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Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 9: Nervous System Effects

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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

ABCD	Amsterdam-Born Children and Their Development Study
AARP	American Association of Retired People
ABCL	Adult Behavior Checklist
AD	Alzheimer's disease
ADOS	Autism Diagnostic Observation Schedule
ADHD	attention-deficit/hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
ADRD	Alzheimer's disease and related dementias
AIC	Akaike Information Criterion
ALS	amyotrophic lateral sclerosis
ALSWH	Australian Longitudinal Study on Women's Health
ANT	attention network test
APOE	apolipoprotein E
APP	amyloid precursor protein
AQS	Air Quality System
ASBQ	Adult Social Behavior Questionnaire
ASD	Autism spectrum disorder
ASQ	Ages and Stages Questionnaires
A-TAC	Autism - Tics
ATP	adenosine triphosphate
avg	average
β	beta
BACE1	beta-secretase 1
BC	Black Carbon
BDI	Bayley Development Index
BHIS	Belgian Health Interview Survey
BiB	Born in Bradford
BL	bronchial lavage
BMI	body mass index
BORN	Better Outcomes Registry & Network
BSID	Bayley Scales of Infant Development
CANDLE	Conditions Affecting Neurocognitive Development and Learning in Early Childhood
CANS-ASP	Ontario Ministry of Children and Youth Services' Child and Adolescent Needs and Strengths - Autism Spectrum Profile
CANUE	Canadian Urban Environmental Health Consortium
CASI	Cognitive Abilities Screening Instrument
CAST	Childhood Autism Spectrum Test
CATSS	Child and Adolescent Twin Study in Sweden
CBCL	Child Behavior Checklist
CCHS	Canadian Community Health Survey
CC MET	two C-alleles of the gene encoding the MET receptor tyrosine kinase promoter variant rs1858830
CCW	Chronic Conditions Warehouse
CDPH	California Department of Public Health
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Center for Epidemiological Studies Depression Scale
CES-D-9	Center for Epidemiologic Studies Depressive 9-item scale
CHARGE	Childhood Autism Risks from Genetics and the Environment
CHF	congestive heart failure
CI	confidence interval
CIND	cognitive impairment non-dementia
CMAQ	Community Multiscale Air Quality
CMAQ-urban	Urban Community Multiscale Air Quality
CNS	central nervous system
CNV	copy number variation
CO	carbon monoxide
COI	child opportunity index
CONSTANCES	Cohorte des consultants des Centres d'examens de santé
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CPRS	Comprehensive Psychopathological Rating Scale
CPT	continuous performance test
CSBQ	Children's Social Behavior Questionnaire
CTMs	chemical transport modeling
CV	cross-validation
CVD	cardiovascular disease
CVLT	California Verbal Learning Test
d	square distance
DBP	diastolic blood pressure
DDST	Denver Developmental Screening Index
df	degrees of freedom
DID	difference-in-difference
DLM	distributed lag model
DLNMs	distributed lag non-linear models
DLPFC	dorsolateral prefrontal cortex
DMST	Digit Memory Span Test
DNA	Deoxyribonucleic acid
DNBC	Danish National Birth Cohort
DNPR	Danish National Patient Register
DS	Digit Span
DSC	Digit Symbol Coding
DSM	Diagnostic and Statistical Manual
Dx	diagnosis
EARLI	Early Autism Risk Longitudinal Investigation
ED	emergency department

EDEN	´Etude des D´eterminants pr´e-et postnatals du d´eveloppement et de la sant´e de l'Enfant
EE	effect estimate
EC	elemental carbon
e.g.	exempli gratia (for example)
ELA	English Language Arts
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ELF	epithelial lining fluid
ELSA	English Longitudinal Study of Ageing
EMM	effect measure modification
EPIC-NL	Dutch European Investigation into Cancer and Nutrition
EPM	elevated plus maze
EPINEF	Environmental Pollution-Induced Neurological Effects
ESCAPE	European Study of Cohorts for Air Pollution Effects
etc.	et cetera
EPA	Environmental Protection Agency
EPM	elevated plus maze
E-Risk	Environmental Risk
ETS	environmental tobacco smoke
F	female(s)
FEV1	forced expiratory volume in 1 second
FPN	fronto-parietal network
FSIQ	full-scale intelligence quotient
FST	forced swim test
FTD	Frontotemporal Dementia
FVC	forced vital capacity
g	gram(s)
GAD	Generalized Anxiety Disorder
GAD-7	generalized anxiety disorder 7-item
GASPII	Gene and Environment Prospective Study on Infancy in Italy
GCI	general cognitive index
GCS	global cognitive score
GD	gestational day
GDS	Geriatric Depression Scale
GDS-15	15-item Geriatric Depression Scale
GEE	generalized estimating equation
GEMS	Ginkgo Evaluation of Memory Study
GHQ	General Health Questionnaire
GINIplus	German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy
GM	gray matter
HA	hospital admission
HCUP	Health Cost and Utilization Project
HECT	Hand-Eye Coordination Test
HELIX	Human Early-life Exposome project
HNR	Heinz Nixdorf Recall
HR	hazard ratio
hr	hour(s)
HRT	hypertension
ICD	International Classification of Diseases
ICD-(CM)	International Classification of Diseases-(Clinical Modification)
IDW	Inverse distance weighting
IHD	ischemic heart disease
ILS	Italian Longitudinal Study
INMA	INfancia y Medio Ambiente
IPL	inferior parietal lobule
IPW	inverse probability weighted
IQ	intelligence quotient
IQR	interquartile range
IRR	incidence rate ratio
ISA	Integrated Science Assessment
K10	Kessler psychological distress scale
KPSC	Kaiser Permanente Southern California
L	liter(s)
LGI	local gyrification index
LHID2000	Longitudinal Health Insurance Database 2000
LISA	Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Childhood
LOOCV	leave-one-out cross-validation
LRT	likelihood-ratio test.
LSOAs	Lower Super Output Areas
LTA	lifetime average
LUR	Land use regression
M	male
m	milligram
M/F	male/female
m	meter(s)
MA	moving average
MatCH	Mothers and their Children's Health
Max	Maximum
MCDI	McArthur Communicative Development Inventory
MCI	mild cognitive impairment
MDD	major depressive disorder
MESA	Multi-Ethnic Study of Atherosclerosis
MESA-air	Multi-Ethnic Study of Atherosclerosis and Air Pollution study
mL	milliliter
mo	month(s)
MoBa	Norwegian Mother and Child Cohort Study
MRI	magnetic resonance imaging
ms	milliseconds
MS	multiple sclerosis
MSCA	McCarthy Scales of Children's Abilities
MSE	mean square error
MWM	Morris water maze
N	Population size
NACRS	National Ambulatory Care Reporting System
NDVI	Normalized Difference Vegetation Index
NEPSY	Neuropsychological Assessment
NES	Neurobehavioral Evaluation System

NHIRD	National Health Insurance Database
NHIS	National Health Insurance Service or National Health Interview Survey
NHS	National Health Service
NIH	National Institutes of Health
NO	nitric oxide
NO_2	nitrogen dioxide
NO_X	oxides of nitrogen
NOMAS	Northern Manhattan Study
NR	Not reported
nSES	neighborhood socioeconomic status
O_3	ozone
OFT	open field test
ONPHEC	Ontario Population Health and Environment Cohort
OP^{DTT}	dithiothreitol
OR	odds ratio
P	percentile
PAGE study	Parkinson's, Genes, and Environment study
PC4	four digit postal code level
PCC/P	posterior cingulate cortex and precuneus
PD	Parkinson's disease
PDF	probability density function
PDP	Pervasive Developmental Problems
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PELAGIE	Perturbateurs Endocriniens, ´Etude Longitudinale sur les Anomalies de la Grossesse, l'Infertilite et l'Enfance
PHM	Dutch Public Health Monitor
PHQ	Patient Health Questionnaire
PM	particulate matter
P.M.	post meridiem
$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm
PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 µm
PND	postnatal day
ppb	parts per billion
ppm	parts per million
PRS	polygenic risk score
Q	quantile (could be quartile or quintile)
R	Organic radical
r^2	coefficent of determination
RANCH	Road Traffic and Aircraft Noise Exposure and Children's Cognition and Health
REPRO_PL	Polish Mother and Child Cohort Study
RERI	relative excess risk due to interaction
RGS	rat grimace scale
RHEA	Mother and Child Cohort in Crete
RMSE	root mean square error
RR	relative risk or risk ratio
SALIA	Study on the influence of Air pollution on Lung function, Inflammation and Aging
SALSA	Sacramento Area Latino Study on Aging
SAT	Switching Attention Test
SBI	subclinical brain infarct
SBP	systolic blood pressure
SCHIF	Shape Constrained Health Impact Function
SCL-90-R	Symptom Checklist-90-Revised
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
SDST	Symbol Digit Substitution Test
SE	standard error
SEDA	Stanford Education Data Archive
SES	socioeconomic status
SF-36	Short Form Health Survey-36
SGDS-K	Geriatric Depression Scale-Short Form Korean Version
SNAC-K	Swedish National Study of Aging and Care-Kungsholmen
SO_2	sulfur dioxide
SPM	suspended particulate matter
SRS	Social Responsiveness Scale
SRTT	Simple Reaction Time Test
T	tertile
t	time
TCBV	total cerebral volume
TICS	Telephone Interview for Cognitive Status
TICS-M	Telephone Interview for Cognitive Status-Modified
TMTB	Trail Making Test Part B
TRAILS	TRacking Adolescents' Individual Lives Survey
UEBMI	urban employee-based basic medical insurance
µg	microgram
U.K.	United Kingdom
UKHLS	U.K. Household Longitudinal Study
µm	Micrometer
URBMI	urban resident-based basic medical insurance
U.S.	United States
USV	ultrasonic vocalizations
VAD	Vascular Dementia
VCP	Visuo-construction performance
VETSA	Vietnam Era Twin Study of Aging
vs.	versus
WHI	Women's Health Initiative
WHICAP	Washington Heights–Inwood Community Aging Project
WHIMS	Women's Health Initiative Memory Study
WHIMS-ECHO	Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes
WHIMS-MRI	Women's Health Initiative Memory Study Magnetic Resonance Imaging
WHO	World Health Organization

WISC	Wechsler Intelligence Scale for Children
WMHV	log-white matter hyperintensity volume
wk	week(s)
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
yr	year(s)
ZCTA	Zip code tabulation area

CHAPTER 9 Nervous System Effects

Summary of Causality Determinations for Oxides of Nitrogen Exposure and Nervous System Effects

This chapter characterizes the scientific evidence that supports causality determinations for oxides of nitrogen exposure and nervous system effects. 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 Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen, Volume 2 (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
Nervous System Effects – Long-term Exposure	Suggestive of, but is not sufficient to infer, a causal relationship
Nervous System Effects – Short-term Exposure	Inadequate 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.

9.1 Introduction

9.1.1 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 contain a causality determination for oxides of nitrogen exposure and nervous system effects. Studies on neurodevelopmental outcomes were discussed in the long-term exposure and Reproductive and Developmental Effects Section [see Section 6.4, U.S. EPA (2016)] and considered under the postnatal development causality determination alongside studies on physical development. At that time, the evidence was inadequate to infer the presence or absence of a causal relationship between oxides of

nitrogen exposure and postnatal development, primarily resulting from limited and inconsistent epidemiologic and toxicological evidence. Studies on neurodevelopment evaluated cognitive function, attention-related behaviors, motor function, psychological distress, and autism spectrum disorder (ASD). This evidence is briefly summarized below.

While cognitive function was the most well-examined endpoint, studies did not consistently find associations between ambient NO_2 exposure and cognitive decrements. van Kempen et al. (2012) reported that ambient NO_2 exposure at home was not associated with decrements in either memory or attention in school-age children, while exposure to ambient NO_2 at school was associated with decrements in memory but not attention. Associations of prenatal residential NO_2 and cognition in school-age children and infants were also inconsistent among four Spanish cohorts (Guxens et al., 2014; Guxens et al., 2012), and additional studies of ambient NO_2 and cognitive function in school-age children found no significant associations (Clark et al., 2012; Freire et al., 2010). Morales et al. (2009) reported that indoor NO_2 exposure in early life was inversely associated with cognitive function and attention in school-age children. No toxicological studies of cognitive function or attention were available.

The evidence for other neurodevelopmental endpoints was similarly inconsistent or limited. Prenatal NO_2 exposure was associated with decreased motor function in children 1 to 6 years of age in a pooled analysis of six European cohorts, but cohort-specific analyses indicated that this association was not consistent across the individual cohorts examined (Guxens et al., 2014). Concurrent NO_2 exposure was not associated with fine motor skill decrements in 4- to 11-year-old children, but gross motor function in 4-year-old children was inversely associated with ambient home NO_2 (van Kempen et al., 2012; Freire et al., 2010). Toxicological studies found inconsistent effects on motor function endpoints (e.g., righting reflex, postural gait, locomotor activity) resulting from developmental NO_2 exposure (Di Giovanni et al., 1994; Tabacova et al., 1985). Gestational NO_2 exposure decreased ultrasonic vocalizations in rat pups, an indication of emotionality, while an epidemiologic study did not find associations between NO_2 exposure and psychological distress (Clark et al., 2012; Di Giovanni et al., 1994). Finally, two case-control studies of children in California found that prenatal ambient NO_2 exposure was associated with higher odds ratios for ASD (Becerra et al., 2013; Volk et al., 2013).

A strength of many of the epidemiologic studies in the 2016 Oxides of Nitrogen ISA was the use of well-validated land use regression (LUR) models to estimate ambient NO_2 exposures at children's homes or schools. These studies also assessed neurodevelopment with widely used, structured neuropsychological tests, and some of the reported associations between NO_2 exposure and neurodevelopmental outcomes even after adjusting for socioeconomic status indicators and birth outcomes. However, spatially correlated factors with NO_2 in ambient air, such as traffic noise, $PM_{2.5}$, and carbon monoxide were inconsistently considered by epidemiologic studies, and other relevant copollutants—such as lead, benzene, and polycyclic aromatic hydrocarbons—were not evaluated in any of the studies. The potential for differential exposure measurement error between the residential NO_2 and

central site copollutant measurements adds additional uncertainty. Furthermore, toxicological evidence supporting the biological plausibility of the epidemiologic findings was limited.

9.1.2 Chapter Organization and Conventions

This chapter evaluates recent evidence examining the relationship between oxides of nitrogen exposure and nervous system 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 recent studies evaluated in this chapter (see Section 9.2), an assessment of the recent evidence for nervous system effects following oxides of nitrogen exposure (see Sections 9.3 to 9.8), a discussion of biological plausibility (see Section 9.9), a summary of evidence for the lifestages and population (see Section 9.10, Table 9-1), and a discussion of the causality determinations for long-term (see Section 9.9.11.1, Table 9-2) and short-term (see Section 9.11.2, Table 9-3) oxides of nitrogen exposure and nervous system 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.

9.1.2.1 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 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 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 "Copollutants" 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 is relatively low (e.g., correlation coefficent rho (ρ)<0.4). However, when correlations are high (e.g., ρ>0.7), collinearity between pollutants make 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. Additionally, exposure measurement error can contribute to effect transfer in copollutant models from the pollutant measured with more error to the better measured pollutant (Evangelopoulos et al., 2021).

Throughout this chapter, short-term exposure to oxides of nitrogen is assumed to be approximately 30 days or less, while long-term exposure to oxides of nitrogen is assumed to be approximately more 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 average, 8-hour maximum, 1-hour maximum) and oxide of nitrogen. For 24-hour average, effect estimates were scaled to a 20 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 the 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

[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.

polluted year) concentrations among monitors in the State and Local Air Monitoring Stations network. Long-term averages of ambient oxides of nitrogen 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 μg/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 μg/m^3 at a national scale for the United States or other countries. Therefore, the ISA presents effect estimates based on μg/m^3 of NO_X as they are reported in their respective studies.

9.1.2.2 Animal Toxicological Studies

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

9.2 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 the 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

[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 recent 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).

Nitrogen ISA, including some 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 nervous system effects, 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).

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 nervous system 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]

[3]Epidemiologic studies examining associations with NO_2 in ambient air 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 U.S. during the most recent 15 years of available data (i.e., 2008 to 2022) (U.S. EPA, 2023). Studies reporting average NO_2 exposures greater than 22 ppb are considered for inclusion in the ISA if they meet additional study quality criteria described in the Process Chapter (see Chapter 14).
[4]Five ppm is approximately two orders of magnitude higher than peak NO_2 concentrations in ambient air in the U.S. 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 Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (U.S. EPA, 2016). Experimental studies investigating the effects of concentrations greater than 5 ppm may be considered for inclusion in the ISA if they provide insight into biological plausibility.

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

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

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

9.3 Neurodevelopmental Effects

Neurodevelopmental effects refer to adverse outcomes related to impairments in the formation and maturation of the nervous system. In the 2016 Oxides of Nitrogen ISA, prenatal, early life, or concurrent (i.e., school-age) NO_2 exposure was examined in a limited number of epidemiologic studies evaluating cognitive function, attention-related behaviors, aggressive behaviors, motor function, and ASD (U.S. EPA, 2016), which are summarized in Section 9.1. Overall, associations between NO_2 in ambient air and neurodevelopmental effects were generally inconsistent across the available studies, and consideration of copollutants and other confounding factors was absent or limited. Recent studies conducted in the United States and across Europe add to this evidence. The evaluation of available evidence for neurodevelopmental effects is organized into five sections: cognitive function (see Section 9.3.1), motor function (see Section 9.3.2), ASD (see Section 9.3.3), and externalizing behaviors (e.g., attention-deficit/hyperactivity disorder (ADHD), aggression) (see Section 9.3.4). Section 9.3.5 presents an integrated synthesis across lines of evidence for neurodevelopmental effects.

9.3.1 Cognitive Function

Cognitive function refers to a broad range of mental processes, including memory, learning, attention, problem-solving, and language. These processes begin developing in infancy, continuing through adolescence and into adulthood. Key epidemiologic studies from the 2016 Oxides of Nitrogen ISA and recent PECOS-relevant epidemiologic studies have evaluated associations between long-term exposure to oxides of nitrogen and multiple facets of cognitive function in infants, children, and adolescents, including cognitive development, attention, intelligence, and academic performance. A single recent epidemiologic study investigated short-term oxides of nitrogen exposure and attention deficits. Recent PECOS-relevant animal toxicological studies are limited to tests of spatial learning and memory using the Morris water maze paradigm. These epidemiologic studies and animal toxicological studies examining cognitive function are discussed in Sections 9.3.1.1 and 9.3.1.2, respectively. For studies of cognitive function in adulthood, refer to Section 9.5.1.

9.3.1.1 Epidemiologic Studies of Cognitive Function

Several national or multi-country European cohort studies of cognitive function were assessed in the 2016 Oxides of Nitrogen ISA. These studies examined cognitive function in school-aged children and mental development in infants. Overall, the evidence was limited, and study results did not consistently indicate associations between long-term NO_2 exposure and cognitive function. van Kempen et al. (2012) assessed cognitive performance using select tests from the Neurobehavioral Evaluation System (NES) that measured memory, attention locomotion, and perceptual coding to examine the association with LUR predicted annual average NO_2 exposure outside the home and the school (Cross-Validation [C-V] r^2: 0.85). Annual average NO_2 exposure at school, not at home, was associated with poorer performance on the test of memory after adjustment for noise. Neither school nor home NO_2 exposure was associated with the ability to process information. Results from a similar study of reading comprehension and memory among school children in the United Kingdom, in which aircraft noise was considered as a potential confounder, reported no association between NO_2 exposure at school and cognitive function (Clark et al., 2012). In this study annual average NO_2 exposure from traffic-related sources was estimated at the school zip code level using a hybrid approach that combined emissions, dispersion and LUR methods.

An imprecise inverse association (Confidence Intervals (CI) include the null value) between prenatal NO_2 exposure and mental development (Bayley Mental Development Index (BMDI) and Bayley Scales of Infant Development (BSID)) in infants enrolled in the Spanish Children's Health and Environment INfancia y Medio Ambiente (INMA) mother and child cohort study was observed (β: -0.95 [95% CI: -3.90, 1.89] per doubling of NO_2 exposure during pregnancy) (Guxens et al., 2012). The association was stronger among infants whose mothers reported low intakes of fruits/vegetables during pregnancy (β: -4.13 [95% CI: -7.06, -1.25] per doubling of NO_2 exposure during pregnancy). The findings from INMA were generally consistent with Guxens et al. (2014) in which data from six European cohorts was analyzed, including INMA. The association of prenatal NO_2 exposure with general cognition in infants and children (one to six years) was also negative and included the null value (β: -0.43 [95% CI: -1.81, 0.94]) but this study did not examine modification by maternal antioxidant intake. A small decrease in general cognition (β: -0.16 [95% CI: -0.71, 0.39] per 20 $\mu g/m^3$) was also observed with prenatal NO_X exposure in the Guxens et al. (2014) study, although the CI included the null value. Although NO_2 exposures were estimated from LUR models that varied in performance across locations, the findings across studies did not appear to be related to model performance (U.S. EPA, 2016). Uncertainty in the evidence was due to the lack of examination of potential confounding by copollutants, despite their moderate to high correlations with NO_2 (U.S. EPA, 2016).

Recent studies of school-aged children and infants add to the evidence base. These recent studies are summarized below, and study-specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are presented in Table 9-4, Table 9-5, and Appendix A – Appendix Table 9-1.

United States Studies

- Lu et al. (2021) examined the association, using generalized difference-in-difference (DID) models, between NO_2 exposure and district-wide average score on standardized English Language Arts (ELA) and Math tests. Third to eighth grade students in the United States, are required to take standardized tests from as part of state-wide assessments. NO_2 exposure was estimated using an ensemble model (Di et al., 2020) incorporating predictor variables including satellite-based estimates of NO_2, land cover variables, meteorological variables, and simulation results from chemical transport models while also integrating multiple machine learning algorithms. The cross-validated r^2 was 0.788 overall, with a spatial r^2 of 0.844, and a temporal r^2 of 0.729. The single pollutant results, which are shown in Figure 9-1, were adjusted for four classes of time-varying covariates derived from the 5-year estimates of the American Community Survey and the Common Core of Data including student racial/ethnic compositions, student-level socioeconomic status (SES), urbanicity, and school district-level SES. NO_2 exposure was associated with lower math and ELA scores in these single pollutant models. Associations in these fully adjusted models, which simultaneously included $PM_{2.5}$ and ozone were attenuated compared to single pollutant models (see Section 9.3.1.1.3). The strength of the DID analysis relies on the parallel trend assumption, which was not tested due to the lack of data over the years where the air pollution concentrations remained constant. In addition, confounding may not be adequately controlled because the covariates were averaged over 5 years while NO_2 exposure was estimated for the 12-month period that preceded the testing date.

List of abbreviations in alphabetical order: ELA = English Language Arts; NO_2 = nitrogen dioxide.
Source: Lu et al. (2021). Copyright permission pending.

Figure 9-1 Association of 12-month Average NO_2 Exposure with Lower Achievement Among U.S. Children: A Nationwide Panel Study of School Districts.

- Morgan et al. (2023) examined Latino mother and infant pairs enrolled in the Southern California Mother's Milk Study to determine the association of prenatal NO_2 exposure with neurodevelopment at age 2, assessed using the BSID. NO_2 concentration was estimated at each participant's geocoded residential address based on inverse distance weighting (IDW) of up to four Air Quality System (AQS) stations within 50 km of the home (leave one out validation, coefficient of determination $r^2 = 0.73$ (Eckel et al., 2016)). Prenatal exposure was associated with a decrease in composite cognitive score (β: -2.88 [95% CI: -10.78, 5.02]) and composite language score (β: -1.36 [95% CI: -8.31, 5.6]), though associations were imprecise (n = 161 mother-infant pairs).
- In another U.S. study, Loftus et al. (2019) used prospective data collected from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study to examine the association between annual average NO_2 concentration with full-scale intelligence quotient (FSIQ), verbal and nonverbal intelligence quotient (IQ), and

several subscales assessed using the Stanford Binet Intelligence Scales at age 4 to 6 years. Only FSIQ results were reported for NO_2. A validated (C-V r^2: 0.79 to 0.89) national universal kriging model that combined monitoring data with LUR predicted the annual average NO_2 concentration at the participant's geocoded residential address. This study reported a positive, imprecise association in fully adjusted models (β: 2.3 [95% CI: -1.9, 6.5]).

European Studies

- Binter et al. (2022) examined the association of prenatal and childhood NO_2 concentrations with verbal and nonverbal cognitive abilities in the Human Early-life Exposome project (HELIX), a consortium of four European birth cohorts (United Kingdom, France, Spain, Greece). The LUR model developed for European Study of Cohorts for Air Pollution Effects (ESCAPE) was used to estimate NO_2 concentrations (Beelen et al., 2013). Because different assessment instruments (i.e., British Picture Vocabulary Scale, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), McCarthy Scales of Children's Abilities) were used across cohorts, metrics indicating verbal and nonverbal abilities were derived. Little evidence of an association with NO_2 exposure was observed. The associations of prenatal NO_2 concentration with nonverbal and verbal abilities were essentially null (0.2 point increase [95% CI: -1.18, 1.57] and 0.4 point decrease [95% CI: -1.7, 0.9], respectively). Associations of childhood NO_2 concentration with nonverbal and verbal abilities that also included the null value were observed (0.5-point increase [95% CI: -0.65, 1.72] and 0.8 point decrease [95% CI: -1.8, 0.3], respectively).
- Guilbert et al. (2023) used data from two French birth cohorts to examine the association of NO_2 exposures with general, verbal, and nonverbal abilities assessed using the WPPSI, subtests of the Neuropsychological Assessment (NEPSY), and the Wechsler Intelligence Scale for Children (WISC). NO_2 exposure at the residence were estimated within a 4 km x 4 km grid combining measurements with chemical transport model predictions and relying on a kriging procedure for spatial interpolation. The model showed good performance in urban areas (i.e., bias not exceeding -3.5%) while lower performance (i.e., 60–80% overestimation depending on the year) was achieved in rural areas where the monitor coverage was less dense. The study examined associations over time (gestational weeks and postnatal months [0–57 months]) to identify exposure windows that may confer susceptibility. Overall, the study reported inconsistent associations that fluctuated in direction and precision during the time periods studied.
- A recent analysis of the INMA cohort (Lertxundi et al., 2019) extends that of Guxens et al. (2012) who previously reported a small association (CIs included the null value) between prenatal NO_2 exposure and impaired mental development in infants. Data were obtained at birth for 2,021 mother-child pairs, and cognitive function was measured using the McCarthy Scales of Child Development between age 4 and 6 years old. Residential NO_2 exposure during the entire pregnancy was estimated using an LUR model that captured between 60 and 88% of the variability in the annual average NO_2 concentration. The association between prenatal NO_2 exposure and the general cognitive index (GCI) derived from the McCarthy scales was close to the null value (β: -1.32 [95% CI: -3.2, 0.56]) for the children overall. An association with decreased GCI was observed in males (β: -3.58 [95% CI: -6.76, -0.39]) but not in females (β: 1.51 [95% CI: -0.847, 3.857]).
- Compa et al. (2023) examined the association of long-term NO_2 exposure with performance on tests of attention among school children (10–13 years old) living in Poland with and without ADHD (NeuroSmog case-control study). NO_2 exposures were estimated using validated LUR models with a resolution of 125 × 125 meters (5-fold C-V: 0.85). The

outcome was ascertained using the attention network test (ANT), which assesses alerting, orienting, and executive control, and the continuous performance test (CPT), which assesses the efficiency of executive attention. Among children with ADHD, but not among typically developing children, annual average NO_2 exposure was associated with less efficient orienting of attention on the ANT and improved performance (more correct rejections) on the CPT. These associations persisted after adjustment for PM_{10}. Compa et al. (2023) also conducted an analysis of the effect of short-term NO_2 exposure on performance on tests of attention. The study reported that daily mean NO_2 exposure from 1 to 7 days before the attention test was administered was associated with worse executive attention on the ANT but faster response time and fewer omission errors in the neurotypical group. No associations between short-term NO_2 exposure and performance on tests of attention were observed in the children with ADHD.

Recent studies summarized above present additional analyses evaluating the lifestages and populations that may be at higher risk of NO_2-associated cognitive effects, the potential influence of copollutants on reported associations with cognitive effects, and the appropriate exposure windows for examining cognitive effects. The evidence on these topics is discussed in greater detail below in Sections 9.3.1.1.1, 9.3.1.1.2, and 9.3.1.1.3, respectively. Section 9.3.1.1.4 presents a summary of findings from epidemiologic studies of cognitive effects and of the remaining uncertainties in the epidemiologic evidence.

9.3.1.1.1 Lifestages and Populations

Limited information from a single study in the 2016 Oxides of Nitrogen ISA observed that associations between NO_2 exposure during pregnancy and impaired mental development in infants were larger in those born to mothers with low fruit intake, those born to mothers with low Vitamin D and those who were never breastfed (Guxens et al., 2012). The recent studies summarized above also examine factors that may confer a higher risk of NO_2-related cognitive effects. Analyses of these factors are summarized below and in Table 9-4.

- Lu et al. (2021) examined the association between annual average NO_2 exposure and academic test scores (ELA and Math) among third to eighth grade students in the United States at the school district level. This study examined effect measure modification by school district racial/ethnic composition, school district SES, and grade in school by adding interaction terms between NO_2 exposure and the potential modifiers. These analyses indicated that the inverse association between NO_2 exposure and test scores was stronger in school districts with higher SES and weaker in school districts with lower SES. The inverse association of NO_2 exposure with math test scores was weaker in districts with a higher percentage of Hispanic/Latino students. In addition, the inverse association of ELA score with NO_2 was weaker at higher grades indicating less of an effect of NO_2 exposure in older students while the opposite was true for the association with math test scores (i.e., the association was stronger in older students). No statistical evidence of an interaction between NO_2 exposure and school districts with higher proportion of Black students was observed.
- Loftus et al. (2019) used prospective data collected from the CANDLE cohort to examine the association of prenatal NO_2 exposure with FSIQ. This study reported a positive association in

the fully adjusted model (β: 2.3 [95% CI: -1.9, 6.5]), although confidence intervals included the null value. There was no evidence that this association was modified in stratified analyses examining the pattern of associations by maternal race, insurance status, and maternal fruit and vegetable intake (i.e., NO_2 exposure was not associated with a decrement in IQ in any of the strata that were examined).

- A recent analysis of the INMA cohort (Lertxundi et al., 2019) found little evidence of an association between prenatal NO_2 exposure and GCI derived from the McCarthy scales (β: -1.32 [95% CI: -3.2, 0.56]) among the children enrolled in the study overall. The inverse association persisted in males (β: -3.58 [95% CI: -6.76, -0.39]) but not in females (β: 1.505 [95% CI: -0.85, 3.86]).

Recent studies expand the literature, but the evidence remains limited overall and lacks consistency. Studies of prenatal and childhood NO_2 exposure and cognitive effects report mixed findings regarding effect measure modification by SES, indicated by parental occupation or participation in free lunch programs, and other indicators of disadvantage measured at the school district level (see Table 9-4) (Lu et al., 2021; Loftus et al., 2019; Guxens et al., 2012). The literature that examined modification by sex or race was also sparse or did not indicate differences across groups. A U.S. study (Loftus et al., 2019) observed a positive association between prenatal NO_2 exposure and FSIQ that was attenuated and became null in the high fruit and vegetable group, providing little support for the study by Guxens et al. (2012).

Table 9-4 Epidemiologic Studies Evaluating Effect Measure Modification between Long-Term Nitrogen Dioxide Exposure and Cognitive Function in Infants and Children

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Lifestage					
†Lu et al. (2021) Outcome: Academic Achievement	SEDA 2010–2016	Higher grade in school (integer value) Interaction term, β[c]: Math: -0.00273, p≤0.05	Lower grade in school (integer value) (The interaction term in the EMM Reference Factor column indicates that the decrease in academic achievement is larger at higher grades. The downward arrow in the Direction of EMM column indicates that the inverse association is smaller in magnitude at lower grades compared to the higher grades.)	↓	School district-level
		ELA: 0.00268, p≤0.01	Lower grade in school (integer value) (The interaction term in the EMM Reference Factor column indicates that the decrease in academic achievement is smaller at higher grades. The upward arrow in the Direction of EMM column indicates that the inverse association is larger in magnitude at lower grades compared to the higher grades.)	↑	School district-level
Nutritional Status					
Guxens et al. (2012) Outcome: BSID	INMA Enrollment: 2003–2008 Follow-up: birth to 2 years of age	β (standardized score) (95% CI)[c] Med/High Fruit and Vegetable: 0.25 (-3.63, 4.12)	β (standardized score) (95% CI)[c] Low Fruit and Vegetable: -4.13 (-7.06, -1.21)	↑	Individual
		β (standardized score) (95% CI)[c] Breast Feeding ≥6 mo: -0.61 (-2.97, 1.75)	β (standardized score) (95% CI)[c] No Breast Feeding: -3.47 (-7.82, 0.98)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
		β (standardized score) (95% CI)[c] Breast Feeding ≥6 mo: -0.61 (-2.97, 1.75)	β (standardized score) (95% CI)[c] Breast Feeding <6 mo: -0.71 (-4.06, 2.65)	≈	Individual
		β (standardized score) (95% CI)[c] High Vitamin D: -0.11 (-2.72, 2.49)	Low Vitamin D: -2.49 (-6.87, 1.89) Med Vitamin D: -0.55 (-3.48, 2.39)	↑	Individual
†Lertxundi et al. (2019) Outcome: McCarthy GCI	INMA Enrollment: 2004–2008 Follow-up: 4–6 years	β (standardized score) (95% CI)[b] ≥4 mo: -0.94 (-3.29, 1.41)	β (standardized score) (95% CI)[b] <4 mo or only bottle: -1.88 (-5.17, 1.41)	↑	Individual
†Loftus et al. (2019) Outcome: FSIQ	CANDLE	High Maternal Fruit and Vegetable intake (>median) (Figure Only)	Low Maternal Fruit and Vegetable intake (<median) (Figure Only)	≈	Individual
		Higher Plasma Folate (Figure Only)	Lower Plasma Folate (Figure Only)	≈	Individual
Race/Ethnicity					
†Lu et al. (2021) Outcome: Academic Achievement	SEDA 2010–2016	Higher proportion of Black students Interaction term, β[c]: Math: 0.00035, p≥0.10 ELA: 0.00061, p≥0.10	β (score) (95% CI)[c] Lower proportion of Black students	≈	School-district level
		Higher proportion of Hispanic/Latino students Interaction term, β[c]: Math: 0.00134, p≤0.05	Lower proportion of Hispanic/Latino students	↑	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			(The interaction term in the EMM Reference Factor column indicates that the decrease in academic achievement is smaller at when there is a higher proportion of Hispanic/Latino Students. The upward arrow in the Direction of EMM column indicates that the inverse association is larger in magnitude when there is a lower proportion of Hispanic/Latino students compared to a higher proportion.)		
Sex					
†Lertxundi et al. (2019)	INMA Enrollment: 2004–2008 Follow-up: 4–6 years	β (standardized score) (95% CI)[b] Male: -3.58 (-6.76, -0.39)	β (standardized score) (95% CI)[b] Female: 1.51 (-0.85, 3.86)	↓	Individual
Socioeconomic Status					
Guxens et al. (2012) Outcome: BSID	INMA Enrollment: 2003–2008 Follow-up: childbirth to 2 years of age	β (standardized score) (95% CI)[c] High SES (occupation): -1.57 (-3.76, 0.62)	β (standardized score) (95% CI)[c] Low SES (occupation): -1.02 (-5.23, 3.19) Med SES (occupation): 0.16 (-3.79, 4.11)	↓	Individual
		β (standardized score) (95% CI)c High SES (maternal education = university): -0.72 (-3.93, 2.49)	β (standardized score) (95% CI)[c] Low SES (maternal education = primary school or less): -0.90 (-6.54, 4.73) Medium SES (maternal education = secondary school only): -2.22 (-5.13, 0.70)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Lu et al. (2021)	SEDA 2010–2016	Higher SES (Composite index >0) Interaction term, β: Math: -0.00528, p≤0.01 ELA: -0.00293, p≤0.01	Lower SES (Composite index ≤0) (The interaction terms in the EMM reference factor column indicate that the decrease in academic achievement is larger in the higher SES group. The downward arrow in the Direction of EMM column indicates that the inverse association is smaller in magnitude in the lower SES group compared to the higher SES group.)	↓	School-district level
†Loftus et al. (2019)	CANDLE Enrollment: 2006–2011 Follow-up: 4–6 yr	Higher SES (private insurance)	Lower SES (Medicaid/Medicare only)	≈ (Figure Only)	Individual

List of abbreviations in alphabetical order: BSID = Bayley Scales of Infant Development; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CI = confidence interval; ELA = English language arts; EMM = effect measure modifier; FSIQ = full scale intelligence quotient; GCI = general cognitive index; INMA = INfancia y Medio Ambiente; mo = month; SEDA = Stanford Education Data Archive; SES = socioeconomic status; yr = year(s)

[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 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.

9.3.1.1.2 Copollutants

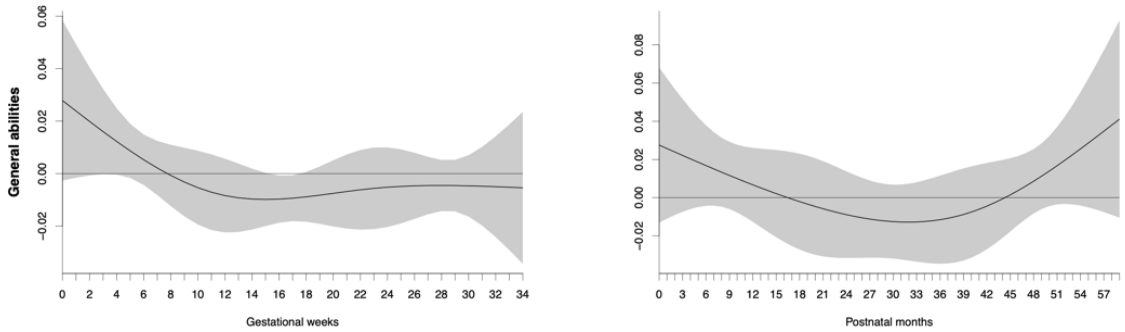
A limited body of evidence on long-term exposure to oxides of nitrogen and neurodevelopmental effects was assessed in the 2016 Oxides of Nitrogen ISA. No studies examined potential confounding by traffic-related copollutants. Recent studies can be drawn upon to assess the independent effect of NO_2 on cognitive function, but the evidence remains limited overall. Lu et al. (2021) examined the association between NO_2 exposure during the 12 months preceding testing and the average academic test scores (ELA and Math) of third to eighth grade students in the United States. The authors reported that a 7.3 ppb interquartile range (IQR) increase in NO_2 exposure was associated with a -0.004 standard deviation (95% CI: -0.006, -0.002) lower average math test score, and a -0.012 standard deviation (95% CI: -0.014, -0.01) lower average ELA test score in models that adjusted for $PM_{2.5}$ and ozone in addition to four classes of time varying covariates (student racial/ethnic compositions, student-level SES, urbanicity, and school district-level SES). The small negative associations of NO_2 with both average math and ELA score in the copollutant adjusted models were attenuated compared to the single pollutant results (see Figure 9-1) but remained. A small number of studies reported that associations did not change after adjustment for PM_{10} (Compa et al., 2023) or noise (Clark et al., 2012; van Kempen et al., 2012). Moderate correlations between noise and traffic pollutants including black carbon (BC) have been observed in multiple studies in Europe and the United States (see Chapter 2, Section 2.4.3.1), suggesting that controlling for traffic noise may also control, in part, for other traffic-related pollutants.

9.3.1.1.3 Exposure Windows

Studies of infant development typically examined NO_2 exposure during pregnancy. For studies of other neurocognitive effects, prenatal exposures, or annual average or multi-year average exposures during childhood, were generally examined. A small number of studies compared multiple exposure windows during pregnancy and childhood.

- A European multi-country study that is part of the ESCAPE project examined both prenatal and childhood (through age four to five years) NO_2 exposure, reporting a larger decrement in verbal abilities in association with childhood exposure (β: -0.8 [95% CI: -1.8, 0.3]) than with prenatal exposure (β:-0.4 [95% CI: -1.7, 0.9]) (Binter et al., 2022).
- Guilbert et al. (2023) used data from two French birth cohorts to examine the association of NO_2 exposure during the gestational (zero to 34 weeks) and postnatal periods (zero to 57 months) with cognitive abilities in childhood measured using the WPPSI or subtests from the NEPSY-II depending on the cohort (see Figure 9-2). Plots showing the effect of a 10 $\mu g/m^3$ increase in NO_2 during the gestational and postnatal periods indicated that increasing NO_2 exposure in early pregnancy was associated with small increases in general cognitive abilities. Associations were negative (i.e., increases in NO_2 exposure were associated with decreases in cognitive abilities) during later periods of pregnancy, but confidence overlapped with the null value. The pattern of associations between postnatal exposure and cognitive abilities had similarly wide confidence intervals, with trends toward increases in cognitive

abilities associated with increases in NO_2 exposure during the early and later months of the childhood period.



Note: Effect estimates presented are from fully adjusted models that include variables for recruitment center, maternal education, age, body mass index (BMI), fish consumption, parity, child sex, prenatal tobacco exposure, breastfeeding, child stimulation through maternal interactions, HOME, method of childcare, age at the cognitive test and the French European Deprivation Index.
Source: Guilbert et al. (2023). Copyright permission pending.

Figure 9-2 Lag-Specific Effect (β Coefficient) of a 10 µg/m^3 Increase in NO_2 Concentration on Children's General Cognitive Abilities. Shaded Areas Represent the 95% CI of the Estimate.

- Morgan et al. (2023) examined Latino mother and infant pairs enrolled in the Southern California Mother's Milk Study to determine the association of prenatal NO_2 exposure with neurodevelopment at age 2 assessed using the BSID. Although the associations with both composite and subscale scores were consistently negative in analyses of NO_2 exposure during each month of pregnancy, most confidence intervals included the null value. The authors report a decrease in BSID composite score in association with ninth month NO_2 exposure of β: -1.76 (95% CI: -3.50, -0.03) per 2.43 ppb increase in NO_2, however.

Overall, the limited number of studies that compare NO_2 exposure windows during pregnancy and early childhood report associations with confidence intervals that include the null value that do not reveal a clear pattern. These studies do not identify a window that is most strongly associated with cognitive effects in infants and children.

9.3.1.1.4 Conclusions and Remaining Uncertainties

Recent studies examine long-term (i.e., pregnancy and postnatal) NO_2 exposure and cognitive effects in infants and children (2–13 years old) (see Table 9-5). Cognitive effects were assessed using a variety of instruments that measured performance on tests of attention, infant development, cognitive ability, and academic achievement. A small number of studies of infant development report decreased performance on assessments of cognitive development with increasing prenatal NO_2 exposure, but confidence intervals generally include the null value. The available studies of cognitive abilities in childhood lacked consistency in both direction and magnitude. Although the evidence is limited overall, NO_2-associated cognitive effects were consistently observed in studies of infant development. Despite

some limitations related to confounder control, a recent study of academic achievement by Lu et al. (2021) reports small decreases in average ELA and math test scores in association with 12-month average NO_2 exposure at school that remained after adjustment for $PM_{2.5}$ and ozone. Studies examining performance on neuropsychological tests of attention and cognitive abilities report worse performance in association with higher NO_2 exposure on some tests and subscales, but the evidence is limited to a small number of studies making it difficult to identify patterns. Considerable uncertainty remains, however, regarding the independence of reported associations with NO_2 exposure from confounding by traffic-related pollutants.

Table 9-5 Summary of Evidence Pertaining to the Associations of Long-Term NO_2 and NO_X Exposure with Cognitive Function

Study and Location	Cohort and Population Study Period	Exposure Assessment and Concentration	Pollutant	Outcome Assessment Instrument	Effect Estimate (95% CI)
Academic Achievement					
†Lu et al. (2021) U.S.	SEDA data 3rd–8th grade students 2010–2016 N = 256,192,733 (tests)	Ensemble Annual avg 12.2–14.1 ppb (depending on the year, 2010–2016)	NO_2	Standardized Math Test Score Standardized ELA Test Score	β: -0.005 SD (-0.008, -0.003) β: -0.016 (-0.019, -0.014)
Infant Development					
Guxens et al. (2012) Spain	INMA Infants, 11–23 mo Enrollment: 2000–2008 Follow-up: birth to age 2 N = 1,889	LUR Pregnancy avg Mean: 15.4 ppb	NO_2	Infant mental development, BSID	β: -0.95 (-3.9, 1.89)* per doubling NO_2 concentration
Guxens et al. (2014) Netherlands, Germany, France, Italy, Greece, Spain	ESCAPE Infants and children, 1–6 yr Enrollment: 2003–2008 Follow-up 1–6 yr N = 9,482	LUR Pregnancy avg Median NO_2: 6.1–23.3 ppb (depending on the cohort)	NO_2 NO_X	General Cognition General Cognition (BSID, MCDI, MSCA, or DDST)	β: -0.43 (-1.81, 0.94) β: -0.16 (-0.71, 0.39)* per 20 μg/m³
†Morgan et al. (2023) Southern California	Mother's Milk Study Latino mother infant pairs Enrollment: 2016 Follow-up: 2 yr N = 161	IDW Pregnancy avg Mean: 17.89 ppb	NO_2	BDI-Composite Cognitive BDI-Composite Language	β: -2.88 (-10.78, 5.02) β: -1.36 (-8.31, 5.6)

Study and Location	Cohort and Population Study Period	Exposure Assessment and Concentration	Pollutant	Outcome Assessment Instrument	Effect Estimate (95% CI)
Tests of cognitive abilities in childhood					
†Loftus et al. (2019) Shelby Co., TN, U.S.	CANDLE Enrollment: 2006–2011 Follow-up: 4–6 yr N = 905	Kriging w/ LUR Annual avg Mean: 12.06 ppb	NO_2	FSIQ, Stanford Binet	β: 2.3 (-1.9, 6.5)
†Binter et al. (2022) U.K., France, Spain, Greece, Norway	BiB, EDEN, INMA, RHEA, MoBa Mother infant pairs Enrollment: 2003–2010 Follow-up: 4–5 yr N = 5,403	ESCAPE LUR Pregnancy avg Mean: 11.5 ppb Childhood avg Mean: 13.3 ppb	NO_2 Pregnancy NO_2 Childhood	Nonverbal abilities Verbal abilities Nonverbal abilities Verbal abilities (WPPSI, MSCA, and British Picture Vocabulary Scale)	β: 0.1 (-0.6, 0.8) β: -0.2 (-0.8, 0.5) per 5.1 ppb β: 0.5 (-0.6, 1.6) β: -0.7 (-1.7, 0.3) per 9.3 ppb
†Guilbert et al. (2023) France	EDEN and PELAGIE Mother infant pairs Enrollment: 2003–2006 Follow-up: 5–6 yr N = 1,271	Hybrid w/ Kriging for spatial interpolation Gestational wk Postnatal mo (0–57)	NO_2	General cognitive abilities (WPPSI, subtests of the NEPSY, and the WISC)	See Figure 9-2 in Section 9.3.1.1.2
†Lertxundi et al. (2019) Spain	INMA Mother infant pairs Enrollment: 2004–2008 Follow-up: 4–6 yr N = 2,021	ESCAPE LUR Pregnancy avg Mean: 17.2 ppb	NO_2	McCarthy GCI	β: -0.07 (-0.17, 0.03)
Neuropsychological Tests of Cognitive Function					
(van Kempen et al., 2012) Amsterdam, Netherlands	School children, 9–11 yr (2002) N = 485	Annual avg LUR Mean (School): 16.5 ppb Mean (Home): 16.4 ppb	NO_2 School NO_2 Home	DMST SRTT HECT SDST DMST SRTT HECT SDST	β: -0.3 (-0.54, -0.07) β: -0.17 (-18.7, 18.4) β: 0.113 (-0.03, 0.25) β: 0.094 (-0.13, 0.32) β: 0.169 (0.12, 0.22) β: -3.782 (-21.73, 14.17) β: 0.038 (-0.10, 0.18) β: 0 (-0.2, 0.2)
Clark et al. (2012) London, U.K.	RANCH School children (9–10 years old) (2001–2003) N = 719	Annual avg Hybrid (emissions, dispersion, LUR) Mean: 22.7	NO_2 School	Reading Comprehension Recognition Memory Information Recall	β: 0.01 (-1.43, 1.45) β: -0.09 (-0.77, 0.58) β_l: 0.23 (-0.69, 1.14) β_l: -0.04 (-0.28, 0.21) β: 0.68 (-3.27, 4.69)

Study and Location	Cohort and Population Study Period	Exposure Assessment and Concentration	Pollutant	Outcome Assessment Instrument	Effect Estimate (95% CI)
				Conceptual Recall Working Memory	
†Compa et al. (2023) Poland	Children ages 10–13 with ADHD and their typically developing peers 2020–2022 N = 652	Annual avg LUR 9.6 ppb	NO_2	ANT-derived outcomes that assess efficiency of attention (i.e., alerting, orienting, and executive control) CPT-derived outcomes that assess ability to sustain attention and stop prepotent motor response	Associations with multiple CPT and ANT-derived outcomes presented on figures. Overall, NO_2 was associated with less efficient orienting of attention on the ANT and more correct rejections on the CPT among those with ADHD.

List of abbreviations in alphabetical order: ADHD = attention-deficit/hyperactivity disorder; ANT = attention network test; avg = average; BDI = Bayley Development Index; BiB = Born in Bradford; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood ; CI = confidence interval; CPT = continuous performance test; DDST = Denver Developmental Screening Index; DMST = Digit Memory Span Test; EDEN = ´Etude des D´eterminants pr´e-et postnatals du d´eveloppement et de la sant´e de l'Enfant; ELA = English Language Arts; ESCAPE = European Study of Cohorts for Air Pollution Effects; FSIQ = Full-Scale Intelligence Quotient; GCI = general cognitive index; HECT = Hand-Eye Coordination Test; IDW = inverse distance weighting; INMA = INfancia y Medio Ambiente; LUR = land use regression; MCDI = McArthur Communicative Development Inventory; MoBa = Norwegian Mother and Child Cohort Study; MSCA = McCarthy Scales of Children's Abilities; NEPSY = Neuropsychological Assessment; NO_2 = nitrogen dioxide; NO_X = oxides of nitogen; PELAGIE = Perturbateurs Endocriniens, ´Etude Longitudinale sur les Anomalies de la Grossesse, l'Infertilite et l'Enfance; ppb = parts per billion; RANCH = Road Traffic and Aircraft Noise Exposure and Children's Cognition and Health; RHEA = Mother and Child Cohort in Crete; SDST = Symbol Digit Substitution Test; SEDA = Stanford Education Data Archive; SRTT = Simple Reaction Time Test; WISC = Wechler Intelligence Scale for Children; wk = week(s); WPPSI = Wechsler Preschool and Primary Scale of Intelligence.
†Studies published since the 2016 Oxides of Nitrogen ISA.

9.3.1.2 Animal Toxicological Studies of Cognitive Function

Although humans and rodents often differ in terms of specific behaviors, behavioral parallels can be drawn with consideration for similar functionality and underlying neurological mechanisms. Therefore, while neurobehavioral tasks in rodents rarely directly mimic human behavior, they are useful models to evaluate cognitive function. One of the most widely used rodent behavioral tasks is the Morris water maze (MWM), which assesses hippocampal-dependent spatial learning and memory. In humans, the hippocampus is similarly involved in spatial, semantic, and episodic memory, which are often impacted by disease and injury (Vorhees and Williams, 2014).

There were no toxicological studies evaluating oxides of nitrogen exposure and cognitive function in the 2016 Oxides of Nitrogen ISA. A small number of recent studies evaluated the effects of NO_2 exposure on spatial learning and memory using the MWM. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-2. Section 9.3.1.2.1 presents conclusions from these animal studies and summarizes the remaining uncertainties.

- Pregnant C57BL/6 mice were exposed to 2.5 ppm NO_2 (5 hours/day) throughout gestation and male and female pups were tested for cognitive function on the MWM from postnatal day (PND) 22 to PND 27. During the acquisition (learning) phase, NO_2-exposed males exhibited significantly longer latencies in locating the hidden platform and no effect on swimming speed. During the probe (memory) phase, exposed males swam for significantly less time and distance in the target quadrant and had fewer entries into the target quadrant compared to control animals, indicative of memory deficits (Yan et al., 2020). In contrast, exposed female mice did not show any significant performance impairments in the MWM.
- Yan et al. (2016b) exposed 2-month-old male C57BL/6J mice to 1.3 ppm and 2.7 ppm NO_2 (5 hours/day) for 4 weeks. Mice in the high-dose group took longer to learn where the hidden platform was located during the acquisition phase of the MWM, and the number of mice crossing into the target zone and time spent in the target quadrant significantly decreased compared to controls. Learning and memory dysfunction were less affected in the low-dose group, but these mice still spent significantly less time in the target quadrant during the probe trial compared to the control group, suggesting a potential dose-response relationship.

9.3.1.2.1 Conclusions and Remaining Uncertainties

In summary, recent studies have reported that NO_2 exposure impacts spatial learning and memory performance in male mice, but the evidence is limited. Furthermore, while one study investigated the impacts of gestational NO_2 exposure in mice, the second study investigated NO_2 exposure in young adult mice, which is less comparable to epidemiologic studies in children. Although MWM performance is primarily a function of learning and memory, other impairments, such as decreased motivation, motor deficits, stress, or altered perceptual function may confound the results. Yan et al. (2020) reported that swimming speed was unaffected by NO_2 exposure, suggesting that motor deficits or decreased motivation did not significantly impact the results, however, additional studies which consider these factors could further reduce this uncertainty. The finding that males may be more sensitive to these effects than females requires additional investigation. No PECOS-relevant studies have examined other tests of learning and memory or other aspects of cognitive function (e.g., attention, executive function), the effects of exposures during other sensitive developmental periods (e.g., postnatally), the impacts of various exposure durations, or the effects of multipollutant exposure on this endpoint.

9.3.2 Motor Function

Motor function encompasses a range of voluntary and involuntary movements. The development of motor skills in infants and children progresses sequentially from primitive autonomic responses (e.g., grasp or startle reflex) to increasingly advanced and coordinated actions, categorized into gross and fine motor skills. Gross motor skills include movements such as crawling, walking, and jumping, while fine motor skills involve precise, small-scale movements like writing and manipulating objects. Deficits in motor function can be an important marker of neurological health.

This Section summarizes key evidence from the 2016 Oxides of Nitrogen ISA and recent PECOS-relevant epidemiologic and animal toxicological evidence examining the relationship between long-term exposure to oxides of nitrogen and motor function. No PECOS-relevant studies of short-term exposure were identified. Recent epidemiologic studies (see Section 9.3.2.1) evaluated motor function in children using a variety of behavioral assessments measuring both fine and gross motor skills (e.g., Bayley Scale of Infant Development III, McCarthy Scales of Child Development, Clinal Kinematic Assessment Tool) or parental questionnaires (e.g., Ages and Stages Questionnaire 3). Animal toxicological studies (see Section 9.3.2.2) investigated reflex development, gait abnormalities, and open field behavior.

9.3.2.1 Epidemiologic Studies of Motor Function

Evidence from epidemiologic studies assessed in the 2016 Oxides of Nitrogen ISA did not strongly indicate that NO_2 exposure affects motor function of children (U.S. EPA, 2016). A large multi-country epidemiologic study in Europe, (Guxens et al., 2014) that analyzed data from six cohorts was assessed in the previous ISA. Prenatal NO_2 exposure (i.e., during the pregnancy period) was associated with a decrement in global psychomotor development (β: -1.28 [95% CI: -2.35, -0.21]) as was prenatal NO_X exposure (β: -0.44 [95% CI: -0.95, 0.08] per 20 μg/m^3) in the pooled analysis; however, these associations, which indicated decreased motor function in increasing NO_2 exposure, were limited to half the individual cohorts, and there was no clear pattern of association by gross or fine motor function or by age at which motor function was assessed. In addition, NO_2 was associated with poorer motor function in children in some locations but not in others. Results across a limited number of cross-sectional studies of children also lacked consistency (U.S. EPA, 2016).

Recent studies were conducted in the United States, Europe and Australia that build on the previous evidence. Study-specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Table 9-6 and Appendix A – Appendix Table 9-3. Conclusions and remaining uncertainties in the epidemiologic evidence for motor function are discussed in Section 9.3.2.1.1.

- Morgan et al. (2023) examined Latino mother and infant pairs enrolled in the Southern California Mother's Milk Study to determine the association of prenatal NO_2 exposure with neurodevelopment at age 2, assessed using the BSID. IDW weighting of AQS monitoring data within 50 km of participants homes was used to estimate residential exposure during the pregnancy period. Prenatal NO_2 exposure was associated with an imprecise (n=161) increase in composite motor score that was close to the null value (β: 2.26 [95% CI: -4.59, 9.12]). Associations with fine and gross motor scores were smaller in magnitude, and CIs also included the null value. The largest magnitude association with a specific time window of NO_2 exposure was for the 1st month of pregnancy and indicated a decrease in motor score (β: -0.35 [95% CI: -0.69, -0.002] per 9 ppb).

- Binter et al. (2022) examined the association of prenatal and childhood NO_2 exposure with motor function in four European cohorts combining the results from cohort-specific assessment instruments (i.e., Clinical Kinematic Assessment Tool, Peg moving task, and McCarthy Scales). The LUR model developed for ESCAPE was used to estimate NO_2 concentration (Beelen et al., 2013). Prenatal NO_2 concentration was weakly associated with a decrease in fine motor abilities (β: -1.4 [95% CI: -2.8, 0.1]) and a null association with gross motor abilities (β: 0 [95% CI: -1.5, 1.5]) was observed. The associations of childhood NO_2 concentration with fine and gross motor abilities (assessed at age 4–5 years old) encompassed the null value (β: 0.43 [95% CI: -0.75, 1.61] and β: -0.8 [95% CI: -2, 0.5], respectively).
- A recent analysis of the INMA cohort, which includes data for mother-child pairs, was conducted. Motor function was measured using the McCarthy Scales of Child Development between ages 4 and 6 years old (Lertxundi et al., 2019). Residential NO_2 exposure during the entire pregnancy was estimated using an LUR model that captured between 60 and 88% of the variability in the annual average NO_2 concentration. A small negative association (CIs included the null value) between prenatal NO_2 exposure and motor function was observed (-0.07 [95% CI: -0.21, 0.07], per 1 $\mu g/m^3$ NO_2). The association was stronger in males (β: -0.15 [95% CI: -0.28, -0.02] per 1 $\mu g/m^3$ NO_2) compared to females (β: -0.07 [95% CI: -0.33, 0.20] per 1 $\mu g/m^3$ NO_2).
- Ahmed et al. (2022) examined the association of residential NO_2 exposure during the prenatal period, the first year of life and over the child's lifetime with developmental delays including motor function in the Australian Mothers and their Children's Health (MatCH) study. Delays in fine and gross motor function was assessed between 1 and 66 months of age using the Ages and Stages Questionnaire (ASQ-3). NO_2 exposure was estimated at the mother's residence using a LUR model that captured 88% (Root Mean Square Error [RMSE] = 1.4 ppb) of the spatial variation across Australia and 66% of annual NO_2 (RMSE: 2 ppb) at independent validation sites. NO_2 exposure was not associated with developmental delay across the exposure periods examined. For example, the associations between NO_2 exposure during pregnancy and the child's lifetime with gross motor delay were OR: 0.97 (95% CI: 0.9, 1.03) and OR: 0.98 (95% CI: 0.91, 1.06), respectively.

9.3.2.1.1 Conclusions and Remaining Uncertainties

Overall, the limited body of literature does not provide clear evidence for an association between NO_2 exposure and motor function in studies of neurodevelopment. Most effect estimates are close to the null value and confidence intervals generally include the null value. As noted in the 2016 Oxides of Nitrogen ISA, there was a lack of consistency in the magnitude and direction of the associations across countries and age groups in a multi-country European study (Guxens et al., 2014). Recent studies in populations with mean or median concentrations (childhood or pregnancy avg) ranging from 6 to 23.3 ppb (see Table 9-6) do not reveal a clear pattern of associations. The few studies available have not identified populations that may be at higher risk, the shapes of concentration-response relationships, the potential influence of copollutant confounding on associations, or the most influential exposure windows. These gaps in the literature contribute to considerable uncertainty in the relationship between NO_2 exposure and decrements in motor function.

Table 9-6 Summary of Evidence Pertaining to the Associations of Long-Term NO_2 and NO_X Exposure with Motor Function

Study and Location	Cohort and Population Study Period	Exposure Assessment and Concentration	Pollutant	Outcome Assessment Instrument	Effect Estimate (95% CI)
Guxens et al. (2014) Netherlands, Germany, France, Italy, Greece, Spain	ESCAPE Infants and children, 1–6 yr Enrollment: 2003–2008 Follow-up 1–6 yr N = 9482	LUR Pregnancy avg Median NO_2: 6.1–23.3 (depending on the cohort)	NO_2 NO_X	BSID-Global Psychomotor	β: -0.68 (-1.25, -0.11) β: -0.44 (-1.25, -0.11)
†Morgan et al. (2023) So. California	Mother's Milk Study Latino mother infant pairs Enrollment: 2016 Follow-up: 2 yr N = 161	IDW Pregnancy avg Mean: 17.89 ppb	NO_2	Composite Motor BSID	β: 0.55 (-1.11, 2.22)
†Binter et al. (2022) U.K., France, Spain, Greece, Norway	BiB, EDEN, INMA, RHEA, MoBa Mother infant pairs Enrollment: 2003–2010 Follow-up: 4–5 yr N = 5,403	ESCAPE LUR Pregnancy avg 11.5 ppb Childhood avg 13.3 ppb	NO_2 Pregnancy NO_2 Childhood	Fine Motor Gross Motor Fine Motor Gross Motor (cohort-specific instruments)	β: -0.7 (-1.4, 0.1) β: 0 (-0.8, 0.7) β: 0.4 (-0.7, 1.5) β: -0.7 (-1.9, 0.5)
†Lertxundi et al. (2019) Spain	INMA Mother infant pairs Enrollment: 2004–2008 Follow-up: 4–6 yr N = 2021	ESCAPE LUR Pregnancy avg 17.2 ppb	NO_2	MSCA Motor	β: -0.07 (-0.21, 0.07)
Ahmed et al. (2022)	MatCH Mother-child pairs Enrollment: 1996 Follow-up: 2012–2013 N = 1,265	LUR Pregnancy avg Mean: 6.8 ppb Childhood lifestages Mean: 6 ppb	NO_2 Prenatal NO_2 Child 1st yr	ASQ-3	Moderate vs. Low: β: 1.12 (0.6, 2.07) High vs. Low: β: 0.77 (0.39, 1.54) Moderate vs. Low: β: 1.29 (0.65, 2.54) High vs. Low: β: 0.59 (0.26, 1.33)

List of abbreviations in alphabetical order: ASQ-3 = Ages and Stages Questionnaire version 3; BiB = Born in Bradford; BSID = Bayley Scales of Infant Development; EDEN = ´Etude des déterminants pré et post natals du développement de la santé de l'enfant; ESCAPE = European Study of Cohorts for Air Pollution Effects; IDW = inverse distance weighting; INMA = INfancia y Medio Ambiente; LUR = land use regression; MatCH = Mothers and their Children's Health; MoBa = Norwegian Mother and Child Cohort Study; MSCA = McCarthy Scales of Children's Abilities; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; ppb = parts per billion; RHEA = Mother and Child Cohort in Crete; yr = year(s).
†Studies published since the 2016 Oxides of Nitrogen ISA.

9.3.2.2 Animal Toxicological Studies of Motor Function

Understanding neurodevelopmental disorders often depends on insights gained from animal models. In human infants, abnormal reflexes reflect a disruption in typical nervous system development and often predict developmental disabilities. Although the timing of developmental milestones differs between rodents and humans, both species undergo a considerable period of postnatal development that is fundamentally comparable. Similarly, gait abnormalities in rodents can provide insights into human gait issues, despite differences in limb utilization (i.e., bipedal vs. quadrupedal gait). Observing similar patterns and motor disturbances in rodents can provide insight into the potential effects of toxicant exposure on neurodevelopmental disorders in humans.

There was limited toxicological evidence available to support effects on motor function in the 2016 Oxides of Nitrogen ISA. In a study of Wistar rats, NO_2 exposure during gestation (0.03, 0.05, 0.53, and 5.32 ppm for 6 hours per day) impaired reflex and gait development in the pups, evidenced by statistically significant changes in surface righting abilities (on PND 7), negative geotaxis (on PND 9), auditory startle response (on PND 14), air righting (on PND 14 and PND 18), and hindlimb support (on PND 18) (Tabacova et al., 1985). These effects were primarily detected in the highest exposure group (5.3 ppm), but early motor development tests (i.e., surface righting and negative geotaxis) were also significantly altered at lower exposure levels (0.53 and 0.05 ppm). Tabacova et al. (1985) also assessed open field behavior in these animals across developmental time points (PNDs 9, 14, 21, 30, and 60). On PND 9, pups had significantly reduced locomotor activity and increased passivity (5.32 ppm exposure group), significantly decreased head raisings (5.32 and 0.53 ppm exposure groups), and postural and gait deficits (0.05 ppm exposure and above). By PND 14, only deficits in posture and gait persisted. However, on PND 30 and PND 60, decreased locomotor activity reappeared in male rats (5.32 ppm exposure group). Rearing was also decreased on PND 30 in males (5.32 and 0.53 ppm exposure groups). Another study, Di Giovanni et al. (1994), demonstrated that gestational exposure to NO_2 (1.5 and 3.0 ppm continuously) did not significantly affect motor activity levels in male Wistar rat pups on PNDs 14 and 21. No recent PECOS-relevant studies have investigated NO_2 exposure on motor development, but recent studies of motor activity are discussed below, including studies in young adult rodents. While adult studies are not fully comparable to human neurodevelopmental effects, they may provide additional insight for this endpoint due to the limited availability of evidence. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-4. Section 9.3.2.2.1 provides additional discussion of dose-response information from these studies, and Section 9.3.2.2.2 presents conclusions and summarizes remaining uncertainties in the evidence.

- Li et al. (2022a) exposed pregnant C57BL/6J mice to 2.5 ppm NO_2 (5 hours/day) throughout gestation and measured the pups' behavior in an open field apparatus. During the 10-minute observation period, the total distance traveled was not significantly affected by the treatment condition. Another study by Li et al. (2021) reported similar results after exposing 7-week-old male and female C57BL/6J mice to 2.5 ppm NO_2 (5 hours/day) for 28 days.

- In 7-week-old female Sprague Dawley rats exposed to 0.5, 5, or 10 ppm NO_2 (4 hours/day), general activity was significantly increased in the medium- and high-dose groups after 3, 6, 9, 12, and 15 days of exposure (Ye et al., 2022). Activity was defined as head scratching, self-grooming, circling, climbing, back-and-forth movement, and tail biting. This study did not test male rats.

9.3.2.2.1 Dose Response

A clear dose-response relationship can inform and may strengthen conclusions on causality. Many of the motor deficits reported by Tabacova et al. (1985) appear to follow a dose-response relationship, although statistical significance was generally reached only in the highest exposure group (5.32 ppm). The most sensitive endpoints, negative geotaxis and postural and gait deficits, were significantly altered at 0.05 ppm NO_2 and above, with the magnitude of the effect increasing across dosing groups. None of the measured endpoints were affected at the lowest exposure level (0.03 ppm). Ye et al. (2022) also reported that the magnitude of hyperactivity increased along with increasing NO_2 exposure (0.5, 5, and 10 ppm). However, the two studies are present inconsistent motor activity findings, with one reporting decreased activity and the other reporting increased activity, which complicates the overall interpretation of these relationships. The other reviewed studies provide little insight into dose-response, since they either did not report group-specific information (Di Giovanni et al., 1994) or only examined a single exposure level (Li et al., 2022a; Li et al., 2021).

9.3.2.2.2 Conclusions and Remaining Uncertainties

In summary, evidence from a single study suggests that gestational NO_2 exposure alters neuromotor development, evidenced by deficits in reflexes, posture, and gait during developmental timepoints (PNDs 9–18) at exposure levels as low as 0.05 ppm. No recent studies have attempted to replicate these findings. General motor activity was also measured during development and into adulthood by multiple studies with mixed results. There is some evidence that gestational NO_2 exposure reduced motor activity in postnatal and adolescent rats, but this was not consistent across time points or studies. Exposure to NO_2 in 7-week-old rodents, which are typically considered young adults, increased motor activity in one study, but additional studies did not find a significant effect. These discordant results may be explained by differences in study design or endpoint measurement methods, and additional studies could alter these conclusions. No PECOS-relevant studies have examined other elements of motor function (e.g., coordination, balance, fine motor skills, strength), the effects of exposures during other sensitive developmental periods (e.g., postnatally), the impacts of various exposure durations, or the effects of multipollutant exposure on this endpoint.

9.3.3 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities. Improvements in diagnostic tools, changes in diagnostic criteria, and increased awareness of ASD have contributed to substantial increases in diagnosis rates in the past two decades. To account for this, studies in this review have identified associations between oxides of nitrogen and ASD diagnoses across a wide range of ages and birth years, and recent studies adjusted for calendar year or birth year in their models. Section 9.3.3.1 summarizes key evidence from the 2016 Oxides of Nitrogen ISA and recent PECOS-relevant epidemiologic evidence examining the relationship between long-term oxides of nitrogen exposure and ASD risk. Section 9.3.3.2 summarizes PECO-relevant animal toxicological evidence evaluating aspects of social communication and repetitive behaviors that may provide insight into ASD in humans.

9.3.3.1 Epidemiologic Studies of Autism Spectrum Disorder

Recent U.S. case-control studies in the 2016 Oxides of Nitrogen ISA evaluated associations between long-term NO_2 exposure and risk of ASD diagnosis (Volk et al., 2014; Volk et al., 2013) in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. NO_2 exposure during each trimester of pregnancy, the entire pregnancy, and the first postnatal year was positively associated with risk of ASD diagnosis (Volk et al., 2013). Furthermore, exposure to higher concentrations of NO_2 were associated with higher odds of ASD diagnosis in children with two C-alleles of the gene encoding the MET receptor tyrosine kinase promoter variant rs1858830 (CC MET) genotype, compared with the CG or GG genotype (Volk et al., 2014). The CC MET genotype is associated with decreased MET protein in the brain and has been associated with ASD risk. However, there were concerns regarding the adequacy of the CALINE4 line-source air quality dispersion model used in the studies for capturing the spatial heterogeneity of NO_2 concentrations, and the high correlation of NO_X with EC and CO ($r \sim 0.99$) using this model in previous studies complicated inference about the independent contribution of NO_2.

Recent studies evaluated associations with ASD in additional populations that may be at increased risk and compared across different time windows of exposure. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Figure 9-3, and Appendix A – Appendix Table 9-5.

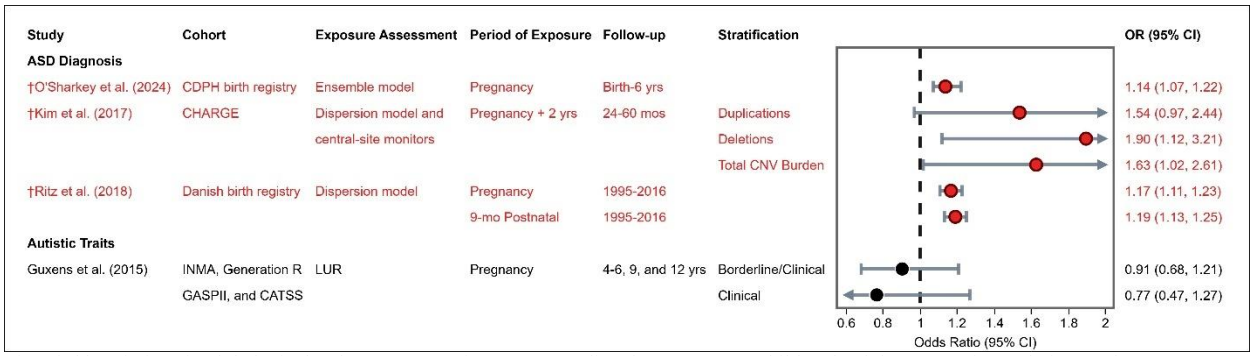
- Recent studies extended the results of the CHARGE studies by evaluating interactions by the level of copy number variation (CNV) burden and folic acid intake (Goodrich et al., 2017; Kim et al., 2017). Kim et al. (2017) observed positive associations between ASD diagnosis between 24–60 months of age and NO_2 exposure spanning pregnancy through the first two postnatal years (OR duplications: 1.54 [95% CI: 0.97, 2.44]; OR deletions: 1.90 [95% CI: 1.12, 1.3.21]; OR total CNV burden: 1.32 [95% CI: 1.01, 1.73] per 1 standard deviation (SD) (5.7 ppb) increase in NO_2). No evidence for interaction was observed. In contrast, Goodrich

et al. (2017) reported an imprecise positive association among those with low folic acid intake (OR low folic acid: 1.53 [95% CI: 0.91, 2.56] per 2 SD (9.5 ppb) increase in NO_2) and a negative imprecise association among those with high folic acid intake (OR high folic acid: 0.74 [95% CI: 0.46, 1.19] per 2 SD (9.5 ppb) increase in NO_2) for NO_2 exposure in the first trimester. A couple of California studies replicated the abovementioned issues in exposure assessment methods from the older CHARGE studies by using the CALINE4 dispersion model with monthly air quality data based on 24-hour average concentrations obtained from monitors 5 km from homes, if available, or assigning concentrations by IDW over a 50 km area, and they furthermore did not report what proportion of subjects were assigned at each scale.

- Recent large U.S. studies evaluated associations between prenatal NO_2 modeled using ensemble machine learning methods and ASD diagnosis using large administrative datasets in Southern California. Using a case-control design, O'Sharkey et al. (2024) reported a positive association (OR: 1.14 [95% CI: 1.07, 1.22] per 10 ppb increase in NO_2) between NO_2 exposure during pregnancy and ASD diagnosis between birth to age 6 years identified from the California Department of Developmental Services Client Development Evaluation Report according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5. The authors evaluated sex, maternal education, maternal nativity, maternal race/ethnicity, and neighborhood socioeconomic status (nSES) as potential modifiers. Those with low nSES and low maternal education appeared to have stronger positive associations between NO_2 exposure and ASD risk. Adjustment for $PM_{2.5}$ resulted in attenuated effect estimates with confidence interval crossing the null. Rahman et al. (2022) conducted a retrospective cohort study and observed a null association (hazard ratio [HR]: 0.99 [95% CI: 0.90, 1.09] per 17.4 ppb increase in NO_2) between weekly averages of maternal gestational exposure and ASD diagnosis (International Classification of Diseases [ICD]-9 codes 299.0, 299.1, 299.8, and 299.9; ICD-10 codes F84.0, F84.3, F84.5, F84.8, and F84.9). Rahman et al. (2022) adjusted for season but not smoking in their analysis.
- Pagalan et al. (2018) reported positive associations between ASD diagnosis (median age 4.2-years) and median monthly NO exposure (OR for NO: 1.07 [95% CI: 1.01, 1.13] per IQR (10.7 ppb) of NO) and NO_2 exposure (OR for NO_2: 1.06 [95% CI: 0.99, 1.12] per IQR (4.8 ppb) of NO_2) exposures in a small population-based birth cohort in Vancouver, Canada. This study used well-validated LUR models at 10 m^2 spatial resolution. Stronger associations were observed for male children (OR for NO: 1.09 [95% CI: 1.02, 1.15] per IQR (10.7 ppb) of NO; OR for NO_2: 1.07 [95% CI: 1.00, 1.13] per IQR (4.8 ppb) of NO_2), while estimates were null in female children (OR for NO: 0.98 [95% CI: 0.83, 1.13] per IQR (10.7 ppb) of NO; OR for NO_2: 1.00 [95% CI: 0.86, 1.16] per IQR (4.8 ppb) of NO_2). There were no differences by trimester of exposure.
- A matched case-control study in Ontario, Canada (Murphy et al., 2024) reported consistent and strong positive associations between weekly average NO_2 exposure during different pregnancy windows from 13 weeks preconception to delivery and ASD diagnosis among children aged 2–6 years. Associations were strongest in early-to-mid pregnancy and decreased towards delivery. Further details on results using distributed lag non-linear models (DLNMs) are provided in Section 9.3.3.1.3.
- A Danish population-based case-control study (Ritz et al., 2018) also observed positive associations between ASD diagnosis and NO_2 exposure during pregnancy (OR prenatal: 1.17 [95% CI: 1.11, 1.23] per 10 ppb increase in NO_2) and 9 months after birth (OR postnatal: 1.19 [95% CI: 1.13, 1.25]). ASD cases in this cohort were born between 1989–2013 and diagnosed between 1996–2016. Exposure was modeled using a 1 km x 1 km dispersion model.

- A national cohort study in Taiwan (Wang et al., 2021a) reported an increased risk of ASD diagnosis (median age 5.66 years) in association with NO_2 exposures averaged over each trimester of pregnancy and the entire period of gestation (HR entire pregnancy: 1.39 [95% CI: 1.19, 1.62] per 10 ppb increase in NO_2) in Cox proportional hazard models adjusted for only sex and calendar year. Further adjustment for comorbidities including bipolar disorder, depressive disorder, phobic disorder, obsessive compulsive disorder, intellectual disabilities, and preterm birth slightly strengthened the magnitude of the associations.
- A small (n = 126) cohort study (Bragg et al., 2024) in 4 U.S. cities evaluated mother-child pairs with a previous child diagnosed with ASD. The authors reported null results between NO_2 exposures during pregnancy and two measures of ASD outcomes at 36 months of age: ASD diagnosis and autistic traits assessed using the Social Responsiveness Scale (SRS) [b for SRS: -0.01 (95% CI: -0.77, 0.83); OR for ASD diagnosis: 1.00 (95% CI: 0.92, 1.08) per 1 ppb increase in NO_2]. Exposure to NO_2 was derived using an ensemble model.
- Recent cohort studies in European populations did not provide evidence for positive associations between NO_2 exposure modeled using ESCAPE LUR models and autistic traits and symptoms. Li et al. (2023b) reported very small but precise negative associations [β: -0.0120 (95% CI: -0.0210, -0.0032) per IQR increase in NO_2] with NO_2 concentrations in linear mixed models adjusted for the interaction between environmental exposures and follow-up time in a Dutch cohort of children and young adults (10–28 years). These associations attenuated to null in sensitivity analyses adjusting for multiple testing using the Benjamini-Hochberg procedure. Guxens et al. (2015) also reported null associations between NO_2 exposure and autistic traits in the borderline/clinical range in three birth cohorts in the Netherlands (age 6 years), Italy (age 4 years), and Spain (age 4–5 years), and one longitudinal twin study in Sweden (age 9 or 12 years) that were part of the ESCAPE project.

Of the studies discussed above present additional analyses evaluating the lifestages and populations that may be at increased risk of NO_2-associated ASD, the potential influence of copollutants on reported associations with ASD, and the appropriate NO_2 exposure windows for examining associations with ASD. The evidence on these topics is discussed in greater detail below in Sections 9.3.3.1.1, 9.3.3.1.2, and 9.3.3.1.3, respectively. Section 9.3.3.1.4 presents conclusions from epidemiologic studies of ASD and discusses the remaining uncertainties in the epidemiologic evidence.



List of abbreviations in alphabetical order: ASD = autism spectrum disorder; CATSS = Child and Adolescent Twin Study in Sweden; CDPH = California Department of Public Health; CHARGE = Childhood Autism Risks from Genetics and Environment; CI = confidence interval; GASPII = Gene and Environment Prospective Study on Infancy in Italy; INMA = INfancia y Medio Ambiente; LUR = land use regression; mo = month; OR = odds ratio; yr = year(s).
Note: Red = recent studies and those not included in 2016 Oxides of Nitrogen ISA. Results are standardized to a 10 ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 9-3 Associations between long-term nitrogen dioxide exposure and ASD diagnosis or autistic traits.

9.3.3.1.1 Lifestages and Populations

A few studies assessed sex in stratified analyses of the relationship between exposure to oxides of nitrogen and ASD diagnosis and traits, which are summarized below and in Table 9-7.

Recent studies evaluated differences in ASD risk associated with exposure to oxides of nitrogen between male and female children but did not find strong support for sex differences.

- In Pagalan et al. (2018), positive associations with both NO and NO_2 were slightly increased in males while these associations were null in females. The confidence intervals for ORs in female children were twice that in male children, which is likely derived from the much smaller number of ASD cases among females (n = 216) vs. among males (n = 1,091).
- Ritz et al. (2018) observed positive associations between 9 months postnatal NO_2 exposure and ASD diagnoses that did not differ between males and females. O'Sharkey et al. (2024) also did not report differences between males and females for the association between entire pregnancy NO_2 exposure and ASD diagnosis.
- Rahman et al. (2022) observed null associations for both males (HR: 1.00 [95% CI: 0.90, 1.11]) and females (HR: 0.94 [95% CI: 0.74, 1.15]) per 17.4 ppb increase in weekly averages of maternal gestational NO_2 exposure and ASD diagnosis.
- Guxens et al. (2015) reported null associations for both males and females between NO_2 and NO_X exposure during pregnancy and autistic traits. ORs among females (OR for NO_2: 0.85 [95% CI: 0.65, 1.11] per 5.3 ppb increase in NO_2; OR for NO_X: 0.91 [95% CI: 0.70, 1.10] per 16.3 ppb increase in NO_X) tended to be slightly negative compared to ORs among males (OR for NO_2: 1.02 [95% CI: 0.82, 1.27] per 5.3 ppb increase in NO_2; OR for NO_X: 1.10 [95% CI: 0.86, 1.40] per 16.3 ppb increase in NO_X).

A single study from the 2016 Oxides of Nitrogen ISA reported evidence of a synergistic multiplicative interaction by MET genotype such that those with the CC MET genotype in the top NO_2

exposure quartile (≥17.5 ppb) had increased odds (OR: 3.6 [95% CI: 1.3, 12.7]) of ASD diagnosis compared to those with the CG/GG genotype in the bottom three exposure quartiles (Volk et al., 2014). One recent study evaluated the interaction between NO_2 exposure and the level of CNV burden across the genome in association with ASD diagnosis. There were no stratified analyses, but the association between NO_2 exposure in the first postnatal year and ASD diagnoses was strongest among those with low CNV duplication burden (Kim et al., 2017). Overall, there was no statistical evidence for an interaction between NO_2 exposure and CNV burden.

Certain lifestyle factors such as prenatal diet has been associated with ASD and may interact with environmental exposures to affect neurodevelopmental outcomes. Subgroups stratified by maternal folic acid intake was evaluated in one study. Goodrich et al. (2017) reported a positive but imprecise association among pregnant women with low folic acid intake (<800 µg) (OR low folic acid: 1.53 [95% CI: 0.91, 2.56] per 2 SD (9.5 ppb) increase in NO_2) and a negative, imprecise association among those with high folic acid intake (OR high folic acid: 0.74 [95% CI: 0.46, 1.19] per 2 SD (9.5 ppb) increase in NO_2) in the first trimester. These results were somewhat attenuated, with effect estimates closer to the null, when using NO_2 exposure during the second trimester, and there was no difference in the level of folic acid intake during the third trimester.

O'Sharkey et al. (2024) evaluated maternal education, maternal nativity, maternal race/ethnicity, and nSES as potential modifiers. Those who had low nSES, had U.S.-born mothers, and had low maternal education appeared to have stronger positive associations between NO_2 exposure and the likelihood of ASD diagnosis.

The impact of urbanicity on associations between NO_2 and ASD diagnosis was evaluated in one study. Ritz et al. (2018) observed that the OR remained positive among those living in large cities (OR urban: 1.12 [95% CI: 1.04, 1.22]), while attenuating to null among those living in rural/provincial towns (<10,000 people) (OR rural: 1.02 [95% CI: 0.89, 1.15]). A similar pattern was observed for $PM_{2.5}$ and PM_{10}, which may indicate stronger associations with locally generated traffic-related air pollutants than with long-ranged transported PM and NO_2.

Table 9-7 Epidemiologic Studies Evaluating Effect Measure Modification between Long-Term NO, NO_2, and NO_X Exposure and Autism Spectrum Disorder

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Sex						
†Guxens et al. (2015)	GASPII, CATSS, Generation R, INMA	Autistic Traits Score within Borderline/	OR (95% CI)[b] NO_2	OR (95% CI)[b] NO_2	↑	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Enrollment: 1992-2008 Follow-up: age 4–10 yr	Clinical Range	Female: 0.74 (0.45, 1.22)	Male: 1.04 (0.69, 1.57)		
			OR (95% CI)[c] NO_X Female: 0.91 (0.70, 1.10)	OR (95% CI)[c] NO_X Male: 1.10 (0.86, 1.40)	↑	Individual
†O'Sharkey et al. (2024)	CDPH birth registry Enrollment: January 2016–December 2019	ASD Dx	OR (95% CI)[b] Girls: 1.17 (1.03, 1.33)	OR (95% CI)[b] Boys: 1.14 (1.07, 1.22)	≈	Individual
†Pagalan et al. (2018)	British Columbia Provincial Health Insurance Program Enrollment: 2004–2009 Follow-up: through December 2014	ASD Dx	OR (95% CI)[c] NO_2 Female: 1.00 (0.86, 1.16)	OR (95% CI)[c] NO_2 Male: 1.07 (1.00, 1.13)	↑	Individual
			NO Female: 0.98 (0.83, 1.13)	NO Male: 1.09 (1.02, 1.15)	↑	Individual
†Rahman et al. (2022)	KPSC Enrollment: January 2001–December 2014 Follow-up: Age 18 mo–December 2019	ASD Dx	HR (95% CI)[c] Female: 0.93 (0.73, 1.15)	HR (95% CI)[c] Male: 1.00 (0.90, 1.11)	≈	Individual
†Ritz et al. (2018)	Danish Medical Birth Registry Enrollment:	ASD Dx	OR (95% CI)[b] Female: 1.21 (0.99, 1.47)	OR (95% CI)[b] Male: 1.10 (0.98, 1.24)	↓	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	1996–2016 Birth: 1989–2013					
Genetics						
†Kim et al. (2017)	CHARGE Enrollment: 2003–NR	ASD Dx	OR (95% CI)[b] Total CNV Burden: 1.63 (1.02, 2.61)	OR (95% CI)[b] Deletions: 1.90 (1.12, 3.21)	↑	Individual
				Duplications: 1.54 (0.97, 2.44)	≈	Individual
Behavioral Factors: Diet						
†Goodrich et al. (2017)	CHARGE Enrollment: 2003–NR	ASD Dx - 1st Trimester	OR (95% CI)[c] High Folate: 0.74 (0.46, 1.19)	OR (95% CI)[c] Low Folate: 1.53 (0.91, 2.56)	↑	Individual
		ASD Dx – 2nd Trimester	High Folate: 0.88 (0.57, 1.38)	Low Folate: 1.25 (0.73, 2.14)	↑	Individual
		ASD Dx – 3rd Trimester	High Folate: 1.19 (0.74, 1.92)	Low Folate: 1.04 (0.64, 1.71)	↓	Individual
Socioeconomic Status: Education						
†O'Sharkey et al. (2024)	CDPH birth registry Enrollment: January 2016–December 2019	ASD Dx	OR (95% CI)[b] At Least Some College: 1.05 (0.96, 1.16)	OR (95% CI)[b] ≤12th Grade: 1.26 (1.09, 1.46)	↑	Individual
				High School Graduate: 1.20 (1.07, 1.34)	↑	Individual
Socioeconomic Status: Neighborhood Composite						
†O'Sharkey et al. (2024)	CDPH birth registry Enrollment: January 2016–December 2019	ASD Dx	OR (95% CI)[b] High nSES: 1.11 (0.95, 1.30)	OR (95% CI)[b] Low nSES: 1.29 (1.17, 1.43)	↑	Block Group
				Medium nSES: 1.00 (0.91, 1.10)	↓	Block Group
Region/Urbanicity						
†Ritz et al. (2018)	Danish Medical Birth Registry	ASD Dx	OR (95% CI)[b] Provincial/Rural: 1.03 (0.84, 1.28)	OR (95% CI)[b] Large Cities: 1.21 (1.06, 1.38)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Enrollment: 1996–2016 Birth: 1989–2013					

List of abbreviations in alphabetical order: ASD = autism spectrum disorder; CATSS = Child and Adolescent Twin Study in Sweden; CDPH = California Department of Public Health; CHARGE = Childhood Autism Risks from Genetics and Environment; CI = confidence interval; CNV = copy number variation; Dx = diagnosis; EMM = effect measure modification; GASPII = Gene and Environment Prospective Study on Infancy in Italy; HR = hazard ratio; INMA = INfancia y Medio Ambiente; KPSC = Kaiser Permanente Southern California; nSES = neighborhood socioeconomic status; NO = nitric oxide; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; NR = not reported; OR = odds ratio; yr = year(s).
[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 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.

9.3.3.1.2 Copollutants

A single U.S. study evaluated the influence of a copollutant on the association between NO_2 and ASD diagnosis. O'Sharkey et al. (2024) reported attenuation of associations to null in the overall population (OR single pollutant: 1.05 [95% CI: 1.02, 1.07] vs. OR copollutant: 1.01 [95% CI: 0.99, 1.04] per 3.71 ppb of NO_2) and in subgroups stratified by sociodemographic characteristics with the inclusion of $PM_{2.5}$ in the model (Pearson's $\rho = 0.28$).

A Canadian case-control study (Murphy et al., 2024) reported strengthened associations for ASD with increasing NO_2 exposure across stages from preconception to delivery in multipollutant models including $PM_{2.5}$ and O_3. Pearson's correlation coefficients between NO_2 and O_3 ranged from -0.31 to -0.26, while correlation coefficients between NO_2 and $PM_{2.5}$ were between 0.41 and 0.46.

9.3.3.1.3 Exposure Windows

The critical period of exposure to air pollution for the development of ASD is unclear; however, the majority of those with ASD are diagnosed before 3 years of age, and most symptoms persist into adulthood. Therefore, exposure to neurotoxicants during pregnancy, birth, and early childhood years is of particular relevance. One case-control study in the 2016 Oxides of Nitrogen ISA reported strong positive associations for NO_2 exposure during each trimester of pregnancy, the full pregnancy period, and the first postnatal year (Volk et al., 2013). The associations were stronger for later exposures compared to earlier exposures. A few recent studies also evaluated associations during pregnancy and early childhood, but no clear pattern is apparent.

- In Pagalan et al. (2018), associations during the first trimester of pregnancy were slightly stronger for both NO (OR: 1.06 [95% CI: 1.01, 1.11] per IQR (10.7 ppb) increase in NO) and NO_2 (OR: 1.06 [95% CI: 1.00, 1.12] per IQR (4.8 ppb) increase in NO_2) compared to associations during the second and third trimesters and during the full pregnancy. However, the differences were marginal.
- Ritz et al. (2018) reported similar positive results for NO_2 exposure during pregnancy (OR: 1.10, [95% CI: 1.06, 1.13] per IQR increase in NO_2) and 9 months after birth (OR: 1.11, CI: (1.07, 1.14) per IQR increase in NO_2). There was no difference in associations by exposures during different trimesters of pregnancy.
- Using DLNMs with two knots, Murphy et al. (2024) reported the strongest positive associations for weekly average NO_2 exposure and ASD diagnosis during early-to-mid pregnancy that decreased in magnitude towards delivery. The preconception period OR was 1.2 (95% CI: 1.1, 1.2) and the gestational period OR was 2.5 (95% CI: 2.2, 2.8).
- In Wang et al. (2021a), associations between ASD diagnosis and NO_2 concentrations were strongest in the first trimester of pregnancy (HR: 1.34 [95% CI: 1.19, 1.52] per 10 ppb increase in NO_2) and remained positive but attenuated in the second (HR: 1.22 [95% CI: 1.07, 1.38]) and third trimesters (HR: 1.18 [95% CI: 1.04, 1.34]).
- Although all associations were imprecise, Goodrich et al. (2017) observed the strongest associations with NO_2 exposure during the first trimester and weaker associations in subsequent trimesters in analyses stratified by folic acid intake.
- Among those with low CNV burden, associations of ASD risk and NO_2 exposure during the first postnatal year were generally the strongest compared to associations using NO_2 exposure during pregnancy and during the second postnatal year (Kim et al., 2017).
- Rahman et al. (2022) used a distributed lag model in a Cox proportional hazard regression to model associations between weekly NO_2 gestational exposures and ASD diagnosis. The authors did not identify a critical window of exposure, although associations with exposures in the first trimester of pregnancy were generally positive while associations became inverse at later exposures.

9.3.3.1.4 Conclusions and Remaining Uncertainties

Recent available U.S. case-control studies from the 2016 Oxides of Nitrogen ISA reported positive associations between NO_2 exposures and ASD diagnosis, but deficiencies in the exposure assessment method limited the strength of inference from this evidence. Recent studies expanded the analyses within the same population by assessing effect modification by folic acid intake and CNV burden, but, as above, the same uncertainty regarding the exposure model used and high correlations with other pollutants remained unresolved. One longitudinal cohort study in Canada and a case-control study in Denmark also reported positive associations between NO_2 or NO and ASD diagnosis, but one cohort study reported null associations. For autistic traits, one small U.S. cohort study and a couple of cohort studies in multiple European countries observed null associations with NO_2 exposure. Calendar time or birth year was considered in some studies to account for changes in ASD diagnostic criteria over time (Rahman et al., 2022; Wang et al., 2021a; Pagalan et al., 2018; Ritz et al., 2018). Recent studies evaluated the potential for effect modification by sex, birth year, urbanicity, CNV burden, CC MET genotype, or

nutrient intake, but there is not sufficient evidence to conclude the presence of increased risk in these subgroups. Studies comparing estimates based on exposures across trimesters of pregnancy or before and after birth supported a trend towards stronger associations with NO_2 exposures in early to mid-pregnancy, compared to later in pregnancy or postnatal periods. However, uncertainties in the overall body of epidemiologic evidence for the relationship between NO_2 and ASD limit confidence in conclusions regarding exposures during a particular developmental period.

Several other uncertainties remain. Because NO_X and NO_2 are often highly correlated with other pollutants, there is potential for copollutant confounding, which has only been evaluated in recent studies. On study reported strengthened associations after adjustment for $PM_{2.5}$ and O_3 simultaneously while the other reported attenuated results after $PM_{2.5}$ adjustment. In addition, recent studies have not examined the shape of the concentration-response function for the relationship between oxides of nitrogen and ASD.

9.3.3.2 Animal Toxicological Studies of Autism Spectrum Disorder

Rodent models are not capable of fully reproducing complex human disorders. Rather, they aim to mimic specific aspects of the human disorder, such as the symptomology, underlying pathophysiology, or both to test hypotheses about the human condition. Some components of ASD, like speech deficits and impaired theory of mind, cannot be tested in rodents; however, the core features of ASD do have behavioral correlates in rodents, indicated by changes in rodents' natural social behaviors and increases in repetitive, ritualistic behaviors that are resistant to change. Studies that find co-occurring deficits across both domains are presumptively more relevant to human ASD than results from single behavioral assays.

Toxicological studies of rodent behavior which are relevant to features in ASD fall into three main categories: abnormal social interactions, impairments in social communication, and repetitive or ritualistic behaviors (Crawley, 2007). A single study reviewed in the 2016 Oxides of Nitrogen ISA investigated the effect of gestational NO_2 exposure (1.5 and 3.0 ppm continuously) on pup ultrasonic vocalizations (USVs) (Di Giovanni et al., 1994). USVs, which are emitted by pups when isolated from their mother and siblings, serve as early indicators of emotional state and social communication. The authors reported that the duration of USVs was significantly decreased only in the high-dose exposure group on PND 10 and PND 15, but other USV parameters (e.g., rate of calls, frequency range) were not affected. No additional studies are available to inform deficits in social communication, but a single recent study investigated repetitive behaviors. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-6. Section 9.3.3.2.1 summarizes conclusions and remaining uncertainties from this animal evidence.

- Exposure to 2.5 ppm NO_2 (5 hours/day) for four weeks in 7-week-old C57Bl/6J mice significantly increased marble burying behavior in males but not females (Li et al., 2021). Rodents innately engage in burying behaviors in their home cage but increases in this behavior can be reflective of a repetitive behavior that is highly resistant to change (Thomas et al., 2009).

9.3.3.2.1 Conclusions and Remaining Uncertainties

A small number of animal toxicological studies evaluated the impact of NO_2 exposures on behaviors that may be relevant for ASD. The evidence suggests that NO_2 exposure may alter postnatal social communication and increase repetitive behaviors in young adults. However, the available studies have not fully characterized the effect of NO_2 on behaviors relevant to ASD in rodents. While USVs are relevant for social communication in pups, it is not clear if social communication deficits would persist past the postnatal period, and the impact of NO_2 on other aspects of social behavior in juvenile and adult rodents has not been evaluated (e.g., social approach, social preference, play behavior, aggression). Findings in the marble burying assay suggested that males may be more sensitive to NO_2 exposure than females, which should be further considered along with additional tests of repetitive, ritualistic behavior. Studies that assess both behavioral domains would be particularly informative. More broadly, the impact of NO_2 exposure during other sensitive developmental periods (e.g., postnatally), the duration of NO_2 exposure, the dose-response relationship, and multipollutant exposure on these endpoints need further investigation.

9.3.4 Externalizing Behaviors

Externalizing behaviors are a cluster of outwardly directed actions including hyperactivity, impulsivity, defiance, and aggression. In children, these behaviors may be signs of disorders such as ADHD, conduct disorder, and oppositional defiant disorder. Section 9.3.4.1 summarizes recent PECO-relevant epidemiologic evidence examining the relationship between long-term oxides of nitrogen exposure and ADHD diagnoses, ADHD symptoms, and related externalizing behavior measures (e.g., attention). Section 9.3.4.2 summarizes the supporting animal toxicological evidence on hyperactivity. Section 9.3.4.3 summarizes recent epidemiologic evidence examining long-term oxides of nitrogen exposure and aggressive behavior. There were no PECOS-relevant animal toxicological studies of aggression.

9.3.4.1 Epidemiologic Studies of Externalizing Behaviors – ADHD and Related Behaviors

No studies of attention-related behaviors and hyperactivity from previous reviews met PECOS criteria for the current ISA. Recent studies reported some evidence for associations between long-term NO_2 exposures and ADHD diagnoses (Yuchi et al., 2022; Thygesen et al., 2020; Min and Min, 2016). Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 9-7 and Figure 9-4.

- In a birth cohort of all live births in Vancouver, Canada in 2000–2001, Yuchi et al. (2022) reported a null association (HR: 1.01 [95% CI: 0.96, 1.07]) between NO_2 exposure during the

first three years of life assessed using well-validated national LUR models (r^2 = 0.73) and ADHD incidence. ADHD diagnoses were ascertained among children ages 3–10 years from hospital record diagnoses, physician visits from the universal health insurance plan, and pharmacy prescriptions.

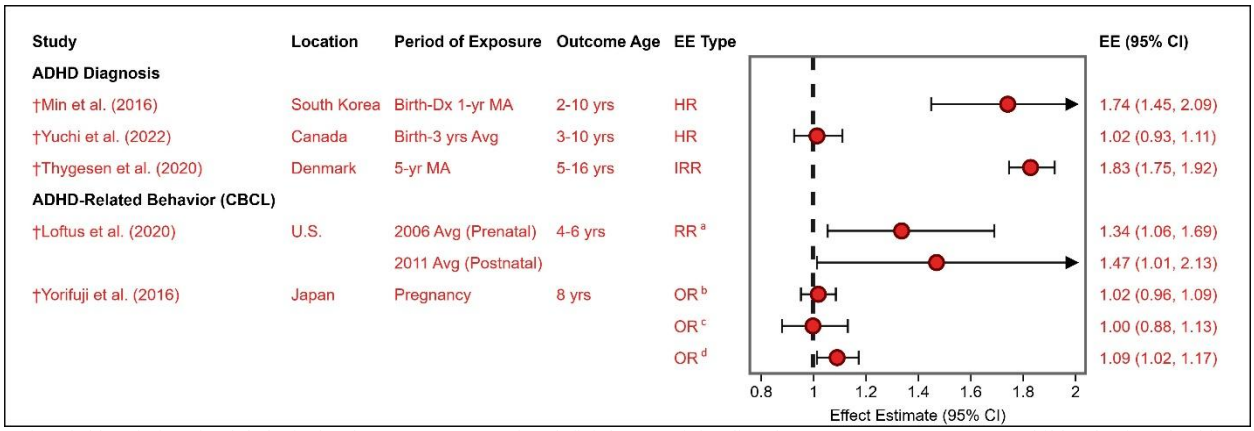
- A cohort study in Denmark (Thygesen et al., 2020) observed a positive association between NO_2 exposure averaged over the first 5 years of life and ADHD incidence diagnosed with ICD-10-DCR codes F90 times or F98.8 between ages 5–16 years [incidence rate ratio (IRR): 1.38 [95% CI: 1.35, 1.42] per 5.3 ppb increase]. The IRR remained stable after further adjustment for additional variables like parental psychiatric history and obstetrical factors. An approximately linear positive relationship was reported in analyses by quintiles of NO_2. NO_2 concentrations were modeled using a dispersion model on a 1 km x 1 km scale.
- Min and Min (2016) conducted a cohort study using a sample extracted from the National Health Insurance Service in South Korea. Annual average NO_2 concentrations from birth to diagnosis (or end of study) were positively associated with risk of ADHD incidence between ages 2–10 years (HR: 1.03 [95% CI: 1.02, 1.04) per 0.53 ppb increase), adjusting for sex, metropolitan area, and household income. On stratifying by tertiles of NO_2 concentrations, the HR for ADHD compared to the first tertile for those in the highest tertile (≥30.59 ppb) was 2.12 (95% CI: 1.56, 2.89), while the HR for those in the second tertile (21.57–30.59 ppb) was 1.44 (95% CI: 1.31, 2.43).

Evidence for effects on ADHD symptoms and externalizing behavior were mixed (Li et al., 2023b; Loftus et al., 2020; Yorifuji et al., 2016).

- A cohort study of U.S. preschool-age children reported an RR of 1.34 (95% CI: 1.06, 1.69) for a 1-unit increase in raw scores of the externalizing behavior scale per 10 ppb increase in prenatal NO_2 and an RR of 1.47 (95% CI: 1.01, 2.13) per 10 ppb increase in postnatal NO_2 (Loftus et al., 2020). Externalizing behavior (e.g., aggression, attention problems, and hyperactivity) in this study was assessed using the Child Behavior Checklist (CBCL), which is a reliable and well-validated parent-reported measure of problem behaviors in children, at a mean age of 4.3 (SD: 0.4) years.
- A Dutch cohort study (Li et al., 2023b) recruited children aged 10–12 years and followed them every 2–3 years until ages 24–28 years, assessing ADHD symptoms using the CBCL for ages 10–18 years and the Adult Behavior Checklist (ABCL) at the 5th follow-up visit (mean age 22.23 years). Using linear mixed models adjusting for the interaction between environmental exposures and follow-up time, the authors reported a small negative association (β: -0.0161 [95% CI: -0.0301, -0.0021] per IQR increase in NO_2) between NO_2 exposures using ESCAPE LUR models, but these associations attenuated to null in sensitivity analyses adjusting for multiple testing.
- Yorifuji et al. (2016) evaluated associations between 9-month prenatal NO_2 exposure and three attention-related behaviors assessed at age 8 years with the CBCL in a Japanese birth cohort. The authors observed null associations for interrupting people and inability to wait his/her turn during play, while reporting an increase in the odds of failing to pay attention when crossing a street (OR: 1.10 [95% CI: 1.02, 1.19] per 10.8 ppb increase in NO_2).

Several of the studies discussed above present additional analyses evaluating the shape of the concentration-response function for NO_2 exposure and externalizing behavior, the lifestages and populations that may be at increased risk of NO_2-associated externalizing behavior, the potential influence of copollutants on reported associations, and/or the critical NO_2 exposure windows. These analyses are

discussed below in Sections 9.3.4.1.1, 9.3.4.1.2, 9.3.4.1.3, and 9.3.4.1.4, respectively. Section 9.3.4.1.5 presents conclusions from epidemiologic studies of externalizing behavior and discusses the remaining uncertainties in that evidence.



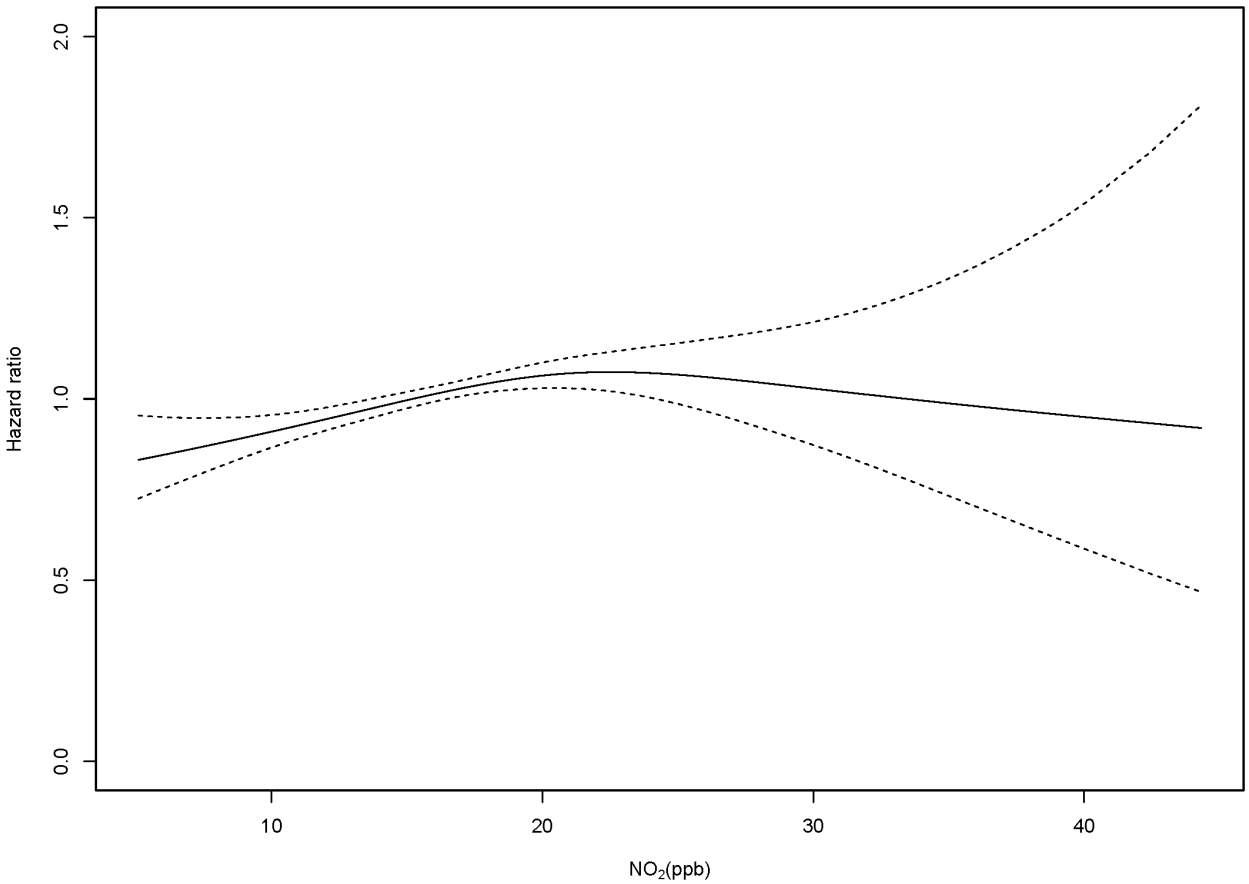
List of abbreviations in alphabetical order: ADHD = attention deficit hyperactivity disorder; avg = average; CBCL = Child Behavior Checklist; CI = confidence interval; EE = effect estimate; HR = hazard ratio; IRR = incidence rate ratio; LUR = land use regression; MA = moving average; OR = odds ratio; RR = risk ratio; yr = year(s).
Notes: Red = recent studies and those not included in 2016 Oxides of Nitrogen ISA. Results are standardized to a 10 ppb increase in NO_2.
[a]Outcome assessed is externalizing behavior.
[b]Outcome assessed is interrupting people.
[c]Outcome assessed is inability to wait his/her turn during play.
[d]Outcome assessed is not paying attention when crossing a street.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 9-4 Associations between long-term nitrogen dioxide exposure and ADHD diagnosis or ADHD-related behaviors.

9.3.4.1.1 Concentration-Response

A few recent studies provide some evidence regarding the shape of the concentration-response curve for the relationship between oxides of nitrogen and ADHD diagnoses and attention-related behavior. The association appears to be approximately linear at low concentrations of NO_2 with high imprecision at concentrations greater than 20 ppb.

- Yuchi et al. (2022) showed a linearly increasing association between 3-year average NO_2 exposure and ADHD incidence below approximately 20 ppb of NO_2 and great uncertainty at higher concentrations of NO_2, indicated by wide confidence intervals in the exposure-response curve below (see Figure 9-5), likely due to lack of data at these levels of NO_2. This uncertainty may have contributed to the null result when NO_2 exposure was averaged across the entire cohort.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Source: Yuchi et al. (2022). Copyright permission pending.

Figure 9-5 Exposure-Response Curve between Nitrogen Dioxide (NO_2) and ADHD.

- Another study (Thygesen et al., 2020) reported a positive linear relationship between increasing quintiles (Q1: 2.33–6.06 ppb; Q2: 6.06–7.47 ppb; Q3: 7.48–9.15 ppb; Q4: 9.15–11.31; Q5: 11.31–30.63 ppb) of NO_2 exposure averaged over 0–5 years of age and ADHD diagnosis between 5–16 years of age (IRR Q2 vs. Q1: 1.22 [95% CI: 1.16, 1.28]; IRR Q3 vs. Q1: 1.30 [95% CI: 1.24, 1.37]; IRR Q4 vs. Q1: 1.47 [95% CI: 1.40, 1.55]; IRR Q5 vs. Q1: 1.70 [95% CI: 1.61, 1.78]).
- Min and Min (2016) reported a monotonic increase in risk of ADHD by increasing tertiles of NO_2 concentrations from birth to diagnosis or end of study (HR for 21.57–30.59 ppb of NO_2: 1.44 [95% CI: 1.31, 2.43]; HR for NO_2 ≥30.59 ppb: 2.12 [95% CI: 1.56, 2.89]).
- In analyses stratified by exposure quartiles, one cohort study in Japan observed a positive approximately linear relationship that flattened in the fourth quartile between prenatal NO_2 exposure and failure to pay attention when crossing a street (OR Q2 vs. Q1: 1.08 [95% CI: 0.97, 1.20]; OR Q3 vs. Q1: 1.17 [95% CI: 1.05, 1.31]; OR Q4 vs. Q1: 1.17 [95% CI: 1.00, 1.37]) (Yorifuji et al., 2016).

9.3.4.1.2 Lifestages and Populations

Sex

- A U.S. cohort study did not report any difference by sex in associations between pre- and postnatal NO_2 exposure and externalizing behavior scores (quantitative results not presented) (Loftus et al., 2020).

Race

- Associations between pre- and postnatal NO_2 exposure and externalizing behavior in a U.S. cohort study did not differ by maternal race (quantitative results not presented) (Loftus et al., 2020).

Socioeconomic status

- Loftus et al. (2020) reported stronger associations between postnatal NO_2 exposure and externalizing behavior scores among those with Medicaid or no insurance compared to those with private insurance (quantitative results not presented). Similar results were observed when low vs. high income was used as the SES variable.

Urbanicity

- Thygesen et al. (2020) reported that stratification by degree of urbanization at birth resulted in stronger associations in less urban municipalities, while the most urban areas had attenuated but still positive associations with ADHD incidence (IRR Capital: 1.26 [95% CI: 1.00, 1.59]; IRR Capital suburb: 1.39 [95% CI: 1.15, 1.68]; IRR Municipalities with a town >100,000 residents: 1.50 [95% CI: 1.17, 1.92]; IRR Municipalities with a town 10,000–100,000 residents: 1.57 [95% CI: 1.40, 1.75]; IRR Municipalities with a town <10,000 residents: 2.96 [95% CI: 2.61, 3.36] per 10 ppb increase in NO_2).

Maternal folate during pregnancy

- Loftus et al. (2020) reported imprecise trends of stronger positive associations between pre- and postnatal NO_2 and externalizing behavior scores among children with low maternal folate during pregnancy (quantitative results not presented).

9.3.4.1.3 Copollutants

A few studies assessed the influence of copollutants on the associations between NO_2 and ADHD diagnoses and symptoms.

- Thygesen et al. (2020) reported that the positive association between NO_2 and ADHD incidence in the single pollutant model (IRR: 1.83 [95% CI: 1.75, 1.92] per 10 ppb increase in NO_2) remained the same after adjusting for $PM_{2.5}$ in the two-pollutant model (IRR: 1.76 [95% CI: 1.66, 1.86] per 10 ppb increase in NO_2). Furthermore, the effect of NO_2 exposure on ADHD risk was approximately the same magnitude across quintiles of $PM_{2.5}$.
- In one Japanese cohort, a positive association between 9-month prenatal NO_2 exposure and scores on an attention problem item on the CBCL (failing to pay attention when crossing a street) attenuated to the null in a multipollutant model with both suspended particulate matter (SPM) and sulfur dioxide (SO_2) included (Yorifuji et al., 2016).

- Yuchi et al. (2022) conducted analyses with two-exposure and multi-exposure models adjusting for greenness (vegetation percentage in 250 m radius of residence) and noise levels and observed that associations remained null.

9.3.4.1.4 Exposure Windows

Because ADHD is a neurodevelopmental disorder that often begins in childhood and may persist into adulthood, it is important to identify critical periods of exposure for ADHD and attention-related behavior problems. Only one recent study evaluated associations across different exposure windows. Loftus et al. (2020) assessed the relationship between NO_2 in the 9 months before (prenatal) and after (postnatal) birth and externalizing behavior. The association with postnatal NO_2 (RR: 1.34 [95% CI: 1.06, 1.69] per 10 ppb) had a somewhat greater magnitude compared to the association with prenatal NO_2 (RR: 1.47 [95% CI: 1.01, 2.13] per 10 ppb), although the confidence intervals for the two associations were largely overlapping with each other. Associations for both exposure windows were positive.

9.3.4.1.5 Conclusions and Remaining Uncertainties

There were no studies evaluating the effects of oxides of nitrogen on ADHD and related behaviors meeting the current PECOS criteria in previous ISAs. A few recent studies provide some evidence regarding the relationship between NO_2 exposure and ADHD in children and adolescents. Two of these studies reported positive associations in Danish and Korean cohorts (Thygesen et al., 2020; Min and Min, 2016), while one Canadian study reported a null result (Yuchi et al., 2022). The concentration-response relationship in all three studies showed a positive linear relationship between increasing concentrations of NO_2 and ADHD risk, with increasing imprecision at NO_2 exposures above approximately 20 ppb in Yuchi et al. (2022). Urbanicity may modify the effect of NO_2 on ADHD incidence (Thygesen et al., 2020), and other factors like sex, race, SES, and prenatal maternal factors need further evaluation. Copollutants such as $PM_{2.5}$, SPM, and SO_2 and coexposures including greenness, and noise have been assessed, but there is insufficient evidence to make a conclusion regarding their influence on the relationship between NO_2 exposure and ADHD. Uncertainties regarding the critical window of NO_2 exposure in the etiology of ADHD remain an important consideration.

9.3.4.2 Animal Toxicological Studies of Externalizing Behaviors – ADHD and Related Behaviors

Animal models are not capable of fully reproducing complex human disorders. Rather, they aim to mimic specific facets of the human disorder, such as the symptomology, underlying pathophysiology, or both. The defining behaviors of ADHD—inattention, hyperactivity, and impulsivity—can each be measured in rodent models. To date, no PECOS-relevant studies have investigated the effect of oxides of nitrogen exposure on attention or impulsivity in animals, but some evidence is available that informs

hyperactivity. Tabacova et al. (1985) exposed Wistar rat dams to 0.03–5.32 ppm NO_2 (6 hours/day) throughout gestation and observed the pups for deficits in neuromotor development and motor activity (see Section 9.3.2.2). No evidence of hyperactivity was reported; rather, the authors reported significantly reduced open field locomotor activity in the 5.32 ppm exposure group on PND 9, PND 30 (males only), and PND 60 (males only). Rearing was also significantly decreased on PND 30 in males. In contrast, Di Giovanni et al. (1994) reported no significant effects on motor activity in male Wistar rat pups exposed to NO_2 during gestation (1.5 and 3.0 ppm continuously). Recent PECOS-relevant studies investigating developmental NO_2 exposure and motor activity are discussed below. Recent studies in adult animals, while not fully analogous to human neurodevelopmental studies, are also discussed below to provide additional insight into this endpoint. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-8. Section 9.3.4.2.3 presents conclusions based on the animal data and summarizes the remaining uncertainties in the evidence.

- Li et al. (2022a) exposed pregnant C57BL/6J mice to 2.5 ppm NO_2 (5 hours/day) throughout gestation and measured the pups' behavior in an open field apparatus. During the 10-minute observation period, the total distance traveled was not significantly affected by the treatment condition. Another study by Li et al. (2021) reported similar results after exposing 7-week-old male and female C57BL/6J mice to 2.5 ppm NO_2 (5 hours/day) for 28 days.
- In 7-week-old female Sprague Dawley rats exposed to 0.5, 5, or 10 ppm NO_2 (4 hours/day), general activity was significantly increased in the medium- and high-dose groups after 3, 6, 9, 12, and 15 days of exposure (Ye et al., 2022). The observed hyperactivity appeared to increase across repeat testing days, though it is challenging to parse if this observation is a result of increased familiarity or continued NO_2 exposure. Activity was defined as head scratching, self-grooming, circling, climbing, back-and-forth movement, and tail biting. This study did not test male rats.

9.3.4.2.1 Dose Response

The presence of a dose-response relationship informs and may strengthen causality determinations. Ye et al. (2022) demonstrated that the magnitude of hyperactivity increased as NO_2 exposure increased (0.5, 5, and 10 ppm), indicating a biological effect gradient. Despite contrasting findings, the hypoactivity reported by Tabacova et al. (1985) also seemed to follow a dose-response relationship, though inference is limited as some endpoints were only tested at two dose levels. The other reviewed studies are not informative to dose-response, as they either did not report group-specific information (Di Giovanni et al., 1994) or only investigated a single dose (Li et al., 2022a; Li et al., 2021).

9.3.4.2.2 Relevance of Animal Responses to Human Responses

Behaviors associated with ADHD (e.g., hyperactivity, inattention, and impulsivity) can be measured in rodents, and the inferences drawn from these findings can be strengthened if disease-similar neurological alterations are demonstrated, like the dopaminergic dysfunction seen in ADHD. The studies

reviewed above focused only on rodent activity. In ADHD, hyperactivity is typically more prevalent in familiar environments as opposed to novel environments (Sagvolden and Sergeant, 1998; Sleator and Ullmann, 1981); therefore, rodent behavioral tests replicating this observation are likely more relevant. The studies reviewed above were all conducted in novel environments, though familiarity should increase over time in the studies that measured activity across multiple days. The hyperactivity reported by Ye et al. (2022) did appear to increase across repeat testing days, though it is difficult to parse if this observation is a result of increased familiarity or continued NO_2 exposure.

9.3.4.2.3 Conclusions and Remaining Uncertainties

Taken together, there is minimal toxicological evidence to suggest that NO_2 exposure may cause hyperactivity. While a single study demonstrated that motor activity was increased in young adult rats after exposure to NO_2, other studies reported no significant effects on motor activity. Furthermore, one study of gestational NO_2 exposure reported decreased activity. These discordant results may be explained by differences in study design or endpoint measurement methods, so additional studies, particularly those focusing on activity in novel and familiar environments, could alter these conclusions. Exposure during other sensitive developmental periods (e.g., postnatally), the impact of varying exposure duration, and the impact of multipollutant exposures have not been investigated for this endpoint. Additionally, the effect of NO_2 on other behavioral elements of ADHD, like inattention and impulsivity, has not been investigated in animal models.

9.3.4.3 Epidemiologic Studies of Externalizing Behaviors – Aggression

Previous ISAs for oxides of nitrogen did not include any studies on aggressive behavior. Two recent cohort studies investigated the relationship between NO_2 exposure and aggression in children. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 9-7.

- A study of eight European birth cohorts (Jorcano et al., 2019) evaluated aggressive symptoms using the CBCL (age 7–10 years) in some cohorts and the Strengths and Difficulties Questionnaire (SDQ) (age 7–11 years) in other cohorts, using validated and standard cutoffs to classify symptoms in the borderline/clinical range and in the clinical range. Annual average NO_2 and NO_X exposures were estimated using LUR models from the ESCAPE project in seven of the cohorts and using universal kriging methods in one cohort. Two exposure windows were selected for analysis: during pregnancy (prenatal period) and from birth until outcome assessment (postnatal period). The authors reported null associations between pre- and postnatal NO_2 and NO_X exposures and aggressive symptoms in the borderline/clinical range [OR prenatal NO_2: 1.07 (95% CI: 0.97, 1.19) per 5.31 ppb NO_2; OR prenatal NO_X: 1.03 (95% CI: 0.95, 1.12) per 16.30 ppb NO_X; OR postnatal NO_2: 0.93 (95% CI: 0.82, 1.06) per 5.31 ppb NO_2; OR postnatal NO_X: 0.91 (95% CI: 0.78, 1.06) per 16.30 ppb NO_X]. In analyses stratified by the assessment tool (CBCL or SDQ) for aggressive

symptoms, associations in cohorts in which the SDQ was used were positive [OR prenatal NO_2:1.16 (95% CI: 1.05, 1.26) per 5.31 ppb NO_2; OR prenatal NO_X:1.14 (95% CI: 1.03, 1.21) per 16.30 ppb NO_X]. Associations were null in cohorts in which the CBCL was used. This discrepancy may be attributed to the fact that more children were in the cohorts that used the SDQ compared to those that used the CBCL. Furthermore, the proportion of children with aggressive symptoms in the borderline/clinical range tended to be higher when the SDQ was used compared to when the CBCL was used.

- A Japanese birth cohort study (Yorifuji et al., 2016) evaluated associations between NO_2 exposure during pregnancy and four aggressive behaviors (e.g., lying, destroying toys and/or books, hurting other people, and causing disturbances in public) assessed using the CBCL. The authors observed a positive association between an IQR (10.8 ppb) increase in NO_2 exposure and lying frequency [OR lying: 1.07 (95% CI: 1.00, 1.15)] while results for other aggressive behaviors were null.

The studies summarized above present additional analyses evaluating the shape of the concentration-response function for NO_2 and aggression, the potential influence of copollutants on reported associations, and/or the critical NO_2 exposure windows. These analyses are discussed below in Sections 9.3.4.3.1, 9.3.4.3.2, and 9.3.4.3.3, respectively. Section 9.3.4.3.4 presents conclusions from the epidemiologic evidence and summarizes the remaining uncertainties in this evidence.

9.3.4.3.1 Concentration-Response

The concentration-response relationship between NO_2 and antisocial behavior was evaluated in one study. Comparing the second, third, and fourth quartiles to the first quartile, increased associations were reported between prenatal NO_2 and lying frequency, [OR Q2 vs. Q1: 1.10 (95% CI: 1.01, 1.20); OR Q3 vs. Q1: 1.12 (95% CI: 1.02, 1.23); OR Q4 vs. Q1:1.09 (95% CI: 0.95, 1.25)] and destroying toys and/or books [OR Q2 vs. Q1: 1.11 (95% CI: 0.98, 1.26); OR Q3 vs. Q1: 1.14 (95% CI: 0.99, 1.32); OR Q4 vs. Q1: 1.12 (95% CI: 0.90, 1.40)], but not for hurting other people and causing disturbances in public (Yorifuji et al., 2016).

9.3.4.3.2 Copollutants

One Japanese cohort study (Yorifuji et al., 2016) reported a positive association between 9-month prenatal NO_2 exposure and lying frequency, which attenuated to the null in a multipollutant model adjusting for both SPM and SO_2.

9.3.4.3.3 Exposure Windows

Jorcano et al. (2019) did not observe an association between NO_2 or NO_X concentrations during the prenatal (entire pregnancy) or postnatal (birth to assessment) periods and the odds of having

borderline/clinically significant symptoms of aggression. Stratification by the type of outcome assessment tool used by each of the cohorts in the study resulted in positive associations for prenatal NO_2 and NO_X exposures, while associations for postnatal exposures remained null. See Section 9.3.4.3 for additional details.

9.3.4.3.4 Conclusions and Remaining Uncertainties

A small number of recent epidemiologic studies assessing the relationship between oxides of nitrogen and aggressive behavior were identified in the current review. The results of the studies were mostly null, and a single positive association between prenatal NO_2 exposure and lying frequency also attenuated to the null after adjusting for SPM and SO_2. Many uncertainties remain regarding the shape of the concentration-response function, potential confounding by copollutants, the critical exposure window, the lifestages and populations at highest risk, and discrepancies by the type of assessment used to evaluate conduct disorder and aggressive behavior.

9.3.5 Synthesis Across Lines of Evidence

The neurodevelopmental effects of oxides of nitrogen have been investigated across several endpoints, including cognitive function, motor development, ASD, and externalizing behaviors such as ADHD and aggression. A limited number of neurodevelopmental effect studies were evaluated in the 2016 Oxides of Nitrogen ISA in the Reproductive and Developmental Effects Section [see Section 6.4, (U.S. EPA, 2016)]. At the time, associations with NO_2 were inconsistent for cognitive function, attention, motor function, psychological distress, and ASD. Since that assessment, additional epidemiologic and animal toxicological studies have expanded the evidence base.

Epidemiologic research in infants and children (2–13 years old) most consistently links long-term prenatal and postnatal NO_2 exposure—averaging between 6.1 and 23.3 ppb—with impairments in infant development and academic achievement. Studies focusing on childhood cognitive abilities and neuropsychological tests lacked consistency, and limited adjustment for other pollutants makes it unclear whether the observed effects are independently associated with exposure to oxides of nitrogen. Controlled exposures to NO_2 in rodent studies consistently impaired spatial learning and memory in a small number of studies, which is supportive of the human evidence, however these studies were conducted at exposure levels above typical ambient conditions (1.33–2.5 ppm).

Evidence for the effects of oxides of nitrogen on motor function is inconclusive. Most epidemiologic studies report near null associations between NO_2 exposure (6–23.3 ppb) and motor function, with no clear pattern of association. A single study in rodents demonstrated that near-ambient gestational NO_2 exposures (53 ppb and above) alter some aspects of early neuromotor development, but these findings have not been replicated, and general motor activity results remain mixed.

Studies of ASD yielded generally positive results. Many case-control and longitudinal analyses have reported positive associations between NO_2 concentrations and ASD diagnoses in United States (O'Sharkey et al., 2024; Kim et al., 2017; Volk et al., 2014; Volk et al., 2013), Canadian (Murphy et al., 2024; Pagalan et al., 2018), Danish (Ritz et al., 2018), and Taiwanese (Wang et al., 2021a) populations. A few longitudinal studies in the U.S. and European countries reported null (Bragg et al., 2024; Rahman et al., 2022; Guxens et al., 2015) or negative (Li et al., 2023b) associations. In several of these investigations reporting null or negative results, the authors examined autistic traits (Bragg et al., 2024; Li et al., 2023b; Guxens et al., 2015), and associations with ASD diagnoses were evaluated in just two studies (Bragg et al., 2024; Rahman et al., 2022). The lack of consistent adjustment for copollutants and the absence of concentration-response analyses complicate the interpretation. Toxicological studies investigating behaviors relevant to ASD are sparse, but the available data suggests possible effects on social communication and repetitive behaviors.

Epidemiologic investigations of externalizing behaviors such as ADHD show a positive linear relationship between increasing NO_2 concentrations and ADHD risk in some cohorts, though the evidence is not uniform across populations. Limited research in animal models provides little support for the effect of NO_2 on hyperactivity, and there has been no investigation into other behavioral components of ADHD. Evidence for aggression is even less compelling, with a small number of epidemiologic studies reporting mostly null associations and no supportive toxicological data available.

9.4 Psychiatric Disorders and Symptoms

Non-developmental psychiatric disorders are not directly related to developmental problems and often emerge in adolescence or adulthood, although they may also sometimes manifest in children—in these cases, symptoms are often more severe and enduring. Non-developmental psychiatric disorders evaluated by studies meeting PECOS criteria in this review include depressive disorders, anxiety disorders, and schizophrenia. Other disorders, such as bipolar disorder, eating disorders, dissociative disorders, substance use disorders, or personality disorders were not evaluated by PECOS-relevant studies. This Section discusses the available epidemiologic and animal toxicological evidence for anxiety, depression, psychological distress, and related symptoms and measures of general mental or emotional wellbeing (see Section 9.4.1) and the available epidemiologic evidence for schizophrenia and psychosis (see Section 9.4.2). Section 9.4.3 presents an integrated synthesis across lines of evidence for non-developmental psychiatric disorders and symptoms.

9.4.1 Anxiety, Depression, Psychological Distress, and Related Symptoms

Anxiety, depression, and psychological distress are common mental health conditions that can significantly affect individuals' quality of life. These conditions present with a range of symptoms

including excessive worry, persistent sadness, irritability, and fatigue. Section 9.4.1.1 summarizes key evidence from the 2016 Oxides of Nitrogen ISA and recent PECOS-relevant epidemiologic studies examining the relationship between oxides of nitrogen exposure and outcomes related to anxiety, depression, and psychological distress in children, adolescents, and adults. Most of these outcomes have been evaluated in the context of long-term exposures, though some epidemiologic studies have additionally evaluated associations between short-term exposures and hospital admissions for these conditions. Section 9.4.1.2 discusses evidence from the 2016 Oxides of Nitrogen ISA and recent animal toxicological studies that have evaluated anxiety-like and depression-like behaviors in rodent models using the open field test, elevated plus maze, and forced swim test.

9.4.1.1 Epidemiologic Studies of Anxiety, Depression, Psychological Distress, and Related Symptoms

Among children

One study from the previous review evaluated psychological distress among 9–10-year-old U.K. children using the SDQ and reported a null association with NO_2, which was unchanged after adjustment for aircraft and road traffic noise (Clark et al., 2012). Recent studies of children and adolescents ranging 4–20 years of age reported generally positive but imprecise associations between oxides of nitrogen and measures of depression and anxiety. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are described below and summarized in Appendix A – Appendix Table 9-9.

- Jorcano et al. (2019) evaluated depressive and anxiety symptoms using the CBCL (age 7–10-years) or SDQ (age 7–11 years) in eight European cohorts, using validated and standard cutoffs to classify symptoms in the borderline/clinical range and in the clinical range. Annual average NO_2 and NO_X exposures were estimated using LUR models from the ESCAPE project in seven of the cohorts and using universal kriging methods in one cohort. Two exposure windows were selected for analysis: during pregnancy (prenatal period) and from birth until outcome assessment (postnatal period). The authors observed an imprecise increase in depressive and anxiety symptoms in the borderline/clinical range associated with a 10 ppb increase in prenatal NO_2 exposure (OR: 1.04 [95% CI: 0.90, 1.19]) or with a 20 $\mu g/m^3$ increase in prenatal NO_X exposure (OR: 1.02 [95% CI: 0.95, 1.11]) but not for postnatal NO_2 (OR: 0.85 [95% CI: 0.69, 1.06]) or NO_X exposure (OR: 0.93 [95% CI: 0.79, 1.09]).
- A small cohort study of U.S. children reported positive but imprecise associations between internalizing behavior scores and prenatal [RR: 1.16 (95% CI: 0.89, 1.52)] and postnatal [RR: 1.34 (95% CI: 0.84, 2.14)] per 10 ppb increase in NO_2 exposure (Loftus et al., 2020). Internalizing behavior (e.g., depression, anxiety, and social withdrawal) in this study was assessed using the CBCL at a mean age of 4.3- (SD: 0.4) years. In this study, prenatal exposure covered the duration of pregnancy and postnatal exposure covered the first 9-months after birth.
- One cross-sectional study in Chinese adolescents (age 10–20 years) also observed null associations between annual concentrations of NO_2 estimated with an ensemble regression

model (r^2: 0.84) and depressive symptoms evaluated with the Center for Epidemiologic Studies Depressive 9-item scale (CES-D-9) and anxiety symptoms evaluated with the generalized anxiety disorder 7-item scale (GAD-7) (Jiang et al., 2023). The odds ratio for reporting CES-D score ≥10 per IQR increase in NO_2 was 1.00 (95% CI: 0.99, 1.09) and 0.99 (95% CI: 0.99, 1.01) for GAD-7 score ≥5. There was no difference by child sex or age in stratified analyses.

Among adults

No studies in the 2016 Oxides of Nitrogen ISA examined associations between oxides of nitrogen exposure and anxiety, depression, or psychological distress in adults. Recent studies have examined associations with these outcomes in adult populations. These studies are described below and summarized in Appendix A – Appendix Table 9-9 and Figure 9-6.

U.S. cohort studies provide some evidence for an association between NO_2 exposure and emotional distress or depression in older adults.

- A study of women 65 years of age or older in the Women's Health Initiative Memory Study (WHIMS) reported a null association [β: -0.028 (95% CI: -0.061, 0.005) per 10 ppb increase] between annual average NO_2 exposure in the 3 years prior to the baseline and a latent emotional distress factor combining scores from the 6-item CES-D and the 5-item emotional wellbeing scale from the Short Form Health Survey-36 (SF-36) (Petkus et al., 2021a).
- Petkus et al. (2021b) conducted an extension study to Petkus et al. (2021a) limiting the analysis to women 80 years of age or older. Depressive symptoms were measured with a T-score from the 15-item Geriatric Depression Scale (GDS-15). For each 10 ppb increase in NO_2, the depressive symptoms T-score increased by 0.301 (95% CI: 0.109, 0.492) for remote NO_2 exposure (average annual NO_2 concentrations in the 3-year period 10 years prior to baseline assessment), and by 0.238 (95% CI: -0.038, 0.513) for recent NO_2 exposure (average annual NO_2 concentrations in the 3-year period immediately preceding the baseline assessment). Associations for recent NO_2 exposures were attenuated in sensitivity analyses excluding women who developed dementia during the study period or self-reported a history of depression prior to the baseline, but they remained strong for remote exposures, suggesting a potential accumulation of neurotoxic insults from air pollution. NO_2 concentrations in both Petkus et al. (2021a) and Petkus et al. (2021b) were estimated using a well-validated kriging model (cross-validated r^2: 0.84).
- Petkus et al. (2022) evaluated the role of gray matter volume in specific regions (i.e., prefrontal cortex, anterior cingulate gyrus, insula amygdala, limbic medial temporal lobe, hippocampus, thalamus and basal ganglia) in mediating the association between NO_2 exposure and depressive symptoms, as assessed by the Geriatric Depression Scale (GDS-15), among older women enrolled in the WHIMS. Residential NO_2 exposure during the 3-year period prior to the magnetic resonance imaging (MRI) assessment was estimated using universal kriging models (r^2: 0.85). The annual linear change in depressive symptoms scores across each year of follow-up increased by 0.023 SD (95% CI: 0.004, 0.043) per 7.80 ppb increase in NO_2 exposure. The association for baseline symptoms was null (β: -0.073 [95% CI: -0.164, 0.017] per 7.80 ppb increase). Mediating effects of brain volume are described in Section 9.8.1.
- A study of Medicare beneficiaries used an ensemble model to estimate NO_2 concentrations by zip code and determined the year of first diagnosis of depression through Medicare claims (Qiu et al., 2023a). A 5 ppb increase in 5-year average NO_2 (including current and past 5-

years of exposure) was associated with an HR of 1.008 (95% CI: 1.005, 1.011) for depression diagnosis risk. Two- and three-pollutant models with $PM_{2.5}$ and O_3 produced similar results. Restricting to levels of NO_2 <53 ppb also did not change the association.

Recent cohort studies analyzed data collected for the UK Biobank study, which enrolled approximately 500,000 adults aged 40–69 years from population-based registries (2006–2010). Biobank data includes demographic, medical, interview and clinical exam data. The extensive data collection allowed for consideration of a wide range of potential confounders including age, sex, race/ethnicity, educational attainment, annual household income, self-rated health, body mass index (BMI), smoking history, and frequency of alcohol use. The following studies reported mostly positive associations between NO_2 and NO_X and incident anxiety, depression, and other mental disorders ascertained through ICD-9 and ICD-10 codes.

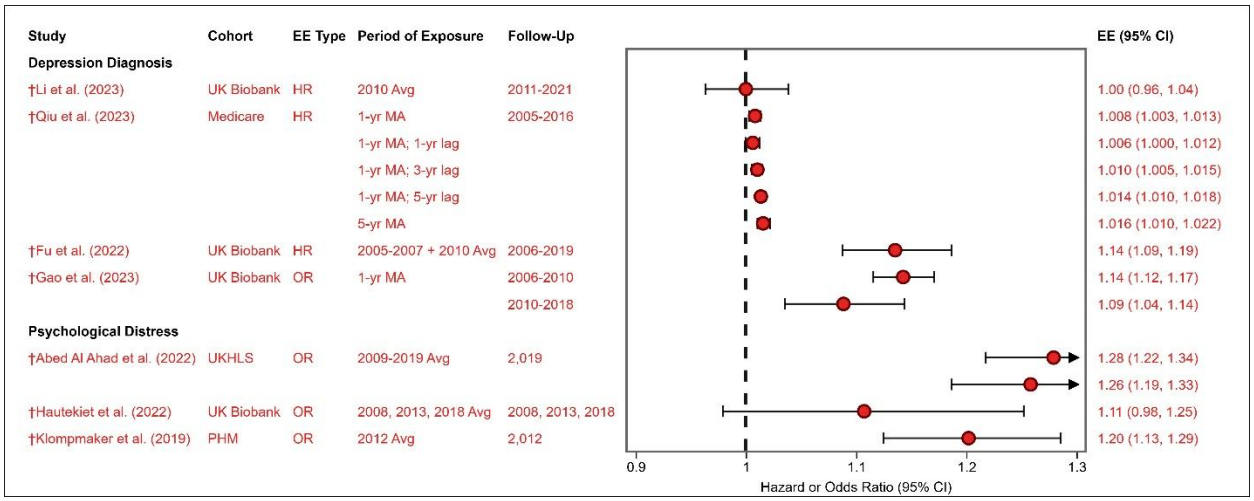
- Feng et al. (2023) observed consistently positive associations between NO_2 and NO_X annual averages and first occurrence of depressive disorders (ICD-10 codes F32–33), anxiety disorders (ICD-10 codes F40–41), and mental disorders (ICD-10 codes F00–99) among people with preexisting prediabetes and diabetes, with follow-up until the beginning of 2022. Diagnoses were identified from primary care, hospital admission, and the United Kingdom National Health Service databases. To model exposure, the authors interpolated annual average concentrations during 2006–2021 from 1 km x 1 km concentration maps estimated using Defra's dispersion model with inputs from the National Atmospheric Emissions Inventory. In additional, patient residential history was accounted for by using a time-weighted approach to calculate annual average exposure based on the time spent at each home address. Using Cox models with inverse probability weighted (IPW) time-varying covariates, associations with NO_2 tended to be slightly stronger than associations with NO_X [HR NO_2 depressive disorders: 1.12 (95% CI: 1.05, 1.20); HR NO_2 anxiety disorders: 1.21 (95% CI: 1.13, 1.29); HR NO_2 mental disorders: 1.18 (95% CI: 1.15, 1.22); HR NO_X depressive disorders: 1.05 (95% CI: 0.98, 1.12); HR NO_X anxiety disorders: 1.18 (95% CI: 1.11, 1.25); HR NO_X mental disorders: 1.16 (95% CI: 1.13, 1.19) per IQR increase (IQR NR)]. In comparison, unweighted estimates were slightly attenuated. Effects were stronger among those with diabetes compared to prediabetes.
- Fu et al. (2022) similarly observed positive associations between NO_2 and NO_X exposure and inpatient diagnosis of depression (ICD-10 code F32) [HR for NO_2: 1.14 (95% CI: 1.09, 1.19) per 10 ppb increase in NO_2; HR for NO_X: 1.04 (95% CI: 1.03, 1.05) per 10 $\mu g/m^3$ increase in NO_X]. Furthermore, the authors reported a monotonic increase in associations by tertiles of pollutant concentrations. Exposures were estimated using an LUR model from the ESCAPE project using measured concentrations from 2010 for NO_X (leave-on-out cross-validation r^2 = 0.88) and averaged values from 2005–2007 and 2010 for NO_2 (r^2 = 0.87). Fu et al. (2022) did not consider residential history or time spent at home in their exposure assessment. Follow-up lasted from baseline until the end of 2019.
- Gao et al. (2023) evaluated associations between NO_2 and NO_X and depression (ICD-9 code 311; ICD-10 codes F32–F33) and anxiety (ICD-9 code 300; ICD-10 codes F40–F41) diagnoses and syndromes. Exposures were estimated using the same ESCAPE LUR models used by Fu et al. (2022). Depression and anxiety at baseline were assessed with the Patient Health Questionnaire (PHQ)-4, syndromes of depression and anxiety were assessed using a 7-year online survey in 2016-2017 (PHQ-9 and the Generalized Anxiety Disorder [GAD]-7 questionnaires), and incident diagnoses were assessed through the 7-year survey and hospital records with follow-up until the end of 2018. Associations were positive for prevalent

depression (OR per 10 ppb increase in NO_2: 1.14 [95% CI: 1.12, 1.17]; OR per 16.53 μg/m^3 increase in NO_X: 1.06 [95% CI: 1.05, 1.08]) and anxiety (OR per 10 ppb increase in NO_2: 1.05 [95% CI: 1.03, 1.08]; OR per 16.53 μg/m^3 increase in NO_X: 1.04 [95% CI: 1.02, 1.06]). Results were similarly positive for incident diagnoses of depression (OR per 10 ppb increase in NO_2: 1.09 [95% CI: 1.04, 1.14]; OR per 16.53 μg/m^3 increase in NO_X: 1.03 [95% CI: 1.00, 1.05]) and anxiety (OR per 10 ppb increase in NO_2: 1.07 [95% CI: 1.04, 1.10]; OR per 16.53 μg/m^3 increase in NO_X: 1.04 [95% CI: 1.01, 1.06]). In analyses by specific syndromes of depression and anxiety, the authors reported positive associations for suicidal ideation, feelings of inadequacy, fatigue, depressed mood, cognitive problems, and anhedonia among depressive symptoms, and worrying control, generalized worrying, foreboding, and anxiety feeling among anxiety symptoms.

- Based on comparing quartiles of air pollutant exposures, Yang et al. (2023) reported positive associations between NO_2 and NO exposure and incidence of depression (ICD-10 codes F32–F33) (OR Q2 vs. Q1 for NO_2: 1.11 [95% CI: 1.06, 1.17]; OR Q3 vs. Q1 for NO_2: 1.15 [95% CI: 1.09, 1.22]; OR Q4 vs. Q1 for NO_2: 1.14 [95% CI: 1.07, 1.21]; OR Q2 vs. Q1 for NO_X: 1.07 [95% CI: 1.02, 1.13]; OR Q3 vs. Q1 for NO_X: 1.11 [95% CI: 1.06, 1.17]; OR Q4 vs. Q1 for NO_X: 1.12 [95% CI: 1.06, 1.18]). Positive associations were also reported for anxiety (ICD-10 codes F40–F48) (OR Q2 vs. Q1 for NO_2: 1.06 [95% CI: 1.01, 1.11]; OR Q3 vs. Q1 for NO_2: 1.10 [95% CI: 1.05, 1.15]; OR Q4 vs. Q1 for NO_2: 1.08 [95% CI: 1.03, 1.15]; OR Q2 vs. Q1 for NO_X: 1.09 [95% CI: 1.04, 1.14]; OR Q3 vs. Q1 for NO_X: 1.13 [95% CI: 1.08, 1.18]; OR Q4 vs. Q1 for NO_X 1.08 [95% CI: 1.03, 1.14]). NO_2 exposure was estimated using the previously described ESCAPE LUR model while NO exposure was estimated by subtracting NO_2 from the NO_X concentrations estimated from the LUR model. Follow-up lasted until February 2020.
- Li et al. (2023a) reported null results for incident major depressive disorder (MDD) associated with continuous and quartile-stratified NO_2 annual averages [HR continuous: 1.00 (95% CI: 0.98, 1.02) per 5.31 ppb NO_2] and positive results with NO_X annual averages [HR continuous: 1.02 (95% CI: 1.01, 1.05) per 20 μg/m^3 NO_X]. NO_2 and NO_X annual averages were estimated using ESCAPE LUR models. Sensitivity analyses using time-varying exposure also showed positive associations for both NO_2 and NO_X. Participants were followed up between January 2011 to January 2021.
- In another U.K. cohort called Understanding Society: The U.K. Household Longitudinal Study (UKHLS), Abed Al Ahad et al. (2022) conducted a panel study reporting positive associations between annual mean NO_2 concentration estimated with dispersion models at two geographical scales (i.e., coarse council areas in Scotland and smaller data zones called Lower Super Output Areas (LSOAs) comprising 400–1200 households each) and odds of poor mental well-being evaluated using the General Health Questionnaire (GHQ-12), which is a screening tool for non-psychotic psychiatric illness [OR LSOAs: 1.28 (95% CI: 1.22, 1.34); OR local authority: 1.26 (95% CI: 1.19, 1.33)] using a cut-off score of 2 (out of 12). Decomposing the effects into between effects across LSOAs and council areas and within effects across years within each LSOA and council area, associations for between effects remained similar to the overall air pollution effect, while those for within effects attenuated to the null, implying that variation in pollution across different locations was driving poor mental well-being rather than variation across time within each location.

A few cohort and cross-sectional studies in other European countries and one study in South Korea report mostly positive associations between oxides of nitrogen and diagnosis or measures of anxiety, depression, and psychological distress in adults.

- Wu et al. (2023) observed a positive association between annual NO_X exposure estimated from 1990–2011 with a well-validated dispersion model ($r^2 = 0.99$) and depression diagnosis among older adults (age ≥60 years) in the Swedish National Study of Aging and Care-Kungsholmen (SNAC-K) cohort [HR: 1.26 (95% CI: 1.01, 1.58) per 10 μg/m^3 increase in NO_X]. Analyses using IPW demonstrated similar results, indicating that potential bias due to drop-out of participants during follow-up assessments was negligible. Major or minor depression was diagnosed between 2001–2013 by trained physicians using the Comprehensive Psychopathological Rating Scale (CPRS) and diagnostic criteria based on the DSM-IV-TR.
- A study in the French Cohorte des consultants des Centres d'examens de santé (CONSTANCES) cohort reported positive associations between long-term NO_2 exposure and depressive symptoms evaluated with the self-administered CES-D (Sakhvidi et al., 2022) [IRR CES-D total score: 1.030 (95% CI: 1.017, 1.044) per 10 ppb increase in NO_2]. 2010 annual average NO_2 at 100 x 100 m spatial resolution was estimated with the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) LUR model, which combined monitoring data, satellite remote sensing data, predictions from chemical transport models, and land use data (hold-out validation $r^2 = 0.575$). CES-D questionnaires were administered between 2012–2020.
- A cross-sectional study in Belgium (Hautekiet et al., 2022) observed mostly positive associations between annual average NO_2 exposure estimated using a spatiotemporal interpolation model (leave-one-out cross-validation $r^2 = 0.78$) and self-rated mental health, ascertained through the General Health Questionnaire (GHQ-12), Symptom Checklist-90-Revised (SCL-90-R), the SF-36, and individual questions in the Belgian Health Interview Survey. The authors reported increased odds for psychological distress [OR: 1.11 (95% CI: 0.98, 1.25)], suboptimal vitality [OR: 1.24 (95% CI: 1.06, 1.44)], and poor self-rated health [OR: 1.26 (95% CI: 1.11, 1.42)] per 10 ppb increase in NO_2. Results for other outcomes including severe psychological distress, suicidal ideation in the past 12 months, depressive disorder, and generalized anxiety disorder were positive but imprecise.
- In a Dutch cross-sectional study, a 10 ppb increase in annual average NO_2 exposure was associated with increased odds of self-reporting severe psychological distress (Kessler psychological distress scale (K10) score ≥30) or being prescribed anxiolytics, hypnotics and sedatives, or antidepressants, based on the national obligatory health insurance database [OR distress: 1.20 (95% CI: 1.13, 1.29); OR anxiolytics: 1.37 (95% CI: 1.25, 1.50); OR hypnotics and sedatives: 1.34 (95% CI: 1.17, 1.54); OR antidepressants: 1.07 (95% CI: 1.01, 1.14)] (Klompmaker et al., 2019). NO_2 exposure was estimated using ESCAPE LUR models based on 2009 measurements, and NO_2 concentrations >80 μg/m^3 were set to 80 μg/m^3.
- One South Korean cross-sectional study among adults aged 50 years or older observed a slight increase in depressive symptoms scores (β: 0.0120 [95% CI: 0.0060, 0.0181]) evaluated with the Korean Geriatric Depression Scale Short Form (SGDS-K) per 10 ppb increase in five-year average NO_2 estimated using a universal kriging exposure prediction model with an r^2 of 0.82 (Kim et al., 2020).



List of abbreviations in alphabetical order: avg = average; CI = confidence interval; EE = effect estimate; HR = hazard ratio; LUR = land use regression; MA = moving average; OR = odds ratio; PHM = Dutch Public Health Monitor; UKHLS = Understanding Society: The UK Household Longitudinal Study; yr = year(s).
Note: Red = recent studies and those not included in 2016 Oxides of Nitrogen ISA. Results are standardized to a 10 ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 9-6 Associations between long-term nitrogen dioxide exposure and depression diagnosis or psychological distress scores among adults.

Hospitalizations

Recent time-series and case-crossover studies from the United States, Canada, Belgium, and China reported generally positive associations between short-term exposure to oxides of nitrogen and hospital admissions for psychiatric disorders at lags ranging from 0 to 7 days. These studies are described below and summarized in Appendix A – Appendix Table 9-9 and Figure 9-7.

- Gu et al. (2020) conducted a time-series analysis to assess short-term exposure to NO_2 and lagged daily hospital admissions for depression among patients covered by the urban employee-based basic medical insurance system (UEBMI) and the urban resident-based basic medical insurance system (URBMI) in 75 Chinese cities during 2013–2017. UEBMI covers urban employees and retirees while URBMI covers those without previous employment history and unemployed adults. The authors reported a 1.78% (95% CI: 0.73%, 2.83%) increase in daily hospital admissions for depression at lag 01 per 5.31 ppb increase in NO_2. Daily mean concentrations were obtained by averaging monitoring measurements from all central site monitors in each city.
- Analyzing a subset from Gu et al. (2020), (Ma et al., 2022), utilized data from 57 Chinese cities with hospitalization expenditure and length of hospital stay data. The authors reported a 7.15% (95% CI: 2.92%, 11.38%) increase in depression admissions per 10 ppb increase in NO_2 at lag 02 days. Daily NO_2 concentrations were calculated by averaging measurements from all central site monitors in each city. Subgroup analyses by sex, age, and insurance type (UEBMI vs. URBMI) did not show evidence for effect modification.
- Szyszkowicz et al. (2016) reported sex-stratified ORs for the risk of emergency department (ED) visits for depression among Ontario residents in a multi-city case-crossover study. NO_2 exposure at single-day lags of 0 to 8 days were calculated by averaging measurements across all central site monitors within 35 km of each patient's 3-digit postal code. Associations were

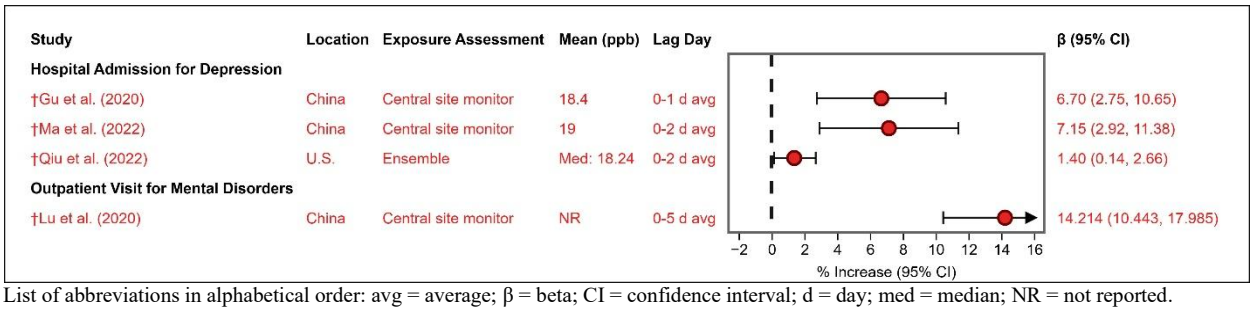
strongest at lag 0, and female participants were at higher risk for ED visits than males (OR male = 1.034 [95% CI: 0.972, 1.099]; OR female = 1.059 [95% CI: 1.006, 1.114] per 1 ppb increase in lag0 NO_2).

- Qiu et al. (2022) evaluated associations between NO_2 exposure with single-day and cumulative-day lags ranging from 0 to 6 days and hospital admissions for depression in Medicare enrollees in a case-crossover design. A 5 ppb increase in lag02 NO_2 was associated with a 0.35% increase (95% CI: 0.03%, 0.66%) in depression-related admissions. NO_2 exposure was estimated for 2000–2016 using an LUR model combining AQS ground monitoring measurements, satellite data, meteorological data, chemical transport model predictions, and 1 km x 1 km land use data (cross-validation $r^2 = 0.79$).
- Lu et al. (2020) conducted a case-crossover study of children and adults in 13 urban Chinese centers. The authors reported positive associations between daily NO_2 at lag 05 days and outpatient visits for mental disorders (depression and anxiety consisted 89.97% of the total visits) (β: 14.214 [95% CI: 10.443, 17.985] per 20 ppb increase in NO_2).

One Italian study assessed long-term exposure to oxides of nitrogen and hospital admissions and found a null association with hospitalization risk.

- Gandini et al. (2018) examined NO_2 and first hospital admissions for mental, behavioral and neurodevelopmental disorders (ICD-9 code 290–319) from the Italian Longitudinal study, which sampled patients from the 1999 to 2000 National Health Interview Survey for mortality and hospitalization follow-up in 2001–2008. Monitoring data for NO_2 were available at the municipality level for the years 1999, 2003, 2005, and 2007, and annual exposure was calculated as the mean exposure of the years for which data was available prior to first hospitalization. In Cox proportional hazard models adjusted for individual sociodemographic characteristics, behavior, and urbanization, NO_2 was not associated with hospital admissions for mental, behavioral and neurodevelopmental disorders (HR: 0.98 [95% CI: 0.88, 1.09] per 10 ppb NO_2).

A few of the studies summarized above include additional analyses examining the shape of concentration-response functions between NO_2 exposures and psychiatric effects, the lifestages and populations at higher risk of NO_2-associated psychiatric effects, critical windows of exposure, the potential impacts of copollutants on reported associations, and the lag structure of the associations. These topics are discussed below in Sections 9.4.1.1.1, 9.4.1.1.2, 9.4.1.1.3, 9.4.1.1.4, and 9.4.1.1.5, respectively. Section 9.4.1.1.6 presents conclusions from these studies and summarizes remaining uncertainties in the epidemiologic evidence.



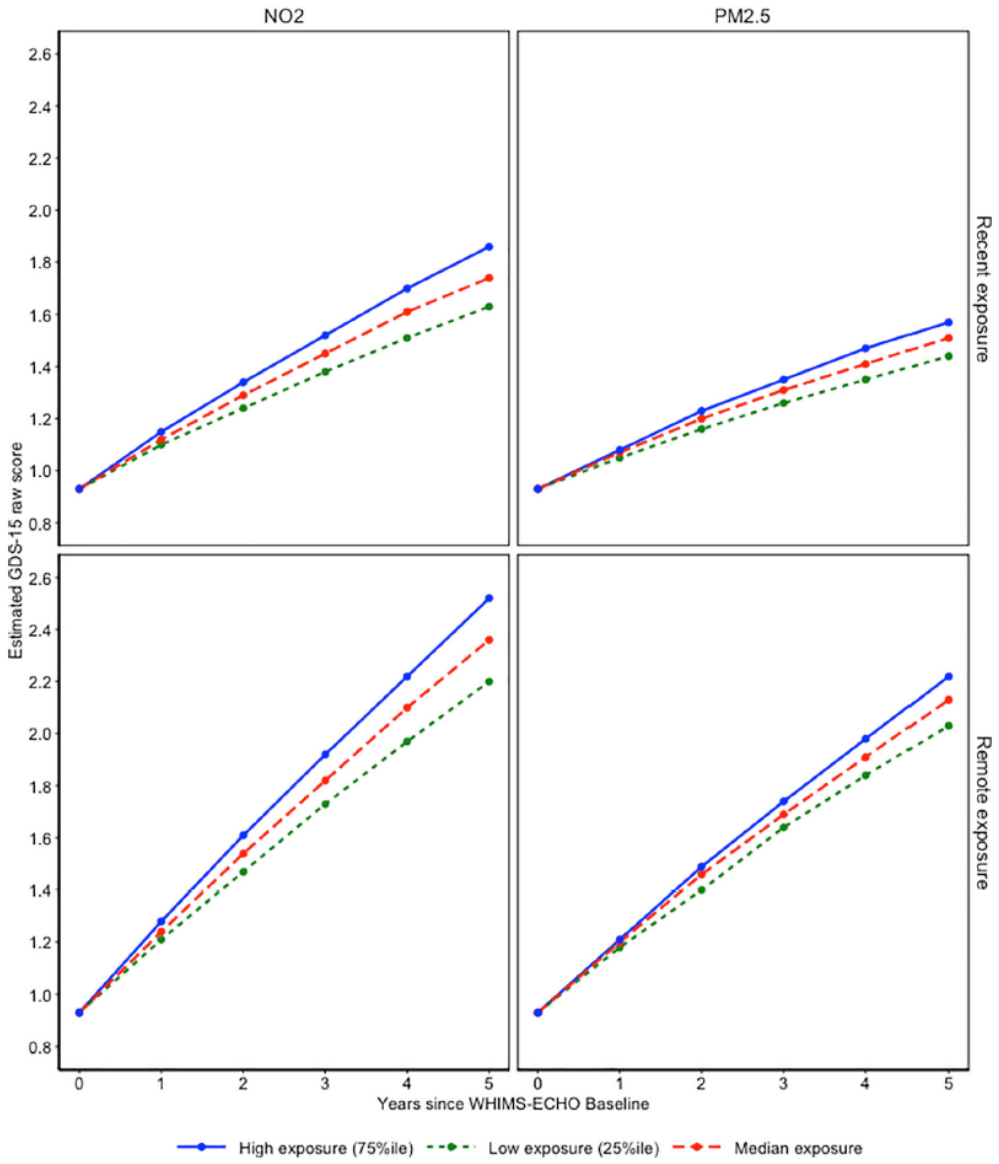
List of abbreviations in alphabetical order: avg = average; β = beta; CI = confidence interval; d = day; med = median; NR = not reported.
Note: Results are standardized to a 10 ppb increase in NO_2.
†Studies published since the 2016 Oxides of Nitrogen ISA.

Figure 9-7 Associations between short-term nitrogen dioxide exposure and hospital admissions for depression or outpatient visits for mental disorders (including depression, anxiety, and others).

9.4.1.1.1 Concentration-Response

A few studies in adults provide evidence on the shape of the relationship between oxides of nitrogen and depression.

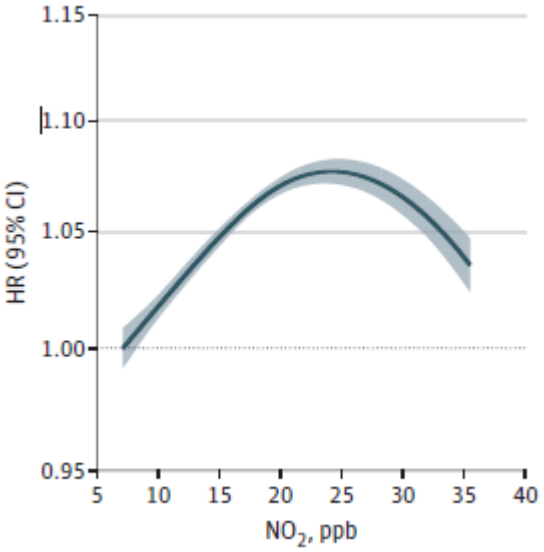
- Petkus et al. (2021b) reported a monotonic increase in depressive symptoms in association with higher concentrations of 3-year NO_2 exposure among women 80–93 years of age. High (75^{th} percentile) exposure was associated with a 24% greater increase in depressive symptoms compared to low (25^{th} percentile) exposure to NO_2 (see Figure 9-8).



List of abbreviations in alphabetical order: GDS-15 = 15-item Geriatric Depression Scale; PM = particulate matter; WHIMS-ECHO = Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes.
Source: Petkus et al. (2021b). Copyright permission pending.

Figure 9-8 Estimated Depressive Symptoms as Measured by the 15-item Geriatric Depression Scale by Pollutants and Exposure Time Period for Low (25th Percentile), Median, and High (75th Percentile) Average 3-Year Exposure.

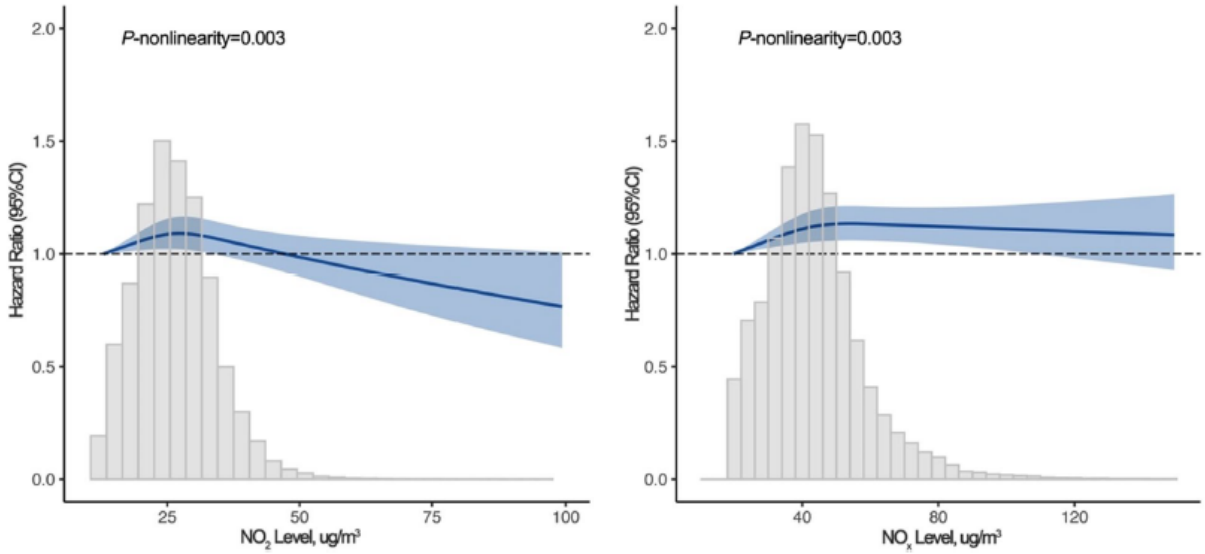
- Another U.S. study showed an upside-down u-shaped concentration-response curve among Medicare beneficiaries, with approximately linear increases in association up to 20 ppb of 5-year average NO_2, and an inverse relationship after 25 ppb (Qiu et al., 2023a) (see Figure 9-9).



List of abbreviations in alphabetical order: CI = confidence interval; HR = hazard ratio; ppb = parts per billion.
Source: Qiu et al. (2023a). Copyright permission pending.

Figure 9-9 Concentration-Response Curve Based on a Tripollutant Model with NO_2, $PM_{2.5}$, and O_3; Concentration Ranges Are Between the 5th and 95th Percentiles.

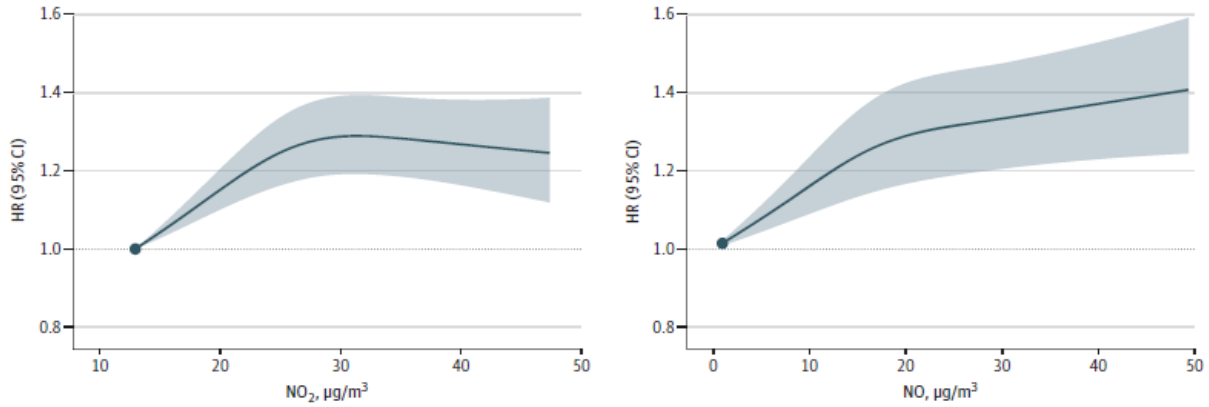
- Fu et al. (2022) observed a monotonic increase in risk of incident depression diagnosis associated with increasing tertiles of annual average NO_2 (HR T2 vs. T1: 1.11 [95% CI: 1.06, 1.16]; HR T3 vs. T1: 1.14 [95% CI: 1.09, 1.19] per 5.31 ppb increase in NO_2) and NO_X (HR T2 vs. T1: 1.10 [95% CI: 1.06, 1.15]; HR T3 vs. T1: 1.16 [95% CI: 1.12, 1.21] per 10 $\mu g/m^3$ increase in NO_X) concentrations among UK Biobank participants.
- Another study in UK Biobank participants reported linearly increasing associations for the risk of incident MDD diagnosis that plateaued at 25 $\mu g/m^3$ (13.3 ppb) and 50 $\mu g/m^3$ of annual averages of NO_2 and NO_X, respectively (Li et al., 2023a). However, there is also increasing uncertainty at higher concentrations, resulting from fewer available data at these concentrations (see Figure 9-10).



List of abbreviations in alphabetical order: CI = confidence interval.
Source: Li et al. (2023a). Copyright permission pending.

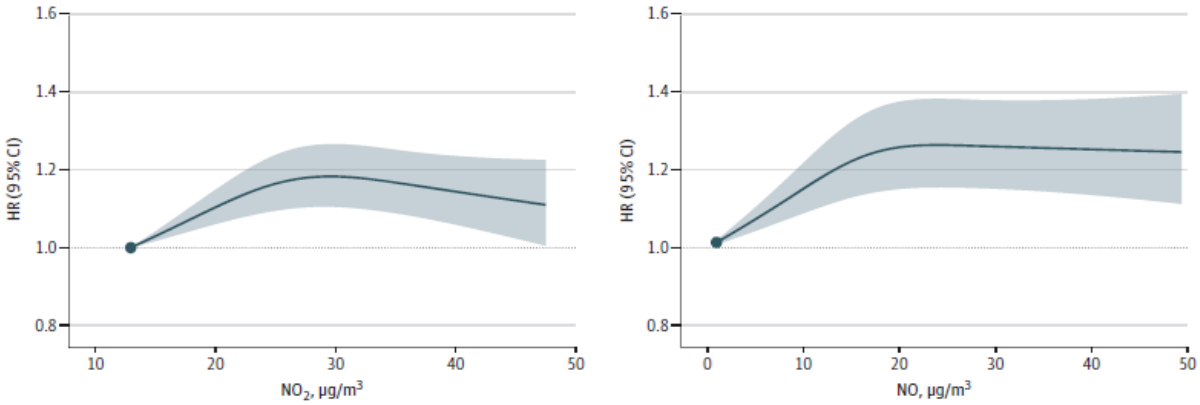
Figure 9-10 Dose-Response Relationship of Annual Exposure to NO_2 (Left) and NO_X (Right) and Incident MDD; Hazard Ratio (HR) for Continuous Air Pollution Is Modeled Using Restricted Cubic Splines.

- Another UK Biobank study reported linear relationships between annual average NO_2 and NO_X exposure and incident diagnoses for depression and anxiety that plateaued at higher concentrations (Yang et al., 2023) (see Figure 9-11 and Figure 9-12).



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

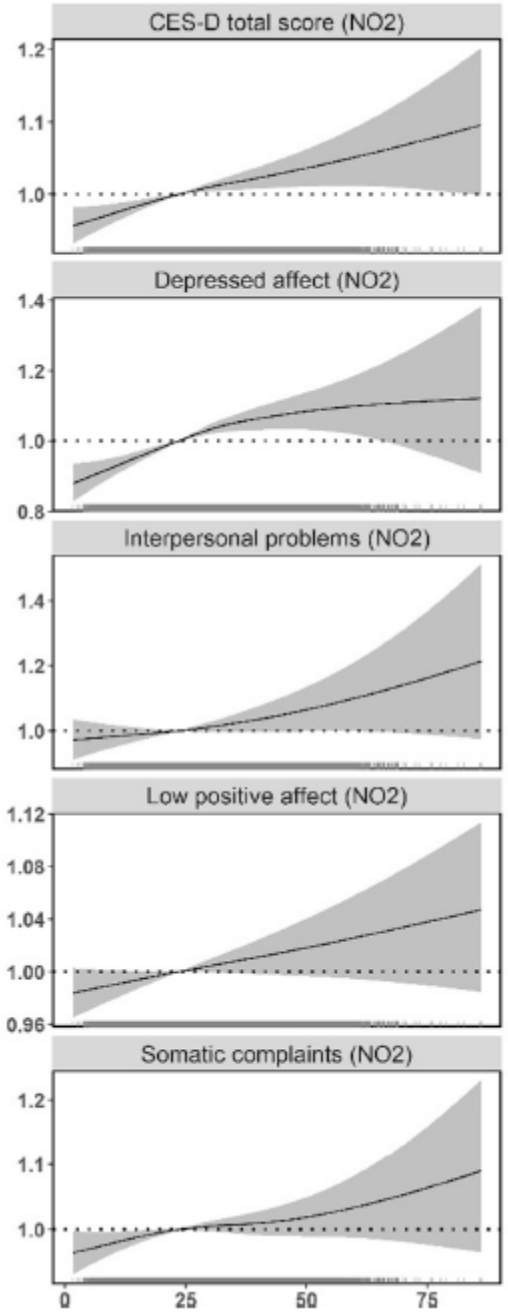
Figure 9-11 Dose-Response Relationship of Annual Exposure to NO_2 (Left) and NO_X (Right) and Incident Depression.



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

Figure 9-12 Dose-Response Relationship of Annual Exposure to NO_2 (Left) and NO_X (Right) and Incident Anxiety.

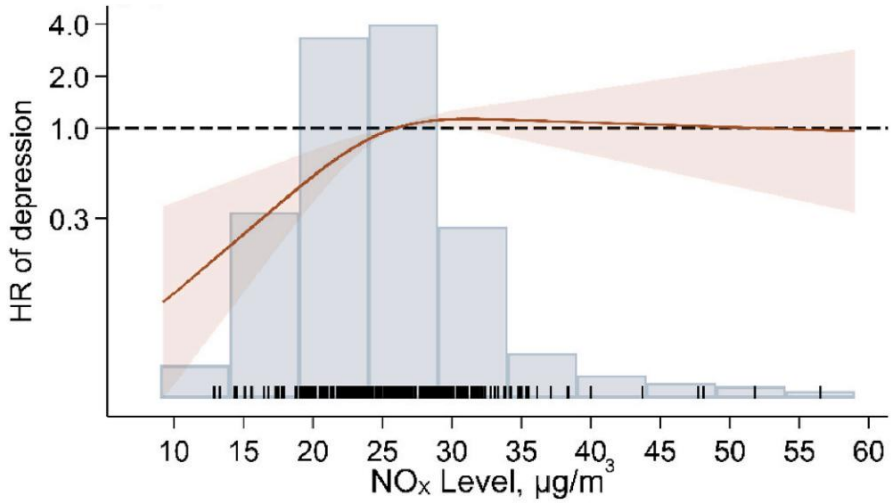
- Sakhvidi et al. (2022) reported approximately linear positive relationships between 2010 annual average NO_2 exposure and CES-D total score and four dimensions of the CES-D (depressed affect, interpersonal problems, low positive affect, and somatic complaints) in exposure-response analyses with a restricted cubic spline function. However, there is large uncertainty above the 95th percentile of NO_2 (see Figure 9-13).



List of abbreviations in alphabetical order: CES-D = Centre of Epidemiologic Studies Depression questionnaire.
Source: Sakhvidi et al. (2022). Copyright permission pending.

Figure 9-13 Incidence Rate Ratios for the Association Between Annual Exposure to NO_2 and Self-Reported Depressive Symptoms (CES-D Scores).

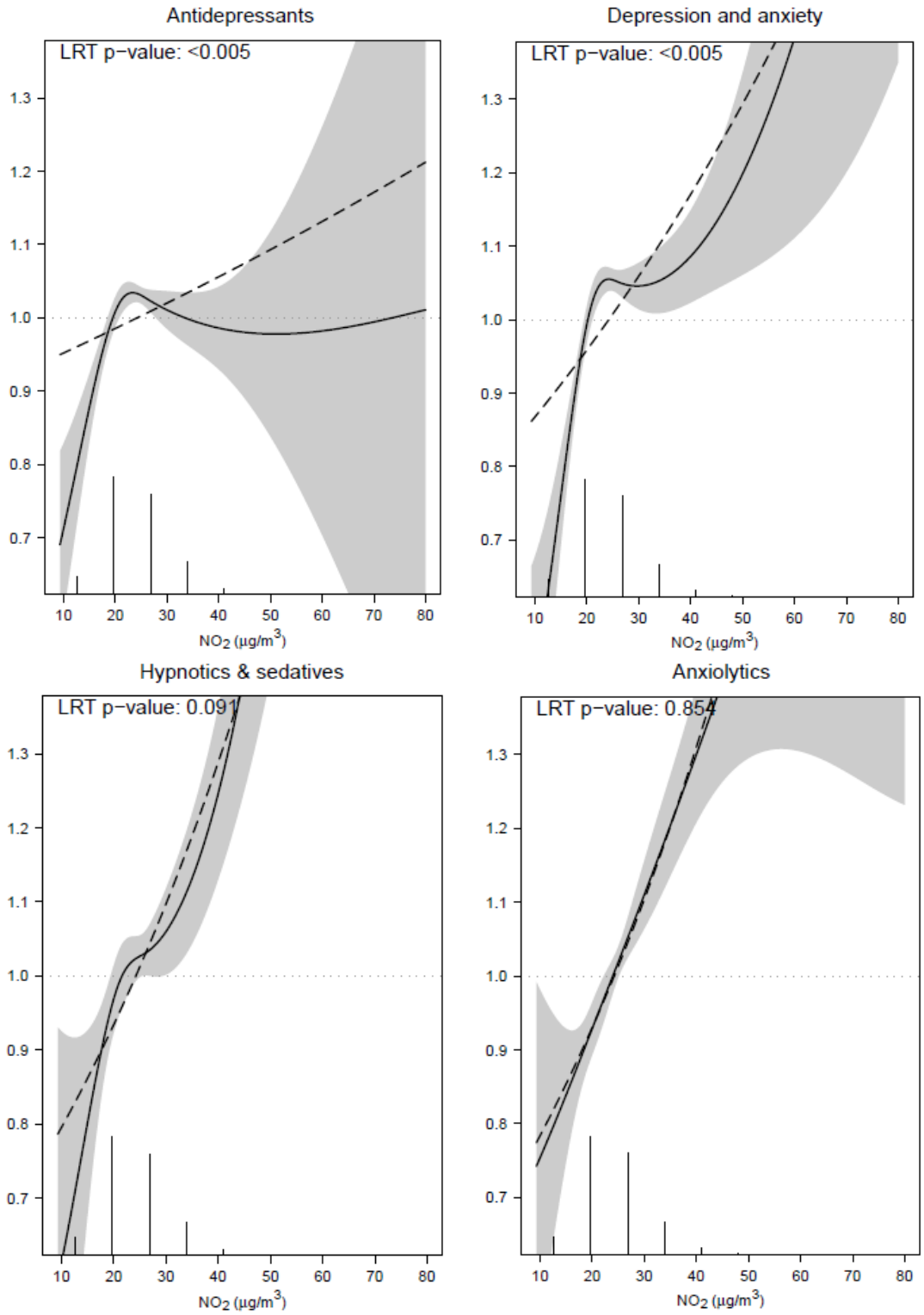
- Wu et al. (2023) reported a supralinear positive relationship between exposure to NO_X modeled as a time-varying covariate and incident depression diagnoses, with hazard rising sharply at low to medium levels of NO_X and plateauing around 30 µg/m^3. The reference group for the exposure-response analysis was the mean NO_X concentration (26 µg/m^3) (see Figure 9-14).



List of abbreviations in alphabetical order: HR = hazard ratio.
Source: Wu et al. (2023). Copyright permission pending.

Figure 9-14 Hazard Ratios for the Association Between Exposure to NO_X (Reference Group: 26 µg/m^3) and Incident Depression.

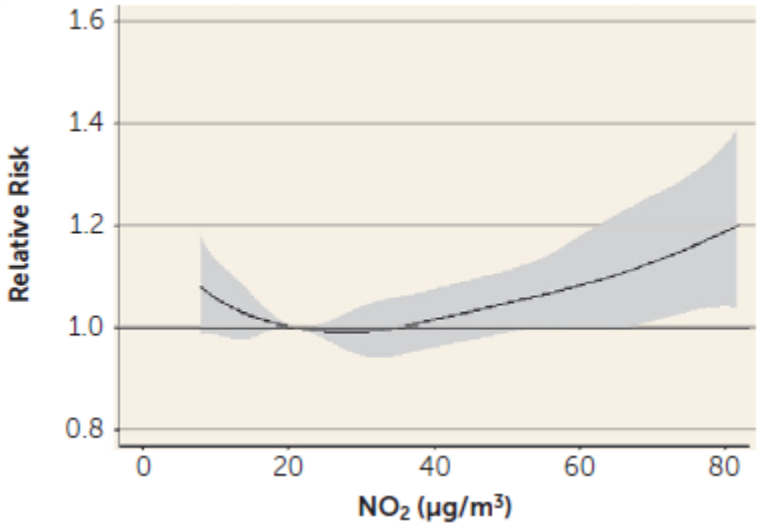
- Klompmaker et al. (2019) observed approximately linear positive relationships between annual average NO_2 exposure and odds of reporting depression and anxiety or being prescribed anxiolytics or hypnotics/sedatives, and a supralinear relationship for being prescribed antidepressants (see Figure 9-15).



List of abbreviations in alphabetical order: LRT = likelihood-ratio test.
Source: Klompmaker et al. (2019). Copyright permission pending.

Figure 9-15 Concentration-Response Curves for the Odds of Poor Mental Health in Association with Long-Term NO_2.

- Using a natural cubic spline with 6 degrees of freedom, Gu et al. (2020) observed a linearly increasing relationship between NO_2 concentrations at lag 01 days and depression-related hospital admissions at concentrations above 21.26 ppb (see Figure 9-16).



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

Figure 9-16 Concentration-Response Curve for NO_2 (Lag 01) and the Risk for Daily Hospital Admissions for Depression.

9.4.1.1.2 Lifestages and Populations

A few of the recent studies summarized above also examine factors that may confer a higher risk of diagnoses, symptoms, and hospitalizations for depression, anxiety, and psychological distress related to exposure to oxides of nitrogen. Analyses of these factors are summarized below and in Table 9-8 for long-term exposures to oxides of nitrogen and Table 9-9 for short-term exposures.

Among children

- One study in children assessed the relationship between NO_2 exposure and internalizing behavior in different populations (Loftus et al., 2020). Stronger positive associations were observed in boys compared to girls, children with Black mothers compared to those with non-Black mothers, children with Medicaid/no insurance at enrollment, children in low-income families, and children whose mothers had low folate concentrations during pregnancy.

Among adults

Short-Term Exposure: Sex

- Szyszkowicz et al. (2016) reported stronger associations for the risk of hospitalization for depression for females compared to males (OR male: 1.034 [95% CI: 0.972, 1.099]; OR female: 1.059 [95% CI: 1.006, 1.114] per 20 ppb increase in lag0 NO_2). This sex difference was consistent across lag periods of up to 8 days.
- Lu et al. (2020) reported a greater risk of hospital outpatient visits for mental disorders associated with a 20 ppb increase in NO_2 exposure averaged 0–5 days before the outcome

(lag 05) among male (β: 16.682 [95% CI: 10.827, 22.538]) compared to female participants (β: 12.573 [95% CI: 7.639, 17.507]).

- Gu et al. (2020) reported a stronger association between a 5.31 ppb increase in 0–1 day lagged cumulative NO_2 exposure and daily hospital admissions for male participants compared to female participants.
- Qiu et al. (2022) reported a stronger association between NO_2 exposure at 02 day lag and daily depression-related hospital admissions for male Medicare beneficiaries compared to female beneficiaries.

Long-Term Exposure: Sex

- Qiu et al. (2023a) reported a positive association between 5-year average NO_2 and depression risk among male but not female Medicare beneficiaries.
- Male participants in a UK Biobank study were more likely than female participants to develop depression or anxiety at higher quartiles of exposure to NO_2 (Yang et al., 2023).
- Sakhvidi et al. (2022) observed stronger associations between NO_X and depressive symptoms among male French participants compared to female participants (quantitative results not presented).
- Hautekiet et al. (2022) reported that male participants in a cross-sectional Belgian study were more likely than female participants to report NO_2-associated psychological distress, while the opposite was true for NO_2-associated depressive disorder and generalized anxiety disorder.

Short-Term Exposure: Age

- Lu et al. (2020) observed increased risk of outpatient visits for mental disorders per 20 ppb increase in NO_2 at lag 05 days among patients aged 15–34 years (β: 16.182 [95% CI: 8.445, 23.919]), 35–64 years (β: 15.076 [95% CI: 10.067, 20.084]), and ≥65 years (β: 14.033 [95% CI: 3.869, 24.198]). The magnitude of associations was similar across the age groups.

Long-Term Exposure: Age

- Participants in a UK Biobank study who were at least 65 years of age or older were more likely than their counterparts to develop depression or anxiety associated with annual average NO and NO_2 exposure. The difference in associations by age stratification was strongest for depression diagnosis at the 4^{th} quartiles vs. the 1^{st} quartiles of NO (HR younger: 1.10 [95% CI: 1.03, 1.17]; HR older: 1.19 [95% CI: 1.04, 1.35]) and NO_2 (HR younger: 1.10 [95% CI: 1.03, 1.18]; HR older: 1.29 [95% CI: 1.12, 1.49]) concentrations (Yang et al., 2023).
- Associations between NO_2 and psychological distress and suicidal ideation were strongest among those who were 60 years of age or older compared to younger individuals in a cross-sectional Belgian study (see Table 9-8) (Hautekiet et al., 2022).
- A cross-sectional study in the Netherlands (Klompmaker et al., 2019) observed stronger associations among those aged ≥65 years compared to those younger than 65 years for the odds of psychological distress (OR younger: 1.12 [95% CI: 1.04, 1.22]; OR older: 1.43 [95% CI: 1.26, 1.50]) or being prescribed anxiolytics (OR younger: 1.20 [95% CI: 1.04, 1.39]; OR older: 1.61 [95% CI: 1.39, 1.87]) or hypnotics/sedatives (OR younger: 1.26 [95% CI: 1.03, 1.53]; OR older: 1.49 [95% CI: 1.24, 1.79]) per 10 ppb increase in NO_2 exposure. Associations did not differ by age for antidepressant prescriptions (OR younger: 1.07 [95% CI: 1.00, 1.15]; OR older: 1.10 [95% CI: 1.00, 1.20]). Differences in the magnitude of associations by age remained robust models adjusting for noise and greenness.

Long-Term Exposure: Race/Ethnicity

- Associations were stronger for Black participants compared to white participants among Medicare beneficiaries, and for those living in ZIP codes with a low proportion of Hispanic individuals as opposed to a high proportion (Qiu et al., 2023a).
- Medicare enrollees living in ZIP codes with a low-median percentage of Hispanic individuals had a higher risk for depression-related hospital admissions associated with lag 02 day NO_2 exposure than those living in areas with a high Hispanic percentage (Qiu et al., 2022).

Short-Term Exposure: Socioeconomic Status

- (Gu et al., 2020) reported a stronger association between a 5.31 ppb increase in 0–1 day lagged cumulative NO_2 exposure and daily hospital admissions for male participants compared to female participants, in patients ≥65 years of age compared to younger patients, and those with the URBMI, which covers urban residents without previous employment history and unemployed adults, compared to those with the UEBMI, which covers urban employees and retirees.
- Medicare enrollees living in ZIP codes with median-high incomes had an increased risk for depression-related hospital admissions associated with lag 02 day NO_2 exposure compared to those living in lower income areas (Qiu et al., 2022).

Long-Term Exposure: Socioeconomic Status

- In subgroup analyses among Medicare beneficiaries, associations between 5-year NO_2 exposure and depression were strongest for those who were eligible for Medicaid, those living in ZIP code areas with a high proportion of households under the federal poverty line, and those in less privileged neighborhoods, as assessed with the income extreme index, compared to their counterparts (Qiu et al., 2023a).
- Among UK Biobank participants, those with a university/college degree were at higher risk of depression but not anxiety at higher concentrations of NO_2 (Yang et al., 2023).
- In the French CONSTANCES cohort, stronger associations were reported between NO_X and depressive symptoms for those with low and middle vs. high education, low vs. high income, living in areas of high vs. low deprivation, and individuals who were unmarried, separated or divorced, or widowed vs. individuals who were married or in a partnership (quantitative results not presented) (Sakhvidi et al., 2022).
- A cross-sectional study among Korean adults aged 50 years or older observed a greater increase in depressive symptoms scores per 10 ppb increase in five-year average NO_2 for married men compared to unmarried men. The opposite pattern was observed among women, such that unmarried women had a stronger association than married women (Kim et al., 2020).

Long-Term Exposure: Region/Urbanicity

- In a cohort of U.S. Medicare beneficiaries, Qiu et al. (2023a) observed the strongest associations between 5-year NO_2 exposure and depression among those living in areas with the lowest population density compared to those living in areas with higher population density.

Long-Term Exposure: Comorbidities

- A U.S. cohort study of women ≥80 years of age observed substantial attenuation of positive associations between recent NO_2 exposures (3-year period just before baseline) and

depressive symptoms when excluding women who developed dementia during the study or reported a history of depression prior to baseline (Petkus et al., 2021b). Associations with remote NO_2 exposure (10 years prior) were attenuated to a lesser extent.

- Subgroup analyses by comorbidities in a cohort of Medicare beneficiaries showed a larger risk of depression diagnosis associated with 5-year NO_2 exposure among those with Alzheimer's disease, dementia, hypertension, stroke, congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD), and cancer compared to those without these comorbidities (Qiu et al., 2023a).
- A study among U.K. patients with prediabetes and diabetes reported an increased risk of anxiety and depression in association with NO_2 and NO_X exposure (Feng et al., 2023). Furthermore, those with diabetes had stronger associations than those with prediabetes.

Long-Term Exposure: Behavior

- Wu et al. (2023) reported a greater increase in incident depression in association with NO_X exposure among those who were socially inactive (HR: 1.33 (95% CI: 1.01, 1.76) per 10 $\mu g/m^3$ increase in NO_X] compared to those who were socially active (HR: 1.09 [95% CI: 0.71, 1.66]).

Short-Term Exposure: Season

- Lu et al. (2020) reported a greater increase in risk per 20 ppb of 0–5 day cumulative average NO_2 exposure and outpatient visits for mental disorders during the cold season (β: 21.872 [95% CI: 17.170, 26.574]) as opposed to the warm season (β: -4.772 [95% CI: -11.660, 2.117]).
- The percent increase in daily hospital admissions for depression using hospitalization data from 57 Chinese cities was higher in the cold season (β: 7.04% [95% CI: 0.15%, 13.92%]) compared to the warm season (β: -6.92% [95% CI: -15.81%, 1.96%]) per 20 ppb increase in NO_2 at lag 02 (Ma et al., 2022).

Table 9-8 Epidemiologic Studies Evaluating Effect Measure Modification between Long-Term NO, NO_2, and NO_X Exposure and Anxiety, Depression, and Psychological Distress

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Sex						
†Hautekiet et al. (2022)	BHIS 2008, 2013, 2018	Psychological Distress	OR (95% CI)[b] Female: 1.05 (0.91, 1.22)	OR (95% CI)[b] Male: 1.18 (1.00, 1.39)	↑	Individual
		Severe Psychological Distress	Female: 1.02 (0.85, 1.22)	Male: 1.14 (0.93, 1.41)	↑	Individual
†Kim et al. (2020)	EPINEF March 2014–November	Depressive Symptoms	β (Score) (95% CI)[b] Female: 0.0130 (0.0065, 0.0195)	β (Score) (95% CI)[b] Male: 0.0098 (0.0034, 0.0162)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	2017					
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] Female: 1.002 (0.993, 1.011)	HR (95% CI)[b] Male: 1.036 (1.029, 1.043)	↑	Individual
Age						
†Yang et al. (2023)	UK Biobank Enrollment: 2006–2010 Follow-up: through February 2020	Depression Dx - Q4 vs. Q1	HR (95% CI)[c] NO_2 <65 yr: 1.10 (1.03, 1.18)	HR (95% CI)[c] NO_2 ≥65 yr: 1.29 (1.12, 1.49)	↑	Individual
			NO <65 yr: 1.10 (1.03, 1.17)	NO ≥65 yr: 1.19 (1.04, 1.35)	↑	Individual
†Hautekiet et al. (2022)	BHIS 2008, 2013, 2018	Psychological Distress	OR (95% CI)[b] 15-29 yr: 1.04 (0.81, 1.32)	OR (95% CI)[b] 30-44 yr: 1.00 (0.80, 1.25)	≈	Individual
				45-59 yr: 1.22 (0.97, 1.53)	↑	Individual
				≥60 yr: 1.11 (0.90, 1.36)	↑	Individual
		Severe Psychological Distress	15-29 yr: 0.97 (0.68, 1.37)	30-44 yr: 1.00 (0.76, 1.31)	≈	Individual
				45-59 yr: 1.07 (0.81, 1.41)	↑	Individual
				≥60 yr: 1.14 (0.89, 1.47)	↑	Individual
†Klompmaker et al. (2019)	PHM 2012	Psychological Distress	OR (95% CI)[b] <65 yr: 1.12 (1.04, 1.22)	OR (95% CI)[b] ≥65 yr: 1.43 (1.26, 1.62)	↑	Individual
		Anxiolytics	<65 yr: 1.20 (1.04, 1.39)	≥65 yr: 1.61 (1.39, 1.87)	↑	Individual
		Hypnotics and Sedatives	<65 yr: 1.26 (1.03, 1.53)	≥65 yr: 1.49 (1.24, 1.79)	↑	Individual
		Antidepressants	<65 yr: 1.07 (1.00, 1.15)	≥65 yr: 1.10 (1.00, 1.20)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Marital Status						
†Kim et al. (2020)	EPINEF March 2014–November 2017	Depressive Symptoms	β (Score) (95% CI)[b] Married: 0.0103 (0.0052, 0.0155)	β (Score) (95% CI)[b] Unmarried: 0.0194 (0.0044, 0.0344)	≈	Individual
		Depressive Symptoms - Male	Married: 0.0105 (0.0043, 0.0168)	Unmarried: -0.0070 (-0.0534, 0.0395)	≈	Individual
		Depressive Symptoms - Female	Married: 0.0090 (0.0020, 0.0160)	Unmarried: 0.0222 (0.0059, 0.0385)	↑	Individual
Pre-existing Diseases/Comorbidities						
†Feng et al. (2023)	UK Biobank Enrollment: 2006–2010 Follow-up: Through December 2019	Mental Disorders Dx	HR (95% CI)[b] NO_2 Prediabetes: 1.18 (1.13, 1.23)	HR (95% CI)[b] NO_2 Diabetes: 1.19 (1.13, 1.25)	≈	Individual
		Depressive Disorders Dx	Prediabetes: 1.11 (1.00, 1.23)	Diabetes: 1.12 (1.02, 1.23)	≈	Individual
		Anxiety Disorders Dx	Prediabetes: 1.19 (1.06, 1.33)	Diabetes: 1.21 (1.12, 1.32)	≈	Individual
		Mental Disorders Dx	HR (95% CI)[c] NO_X Prediabetes: 1.15 (1.11, 1.19)	HR (95% CI)[c] NO_X Diabetes: 1.17 (1.12, 1.23)	≈	Individual
		Depressive Disorders Dx	Prediabetes: 1.04 (0.94, 1.15)	Diabetes: 1.09 (1.01, 1.19)	↑	Individual
		Anxiety Disorders Dx	Prediabetes: 1.16 (1.05, 1.28)	Diabetes: 1.18 (1.10, 1.27)	≈	Individual
†Petkus et al. (2021b)	WHIMS-ECHO Enrollment: 2008 Follow-up: 2008–2016	Depressive Symptoms – Recent Exposure	β (Score) (95% CI)[b] Entire Cohort: 0.238 (-0.038, 0.513)	β (Score) (95% CI)[b] No Dementia: 0.154 (-0.161, 0.469)	↓	Individual
		Depressive Symptoms – Remote Exposure	Entire Cohort: 0.301 (0.109, 0.492)	No Dementia: 0.209 (0.024, 0.395)	↓	Individual
†Qiu et al. (2023a)	Medicare Enrollment:	Depression Dx	HR (95% CI)[b] Without AD: 1.008 (1.002, 1.014)	HR (95% CI)[b] With AD: 1.055 (1.041, 1.068)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	2000–2016 Follow-up: 2005-2016 (median 4 yr)		Without Cancer: 1.012 (1.006, 1.018)	With Cancer: 1.018 (1.008, 1.028)	≈	Individual
			Without CHF: 1.000 (0.994, 1.006)	With CHF: 1.036 (1.028, 1.045)	↑	Individual
			Without COPD: 1.004 (0.997, 1.011)	With COPD: 1.026 (1.017, 1.035)	↑	Individual
			Without Dementia: 1.000 (0.994, 1.006)	With Dementia: 1.051 (1.041, 1.060)	↑	Individual
			Without Diabetes: 1.004 (0.998, 1.010)	With Diabetes: 1.022 (1.014, 1.030)	↑	Individual
			Without HRT: 0.970 (0.960, 0.980)	With HRT: 1.016 (1.010, 1.022)	↑	Individual
			Without Stroke: 1.008 (1.002, 1.014)	With Stroke: 1.024 (1.015, 1.033)	↑	Individual
Race/Ethnicity						
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] White: 1.012 (1.006, 1.018)	HR (95% CI)[b] Black: 1.071 (1.057, 1.086)	↑	Individual
				Other Race: 0.945 (0.931, 0.958)	↓	Individual
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] High Hispanic Proportion: 0.996 (0.990, 1.002)	HR (95% CI)[b] Low Hispanic Proportion: 1.044 (1.035, 1.054)	↑	ZIP code
Region/Urbanicity						
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] Population Density Q1: 1.065 (1.051, 1.080)	HR (95% CI)[b] Population Density Q2: 1.059 (1.046, 1.072)	≈	ZIP code
				Population Density Q3: 1.000 (0.989, 1.011)	↓	ZIP code
				Population Density Q4: 0.955 (0.946, 0.963)	↓	ZIP code

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Socioeconomic Status: Income						
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] Income Extreme Index Quintile 1: 1.026 (1.015, 1.037)	HR (95% CI)[b] Income Extreme Index Quintile 2: 1.030 (1.020, 1.040)	≈	ZIP code
				Income Extreme Index Quintile 3: 1.018 (1.008, 1.028)	≈	ZIP code
				Income Extreme Index Quintile 4: 1.014 (1.005, 1.023)	≈	ZIP code
				Income Extreme Index Quintile 5: 0.986 (0.977, 0.995)	↓	ZIP code
Socioeconomic Status: Insurance Status						
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] Medicaid ineligible: 1.006 (1.000, 1.012)	HR (95% CI)[b] Medicaid eligible: 1.061 (1.051, 1.071)	↑	Individual
Socioeconomic Status: Poverty						
†Qiu et al. (2023a)	Medicare Enrollment: 2000–2016 Follow-up: 2005–2016 (median 4 yr)	Depression Dx	HR (95% CI)[b] Less Poor: 1.012 (1.006, 1.018)	HR (95% CI)[b] Poor: 1.018 (1.008, 1.028)	↑	ZIP code

List of abbreviations in alphabetical order: AD = Alzheimer's Disease; BHIS = Belgian Health Interview Survey; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; Dx = diagnosis; EMM = effect measure modification; EPINEF = Environmental Pollution-Induced Neurological Effects; HR = hazard ratio; HRT = hypertension; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; NO = nitric oxide; OR = odds ratio; PHM = Dutch Public Health Monitor; Q = quartile; WHIMS-ECHO = Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; yr = year(s).

[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of anxiety, depression, or psychological distress) 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) indicates 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.

Table 9-9 Epidemiologic Studies Evaluating Effect Measure Modification between Short-Term NO_2 Exposure and Hospitalization for Depression or Mental Disorders

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Sex						
†Gu et al. (2020)	UEBMI and URBMI January 2013–December 2017	HA for Depression - lag 01	β (% change) (95% CI)[b] Female: 7.87 (1.92, 13.81)	β (% change) (95% CI)[b] Male: 10.76 (4.59, 16.93)	↑	Individual
†Lu et al. (2020)	14 Chinese cities January 2013–December 2015	Hospital Outpatient Visit for Mental Disorders (Depression, Anxiety, Others) – lag 05	β (% change) (95% CI)[b] Female: 12.573 (7.639, 17.507)	β (% change) (95% CI)[b] Male: 16.682 (10.827, 22.538)	↑	Individual
†Ma et al. (2022)	UEBMI and URBMI January 2013–December 2017	HA for Depression - lag 02	β (% change) (95% CI)[b] Female: 7.07 (2.39, 11.76)	β (% change) (95% CI)[b] Male: 8.02 (3.42, 12.61)	≈	Individual
†Qiu et al. (2022)	Medicare January 2000–December 2016	HA for Depression - lag 02	β (% change) (95% CI)[b] Female: 1.04 (-2.40, 4.48)	β (% change) (95% CI)[b] Male: 2.08 (-0.10, 4.26)	↑	Individual
†Szyszkowicz et al. (2016)	NACRS April 2004–December 2011	ED Visit for Depression - lag 0	OR (95% CI)[b] Female: 1.059 (1.006, 1.114)	OR (95% CI)[b] Male: 1.034 (0.972, 1.099)	↓	Individual
		ED Visit for Depression - lag 1	Female: 1.029 (0.978, 1.082)	Male: 0.982 (0.924, 1.045)	≈	Individual
		ED Visit for Depression - lag 5	Female: 0.974 (0.927, 1.023)	Male: 0.991 (0.933, 1.053)	≈	Individual
		ED Visit for Depression - lag 8	Female: 1.000 (0.952, 1.050)	Male: 0.967 (0.911, 1.027)	≈	Individual
Age						
†Gu et al. (2020)	UEBMI and	HA for	β (% change) (95%	β (% change) (95%	↑	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	URBMI January 2013–December 2017	Depression - lag 01	CI)[b] 19-39 yr: 6.25 (-2.97, 15.47)	CI)[b] 40-64 yr: 8.96 (2.86, 15.05)		
				≥65 yr: 15.77 (7.71, 23.82)	↑	Individual
†Lu et al. (2020)	14 Chinese cities January 2013–December 2015	Hospital Outpatient Visit for Mental Disorders (Depression, Anxiety, Others) - lag 05	β (% change) (95% CI)[b] 0–14 yr: -1.178 (-17.492, 15.136)	β (% change) (95% CI)[b] 15-34 yr: 16.182 (8.445, 23.919)	↑	Individual
				35-64 yr: 15.076 (10.067, 20.084)	↑	Individual
				≥65 yr: 14.033 (3.869, 24.198)	↑	Individual
†Ma et al. (2022)	UEBMI and URBMI January 2013–December 2017	HA for Depression - lag 02,	β (% change) (95% CI)[b] 19–39 yr: 7.94 (2.77, 13.11)	β (% change) (95% CI)[b] 40–64 yr: 7.49 (3.07, 11.91)	≈	Individual
				≥65 yr: 8.47 (3.71, 13.23)	↑	Individual
Season						
†Lu et al. (2020)	14 Chinese cities January 2013–December 2015	Hospital Outpatient Visit for Mental Disorders (Depression, Anxiety, Others) - lag 05	β (% change) (95% CI)[b] Cold Season: 21.872 (17.170, 26.574)	β (% change) (95% CI)[b] Warm Season: -4.772 (-11.660, 2.117)	↓	Individual
†Ma et al. (2022)	UEBMI and URBMI January 2013–December 2017	HA for Depression - lag 02	β (% change) (95% CI)[b] Cold Season: 7.04 (0.15, 13.92)	β (% change) (95% CI)[b] Warm Season: -6.92 (-15.81, 1.96)	↓	Individual
Socioeconomic Status: Employment Status						
†Gu et al. (2020)	UEBMI and URBMI January 2013–	HA for Depression - lag 01	β (% change) (95% CI)[b] UEBMI (employed or retired): 4.89 (0.47, 9.31)	β (% change) (95% CI)[b] URBMI (no employment history): 4.63 (-	↓	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	December 2017			2.18, 11.44)		
†(Ma et al., 2022)	UEBMI and URBMI January 2013–December 2017	HA for Depression - lag 02	β (% change) (95% CI)[b] UEBMI (employed or retired): 7.83 (3.58, 12.08)	β (% change) (95% CI)[b] URBMI (no employment history): 4.63 (-1.09, 10.35)	↓	Individual
Socioeconomic Status: Neighborhood Income						
†Qiu et al. (2022)	Medicare January 2000–December 2016	HA for Depression - lag 02	β (% change) (95% CI)[b] High-Median Income: 1.68 (0.26, 3.10)	β (% change) (95% CI)[b] Low Income: 0.08 (-3.26, 3.42)	↓	ZCTA
Race/Ethnicity: Neighborhood						
†Qiu et al. (2022)	Medicare January 2000–December 2016	HA for Depression - lag 02	β (% change) (95% CI)[b] Median-Low Hispanic: 1.72 (0.12, 3.32)	β (% change) (95% CI)[b] High Hispanic: 0.96 (-2.10, 4.02)	↓	ZCTA

List of abbreviations in alphabetical order: CI = confidence interval; ED = emergency department; HA = hospital admission; NACRS = National Ambulatory Care Reporting System; NO_2 = nitrogen dioxide; OR = odds ratio; UEBMI = Urban Employee-Based Basic Medical Insurance; URBMI = Urban Resident-Based Basic Medical Insurance; yr = year(s); ZCTA = Zip code tabulation area.
[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of hospitalization for depression or mental disorders) 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) indicates 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.

9.4.1.1.3 Exposure Windows

Depressive and anxiety disorders are frequently linked to childhood experiences, so a consideration of the timing of exposures can help inform inferences about the biological plausibility of the associations. Loftus et al. (2020) evaluated internalizing behavior among preschool-age U.S. children in association with prenatal (pregnancy) and postnatal (birth to 9 months) exposures to NO_2. While all associations were positive but imprecise, with confidence intervals including the null, associations with postnatal exposures tended to be greater in magnitude than prenatal exposures. Another cohort study in European children seven to 11 years of age observed null associations between both prenatal and postnatal exposures to NO_2 and NO_X and the odds of having depressive and anxiety symptoms in the

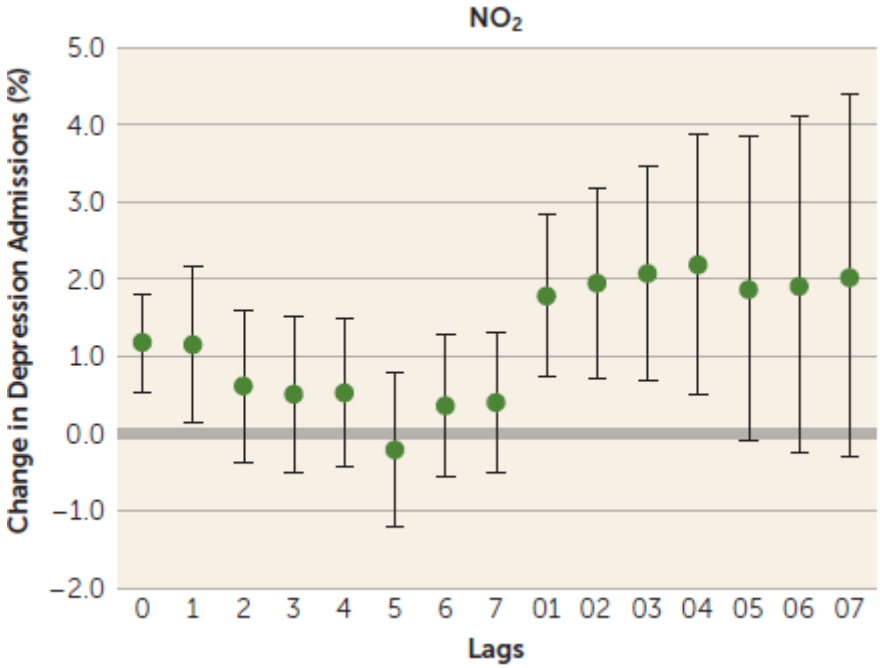
borderline/clinical range, according to CBCL and SDQ scores (Jorcano et al., 2019). However, associations with postnatal exposures were nearly inverse.

9.4.1.1.4 Copollutants

- In a study of U.K. participants, the risk of co-incident depression and anxiety disorders was not substantially changed from the single pollutant results by including $PM_{2.5}$, PM_{10}, NO_2, and NO_X in a multipollutant model [HR for NO_2 single pollutant: 1.05 (95% CI: 1.03, 1.06); HR for NO_2 multipollutant: 1.06 (95% CI: 1.01, 1.10) per 5.31 ppb increase NO_2; HR for NO_X single pollutant: 1.05 (95% CI: 1.04, 1.06); HR for NO_X multipollutant: 1.03 (95% CI: 1.01, 1.07) per 10 $\mu g/m^3$ increase NO_X] (Gao et al., 2023).
- Adjusting for greenness or noise in multi-exposure models or adjusting for $PM_{2.5}$ and oxidative potential of PM using dithiothreitol (OP^{DTT}) in two-pollutant models in a Dutch cross-sectional study slightly attenuated results from the single pollutant models, but associations remained positive (Klompmaker et al., 2019).
- In two-pollutant models, the NO_2 association in Gu et al. (2020) slightly attenuated but remained positive for daily hospital depression admissions at lag 01 after adjusting for $PM_{2.5}$ (IRR: 1.018 [95% CI: 1.007, 1.029]) and PM_{10} (IRR: 1.017 [95% CI: 1.005, 1.029]).
- Lu et al. (2020) reported an increased risk of outpatient visits for mental disorders associated with 20 ppb increase in lag 05 day NO_2 (β: 14.214 [95% CI: 10.443, 17.985]). Associations did not change in copollutant analyses with $PM_{2.5}$ (β: 15.068 [95% CI: 10.690, 19.447]) and PM_{10} (β: 14.240 [95% CI: 9.788, 18.692]), which were moderately correlated with NO_2 (Pearson's $\rho = 0.65$ and 0.60, respectively).
- One panel study reported positive associations between annual mean NO_2 concentrations and psychological distress (OR LSOAs: 1.28 [95% CI: 1.22, 1.34]; OR local authority: 1.26 [95% CI: 1.19, 1.33] per 10 ppb increase in NO_2) using a cut-off score of GHQ-12 ≥2 (out of 12) (Abed Al Ahad et al., 2022). These associations were robust with slight attenuation in copollutant models with SO_2 (Pearson's $\rho = 0.37$) [OR LSOAs: 1.26 (95% CI: 1.20, 1.32); OR local authority: 1.24 (95% CI: 1.16, 1.32)]. However, there was no evaluation of copollutant confounding by PM_{10} ($\rho = 0.76$–0.77) and $PM_{2.5}$ ($\rho = 0.79$–0.81), which were more strongly correlated with NO_2 and NO_X and may contribute to residual confounding.

9.4.1.1.5 Lag Structure

- Gu et al. (2020) reported positive associations between NO_2 concentrations and daily hospital admissions for depression at lag days 0 and 1. Associations at lags ranging from 2 to 5 days were imprecise. (Ma et al., 2022) reported similar results in a smaller subset of the patients analyzed in Gu et al. (2020) who had hospitalization expenditure and length of hospital stay data. Daily hospital admissions for depression increased by 1.50% (95% CI: 0.71, 2.30) at lag 0 and 1.09% (95% CI: 0.11, 2.08) at lag 1 per 5.31 ppb increase in NO_2 (see Figure 9-17).



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

Figure 9-17 Percent Changes in Daily Hospital Admissions for Depression per 5.31 ppb Increase in NO_2 at Different Lag Days.

- Szyszkowicz et al. (2016) reported the strongest sex-stratified associations between NO_2 and hospitalizations for depression at lag 0. Results were attenuated in analyses using single-day lags of 1 to 8 days.
- Qiu et al. (2022) observed the largest magnitude of associations for depression hospital admissions with a 5 ppb increase in single-day lagged NO_2 exposures at lag 0 day that attenuated to null at lag 4 and became nearly inverse at lag 6. Using cubic constrained distributed lag models, the authors identified lag 02 days as the critical exposure window with the strongest association across all single-day and cumulative-day exposure periods.

One study evaluated long-term exposure lags for the relationship between NO_2 exposures and depression.

- Petkus et al. (2021b) reported increases in depressive symptoms in association with 3-year annual NO_2 exposures both immediately before (recent) and 10 years before (remote) the baseline assessment. Associations were stronger for remote NO_2 exposures than for recent exposures. Associations remained robust in sensitivity analyses excluding women who had stroke or developed dementia during follow-up or reported a history of depression before baseline, and in analyses stratified by years since the baseline assessment.

9.4.1.1.6 Conclusions and Remaining Uncertainties

The 2016 Oxides of Nitrogen ISA included one study evaluating associations between NO_2 exposure and psychological distress in children, and no studies evaluating such associations in adult populations. Recent studies have examined children, adolescents, and adults. Among children, a couple recent studies report positive but imprecise associations for a wide range of ages; however, the evidence is sparse. One study of children provided some evidence for effect modification by various characteristics, including child sex, maternal race, pregnancy factors, and SES. The strongest associations were observed in males, children with Black mothers, children from lower-SES families, and children whose mothers had low folate concentrations during pregnancy. Postnatal exposures may be more relevant than prenatal exposures, but the direction of effect is unclear. Studies assessing effects in adults reported generally positive associations and were mostly conducted among older adults (≥50 years). Many of these studies observed supralinear concentration-response relationships between exposure to NO, NO_2, and NO_X and diagnoses and symptoms of depression, anxiety, and/or psychological distress. These studies demonstrated steeper slopes at low to medium exposure concentrations, and a plateauing or inversion of the relationship at higher concentrations. However, the exposure concentration at which this shift occurs differs among the studies, and it may be attributed to the small numbers of observations at higher concentrations of oxides of nitrogen and the resulting wide confidence intervals. Recent studies assessing various lags ranging from 0 to 7 days among short-term exposures identified the strongest positive associations at lags 0–2 days, which were attenuated at later lag days. There was only one long-term exposure study (Petkus et al., 2021b) that evaluated the lag-structure of associations, which suggested that remote exposures occurring a decade before incidence of depression have greater effects than more recent exposures for long-term exposures lasting longer than one month. A few studies evaluated confounding by OP^{DTT}, copollutants such as $PM_{2.5}$, PM_{10}, and other oxides of nitrogen, and co-exposures to factors such as greenness, noise, and reported little to no change in associations after adjustment. Recent studies also observed generally stronger effects for depression among those who were male, older, lower SES, and had preexisting conditions such as cardiovascular diseases, dementia, or diabetes. Depression and anxiety disorders are frequently comorbid with other conditions, so consideration of comorbidities by other mental and physical health conditions can help inform inference about biological plausibility

9.4.1.2 Animal Toxicological Studies of Anxiety and Depression

While subjective emotions like anxiety and depression cannot be directly measured in rodents, many tests have been developed to evaluate innate behaviors that may resemble the human condition. Of these tests, the elevated plus maze (EPM) and forced swim test (FST) are the most widely used for evaluating anxiety- and depression-like behavior, respectively. The EPM and similar tests are designed to exploit the approach-avoidance conflict, wherein rodents must balance their motivation to explore novel environments (to gather food and resources) with the need to evade predators and other threats. In contrast, the FST models behavioral despair. When rodents are subjected to an inescapable aversive

stimulus, they typically attempt to escape, but eventually cease these attempts and become immobile. Increased immobility time is typically considered analogous to depressive behavior; however, this interpretation has been questioned and alternative interpretations, that this behavior reflects maladaptive coping or an anxiety-like phenotype, have been suggested (Anyan and Amir, 2018; Molendijk and de Kloet, 2015). Despite these considerations, both the EPM and FST are sensitive to known anxiolytic and antidepressant drugs, thus having some predictive validity for the human conditions (Lucki, 1997; Rodgers and Dalvi, 1997).

There was limited toxicological evidence available to support the effect of NO_2 on anxiety-like behavior in the 2016 Oxides of Nitrogen ISA. Wistar rat pups exposed to NO_2 (0.03 to 5.32 ppm, six hours/day) showed no significant changes in several measures of anxiety-like behavior in the open field including self-grooming, defecation, or object exploration on PND 21, 30, or 60 (Tabacova et al., 1985). However, on PND 30, male rat pups exhibited a significant reduction in rearings, which may indicate decreased exploratory motivation (an anxiety-like phenotype), but this metric can be confounded by other factors including motor deficits (see Section 9.3.2.2). There was no clear indication of a dose-response gradient for any of these endpoints. Recent studies relevant to anxiety- and depression-like behavior have utilized the open field test (OFT), EPM, and FST. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-10. Conclusions from the animal evidence and remaining uncertainties are discussed in Section 9.4.1.2.1.

- Male and female offspring of pregnant C57BL/6J mice, that were exposed to 2.5 ppm NO_2 (5 hours/day) throughout gestation, were tested for anxiety-like behavior in the OFT and EPM from PND 21 to PND 23 (Li et al., 2022a). Male mice spent significantly less time in the center of the open field arena compared to untreated controls. Increased thigmotaxis (i.e., a tendency to remain close to the walls of the arena) is associated with an anxiety-like phenotype. An anxiogenic effect of NO_2 was also observed in the EPM in male mice, evidenced by significantly increased time spent in the closed arms of the maze concomitant with significant decreases in the time spent in the open arms of the maze. No significant effects were found in NO_2-treated female mice.
- Li et al. (2021) exposed 7-week-old male and female C57BL/6J mice to 2.5 ppm NO_2 (5 hours/day) for four weeks followed by testing in the OFT and EPM. Similar to Li et al. (2022a), NO_2 exposure increased thigmotaxis in the OFT and increased preference for the closed arms in the EPM in male, but not female, mice.
- These studies also reported that immobility time in male mice significantly increased in the FST compared to untreated controls, which is traditionally interpreted as depression-like behavior (Li et al., 2022a; Li et al., 2021).

9.4.1.2.1 Conclusions and Remaining Uncertainties

Taken together, the animal evidence is mixed with two recent studies providing support for anxiety-like and depression-like behaviors following NO_2 exposures in juvenile or young adult male mice, but not females. Recent studies are inconsistent with the single previously reviewed study, which

provided little evidence that NO_2 increases anxiety-like behaviors. These studies assessed behavior using different tests and metrics, which may contribute to the discordant findings. Further studies should build on these findings, examining alternative exposure paradigms and delineating a potential dose-response relationship. Moreover, there is a significant gap in understanding the potential impact of NO_2 on female mice, as current data is insufficient to draw definitive conclusions about sex-specific differences. No data is available on the effects of multipollutant exposure on this endpoint.

9.4.2 Schizophrenia and Psychosis

Schizophrenia is a chronic psychiatric disorder characterized by psychosis, disorganized speech, impaired emotional expression, and abnormal motor behavior. While psychosis is a core feature of schizophrenia, it can manifest for a variety of reasons and broadly refers to hallucinations and delusions that disrupt an individual's grasp on reality. Section 9.4.2.1 summarizes recent PECOS-relevant epidemiologic evidence examining the relationship between long-term oxides of nitrogen exposure and schizophrenia incidence, psychotic experiences and symptoms, and hospitalizations for psychotic disorders. A single short-term study of hospitalizations for schizophrenia is also reviewed. No PECOS-relevant animal toxicological studies were available.

9.4.2.1 Epidemiologic Studies of Schizophrenia and Psychosis

There were no studies evaluating the relationship between oxides of nitrogen exposure and schizophrenia and psychosis in the previous ISA. Recent studies examine associations among adolescents and adults. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 9-11.

- In a Danish national cohort, Antonsen et al. (2020) observed increased incidence rate ratios of schizophrenia diagnosis per 10 ppb increase in daily NO_2 concentrations averaged from birth to age 10 years (IRR: 1.41 [95% CI: 1.17, 1.70]). The authors also reported a positive association for each 10 $\mu g/m^3$ increase in NO_X (IRR: 1.06 [95% CI: 1.02, 1.10]). Exposure was estimated with dispersion models at a 1 km x 1 km spatial resolution. Participants were followed up between ages 10–37 years.
- Newbury et al. (2019) conducted a cross-sectional analysis of psychotic experiences and symptoms in English and Welsh adolescent twin pairs. At 18 years of age, participants were interviewed on their experiences since age 12 years on seven items relating to delusions and hallucinations and six items on unusual experiences drawing from two validated screening tools for psychosis. The authors reported positive associations between the odds for psychotic experiences and exposure to continuous annual mean NO_2 [OR: 1.01 (95% CI: 1.00, 1.03)] and NO_X [OR: 1.01 (95% CI: 1.00, 1.02)]. Dichotomizing at different concentrations of exposure and stratifying by quartiles of exposure demonstrated stronger associations at higher concentrations of NO_2 and NO_X. Dichotomizing at the highest quartile of exposure resulted in

an OR of 1.71 (95% CI: 1.28, 2.28) for NO_2 and 1.72 (95% CI: 1.30, 2.29) for NO_X. NO_2 and NO_X were modeled for 2012 using the local-scale Community Multiscale Air Quality (CMAQ-urban) Modeling System.

Hospitalizations

A single U.S. case-crossover study reported generally positive associations between short-term exposure to oxides of nitrogen and hospital admissions for schizophrenia.

- Qiu et al. (2022) evaluated associations between daily NO_2 exposures with single-day and cumulative lags ranging from 0 to 6 days and hospital admissions for schizophrenia for Medicare enrollees. Using cubic constrained distributed lag models, the authors identified lag 02 days as the critical exposure window for their main analyses. A 20 ppb increase in lag 02 NO_2 was associated with a 2.56% increase (95% CI: 0.80%, 4.32%) in schizophrenia-related admissions. Refer to Section 9.4.1.1 for additional study details.

One recent study assessed long-term exposure to oxides of nitrogen and hospital admissions in a U.S. population and found positive associations with hospitalization risk for schizophrenia.

- Qiu et al. (2023b) examined the association between annual average residential NO_2 exposure and risk of hospitalization for psychotic disorders in U.S. residents using high-resolution air pollution models integrating machine learning, land use, meteorology, and chemical transport models. A zero-inflated negative binomial regression model was adjusted for key confounders including copollutants, demographic, socioeconomic, and meteorological factors. In single pollutant models, each 10 ppb increase in NO_2 was associated with a positive and precise increase in hospitalization risk (RR: 1.18 [95% CI: 1.16, 1.20]).

A few of the studies summarized above include additional analyses examining the shape of concentration-response functions between NO_2 exposures and psychiatric effects, the lifestages and populations at higher risk of NO_2-associated effects, the potential impacts of copollutants on reported associations, and the lag structure of the associations. These topics are discussed below in Sections 9.4.2.1.1, 9.4.2.1.2, 9.4.2.1.3, and 9.4.2.1.4, respectively. Section 9.4.2.1.5 presents conclusions from these studies and summarizes remaining uncertainties in the epidemiologic evidence.

9.4.2.1.1 Concentration-Response

Newbury et al. (2019) conducted analyses with categories of exposure dichotomized at World Health Organization (WHO) thresholds (NO_2: 21.3 ppb; NO_X: 30 μg/m^3), WHO means (NO_2: 10.7 ppb; NO_X: 25.79 μg/m^3), and the highest quartiles (NO_2: 13.8 ppb; NO_X: 33.0 μg/m^3) of exposure, as well as analyses by quartiles of exposure. The associations were negative for the 2nd quartile compared to the 1st quartile [OR for NO_2 Q2 vs. Q1: 0.70 (95% CI: 0.50, 0.99); OR for NO_X Q2 vs. Q1: 0.65 (95% CI: 0.46, 0.91)] and steadily increased to become positive comparing the 4th quartile to the 1st quartile [OR for NO_2 Q4 vs. Q1: 1.41 (95% CI: 0.98, 2.03); OR for NO_X Q4 vs. Q1: 1.37 (95% CI: 0.97, 1.92)]. The OR for psychotic experiences in association with NO_2 dichotomized at 13.82 ppb was 1.71 (95% CI: 1.28, 2.28), while the OR for NO_X dichotomized at 33.0 μg/m^3 was 1.72 (95% CI: 1.30, 2.29).

9.4.2.1.2 Lifestages and Populations

A few of the recent studies summarized above also examine factors that may confer a higher risk of schizophrenia diagnoses or hospitalizations for psychotic disorders related to exposure to oxides of nitrogen. Analyses of these factors are summarized below and in Table 9-10 for long-term exposures to oxides of nitrogen.

- Antonsen et al. (2020) did not find evidence for effect modification by sex of the relationship between NO_2 and NO_X exposure and schizophrenia incidence by age 37 years [IRR for NO_2 males: 1.21 (95% CI: 1.06, 1.38); IRR for NO_2 females: 1.20 (95% CI: 1.02, 1.39); IRR for NO_X males: 1.06 (95% CI: 1.01, 1.12); IRR for NO_X females: 1.06 (95% CI: 1.00, 1.12) per 5.31 ppb increase in NO_2 or 10 $\mu g/m^3$ increase in NO_X].
- Qiu et al. (2023b) observed increased risks for psychotic disorder-related hospital admissions associated with a 10 ppb increase in exposure to NO_2 among male patients (compared to female) (RR male: 1.22 [95% CI: 1.19, 1.24]; RR female: 1.16 [1.14, 1.18]), older individuals (compared to those aged <30 years) (RR older: 1.11 [95% CI: 1.10, 1.13]; RR younger: 1.00 [95% CI: 0.98, 1.02]), those residing in areas with a high proportion of households under the federal poverty line (compared to low-poverty) (RR high poverty: 1.20 [95% CI: 1.17, 1.22; RR low poverty: 1.15 [95% CI: 1.12, 1.17]), and those residing in neighborhoods with a lower proportion of Black individuals (compared to high Black population density) (RR low Black proportion: 1.11 [95% CI: 1.09, 1.14]); RR high Black proportion: 1.05 [95% CI: 1.01, 1.08]). There was weaker evidence for effect modification by Hispanic population percentage.
- Qiu et al. (2022) identified heterogeneity in associations between cumulative lag 02 day NO_2 exposure and hospital admissions for schizophrenia by ZIP code tabulation area (ZCTA)-level Hispanic ethnicity proportion, with a strong positive association among those in ZCTAs with median to low proportion of Hispanic individuals (β: 4.08 [95% CI: 1.84, 6.32] per 20 ppb increase in NO_2) while the association among those in high-proportion Hispanic neighborhoods was null (β: 0.16 [95% CI: -4.08, 4.40]).

Table 9-10 Epidemiologic Studies Evaluating Effect Measure Modification between Long-Term NO and NO_2 Exposure and Schizophrenia and Psychotic Disorder

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Age						
†Qiu et al. (2023b)	HCUP 2002–2016	HA for Psychotic Disorder	RR (95% CI)[b] <30 yr: 1.00 (0.98, 1.02)	RR (95% CI)[b] ≥30 yr: 1.11 (1.10, 1.13)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	Outcome	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Race/Ethnicity: Neighborhood						
†Qiu et al. (2023b)	HCUP 2002–2016	HA for Psychotic Disorder	RR (95% CI)[b] Lower Black Population Density: 1.11 (1.09, 1.14)	RR (95% CI)[b] Higher Black Population Density: 1.05 (1.01, 1.08)	≈	ZIP code
			Low Hispanic Areas: 1.18 (1.16, 1.21)	High Hispanic Areas: 1.17 (1.14, 1.19)	≈	ZIP code
Sex						
†Antonsen et al. (2020)	Danish Civil Registration System Enrollment: January 1980–December 1984	Schizophrenia Dx	IRR (95% CI)[b] NO_2 Female: 1.41 (1.05, 1.89)	IRR (95% CI)[b] NO_2 Male: 1.43 (1.12, 1.83)	≈	Individual
			NO IRR (95% CI)[c] Female: 1.06 (1.00, 1.12)	NO IRR (95% CI)[c] Male: 1.06 (1.01, 1.12)	≈	
†Qiu et al. (2023b)	HCUP 2002–2016	HA for Psychotic Disorder	RR (95% CI)[b] Female: 1.16 (1.14, 1.18)	RR (95% CI)[b] Male: 1.22 (1.19, 1.24)	≈	Individual
Socioeconomic Status: Neighborhood Poverty						
†Qiu et al. (2023b)	HCUP 2002–2016	HA for Psychotic Disorder	RR (95% CI)[b] Low Poverty: 1.15 (1.12, 1.17)	RR (95% CI)[b] High Poverty: 1.20 (1.17, 1.22)	≈	ZIP code

List of abbreviations in alphabetical order: CI = confidence interval; Dx = diagnosis; EMM = effect measure modification; HA = hospital admission; HCUP = Health Cost and Utilization Project; IRR = incidence rate ratio; NO_2 = nitrogen dioxide; NO = nitric oxide; RR = risk ratio; yr = year(s).

[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of anxiety, depression, or psychological distress) 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) indicates 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.

9.4.2.1.3 Copollutants

- In a copollutant analysis including both NO_2 and NO_X simultaneously, one Danish cohort study observed slight attenuation of the estimated positive association for exposure to NO_2 and schizophrenia incidence rate [IRR for NO_2: 1.20 (95% CI: 1.09, 1.33); IRR for NO_{2+} NO_X: 1.19 (95% CI: 0.98, 1.44) per 5.31 ppb increase in NO_2], while the positive association for NO_X became null [IRR for NO_X: 1.06 (95% CI: 1.02, 1.10); IRR for NO_X + NO_2: 1.01 (95% CI: 0.93, 1.08) per 10 μg/m^3 increase in NO_X], suggesting that NO_X exposure did not contribute to schizophrenia incidence beyond that explained by NO_2. The two pollutants were highly correlated (Pearson ρ = 0.90), while the correlations with $PM_{2.5}$ and PM_{10} for NO_2 and NO_X were below 0.5 (Antonsen et al., 2020).
- Newbury et al. (2019) observed an increase in the association between NO_X dichotomized at the highest quartile and psychotic experiences in a copollutant model with $PM_{2.5}$ [OR: 1.82 (95% CI: 1.22, 2.71)].
- Qiu et al. (2023b) employed multi-exposure models including $PM_{2.5}$, temperature, and cumulative precipitation. Associations between annual average NO_2 exposure and depression diagnosis remained positive but were attenuated compared to the single pollutant model (RR: 1.18 [95% CI: 1.16, 1.20] per 10 ppb increase in NO_2) when adjusting for $PM_{2.5}$ (RR: 1.20 [95% CI: 1.18, 1.23]).

9.4.2.1.4 Lag Structure

- Qiu et al. (2022) observed the largest magnitude of associations for schizophrenia hospital admissions per a 5 ppb increase in single-day lagged NO_2 exposures at lag 0 day that attenuated to null at lag 4 and became nearly inverse at lag 6. Using cubic constrained distributed lag models, the authors identified lag 02 days as the critical exposure window with the strongest association across all single-day and cumulative-day exposure periods.

9.4.2.1.5 Conclusions and Remaining Uncertainties

Schizophrenia and psychosis were not evaluated in the 2016 Oxides of Nitrogen ISA. The current review includes one cohort and one cross-sectional study in adolescents and young adults that observed positive associations between increasing concentrations of oxides of nitrogen and psychotic symptoms and schizophrenia incidence. There is some evidence for copollutant confounding between NO_2, NO_X, and $PM_{2.5}$; however, there is uncertainty regarding the extent and direction of confounding effects as well as the influence of other copollutants highly correlated with oxides of nitrogen. One study that evaluated associations by sex did not find differences between males and females. More investigation into the potential for effect modification by sex in addition to other characteristics like age, urbanicity, and SES may help inform conclusions about this relationship. One study assessed the effect of stratifying exposure concentrations at various thresholds and observed a general increase in associations with increasing concentrations of oxides of nitrogen, with a dip at medium levels of exposure. Given the relatively small number of studies examining associations with schizophrenia and psychosis, there remain uncertainties in

the concentration-response relationship, the lifestages and populations at highest risk, the impact of traffic-related copollutants on reported associations, and the critical periods of exposure for the development of schizophrenia.

9.4.3 Synthesis Across Lines of Evidence

In the 2016 Oxides of Nitrogen ISA, a single epidemiologic study reported a null association between NO_2 exposure and emotional problems in children. A small number of recent studies in children and adolescents continue to report mostly null associations with depression and anxiety. In adult populations, however, recent evidence consistently links long-term oxides of nitrogen exposure with increases in measures of anxiety, depression, and psychological distress. These positive associations typically persist, though they are often attenuated, in models that adjust for copollutants, greenness, and noise. Many of these studies observed a supralinear concentration-response relationship between NO, NO_2, and NO_X exposure and these endpoints. One study decomposed associations into between-community and within-community analyses. This study reported null associations in within-community analyses, suggesting the potential for residual confounding in between-community comparisons. Limited evidence from toxicological studies suggests that NO_2 exposure may increase anxiety- and depression-like behaviors in male mice; however, this evidence is not entirely consistent, effects were not observed in females, and studies reporting significant effects were conducted using exposure levels above typical ambient conditions (2.5 ppm). Moreover, because animal models cannot fully reproduce complex human psychiatric conditions, the relevance of these findings to human health remains uncertain.

The relationship between oxides of nitrogen exposure and schizophrenia and psychosis is less well understood. One cohort study and one cross-sectional study in adolescents and young adults reported positive associations between oxides of nitrogen exposure and psychotic symptoms or schizophrenia incidence; however, the extent to which these associations are influenced by copollutants remains unclear. No animal toxicological studies have addressed endpoints relevant to schizophrenia and psychosis.

While most of the recent research has concentrated on long-term oxides of nitrogen exposure and psychiatric conditions, several time-series and case-crossover studies have examined short-term exposures. These studies generally report positive associations between short-term increases in oxides of nitrogen and hospital admissions for psychiatric disorders, with the most pronounced effects observed within zero to two days post-exposure.

9.5 Neurodegenerative Disease

Neurodegenerative diseases are chronic conditions that damage and degrade portions of the nervous system over time. This Section discusses the available epidemiologic and animal toxicological

evidence for general cognitive decline (i.e., cognitive function in adults) (see Section 9.5.1), Alzheimer's disease and related dementias (ADRD) (see Section 9.5.2), Parkinson's disease (see Section 9.5.3) and other neurodegenerative diseases (see Section 9.5.4). Section 9.5.5 presents an integrated synthesis across lines of evidence for oxides of nitrogen exposure and neurodegenerative disease.

9.5.1 General Cognitive Decline

Cognitive decline is a common consequence of aging, marked by gradual impairments in cognitive functioning. Greater than normal cognitive decline may be considered mild cognitive impairment (MCI), an intermediate state between normal aging and dementia. Furthermore, MCI is recognized as a significant risk factor for Alzheimer's disease (AD). Recent PECOS-relevant epidemiologic studies (see Section 9.5.1.1) have assessed associations between long-term exposure to oxides of nitrogen and multiple facets of cognitive function in adults including global cognitive functioning, episodic and working memory, processing speed, executive function, and semantic fluency. Animal toxicological studies examining cognitive function have focused on postnatal or young adult rodents and on transgenic AD-model rodents. These studies are discussed in Sections 9.3.1.2 and 9.5.2.2, respectively, and are not included in this section.

9.5.1.1 Epidemiologic Studies of General Cognitive Decline

There were no studies on the effect of long-term exposure to oxides of nitrogen on cognitive function in adults assessed in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). A small number of recent studies comprise the current evidence base. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 9-12.

Two analyses of older women (74–92 years old) enrolled in the Women's Health Initiative Memory Study–Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) were conducted. WHIMS-ECHO includes more than 2000 women residing in the 48 contiguous U.S. states.

- Wang et al. (2021b) assessed episodic memory using the telephone-based California Verbal Learning Test (CVLT), which was modified to define episodic memory as the total number of correct responses across three learning trials. The authors sought to identify latent classes of cognitive trajectories (i.e., hidden subgroups) using latent class mixed models. Analyses were stratified by age and cognitive resilience to account for differences in the trajectories of decline between individuals. Three-year average NO_2 concentration at baseline and 10 years before enrollment was estimated and linked to the participants' residential history using validated (C-V r^2: 0.85) regionalized national universal kriging models with partial least squares regression of geographic covariates in combination with monitoring data. Results indicated some evidence of an association with episodic memory decline among women categorized as fast decliners who were ≤80 years of age (i.e., β: -0.34 points/yr [95% CI: -

0.74, 0.06]), though all associations included the null value (see Section 9.5.1.1.1). In another study, Petkus et al. (2021b) did not find a direct association between NO_2 exposure and episodic memory; however, an indirect effect of NO_2 exposure on episodic memory that was mediated by depressive symptoms was observed.

- Younan et al. (2022) examined the association between improvement in air quality and the rate of cognitive decline. The exposure model used by Wang et al. (2021b) was also used in this study. Air quality improvement was defined at the individual level as a reduction from remote (10 years prior to enrollment) to recent (3 years prior to enrollment) exposures. Cognitive function was assessed using a modified Telephone Interview for Cognitive Status (TICS) instrument and the CVLT. Living in an area with greater estimated NO_2 reduction was associated with slower rates of decline assessed on the TICs and the CVLT in both general cognitive status and episodic memory. In models adjusted for individual and demographic characteristics (not preexisting disease), each 10 ppb increment of improved NO_2 was associated with slower cognitive declines (β: 0.087/year on the TICs [95% CI: 0.023, 0.151] and β: 0.151/year on the CVLT [95% CI: 0.008, 0.295)]. Results pertaining to different populations are discussed in Section 9.5.1.1.

Additional U.S. studies were conducted including an analysis of older adults enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), a study of men participating in the Vietnam Era Twin Study of Aging (VETSA) and analyses of two Manhattan based cohorts (i.e., Washington Heights–Inwood Community Aging Project (WHICAP) and the Northern Manhattan Study (NOMAS)).

- Wang et al. (2023b) examined the association of NO_2 and NO_X with cognitive function in older adults enrolled in MESA. This study used a validated spatiotemporal model to estimate annual average pollutant concentrations for the years 2010–2012. Cognitive function was assessed during this period using standardized and validated tests to measure global cognitive functioning, processing speed, and working memory (Cognitive Abilities Screening Instrument [CASI], Digit Symbol Coding (DSC], and Digit Span (DS], respectively). The difference in CASI score per increase in annual average NO_2 and NO_X was -1.08 (95% CI: -1.59, -0.57) and -0.92 (95% CI: -1.4, -0.43), respectively. The OR for low cognitive function (i.e., lowest 10^{th} percentile of CASI score distribution) was 1.32 (1.1, 1.58) for NO_2 and 1.27 (95% CI: 1.08, 1.49) for NO_X. NO_X was also associated with slower processing speed (β DSC: -2.07 [95% CI: -3.61, -0.54]) and worse working memory (β DS total: -0.41 [95% CI: -0.81, -0.02]).
- Kulick et al. (2020b) used data from WHICAP and NOMAS to examine the association of NO_2 exposure with cognitive decline in older adults. The MESA regionalized universal kriging model was used to estimate NO_2 exposure for the year before enrollment Residential NO_2 exposure was associated with a 0.18 SD lower (95% -0.24, -0.11) GCI score at baseline and a faster decline in GCI (β: -0.05 [95% CI: -0.06, -0.03]) in GCI score between visits.
- Franz et al. (2023) analyzed data collected from men enrolled in the VETSA study to determine if Apolipoprotein E (APOE) status modulates the effect of air pollution on cognition in middle age noting that studies ε4 carriers have found mixed results depending on lifestage of the participants. NO_2 concentration was estimated using the MESA universal kriging method with LUR to derive measures of past (1993–1999) and recent (3 years prior to baseline assessment) NO_2 exposure estimates. The authors examined the association of specific cognitive domains assessed with 16 standard cognitive tests and 24 subtests within a neuropsychological test battery, with recent and past NO_2 exposure. Associations of past and recent NO_2 exposure with episodic memory, speed, executive function, working memory,

general fluency, and semantic fluency were reported. No evidence of associations was observed between past or recent NO_2 exposure with any domain except semantic fluency (β past: -0.137 [95% CI: -0.25, -0.024] and (β recent: -0.195 [95% CI: -0.3265, -0.0635]. Analyses examining the modification of the association by APOE genotype are discussed in Section 9.5.1.1.1.

Recent studies of cognitive effects were conducted in European countries including the United Kingdom, France and Germany.

- Huels et al. (2018) conducted a causal mediation analysis to examine the relationship between back-extrapolated NO_2 exposure at baseline, lung function, and cognitive impairment, using data from women enrolled in the Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) cohort. NO_2 concentration at baseline was estimated using LUR. Visuo-construction performance (VCP), which measures an individual's ability to copy geometric figures, was assessed at follow-up with the CERAD-Plus neuropsychological test battery. An association was reported between NO_2 and VCP (β: -0.26 [95% CI: -0.50, -0.03]) in an adjusted model that included interaction terms for NO_2 and lung function metrics (i.e., forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC). The mediation analysis indicated that the proportion of the association between NO_2 and VCP that was mediated by lung function was 6.2% and this was higher in never smokers (7.2%) and noncarriers of the APOE-ε4 allele (11.2%).
- Zare Sakhvidi et al. (2022) examined data from the French national health insurance system (CONSTANCES cohort), which enrolled adults between 18 and 69 years old. Annual average NO_2 at the time of enrollment was estimated using LUR, which accounted for 59% of the spatial variation in NO_2, at a 100 by 100 m spatial scale. Cognitive function was assessed using a combination of individual neuropsychological tests and a measure of global cognitive score. NO_2 was associated with worse performance on the test of semantic fluency (β: -0.53 SD [95% CI: -0.8, -0.26]), but the association with global cognition in this study indicated an increase in score with increasing NO_2 exposure, although the CI included the null value (β: 0.42 [95% CI: 0.37, 0.47]).
- Tzivian et al. (2017) studied the association of cognitive function among participants in the population-based Heinz Nixdorf Recall (HNR) study using five neuropsychological subtests and an additively calculated global cognitive score (GCS). NO_2 and NO_X concentrations were estimated using LUR models that explained 89% of the variance for NO_2, and 88% of the variance for NO_X. Noise was treated as an effect modifier in the analysis. Annual average NO_2 and NO_X were associated with a decline in GCS that was similar in magnitude across categories of noise level (authors present results in figure only). Because the focus of the paper was on the interaction between air pollution and road-traffic noise, the authors tabulated results for associations among those in the High NO_2/High Noise (β: -0.13 [95% CI: -0.22, -0.05]) and High NO_X /Noise (β: -0.16 [-0.24, -0.07]) groups per 6.62 and 15.65 $\mu g/m^3$, respectively. Notably, the association of noise with GCS was only present when air pollution was high.
- Nußbaum et al. (2020) examined the association of NO_X and NO_2 exposure with neurocognitive test performance and region-specific changes in local gyrification index (LGI) (see Section 9.8.1) among older adults (55–85 years) enrolled in the HNR study. The authors evaluated five cognitive domains, i.e., attention, executive functions, memory, short-term and working memory and language functioning. The study reported evidence that annual average NO_2 and NO_X estimated using the ESCAPE LUR model were most consistently associated with lower test score rank on tests of language (cognitive domain) in minimally adjusted

models. The association with language and tests within each of the domains evaluated were attenuated and essentially null after adjustment for additional covariates including alcohol, smoking, physical activity and SES.

- Cullen et al. (2018) examined the association of NO_2 and NO_X exposure with baseline cognitive function and with change in cognitive function during a 2.8-year follow-up period among participants in UK Biobank, which is a general population cohort. Associations were generally small, included the null value, and were inconsistent in both magnitude and direction.

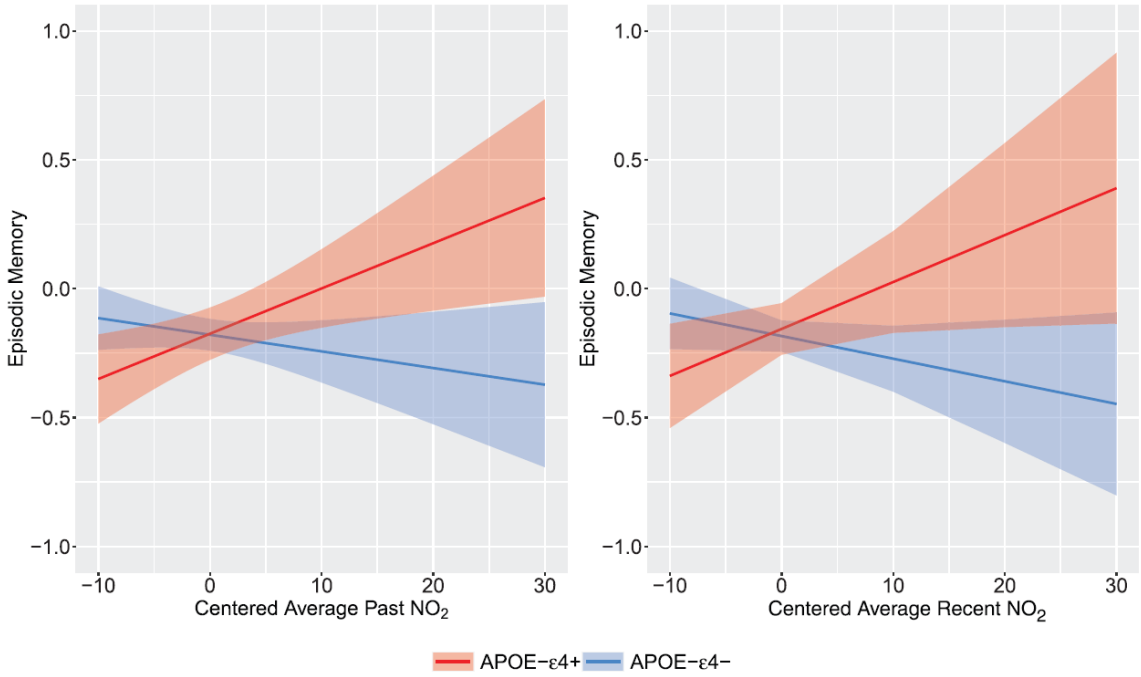
A few of the studies summarized above present additional analyses evaluating the lifestages and populations that may be at higher risk of NO_2-associated cognitive decline. These analyses are discussed in Section 9.5.1.1.1 below. Section 9.5.1.1.2 presents overall conclusions based on the epidemiologic studies of cognitive decline and summarizes the remaining uncertainties in the epidemiologic evidence.

9.5.1.1.1 Lifestages and Populations

Recent U.S. studies examined potential effect measure modification by various modifying factors including pre-existing disease, genetic factors, lifestage, sex, race, and smoking status.

- Wang et al. (2021b) conducted analyses that were stratified by age and cognitive resilience to account for differences in the trajectories of decline between individuals. Although all associations included the null value, results indicated some evidence of an association of recent NO_2 exposure with episodic memory decline among women ≤80- years of age who were categorized as fast decliners (β: -0.34 per year [95% CI: -0.74, 0.06]) compared to women ≤80 years of age who were categorized as slow decliners (β: -0.002 per year [95% CI: -0.082, 0.078]).
- In a study of the WHICAP cohort, Kulick et al. (2020a) examined whether NO_2-related cognitive decline differed across strata defined by APOE-ε4 genotypes. The authors reported that baseline annual average NO_2 exposure in the calendar year before enrollment was associated with a faster rate of cognitive decline among individuals positive for the apolipoprotein E (APOE) ε4 variant (β: -0.08 [95% CI: -0.10, -0.05])) vs. those negative for the variant (β: -0.06 [95% CI: -0.08, -0.04]). This study also reported a larger magnitude cognitive decline in white (β: -0.129 (95% CI: -0.173, -0.084) and Black non-Hispanic (β: -0.1 [95% CI: -0.14, -0.05]) individuals compared Hispanic individuals (β: -0.04 [95% CI: -0.071, -0.009]). Effect measure modification by age, and smoking status was not observed.
- Younan et al. (2022) examined the association of improvement in air quality with cognitive decline. The study reported that reduction in NO_2 concentration (i.e., over a 10-year period) was associated with slower cognitive declines on the TICS and the CVLT. Statistical evidence indicating modification by population characteristics was generally lacking (i.e., evaluated using corrected p-values); however, the association between lower NO_2 exposure and slower decline on the CVLT was stronger in those with APOE-ε4 genotype. In addition, the slower decline on the TICS that was associated with improved NO_2 air quality was stronger among those without hypertension and diabetes.
- In another U.S. study, Franz et al. (2023) analyzed data collected from men enrolled in the VETSA. The authors examined the association of specific cognitive domains with recent and past NO_2 exposure. In a secondary analysis, the study examined whether APOE genotype

modified the observed association. Unexpectedly, APOE-ε4 allele carriers, which are generally associated with accelerated cognitive decline, had better episodic memory at higher NO_2 concentrations (see Figure 9-18).



List of abbreviations in alphabetical order:NO_2 = nitrogen dioxide.
Note: Average NO_2 concentration was centered to avoid multicollinearity.
Source: Franz et al. (2023). Copyright permission pending.

Figure 9-18 Episodic Memory Factor and NO_2 by APOE Interaction.

A limited number of studies examined effect measure modification by factors including pre-existing disease, genetic factors, lifestage, sex, race, and smoking status. Except for APOE-ε4 genotypes, these factors were assessed in single studies precluding comparison across studies. Results from studies examining modification APOE-ε4 genotypes were inconsistent. Kulick et al. (2020a) and Younan et al. (2022) reported a faster rate of cognitive decline among APOE-ε4 positive in the WHICAP and WHIMS-ECHO cohorts; while Franz et al. (2023) reported NO_2 was associated with better episodic memory among APOE-ε4 carriers. Overall, the studies designed to identify population differences are limited.

9.5.1.1.2 Conclusions and Remaining Uncertainties

Recent studies in the United States and Europe contribute to an emerging body of evidence pertaining to the effect of oxides of nitrogen exposures on cognitive decline among adults. Although the evidence remains limited, some studies indicated an association between NO_2 or NO_X exposure and impaired cognitive function. Two analyses of cognitive decline among women enrolled in WHIMS-ECHO (Younan et al., 2022; Wang et al., 2021b) that both used telephone assessments of cognitive

function but different analytical methods (i.e., latent class mixed models vs. linear mixed effect models to examine air quality improvements) provide some support for an association. Low cognitive function was associated with NO_2 and NO_X in the MESA and WHICAP/NOMAS cohorts, but no associations were observed with most cognitive domains (except semantic fluency) among men enrolled in VETSA, a study of twins that was unique in that multiple indicators of each cognitive domain were evaluated. Findings from studies in Europe were inconsistent in direction, and associations generally included the null value. The magnitude of effect estimates is not comparable across studies that use differently scaled outcome assessment instruments. A limited number of studies examined modification by factors including pre-existing disease, genetic factors, lifestage, sex, race, and smoking status. Except for APOE-ε4 genotypes, these factors were assessed in single studies precluding the evaluation of patterns of association across studies. Results examining APOE-ε4 genotypes lacked consistency (see Section 9.5.1.1.1). The interaction between oxides of nitrogen and noise was examined in a study reporting a decline on the GCS; however, associations between annual average NO_2 and NO_X exposures and decline in GCS were similar in magnitude across categories of noise level. Studies evaluating concentration-response functions, and copollutants and exposure windows were not available. Overall, there is an inconsistent pattern association between long-term exposure to oxides of nitrogen and cognitive effects across the available studies. Most studies report using well-validated exposure assessment models to estimate long-term exposure to NO_2 and NO_X. It is not clear from the evidence whether there is an independent effect of oxides of nitrogen or if the observed associations are confounded by noise or traffic-related copollutants.

9.5.2 Alzheimer's Disease and Dementia

Dementia refers to a decline in cognitive functioning severe enough to interfere with daily life, and the most common form of dementia is AD, which is neuropathologically distinguished by amyloid plaques and neurofibrillary tangles in the brain. Section 9.5.2.1 summarizes recent PECOS-relevant epidemiologic evidence examining the relationship between long-term oxides of nitrogen exposure and risk for AD, vascular dementia, a form of dementia that typically develops secondary to cardiovascular disease, and other dementias. Epidemiologic studies have also evaluated hospitalizations from dementia and AD with long- and short-term oxides of nitrogen exposure. Cases are typically ascertained using diagnostic codes (e.g., ICD-9CM: 46.1, 290, 294, 331 or ICD-10: F00–F03, G30 and/or physician medical claims and use of prescription medications for dementia). Section 9.5.2.2 summarizes recent PECO-relevant animal toxicological evidence evaluating AD-related endpoints, including amyloid-β expression and tau phosphorylation.

9.5.2.1 Epidemiologic Studies of Alzheimer's Disease and Dementia

A few studies of older adults and dementia outcomes have been conducted since the 2016 Oxides of Nitrogen ISA. The studies had robust exposure assessment methods and sample sizes, but most studies

did not adjust for other copollutants. These recent studies were conducted in North America, United Kingdom, Europe and Taiwan. Except for a WHIMS-ECHO analysis, most U.S. and Canadian studies provided generally consistent evidence of positive associations between oxides of nitrogen exposure and dementia risk, while European studies were more mixed. Multiple analyses of the UK Biobank study indicated generally positive associations between long term NO_2 exposure and dementia providing some evidence for genetic susceptibility. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 9-13.

- Shi et al. (2021) examined the association between NO_2 exposure and incidence of dementia and AD using data from the Medicare Chronic Conditions Warehouse (2000–2018) cohort. Daily ambient concentrations of NO_2 were estimated from ground monitor observations, satellite data and models, and assigned 5-year moving averages based on ZIP codes of residence. In adjusted Cox proportional hazard models, a 10 ppb increase in NO_2 was positively associated with incident dementia (HR: 1.030 [95% CI: 1.024, 1.036]) and incident AD (1.043 [95% CI: 1.036, 1.050]).
- Ilango et al. (2023) investigated the combined impact of air pollution and the social environment on dementia using data from the Gingko Evaluation of Memory study, which evaluated the dementia status of 2,564 U.S. older adults semiannually from 2000 to 2008. NO_2 exposure was quantified using high-performing spatiotemporal models, and the social environment was assessed at both neighborhood and individual levels. Exposure models demonstrated good performance with NO_2 (r^2 ranging from 0.78 to 0.88), indicating robust exposure assessment capabilities. The authors reported that NO_2 was associated with an increased risk of dementia (HR: 1.39 [95% CI: 1.04, 1.87]), and no consistent evidence of interactions between NO_2 and measures of the social environment.
- Chen et al. (2017) studied nearly 2.1 million adults in Canada and reported that long-term exposure to NO_2 was associated with increased dementia incidence. The authors assigned annual average NO_2 exposure using satellite data combined with land-use regression. A 10 ppb increase in five-year moving average NO_2 concentrations with a two-year lag was positively associated with dementia incidence (HR: 1.07 [95% CI: 1.06, 1.08]).
- Wang et al. (2022) evaluated associations between 3-year average NO_2 exposure immediately before baseline (recent exposure) and 10 years before baseline (remote exposure) and incident all-cause dementia risk among women aged 74–92 years in the WHIMS-ECHO study. Exposure was estimated using a universal kriging model with good validation (r^2 =0.85) and accounted for residential mobility. Associations over 11 years of follow-up was approximately null for recent (HR: 1.02 [95% CI: 0.88, 1.17]) and inverse for remote (HR: 0.86 [95% CI: 0.73, 1.02]) NO_2 exposure, in models incorporating IPW and adjusting for WHIMS enrollment year, demographic variables, socioeconomic factors, neighborhood characteristics, lifestyle factors, hormone use and hormone therapy assignment, cardiovascular risk factors, depression, BMI, and cardiovascular disease (CVD) histories. Results were similar in sensitivity analyses using 1-year average exposure rather than 3-year exposure.
- Yu et al. (2020) investigated the effects of traffic-related NO_X on dementia in older Mexican Americans. Utilizing Cox proportional hazard models, the study adjusted for demographic variables, lifestyle factors, and neighborhood socioeconomic status. A 2.29 ppb increase in traffic-related NO_X was associated with increased incident dementia (HR: 1.2 [95% CI: 1.0,

1.4]). The use of baseline residential addresses to estimate air pollution exposure might not fully account for historical exposure or changes in exposure due to residential mobility. Furthermore, there are limitations in the generalizability of results to other ethnic groups. In another study, Paul et al. (2020) examined the relationship of traffic-related air NO_X exposure with incident dementia and cognitive impairment, cognitive impairment non-dementia (CIND) in older Mexican Americans from the Sacramento Area Latino Study on Aging study. Exposures were estimated using the modified CALINE4 dispersion model for the year of enrollment. After adjustment for census track, individual sociodemographic variables, neighborhood socioeconomic status, urbanicity, and baseline cognitive function score (3 mean square error [MSE] score), a 2.31 ppb increase in annual average traffic-related NO_X concentrations was associated with a faster time to dementia (HR: 1.2 [95% CI: 0.98, 1.47]) and time to dementia or CIND (HR: 1.21 [95% CI: 1.05, 1.40]). In categorical analyses, individuals in the highest traffic-related NO_X tertile (>2.68 ppb) had a faster time to dementia (HR: 1.55 [95% CI: 1.04, 2.33]) and dementia/CIND (HR: 1.45 [95% CI: 1.07, 1.96]) than those in the lower tertiles.

Recent European cohort studies reported mixed findings while a single study from Taiwan indicated an increased risk for dementia.

- An analysis of the SNAC-K, Wu et al. (2022), a study in Sweden, reported a positive association for the relationship between 3-year moving average NO_X exposure and CIND (HR: 1.15 [95% CI: 1.03, 1.29] per 10 $\mu g/m^3$ increase in NO_X) and a positive imprecise association for 3-year moving average NO_X exposure and dementia following CIND (HR: 1.15 [95% CI: 0.91, 1.44]). Exposures were estimated using a dispersion model validated for Stockholm ($r^2 = 0.99$).
- Wood et al. (2022) analyzed a prospective cohort from the English Longitudinal Study of Ageing study (2004–2017) to assess the relationship between long-term NO_2 exposure and dementia incidence among adults aged 50 years and older (n = 8,525). The authors reported null associations estimated from Cox proportional hazard models that were adjusted for age, sex, smoking status, and physical activity.
- Mortamais et al. (2021) reported that NO_2 exposure was not associated with risk of dementia/AD among participants in the three-city study in France. The authors observed null associations across multiple exposure windows and models stratified by potential effect modifiers, including sex, education, genetics, and socioeconomic status.
- Gandini et al. (2018) evaluated the effect of long-term exposure to NO_2 on first hospital admissions for AD in Italy, using a Cox proportional hazard model with robust variance estimation, adjusted for sociodemographic factors, smoking status, physical activity, municipality type, and BMI. A positive but imprecise association was found between NO_2 exposure and AD hospital admissions (HR: 1.12 [95% CI: 0.93, 1.34] per 10 ppb). There were not clear patterns of associations in sensitivity analyses stratified by sex or municipality size.
- Chang et al. (2014) examined the associations between dementia risk and long-term exposure to NO_2 using data from 29,547 Taiwanese adults (2000–2010). The retrospective cohort study, using National Health Insurance Database (NHIRD) data, observed that individuals in the highest NO_2 exposure quartile (Q4), compared to Q1, had increased risk of dementia (HR: 1.54 [95% CI: 1.34, 1.77]) after adjusting for multiple confounders, including sociodemographic characteristics, individual behaviors, and urbanization.

Several recent UK Biobank analyses examined dementia risk estimated using 2010 ESCAPE LUR models. It included demographic, medical, interview and clinical exam data for a subset of

participants (44 to 80 years old) also undergoing brain MRIs. The robust data collection and long follow-up period allowed for extensive confounder adjustment (sociodemographic factors, individual lifestyle choices, and morbidity status), annual household income, self-rated health, BMI, smoking history, and frequency of alcohol use.

- Yuan et al. (2023) examined the associations of NO_X exposure and outcomes such as all-cause dementia, AD, and vascular dementia based among 437,932 UK Biobank participants. The authors utilized ESCAPE LUR models to assign exposure and applied IPW to mimic a randomized controlled trial with respect to several potential confounders, including age, sex, smoking, ethnicity, education level, SES, and alcohol use. Yuan et al. (2023) observed an increased risk of all-cause dementia (HR: 1.14; 95% CI: 1.02, 1.26) and AD (HR: 1.26; 95% CI: 1.08, 1.48) among participants with higher NO_X exposures (≥26.57 ppb) relative to those with lower exposures (<26.57 ppb). A null association was observed for NO_X exposure and vascular dementia. Additionally, the authors reported that participants with a high AD-genetic risk score; and exposure to high NO_X concentrations (≥26.57 ppb) had an increased risk of developing AD compared to those with a low AD-genetic risk score and lower exposures (HR: 2.25 [95% CI: 1.64, 3.09]).
- Parra et al. (2022) analyzed data from 187,194 60 to 69-year-old adult participants of the UK Biobank cohort and reported an increase in dementia risk associated with a 10 ppb increase in annual average NO_2 concentrations at baseline (HR: 1.39 [95% CI: 1.23, 1.58]). Models were adjusted for sociodemographic factors, smoking status, Townsend Deprivation Index, and APOE-e4 status.
- Wang et al. (2023a) assessed the effect of NO_2 and NO_X on the incidence of dementia among 498,660 adults participating in the UK Biobank Study. In primary models adjusted for ages, sex, education, and SES, annual average NO_2 and NO_X concentrations were associated with increased dementia incidence (HR: 1.45 [95% CI: 1.32, 1.59] and HR: 1.01 [95% CI: 1.00, 1.01], respectively). The observed associations were robust after further adjustment for sleep duration, smoking status, social isolation, and drinking status, but were null and much less precise in models further adjusted for BMI, hypertension, diabetes, stroke, depression, hearing impairment, and family history of dementia (HR: 1.00 [95% CI: 0.63, 1.60] per 10 ppb increase in NO_2 and HR: 1.00 [95% CI: 0.99, 1.01] per 1 $\mu g/m^3$ increase in NO_X). Notably, given that insulin resistance is on the pathway through which oxides of nitrogen exposure could cause neurodegenerative disease (Section 9.9), adjustment for diabetes and/or hypertension—which might act as proxies for insulin resistance—may obscure the total effect of oxides of nitrogen exposure on dementia.
- Ma et al. (2023) explored the association between long-term NO_2 exposure on dementia risk among 164,447 older adults, utilizing LUR models to assign long-term exposure to NO_2. The authors reported that NO_2 exposure was associated with increased risk of dementia incidence (HR: 1.09 [95% CI: 1.05, 1.14] per 2.66 ppb increase in long-term NO_2 concentrations at baseline). Ma et al. (2023) also observed a positive interaction between NO_2 exposure and APOE-ε4-related genetic risk on the additive scale, with a relative excess risk due to interaction (RERI) of 0.18 (95% CI: 0.05, 0.31). The interaction results suggest that genetically susceptibility further amplifies the association between NO_2 exposure and dementia risk.
- Chen et al. (2023) examined associations between NO_2 and NO_X exposure and dementia risk in 459,844 UK Biobank participants over a median follow-up of 11.7 years. LUR models were used to estimate long-term exposure at baseline. The authors reported positive associations per IQR increase (increment NR) for NO_2 exposure and all-cause dementia (HR:

1.13 [95% CI: 1.09, 1.16), AD (HR: 1.14 [95% CI: 1.09, 1.20]), and vascular dementia (HR: 1.12 [95% CI: 1.05, 1.20]). NO_X was also positively associated with all-cause dementia (HR: 1.07 [95% CI: 1.04, 1.09]), AD (HR: 1.09 [9% CI: 1.04, 1.14]), and vascular dementia (HR: 1.06 [95% CI: 1.01, 1.12]).

- Zhang et al. (2023b) utilized the UK Biobank to examine the relationship between NO_2 exposure and the dementia risk among 227,840 participants. NO_2 exposure at residential locations was estimated using LUR models, and genetic susceptibility was quantified with a polygenic risk score (PRS). Long-term average NO_2 concentrations at baseline were associated with all-cause dementia (HR: 1.28 [95% CI: 1.17, 1.40] per 10 ppb increase), AD (HR: 1.32 [95% CI: 1.13, 1.55]), and vascular dementia (HR: 1.22 [95% CI: 0.97, 1.55]). NO_X exposure was also positively associated with all-cause dementia (HR: 1.03 [95% CI: 0.99, 1.07] per 16.1 $\mu g/m^3$ increase) and AD (HR: 1.06 [95% CI: 0.99, 1.14]), but not vascular dementia (HR: 0.98 [95% CI: 0.88, 1.08]). Notably, positive predictive values were much higher for all-cause dementia (82.5%) and Alzheimer's disease (71.4%) than vascular dementia (43.8%).

In addition to the studies described above a single U.S. study examined the association of short-term NO_2 exposure with ED visits for AD and a large population-based Canadia cohort study conducted a mediation analysis to estimate the contribution of CVD to the association between 3-year average NO_2 exposure, lagged 5 years, and dementia.

- Zhang et al. (2023a) evaluated short-term exposure to NO_2 and emergency department visits for AD and ADRD across five U.S. states from 2005 to 2015. Exposure to NO_2 was assessed at a 1 km spatial resolution aggregated to the ZIP code level using spatiotemporal models. Statistical analyses utilized a time-stratified case-crossover design with conditional logistical regression adjusted for temperature (6 df natural cubic splines), humidity (6 df natural cubic splines), sociodemographic characteristics, federal holidays, day-of-year time trends (4 df natural cubic splines) and patient-matched controls by ZIP code, day of the week, and year/month. This study analyzed over 7.5 million AD/ADRD emergency department visits and reported a 0.71% (95% CI: 0.32%, 1.11%) increase in emergency department visits associated with a 20 ppb increase in NO_2 concentrations over four days (i.e., lag 0–3).
- Ilango et al. (2020) analyzed data from the Canadian Community Health Survey, in which Canadian-born residents were followed from enrollment (1996-2003) through 2013. Long-term NO_2 exposure (3-year average, lagged 5 years) was associated with dementia risk (HR total: 1.21 [95% CI: 1.02, 1.44], HR direct: 1.19 [95% CI: 1.01, 1.40]), though some of the effect was mediated through CVD in the analysis (HR indirect: 1.04 [95% CI: 1.00, 1.08]).

A few of the studies discussed above present additional analyses evaluating the shape of concentration-response functions for NO_2/ NO_X exposure and dementia, the lifestages and populations that may be at higher risk of oxides of exposure-associated dementia, the potential influence of copollutants on reported associations with dementia, critical exposure windows, and issues related to model specification. The evidence on these topics is discussed in greater detail below in Sections 9.5.2.1.1, 9.5.2.1.2, 9.5.2.1.3, 9.5.2.1.4, and 9.5.2.1.5, respectively. Section 9.5.2.1.6 presents conclusions from epidemiologic studies of AD and dementia and discusses the remaining uncertainties in the epidemiologic evidence.

9.5.2.1.1 Concentration-Response

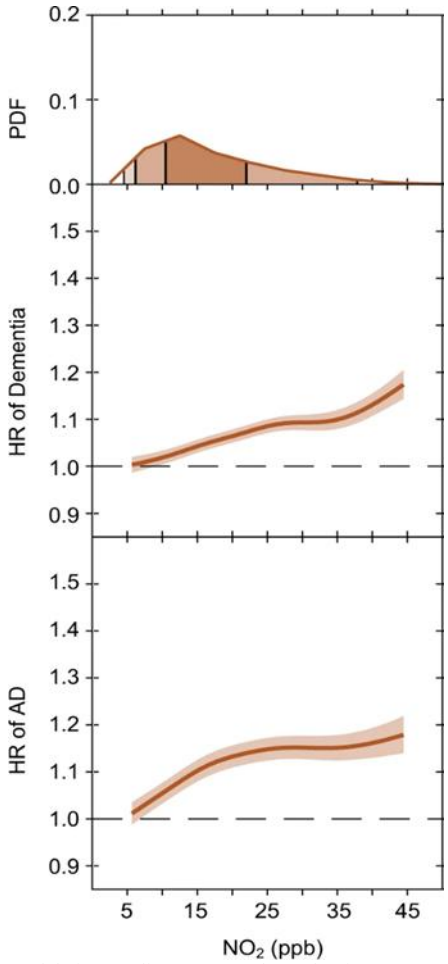
A limited number of studies evaluated the shape of the C-R relationship between long-term NO_2 exposure and dementia/Alzheimer's disease (see Table 9-11). The available studies indicated approximately linear relationships across most of the exposure range, although departures from linearity were observed at relatively high concentrations.

- In multipollutant models, Shi et al. (2021) reported approximately linear positive relationships between NO_2 concentrations and both incident dementia and AD at or below approximately 25 ppb. The curves depart from linearity at higher concentrations, where increases in NO_2 concentrations did not correspond to higher risk (see Figure 9-19).
- Zhang et al. (2023b) observed an approximately linear C-R curve for NO_2 exposure and dementia risk, indicating a monotonic increase in dementia incidence with increasing NO_2 concentrations. The shape of the C-R curve for NO_X was approximately linear across concentrations less than ~40 µg/m^3 (i.e. 21.26 ppb), with a less steep slope at higher concentrations.
- Wang et al. (2023a) examined the shape of the C-R relationship using restricted cubic splines and found that the relationship was approximately linear across the range of concentrations.

Table 9-11 Summary of epidemiologic studies evaluating potential non-linearities in the relationship of long-term NO_2 exposure with Alzheimer's Disease and Dementia

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
†Shi et al. (2021)	Medicare CCW 2000–2018	Mean: 17.1 IQR: 11.6	Penalized spline	Approximately linear with increased HRs for dementia and AD; curve plateaued at higher concentrations
†Wang et al. (2023a)	UK Biobank Baseline: 2006–2010	Median: 9.3 (17.52 µg/m^3) IQR: 3.9 (7.40 µg/m^3)	Restricted cubic spline	Approximately linear
†Zhang et al. (2023b)	UK Biobank 2006–2010	P25–P75 = 11.8–17.4 ppb (22.2–32.7 µg/m^3)	SCHIF	Approximately linear

List of abbreviations in alphabetic order: AD = Alzheimer's disease; CCW=Chronic Conditions Warehouse; HR = hazard ratio; IQR: interquartile range; P = percentile; ppb = parts per billion; NO_2 = nitrogen dioxide; SCHIF=Shape Constrained Health Impact Function.
[a]For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.
[b]There visual representations of the shape of the curve in the corresponding text.
†Studies published since the 2016 Oxides of Nitrogen ISA.



List of abbreviations in alphabetical order: AD = Alzheimer's disease; HR = hazard ratio; PDF = probability density function.
Note: Concentration response curves for NO_2 related to dementia and AD across the 0.5th to 99.5th percentiles, with shaded regions indicating IQR and 95th percentile ranges.
Source: Shi et al. (2021). Copyright permission pending.

Figure 9-19 Concentration Response Curves for NO_2 with Dementia and AD Incidence among Medicare recipients.

9.5.2.1.2 Lifestages and Populations

Recent studies explored the modifying impact of various factors on the association of NO_2/NO_X exposure and ADRD risk. Smoking status, genetic susceptibility, and urban exposure generally modified the associations, with stronger risk in non-smokers, genetically predisposed individuals, and urban populations.

Genetic Factors and Underlying Comorbidities

- Ma et al. (2023) reported a joint effect of NO_2 exposure and APOE-ε4-related genetic risk on dementia incidence that was greater than additive, which indicates positive interaction. There was no evidence of multiplicative interaction.

- In Parra et al. (2022), the associations between NO_2 and NO_X exposures and dementia risk were inconsistently modified by APOE-ε4 allele count. Individuals with one or two alleles had higher risk of NO_2- and NO_X- related risk of vascular dementia than non-carriers. For example, a 10 ppb increase in 10-year moving average NO_2 concentrations was associated with a larger increase in risk of vascular dementia among one-allele carriers (HR: 1.54 [95% CI: 1.02, 2.32]) compared to non-carriers (HR: 1.17 [95% CI: 0.91, 1.50]). For AD, non-carriers had a greater increase in risk (HR: 1.49 [95% CI: 1.07, 2.07] per 10 ppb increase in NO_2 and HR: 1.16 [95% CI: 1.03, 1.29] per 16.02 $\mu g/m^3$ increase in NO_X) compared to one-allele carriers (HR: 1.28 [95% CI: 0.94, 1.74] per 10 ppb increase in NO_2 and HR: 1.08 [95% CI: 0.96, 1.22] per 16.02 $\mu g/m^3$ increase in NO_X) and two-allele carriers (HR: 1.15 [95% CI: 0.67, 1.96] per 10 ppb increase in NO_2 and HR: 1.06 [95% CI: 0.85, 1.31] per 16.02 $\mu g/m^3$ increase in NO_X). There was an increased risk for NO_2-related all-cause dementia across all allele groups, with a slightly larger but much less precise association reported for two-allele carriers (HR: 1.59 [95% CI: 1.10, 2.30]) compared to non-carriers (HR: 1.32 [95% CI: 1.10, 1.59]) or one-allele carriers (HR: 1.39 [95% CI: 1.14, 1.71]). Comparable NO_2-all-cause dementia associations were observed for a 16.02 $\mu g/m^3$ increase in NO_X concentrations among non-carriers (HR: 1.11 [95% CI: 1.04, 1.18]), one-allele carriers (HR: 1.11 [95% CI: 1.03, 1.20]), and two-allele carriers (HR: 1.15 [95% CI: 1.00, 1.33]).
- Yu et al. (2020) reported that dementia risk associated with high traffic-related NO_X exposure was particularly pronounced in Mexican American participants with metabolic dysfunctions. Individuals exposed to traffic-related NO_X (≥3.44 ppb) with hyperglycemia (HR: 2.40 [95% CI: 1.40, 4.00]) had a higher risk of dementia; a null association was reported for those without hyperglycemia (HR: 1.10 [95% CI: 0.57, 2.20]).
- In Zhang et al. (2023b), NO_2 exposure was positively associated with all-cause dementia and AD across low, intermediate, and high genetic risk groups. NO_2 associations with all-cause dementia were comparable across genetic risk groups. For AD, a stronger NO_2 association was observed in the high-risk group (HR: 1.36 [95% CI: 1.09, 1.68]) relative to the low-risk group (HR: 1.15 [95% CI: 0.76, 1.73]), but both estimates were imprecise.

Sex/Race

- Based on figures presented in Shi et al. (2021), Black individuals appeared to have a higher risk for NO_2-associated dementia and AD than white individuals, and males had a higher risk of NO_2-related dementia and AD incidence than females. However, quantitative comparisons between groups were not presented.
- Chang et al. (2014) reported comparable associations between NO_2 exposure and dementia risk in females and males in the highest exposure quartile. Males showed an inverse association in Q3, with lower dementia risk compared to Q1. Females in the third exposure quartile had a slightly increased risk of dementia compared to females in the lowest exposure quartile, but the corresponding 95% CI included the null (HR: 1.11 [95% CI: 0.92, 1.35]).

9.5.2.1.3 Copollutants

- Shi et al. (2021) mutually adjusted for $PM_{2.5}$ and O_3. The observed single pollutant associations between NO_2 and dementia (HR: 1.030 [95% CI: 1.024, 1.036]) and AD (1.043 [95% CI: 1.036, 1.050]) incidence were attenuated but remained positive in multipollutant models (HR: 1.016 [95% CI: 1.01, 1.022] and HR: 1.027 [95% CI: 1.02, 1.034], respectively). In separate copollutant models, NO_2 associations with each neurodegenerative

disease were attenuated but still positive after adjustment for $PM_{2.5}$, and robust (i.e., relatively unchanged) after adjustment for O_3 (quantitative results not provided).

- Wood et al. (2022) conducted copollutant analyses including adjustment for PM_{10}, $PM_{2.5}$, or O_3. The single pollutant NO_2 models indicated null associations with dementia incidence and there was no discernible change in hazard ratios after adjustment for any of the copollutants (data was not presented).

9.5.2.1.4 Exposure Windows

- As described previously, Chen et al. (2017) assigned exposure as a five-year moving average of NO_2 concentrations with a two-year lag. The authors conducted sensitivity analyses varying the lag period and reported that the association between NO_2 exposure and dementia incidence was comparable when extending the lag period to 5 years (HR: 1.06 [95% CI: 1.05, 1.07]). In models with a 10-year lag, the association was slightly attenuated but remained positive (HR: 1.04 [95% CI: 1.02, 1.06]). Notably, the longer lag periods reduced the number of cases available for each analysis.
- Shi et al. (2021) analyzed the association between NO_2 and dementia using different lag periods and 5-year moving averages of NO_2 exposure. The 5-year lag represents NO_2 exposure over a 5-year period, ending five years before outcome assessment; the 10-year lag reflects 5-year average exposure ending ten years before outcome. When using a 5-year average exposure with a 5-year lag, NO_2 was positively associated with dementia (HR: 1.035 [95% CI: 1.028, 1.042]), while estimates weakened at a 10-year lag.
- In Zhang et al. (2023a), same-day NO_2 exposure lag (0) showed the strongest association with a 0.73% (95% CI: 0.44%, 1.01%) increase in emergency department visits for AD and AD-related dementias. Null associations were observed at longer lags (individual days-1 through -3).
- In a Swedish cohort, Wu et al. (2022) reported a positive association for the relationship between 3-year moving average NO_X exposure and CIND (HR: 1.15 [95% CI: 1.03, 1.29] per 10 $\mu g/m^3$ increase in NOx) and a positive imprecise association for 3-year moving average NOx exposure and dementia following CIND (HR: 1.15 [95% CI: 0.91, 1.44]). Associations were stronger using 1-year moving averages of NO_X exposure with 1-year lag (HR CIND: 1.34 [95% CI: 1.21, 1.50]; HR dementia after CIND: 1.43 [95% CI: 1.15, 1.76]). Associations using lags of 2 or 3 years were slightly attenuated compared to associations using a 1-year lag but still stronger than associations using no lag time.

9.5.2.1.5 Model Specification

- (Chen et al., 2017) conducted multiple sensitivity analyses which demonstrated consistent associations between NO_2 exposure and increased dementia risk in analyses restricted to individuals with up to ten years of exposure, excluding those in long-term care, restricted to urban dwellers, and adjusting for North/South and urban/rural residence.
- Ma et al. (2023) implemented restricted analyses using progressively lower concentration cut points and reported that the positive association between NO_2 and dementia risk persisted in analyses restricted to individuals exposed to long-term average NO_2 concentrations below 40, 35, 30, 29, and 28 $\mu g/m^3$ (i.e., 21.26, 18.60, 15.94, 15.41, and 14.88 ppb).

9.5.2.1.6 Conclusions and Remaining Uncertainties

In summary, studies often demonstrated positive associations between oxides of nitrogen exposure and increased risk of dementia across diverse populations and methodologies. Exposure models included validated land-use regression models and associations were adjusted for a wide array of potential confounders (i.e., genetic risk factors, individual and area-level socioeconomic factors). The small number of studies that examine copollutants models show persistent associations even after adjusting for $PM_{2.5}$ and O_3, though some reported attenuation towards the null; genetic predisposition (i.e., APOE-ε4 carriers) and comorbidities (i.e., cardiovascular disease, diabetes) may modify these relationships. Furthermore, associations tend to be stronger in urban/high-traffic areas.

9.5.2.2 Animal Toxicological Studies of Alzheimer's Disease

Although rodents do not develop AD, they are nevertheless pivotal in studying the mechanisms underlying the disease's onset and progression, as these elements are difficult to resolve using postmortem human tissues. Crucial proteins involved in AD pathology, including amyloid-β and tau, are conserved between humans and rodents. However, rodents do not naturally exhibit the amyloid plaques and neurofibrillary tangles that are hallmarks of human AD. To address this, numerous transgenic rodent models have been created to simulate AD pathologies. While no single model encapsulates all facets of AD, they collectively provide critical insights.

There were no animal studies evaluating oxides of nitrogen exposure and AD-related outcomes in the 2016 Oxides of Nitrogen ISA. Recent studies have investigated AD-like pathology in wild-type and transgenic mouse models. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-14. Section 9.5.2.2.2 presents conclusions and summarizes the remaining uncertainties in the animal evidence.

- Yan et al. (2016b) evaluated the effects of NO_2 using 2-month-old wild-type C57BL/6J male mice and 5-month-old amyloid precursor protein (APP)/PS1 transgenic male mice. APP/PS1 mice spontaneously develop amyloid plaques and cognitive deficits in adulthood (Garcia-Alloza et al., 2006). In these mice, a 4-week exposure to 2.7 ppm NO_2 (5 hours/day) significantly increased amyloid-β_{42} deposition in the hippocampus and cortex, increased neuroinflammation and neurodegeneration, and caused learning and memory deficits in the MWM. Increased amyloid-β_{42} deposition and cognitive deficits (see Section 9.3.1.2) were also noted in the wild-type mice.
- In the same study, expression of APP and beta-secretase 1 (BACE1) (a key enzyme that processes APP into amyloid-β) were significantly increased in both mouse models (Yan et al., 2016b) following exposure to 2.7 ppm NO_2, but not following exposure to 1.3 ppm. Although only results from the high-exposure group were significant, results appear to follow a dose-response relationship.
- Expression of tau protein was not significantly affected in 2-month-old male C57BL/6J mice exposed to 1.3 or 2.7 ppm NO_2 (5 hours/day) for 4 weeks, but phosphorylated tau increased in

a dose-dependent manner, reaching significance in the high-dose group (Yan et al., 2016a). Neurofibrillary tangles, a pathological hallmark of AD, are comprised of hyperphosphorylated tau protein aggregates.

9.5.2.2.1 Relevance of Animal Responses to Human Responses

The mice used in Yan et al. (2016b), APP/PS1, express mutant amyloid precursor protein and presenilin-1, which leads to the development of amyloid plaques and cognitive deficits in adulthood (Bilkei-Gorzo, 2014). These mice are well-suited to investigate the amyloidogenic pathway of AD, though they do not manifest tau pathology. Continued development and utilization of diverse rodent models are essential for fully understanding the complexities of AD and the potential impact of environmental pollutants.

9.5.2.2.2 Conclusions and Remaining Uncertainties

A single animal study demonstrated that NO_2 exposure increases expression of amyloidogenic proteins and deposition of amyloid-β. Another study reported that NO_2 exposure increased tau phosphorylation, a precursor to neurofibrillary tangles. Taken together, these studies consistently suggest that exposure to NO_2 may promote AD-like pathology. Further studies should build on these findings. In particular, no toxicological studies investigated NO_2 exposure in females or during sensitive developmental periods (i.e., prenatal and postnatal). Furthermore, the effect of NO_2 exposure in transgenic models other than APP/PS1, particularly those which model tau pathology, is not known. Utilization of other animal models, including nonhuman primates, could be particularly informative for this endpoint.

9.5.3 Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disease caused by a progressive accumulation of abnormal protein aggregates (i.e., Lewy bodies) and loss of dopaminergic neurons, particularly within the substantia nigra. This Section summarizes the recent PECOS-relevant epidemiologic evidence (see Section 9.5.3.1) examining the relationship between long-term and short-term oxides of nitrogen exposure on PD risk and PD hospitalizations. No PECOS-relevant animal toxicological studies were identified.

9.5.3.1 Epidemiologic Studies of Parkinson's Disease

Recent studies investigating the link between NO_2 exposure and PD have reported mixed results. Studies used ICD codes recorded in hospital or outpatient clinic records to ascertain cases of PD (e.g.,

ICD-10 G20). In addition, a review of medical records by a neurologist and/or movement disorder specialist was performed in some studies. While most studies have found positive associations between NO_2 exposure and PD risk, these associations were often small in magnitude and imprecise. Most of the available studies employed rigorous adjustment for confounders, including pollutants and sociodemographic characteristics, and used robust spatial-temporal models. Study-specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are summarized below and in Appendix A – Appendix Table 9-15.

- Ritz et al. (2015) investigated the relationship between long-term exposure to traffic-related air pollution and PD in a case-control study in Denmark with 1,696 PD patients diagnosed between 1996 and 2009 and 1,800 matched controls. Long-term NO_2 and NO_X exposures were assessed using hybrid exposure models to assign exposure based on residential histories from 1971 until diagnosis or index date. Using logistic regression models, adjusted for age, sex, education, smoking history, family history of PD, and occupational exposures, the study reported positive associations between long-term exposure to NO_2 (per 10 ppb increase) and PD risk (OR: 1.73 [95% CI: 1.18, 2.52]) and NO_X (per 7.10 $\mu g/m^3$ increase) and PD risk (OR: 1.06 [95% CI: 1.02, 1.11]).
- Toro et al. (2019) reported null associations between 16-year average residential exposure to NO_2 and PD risk in the Netherlands in the ESCAPE study.
- Lee et al. (2016a) conducted a nationwide case-control study in Taiwan, analyzing NO_X exposure and risk of PD. The study included 11,117 PD patients and 44,468 matched controls. Long-term exposure was estimated using Bayesian Maximum Entropy models with 1 to 5 km grid cell resolution depending on the density of monitoring networks in a given area. In single pollutant continuous exposure models, the authors reported a null association between long-term NO_X exposure and PD per 20 ppb increase (OR: 1.00 [95% CI: 0.96, 1.04]). In a categorical analysis comparing upper quartiles of exposure to the lowest exposure quartile, Lee et al. (2016a) reported increased risk of PD in the highest exposure quartile (OR: 1.10 [95% CI: 1.04, 1.17]), and null or inverse associations corresponding to quartiles two and three, respectively.
- Shin et al. (2018) examined the long-term exposure effects of NO_2 and the incidence of PD in Ontario, Canada from 2001 to 2013. Using health administrative databases, the study followed over 2 million adults aged 55 to 85 years who were free of PD at baseline. NO_2 exposure was estimated at the residential level using national LUR models. In an adjusted single pollutant model, a 10 ppb increase in 5-year moving average NO_2 concentrations with a 2-year lag was positively associated with PD incidence (HR: 1.03 [95% CI: 1.00, 1.06]).
- Liu et al. (2016) investigated the association of long-term exposure to NO_2 and PD risk using a nested case-control analysis within the National Institutes of Health's American Association of Retired People (NIH-AARP) Diet and Health Study in the United States. Exposure levels were estimated from geocoded home addresses, and logistic regression models adjusted for individual sociodemographic factors, caffeine intake, and smoking status. The study reported a null association between annual-average NO_2 concentrations at the end of follow-up and PD risk (OR: 1.01 [95% CI: 0.90, 1.14] per 10 ppb increase in NO_2). The use of temporally misaligned exposure data could result in exposure measurement error since exposures that are assigned after an outcome occurs may not be representative of exposures earlier in the study period.

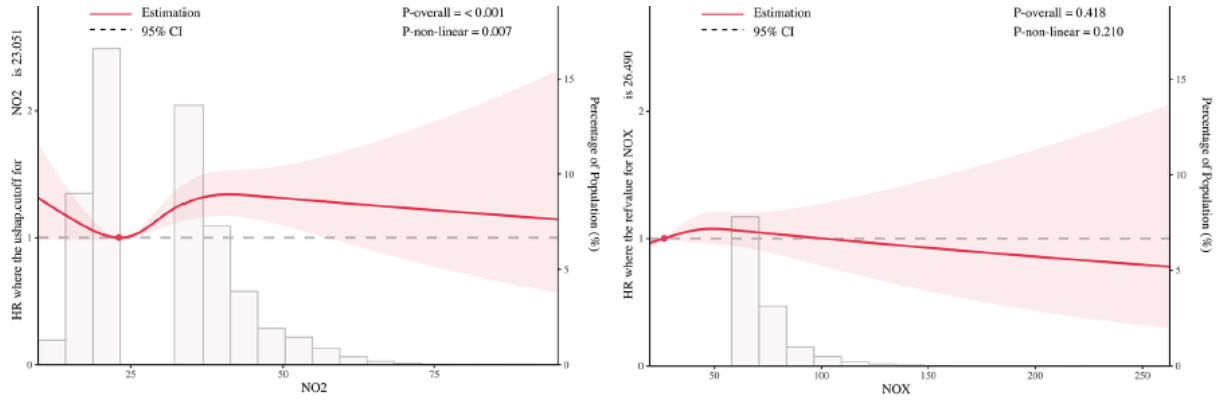
- Salimi et al. (2020) examined the association between long-term exposure to NO_2 and PD risk in a cross-sectional study of over 240,000 older adults in New South Wales, Australia. The authors reported an imprecise positive association between annual average NO_2 exposure and PD prevalence with a 95% CI that includes the null (OR: 1.12 [95% CI: 0.93, 1.34]).
- Huang et al. (2024) examined the associations between long-term NO_2 and NO_X exposure and PD risk among a sample of over 300,000 UK Biobank participants who were free of PD at baseline. The authors used an LUR to assign multi-year average exposures at baseline. In Cox proportional hazard models adjusted for ages, sex, BMI, health behaviors, and SES, a 10 ppb increase in NO_2 was associated with an increase in PD risk (HR: 1.17 [95% CI: 1.04, 1.30]).
- A Dutch case cohort study assessed associations between quartiles of annual average NO_2 and NO_X exposure estimated with ESCAPE LUR models for the year 2009 and PD risk evaluated using a combination of self-report information, registry data, and the Tanner screening questionnaire (Lomme et al., 2023). Positive imprecise associations were reported for all quartiles, and associations were strongest for the highest quartile of exposure (NO_2 range: 28.4–68.4 μg/m^3 [approx. 15.1–36.4 ppb); NO_X range: 41.2–109 μg/m^3) relative to the lowest quartile (NO_2 range: 10.3–19.6 μg/m^3 [approx. 5.5–10.4 ppb]; NO_X range: 17.3–28.1 μg/m^3) (OR for NO_2 Q4 vs. Q1: 1.48 [95% CI: 0.99, 2.25]; OR for NO_X Q4 vs. Q1: 2.08 [95% CI: 1.37, 3.22]).
- Goria et al. (2021) analyzed data on nearly 200,000 PD hospital admissions in 18 urban areas in France from 2009 to 2017. The study assigned NO_2 exposure using the average of current and previous day concentrations (i.e., lag 0–1) from fixed-site monitors. Generalized additive Poisson regression models adjusted for temperature, season, and long-term trends. A positive association was observed between NO_2 and increased PD hospital admissions across all ages (RR: 1.042 [95% CI: 1.021, 1.064]). In seasonal analyses, NO_2 concentrations were associated with increases hospital admissions for PD in the winter (RR: 1.03 [95% CI: 1.00, 1.07]), summer (RR: 1.05 [95% CI: 1.01, 1.10]), and spring (RR: 1.07 [95% CI: 0.98, 1.16]), but not in the fall (RR: 1.01 [95% CI: 0.97, 1.06]).
- Gandini et al. (2018) evaluated associations between long-term NO_2 exposures and first hospital admissions for PD in Italy, using a Cox proportional hazard model with robust variance estimation, adjusted for sociodemographic factors, smoking status, physical activity, BMI, and municipality type. The authors reported a positive but imprecise association between long-term average NO_2 concentrations at baseline and PD hospital admissions (HR: 1.16 [95% CI: 0.89, 1.50] per 10 ppb increase). There were not clear patterns of associations in sensitivity analyses stratified by sex and municipality size.
- Lee et al. (2016b) utilized one of the largest population-based case-control studies of PD, the Danish PASIDA study, to evaluate long-term exposure to NO_2 and NO_X and risk of PD. There was increased risk for PD prevalence overall (OR: 1.45 [95% CI: 0.98, 2015]) with long-term exposure to NO_2 or NO_X (OR: 1.05 [95% CI: 1.00, 1.10]). However, for PD incident cases and their matched controls, the risk was attenuated (NO_2 OR: 1.07 [95% CI: 0.48, 2.36] and NO_X OR: 1.01 [95% CI: 0.92, 1.11]).

A few of the studies discussed above present additional analyses evaluating the shapes of concentration-response functions for NO_2/ NO_X exposure and PD, the lifestages and populations that may be at higher risk of exposure-associated PD, the potential influence of copollutants on reported associations with PD, and issues related to model specification. The evidence on these topics is discussed

in greater detail below in Sections 9.5.3.1.1, 9.5.3.1.2, 9.5.3.1.3, and 9.5.3.1.4, respectively. Section 9.5.3.1.5 presents conclusions from epidemiologic studies of PD and discusses the remaining uncertainties in the epidemiologic evidence.

9.5.3.1.1 Concentration-Response

- Ritz et al. (2015) conducted analyses, using spline models with two knots to assess the shape of the C-R relationship. The authors observed a non-linear C-R curve for NO_2 and PD risk, with approximately linear positive associations below the first knot (~6.3 ppb) and above the second knot (7.9 ppb), and an inverse association between the two knots.
- Huang et al. (2024) used restricted cubic splines to assess the shape of the C-R relationship for NO_2 and PD risk. The authors observed a non-linear C-R relationship, with an inverse association at lower NO_2 concentrations and a positive association that plateaus at higher concentrations (see Figure 9-20).



List of abbreviations in alphabetical order: CI = confidence interval.
Note: Exposure-response relationships for each air pollutant with incidence Parkinson disease among UK Biobank for 312,009 participants (knot = 3, degree of freedom = 9, adjusted for age, sex, BMI, education level, employment status, household income, and Townsend deprivation index.
Source: Huang et al. (2024). Copyright permission pending.

Figure 9-20 Exposure-response relationships between air pollutants and PD risk in the UK Biobank.

9.5.3.1.2 Lifestages and Populations

Genetic Factors

- Huang et al. (2024) assessed the joint effect of genetic risk for PD and NO_2 exposure on PD risk. Individuals with high PRS who were in the highest NO_2 exposure tertile had increased risk of PD incidence relative to individuals in the first tertiles of PRS and NO_2 exposure (HR: 2.414 [95% CI: 1.912, 3.048]). Evidence of an interaction was observed on the multiplicative

scale. A similar gene-environment interaction was reported with genetic risk and NO_X exposure.

Age

- In models stratified by age, younger and older adults (<65 vs. ≥65 years) had comparable NO_2-related PD risk (HR: 1.15 [95% CI: 1.04, 1.27] and 1.17 [95% CI: 1.03, 1.34], respectively) (Huang et al., 2024).
- Lee et al. (2016a) reported stronger associations between long-term NO_X exposure and PD risk among older individuals (≥72 years) (OR: 1.18 [95% CI: 1.10, 1.27]) compared to younger individuals (<72 years) (OR: 1.05 [95% CI: 0.91, 1.20]).

Sex

- In Ritz et al. (2015), comparable positive associations were observed for NO_2 and PD incidence among males (OR: 1.73 [95% CI: 1.05, 2.83]) and females (OR: 1.73 [95% CI: 1.00, 3.00]).
- Huang et al. (2024) evaluated the association between long-term NO_2 exposure and PD risk in models stratified by sex. The authors reported a positive association among males (HR: 1.23 [95% CI: 1.11, 1.36]) and an approximately null association among females (HR: 1.03 [95% CI: 0.89, 1.18]).
- Lee et al. (2016a) reported comparable positive associations between long-term NO_X exposure and PD risk in males (OR: 1.12 [95% CI: 1.01, 1.24]) and females (OR: 1.12 [95% CI: 1.02, 1.23]). Heterogeneity in observed associations was observed by population density, where rural residents (OR: 1.58 [95% CI: 1.53, 1.63]) had higher NO_X- related PD risk than urban residents (OR: 1.11 [95% CI: 1.01, 1.22]).
- In an analysis of Italian Longitudinal Study, there were not clear differences in associations between long-term NO_2 exposure and first hospitalizations for PD across males and females (Gandini et al., 2018).

Smoking Status

- Salimi et al. (2020) observed a positive association between annual average NO_2 concentrations and PD prevalence among past smokers (HR: 1.48 [95% CI: 1.09, 2.01]), and null associations among never smokers or current smokers.
- Liu et al. (2016) reported a null association between NO_2 exposure and PD risk (see Section 9.5.3.1). The association remained null in models stratified by smoking status (i.e., never-smokers and ever-smokers).

9.5.3.1.3 Copollutants

- Lee et al. (2016a) analyzed mutually adjusted multipollutant models including NO_X, SO_2, O_3, and PM_{10}. While the observed association between long-term NO_X exposure and PD risk was null in a single pollutant model, NO_X was positively associated with PD risk after adjustment for SO_2, O_3, and PM_{10} (OR: 1.12 [95% CI: 1.06, 1.19] per 20 ppb). NO_X was negatively correlated with O_3 ($\rho = 0.62$) and had correlation values of 0.39 and 0.05 for SO_2 and PM_{10}, respectively.

- Shin et al. (2018) observed a positive association between long-term exposure to NO_2 and PD risk in single pollutant models that was attenuated to the null after mutually adjusting for O_3 and $PM_{2.5}$ (HR: 1.00 [95% CI: 0.97, 1.03]) in a multipollutant model.
- In Goria et al. (2021), the observed association between short-term NO_2 exposure and hospital admissions for PD was attenuated but remained after adjustment for PM_{10} (RR: 1.023 [95% CI: 0.996, 1.050]). Additionally, the association was robust to adjustment for O_3 (RR: 1.046 [95% CI: 1.025, 1.068]).
- Adjustment for $PM_{2.5}$ in Lomme et al. (2023) somewhat attenuated NO_2 associations with PD risk for all quartiles of exposure relative to the first quartile. Associations were attenuated by a greater magnitude for NO_X associations, but all associations remained positive and imprecise. Adjustment for $PM_{10\text{-}2.5}$ resulted in greater attenuations than for $PM_{2.5}$, although all associations remained positive.

9.5.3.1.4 Model Specification

- Ritz et al. (2015) conducted sensitivity analyses and reported positive associations for PD risk when lagging exposures by 5 years (OR: 1.54 [95% CI: 1.14, 2.06]) or 10 years (OR: 1.63 [95% CI: 1.21, 2.18]) prior to PD onset.
- Salimi et al. (2020) adjusted for additional covariates (alcohol consumption, random intercept for neighborhood effects), and null associations between NO_2 and PD risk were unchanged.
- Shin et al. (2018) conducted sensitivity analyses with longer exposure lags, and associations for NO_2 and PD risk were attenuated to the null when the lag period was extended to 5 years (HR: 1.00 [95% CI: 0.97, 1.03]) or 10 years (HR: 1.01 [95% CI: 0.97, 1.05]). HRs were relatively unchanged when indirectly adjusting for smoking and physical activity.

9.5.3.1.5 Conclusions and Remaining Uncertainties

The associations between NO_2/NO_X exposure and PD remains inconsistent across studies, with some reporting positive and precise associations, particularly in high exposure groups, while most reported null results after adjusting for copollutants. Differences in study design, exposure assessment, confounder adjustments, and regional variations in pollution sources, may contribute to these discrepancies. Studies testing longer exposure lags found weaker associations, and while some evidence supports a linear trend in concentration-response, other studies observed nonlinear relationships. Some evidence suggests stronger associations in specific subpopulations, such as past smokers, urban residents, and individuals with higher genetic risk, but few of these populations have been evaluated in multiple studies.

9.5.4 Other Neurodegenerative Disease

This Section summarizes recent PECOS-relevant epidemiologic evidence (see Section 9.5.4.1) examining the relationship between long-term exposure to oxides of nitrogen and risk of neurodegenerative diseases not discussed in previous Sections—multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). MS is characterized by inflammatory demyelination and axonal degeneration in the central nervous system, while ALS is characterized by a progressive loss of motor neurons. No PECOS-relevant studies of short-term exposure or PECOS-relevant animal toxicological studies were identified. A few of the studies discussed present additional analyses evaluating the shapes of concentration-response functions for oxides of nitrogen exposure and other neurodegenerative diseases, the lifestages and populations that may be at higher risk of exposure-associated other neurodegenerative diseases, the potential influence of copollutants on reported associations with other neurodegenerative diseases, and critical exposure windows. The evidence on these topics is discussed in greater detail below in Sections 9.5.4.1.1, 9.5.4.1.2, 9.5.4.1.3, and 9.5.4.1.4, respectively. Section 9.5.4.1.5 presents conclusions from epidemiologic studies of other neurodegenerative diseases and discusses the remaining uncertainties in the epidemiologic evidence.

9.5.4.1 Epidemiologic Studies of Other Neurodegenerative Diseases

Recent studies on the relationship between air pollution and less common neurodegenerative diseases, such as ALS and MS, showed positive associations with oxides of nitrogen exposure ((Hedström et al., 2023; Seelen et al., 2017), respectively). In contrast, other studies presented null or inverse associations between oxides of nitrogen exposure and ALS or MS ((Parks et al., 2022; Bai et al., 2018), respectively), including multiple sensitivity analyses and copollutant adjustments in one study (Parks et al., 2022). Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 9-16.

- Hedström et al. (2023) analyzed data from two population-based case-control studies and a national outpatient registry of MS cases to assess the association between annual average NO_X exposure and MS risk in Sweden (1990–2018). The authors utilized dispersion modeling with high spatial resolution linked to individual residential histories. Logistic regression models were adjusted for study, age, sex, region, ancestry, smoking, sun exposure, and adolescent BMI. Each 10 µg/m³ increase in NO_X exposure was associated with increased risk of MS (OR: 1.03 [95% CI: 1.02, 1.05]). In analyses of source-specific NO_X, both traffic-related and residential wood combustion NO_X concentrations were positively associated with MS risk.
- Seelen et al. (2017) conducted a population-based case-control study in the Netherlands and examined long-term air pollution exposure and ALS risk. The authors assigned NO_2 and NO_X exposure at residential addresses using a national LUR models and estimated NO_2- and NO_X-related ALS risk in conditional logistic regression models adjusted for age, sex, education, BMI, smoking, alcohol use, urbanization degree, and area-level SES. Increasing concentrations of NO_2 were associated with increased ALS risk; individuals in the highest

exposure quartile (Q4) had a higher risk of ALS than those in the first quartile (OR: 1.74 [95% CI: 1.32, 2.30]). For NO_X exposure, ALS risk was also elevated in Q4 relative to Q1 (OR: 1.38 [95% CI: 1.07, 1.77]).

- In contrast, other recent studies reported null or inverse associations between oxides of nitrogen exposure and MS (Bai et al., 2018) or ALS (Parks et al., 2022). In an analysis of the Ontario Population Health and Environment Cohort that assigned residential exposure to NO_2 using a LUR model, 5-year moving average NO_2 concentrations with a 2-year lag were associated with a decrease in incident MS (HR: 0.92 [95% CI: 0.83, 1.02]) (Bai et al., 2018). Parks et al. (2022) reported a null association between 5-year average NO_X concentrations and odds of ALS in a national population-based cohort in Denmark.

9.5.4.1.1 Concentration-Response

- Hedström et al. (2023), reported monotonically increasing MS risk across increasing quantiles of NO_X exposure.
- Seelen et al. (2017) used spline models to assess the shape of the C-R relationship between long-term oxides of nitrogen exposure and ALS risk. The C-R curve for NO_2 exposure and ALS risk was approximately linear across the range of the exposure distribution. For NO_X, the association was approximately linear at lower concentrations and appeared to plateau at roughly 60 $\mu g/m^3$.

9.5.4.1.2 Lifestages and Populations

- In Hedström et al. (2023), the association between NO_X exposure and MS risk was stronger among never smokers compared to ever smokers. Additionally, males had a higher NO_X-related risk of MS relative to females. A strong interaction was observed between NO_X exposure and the presence of the HLA-DRB*15:01 allele, with carriers observed to be at substantially higher risk of MS when exposed to higher NO_X concentrations.
- In Seelen et al. (2017), stratified analyses indicated that ALS risk associated with NO_2 and NO_X exposure was stronger in patients with bulbar-onset ALS compared to spinal onset. The risk of bulbar-onset ALS was increased for individuals in the highest quartile of NO_2 and NO_X exposure compared to those in the lowest quartiles. Approximately null associations were observed for spinal onset. There was not strong evidence of effect modification by smoking status. ORs for NO_2 and ALS risk were slightly higher among non-smokers compared to current smokers. However, there was a smaller sample size of current smokers, which led to imprecise effect estimates and adds uncertainty to the comparison between groups. A similar pattern was observed for NO_X exposure.

9.5.4.1.3 Copollutants

- Seelen et al. (2017) analyzed copollutant models to evaluate the effects of NO_2 and NO_X on ALS risk while adjusting for $PM_{2.5}$. The NO_2 association with ALS risk (Q4 vs. Q1 OR: 1.74 [95% CI: 1.29, 2.30]) remained robust in the copollutant model adjusted for $PM_{2.5}$ (Q4 vs. Q1 OR: 1.73 [95% CI: 1.29, 2.30]). The single pollutant NO_X association (Q4 vs. Q1 OR: 1.38

[95% CI: 1.07, 1.77]) was also relatively unchanged after adjustment for $PM_{2.5}$ (Q4 vs. Q1 OR: 1.33 [95% CI: 1.02, 1.75]).

9.5.4.1.4 Exposure Windows

- Seelen et al. (2017) conducted multiple sensitivity analyses (recency of exposure, lagging exposure by 1 and 5 years, excluding movers, and removing exposure extrapolation) that yielded similar results to primary models.

9.5.4.1.5 Conclusions and Remaining Uncertainties

The evidence on oxides of nitrogen exposure and other neurodegenerative diseases is limited, with only a couple of studies examining ALS and MS risk. One study reported positive associations between NO_2 and ALS, while another reported a null association between NO_X and MS, which became more precise after adjusting for copollutants. Differences in exposure assessment and confounder adjustments may explain these mixed findings and warrant further research to clarify these relationships.

9.5.5 Synthesis Across Lines of Evidence

The 2016 Oxides of Nitrogen ISA did not evaluate neurodegenerative effects. Recent epidemiologic studies from the United States and Europe report inconsistent associations between long-term exposure to oxides of nitrogen and cognitive decline among adults, but limited adjustment for copollutants makes it unclear whether there is an independent effect of oxides of nitrogen on adult cognitive function. In contrast, research on Alzheimer's disease and dementia shows more consistent positive associations, with many studies reporting increased dementia risk across diverse populations, even after adjusting for confounders such as $PM_{2.5}$ and ozone. Supporting these observations, recent toxicological studies have demonstrated that NO_2 exposure promotes AD-like pathology by elevating expression of amyloid-β, promoting tau phosphorylation, and exacerbating cognitive dysfunction in an AD model, which provides important biological plausibility.

Evidence for other neurodegenerative diseases is less robust. Epidemiologic findings on long-term oxides of nitrogen exposure and Parkinson's disease have been inconsistent; while some studies reported positive associations with PD risk, few adjusted for copollutants, and most studies reported a null association. A single study of short-term exposure reported positive associations between NO_2 and hospital admissions for PD. Studies examining long-term exposure and risk of ALS or MS have produced mixed findings, with one study indicating a positive association for ALS and another showing no association with MS. No animal toxicological studies have addressed these endpoints.

9.6 Other Nervous System Effects

The following Sections discuss the available epidemiologic and animal toxicological evidence for additional nervous system effects that have not been covered previously, including febrile seizures (see Section 9.6.1), peripheral nervous system effects (see Section 9.6.2), and sensory function (see Section 9.6.3) which are each supported by a single line of evidence. Because no Section includes both toxicological and epidemiologic data, an integrated synthesis across lines of evidence has not been included.

9.6.1 Febrile Seizures

This Section summarizes recent PECOS-relevant epidemiologic evidence (see Section 9.6.1.1) examining the relationship between long-term exposure to oxides of nitrogen and febrile seizures, which are brought on by fevers in young children and infants (see Appendix A – Appendix Table 9-17). No PECOS-relevant studies of short-term exposure or PECOS-relevant animal toxicological studies were identified. The evidence summary concludes with a summary of finding and remaining uncertainties (see Section 9.6.1.1.1).

9.6.1.1 Epidemiologic Studies of Febrile Seizures

In an analysis of the Danish National Birth Cohort, Hjortebjerg et al. (2018) reported that long-term exposure to NO_2 in childhood was associated with febrile seizures (IRR: 1.15 [95% CI: 0.98, 1.35]). The association between prenatal NO_2 exposure and febrile seizures was null (IRR: 1.00 [95% CI: 0.86, 1.17]).

9.6.1.1.1 Conclusions and Remaining Uncertainties

Evidence examining the relationship between oxides of nitrogen exposure and febrile seizures is limited. A single study reported initial evidence of an association between long-term NO_2 exposure and febrile seizures in childhood.

9.6.2 Effects on the Peripheral Nervous System

This Section summarizes recent PECOS-relevant epidemiologic evidence (see Section 9.6.2.1) examining the relationship between long-term exposure to oxides of nitrogen and peripheral nervous system effects. No PECOS-relevant epidemiologic studies of short-term exposure or PECOS-relevant

animal toxicological studies were identified. The evidence summary concludes with a summary of the findings and remaining uncertainties (see Section 9.6.2.1.1).

9.6.2.1 Epidemiologic Studies of Effects on the Peripheral Nervous System

Li et al. (2022b) examined the association of NO and NO_X with microvascular disease including retinopathy and peripheral neuropathy using data from the UK Biobank, a prospective cohort study of approximately 500,000 adults registered with the National Health Service of the United Kingdom. Annual average NO_2 and NO_X concentrations were estimated using the ESCAPE LUR model (C-V r^2 = 87% and 88%, respectively.) The adjusted HRs for the association of NO_2 with peripheral neuropathy was 1.17 (95% CI: 1.11, 1.24) and the association for NO_X was 1.05 (95% CI: 1.00, 1.10) per 41.8 µg/m^3. Neither NO_2 nor NO_X were associated with retinopathy (HR: 1.01 [95% CI: 0.94, 1.09] and HR: 0.99 [95% CI: 0.94, 1.04] per 41.8 µg/m^3). Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 9-17.

9.6.2.1.1 Conclusions and Remaining Uncertainties

The evidence linking oxides of nitrogen exposure to peripheral neuropathy and retinopathy is limited, with a single cross-sectional study reporting a positive association with the former and a null association with the latter.

9.6.3 Sensory Function

This Section summarizes recent PECOS-relevant animal toxicological evidence examining the relationship between exposure to oxides of nitrogen and sensory function. Notably, the only aspect of sensory function evaluated in PECOS-relevant studies was nociception, the sensory process wherein noxious stimuli are detected by specialized neurons that signal the central nervous system (CNS) to perceive pain. Furthermore, no PECOS-relevant epidemiologic evidence was identified. Animal toxicological studies (see Section 9.6.3.1) have evaluated nociception using the Von Frey test and the rat grimace scale (RGS). The evidence Section concludes with a summary of findings and an analysis of remaining uncertainties (see Section 9.6.3.1.1).

9.6.3.1 Animal Toxicological Studies of Sensory Function

In the 2016 Oxides of Nitrogen ISA, there was no toxicological evidence available evaluating effects on sensory function. Recently, a small number of studies have evaluated the effect of NO_2 on

nociception. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-18.

- Ye et al. (2022) exposed 7-week-old female Sprague Dawley rats to NO_2 (0.5, 5, or 10 ppm for 4 hours/day) and examined their mechanical pain thresholds using the von Frey test after 3, 6, 9, 12, and 15 days of exposure. Compared to untreated controls, the threshold for pain was significantly decreased in the medium- and high-dose groups on each testing day. This result was replicated in a follow-up study utilizing the same methodology (i.e., 7-week-old female Sprague Dawley rats exposed to 5 ppm NO_2, 4 hours/day for 15 days) (Ye et al., 2024).
- The same studies also utilized the RGS to score changes in facial expression as a means of quantifying pain. Rats had significantly increased RGS scores on all testing days (3, 6, 9, 12, and 15 days of exposure) in response to 0.5 ppm exposure and higher (Ye et al., 2024; Ye et al., 2022). The authors reported that scores on the RGS and the mechanical pain thresholds followed an apparent dose-response relationship as NO_2 exposure increased (0.5, 5, and 10 ppm).

9.6.3.1.1 Conclusions and Remaining Uncertainties

In summary, there is limited evidence to suggest that NO_2 exposure may alter nociception, increasing sensitivity to pain.

9.7 Mortality

This Section summarizes recent PECOS-relevant epidemiologic evidence (see Section 9.7.1) examining the relationship between long- or short-term exposure to oxides of nitrogen and mortality from diseases of the nervous system. No PECOS-relevant animal toxicological studies were identified. Because this Section only discusses epidemiologic data, an integrated synthesis across lines of evidence has not been included.

9.7.1 Epidemiologic Studies of Mortality

Recent studies have examined the impact of oxides of nitrogen exposure on mortality related to nervous system diseases. Studies conducted in Europe reported findings that varied depending on the methodological approaches used. ELAPSE analyses reported a positive association of NO_2 exposure with mortality from PD and psychiatric disorders while inconsistent findings for dementia mortality were reported. Associations reported in other studies were largely null. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 9-19.

ELAPSE is a collaborative research effort that aimed to analyze the long-term health impacts of low air pollution concentrations across several European countries.

- A study of a Danish national administrative cohort examined the risk of mortality from dementia and psychiatric disorders associated with annual average NO_2 concentrations estimated at the residential level using the ESCAPE LUR model (So et al., 2022). NO_2 was positively associated with dementia mortality (HR: 1.10 [95% CI: 1.06, 1.14] per 10 ppb) and psychiatric disorder mortality (HR: 1.48 [95% CI: 1.38, 1.58]) in single pollutant models.
- As part of the ELAPSE study, Cole-Hunter et al. (2023) analyzed data from over 250,000 participants pooled across seven European cohorts. LUR models were used to assign exposure at the residential level. The authors reported a positive but imprecise association between long-term NO_2 exposure and PD mortality in a single pollutant model (HR: 1.16 [95% CI: 0.91, 1.74]).
- In the same population as Cole-Hunter et al. (2023), Andersen et al. (2022) examined the association between long-term NO_2 exposure and mortality from dementia and psychiatric disorders. In the single pollutant models, a 10 ppb increase in long-term NO_2 exposure was associated with an increase in psychiatric disorder mortality (HR: 1.83 [95% CI: 1.25, 2.69]). In contrast, NO_2 concentrations were associated with a decrease in dementia mortality (HR: 0.89 [95% CI: 0.73, 1.09]).

A few other studies that were not part of the ELAPSE project reported mostly null associations between oxides of nitrogen exposure and risk of mortality due to diseases of the nervous system.

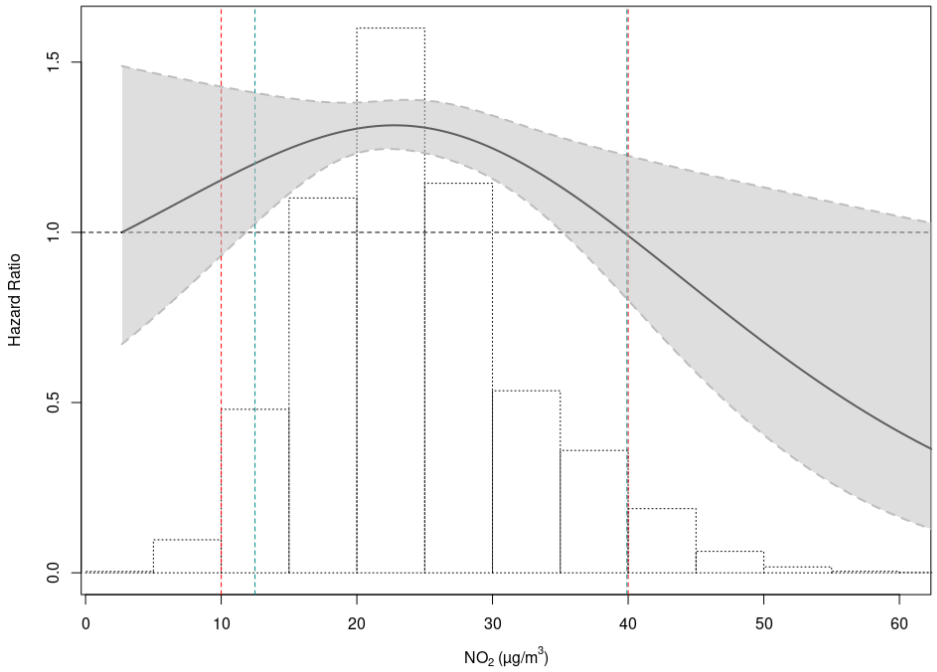
- Kang et al. (2023) conducted a nationwide retrospective cohort study in South Korea to assess long-term NO_2 exposure and neurological disorder mortality using kriging methods with 1-, 3-, and 5-year average exposure windows. Long-term NO_2 exposure was not associated with neurological disease mortality across any of the exposure windows.
- Malek et al. (2023) conducted a nested case-control study within the Women's Health Initiative cohort to assess long-term NO_2 and NO_X exposure and ALS mortality among postmenopausal women. NO_2 and NO_X exposures were estimated using a spatiotemporal model and averaged over 5-, 7.5-, or 10-year periods before ALS deaths. In conditional logistic regression models adjusted for education, smoking, and physical activity, NO_2 and NO_X exposure were not associated with ALS mortality across any of the exposure windows.
- Klompmaker et al. (2020) used a LUR model estimate annual average NO_2 exposure among respondents to a Dutch national health survey (the 2012 Public Health Monitor). The HR for the association between annual average NO_2 exposure and neurodegenerative disease mortality obtained from Cox proportional hazard models that were adjusted for demographic factors, smoking status, and socioeconomic status, was 1.05 (95% CI: 0.86, 1.29). In an analysis of Dutch national administrative cohort, Klompmaker et al. (2021) reported an inverse association between long-term NO_2 exposure estimated at the residential level using a national LUR model and neurodegenerative mortality (HR: 0.982 [95% CI: 0.947, 1.018] per 10 ppb). Both estimates were imprecise with CIs that included the null value.
- In a study of short-term NO_2 exposure, Gariazzo et al. (2023) examined a national dataset from Italy. This study downscaled 5 km x 5 km chemical transport model estimates using machine learning algorithms that integrated spatial and spatiotemporal data. Short-term NO_2 concentrations were inversely associated with decreased nervous disease mortality at lag 0–1 (IRR: 0.77 [95% CI: 0.71, 0.83] per 20 ppb), lag 0–5 (0.71 [95% CI: 0.53, 0.94]), and lag 2–5 (0.84 [95% CI: 0.65, 1.08]).

A few of the studies discussed present additional analyses evaluating the shapes of concentration-response functions for oxides of nitrogen exposure and mortality, the lifestages and populations that may be at higher risk of exposure-associated mortality, the potential influence of copollutants on reported associations with mortality, critical exposure windows, and issues related to model specification. The evidence on these topics is discussed in greater detail below in Sections 9.7.1.1, 9.7.1.2, 9.7.1.3, 9.7.1.4, and 9.7.1.5, respectively. Section 9.7.1.6 presents conclusions from epidemiologic studies of mortality and discusses the remaining uncertainties in the epidemiologic evidence.

9.7.1.1 Concentration-Response

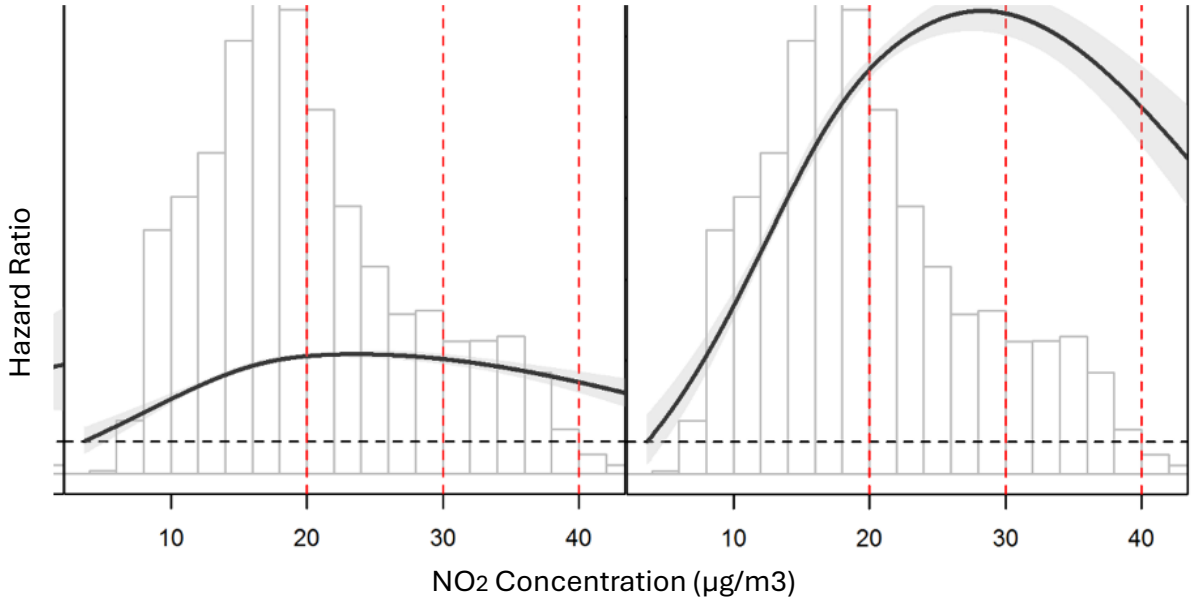
A limited number of studies examined the shape of the C-R relationship for oxides of nitrogen and diseases of the nervous system (see Table 9-12). The C-R relationships were approximately linear at lower concentrations and deviated from linearity at higher concentrations (i.e., plateaued and then became inverse).

- The ELAPSE study Andersen et al. (2022) used natural cubic splines with two degrees of freedom to examine the shape of the C-R relationship between NO_2 exposure and mortality from psychiatric disorders. The C-R curve is approximately linear through the majority of the concentration distribution (see Figure 9-21). There is an inverse association above ~40 $\mu g/m^3$ (21.24 ppb), but there is less confidence in the shape of the C-R relationships at these higher concentrations due to fewer observations, as indicated by wider 95% CIs.
- So et al. (2022) fit models with natural spline terms for NO_2 (3 df) to assess the shape of the C-R relationship with dementia and psychiatric disease mortality (see Figure 9-22). Dementia mortality risk increased approximately linearly with NO_2 exposure at lower concentrations and began to plateau around 20 $\mu g/m^3$ (10.62 ppb). A similar pattern was observed for psychiatric disorder mortality, which had a steeper slope than dementia mortality, indicating a stronger association with NO_2, and a transition to a plateau and then inverse association around 30 $\mu g/m^3$ (15.93 ppb).



Note: Solid black lines indicate hazard ratio values and black dashed lines indicate their 95% confidence intervals. Green dotted lines indicate the 5th and 95th percentiles of air pollutants' concentrations. Red dotted dash lines represent different limited values in EU, U.S., and WHO guidelines (2021 version). The histograms show the distributions of exposures in 2010.
Source: Andersen et al. (2022). Copyright permission pending.

Figure 9-21 Concentration Response Curve for Associations between Long-Term Exposure to NO_2, and Psychiatric Disorder Mortality.



Note: 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.
Note: Associations were obtained from models adjusting 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.
Source: So et al. (2022). Copyright permission pending.

Figure 9-22 Concentration Response Curves for Associations of Long-Term Exposure to NO_2, with Dementia (left) Psychiatric Disorder Mortality (right).

Table 9-12 Summary of Epidemiologic Studies Examining the Concentration-Response Relationship for the Association Between Long-Term NO_2 Exposure and Psychiatric Mortality

Study	Cohort [Enrollment, Follow-up]	Exposure Range[a]	Modeling Method	Shape of Curve[b]
†Andersen et al. (2022) Psychiatric Disorder Mortality	ELAPSE Enrollment: 1985–2005 Follow-up: 2011–2015	Min–Max = 2–38.4 ppb (3.7–72.2 µg/m^3)	Natural cubic splines, 2 df	approximately linear
†So et al. (2022) Dementia Mortality	Danish Administrative Cohort Enrollment: January 2000 Follow-up: through December 2017	Min–Max = 2–38.4 ppb (3.7–72.2 µg/m^3) P25–P75 = 7.76–13.2 ppb (14.6–24.9 µg/m^3)	Natural spline with 3 df	Supralinear, plateau at ~20 µg/m^3 (10.62 ppb)
†So et al. (2022) Psychiatric Disorder Mortality	Danish Administrative Cohort 1 January 2000–31 December 2017	Min–Max = 2–38.4 ppb (3.7–72.2 µg/m^3) P25–P75 = 7.76–13.2 ppb (14.6–24.9 µg/m^3)	Natural spline with 3 df	Approximately linear until ~30 µg/m^3 (15.93 ppb)

List of abbreviations: df = degrees of freedom; ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe; Max = maximum; Min = minimum; NO_2 = nitrogen dioxide; P = percentile; ppb = parts per billion.
[a]For studies with standardized effect estimates, values were converted to ppb, when applicable, and original reported values are noted in parentheses.
[b]There visual representations of the shape of the curve in the corresponding text.
†Studies published since the 2016 Oxides of Nitrogen ISA.

9.7.1.2 Lifestages and Populations

The ELAPSE study Andersen et al. (2022) did not observe effect modification of the association between NO_2 and psychiatric disorder mortality in models stratified by age, sex, weight, smoking, or employment status.

9.7.1.3 Copollutants

In addition to single pollutant models, recent studies examined the association of NO_2 with mortality in models that adjusted for copollutants.

- So et al. (2022) analyzed copollutant models adjusted for $PM_{2.5}$, BC, or O_3. Associations between long-term exposure to NO_2 and both psychiatric disorder mortality and dementia mortality were robust to adjustment for each of the copollutants examined. NO_2 was moderately correlated with $PM_{2.5}$ ($\rho = 0.60$) and O_3 ($\rho = -0.65$), and highly correlated with BC ($\rho = 0.89$).
- Cole-Hunter et al. (2023) reported that the association between NO_2 exposure and PD mortality was attenuated toward the null and imprecise after adjusting for O_3 (HR: 0.87 [95%

CI: 0.54, 1.41]), BC (HR: 1.22 [95% CI: 0.56, 2.63]), or $PM_{2.5}$ (HR: 1.02 [95% CI: 0.67, 1.54]) in copollutant models.

- Andersen et al. (2022) reported that the observed association between long-term NO_2 exposure and mortality from psychiatric disorders (HR: 1.83 [95% CI: 1.25, 2.69]) was robust to adjustment for $PM_{2.5}$ (HR: 1.86 [95% CI: 1.14, 3.03]) or O_3 (HR: 1.83 [1.10, 3.06]) in copollutant models. The association between NO_2 and dementia mortality in a single pollutant model remained null when adjusting for $PM_{2.5}$ or O_3.

9.7.1.4 Exposure Windows

A few studies estimated historical exposures using back-extrapolation methods in sensitivity analyses.

- Andersen et al. (2022) utilized 2010 annual average NO_2 concentrations as the primary exposure measure. However, because follow-up pre-dated 2010, the authors also used back-extrapolated exposure estimates using ratio and difference methods to conduct sensitivity analyses with exposure assigned at the cohort baseline year and as time-varying annual averages. Observed associations were comparable across each of the exposure methods. There was some variation in the magnitude of associations, but there was notable uncertainty in the estimates (i.e., wide 95% CIs) that could explain the variability, and all associations remained directionally consistent.
- As a sensitivity analysis, So et al. (2022) assigned baseline and time-varying exposures by back- and forward-extrapolating the ELAPSE LUR model estimates using a low resolution (26 km x 26 km) exposure model that provides monthly average concentrations dating back to 1990. The authors analyzed Danish national administrative cohort data from 2000 until 2017 and reported comparable positive associations between psychiatric disease mortality and NO_2 concentrations assigned using the primary exposure model (i.e., 2010 average), back-extrapolated baseline exposure (i.e., 2000 average), and back- and forward-extrapolated time-varying exposure estimates that covered the entire study period. For dementia mortality, comparable positive associations were reported for NO_2 concentrations assigned using the primary exposure model and back-extrapolated baseline exposure, but null associations were observed with time-varying exposure.

9.7.1.5 Model Specification

- Andersen et al. (2022) conducted multiple sensitivity analyses to evaluate model robustness, including testing alternative sub-cohort adjustments (i.e., no adjustment, sub-cohort indicator, frailty term, and random intercept). The Akaike Information Criterion suggested that adjusting for sub-cohort differences using strata terms provided the best model fit, though results remaining generally consistent across these adjustments.
- In an analysis of a national administrative cohort in the Netherlands, Klompmaker et al. (2021) evaluated copollutant models that adjusted for the modeled average density of green space surrounding each participant's residence. Greenness is often correlated with air pollutants and can exhibit direct and indirect effects on mortality (Andersson-Molina et al.,

2002). Associations between NO_2 and neurodegenerative disease mortality remained null after adjustment for greenness in co-exposure models.

9.7.1.6 Conclusions and Remaining Uncertainties

Overall, associations between NO_2 exposure and mortality due to nervous system disease are inconsistent, and mostly null in models adjusted for copollutants. Copollutant confounding remains a key uncertainty, as adjustments for $PM_{2.5}$ and BC have led to attenuation of associations, while associations remained robust when adjusted for O_3. One short-term study revealed negative and precise associations between short-term NO_2 exposure and nervous disease mortality, emphasizing the inconsistency of results for long-term and short-term exposures. There is limited research assessing lifestage and population differences.

9.8 Overt Nervous System Toxicity

This Section summarizes key evidence from the 2016 Oxides of Nitrogen ISA and recent PECOS-relevant epidemiologic and animal toxicological evidence examining the relationship between long-term exposure to oxides of nitrogen and overt nervous system toxicity. Overt nervous system toxicity refers to a group of endpoints related to gross anatomy and histopathology of the nervous system. Epidemiologic studies (see Section 9.8.1) have assessed physical changes in the brain using MRI and have provided some information on the potential impact of copollutants (see Section 9.8.1.1). Limited animal toxicological studies (see Section 9.8.2) have measured brain weight and other microanatomical endpoints. Each evidence Section concludes with a summary of findings and an analysis of remaining uncertainties (see Sections 9.8.1.2 and 9.8.2.1 for epidemiologic and toxicological evidence, respectively). Section 9.8.3 provides an integrated synthesis across lines of evidence for overt nervous system toxicity.

9.8.1 Epidemiologic Studies of Overt Nervous System Toxicity

Evidence from recent studies is summarized below. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 9-20.

The recent body of evidence, published since the 2016 Oxides of Nitrogen ISA, includes analyses of two U.S. populations.

- Kulick et al. (2017) conducted a cross-sectional analysis of stroke-free adults (aged 50 years) enrolled in the MRI cohort of the NOMAS. Residential annual average NO_2 and NO_X exposure, estimated using the MESA Air hybrid model combining kriging and LUR, were

associated with slight decreases (all CIs included the null value) in log-white matter hyperintensity volume (WMHV) and total cerebral volume (TCBV). Neither NO_2 or NO_X was associated with a higher odds of subclinical brain infarct (SBI, i.e., lesions 3 mm) in this study.

- Petkus et al. (2022) conducted an analysis to examine whether gray matter volume in specific regions (i.e., prefrontal cortex, anterior cingulate gyrus, insula amygdala, limbic medial temporal lobe, hippocampus, thalamus and basal ganglia) mediates the association between NO_2 exposure and depressive symptoms among women enrolled in WHIMS. Residential NO_2 exposure (3 years prior to the MRI assessment) was estimated using universal kriging models ($r^2 = 0.85$) and reflected the participant's residential history during the 3-year exposure period. The total effect of NO_2 exposure on depressive symptoms estimated from the study is described in (see Section 9.4). The authors reported that the indirect effects of NO_2 on increases in depressive symptoms mediated by smaller volumes of the prefrontal cortex explained 9% of the total effect of NO_2 on increases in depressive symptoms.

Recent studies analyzed data collected for the UK Biobank study in a subset of patients also undergoing brain MRIs (44–80 years of age). The estimates of residential air pollution exposure were derived from 2010 LUR models developed for ESCAPE (Beelen et al., 2013). Although some analyses controlled for inverse distance to a major roadway which may capture noise and components of the traffic mixture, none of the Biobank analyses adjusted for specific traffic-related copollutants. In addition, the analyses relied on annual average pollutant concentrations for 2010 that were estimated from LUR models without accounting for residential history or time spent at home (see Table 9-13).

- Hedges et al. (2020) examined the cross-sectional association of annual average NO_2 and NO_X exposure with thalamic volume, which is associated with cognitive function. This study considered potential confounders including distance to the roadway, which was included as a proxy for noise, and interactions of air pollution with age, sex, education, and overall health. The associations of NO_2 and NO_X with left and right thalamic volume varied slightly depending on the model but were generally weak and included the null value. In models that included an interaction term between NO_2 or NO_X exposure and education, the decrease in thalamic volume associated with the pollutant was larger and CIs did not include the null value. The interaction of having a college degree with NO_2 and NO_X exposure was positive, indicating that educational attainment may offer some degree of protection against the effect of oxides of nitrogen on the thalamus, however.
- Gale et al. (2020) studied the cross-sectional association of air pollution with gray matter volume in the prefrontal cortex (i.e., frontal poles, superior frontal gyri, frontal medial cortex, orbitofrontal cortex, and frontal opercula). This brain region is associated with cognitive and behavioral processes. Annual average NO_2 and NO_X exposures were associated with reduced volume in the prefrontal cortex after adjustment for potential confounders, including distance to the roadway, which was included as a proxy for noise exposure. An interaction with educational attainment was observed in multivariable models. The study controlled for multiple comparisons using multivariate tests.
- In a cross-sectional study that assessed total gray and white matter volume, which is associated with cognitive function and decline, annual average NO_2 and NO_X exposures were associated with reduced total gray matter volume but not with white matter volume (Erickson et al., 2020). This study applied similar methods as the previously described Biobank analyses. Models were not adjusted for distance to roadways.

Several other European studies were conducted.

- In another study of adults, Nußbaum et al. (2020) examined the association of NO_X and NO_2 exposure with neurocognitive test performance (see Section 9.5.1.1) and region-specific changes in LGI value, which is a marker of local brain atrophy assessed using MRI, among adults (55–85 years) enrolled in the 1000BRAINS arm of the HNR study. Decreased LGI indicates local brain atrophy. The authors reported that annual average NO_2 and NO_X concentrations, estimated using the ESCAPE LUR model, were associated with more pronounced local atrophy of the fronto-parietal network (FPN) in three regions of the right brain hemisphere (i.e., inferior parietal lobule [IPL], posterior cingulate cortex and precuneus [PCC/P] and dorsolateral prefrontal cortex [DLPFC]). Decreases in LGI in association with NO_2 and NO_X exposure as indicated by negative β coefficients in Table 9-13 indicate local brain atrophy. Models that simultaneously included NO_2 and noise were not presented; however, noise was positively associated with LGI in a region of the FPN.
- A study of children 6–10 years old in the Netherlands was also conducted. Guxens et al. (2018) examined the association of prenatal air pollution exposure with cortical thickness, total brain volume, cortical gray matter volume, cortical white matter volume, subcortical gray matter volumes, and ventricular volume. The data for this study came from the Generation R cohort, which enrolled maternal-infant pairs from Rotterdam, Netherlands (2002–2006). Prenatal (i.e., during fetal life) exposure to NO_2 was assessed using the LUR developed for the ESCAPE study (Beelen et al., 2013; Cyrys et al., 2012). No associations were reported between prenatal NO_2 exposure and total brain volume or volumes of cortical gray matter, cortical white matter, subcortical gray matter, or ventricular volume (see Table 9-13).

9.8.1.1 Copollutants

Some analyses of the UK Biobank study adjusted for the distance to roadway as a proxy for noise exposure. Moderate correlations between noise and traffic pollutants including BC have been observed in multiple studies in Europe and the United States (see Chapter 2, Section 2.4.3.1), suggesting that controlling for traffic noise may also control, in part, for other traffic-related pollutants. Studies were generally robust to adjustment for noise or distance to roadway potentially strengthening the evidence that the observed brain changes may be independently associated with NO_2 exposure.

9.8.1.2 Conclusions and Remaining Uncertainties

A recent analysis of NOMAS reported small decreases in brain volume (all CIs included the null value) and no association with SBI among stroke-free adults while an analysis of the WHIMS cohort found that brain volume may mediate the association between annual average NO_2 and depressive symptoms observed in their study (see Table 9-13Table 9-). Several analyses of adults enrolled in the UK Biobank study reported associations of NO_2 and NO_X with brain changes on MRIs, while no association was observed in a single study of children. The main strengths of these studies included their large size, extensive evaluation of potential confounders and ascertainment of the brain alterations that may underlie

functional changes in cognition and behavior using MRI; however, the analyses were cross-sectional introducing some uncertainty regarding the temporality of the observed associations. The U.K. Biobank studies adjusted for distance to roadway to control for noise exposure. Although adjustment for distance to a major roadway may have addressed confounding by other traffic pollutants, none of the studies included copollutants in their multivariable models. The extent to which there is an independent effect of oxides of nitrogen on the overt nervous system effects examined remains an uncertainty.

Table 9-13 Summary of Evidence for Long-Term NO_2 and NO_X Exposure and Brain Changes

Study and Location	Cohort and Population (Study Period)	Exposure Assessment		Effect Estimate (95% CI)
†Kulick et al. (2017) Manhattan, NY, U.S.	NOMAS (2003–2008) Adults ≥50 yr N = 1,241	Annual Avg MESA Air Hybrid (Kriging and LUR)	NO_2	Log WMHV β: -0.041 (-0.165, 0.083) TCBV β: -0.008 (-0.507, 0.49) SBI β: 0.97 (0.63, 1.49)
			NO_X	Log WMHV β: -0.024 (-0.098, 0.049) TCBV β: -0.016 (-0.308, 0.276) SBI OR: 0.99 (0.77, 1.26)
†Hedges et al. (2020) U.K.	Biobank study (2006–2010) Adults, 44–80 yr at enrollment N = 18,278.	Annual Avg (2010) ESCAPE LUR	NO_2	L Thalamus Vol β: 0 (-25.5, 25.5) R Thalamus Vol β: -5.08 (-29.45, 19.29)
			NO_X	L Thalamus Vol β: -0.31 (-1, 0.37)* R Thalamus Vol β: -0.52 (-1.17, 0.13)*
†Gale et al. (2020) U.K.	Biobank study (2006–2010) Adults 40–69 yr at enrollment N = 18,288	Annual Average ESCAPE LUR	NO_2	L Pole Vol β: -5.12 (-10.24, 0)* R Pole Vol β: -6.25 (-11.96, -0.54)* L Operculum Cortex β: -0.58 (-1.1, -0.06)* R Operculum Cortex β: 0.05 (-0.46, 0.56)*
			NO_X	L Pole Vol β: -2.92 (-5.51, -0.34)* R Pole Vol β: -3.93 (-6.8, -1.05)* L Operculum Cortex β: -0.39 (-0.66, -0.13)* R Operculum Cortex β: -0.07 (-0.33, 0.18)*
†Erickson et al. (2020)	N = 18,292	Annual Average ESCAPE LUR	NO_2	GM vol β: -103.0 (-180.00, -26.0)* WM vol β: -72.0 (-155.0, 12.0)*
			NO_X	GM vol β: -42.0 (-79.0, -4.0)* WM vol β: -26.0 (-67.0, 15.0)*
†Nußbaum et al. (2020) Ruhr region, Germany	HNR (2006–2016) Adults, 55–85 yr N = 615	Annual Avg ESCAPE LUR		Changes in LGI by Region:
			NO_2	R DLPFC β: -0.04 (-0.09, 0.02) R PCC/P β: -0.07 (-0.14, 0) R IPL β: -0.04 (-0.09, 0.02)
			NO_X	R DLPFC β: -0.01 (-0.02, 0.01)* R PCC/P β: -0.02 (-0.04, -0.01)* R IPL β: -0.02 (-0.03, 0)*

Study and Location	Cohort and Population (Study Period)	Exposure Assessment	Effect Estimate (95% CI)
†Guxens et al. (2018) Rotterdam, Netherlands	Generation R Children 6–10 yr N = 783	Prenatal ESCAPE LUR	Total Brain Vol β: 124 (-1118, 1375)* Cortical GM Vol β: -60 (-853, 733)* Cortical WM Vol β: 199 (-287, 685)* Subcortical GM Vol β: 36 (-17, 89)* Ventricular Vol β: 4, (-57, 64)*

List of abbreviations in alphabetical order: Avg = average; DLPFC = dorsolateral prefrontal cortex; ESCAPE = European Study of Cohorts for Air Pollution Effects; GM = gray matter; HNR = Heinz Nixdorf Recall; L = left; LGI = local gyrification index; LUR = Land Use Regression; IPL = inferior parietal lobule; MESA Air = Multi-Ethnic Study of Atherosclerosis and Air Pollution; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; NOMAS = Northern Manhattan Study; OR = odds ratio; PCC/P = posterior cingulate cortex and precuneus; R = Right; SBI = subclinical brain infarct; TCBV = total cerebral volume; Vol = volume; WHMV = white matter hyperintensity volume; WM = white matter; yr = year(s).
Note: For studies that model the association of annual average concentration with the outcome, effect estimates are standardized to incremental increases of 10 ppb NO_2 and 20 ppb NO_X.
*Results are not standardized.
†Studies published since the 2016 Oxides of Nitrogen ISA.

9.8.2 Animal Toxicological Studies of Overt Nervous System Toxicity

Animal studies can offer insights into the effects on brain structure and function through investigations that cannot be conducted on human subjects. In the 2016 Oxides of Nitrogen ISA, Li et al. (2012) reported decreases in the brain-to-body weight ratio, and histopathological evidence of neuronal damage, characterized by pyknotic nuclei and eosinophilic neurons, to the pallium (also known as the cerebral cortex) resulting from 2.66 or 5.32 ppm NO_2 exposure (6 hours/day) for 7 days in Wistar rats. Recent studies have investigated brain weight and myelination. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 9-21.

- No significant differences in brain weight on PND 1 were reported in male and female C57BL/6 mouse pups whose dams were exposed to 2.5 ppm NO_2 (5 hours/day) throughout gestation (Yan et al., 2020).
- Brain-to-body weight ratio was not significantly affected following 28 days of 2.5 ppm NO_2 exposure (5 hours/day) in male and female 7-week-old C57BL/6J mice (Li et al., 2021).
- Structural alterations in the myelin sheath were noted in the optic nerve, corpus callosum, and cortex of male, but not female, C57BL/6J mouse pups whose dams were exposed to 2.5 ppm NO_2 (5 hours/day) throughout gestation (Li et al., 2022a). This study also demonstrated that gestational NO_2 exposure delayed the maturation of oligodendrocytes, which may underlie the reported effects on myelination.
- Damages to the myelin sheath ultrastructure were also detected in 7-week-old male, but not female, C57BL/6J mice exposed to 2.5 ppm NO_2 (5 hours/day) for 28 days (Li et al., 2021).

9.8.2.1 Conclusions and Remaining Uncertainties

Overall, the evidence is limited regarding the effects of NO_2 exposure on overt nervous system toxicity. A single study reported NO_2 exposure decreased brain-to-body weight ratio in rats, but additional studies in mice have not supported this finding. A small number of studies have reported that both developmental (i.e., gestational) and non-developmental NO_2 exposure result in neuronal damage and impaired myelination in female rodents. However, because these effects were only tested at 2.5 ppm NO_2 exposure and above, there is uncertainty about their persistence at concentrations closer to those found in U.S. ambient air.

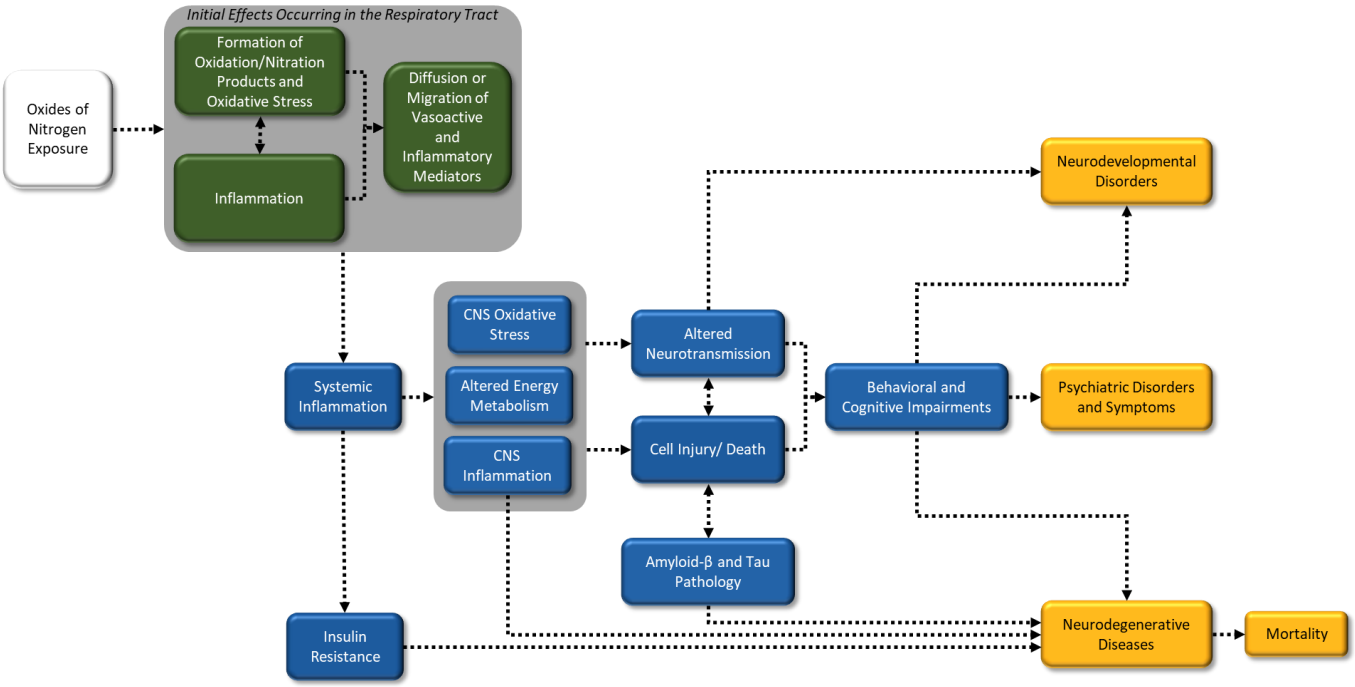
9.8.3 Synthesis Across Lines of Evidence

Overt neurotoxicity has been evaluated by epidemiologic and animal toxicological studies with varying results. Recent epidemiologic studies include analyses of U.S.-based cohorts (NOMAS and WHIMS), several analyses of the UK Biobank data and an analysis of children in the Netherlands. Overall, the limited body of evidence reported some associations between oxides of nitrogen exposure and reductions in region-specific brain volume and indicated that reduced brain volume may partially mediate the association between NO_2 exposure and depression in adults. Multiple analyses of UK Biobank data reported that associations persisted after adjustment for distance to roadway. However, none of the available studies included adjustments for specific traffic-related copollutants, and there are uncertainties regarding the temporality of the observed associations in the cross-sectional analyses. A small number of toxicological studies evaluated brain weight and brain-to-body weight ratios with inconsistent findings. The lack of coherence for this endpoint may stem from differences in exposure duration, species susceptibility, or the sensitivity of the weight-based measures in animal models compared to MRI-based measures in human studies. Despite this, microscopic analyses of rodent brains demonstrated impaired myelination and neurodegeneration, which may translate to structural alterations over time. The existing toxicological evidence utilized NO_2 concentrations well above U.S.-ambient concentrations, which introduces additional uncertainty into the extrapolation of these data.

9.9 Biological Plausibility

This Section describes biological pathways that potentially underlie nervous system effects resulting from exposure to oxides of nitrogen. Figure 9-23 depicts the potential pathways as a continuum of upstream events connected by arrows that may lead to downstream events observed in epidemiologic studies. Evidence supporting these proposed pathways was derived from Sections 9.3 to 9.8 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 exposure to oxides of nitrogen may lead to nervous system

effects 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).



List of abbreviations in alphabetical order: CNS = central nervous system.
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 9-23 Potential Biological Plausibility Pathways for Nervous System 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, including the nervous system.

Although the exact mechanisms linking NO_2 exposure and its initial effects in the respiratory tract to neurotoxicity have not been fully elucidated, current evidence points to three interrelated key pathways: oxidative stress, inflammation, and disrupted energy metabolism. Multiple studies have demonstrated that NO_2 exposure increases reactive oxygen species and diminishes antioxidant capacity in

brain tissue (Ye et al., 2022; Li et al., 2012; Farahani and Hasan, 1991). Mice exposed to NO_2 also exhibit elevated markers of microglial and astrocyte activation (Yan et al., 2016b). These glial cells are the CNS's primary mediators of inflammation, which function in part by releasing pro-inflammatory cytokines. Indeed, cytokines such as TNF-α, Il-1β, and Il-6 have been found to be elevated in brain tissue following NO_2 exposure (Ye et al., 2022; Li et al., 2021). Yan et al. (2016b) demonstrated that this inflammation can be induced though increased COX-2 activity and increased prostaglandin E_2 synthesis (Yan et al., 2016b). Notably, inhibition of monoacylglycerol lipase, which produces the COX-2 substrate arachidonic acid, attenuated these inflammatory responses. In parallel, NO_2 exposure has also been shown to alter mitochondrial morphology, decrease ATP production, and inhibit mitochondrial biogenesis (Yan et al., 2015). Given the brain's high energy demands, such mitochondrial dysfunction can critically undermine neuronal cell function and survival.

Collectively, these key effects may lead to disruptions in neurotransmission. NO_2 exposure elevated levels of the inhibitory neurotransmitter serotonin in both fetal and adult brain tissues (Kreis et al., 2022; Li et al., 2022a). In contrast, levels of hypothalamic noradrenaline were decreased in adult rats exposed to NO_2 (Vyskocil et al., 1985). Furthermore, NO_2 exposure decreased expression of glutamate receptors in the cortex and hippocampus coupled with thinning of the post-synaptic density (Yan et al., 2016a). Developmental exposure to NO_2 also alters the expression of myelin-related proteins (Mbp, Cnp, Tmem10, Mag), delays the maturation of oligodendrocytes (the cells responsible for myelination), and changes the structure of myelin sheaths in multiple brain regions (Li et al., 2022a; Li et al., 2021). Myelin sheaths facilitate quick and efficient electrical transmission along nerve cells, and myelination is an essential step in neurodevelopment. These findings indicate NO_2 exposure causes synaptic dysfunction and impaired neural communication, which in turn may underlie cognitive and behavioral effects.

Excessive damage to cellular lipids, proteins, and Deoxyribonucleic acid (DNA) can trigger cell death. Oxidative damage to brain lipids and proteins, measured by lipid peroxidation and protein carbonylation has been observed following NO_2 exposure (Li et al., 2012; Farahani and Hasan, 1990). Furthermore, NO_2 affects the lipid composition of brain tissues, which could impact cellular structure and function (Farahani and Hasan, 1992, 1990). Li et al. (2012) reported that NO_2 exposure increased the expression of the pro-apoptotic transcription factors (c-fos, c-jun, and p53) and regulatory proteins (Bax). Histopathological analysis of these animals showed damaged neurons characterized by pyknotic nuclei and eosinophilic cytoplasm, and immunohistochemical staining further revealed DNA fragmentation, an indicator of apoptosis. Widespread cell loss in the nervous system can cause functional and structural changes that contribute to cognitive and behavioral effects.

Cell death is also a common element in neurodegenerative diseases. Histochemical analysis of the cortex and hippocampus of AD-model mice showed an increase in degenerating neurons following exposure to NO_2 accompanied with increased neuroinflammation (Yan et al., 2016b). In an epidemiologic study, long-term NO_2 exposure increased plasma levels of Aβ1-40, with the repeated measures analysis showing stronger associations over time (Hajat et al., 2023). Likewise, NO_2 exposure in rodents affected

processing of amyloid precursor protein and increased deposition of amyloid plaques (Yan et al., 2016b). Yan et al. (2020) reported that ApoE, a gene which encodes apolipoprotein E, was significantly upregulated in postnatal male mice exposed to NO_2 during gestation. Apolipoprotein E is a lipid-transport protein that promotes deposition of amyloid-β (Greenwald, 1960). Both Amyloid-β and amyloid plaques are key markers of AD and contribute to cell death in AD (Wirths et al., 2004). Another potential pathway connecting NO_2 exposure and AD involves disrupted insulin signaling. Yan et al. (2016a) reported that NO_2 exposure interfered with the IRS-1/PI3K/AKT insulin signaling pathway, leading to insulin resistance in the CNS and an increase in tau phosphorylation. In humans, hyperphosphorylated tau forms the neurofibrillary tangles present in AD. The effects of NO_2 on insulin signaling are discussed in more detail in Chapter 8 on Metabolic Syndrome and Diabetes.

Together, the proposed pathways support the biological plausibility of epidemiologic evidence of neurological effects and were used to inform causality determinations in this chapter.

9.10 Summary of Lifestages and Populations

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 of nitrogen and nervous system effects, this discussion focuses on long-term exposure studies only. Table 9-1 at the end of this Section Summarizes the evidence for each factor to increase risk of oxides of nitrogen-related health effects.

9.10.1 Long-term Exposure

Sex

Many health conditions and diseases differ by sex, and there is some indication that sex may also influence the relationship between air pollution and health effects. In the 2016 Oxides of Nitrogen ISA, no studies evaluated whether sex modified the associations between oxides of nitrogen exposure and nervous system effects. A limited number of recent epidemiologic studies indicate that associations between oxides of nitrogen exposure and cognitive function (Lertxundi et al., 2019) or ASD (Rahman et al., 2022; Pagalan et al., 2018; Guxens et al., 2015) are stronger in males than in females. Stronger associations in males were more consistently reported in studies examining anxiety, depression, and psychological distress in both children (Loftus et al., 2020) and adults (Qiu et al., 2023a; Yang et al., 2023; Sakhvidi et al., 2022; Gu et al., 2020). Animal toxicological research provides coherence for these findings, with recent studies demonstrating significant effects on cognitive function and anxiety- and depression-like behavior in males but not in females (Li et al., 2022a; Li et al., 2021; Yan et al., 2020). Although the evidence is generally consistent across lines of evidence, uncertainties remain regarding the independent effects of oxides of nitrogen exposure on these health outcomes. Overall, the evidence is suggestive that males may be at increased risk for oxides of nitrogen-related neurodevelopmental and psychiatric effects.

Pre-existing disease/Comorbidities

Individuals with a pre-existing disease may be at higher risk for air pollution-related health effects due to their compromised biological state, with risk varying by disease type and severity. In the 2016 Oxides of Nitrogen ISA, no studies examined whether underlying conditions modified the relationship between oxides of nitrogen exposure and nervous system effects. Recent epidemiologic research consistently indicates conditions such as AD, dementia, congestive heart failure, COPD, diabetes, and hypertension may increase the NO_2-associated risk of depression, anxiety, and related outcomes (Feng et al., 2023; Qiu et al., 2023a; Petkus et al., 2021b). Furthermore, evidence suggests that hyperglycemia may exacerbate the risk of dementia associated with NO_X exposure in a Mexican American population (Yu et al., 2020). No animal toxicological studies have investigated the relationship between comorbidities and NO_2-related nervous system effects. Overall, the evidence is suggestive that pre-existing conditions and comorbidities can heighten susceptibility to oxides of nitrogen-related psychiatric and neurodegenerative effects.

Genetics

Genetic variation contributes to numerous diseases and influences physiological responses. In the 2016 Oxides of Nitrogen ISA, stronger associations for ASD diagnosis were reported in children with the CC MET genotype compared with those having the CC/GG genotype (Volk et al., 2014). Furthermore, a recent study reported that the relationship between NO_2 exposure in the first postnatal year and ASD diagnosis was strongest among individuals with low CNV duplication burden (Kim et al., 2017). For

neurogenerative outcomes, some studies reported that individuals carrying the APOE-ε4 allele, which is associated with elevated risk for AD, experience faster NO_2-related cognitive decline (Younan et al., 2022; Kulick et al., 2020a) or increased NO_2-related ADRD risk (Ma et al., 2023); however, one study reported improved episodic memory (Franz et al., 2023) with increasing NO_2 exposure. Further research in individuals with ADRD suggests that those with higher genetic risk scores may be more vulnerable to NO_2 exposure (Yuan et al., 2023; Zhang et al., 2023b). No animal toxicological studies have investigated the interplay between genetic factors and NO_2-related nervous system effects. Overall, the evidence is suggestive that genetic factors may heighten susceptibility to oxides of nitrogen-related neurodevelopmental, psychiatric, and neurodegenerative effects.

Factors with Inadequate Evidence

Recent studies have examined whether factors such as age, race/ethnicity, SES, maternal nutrition, smoking, and region/urbanicity modify the nervous system effects of oxides of nitrogen exposure.

- A small number of studies suggest that older adults may experience stronger associations between NO_2 exposure and outcomes like depression, anxiety, and physiological distress (Yang et al., 2023; Hautekiet et al., 2022; Klompmaker et al., 2019).
- Additionally, limited evidence indicates that associations with anxiety and depression may be stronger among Black individuals or children with African American mothers (Qiu et al., 2023a; Loftus et al., 2020), although research on cognitive function has not demonstrated clear evidence of modification by race (Lu et al., 2021; Loftus et al., 2019).
- There is also modest support for increased vulnerability to neurodevelopmental outcomes (e.g., ASD, externalizing behaviors) (O'Sharkey et al., 2024; Loftus et al., 2020) and adult depression (Sakhvidi et al., 2022) among individuals with lower SES.
- Limited data further suggest that maternal nutrition status, specifically low prenatal folate, may strengthen the adverse neurodevelopmental effects (e.g., ASD, externalizing behaviors) of NO_2 exposure (Loftus et al., 2020; Goodrich et al., 2017).
- One study reported that smokers face a higher risk of PD in relation to NO_2 exposure (Salimi et al., 2020), while another found that associations with NO_2 exposure and PD remained null in models stratified by smoking status (Liu et al., 2016).
- While there is some evidence of stronger associations between NO_2 exposure and ASD (Ritz et al., 2018) in urban populations, other studies have reported stronger associations in less urban or more rural populations for ADHD (Thygesen et al., 2020).

Overall, the current body of research provides suggestive evidence for the modifying effect of sex, pre-existing diseases or comorbidities, and genetics on the association between oxides of nitrogen exposure and nervous system effects, including cognitive function, ASD, anxiety, depression, psychological distress, cognitive decline, dementia, and AD. The evidence for effect modification by other evaluated factors, including age, race/ethnicity, socioeconomic status, maternal nutritional status, smoking status, and region/urbanicity, is insufficient in quantity and consistency to permit stronger conclusions about how these factors modify oxides of nitrogen-related nervous system effects.

Table 9-1 Summary of Evidence for Lifestages and Populations at Increased Risk of Nervous System Effects from Oxides of Nitrogen Exposure

	Key Evidence	Key References
Suggestive evidence		
Sex	Stronger associations in males for cognitive function and ASD.	†Lertxundi et al. (2019) †Pagalan et al. (2018) †Rahman et al. (2022) †Guxens et al. (2015)
	Stronger associations in males for anxiety, depression, and psychological distress in children and adults.	†Qiu et al. (2023a) †Yang et al. (2023) †Sakhvidi et al. (2022) †Gu et al. (2020) †Loftus et al. (2020)
	Supporting evidence from limited toxicological studies of cognitive function and anxiety- and depression-like behavior.	†Li et al. (2021) †Li et al. (2022a) †Yan et al. (2020)
Pre-existing disease/Comorbidities	Higher risk of anxiety and depression among those with comorbid dementia, cardiovascular disease, and metabolic disease.	†Petkus et al. (2021b) †Qiu et al. (2023a) †Feng et al. (2023)
	Higher risk of AD and dementia among those with metabolic dysfunction.	†Yu et al. (2020)
Genetics	Some evidence of increased risk of cognitive decline, AD, and dementia among APOE genotypes and genetic risk scores.	†Kulick et al. (2020a) †Younan et al. (2022) †Ma et al. (2023) †Yuan et al. (2023) †Zhang et al. (2023b)
	Limited evidence of increased risk of ASD among those with CC MET genotype or low CNV duplication burden.	Volk et al. (2014) †Kim et al. (2017)
Inadequate evidence		
Age	Inconsistent evidence in stratified analyses of cognitive function and anxiety and depression in adults.	†Yang et al. (2023) †Hautekiet et al. (2022) †Klompmaker et al. (2019)
Race/Ethnicity	Limited evidence did not find modification of associations with cognitive function in children by race or ethnicity.	†Lu et al. (2021) †Loftus et al. (2019)
	Limited evidence of stronger associations with anxiety and depression among those with Black mothers	†Loftus et al. (2020) †Qiu et al. (2023a)

	Key Evidence	Key References
Socioeconomic status	Limited support for stronger associations for neurodevelopment and depression among those with lower SES.	†O'Sharkey et al. (2024) †Loftus et al. (2020) †Sakhvidi et al. (2022)
Maternal nutrition status	Limited evidence of stronger adverse effects for mental development, ASD, ADHD among those with low prenatal folate and fruit intake and those with high vitamin B6 intake.	†Goodrich et al. (2017) †Loftus et al. (2020)
Smoking status	Limited, inconsistent evidence of increased risk of PD and AD/dementia by smoking status.	†Salimi et al. (2020) †Liu et al. (2016)
Region/Urbanicity	Limited, inconsistent evidence of increased risk of ASD and ADHD based on region or urbanicity.	†Ritz et al. (2018) †Thygesen et al. (2020)

List of abbreviations in alphabetical order: APOE = apolipoprotein E; AD = Alzheimer's disease; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CNV = copy number variation; PD = Parkinson's disease; SES = socioeconomic status.
†Studies published since the 2016 Oxides of Nitrogen ISA.

9.11 Summary and Causality Determination

9.11.1 Long-term Exposure

Long-term exposure to oxides of nitrogen has been investigated for its potential effects on the nervous system, including neurodevelopmental outcomes, psychiatric disorders and symptoms, neurodegenerative disease, overt effects, and mortality. Although most of the available research is recent, recent epidemiologic and toxicological studies on neurodevelopmental effects were reviewed in the 2016 Oxides of Nitrogen ISA in the Reproductive and Developmental Effects Section [Section 6.4, (U.S. EPA, 2016)]. That evidence was both limited and inconsistent regarding effects on cognitive function, attention, motor function, psychological distress, and ASD. Recent research has expanded our understanding of nervous system effects, though significant uncertainties remain.

Epidemiologic studies of neurodevelopment have reported associations between long-term oxides of nitrogen exposure and diminished cognitive function, reflected most strongly in measures of infant development and academic achievement, and increased risk of ASD (see Table 9-2). However, this evidence is somewhat limited, not entirely consistent, and few studies have examined potential confounding by traffic-related copollutants. A small body of toxicological evidence provides some coherence for these endpoints by demonstrating learning and memory deficits, impairments in social communication and increased repetitive behaviors in studies using exposure concentrations well-above those in the ambient air. Evidence regarding motor function and externalizing behaviors, including ADHD, is less consistent across both lines of evidence.

Among adults, epidemiologic investigations consistently associate long-term oxides of nitrogen exposure with an increased risk of anxiety, depression, and psychological distress. These findings have been observed across diverse cohorts and endpoint metrics, which reinforces these associations. Moreover, these studies report mostly supralinear concentration-response relationships that persist after adjustment for copollutants (i.e., $PM_{2.5}$, PM_{10}) and socioeconomic variables. Toxicological studies align with these findings, reporting anxiety- and depression-like behaviors in males exposed to high NO_2 concentrations. In contrast, evidence linking oxides of nitrogen exposure to schizophrenia and psychosis is more inconsistent, and no evidence is available from experimental studies to provide coherence.

Multiple studies have reported positive associations between oxides of nitrogen exposure and increased risk of ADRD, even after adjustment for potential confounders like particulate matter and ozone in a subset of these studies. Additionally, limited evidence suggests that exposure is associated with impaired cognitive function in adults, and although these deficits do not meet the clinical threshold for dementia, mild cognitive impairment is recognized as a risk factor for ADRD. Experimental findings provide coherence with the above associations by demonstrating that NO_2 exposure can trigger key AD-related pathologies such as amyloid-β accumulation and tau hyperphosphorylation. Furthermore, limited evidence in humans and rodents suggests that exposure to oxides of nitrogen may reduce brain volume in adults, lending further support to these neurodegenerative changes. Results of studies on PD and ALS are less consistent, with methodological variability and a lack of supporting experimental evidence. Studies investigating nervous disease mortality are inconsistent and mostly null in models adjusted for copollutants.

Overall, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between long-term oxides of nitrogen exposure and nervous system effects. While epidemiologic and toxicological studies examining certain neurodevelopmental outcomes, adult psychiatric disorders, and ADRD demonstrate some areas of consistency and coherence, the potential influence of chance, confounding, and other biases cannot be ruled out. The reported effects are generally small in magnitude and are often imprecise, though the consistency in the direction of associations across varied populations and study designs reinforces their significance. In contrast, uncertainties regarding the impact of confounding by copollutants and coexposures remain a key limitation. While several studies reported that associations were robust for these adjustments, a significant number of studies do not consider copollutants or coexposures. Furthermore, very few studies consider the traffic-related copollutants that are typically most strongly correlated with NO_2 and NO_X. This concern is partially mitigated by experimental evidence demonstrating adverse nervous system effects following controlled NO_2 exposures in animals, however, evidence using ambient concentrations of NO_2 is lacking. Nonetheless, the biological plausibility of these associations is shown by studies demonstrating oxidative stress, inflammation, altered neurotransmission, and cell death in response to NO_2, though these pathways lack specificity (i.e., may be shared with other pollutants).

Table 9-2 Summary of Evidence Contributing to the Long-term Causality Determination for Oxides of Nitrogen Exposure and Nervous System Effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Neurodevelopmental Effects			
Multiple epidemiologic studies find associations between exposure to relevant concentrations of oxides of nitrogen and neurodevelopmental effects; however, the evidence is limited and not entirely consistent.	The strongest or most consistent evidence is provided by studies of infant development, academic achievement, and ASD.	Guxens et al. (2012) Guxens et al. (2014) †Morgan et al. (2023) †Lu et al. (2021)	6.1 ppb–23.2 ppb
		Volk et al. (2013) Volk et al. (2014) †Kim et al. (2017) †O'Sharkey et al. (2024) †Pagalan et al. (2018) †Murphy et al. (2024) †Ritz et al. (2018) †Wang et al. (2021a)	10.1–17.0 ppb NO_2 15.3–18.3 ppb NO
	Results from a limited number of studies are inconsistent for endpoints including motor function and externalizing behaviors	Sections 9.3.2 and 9.3.4	
Experimental animal studies provide some support for observations in epidemiologic studies, but coherence is limited overall	Exposure during gestation or young adulthood resulted in learning and memory deficits.	†Yan et al. (2020) †Yan et al. (2016b)	2,500 ppb NO_2
	Limited evidence for ASD and motor function deficits.	†Li et al. (2021) Tabacova et al. (1985)	53 ppb–2,500 ppb NO_2
Chance, confounding and other biases cannot be ruled out	The evaluation of confounding by traffic-related copollutants is limited across the body of evidence.	Sections 9.3.1.1.2, 9.3.3.1.2, 9.3.4.1.3, and 9.3.4.3.2	

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Psychiatric Disorders and Symptoms			
Multiple epidemiologic studies find associations between exposure to relevant concentrations of oxides of nitrogen and psychiatric disorders and symptoms; however, the evidence is limited and not entirely consistent.	The strongest or most consistent evidence is provided by studies of depression and psychological distress in adults.	Section 9.4.1.1	13.0 ppb NO 9.7–16.2 ppb NO_2 27.4–43.7 µg/m^3 NO_X
	Results from a limited number of studies are inconsistent for endpoints including anxiety and depression in children and schizophrenia in adolescents and adults.	Section 9.4.1.1 Section 9.4.2.1	7.4–23.1 ppb NO_2 8.8–20.2 ppb NO_2 25.8–44.1 µg/m^3 NO_X
The concentration-response relationship is well-characterized.	Mostly supralinear and a few linear relationships observed among studies of anxiety and depression in adults.	Section 9.4.1.1.1	
Chance, confounding, and other biases cannot be ruled out.	Evaluation of confounding by traffic-related copollutants is limited across the body of evidence.	Sections 9.4.1.1.4 and 9.4.2.1.3	
Animal toxicological studies provide some support for observations in epidemiologic studies, but coherence is limited overall.	Anxiety- and depression like behaviors in juvenile and young adult animals.	†Li et al. (2021) †Li et al. (2022a)	2,500 ppb NO_2

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Neurodegenerative Disease			
Multiple epidemiologic studies find associations between exposure to relevant concentrations of oxides of nitrogen and neurodegenerative disease; however, the evidence is limited and not entirely consistent.	The strongest evidence is from studies of AD and dementia with support from studies of general cognitive decline.	†Shi et al. (2021) †Chen et al. (2017) †Chen et al. (2023) Chang et al. (2014) †Ilango et al. (2023) †Yu et al. (2020) †Paul et al. (2020) †Wu et al. (2022)	9.3–17.1 ppb NO_2 2.6 ppb; 29.4–43.5 µg/m^3 NO_X
		†Wang et al. (2021b) †Younan et al. (2022) †Wang et al. (2023b) †Kulick et al. (2020b) †Huels et al. (2018) †Zare Sakhvidi et al. (2022) †Tzivian et al. (2017)	10.4–16.0 ppb NO_2 24.3–50.4 µg/m^3 NO_X
	Evidence related to PD and other neurodegenerative diseases is limited and inconsistent.	Sections 9.5.3.1 and 9.5.4.1	
The concentration-response curve is moderately characterized.	Studies indicate a generally near-linear or monotonic increase in dementia risk with rising NO_2 exposure.	Section 9.5.2.1.3	
Chance, confounding and other biases cannot be ruled out.	The evaluation of confounding by traffic-related copollutants is limited across the body of evidence.	Sections 9.5.2.1.5, 9.5.2.1.6, 9.5.3.1.1, and 9.5.3.1.5	
Animal toxicological studies provide some support for observations in epidemiologic studies, but coherence is limited overall	Evidence of AD-like pathologies in wild-type and transgenic mice models.	†Yan et al. (2016b) †Yan et al. (2016a)	2,660 ppb NO_2

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Mortality			
Multiple epidemiologic studies find associations between exposure to relevant concentrations of oxides of nitrogen and mortality from diseases of the nervous system.	The strongest evidence is from generally consistent findings for AD/dementia mortality. Evidence from studies of PD and ALS mortality is mixed.	Section 9.7.1	
The concentration-response curve is moderately characterized.	Studies show mostly positive NO_2 associations with both linear and nonlinear patterns for AD/dementia mortality	Sections 9.7.1.4 and 9.7.1.6	
Chance, confounding and other biases cannot be ruled out.	The evaluation of confounding by traffic-related copollutants is limited across the body of evidence.	Sections 9.7.1.5 and 9.7.1.6	

List of abbreviations in alphabetical order: AD=Alzheimer's disease; ALS = amyotrophic lateral sclerosis; ASD = autism spectrum disorder; NO = nitric oxide; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; ppb = parts per billion; PD = Parkinson's disease.
[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.

9.11.2 Short-term Exposure

Studies of short-term exposure to oxides of nitrogen and nervous system effects remain limited. Nearly all available studies focus on hospitalizations, with the strongest and most consistent evidence emerging from studies of admissions for psychiatric disorders (see Table 9-3). The evidence for hospitalizations due to neurodegenerative disease is sparser, but generally positive associations were reported in single studies of AD and PD admissions. Aside from hospitalizations, a single study reported that short-term NO_2 exposure was associated with poorer executive function in neurotypical school children, and another study reported negative and precise associations between short-term NO_2 exposure and nervous disease mortality. Numerous uncertainties persist regarding exposure- or dose-response relationships, copollutant confounding, and biological plausibility. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between short-term oxides of nitrogen exposure and nervous system effects.**

Table 9-3 Summary of Evidence Contributing to the Short-term Causality Determination for Oxides of Nitrogen Exposure and Nervous System Effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Hospital Admissions			
Evidence is limited and available studies are of limited quality.	The evidence comes from studies of hospital admissions and ED visits for depression.	†Gu et al. (2020) †Ma et al. (In Press) †Szyszkowicz et al. (2016) †Qiu et al. (2022) †Lu et al. (2020)	18.2–19.0 ppb NO_2
	Evidence is limited for studies of hospital admissions for schizophrenia.	†Qiu et al. (2022)	
	Evidence is limited for studies of hospital admissions for AD, dementia and PD.	†Gandini et al. (2018) †Goria et al. (2021)	
Chance, confounding and other biases cannot be ruled out.	The evaluation of confounding by traffic-related copollutants is limited across the body of evidence.	Sections 9.4.1.1.4, 9.4.2.1.3, 9.5.2.1.3, and 9.5.3.1.3	

List of abbreviations in alphabetical order: AD = Alzheimer's disease; ED = emergency department; NO_2 = nitrogen dioxide; PD = Parkinson's disease.

[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.

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