjustment on NO_2-mortality risk estimates and reported similar results across a range of degrees of freedom per year. However, inference was limited by uncertainty as to whether short-term exposure to NO_2 is independently associated with

total mortality. Epidemiologic studies consistently demonstrated that the NO_2-mortality association is robust in copollutant models with particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm (PM_{10}), ozone (O_3), or sulfur dioxide (SO_2). However, NO_2 is often highly correlated with certain other traffic-related pollutants (e.g., carbon monoxide [CO], elemental carbon/black carbon [EC/BC], volatile organic compounds [VOC]), which were not examined in copollutant models, complicating the ability to disentangle the independent effects of NO_2 from those of other measured or unmeasured pollutants associated with traffic, adding uncertainty to the interpretation of the association between NO_2 and total mortality. In addition to copollutant models, studies examined the influence of the extent of temporal adjustment on NO_2-mortality risk estimates and reported similar results across a range of degrees of freedom per year.

At the time of the publication of the 2016 Oxides of Nitrogen ISA, the biological mechanisms that could lead to mortality as a result of short-term NO_2 exposures had not been clearly characterized. This was evident when evaluating the underlying health effects (i.e., cardiovascular effects and respiratory effects) that could lead to cardiovascular (~35% of total mortality) and respiratory (~9% of total mortality) mortality, the contributors to total mortality that had been most thoroughly evaluated.

Epidemiologic studies that examined the relationship between short-term NO_2 exposure and cardiovascular effects found consistent evidence for myocardial infarction, but epidemiologic and experimental evidence for other cardiovascular endpoints were inconclusive. Important uncertainties remained especially in disentangling whether there is an independent effect of NO_2 exposure on cardiovascular effects, given the potential for high correlations between NO_2 and other traffic-related pollutants. Overall, this evidence provided limited coherence and biological plausibility for NO_2-related cardiovascular mortality. For respiratory effects, there was strong support for NO_2-related asthma exacerbation supported by controlled human exposure studies demonstrating increased airway responsiveness in response to short-term NO_2 exposures, as well as epidemiologic studies reporting associations with asthma-related hospital admissions, emergency department (ED) visits, and asthma related symptoms. However, asthma exacerbation is a relatively small contributor to mortality, and the biological mechanisms that could explain the continuum of effects from short-term NO_2 exposures to respiratory-related mortality remained unclear. The 2016 Oxides of Nitrogen ISA concluded that inference from the consistently positive associations observed across various multicity studies was limited by the uncertainty as to whether NO_2 is independently associated with total mortality as well as the uncertainty in the biological mechanism that could lead to NO_2-induced mortality. Thus, the evidence was determined to be suggestive of, but not sufficient to infer, a causal relationship between short-term NO_2 exposure and total mortality.

10.1.2 Chapter Organization and Conventions

This chapter evaluates recent evidence examining the relationship between short-term oxides of nitrogen exposure and total mortality. Its conclusions are drawn from integration of the full body of evidence available in the 2016 Oxides of Nitrogen ISA and the evidence that has become available since the previous ISA. The following sections provide an overview of study inclusion criteria for this chapter (see Section 10.2), summaries of recent evidence (see Sections 10.3 to 10.4), a discussion of biological plausibility (see Section 10.5), a summary of lifestages and population differences (see Section 10.6, Table 10-1), and a discussion of the causality determination for short-term oxides of nitrogen exposure and total mortality (see Section 10.7, Table 10-2). Evidence inventories include study-specific details for the epidemiologic and toxicological studies including, for example, study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are located in Appendix A – Appendix Tables.

10.1.2.1 Epidemiologic Studies

In sections assessing the epidemiologic evidence, this chapter summarizes the evidence from previous ISAs and from recent studies that have become available since the last ISA. When relevant information is available from epidemiologic studies, this chapter additionally includes targeted discussion of concentration-response relationships, effects in particular lifestages and populations, the potential for confounding by copollutants, and other policy-relevant issues.

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

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

To increase 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, 8-hour maximum, or 1-hour maximum were examined in some studies, 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.

Some epidemiologic studies reported effect estimates in terms of micrograms per cubic meter ($\mu g/m^3$) 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 $\mu g/m^3$ at a national scale for the United States or other countries. Therefore, the ISA presents effect estimates based on $\mu g/m^3$ of NO_X as they are reported in their respective studies.

10.2 Scope

The evidence that has become available since the 2016 Oxides of Nitrogen ISA is 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

[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.

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 demonstrate the biological plausibility of oxides of nitrogen associated total mortality, recent studies were only included if they meet all components of the discipline-specific PECOS statements (see below) and satisfy discipline-specific study quality criteria (see Chapter 14).

Short-term Epidemiologic Studies:

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

Exposure: Short-term exposure (less than 30 days) to relevant concentrations of oxides of nitrogen.

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

Outcome: Change in risk (incidence/prevalence) of total mortality effects.

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

10.3 Total (Nonaccidental) Mortality

Since the completion of the 2016 Oxides of Nitrogen ISA, the body of epidemiologic literature that has examined the association between short-term exposure to oxides of nitrogen and mortality has grown. In contrast to the 2016 Oxides of Nitrogen ISA, an increasing number of studies have focused specifically on the associations between short-term exposure to oxides of nitrogen and total mortality. Of

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

the studies identified for inclusion, the majority have been conducted in the United States, Canada, and Europe, with fewer conducted in Asia and other regions.

10.3.1 Total Mortality

The evidence from the 2016 Oxides of Nitrogen ISA indicated consistently positive associations between short-term exposure to oxides of nitrogen, primarily NO_2, and total mortality. Collectively, the evidence from the multicity studies of short-term NO_2 exposures and mortality consistently demonstrated the NO_2-mortality association is robust in copollutant models with PM_{10}, O_3, or SO_2. However, NO_2 is often highly correlated with other traffic-related pollutants, complicating the ability to disentangle the independent effects of NO_2 from those of other measured or unmeasured pollutants associated with traffic, adding uncertainty to the interpretation of the association between NO_2 and total mortality. Furthermore, examination of lifestages and populations indicated that older adults (≥65 years of age), females, individuals with pre-existing cardiovascular or respiratory diseases, and individuals of lower socioeconomic status (SES), specifically lower income and educational attainment, are at greater risk. Studies that examined whether there are seasonal differences in the NO_2-mortality relationship consistently observed greater effects in the warm or summer months in multicity studies conducted in Canada and Europe. However, these results are contradicted by a study conducted in Asia where larger effects were observed in the cold season. These between-study differences in seasonal associations are more than likely a reflection of the different seasonal weather patterns observed between countries.

Several recent studies provide additional, generally consistent support for a positive association between short-term NO_2 exposure and total (nonaccidental) mortality. Recent studies expand the geographic coverage of the evidence base, including a global analysis of mortalities recorded in 398 cities across 16 countries, as well as nationwide and multicity studies conducted in North America, Europe, and Asia. A short, bulleted summary of the recent evidence is provided below, followed by additional discussion of concentration-response relationships in these studies (see Section 10.3.1.1), effects at low concentrations (see Section 10.3.1.2), exposure assessment approaches (see Section 10.3.1.3), lag structure of associations (see Section 10.3.1.4), the lifestages and populations evaluated (see Section 10.3.1.5), potential impacts of copollutants (see Section 10.3.1.6), alternative methods for confounder control (see Section 10.3.1.7), and potential seasonal differences in associations (see Section 10.3.1.8).

- Recent multicity studies in the United States. (Liu et al., 2022; Wei et al., 2021; Schwartz et al., 2018; Schwartz et al., 2017), Canada (Huang et al., 2023), Europe (Corso et al., 2020; Perez et al., 2015), and China (Li et al., 2021; Zhao et al., 2021; Chen et al., 2018), as well as a global analysis of mortality records from 16 countries (Meng et al., 2021), provide evidence of a positive association between short-term NO_2 exposure and total (nonaccidental) mortality (see Appendix A – Appendix Table 10-1). The majority of recent studies used a 24-hour averaging time for NO_2 concentrations, though Liu et al. (2022) and Huang et al. (2023) used 1-hour max and 3-hour max concentrations, respectively.

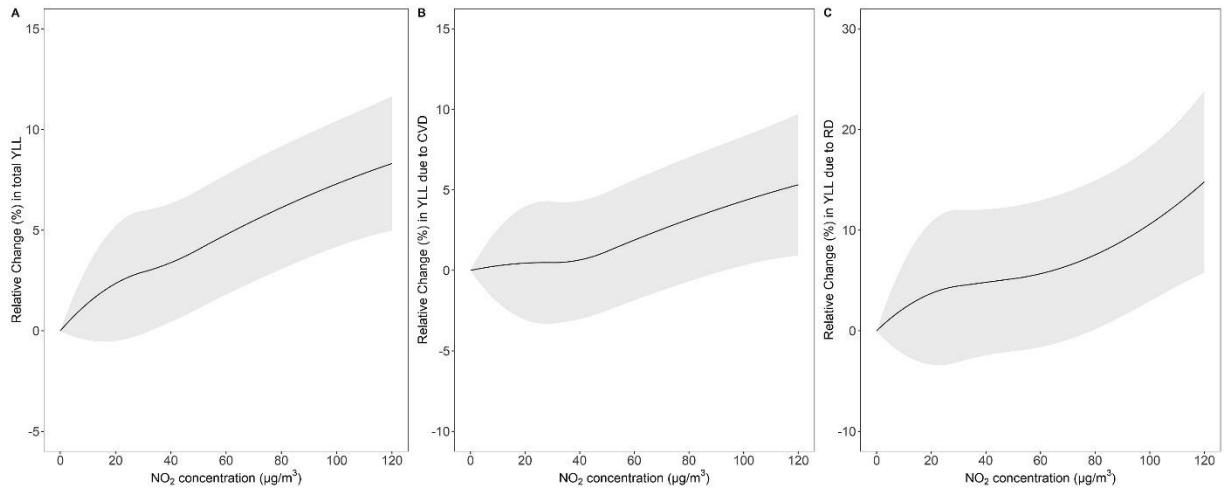
- Studies providing the strongest inference include a U.S. study with state-wide mortality data from seven states (Liu et al., 2022) and a global analysis of mortality and air pollution data from over 360 cities (Meng et al., 2021). In addition to including a large representative sample of the U.S. population, Liu et al. (2022) assigned NO_2 exposure using a high resolution (i.e., 1 km x 1 km) hybrid prediction model with a high out-of-sample predicted R^2 (0.79) and used negative exposure controls to assess the potential for unmeasured confounders (see Section 10.3.1.7). The authors reported positive associations between lag 0–2 1-hour max NO_2 concentrations and all-cause mortality in a traditional case-crossover analysis as well as in a two-stage model adjusting for negative exposure and outcome controls. Meng et al. (2021) used central site monitors to estimate the NO_2-respiratory mortality relationship using data from over 360 cities in the Multi-Country Multi-City Collaborative Research Network database, pooling effect estimates across cities to the country and global level. For the global pooled estimate, Meng et al. (2021) reported an overall increase in total mortality of 1.74% (95% CI: 1.34, 2.14) for every 20 ppb increase in previous day NO_2 concentrations. The authors also observed an increase in NO_2-related mortality risk in each of the 16 countries examined.
- While most recent studies employ traditional study designs and methods to assess the relationship between short-term NO_2 exposure and mortality, a few recent studies have utilized more novel methods to account for potential bias due to confounding (see Section 10.3.1.7). These alternative methods for confounder control include instrumental variables (Schwartz et al., 2018; Schwartz et al., 2017), negative exposure controls (Liu et al., 2022; Schwartz et al., 2018), negative outcome controls (Liu et al., 2022), and generalized propensity scores (GPS) (Wei et al., 2021; Schwartz et al., 2018; Schwartz et al., 2017). Across these studies, which are discussed in more detail in Section 10.3.1.7, short-term NO_2 exposures were consistently associated with increased risk of total mortality. The consistency of results from these novel methods with results from studies using more traditional methods adds further support for an association between short-term NO_2 exposure and mortality that is independent of measured and unmeasured confounders, except for highly correlated copollutants. Given the limitations inherent to disentangling effects of highly correlated covariates in both traditional and alternative approaches to confounder control, notable uncertainties remain regarding potential copollutant confounding, particularly concerning highly correlated traffic-related pollutants (see Section 10.3.1.6).
- Although most recent studies reported positive associations (see Appendix A – Appendix Table 10-1), a recent study in Italy (Gariazzo et al., 2023) and a multi-country study in Europe (Lanzinger et al., 2016) reported negative and null results, respectively. Additionally, a nationwide time series study in Canada reported inconsistent results in models stratified by sex and season [(Shin et al., 2022); Section 10.3.1.8]. Whereas most studies in this chapter estimated NO_2 exposures using central site monitors, Gariazzo et al. (2023) used a hybrid exposure model to estimate NO_2 at a finer spatial resolution (see Section 10.3.1.3).

Overall, recent studies generally demonstrate positive associations between short-term exposure to oxides of nitrogen and increased risk of total (nonaccidental) mortality. Subsequent sections (i.e., Sections 10.3.1.1 to 10.3.1.8) discuss, in more detail, analyses from these studies that provide further context for the conclusions of this chapter.

10.3.1.1 Concentration-Response

In the 2016 Oxides of Nitrogen ISA, multicity studies examined the shape of the concentration-response (C-R) relationship and whether a threshold exists in both a multi- and single-city setting. These studies used different statistical approaches and consistently demonstrated a linear relationship with no evidence of a threshold within the range of NO_2 concentrations currently found in the United States.

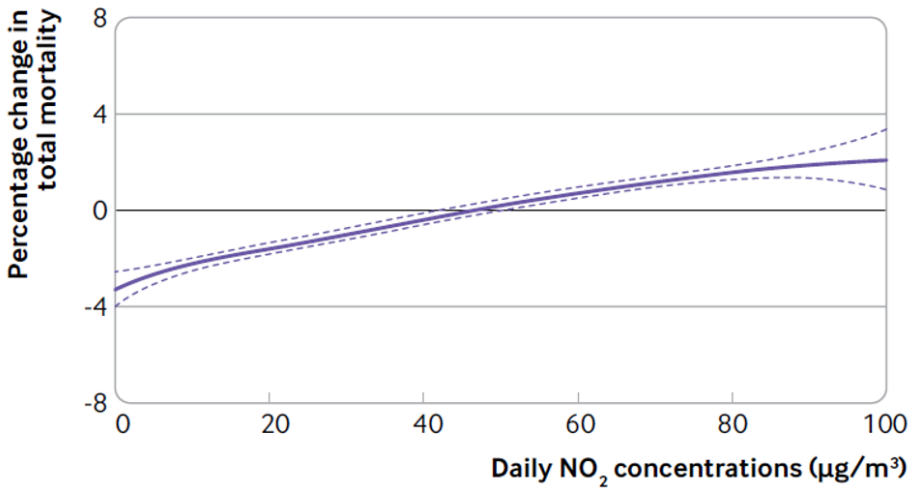
In the recent epidemiologic studies, the evidence is limited overall but findings are similar to those in the 2016 Oxides of Nitrogen ISA. The few studies that examined C-R relationships report a generally linear relationship between short-term NO_2 exposure and total mortality (Li et al., 2021; Meng et al., 2021; Zhao et al., 2021). More specifically, Li et al. (2021) evaluated the C-R relationship between lag days 0–1 and years of life lost (YLL) in 48 cities in China by using B-spline with two knots and then estimated the pooled C-R relationship with multivariate meta-analysis (see Figure 10-1). Results indicate generally linear relationships with total YLL and with YLL due to cardiovascular or respiratory disease.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; CVD = cardiovascular diseases; RD = respiratory diseases; YLL = years life lost; $\mu g/m^3$ = micrograms per cubic meter.
Notes: The upper and lower gray areas show the 95% confidence interval. Total, nonaccidental causes.
Source: Li et al. (2021). Copyright permission pending.

Figure 10-1 Pooled concentration-response curves for associations of nitrogen dioxide concentrations at lag 0–1 day with daily years life lost in 48 major cities, China, 2013 to 2017

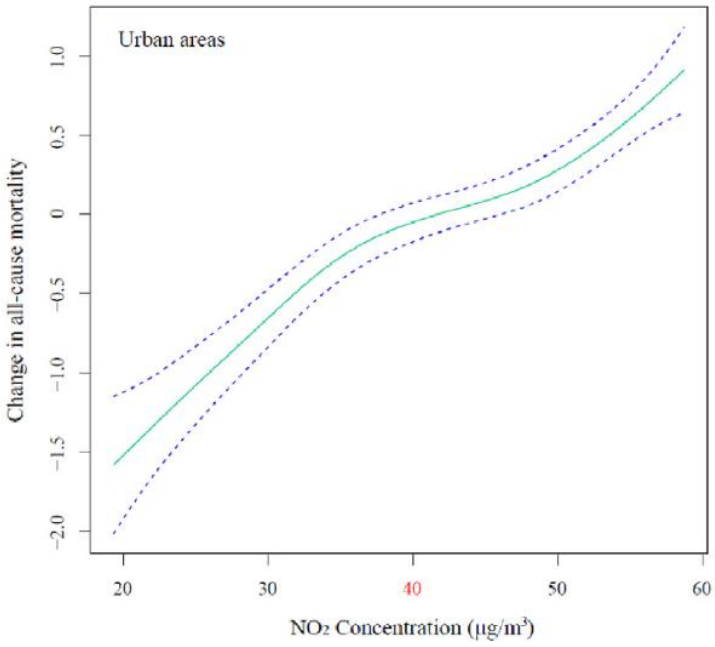
Meng et al. (2021) report C-R curves for the relative change of the mean effect of NO_2 on total mortality (see Figure 10-2). The association between estimated NO_2 and total mortality indicates a positive and approximately linear C-R curve, without a discernible threshold.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; µg/m^3 = micrograms per cubic meter.
Note: The vertical scale can be interpreted as the relative change of the mean effect of NO_2 on mortality; the fraction of the curve below zero denotes a smaller estimate than the mean effect.
Source: Adapted from Meng et al. (2021). Copyright permission pending.

Figure 10-2 Concentration-response curve between nitrogen dioxide concentrations (lag 1) and total mortality

Lastly, Zhao et al. (2021) estimated the C-R relationship for the change in NO_2-associated mortality by fitting generalized additive models (the C-R curves were adjusted with all the covariates). Across the range of estimated NO_2 concentrations, there was an approximately linear shape (see Figure 10-3).

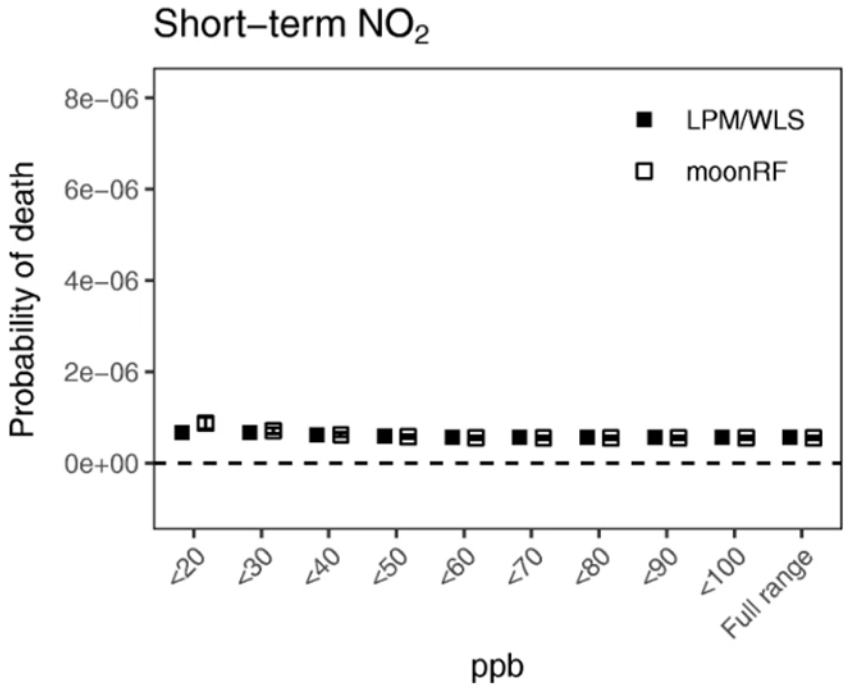


List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; $\mu g/m^3$ = micrograms per cubic meter.
Note: The green line represents the C-R curve and the blue lines show pointwise 95% CIs.
Source: Zhao et al. (2021). Copyright permission pending.

Figure 10-3 C-R curve of nitrogen dioxide and change in total (all-cause) mortality in urban areas in China

10.3.1.2 Low Exposure Analyses

In addition to studies that use flexible splines to examine the shape of the concentration-response relationship across the entirety of the concentration distribution, a recent study utilized restricted analyses to assess the association between short-term NO_2 exposure and total mortality below increasingly stringent concentration cut points (Wei et al., 2021). In this study of Medicare beneficiaries in Massachusetts, the magnitude of the observed association in the full population was comparable to the associations in each of the low exposure subsets ranging from <100 ppb to <20 ppb in 10 ppb increments (see Figure 10-4). Notably, the median, 95th percentile, and maximum 24-hour average NO_2 concentrations in this study were 19.2, 35.0, and 64.6 ppb, respectively. As a result, there are no differences between the full study population and the population subsets with concentration cut points down to <70 ppb, and only minimal differences are present in the subsets with concentration cut points down to <40 ppb.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; LPM = linear probability model; moonRF = m-out-of-n random forests; ppb = parts per billion; WLS = weighted least squares.
Note: "Full range" indicates the analysis was performed on the full dataset.
Source: Adapted from Wei et al. (2021). Copyright permission pending.

Figure 10-4 Probabilities of death (and 95% CIs) attributable to a 1 ppb increase in nitrogen dioxide at concentrations below increasingly stringent cut points

10.3.1.3 Evaluation of Exposure Assessment Techniques

An important uncertainty in air pollution epidemiology is the potential for exposure measurement error resulting from the various methods used to estimate exposure. Chapter 2 provides a thorough discussion of the bias resulting from exposure assessment methods common to the epidemiologic literature and their impact on the inferences that can be drawn about health effects. In the 2016 Oxides of Nitrogen ISA, all the epidemiologic studies examining the relationship between short-term NO_2 exposure and total (nonaccidental) mortality used fixed or central-site monitors to assign exposure. These exposure surrogates included single monitors and unweighted or population-weighted averages of multiple monitors. The use of central site monitors in time-series and case-crossover studies is likely to bias effect estimates toward the null and reduce precision (Chapter 2) and is unlikely to explain the consistent positive associations reported across studies in the 2016 Oxides of Nitrogen ISA.

Similar to studies from the 2016 Oxides of Nitrogen ISA, recent studies mostly use central site monitors to provide a surrogate for NO_2 exposure. This is common for time-series and case-crossover studies, which tend to rely on temporal variability in exposure, rather than spatial variability, to assess health effects. However, given the potential for finer scale spatiotemporal variation than is captured solely

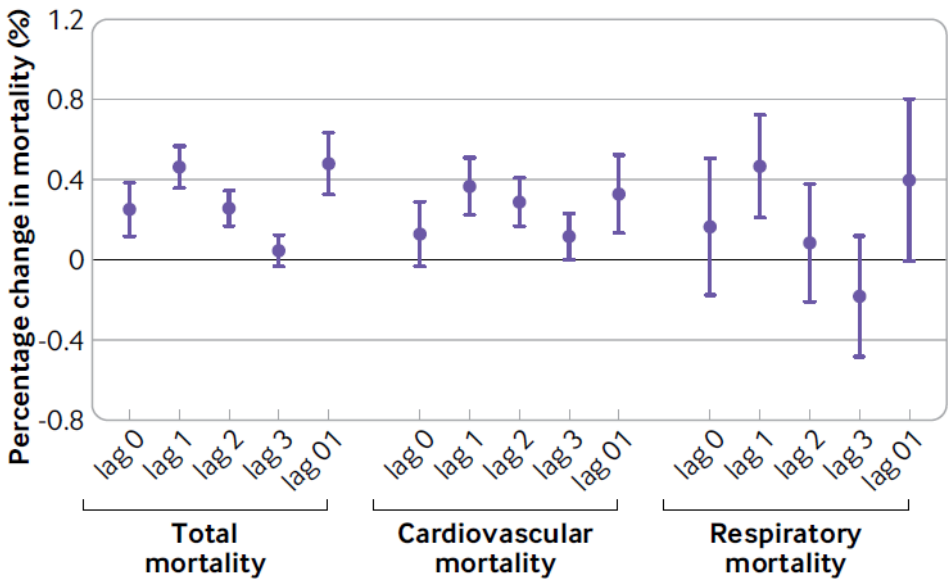
by air quality monitors, some recent studies have assigned exposure using hybrid prediction models that incorporate satellite observations, chemical transport models, and spatiotemporal data in addition to monitoring data (Gariazzo et al., 2023; Liu et al., 2022; Wei et al., 2021). In each study, models were used to estimate exposures at a fine spatial scale (i.e., 1-km^2 grid cells) and the resulting exposure grids were aggregated to larger spatial domains. Wei et al. (2021) and Liu et al. (2022) used unweighted averages to aggregate exposure to ZIP Codes of residence in Massachusetts, U.S., or 12-km grid cells across seven U.S. states, respectively, whereas Gariazzo et al. (2023) used population-weighted averages to aggregate exposure to the municipal level across the entirety of Italy. Because Wei et al. (2021) and Liu et al. (2022) employed novel model specifications to control for potential confounders (see Section 10.3.1.7), the magnitudes of the observed effect estimates are not directly comparable to the magnitudes of the effect estimates from the monitor-based studies in the United States. However, consistent with the monitor-based studies, Wei et al. (2021) and Liu et al. (2022) reported positive associations between short-term NO_2 exposure and all-cause mortality. In contrast, Gariazzo et al. (2023) reported an inverse association between model-predicted short-term NO_2 concentrations and total mortality in Italy. Notably, cross-validation indicated better predictive performance for the model used in the U.S. studies ($R^2 = 0.79$) (Liu et al., 2022; Wei et al., 2021) relative to the model used in the nationwide study in Italy ($R^2 = 0.6$) (Gariazzo et al., 2023).

In summary, a few recent studies employed more spatially refined exposure assessment methods to better account for the spatiotemporal variation in NO_2 concentrations. Study results were generally consistent with results from studies assigning exposure from central site monitors. Together, the pattern of consistent positive associations observed across studies reduces the likelihood that the findings are due to exposure measurement error.

10.3.1.4 Lag Structure of Associations

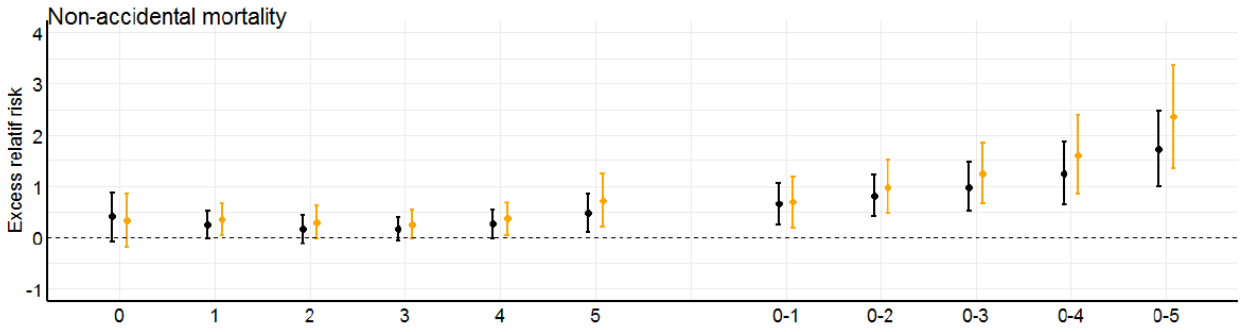
The 2016 Oxides of Nitrogen ISA found consistent evidence across studies indicating that positive NO_2-mortality associations were observed for immediate single-day lags (i.e., 0 to 1 days) as well as cumulative lags indicative of prolonged effects (U.S. EPA, 2016). Many recent studies of total (nonaccidental) mortality defined lags a priori as multiday averages of 0-1 or 0-2 days, as informed by previous studies described in the 2016 Oxides of Nitrogen ISA. A few recent studies examined the impact of different lag structures on the association between short-term NO_2 exposure and total mortality. Recent studies that considered lag structure of associations focused on a small number of lags ranging from 0 to 5 days. These studies included a global analysis of respiratory mortality and air pollution data from 362 cities (Meng et al., 2021), a large time-series analysis of mortality in Canada (Shin et al., 2022), and a time series analysis of 18 cities in France (Corso et al., 2020). Recent studies are somewhat inconsistent, with a couple of studies indicating more immediate effects of short-term NO_2 exposure (Shin et al., 2022; Meng et al., 2021), and another indicating prolonged effects up to five days (Corso et al., 2020).

- Meng et al. (2021) observed mostly positive associations between NO_2 exposure and total or cause-specific mortality across single day lags ranging from 0 to 3 days, as well as the moving average of NO_2 concentrations on the same day and previous day (i.e., lag 0–1; see Figure 10-5). The magnitudes of effect estimates were larger at earlier single day lags (i.e., lags 0 through 2) compared to lag 3, and the strongest associations were observed at lags 1 and 0-1.
- Shin et al. (2022) stratified models of short-term NO_2 exposure and total mortality by season and sex. While inverse associations were reported in the year-round analyses for males and females, the authors noted larger increases in total mortality risk for males and females in the warm season associated with higher same-day (i.e., lag 0) NO_2 concentrations compared to lag 1 and lag 2 exposures.
- In contrast to results from Meng et al. (2021) and Shin et al. (2022) that suggest a stronger immediate effect of NO_2 concentrations on mortality, Corso et al. (2020) observed comparable positive associations between NO_2 and non-accidental mortality across single day lags ranging from 0 to 5 days (see Figure 10-6). Additionally, the authors reported stronger associations with cumulative NO_2 exposure, with lag 0–5 resulting in the strongest effect estimates (Corso et al., 2020).
- Lanzinger et al. (2016) and Gariazzo et al. (2023) also evaluated multiple lags, but neither study observed strong evidence of a positive association across single-day or cumulative lags ranging from 0 to 5 days.



Note: Lags indicate the time difference between the NO_2 exposure and the outcome. Lag 0 = the present day; lag 1 = the previous day; lag 2 = the day before lag 1; lag 3 = the day before lag 2; lag 0–1 = the two-day moving average of the present day and the previous day
Source: Adapted from Meng et al. (2021).Copyright permission pending.

Figure 10-5 Relative risks of total, cardiovascular, and respiratory mortality associated with a 10 µg/m³ increase in nitrogen dioxide on different lag days for nitrogen dioxide



Note: black effect estimates and 95% confidence intervals represent results from entire study population; orange effect estimates and 95% confidence intervals represent results for those aged 75 years and over.
Source: Adapted from Corso et al. (2020). Copyright permission pending.

Figure 10-6 Excess relative risk and 95% confidence intervals for non-accidental deaths associated with a 5.31 ppb increase of nitrogen dioxide concentrations in single pollutant models (18 areas, metropolitan France, 2010 to 2014)

10.3.1.5 Lifestages and Populations

In the 2016 Oxides of Nitrogen ISA, there was a limited number of studies that examined potential effect measure modifiers of the oxides of nitrogen and mortality relationship. There was limited evidence that reported associations of short-term exposure to NO_2 with total mortality in most studies were larger in adults ages 65 or older than in younger adults, with evidence pointing to elevated risk among the oldest adults ages greater than 75 or 85 years (U.S. EPA, 2016). Overall, in the recent evidence, there were a limited number of studies that evaluated potential differences among lifestages and populations in the associations between short-term exposure to oxides of nitrogen and total mortality.

Lifestages

Among the recent epidemiologic studies, there were only a few studies that evaluated the effect of lifestage on the associations between short-term exposure to NO_2 and total mortality (Huang et al., 2023; Liu et al., 2022; Li et al., 2021; Corso et al., 2020; Perez et al., 2015). Overall, the effect of lifestage on the associations between short-term exposure to NO_2 and total mortality reported generally positive associations for older adults, but a single study reported no change in association comparing lifestages. Li et al. (2021) reported increasing YLL with increasing age (age 0 to 64 years, 65 to 74 years, and ≥75) among 48 Chinese cities, with older adults over 75 years reporting the higher YLL (YLL: 0.79 [95% CI: 0.58, 0.99] per 5.31 ppb increase in NO_2 for lag 0–1 days) (see Table 10-3). Among 47 Census divisions in Canada, (Huang et al., 2023) reported that associations between short-term exposure to NO_2 (estimated as the 3-hour maximum) and all-cause mortality was stronger among older adults aged >65 years (national risk: 0.91% [95% high density interval (HDI): 0.17, 1.08] per 12.8 ppb increase in NO_2), when compared to adults aged <65 years (national risk: 0.17% [95% CI: 0.00, 0.79]). Corso et al. (2020)

reported excess relative risk (ERR) for non-accidental deaths associated with short-term exposure to NO_2 (lag 0–1 days) for older adults (≥75 years) of 1.44 (95% CI: 0.63, 1.66) per 5.31 ppb increase in NO_2, compared to the total population (ERR: 0.75 [95% CI: 0.40, 1.10]) among 18 metropolitan areas in France, but the associations were imprecise with the CIs including the null. However, Perez et al. (2015) reported similar daily number of mortality cases for all ages, ≥65 years, and ≥75 years for short-term exposure to NO_2 (lag day 1–2) in Switzerland. Liu et al. (2022) reported no evidence of effect measure modification for age groups (<45 yrs, 45 to 65 yrs, 65 to 75 yrs, ≥75 yrs) on the associations between exposure to NO_2 and all-cause mortality among participants in seven U.S. states.

Sex

Among the recent epidemiological studies, the evidence remains limited and inconsistent. While Li et al. (2021) reported stronger associations in females (YLL: 0.78% [95% CI: 0.60, 0.97] per 5.31 ppb increase in NO_2 for lag 0–1) compared to males (YLL: 0.56 [95% CI: 0.35, 0.76]) in China, Shin et al. (2022) reported similar associations for males and females among participants in Canada and Liu et al. (2022) reported no evidence of effect measure modification by sex among participants in seven U.S. states (see Table 10-3).

Socioeconomic Status

Only a few recent epidemiologic studies evaluated the impact of education, a proxy measurement for SES, on the associations between short-term exposure to NO_2 and total mortality (see Table 10-3). In a study in China, Li et al. (2021) reported no evidence of effect modification by educational attainment, less education attainment (≤9 years) compared more educational attainment (>9 years). In a study of participants in seven U.S. states, there was no evidence of effect measure modification by education (<high school, high school, >high school) on the associations between short-term exposure to NO_2 and total mortality.

10.3.1.6 Copollutants

In the recent epidemiologic studies, there were several studies that examined the potential impacts of confounding by copollutants on the associations between exposure to oxides of nitrogen and total mortality. The examination of confounding by copollutants is informative to determine an independent effect on mortality from exposure to oxides of nitrogen. However, in copollutant models, there may be multicollinearity issues due to high correlations typically seen between NO_2 concentrations and traffic-related copollutants, such as CO, BC, VOCs, and were not extensively evaluated in the recent epidemiologic studies. Of the copollutants that were evaluated, PM_{10}, $PM_{2.5}$, SO_2, O_3, and CO, were the most common. Overall, the associations were relatively unchanged when co-adjusting for other copollutants. Evidence from recent studies is summarized in the bullets below and selected results are in Table 10-3.

- Among the studies that evaluated the potential confounding by PM_{10} on the associations between short-term exposure to NO_2 and total mortality, the positive associations were relatively unchanged when adjusted for PM_{10} compared to the single pollutant model with NO_2 alone, with low to moderate correlations (ρ = 0.05 to 0.77), in co-adjusted models (Gariazzo et al., 2023; Meng et al., 2021; Corso et al., 2020; Perez et al., 2015).
- Overall, there was general pattern of relatively unchanged positive associations among the studies that evaluated the potential confounding by $PM_{2.5}$ on the associations between short-term exposure to NO_2 and total mortality (Gariazzo et al., 2023; Li et al., 2021; Meng et al., 2021), but a single study reported attenuation of the association (Liu et al., 2022), compared to the single pollutant model with NO_2 alone. All of these studies co-adjusted for $PM_{2.5}$, with correlations relatively low (ρ <0.4), although a single study reported a moderate correlation (ρ = 0.65) (Li et al., 2021).
- Liu et al. (2022) reported attenuation in all-cause mortality when co-adjusting for $PM_{2.5}$ in a two-pollutant model (% increase: 0.18% [95% CI: -0.02, 0.37] per 10 ppb increase in NO_2) and when co-adjusting for $PM_{2.5}$ and O_3 in a three-pollutant model (% increase: 0.19% [95% CI: -0.01, 0.38] per 10 ppb increase in NO_2), compared to the single pollutant model with NO_2 alone (% increase: 0.35% [95% CI: 0.17, 0.53] per 10 ppb increase in NO_2).
- Overall, there was general pattern of association of relatively unchanged associations among the recent studies that evaluated the potential confounding by O_3, compared to the single pollutant model with NO_2 alone (Liu et al., 2022; Li et al., 2021; Meng et al., 2021). However, Corso et al. (2020) reported increased excess relative risk when co-adjusted for O_3, but wide CIs that include the null (ERR: 1.12 [95% CI: 0.63, 1.61] per 5.31 ppb increase in NO2) and correlation was not reported.
- There were a few recent studies that evaluated the potential confounding by SO_2 and CO (Li et al., 2021; Meng et al., 2021). Overall, the positive associations were relatively unchanged whether co-adjusted for SO_2 or CO, despite the moderate correlations (ρ = 0.5 to 0.6), compared to the single pollutant model with NO_2 alone.

Lastly, Wei et al. (2021) used a linear probability model (LPM) and two GPS based approaches, weighted least squares (WLS) and m-out-of-n random forest (moonRF), to assess the additive effects of exposure to NO_2, $PM_{2.5}$, and O_3 on total mortality. While the annual number of early deaths for short-term exposure to NO_2 were increased, the association is not for independent effect of exposure to NO_2, but rather the additive effect of exposure to NO_2, $PM_{2.5}$, and O_3 on total mortality.

Table 10-3 Epidemiologic studies evaluating copollutants on the associations between short-term exposure to NO_2 and total mortality

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (r2)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
Exposure to NO_2						
†Corso et al. (2020)	2010–2014	PM_{10}; O_3	PM_{10}: NR O_3: NR	Generalized additive Poisson regression models	PM_{10}: ≈	RR (95% CI)[b] Non-accidental mortality 2.85 (1.52, 4.21) Non-accidental mortality coadjusted for PM_{10}: 2.20 (0.57, 3.86) Non-accidental mortality, ≥75 years, coadjusted for PM_{10}: 3.01 (0.99, 5.06) Non-accidental mortality, cold period, coadjusted for PM_{10}: 0.34 (-1.57, 2.28) Non-accidental mortality, cold period, ≥75 years, coadjusted for PM_{10}: 1.06 (-1.29, 3.46) Non-accidental mortality, warm period, coadjusted for PM_{10}: 5.10 (1.42, 8.91) Non-accidental mortality, warm period, ≥75 years, coadjusted for PM_{10}: 6.19 (0.88, 11.78)
					O_3: ↑	RR (95% CI)[b] Non-accidental mortality 2.85 (1.52, 4.21) Non-accidental mortality coadjusted for O_3: 4.28 (2.40, 6.20) Non-accidental mortality, ≥75 years, coadjusted for O_3: 5.65 (3.22, 8.12) Non-accidental mortality, cold period, coadjusted for O_3: 1.13 (-0.63, 2.93) Non-accidental mortality, cold period, ≥75 years, coadjusted for O_3: 2.24 (-0.11, 4.64) Non-accidental mortality, warm period, coadjusted for O_3: 9.90 (6.23, 13.69) Non-accidental mortality, warm period, ≥75 years, coadjusted for O_3: 11.68 (9.33, 14.09)
†Gariazzo et al. (2023)	2013–2015	PM_{10}; $PM_{2.5}$	PM_{10}: 0.05 $PM_{2.5}$: 0.06	Time series and pooled analysis	≈	HR (95% CI)[c] Total (natural) mortality, lag 0–5: -0.77 (-1.67, 0.14) Total (natural) mortality, lag 0–5,

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (r2)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						coadjusted for PM_{10}: -0.62 (-1.53, 0.29) Total (natural) mortality, lag 0–5, coadjusted for $PM_{2.5}$: -0.63 (-1.53, 0.29)
†Li et al. (2021)	2013–2017	$PM_{2.5}$; SO_2; O_3; CO	$PM_{2.5}$: 0.68 SO_2: 0.64 O_3: -0.25 CO: 0.69	Generalized additive model and meta-analysis	≈	HR (95% CI)[b] Total mortality: 2.47 (1.90, 3.04) Years life lost: 2.43 (1.78, 3.08) Total mortality, coadjusted for $PM_{2.5}$: 1.67 (0.79, 2.55) Total mortality, coadjusted for SO_2: 2.28 (1.57, 2.99) Total mortality, coadjusted for O_3: 2.20 (1.67, 2.74) Total mortality, coadjusted for CO: 1.89 (1.00, 2.80) Years life lost, coadjusted for $PM_{2.5}$: 1.93 (0.96, 2.91) Years life lost, coadjusted for SO_2: 2.62 (1.84, 3.41) Years life lost, coadjusted for O_3: 2.12 (1.53, 2.72) Years life lost, coadjusted for CO: 1.97 (0.98, 2.97)
†Liu et al. (2022)	2000–2015	O_3; $PM_{2.5}$	O_3: NR $PM_{2.5}$: NR	Conditional logistic regression	≈	HR (95% CI)[c] All-cause mortality: 0.35 (0.17, 0.53) All-cause mortality - copollutant model with O_3: 0.34 (0.16, 0.53) All-cause mortality - copollutant model with $PM_{2.5}$: 0.18 (-0.02, 0.37)
†Meng et al. (2021)	1973–2018	PM_{10}; $PM_{2.5}$; O_3; SO_2; CO	PM_{10}: 0.34 $PM_{2.5}$: 0.38 O_3: -0.24 SO_2: 0.42 CO: 0.56	Quasi-Poisson generalized linear regression model & meta-analytic approach	≈	HR (95% CI)[b] Total mortality: 1.74 (1.34, 2.14) Total mortality, coadjusted for PM_{10}: 1.44 (0.96, 1.91) Total mortality, coadjusted for $PM_{2.5}$: 1.40 (0.96, 1.84) Total mortality, coadjusted for O_3: 1.78 (1.38, 2.18) Total mortality, coadjusted for SO_2: 1.70 (1.30, 2.10) Total mortality, coadjusted for CO: 1.82 (1.38, 2.26)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (r2)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
†Perez et al. (2015)	1995–2010	PM_{10}	PM_{10}: NR	Poisson regression	≈	HR (95% CI)[b] Daily mortality: 1.40 (0.20, 2.62) Daily mortality - coadjusted for PM_{10}: 1.00 (-0.39, 2.42) Daily mortality, Ages ≥65 - coadjusted for PM_{10}: 3.84 (-3.15, 11.33) Daily mortality, Ages ≥75 - coadjusted for PM_{10}: 0.60 (-0.89, 2.12)

List of abbreviations: CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; $PM_{2.5}$ = 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; RR = rate ratio; SO_2 = sulfur dioxide

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

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

[c]Estimates are not standardized.

†Studies published since the 2016 Oxides of Nitrogen ISA.

10.3.1.7 Alternative Methods for Confounder Control

Of the studies that examined short-term NO_2 exposure and mortality, multiple studies seek to mimic randomized experiments and reduce the potential bias of effects due to confounding through the use of study design and statistical methods (Liu et al., 2022; Wei et al., 2021; Schwartz et al., 2018; Schwartz et al., 2017). These alternative methods for confounder control are often referred to in the scientific literature as causal inference methods.[3] Alternative methods for confounder control that attempt to eliminate/reduce confounding are complementary to established methods and can be integrated with other epidemiology methods along with those in other disciplines (e.g., toxicology) to provide a more holistic view of causality and biological plausibility (Pearce et al., 2019). Recent epidemiologic studies used methods such as instrument variables, GPS, marginal structural model, and negative exposure control analysis. The results from studies utilizing these alternative methods for confounder control provide support for the associations reported from traditional epidemiologic studies. Evidence from recent studies is summarized in the bullets below, with additional details describing the alternative methods for confounder control.

[3]To prevent confusion with the main scientific conclusions presented within an ISA (i.e., the causality determinations), this document refers to such studies as employing alternative methods for confounder control.

- Schwartz et al. (2017) utilized an instrument variable approach to estimate the associations between exposure to NO_2 and mortality in the Boston, Massachusetts, U.S., area. An instrument variable is a variable that is only related to the outcome through the exposure of interest. Schwartz et al. (2017) used four instrument variables (planetary boundary layer and wind speed each at lag 0 and lag 1) and regressed NO_2 against the four variables first, and used that result (the variation in NO_2 explained by the four instrumental variables) to generate a single instrumental variable for regression on the outcome. An IQR increase in the instrument for NO_2 was associated with a 0.62% (95% CI: -0.12, 1.64) increase in daily deaths. Limitations inherent to this study include assumptions of a valid instrument, that the instrumental variable controls for unmeasured confounding, all-cause mortality includes death unrelated to NO_2 thus decreasing power, and importantly exposures were measured at a single site (Schwartz et al., 2017). Additionally, wind speed is directly associated with apparent temperature, which can impact both the exposure and the outcome, so there should be caution with interpreting the results of this study. Furthermore, there were only results for the instrument of NO_2 and there were no additional results (e.g., for the lag models) or a comparison to traditional methods to verify whether this alternative method for confounder control provides support for an independent effect of NO_2 and daily deaths.
- Schwartz et al. (2018) used two alternative methods for confounder control, a marginal structural model and a negative exposure control analysis, compared to a traditional time series to estimate the effects of exposure to NO_2 on mortality in 135 U.S. cities. Marginal structural models estimate the marginal effects of exposure by using inverse probability weights of time-varying exposures to render the exposure independent of the measured covariates. Marginal structural models assume that there are no unmeasured confounders. If the exposure is independent of covariates, its effect on the outcome cannot be confounded by them and resulting estimates do not depend on the distributions of confounders. Negative exposure control identifies a negative exposure variable, which is likely to be correlated with unmeasured potential confounders but could not be a cause of the outcome of interest. Negative exposure controls serve as instruments for the unmeasured confounders. If such confounders exist, control for the negative exposure would be expected to reduce or eliminate the estimated effect of the exposure of interest. If no such confounders exist, then control for the negative exposure would be expected to result in no change in the association between the exposure and outcome, which indicates no confounding by any measured or unmeasured variables. In the conventional time series analysis, there was a 0.38% (95% CI: 0.08, 0.69) change in daily mortality per a 10 ppb increase in NO_2. The results of the marginal structure model show an estimated percentage change in daily mortality of 2.59% (95% CI: 1.78, 3.40), while the negative exposure control model reported an estimated percentage change in daily mortality of 2.62% (95% CI: 1.81, 3.43). The results of the two alternative methods for confounder control models agreed with the conventional time series analysis.
- Among Medicare beneficiaries, Wei et al. (2021) used a linear probability model (LPM) and two GPS based approaches, weighted least squares (WLS) and m-out-of-n random forest (moonRF), to assess the additive effects of exposure to NO_2, $PM_{2.5}$, and O_3 on total mortality. Overall, the LPM and WLS models produced equivalent results and similar results to the moonRF models. The annual number of early deaths for short-term exposure to NO_2 was 167 (95% CI: 156, 179) per 1 ppb increase in NO_2 for LPM/WLS model and 163 (95% CI: 151, 174) per 1 ppb increase in NO_2 for moonRF. However, these estimated annual number of early deaths are not showing an independent effect of exposure to NO_2, but rather the additive effect of exposure to NO_2, $PM_{2.5}$, and O_3 on total mortality.
- Liu et al. (2022) used logistic regression and two alternative methods for confounder control, a double negative control model and two-stage approach, which is similar to two-stage least

squares, to quantify the associations between daily NO_2 exposure and total mortality in seven U.S. states. While an independent effect between exposure to NO_2 and total mortality was reported using logistic regression (percent increase of 0.35% [95% CI: 0.17, 0.53] per 10 ppb increase in NO_2 exposure at lag 0–2 days), the use of two alternative methods for confounder control resulted in less precise estimates (see Appendix Table 10-1).

Overall, the recent epidemiologic studies that utilized alternative approaches for confounder control provide additional support for the relationship between short-term NO_2 exposure and mortality described in previous and recent studies (e.g., more traditional studies). A key aspect of the alternative approaches for confounder control is accounting for unmeasured confounders, which may bias the associations reported in more traditional studies. Since the findings from the more traditional studies are similar to those utilizing alternative approaches for confounder control, there is evidence of an independent association of short-term exposure to NO_2 and total mortality.

10.3.1.8 Examination of Seasonal Differences and Temperature as a Modifying Factor

A limited number of studies evaluated in the 2016 Oxides of Nitrogen ISA examined seasonal differences in the NO_2-total mortality relationship and indicated stronger associations in the warm season compared to the cold season (Shin et al., 2012; Stieb et al., 2008; Bellini et al., 2007). A couple of recent multicity studies provide some additional support for stronger associations between short-term NO_2 exposure and total (nonaccidental) mortality in the warm season.

Corso et al. (2020) analyzed the association between short-term NO_2 exposure and total mortality in 18 French cities. The authors reported increased risk of mortality associated with 24-hour average NO_2 concentrations in the warm season and null association in the cold season. For example, in the total population, the lag 0–1 ERR during the warm season is 2.65 (95% CI: 1.82; 3.48), while the lag 0–1 ERR for the cold season is 0.01 [95% CI: -0.41; 0.42]. This pattern holds for copollutant models (see Section 10.3.1.6) and stratified analyses for those ≥75 years of age [see Section 10.3.1.5; (Corso et al., 2020)]. Shin et al. (2022) stratified models of short-term NO_2 exposure and total mortality by season and sex. Similarly, a recent analysis of NO_2-related mortality in 24 Canadian cities provides additional evidence of stronger associations with same-day NO_2 concentrations in the warm season relative to the cold season, as observed in sex-stratified models (Shin et al., 2021). Seasonal differences are not apparent with longer exposure lags (i.e., one or two days). Notably, this study analyzes the same population, with eight additional years of follow-up, as the Shin et al. (2012) study evaluated in the 2016 Oxides of Nitrogen ISA. Consequently, the results are not independent of the previous findings.

While seasonal analyses indirectly account for the role of temperature on the NO_2-mortality association, most studies do not directly address whether higher or lower temperatures modify the NO_2-mortality association. In one recent study that did examine effect modification by temperature, Li et al. (2021) included quartiles for average temperature in a meta-regression that pooled city-specific estimates YLL associated with short-term NO_2 concentrations across 48 cities in China. The authors reported

consistent evidence of positive associations between lag 0–1 24-hour average NO_2 concentrations and YLL across each temperature quartile, with larger increases in YLL estimates among the cities in the higher temperature quartiles (Q2: 0.62 [95% CI: 0.41, 0.83]; Q3: 0.69 [95% CI: 0.47, 0.92]; and Q4: 0.52 [95% CI: 0.10, 0.94]) relative to quartile 1 (0.24 [95% CI: 0.04, 0.44]).

10.4 Cause-Specific Mortality

Among the epidemiologic studies in the 2016 Oxides of Nitrogen ISA that examined the relationship between short-term NO_2 exposure and cardiovascular effects, there was consistent evidence for myocardial infarction, but epidemiologic and experimental evidence for other cardiovascular endpoints was inconclusive. However, important uncertainties remained especially in disentangling whether there is an independent effect of NO_2 on cardiovascular effects, which is the same uncertainty in total mortality studies. Overall, the evidence provided limited coherence and biological plausibility for NO_2-related cardiovascular mortality. For respiratory effects, there was strong evidence for NO_2-related asthma exacerbation supported by controlled human exposure studies demonstrating increased airway responsiveness in response to short-term NO_2 exposures as well as epidemiologic studies reporting associations with asthma-related hospital admissions, ED visits, and symptoms among the studies in the 2016 Oxides of Nitrogen ISA. However, the biological mechanism that explains the continuum of effects that could lead to respiratory-related mortality also remained unclear. Additionally, studies that examined the association between short-term NO_2 exposures and mortality rely on central site monitors, which may contribute to exposure measurement error and underestimate NO_2 effects if the temporal variation in measured ambient NO_2 concentrations does not fully reflect variation in people's ambient NO_2 exposure. Taken together, inference from the consistently positive associations observed across various multicity studies in the 2016 Oxides of Nitrogen ISA was limited by the uncertainty as to whether NO_2 is independently associated with total mortality as well as the uncertainty in the biological mechanism that could lead to NO_2-induced mortality.

Since the 2016 Oxides of Nitrogen ISA, a number of recent studies have been published that examine associations between exposure to oxides of nitrogen and cause-specific mortality. Most studies focus on respiratory mortality and cardiovascular mortality, though there was a single study of metabolic mortality examined. The studies that examine the associations between short-term NO_2 exposure and cause-specific mortality outcomes, such as respiratory or cardiovascular mortality, provide additional evidence for NO_2-related health effects, specifically, whether there is evidence of an overall continuum of respiratory and cardiovascular effects that could lead to mortality in some people.

10.4.1 Respiratory Mortality

Several multicity epidemiologic studies evaluated in the 2016 Oxides of Nitrogen ISA reported consistent positive associations between short-term NO_2 exposure and respiratory mortality. Positive associations were observed in multicity studies conducted in Asia (Chen et al., 2012; Wong et al., 2008) and Italy (Faustini et al., 2013; Chiusolo et al., 2011; Bellini et al., 2007), as well as a meta-analysis of studies conducted in Asian cities (Atkinson et al., 2012). A large number of recent epidemiologic studies support and extend conclusions from the 2016 Oxides of Nitrogen ISA that indicated an association between short-term NO_2 exposure and respiratory mortality. Recent evidence is provided by studies with greater geographic diversity, including several multicity studies in North America and analyses of a large dataset collected from over 360 cities in 16 different countries across the world. The recent evidence base also includes expanded evaluation of the C-R relationship that suggests an approximately linear relationship between short-term NO_2 exposure and respiratory mortality with no evidence of a threshold. Additionally, whereas studies evaluated in the 2016 Oxides of Nitrogen ISA utilized central site monitors, a few recent studies reported positive associations between respiratory mortality and short-term NO_2 concentrations estimated using more spatially refined hybrid prediction models. Most of the evaluated studies of respiratory mortality defined lags a priori as multiday averages of 0–1 or 0–2 days. In contrast to studies described in the 2016 Oxides of Nitrogen ISA that examined alternative lag structures and reported equivocal results, recent studies revealed a consistent pattern of stronger associations at earlier lags (e.g., 0 and 1 days) with decreasing magnitudes of associations at later lags. For further details on recent epidemiologic studies examining short-term NO_2 exposures and respiratory mortality, refer to Chapter 3, Section 3.8.

10.4.2 Cardiovascular Mortality

The evidence evaluated in the 2016 Oxides of Nitrogen ISA supported a positive association between short-term increases in NO_2 exposure and cardiovascular mortality outcomes. Several multicity studies consistently reported positive associations between short-term NO_2 exposure and cardiovascular mortality in Asia (Chen et al., 2013; Chen et al., 2012; Wong et al., 2008) and Europe (Chiusolo et al., 2011; Bellini et al., 2007); these associations were slightly greater in magnitude than the associations with total mortality. Many recent epidemiologic studies further evaluate the relationship between short-term NO_2 exposure and cardiovascular mortality. In contrast to the findings of the 2016 Oxides of Nitrogen ISA, recent epidemiologic evidence indicates generally inconsistent associations between short-term NO_2 exposure and cardiovascular mortality. These studies include a wider geographic coverage than previously reported, including multi-country studies across over 300 cities, as well as additional multicity studies conducted across North America, Europe, and Asia. Several studies also evaluated potential confounding by copollutant exposure, such as $PM_{2.5}$ and O_3.

Recent studies among large patient populations conducted in the United States, Canada, Brazil, Europe, and Asia reported inconsistent evidence of an association between short-term NO_2 and cardiovascular mortality. Main findings included null effect estimates, negative and positive effect estimates with 95% CIs containing the null, negative and positive effect estimates with 95% CIs excluding the null. Recent studies included time series and case-crossover analyses, with little variation in model specifications. Models typically included adjustments for temporal trends, temperature, humidity, day-of-week, holidays, and vacation periods using flexible splines and categorical variables. For further details on recent epidemiologic studies examining short-term NO_2 exposures and cardiovascular mortality, refer to Chapter 5, Section 5.11.

10.4.3 Metabolic Mortality

Overall, among the recent epidemiologic evidence, the evidence is limited for short-term exposure to NO_2 and metabolic mortality. There was only a single study recent epidemiologic study evaluated the association 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. This study reports an increased NO_2-associated risk for metabolic mortality that is modified by sex, with strong associations in males but not females. For further details on this recent epidemiologic study examining short-term NO_2 exposures and metabolic mortality, refer to Chapter 8, Section 8.8.

10.5 Biological Plausibility

Chapters 3, 5, 8, 9, and 13 of this ISA include evidence evaluating the biological plausibility by which short-term NO_2 exposure may lead to the morbidity effects that can contribute to total (nonaccidental) mortality. The largest contributors to total nonaccidental mortality are respiratory- and cardiovascular-related effects, discussed in Section 3.8 and Section 5.11, respectively. The evidence supporting the biological plausibility of respiratory and cardiovascular effects of short-term NO_2 exposure is derived from animal toxicological, controlled human exposure, and epidemiologic studies.

Chapter 3 characterizes the available evidence by which inhalation exposure to NO_2 could progress from initial events to effects in the respiratory system, such as the exacerbation of respiratory disease (i.e., asthma, COPD) and susceptibility to respiratory infections. However, there are some uncertainties in the evidence for the continuum of effects that could ultimately lead from exposure to mortality. The strongest evidence supporting a causal relationship between short-term NO_2 exposures and respiratory effects is for asthma exacerbation, which is only a minor contributor to respiratory mortality. The primary causes of non-malignant respiratory mortality are chronic obstructive pulmonary disease (COPD) and respiratory infection (e.g., influenza and pneumonia) (NHLBI, 2017). For COPD, the

leading cause of non-malignant respiratory mortality, there is limited and inconsistent experimental evidence supporting epidemiologic evidence of associations between short-term NO_2 exposure and COPD exacerbation. In contrast, whereas there is strong experimental evidence that short-term exposure to relevant NO_2 concentrations impairs host resistance to bacterial and viral infection in monkeys and mice, epidemiologic evidence for pneumonia and influenza is limited and inconsistent.

Chapter 5 outlines the available evidence for plausible mechanisms by which inhalation exposure to NO_2 could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as myocardial infarction (MI), ischemic heart disease (IHD), and stroke. Although epidemiologic studies provide generally consistent evidence of positive associations between short-term increases in NO_2 concentrations and coronary events, including MI, there is a lack of coherence with experimental evidence and limited support for biological plausibility. Thus, the evidence remains "suggestive of, but not sufficient to infer," a causal relationship between short-term NO_2 exposure and cardiovascular effects.

Thus, although the available evidence strongly supports potential biological pathways by which short-term NO_2 exposures could result in exacerbation of respiratory disease (i.e., asthma), there is a lack of coherence in results between experimental and epidemiologic studies of respiratory and cardiovascular outcomes that are the largest contributors to mortality (e.g., COPD and MI). This lack of coherence contributes to considerable uncertainty in the degree to which observed associations between short-term NO_2 exposure and total (nonaccidental) mortality reflect a causal relationship.

10.6 Summary of Lifestages and Population

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,[4] extrinsic,[5] 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 Volume 2 of the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (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

[4]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.
[5]Extrinsic factors (e.g., nutritional status) and exposure-related factors (e.g., working outdoors, living near roadways or other pollution sources) can also contribute to increased risk, and many of the characteristics commonly used to classify populations potentially at increased risk (e.g., race, SES, educational attainment) are surrogates for the combined impact of several intrinsic, extrinsic, and exposure-related factors.

concentrations within the same study design. For the evaluation of these studies, important considerations include whether the stratified analyses were planned a priori or were post hoc analyses, whether the study conducted multiple comparisons, and whether there were small sample sizes in individual strata. These study design issues can increase the probability of finding associations by chance or reduce 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. Table 10-1 at the end of this section summarizes the evidence for each factor to increase risk of NO_2-related health effects.

10.6.1 Sociodemographic Factors

Sociodemographic factors encompass the broad categories of lifestages (e.g., children, adults), SES, race/ethnicity, sex, residence in urban area, and/or proximity to roadways.

Lifestages

In the 2016 Oxides of Nitrogen ISA, there was a limited number of studies that examined potential effect measure modifiers of the oxides of nitrogen and mortality relationship. There was limited evidence that reported associations of short-term exposure to NO_2 with total mortality in most studies were larger in adults ages 65 or older than in younger adults, with evidence pointing to elevated risk among the oldest adults with ages greater than 75 or 85 years (U.S. EPA, 2016). Among the recent epidemiologic studies, there were only a few studies that evaluated the effect of lifestage on the associations between short-term exposure to NO_2 and total mortality (Huang et al., 2023; Liu et al., 2022; Li et al., 2021; Corso et al., 2020; Perez et al., 2015). Overall, the effect of lifestage on the associations between short-term exposure to NO_2 and total mortality reported generally positive associations for older adults, with a few recent studies reporting no change in association comparing lifestages, but the evidence is limited. Among the recent studies, a few studies reported stronger associations when evaluating the effect of older adults aged 75 years or older (Li et al., 2021; Corso et al., 2020) with additional evidence of effects for older adults aged 65 year or older (Huang et al., 2023; Li et al., 2021; Corso et al., 2020). Overall, the recent evidence is limited and there is inadequate evidence for effects of lifestages on the associations between short-term exposure to NO_2 and total mortality.

Sex

In the 2016 Oxides of Nitrogen ISA, there was a limited number of studies that evaluated the effect of sex on the associations between short-term exposure to NO_2 and total mortality, with inconsistent associations overall. Among the recent epidemiologic studies, the evidence remains limited and inconsistent. While a single recent study in China reported stronger associations in females compare

to males (Li et al., 2021), a recent study in Canada and another among seven U.S. states reported no evidence of effect measure medication by sex (Liu et al., 2022; Shin et al., 2022). Overall, the recent evidence is limited and there is inadequate evidence for effects of sex on the associations between short-term exposure to NO_2 and total mortality.

Socioeconomic Status

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. Persons with lower SES generally have been found to have a higher prevalence of pre-existing diseases, less access to resources such as healthcare, and possibly increased nutritional deficiencies. Neighborhoods comprising low SES populations are characterized as having fewer resources and more psychosocial stressors and air pollution sources (Diez Roux and Mair, 2010; O'Neill et al., 2003); thus, community-level SES may influence health. Any or a combination of these factors could link low SES to increased risk for NO_2-related health effects.

In the 2016 Oxides of Nitrogen ISA, there were a few studies available that evaluated the potential for SES to modify the associations between short-term exposure to oxides of nitrogen and total mortality. Several studies in various countries found larger associations for short-term NO_2 exposure with total mortality in low SES compared to high SES groups as indicated by education, income, or employment. The increased risk for low SES was observed with both individual- and community-level SES indicators. In the recent evidence, there was only a single study that evaluated the potential for SES to modify the associations between short-term exposure to oxides of nitrogen and total mortality. Li et al. (2021) reported no evidence of effect modification by less education attainment (≤9 years) compared more educational attainment (>9 years) among participants in China. Among study of participants in seven U.S. states, there was no evidence of effect measure modification by education (<high school, high school, >high school) (Liu et al., 2022). Overall, there was limited and inadequate evidence of effect measure modification of SES on the associations between short-term exposure to oxides of nitrogen and total mortality.

Table 10-1 Summary of evidence for lifestages and population differences of total mortality from short-term exposure to oxides of nitrogen

	Key Evidence	Key References
Suggestive evidence		
Lifestage	Generally positive associations for 75 years or older and 65 years and older	†Li et al. (2021); †Corso et al. (2020); †Huang et al. (2023); †Liu et al. (2022)

	Key Evidence	Key References
Inadequate evidence		
Sex	Limited and inconsistent evidence	†Li et al. (2021); †Shin et al. (2022); †Liu et al. (2022)
Socioeconomic status	Limited evidence	†Li et al. (2021); †Liu et al. (2022)

†Studies published since the 2016 Oxides of Nitrogen ISA.

10.7 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA concluded that evidence was "suggestive of, but not sufficient to infer, a causal relationship" between short-term exposure to NO_2 and total (nonaccidental) mortality. This conclusion was based primarily on evidence from multicity epidemiologic studies conducted in the United States, Canada, Europe, and Asia, which generally reported positive associations with total mortality, as well as deaths due to respiratory and cardiovascular disease. Despite consistent positive associations between short-term NO_2 exposure and total mortality, the evidence is limited by the inability to discern the independent effect of NO_2 from the potential effect of the traffic-related pollution mixture, or components of that mixture, due to a limited number of studies evaluating copollutant models with traffic-related pollutants, as well as limited confidence in copollutant models adjusted for highly correlated pollutants. Additionally, there is uncertainty in the evidence supporting an independent effect of long-term NO_2 exposure on the cardiovascular and respiratory morbidity outcomes that are major underlying causes of mortality.

Recent multicity and nationwide epidemiologic studies continue to provide generally consistent evidence of positive associations between short-term NO_2 exposures and total (nonaccidental) mortality. Recent evidence of positive associations includes a global analysis of mortalities across 16 countries (Meng et al., 2021) and several studies utilizing alternative methods for confounder control (Liu et al., 2022; Wei et al., 2021; Schwartz et al., 2018; Schwartz et al., 2017; Section 10.3.1.7). A few recent studies examined the shape of the C-R relationship and reported an approximately linear relationship with no evidence of a threshold (see Section 10.3.1.1). Similarly, positive associations of comparable magnitude were observed at progressively lower concentration cut points in a restricted analysis of Medicare beneficiaries in Massachusetts, U.S., (Wei et al., 2021; Section 10.3.1.2). Consistent with the evidence presented in the 2016 Oxides of Nitrogen ISA, a few recent studies that examined potential seasonal differences in the NO_2-mortality relationship reported stronger associations in the warm season or summer months relative to the cold season (see Section 10.3.1.8). Recent evidence also expands on the exposure assessment methods used to assign NO_2 exposure (see Section 10.3.1.3). A few recent studies employed hybrid prediction models to better account for the spatiotemporal variation in NO_2

concentrations and reported results that were generally consistent with results from studies assigning exposure from central site monitors. Together, the pattern of consistent positive associations observed across studies reduces the likelihood that exposure measurement error substantially impacts study results. Although the body of epidemiologic evidence is mostly consistent, key uncertainties and data gaps related to copollutant confounding and biological plausibility remain.

It remains difficult to disentangle the potential independent effect of NO_2 from the effect of the traffic-related pollution mixture or components of that mixture. Consistent with the conclusions of the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), several recent studies report that associations between short-term NO_2 exposure and total mortality are robust (i.e., unchanged) or attenuated but still positive after adjustment for $PM_{10-2.5}$, $PM_{2.5}$, SO_2, or O_3. NO_2 correlations with copollutants ranged from moderate to high, which may produce unstable effect estimates and limit the confidence in copollutant model results due to multicollinearity. Additionally, a lack of evaluation of potential confounding by highly correlated traffic-related pollutants (e.g., EC, CO, or UFP), often due to concerns with multicollinearity, precludes conclusions on the association between short-term NO_2 exposure and total mortality relative to those copollutants. There is also uncertainty in the continuum of effects that could ultimately lead from short-term NO_2 exposure to mortality (see Section 10.5). While there is some evidence that short-term NO_2 exposures are associated with cardiovascular and respiratory mortality, there is not clear evidence that short-term NO_2 exposure has an independent effect on the exacerbation of cardiovascular and respiratory morbidity outcomes that are major underlying causes of mortality, such as MI, CHD, or COPD (see Chapters 3 and 5).

Overall, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between short-term exposure to oxides of nitrogen and total (nonaccidental) mortality. Although epidemiologic studies provide generally consistent evidence of a positive association between short-term oxides of nitrogen exposures and total mortality, there is notable uncertainty as to whether the association is indicative of an effect of ambient air NO_2 exposure on mortality independent of other air and traffic-related pollutants. There is additional uncertainty in the continuum of effects that could lead from short-term NO_2 exposure to mortality. The evidence for the relationship between short-term exposure to NO_2 and total mortality is summarized in Table 10-2, using the framework for causality determinations 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).

Table 10-2 Summary of evidence contributing to causality determinations for short-term oxides of nitrogen exposure and total mortality

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Generally consistent epidemiologic evidence from multiple, high-quality studies at relevant NO_2 concentrations	Increases in mortality in multicity studies conducted in the United States, Canada, Europe, and Asia.	Section 10.3.1 Stieb et al. (2008) Shin et al. (2012) †Liu et al. (2022) †Meng et al. (2021)	Mean 24-h avg: 7.44 to 25.0 ppb Mean 1-h max: 21.2 ppb Mean 3-h max: 13.1 to 19.1 ppb
Generally consistent positive epidemiologic evidence for associations between NO_2 exposure and total mortality across exposure assessment methods	While most studies assigned exposure from central site monitors, a few recent studies reported positive associations between total mortality and short-term NO_2 exposure estimated from hybrid prediction models.	Section 10.3.1.3	Mean 24-h avg: 6.27 to 21.2 ppb Mean 1-h max: 21.2 ppb Mean 3-h max: 13.1 to 19.1 ppb
Uncertainty regarding potential copollutant confounding	NO_2 associations were robust or attenuated but still positive after adjustment for $PM_{10-2.5}$, $PM_{2.5}$, SO_2, or O_3. Confounding by highly correlated traffic-related pollutants (e.g., EC, UFPs) was not examined. Moderate to high correlations limit confidence in model results for some copollutants.	Section 10.3.1.6	Mean 24-h avg: 6.27 to 21.2 ppb
Limited biological plausibility from studies of respiratory and cardiovascular morbidity	A lack of coherence between experimental and epidemiologic studies of short-term NO_2 exposure and respiratory and cardiovascular morbidity outcomes that support pathways for mortality.	Section 10.5 Chapters 3 and 5	

List of abbreviations in alphabetical order: avg = average; EC = elemental carbon; h = hour; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{10 \text{ or } 2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm or 2.5 μm; ppb = part per billion; UFP = ultra fine particles; SO_2 = sulfur dioxide.

[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.

10.8 References

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