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Supplement to the 2019 Integrated Science Assessment for Particulate Matter

Office of Research and Development
Center for Public Health & Environmental Assessment, Research Triangle Park, NC

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ACRONYMS AND ABBREVIATIONS

Acronym/ Abbreviation	Meaning
AARP	American Association of Retired Persons
ABI	ankle-brachial index
ACS	American Cancer Society
adj	adjustment
AF	atrial fibrillation
Ag Health	Agricultural Health Study
AHSMOG	Adventist Health Study and Smog
AIC	Akaike information criterion
AL	Alabama
AMI	acute myocardial infarction
AN	ammonium nitrate
AOD	aerosol optical depth
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
AQCD	Air Quality Criteria Document
AQS	Air Quality System
AS	ammonium sulfate
ASD	autism spectrum disorder
avg	average
BAD	bronchial artery diameter
BASIC	Brain Attack Surveillance in Corpus Christi
BC	black carbon
b_{ext}	light extinction coefficient
BME	Bayesian maximum entropy
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CA	California
CAC	coronary artery calcification
CAD	coronary artery disease
Cancer Prev	cancer prevention
CanCHEC	Canadian Census Health and Environment Cohort
CAN-Marg	Canadian Marginalization Index
CAPs	concentrated ambient particles
CASAC	Clean Air Scientific Advisory Committee
CATHGEN	Catheterization Genetics study
CBSA	core-based statistical area
CBVD	cerebrovascular disease
CCHEC	Canadian Census Health and Environment Cohort
CCHS	Canadian Community Health Survey
CFR	case fatality rate
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
cIMT	carotid intima-media thickness
CM	coarse mass
CMA	census metropolitan area size
CMAQ	Community Multiscale Air Quality model
CMR	cardiovascular mortality rate
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
C-R	concentration-response
CSN	Chemical Speciation Network
CTM	chemical transport model
CTS	California Teachers Study
C-V	cross-validation
CVD	cardiovascular disease
DBP	diastolic blood pressure
DC	District of Columbia
DE	diesel exhaust
df	degrees of freedom

Acronym/ Abbreviation	Meaning
DID	difference-in-difference
DNA	deoxyribonucleic acid
DOW	day of week
DRAM	doubly robust additive model
DVT	deep vein thrombosis
EC	elemental carbon
ECG	electrocardiogram
ED	emergency department
EFFECT	Enhanced Feedback for Effective Cardiac Treatment
EJ	environmental justice
EPA	Environmental Protection Agency
ESCAPE	European Study of Cohorts for Air Pollution Effects
ESRD	end-stage renal disease
exp	exposure
FA	filtered air; fatty acid
FD	find dust
FEV_1	forced expiratory volume in 1 second
FMD	flow-mediated dilation
FVC	forced vital capacity
GA	Georgia
GAM	generalized additive model
GLM	generalized linear model
GEOS-Chem	Goddard Earth Observing System-Chem
GP	general practitioner
GPS	generalized propensity score
GWR	geographically weighted regression
h	hour(s)
HA	hospital admission
HDL-c	High-density lipoprotein cholesterol
Health Prof	health professionals
HeartSCORE	Heart Strategies Concentration on Risk Evaluation
HEI	Health Effects Institute
HEPA	high efficiency particle filter
HF	heart failure; high frequency
HHD	hypertensive heart disease
HISA	Highly Influential Scientific Assessment
HNR	Heinz Nixdorf Recall (study)
HPFU	Health Professionals Follow-Up Study
HR	hazard ratio
HRV	heart rate variability
HS	hemorrhagic stroke
HSC	Harvard Six Cities
HYSLPLIT	HYbrid Single-Particle Lagrangian Integrated Trajectory
IAD	inter-adventitial diameter
ICD-10	International Classification of Disease version 10
ICD-9	International Classification of Disease version 9
ICU	intensive care unit
IDW	inverse distance weighting
IHD	ischemic heart disease
IL	Illinois
IMPROVE	Interagency Monitoring of Protected Visual Environments
InMAP	Intervention Model for Air Pollution
IPTW	inverse probability of treatment weighting
IPW	inverse probability weighting
IQR	interquartile range
IRD	Index of Racial Dissimilarity
IRP	Integrated Review Plan
IRR	incidence rate ratio
IS	ischemic stroke
IV	instrumental variable
JHS	Jackson Heart Study
km	kilometer(s)
km2	square kilometer(s)
LDH	lactate dehydrogenase

Acronym/ Abbreviation	Meaning
LDL-c	low-density lipoprotein cholesterol
LF	low frequency
LUR	land use regression
LUR-BME	land use regression—Bayesian maximum entropy
LV	left ventricular
m^2	Square meter(s)
MAP	mean arterial pressure
MAPLE	mortality-air pollution associations in low-exposure environments
max	maximum
MCAPS	Medicare Cohort Air Pollution Study
MCC	Multi-City Multi-Country Collaborative Research Network
mCCHS	Canadian Community Health Survey—mortality cohort
MCM	multi-cause multicity
MD	Maryland
MESA	Multi-Ethnic Study of Atherosclerosis
mg	milligram(s)
MI	myocardial infarction
min	minimum
MINAP	Myocardial Ischemia National Audit Project
MISR	Multiangle Imaging Spectroradiometer
MISS	monotonically increasing smoothing splines
mm Hg	millimeters of mercury
mo	month(s)
MO	Missouri; month
MR	mortality ratio
MRR	mortality risk ratio
NAAQS	National Ambient Air Quality Standards
NAPS	National Air Pollution Surveillance System
NC	number concentration; North Carolina

Acronym/ Abbreviation	Meaning
NCHS	National Center for Health Statistics
NEI	National Emissions Inventory
NH	non-Hispanic
NHIS	National Health Interview Survey
NHS	Nurses' Health Study
NIH	National Institutes of Health
NIH-AARP	National Institutes of Health–American Association of Retired Persons (diet and health cohort)
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NN	Normal-to-Normal
NO_2	nitrogen dioxide
NO_3	nitrate
NO_X	oxides of nitrogen ($NO + NO_2$)
NPMs	neighborhood PM monitors
NR	not reported
NSTEMI	non-ST segment elevation MI
O_3	ozone
OC	organic carbon
OHCA	out-of-hospital cardiac arrest
OLS	ordinary least squares
OM	organic matter
OMB	Office of Management and Budget
ONPHEC	Ontario Population Health and Environment Cohort
OR	odds of recurrent
Ox	Redox weighted average of NO_2 and O_2
PA	Pennsylvania
PAH	polycyclic aromatic hydrocarbon(s)
PE	prediction error
PEF	peak expiratory flow
PM	particulate matter

Acronym/ Abbreviation	Meaning
PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 um
$PM_{10–2.5}$	particulate matter with a nominal mean aerodynamic diameter greater than 2.5 um and less than or equal to 10 um
$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 um
POM	particulate organic matter
ppb	parts per billion
ppm	parts per million
PQAPP	Program-level Quality Assurance Project Plan
PREMIER	Prospective Registry Evaluating Myocardial Infraction: Events and Recovery
QA	quality assurance
QAPP	quality assurance project plans
QRS	time interval between the beginning of the Q wave and the peak of the S wave
r	correlation coefficient
R^2	coefficient of determination
RAMP	Real-time Affordable Multi-Pollutant
RC	regression calibration
RCS	restricted cubic splines
redox	reduction-oxidation
REGARDS	REasons for Geographic and Racial Differences in Stroke
re-HA	Readmission to the hospital
RF	radiative forcing
RH	relative humidity
RMSS	root mean square standardized
RR	relative risks
RRS	racial residential segregation
RV	right ventricular
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	surface area concentration
SCHIF	Shape Constrained Health Impact Function
SD	standard deviation
SDI	social deprivation index
SDNN	standard deviation of NN
SE	standard error
SED	socioeconomic deprivation
SEIR	susceptible-exposed-infected-recovered
SES	socioeconomic status
SHS	second-hand smoke
SHV	Social and Health Vulnerability
sICAM	soluble intercellular adhesion molecule 1
SO_2	sulfur dioxide
SO_4	sulfate
SPARCS	New York State Department of Health Statewide Planning and Research Cooperative System
SPE	standardized prediction error
ST	beginning of S wave to end of T wave
STEMI	ST elevated myocardial infarction
sVCAM	Soluble vascular cell adhesion molecule 1
SHV	Social Health Vulnerability
SWAN	Study of Women's Health Across the Nation
TRAP	traffic-related air pollution
TrIPS	Trucking Industry Particle Study
TRIUMPH	Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction
TX	Texas

Acronym/ Abbreviation	Meaning
UFIREG	Ultrafine Particles—An Evidence-Based Contribution to the Development of Regional and European Environmental and Health Policy
UFP	ultrafine particle
U.S.	United States of America
U.S. EPA	U.S. Environmental Protection Agency
USRDS	U.S. Renal Data System
W	west
WHI	Women's Health Initiative
WHO	World Health Organization
WS Fe	water-soluble iron
yr	year(s)
ZIP	Zone Improvement Plan

EXECUTIVE SUMMARY

In June 2021, the U.S. Environmental Protection Agency (EPA) announced it will reconsider the December 2020 decision to retain the particulate matter (PM) National Ambient Air Quality Standards (NAAQS). As part of the reconsideration process, EPA indicated that it would develop a supplement to the 2019 Integrated Science Assessment for PM (2019 PM ISA) to thoroughly evaluate the most up-to-date science that became available after the literature cutoff date of the 2019 PM ISA that could either further inform the adequacy of the current PM NAAQS or address key scientific topics that have evolved since the 2020 PM NAAQS review was completed.

Within this Supplement, EPA presents an evaluation of recent studies (i.e., published since the literature cutoff date of the 2019 PM ISA) that potentially are of greatest relevance to the reconsideration of the PM NAAQS in the context of the findings of the 2019 PM ISA. The studies that formed the basis of the evaluation consist of U.S. and Canadian studies, specifically: (a) epidemiologic studies for health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term $PM_{2.5}$ exposure[1] and cardiovascular effects and mortality); (b) epidemiologic studies that employed statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control)[2] or conducted accountability analyses; (c) studies that address key scientific topics that have evolved since the literature cutoff date for the 2019 PM ISA, including experimental studies conducted at near-ambient $PM_{2.5}$ concentrations, epidemiologic studies that examined the association between $PM_{2.5}$ exposure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) death, and epidemiologic or exposure studies that examined disparities in $PM_{2.5}$ exposure or health risks by race and ethnicity or socioeconomic status; and (d) studies that examined public preferences for visibility impairment and/or developed methodologies or conducted quantitative analyses of light extinction. This Supplement to the 2019 PM ISA does not represent a full multidisciplinary evaluation of evidence that results in the formation of weight-of-evidence conclusions (i.e., causality determinations), but instead puts the results of recent studies that encompass specific criteria in the context of the scientific conclusions presented within the 2019 PM ISA. As such, the Supplement indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with

[1] Consistent with the scope of the 2019 PM ISA (Section P.3.1), short-term exposures are defined as those exposures occurring over hours up to 1 month, while long-term exposures are defined as those exposures occurring over 1 month to years.

[2] In the peer-reviewed literature, these epidemiologic studies are often referred to as causal inference studies or studies that used causal modeling methods. For the purposes of this Supplement this terminology is not used to prevent confusion with the main scientific conclusions (i.e., the causality determinations) presented within an ISA. In addition, as is consistent with the weight-of-evidence framework used within ISAs and discussed in the Preamble to the Integrated Science Assessments, an individual study on its own cannot provide the evidence needed to make a causality determination, but instead represents a piece of the overall body of evidence.

and reduces uncertainties), or does not support (is not consistent with) the causality determinations detailed in the 2019 PM ISA for the health effects categories evaluated within this Supplement.

This Supplement to the 2019 PM ISA finds that recent studies further support, and in some instances extend, the evidence that formed the basis of the causality determinations presented within the 2019 PM ISA that characterizes relationships between PM exposure and health (i.e., cardiovascular effects and mortality) and welfare effects (i.e., visibility impairment). In brief, this Supplement finds the following:

- Recent U.S. and Canadian epidemiologic studies examining short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality provide evidence that further supports, and in some instances extends, the evidence that contributed to the conclusion of a *causal relationship* detailed in the 2019 PM ISA. Relative to the studies evaluated in the 2019 PM ISA, many of the studies report positive associations at lower $PM_{2.5}$ concentrations (i.e., annual $PM_{2.5}$ concentrations ranging from 5.9 to 16.5 micrograms per cubic meter ($\mu g/m^3$); mean 24-hour avg $PM_{2.5}$ concentrations ranging from 7.1 to 15.4 $\mu g/m^3$).
    - Recent U.S. and Canadian epidemiologic studies examining short- and long-term $PM_{2.5}$ exposure and cardiovascular effects provide evidence that is consistent with the studies evaluated in the 2019 PM ISA. Studies examining short-term $PM_{2.5}$ exposure report consistent positive associations for cardiovascular-related emergency department (ED) visits and hospital admissions, specifically for ischemic heart disease (IHD), myocardial infarction (MI), and heart failure (HF). For long-term exposure, strong evidence remains for cardiovascular-related mortality with support from studies of cardiovascular morbidity outcomes including coronary heart disease (CHD), stroke, and atherosclerosis progression, among individuals with preexisting diseases or patients followed after a cardiac event or procedure. Associations persisted across studies conducted in different geographic locations, populations with diverse demographic characteristics, and study designs (i.e., different exposure assessment methods, and confounder control).
    - Relatively few recent U.S. and Canadian epidemiologic studies examined short-term $PM_{2.5}$ exposure and mortality; however, these studies continue to provide evidence of positive associations with both all-cause and total (nonaccidental) mortality as well as with cause-specific mortality outcomes.
    - A number of recent long-term $PM_{2.5}$ exposure and mortality studies conducted in cohorts consisting of populations with diverse demographic characteristics and encompassing large geographic areas report consistent, positive associations, with most reporting mean annual $PM_{2.5}$ concentrations ranging from 5.9 to 11.65 $\mu g/m^3$.
        - Across epidemiologic studies examining both cardiovascular effects and mortality, sensitivity analyses as well as individual studies further inform uncertainties in the evidence base (i.e., copollutant confounding, control for confounders such as temporal trends and temperature, and the concentration-response [C-R] relationship). Such analyses increase confidence in the relationship for both short- and long-term $PM_{2.5}$ exposures and both health effect categories, and further support the causality determinations presented in the 2019 PM ISA.
        - Since the completion of the 2019 PM ISA, numerous U.S. and Canadian epidemiologic studies conducted accountability analyses or employed statistical approaches that attempt to account more extensively for confounders and are

more robust to model misspecification (i.e., used alternative methods for confounder control) to examine both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality. These studies, which used a variety of statistical methods to control for confounding bias, consistently report positive associations, which further supports the broader body of epidemiologic evidence for both cardiovascular effects and mortality.

  - Several recent U.S. and Canadian studies provide additional insight on the health effects of $PM_{2.5}$, including a recent controlled human exposure study conducted at near-ambient concentrations, which provided initial evidence of both lung and cardiac function changes in young, healthy participants.
  - In response to the global COVID-19 pandemic, numerous studies provide initial assessments of short- and long-term $PM_{2.5}$ exposure and SARS-CoV-2 infection and COVID-19 death. While some of these studies report initial evidence of positive associations, these studies are subject to methodological limitations and require additional exploration.
  - The 2019 PM ISA provided evidence that specific lifestages and populations are at increased risk of a $PM_{2.5}$-related health effect. Recent U.S. and Canadian epidemiologic studies support and expand the evidence base within the 2019 PM ISA and indicate that there are both $PM_{2.5}$ exposure and health risk disparities by race and ethnicity among minority populations, specifically Black populations. Additionally recent evidence supports the evidence presented in the 2019 PM ISA that there may be $PM_{2.5}$ exposure and health risk disparities by socioeconomic status (SES), specifically among people of low SES.

- Recent studies continue to support a relationship between PM and visibility impairment and provide additional insights on the impact of choice of metric on preference study results, impacts of changing PM composition on the relationship between PM and visibility impairment, and alternative approaches to estimating light extinction.

1. INTRODUCTION AND SCOPE

1.1. Introduction

The U.S. Environmental Protection Agency (EPA) completed the Integrated Science Assessment for Particulate Matter (PM ISA) in December 2019 (hereafter referred to as the 2019 PM ISA) (U.S. EPA, 2019). The 2019 PM ISA builds upon the evidence evaluated and scientific conclusions presented in prior assessments, including the 2009 PM ISA (U.S. EPA, 2009) and earlier assessments, e.g., 2004 PM Air Quality Criteria Document [AQCD; (U.S. EPA, 2004)] and 1996 PM AQCD (U.S. EPA, 1996). Within the 2019 PM ISA, evidence spanning scientific disciplines (e.g., atmospheric chemistry, exposure science, animal toxicological, human clinical, epidemiology) was evaluated to assess the causal nature of relationships between short- and long-term[3] PM exposure and health and PM and nonecological welfare effects using a weight-of-evidence approach extensively detailed in the *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015) and the Appendix of the 2019 PM ISA.[4]

The key science judgments (i.e., causality determinations) detailed within the 2019 PM ISA directly informed the development of conclusions outlined within the *Policy Assessment for the Review of the PM NAAQS* (2020 PM PA) (U.S. EPA, 2020b). These key science judgments formed the basis of the discussion on potential alternative primary and secondary National Ambient Air Quality Standards (NAAQS) for PM within the 2020 PM PA and were considered in EPA's final decision in the 2020 review to retain the PM NAAQS (see Section 1.3.5, (U.S. EPA, 2022)).

On June 10, 2021, EPA announced it is reconsidering the December 2020 decision to retain the PM NAAQS "because available scientific evidence and technical information indicate that the current standards may not be adequate to protect public health and welfare, as required by the Clean Air Act. EPA explained that as part of the reconsideration process " the agency will develop a supplement to the 2019 [PM ISA] that will take into account the most up-to-date science" (EPA Press Office, 2021).[5] As a result, the evidence presented within the 2019 PM ISA, along with the targeted identification and evaluation of new scientific information in this Supplement, provide the scientific basis to support a robust and thorough reconsideration of the 2020 PM NAAQS.

[3] Consistent with the scope of the 2019 PM ISA (Section P.3.1), short-term exposures are defined as those exposures occurring over hours up to 1 month, whereas long-term exposures are defined as those exposures occurring over 1 month to years.

[4]Hereafter welfare effects refers to nonecological welfare effects, unless otherwise noted. The ecological effects resulting from the deposition of PM and PM components are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen, oxides of sulfur, and PM (U.S. EPA, 2020a).

[5] See Section 1.4 of the Policy Assessment for the Reconsideration of the National Ambient Air Quality Standards for Particulate Matter for additional details (U.S. EPA, 2022).

1.2. Rationale and Scope

In completing the review of the PM NAAQS in December 2020, EPA provisionally considered numerous studies published after the literature cutoff date (approximately January 2018) for the 2019 PM ISA. In reviewing these studies, as explained in *Responses to Significant Comments on the 2020 Proposed Decision on the National Ambient Air Quality Standards for Particulate Matter*, EPA "concluded that none of the studies materially change any of the broad scientific conclusions of the ISA regarding the health and welfare effects of PM or warrant reopening the air quality criteria for this review" (U.S. EPA, 2020c).

To inform the reconsideration of the PM NAAQS, EPA determined that a thorough evaluation is warranted of some studies that became available after the literature cutoff date of the 2019 PM ISA that could either further inform the adequacy of the current PM NAAQS or address key scientific topics that have evolved since the literature cutoff date for the 2019 PM ISA. Additionally, the evaluation of recent studies identified would occur in the form of a supplement and EPA would rely on the Supplement to the 2019 PM ISA and the 2019 PM ISA as the scientific foundation for the reconsideration, rather than revising the 2019 PM ISA or developing a new PM ISA. To facilitate the identification and evaluation of recent studies that warrant review, the developed a rationale (Section 1.2.1) and scope (Section 1.2.2) for this Supplement to the 2019 PM ISA to focus on specific PM-related health and welfare effects most pertinent to EPA in support of the reconsideration of the primary and secondary PM NAAQS. This targeted approach to developing the Supplement to the 2019 PM ISA for the purpose of reconsidering the 2020 PM NAAQS decision does not reflect a change to EPA's approach for developing ISAs for NAAQS reviews.

1.2.1. Rational for Inclusion of Health and Welfare Effects

The causality determinations presented within the 2019 PM ISA (discussed in Section 2), in combination with the characterization of the science with respect to the health and welfare effects of PM presented in the 2020 PM PA, form the basis of the rationale for the health and welfare effects evaluated within this Supplement. The following section provides specific details on the rationale for the types of evidence included, which ultimately forms the basis of the scope that governs the studies considered for inclusion in this Supplement.

In selecting the health effects to evaluate within this Supplement, the primary rationale is based on the causality determinations for health effect categories presented in the 2019 PM ISA, and the subsequent use of the health effects evidence in the 2020 PM PA (U.S. EPA, 2020b). "In considering the public health protection provided by the current primary $PM_{2.5}$ standards, and the protection that could be provided by alternatives, [EPA, within the 2020 PM PA] emphasized health outcomes for which the ISA determined that the evidence supports either a *causal* or a *likely to be causal relationship* with $PM_{2.5}$

exposures" (U.S. EPA, 2020b). Although the 2020 PM PA initially focused on this broader set of evidence, the basis of the discussion on potential alternative standards primarily focused on health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality) as reflected in Figures 3-7 and 3-8 of the 2020 PM PA (U.S. EPA, 2020b). Therefore, within this Supplement the focus is only on the health effects evidence for which the 2019 PM ISA concluded a *causal relationship.*

In addition, this Supplement also considers recent health effects evidence that addresses key scientific topics for which the literature has evolved since the 2020 PM NAAQS review was completed, specifically since the literature cutoff date for the 2019 PM ISA. These key scientific topics include experimental studies conducted at near-ambient concentrations, epidemiologic studies that employed statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control)[6] or conducted accountability analyses, studies that assess the relationship between $PM_{2.5}$ exposure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) death; and in accordance with recent EPA goals on addressing environmental justice [e.g., U.S. EPA (2021)], studies that examine disparities in $PM_{2.5}$ exposure and the risk of health effects by race/ethnicity and socioeconomic status (SES).

In identifying the studies to consider for inclusion within this Supplement, the focus was on those studies conducted in locations that were most informative to the reconsideration of the 2020 PM NAAQS. This criterion resulted in an assessment of the scientific literature that is more refined compared with the 2019 PM ISA. While the 2019 PM ISA considered and included studies conducted globally when evaluating the evidence and forming causality determinations, the rationale for the scope of this Supplement is directly informed by policy considerations surrounding the types of scientific information included in the 2020 PM PA. In addition to focusing on studies for health effect categories for which the 2019 PM ISA concluded *causal* or a *likely to be causal relationship*, as noted above, the 2020 PM PA also focused on a narrower set of studies conducted in locations that are most relevant to informing the level, form, averaging time, and indicator of the NAAQS for PM. Specifically, the 2020 PM PA states that the emphasis is on "multicity studies that examine health effect associations in the U.S. or Canada, as such studies examine potential associations over large geographic areas with diverse atmospheric conditions and population demographics (e.g., U.S. EPA (2019), Sections 11.1 and 11.2). Additionally, studies examining associations outside the U.S. or Canada reflect air quality and exposure patterns that may be less typical of the U.S., and thus less likely to be informative for purposes of reviewing the

[6] In the peer-reviewed literature, these epidemiologic studies are often referred to as causal inference studies or studies that used causal modeling methods. For the purposes of this Supplement, this terminology is not used to prevent confusion with the main scientific conclusions (i.e., the causality determinations) presented within an ISA. In addition, as is consistent with the weight-of-evidence framework used within ISAs and discussed in the Preamble to the Integrated Science Assessments, an individual study on its own cannot inform causality, but instead represents a piece of the overall body of evidence.

NAAQS" (U.S. EPA, 2020b).[7] Therefore, within this Supplement the studies considered for inclusion are limited to those studies conducted in the U.S. and Canada. However, it is the combination of the scientific evidence detailed in the 2019 PM ISA and this Supplement that forms the complete scientific record informing the reconsideration of the 2020 PM NAAQS.

Consistent with the rationale for the health effects, the selection of welfare effects to evaluate within this Supplement is based on the causality determinations reported in the 2019 PM ISA and the subsequent use of scientific evidence in the 2020 PM PA. The 2019 PM ISA concluded a *causal relationship* for each of the welfare effects categories evaluated (i.e., visibility, climate effects, and materials effects). While the 2020 PM PA considered the broader set of evidence for these effects, for climate effects and material effects, it concluded that there remained "substantial uncertainties with regard to the quantitative relationships with PM concentrations and concentration patterns that limit[ed] [the] ability to quantitatively assess the public welfare protection provided by the standards from these effects" (U.S. EPA, 2020b). Given these uncertainties and limitations, the basis of the discussion on conclusions regarding the secondary standards in the 2020 PM PA primarily focused on visibility effects. Therefore, this Supplement focuses only on visibility effects in evaluating newly available scientific information, and consistent with the health effects rationale, is limited to studies conducted in the U.S. and Canada.

1.2.2. Scope

Building on the rationale presented in Section 1.2.1, the scope of this Supplement provides specific criteria for the types of studies considered for inclusion within the Supplement. Specifically, studies must be peer reviewed and published between approximately January 2018 and March 2021, and satisfy the following criteria:

Health Effects

- U.S. and Canadian epidemiologic studies for health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality)
    - U.S. and Canadian epidemiologic studies that employed alternative methods for confounder control or conducted accountability analyses (i.e., examined the effect of a policy on reducing $PM_{2.5}$ concentrations)[8]

Key Scientific Topics

- Experimental studies (i.e., controlled human exposure and animal toxicological) conducted at near-ambient $PM_{2.5}$ concentrations experienced in the U.S.

[7] This emphasis on studies conducted in the U.S. or Canada is consistent with the approach in previous reviews of the PM NAAQS (U.S. EPA (2011), section 2.1.3).
[8]These studies do not include studies that instituted a specific action or intervention to reduce or mitigate exposure, such as the installation of high efficiency particle filters (HEPA) or indoor air cleaners.

- U.S.- and Canadian-based epidemiologic studies that examined the relationship between $PM_{2.5}$ exposures and SARS-CoV-2 infection and COVID-19 death
- At-risk populations
    - U.S.- and Canadian-based epidemiologic or exposure studies examining potential disparities in either $PM_{2.5}$ exposures or the risk of health effects by race/ethnicity or SES

Welfare Effects

- U.S. and Canadian studies that provide new information on public preferences for visibility impairment and/or developed methodologies or conducted quantitative analyses of light extinction

Given the scope of this Supplement (i.e., not focusing on the broader body of experimental studies), it is important to recognize the evaluation conducted does not encompass the full multidisciplinary evaluation presented within the 2019 PM ISA as described in the *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015) that would result in weight-of-evidence conclusions on causality (i.e., causality determinations). Additionally, this scope does not allow for the evaluation of recent studies for health effect categories from the 2019 PM ISA for which a *likely to be causal relationship* was concluded nor an assessment as to whether recent evidence may strengthen the causality determination to a *causal relationship*.[9] Therefore, this Supplement critically evaluates and provides key study-specific information for only those recent studies deemed to be of greatest significance for impending regulatory decisions regarding the PM NAAQS in the context of the body of evidence and scientific conclusions presented in the 2019 PM ISA. As such, the Supplement indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with and reduces uncertainties), or does not support (is not consistent with) the causality determinations described in the 2019 PM ISA.

1.3. Development of the Supplement

The process used in developing this Supplement is consistent with the 2019 PM ISA as captured in the Preface and Appendix of the 2019 PM ISA. Because this Supplement builds on the 2019 PM ISA, that process is not reiterated but instead is cross referenced. Within the 2019 PM ISA, the Preface provides a detailed description of the process for developing ISAs (Section P.3.), including a discussion of the scope of the ISA (Section P.3.1.) and how evidence is evaluated (Section P.3.2.). A more detailed description of the process of evaluating evidence in ISAs is described in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015) with information specific to the PM ISA in the Appendix of the 2019 PM ISA. Specifically, the Appendix describes in detail the various steps that encompassed the development of the PM ISA. These steps include the literature search and the evaluation of individual study quality, which details scientific considerations for evaluating the strength of inference from studies

[9] The narrow scope also does not allow for the evaluation of recent studies for health effect categories from the 2019 PM ISA where *suggestive of, but not sufficient to infer, a causal relationship* and *inadequate to infer the presence or absence of a causal relationship* was concluded.

that examined the health effects of PM (2019 PM ISA, Section A.3.2., Table A-1). The information presented in Table A-1 in the 2019 PM ISA, which includes the identification and rationale behind advantageous study characteristics (e.g., study design, study population, exposure assessment) as well as information on the selection of results to present from individual studies, was relied upon in the process of considering and identifying recent studies evaluated within this Supplement.

1.4. Organization of the Supplement

The Supplement to the 2019 PM ISA is not intended to be a stand-alone document, but instead to build on the established scientific record regarding the health and welfare effects of PM presented in the 2019 PM ISA and prior assessments. As a result, this Supplement evaluates selected recent studies (i.e., studies published since the literature cutoff date of the 2019 PM ISA and that fall within the scope as outlined above) in the context of the scientific conclusions presented in the 2019 PM ISA.

This Supplement includes chapters and sections incorporated verbatim from the 2019 PM ISA to provide the background information and scientific conclusions necessary to put recent studies in the appropriate context. Section 2 of this Supplement consists of the Integrated Synthesis chapter (Chapter 1) of the 2019 PM ISA, which integrates and summarizes the overall scientific conclusions of the 2019 PM ISA. Section 3 represents the evaluation of the health effects evidence (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality) that falls within the scope of this Supplement. The organization of Section 3 is consistent with the overall organization of the health effects discussion in the 2019 PM ISA, which includes separate discussions of the evidence organized in relation to exposure duration (i.e., short- or long-term exposure) and then within the exposure duration sections discussions organized around specific health effects (e.g., myocardial infarction, nonaccidental mortality) and specific issues of importance (e.g., copollutant confounding, concentration-response relationship). In addition, within each section of Section 3, the summary and causality determination from the 2019 PM ISA is presented to capture the scientific conclusions of the ISA, which recent literature builds upon. The sections that follow in Section 3 evaluate and integrate the evidence from recent studies and ultimately assess the results of recent studies in the context of the causality determinations presented in the 2019 PM ISA. Additionally, Section 3 evaluates recent studies that assess key science topics that have evolved since the completion of the 2019 PM ISA. Study-specific details for the epidemiologic studies evaluated in Section 3, such as information on study population, exposure assessment, $PM_{2.5}$ concentrations, and confounder control (e.g., copollutants) are detailed in tables presented in Section 3. Section 4 consists of an evaluation of recent studies that inform visibility effects and is organized similar to the health effects chapter. Therefore, Section 4 first presents the summary and causality determination from the 2019 PM ISA, then evaluates recent studies, and concludes by assessing new evidence in the context of the conclusions for visibility impairment presented in the 2019 PM ISA. Finally, Section 5 provides a summary and presents overarching conclusions based on the evaluation of recent studies within this Supplement.

2. OVERVIEW OF MAIN CONCLUSIONS OF THE 2019 INTEGRATED SCIENCE ASSESSMENT FOR PARTICULATE MATTER

Overall Conclusions of the 2019 Particulate Matter (PM) Integrated Science Assessment (ISA)

- Evidence spanning scientific disciplines (i.e., atmospheric chemistry, exposure science, dosimetry, epidemiology, controlled human exposure, and animal toxicology) built upon evidence detailed in the 2009 PM ISA and reaffirmed a *causal relationship* between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and total (nonaccidental) mortality, and a *likely to be causal relationship* for respiratory effects.
- Experimental and epidemiologic evidence supported a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and nervous system effects.
- Evidence, primarily from studies of lung cancer incidence and mortality, in combination with the decades of research on the mutagenicity and carcinogenicity of PM supported a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and cancer.
- Remaining uncertainties and limitations in the scientific evidence contributed to a *suggestive of, but not sufficient to infer, a causal relationship* and *inadequate to infer the presence or absence of a causal relationship* for all other exposure, size fraction, and health effects category combinations.
- Evidence built upon and reaffirmed that there is a *causal relationship* between PM and the nonecological welfare effects: visibility impairment, climate effects, and materials effects.
- The assessment of PM sources and components confirmed and continued to support the conclusion from the 2009 PM ISA: *Many* $PM_{2.5}$ *components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is more strongly related with health effects than* $PM_{2.5}$ *mass*.
- Many populations (e.g., healthy, diseased) and lifestages (e.g., children, older adults) have been shown to be at risk of a health effect in response to short- or long-term PM exposure, particularly $PM_{2.5}$. However, of the populations and lifestages examined, scientific evidence indicated that only some populations may be at *disproportionately increased risk* of a $PM_{2.5}$-related health effect, including minority populations (often defined as non-White populations within individual studies), children, people with specific genetic variants in genes in the glutathione transferase pathway, people who are overweight or obese, people with preexisting cardiovascular and respiratory diseases, people of low socioeconomic status (SES), and people who smoke or were former smokers. Inadequate evidence exists to determine whether having diabetes, being in an older lifestage (i.e., older adults), residential location (including proximity to source and urban residence), sex, or diet increase the risk of $PM_{2.5}$-related health effects.

2.1. Health Effects

The 2019 Integrated Science Assessment for Particulate Matter (2019 PM ISA) evaluated relationships between short-term and long-term exposures to PM (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFPs) and an array of health effects described in epidemiologic, controlled human exposure, and animal toxicological studies. In the assessment of the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix to the 2019 PM ISA. Short-term exposures are defined as those with durations of hours up to 1 month, with most studies examining effects related to exposures in the range of 24 hours to 1 week. Long-term exposures are defined as those with

durations of more than 1 month to years. As detailed in the Preface of the 2019 PM ISA, the evaluation of the health effects evidence focuses on exposures conducted at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments (up to 2 mg/m^3, which is one to two orders of magnitude above ambient concentrations), and studies that (1) include a composite measure of PM[10] or (2) apply some approach to assess the direct effect of a specific PM size-fraction when the exposure of interest is a source-based mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke).

Consistent with the Integrated Synthesis chapter (Chapter 1) of the 2019 PM ISA, the subsequent sections and accompanying table (Table 2-2) summarize the key evidence that informed the causality determinations for relationships between PM exposure and health effects detailed in the 2019 PM ISA, specifically those relationships for which it was determined that a *causal* or *likely to be causal relationship* exists (Table 2-1). While the following sections of this chapter focus on health effects categories for which the evidence supported a *causal* or *likely to be causal relationship,* this Supplement as reflected in the Scope (Section 1.2.2) focuses on a narrower evidence base in subsequent chapters. These causality determinations draw from evidence related to the biological plausibility of PM-related health effects and the broader health effects evidence described in detail within the 2019 PM ISA in Chapter 5−Chapter 11, as well as information on dosimetry in Chapter 4 and exposure assessment in Chapter 3. Those relationships between PM and health effects for which the 2019 PM ISA concluded that the evidence supported a causality determination of *suggestive of, but not sufficient to infer, a causal relationship* or *inadequate to infer the presence or absence of a causal relationship* are not discussed within this chapter, but are more fully discussed in the 2019 PM ISA.

[10]Composite measures of PM may include mass, volume, surface area, or number concentration.

Table 2-1 *Causal* and *likely to be causal* causality determinations for short- and long-term $PM_{2.5}$ exposure.

Size Fraction	Health Effects Category	Exposure Duration	Causality Determination	Section
$PM_{2.5}$	Respiratory	Short-term	Likely to be causal	2.1.1.1.1
		Long-term	Likely to be causal	2.1.1.1.2
	Cardiovascular	Short-term	Causal	2.1.1.2.1
		Long-term	Causal	2.1.1.2.2
	Nervous system	Long-term	Likely to be causal	2.1.1.3.1
	Cancer	Long-term	Likely to be causal	2.1.1.4.1
	Mortality	Short-term	Causal	2.1.1.5.1
		Long-term	Causal	2.1.1.5.2

$PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm.

2.1.1. Health Effects of $PM_{2.5}$

Substantial scientific evidence exists across disciplines (i.e., animal toxicology, controlled human exposure, and epidemiology) showing that both short- and long-term $PM_{2.5}$ exposure can result in a range of health effects, from changes in circulating biomarkers to mortality. However, the strength of the $PM_{2.5}$ exposure–health effects relationship varies depending on the exposure duration (i.e., short- or long-term) and broad health effects category (e.g., cardiovascular effects, respiratory effects) examined. Across the broad health effects categories examined in the 2019 PM ISA, the evidence supporting biological plausibility varies, but generally includes modulation of the autonomic nervous system and inflammation as part of the pathways leading to overt health effects. Discussions of subsequent events that could occur due to deposition of inhaled $PM_{2.5}$ in the respiratory tract are detailed in the biological plausibility sections of each health chapter in the 2019 PM ISA and summarized in the following sections.

2.1.1.1. Respiratory Effects

Scientific evidence presented in the 2019 PM ISA continues to support the conclusion of the 2009 PM ISA that there is a *likely to be causal relationship* between both short- and long-term $PM_{2.5}$ exposure and respiratory effects. These causality determinations are based on the consistency of findings within disciplines; the coherence of evidence across disciplines, including epidemiologic and animal toxicological studies, with more limited evidence from controlled human exposure studies; and the

evidence supporting biologically plausible pathways for respiratory effects, such as asthma exacerbation, development of asthma, chronic obstructive pulmonary disease (COPD) exacerbation, and respiratory mortality.

2.1.1.1.1. Respiratory Effects Associated with Short-Term $PM_{2.5}$ Exposure

Epidemiologic studies provide strong evidence for overt respiratory effects, including respiratory-related emergency department (ED) visits and hospital admissions and respiratory mortality associated with short-term $PM_{2.5}$ exposure, with coherence provided by some evidence of respiratory effects from experimental studies. Collectively this evidence supported the conclusion of the 2009 PM ISA that there is a *likely to be causal relationship* between short-term $PM_{2.5}$ exposure and respiratory effects (Table 2-2). This conclusion is based on multiple epidemiologic studies demonstrating generally consistent, positive associations with ED visits and hospital admissions for asthma, COPD, and combined respiratory-related diseases, as well as with respiratory mortality. Evidence from animal toxicological studies, although limited, was supportive of and provided biological plausibility for the associations observed in the epidemiologic studies related to exacerbation of asthma and COPD as well as respiratory infection.

Epidemiologic studies evaluated in the 2019 PM ISA continue to provide strong evidence for a relationship between short-term $PM_{2.5}$ exposure and several respiratory-related endpoints, including asthma exacerbation (2019 PM ISA, Section 5.1.2.1), COPD exacerbation (2019 PM ISA, Section 5.1.4.1), and combined respiratory-related diseases (2019 PM ISA, Section 5.1.6), particularly from studies examining ED visits and hospital admissions. The consistent positive associations between short-term $PM_{2.5}$ exposure and asthma and COPD ED visits and hospital admissions across studies that used different approaches to control for the potential confounding effects of weather (e.g., temperature) are supported by epidemiologic studies demonstrating associations with other respiratory-related effects, such as symptoms and medication use that are indicative of asthma and COPD exacerbations (2019 PM ISA, Section 5.1.2.2 and Section 5.1.4.2). The collective body of epidemiologic evidence for asthma exacerbation was more consistent in children than in adults. Epidemiologic studies examining the relationship between short-term $PM_{2.5}$ exposure and respiratory mortality provided evidence of consistent positive associations, indicating a continuum of effects from morbidity to mortality (2019 PM ISA, Section 5.1.9).

Building off the studies evaluated in the 2009 PM ISA, epidemiologic studies evaluated in the 2019 PM ISA expanded the assessment of potential copollutant confounding. There was some evidence that $PM_{2.5}$ associations with asthma exacerbation, combined respiratory-related diseases, and respiratory mortality remain relatively unchanged in copollutant models with gaseous pollutants (i.e., O_3, NO_2, SO_2, with more limited evidence for CO) and other particle sizes (i.e., $PM_{10–2.5}$) (2019 PM ISA, Section 5.1.10.1). The uncertainty as to whether there is an independent effect of $PM_{2.5}$ on respiratory health, was partially addressed by findings from animal toxicological studies.

Animal toxicological studies of short-term $PM_{2.5}$ exposure provided coherence and biological plausibility for asthma and COPD exacerbations by demonstrating asthma-related responses in an animal model of allergic airways disease and enhanced lung injury and inflammation in an animal model of COPD (2019 PM ISA, Section 5.1.2.4.4 and Section 5.1.4.4.3). There was also a broad body of animal toxicological studies examining respiratory effects due to short-term $PM_{2.5}$ exposure, but most of this evidence was from studies conducted in healthy animals, and therefore, does not provide coherence with the results of epidemiologic studies examining effects in people with asthma or COPD. This evidence base also provided consistent evidence for respiratory irritant effects; limited evidence for altered host defense, greater susceptibility to bacterial infection, and allergic sensitization; and some evidence for pulmonary injury, inflammation, and oxidant stress. Controlled human exposure studies conducted in people with asthma or COPD provided minimal evidence of effects due to short-term $PM_{2.5}$ exposure, such as decrements in lung function and pulmonary inflammation. These studies are limited in terms of endpoints evaluated and the size and health status of study subjects.

2.1.1.1.2. Respiratory Effects Associated with Long-Term $PM_{2.5}$ Exposure

Epidemiologic studies provided strong evidence for effects on lung development, with additional evidence for the development of asthma in children due to long-term $PM_{2.5}$ exposure. Evidence from animal toxicological studies, although limited, was supportive of and provided biological plausibility for the associations reported in epidemiologic studies related to lung development and the development of asthma. There was also epidemiologic evidence supporting a decline in lung function in adults in response to long-term $PM_{2.5}$ exposure. Collectively this evidence supported the conclusions of the 2009 PM ISA that there is a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and respiratory effects (Table 2-2).

Epidemiologic studies evaluated in the 2019 PM ISA continued to support an association between long-term $PM_{2.5}$ exposure and several respiratory-related endpoints in children and adults. In children, studies in multiple cohorts provided strong evidence for decrements in lung function growth (2019 PM ISA, Section 5.2.2.1.1). Robust and persistent effects were observed across study locations, exposure assessment methods, and time periods. An animal toxicological study demonstrating impaired lung development resulting from pre- and postnatal $PM_{2.5}$ exposure provided biological plausibility for these findings (2019 PM ISA, Section 5.2.2.1.2). Results of prospective cohort studies in children also provided some evidence for asthma development in children and are supported by other studies examining asthma prevalence in children, childhood wheeze, and pulmonary inflammation (2019 PM ISA, Section 5.2.3). Biological plausibility was provided by an animal toxicological study of long-term $PM_{2.5}$ exposure demonstrating the development of an allergic phenotype and increase in airway responsiveness (2019 PM ISA, Section 5.2.3.3.2). There was limited evidence of increased bronchitic symptoms and hospitalization in children with asthma in relation to long-term $PM_{2.5}$ exposure (2019 PM ISA, Section 5.2.7). In adults, long-term $PM_{2.5}$ exposure was found to be associated with accelerating lung function decline (2019 PM

ISA, Section 5.2.2.2.2). Consistent evidence was observed for respiratory mortality and cause-specific respiratory mortality for COPD and respiratory infection (2019 PM ISA, Section 5.2.10), providing evidence of a continuum of effects in response to long-term $PM_{2.5}$ exposure.

Only a few epidemiologic studies evaluated in the 2019 PM ISA have further examined potential copollutant confounding. There was some evidence that $PM_{2.5}$ associations with respiratory mortality remained robust in models with some gaseous pollutants (2019 PM ISA, Section 5.2.10); however, there was limited assessment of potential copollutant confounding when examining respiratory morbidity outcomes. The uncertainty related to the independence of $PM_{2.5}$ effects was partially addressed by findings of animal toxicological studies. Long-term exposure to $PM_{2.5}$ resulted in oxidative stress, inflammation, and morphologic changes in both upper and lower airways (2019 PM ISA, Section 5.2.8), in addition to the asthma-related and lung development-related effects mentioned above. Epidemiologic studies examining the effects of declining $PM_{2.5}$ concentrations provided additional support for a relationship between long-term $PM_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and bronchitic symptoms in children, and improvement in lung function in adults in association with declining $PM_{2.5}$ concentrations (2019 PM ISA, Section 5.2.11). However, the limited examination of copollutant confounding in studies of declining $PM_{2.5}$ concentrations was a notable uncertainty given the corresponding decline in other pollutants over the time period of the evaluated studies.

2.1.1.2. Cardiovascular Effects

Consistent with the conclusions of the 2009 PM ISA, more recently published scientific evidence further strengthens the conclusion that there is a *causal relationship* between both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects. These causality determinations are based on the consistency of findings within disciplines; coherence among evidence from controlled human exposure, epidemiologic, and animal toxicological studies; and evidence supporting biologically plausible pathways for cardiovascular effects, such as reduced myocardial blood flow, altered vascular reactivity, myocardial infarctions, and cardiovascular mortality.

2.1.1.2.1. Cardiovascular Effects Associated with Short-Term $PM_{2.5}$ Exposure

Strong evidence from epidemiologic studies demonstrating associations between cardiovascular ED visits and hospital admissions in combination with evidence for $PM_{2.5}$-induced cardiovascular effects from controlled human exposure and animal toxicological studies confirmed and extended the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects from the 2009 PM ISA (Table 2-2). This conclusion was based on multiple epidemiologic studies demonstrating associations with cardiovascular effects such as ischemic heart disease (IHD)- and heart failure (HF)-related ED visits

and hospital admissions, as well as cardiovascular mortality. The epidemiologic evidence was supported by experimental studies demonstrating endothelial dysfunction, changes in blood pressure (BP), and alterations in heart function in response to short-term $PM_{2.5}$ exposure. Additional evidence from epidemiologic, controlled human exposure, and animal toxicological studies also provided ample evidence of biologically plausible pathways by which short-term exposure to $PM_{2.5}$ can result in overt cardiovascular effects.

Consistent with the 2009 PM ISA, the strongest evidence comes from epidemiologic studies that reported consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related ED visits and hospital admissions particularly for IHD (2019 PM ISA, Section 6.1.2.1) and HF (2019 PM ISA, Section 6.1.3.1), as well as cardiovascular-related mortality (2019 PM ISA, Section 6.1.9) across studies that used different approaches to control for the potential confounding effects of weather (e.g., temperature). While associations remained relatively unchanged across the copollutants evaluated, the evidence was especially consistent for air pollutants that are not typically associated with traffic (i.e., ozone, SO_2, $PM_{10–2.5}$). In some instances, associations in copollutant models were attenuated, but this was only observed for the traffic-related pollutants (i.e., NO_2, CO), which generally had higher correlations with $PM_{2.5}$ than other copollutants. This evidence from copollutant analyses from studies evaluated in the 2019 PM ISA generally indicates that the associations observed between short-term $PM_{2.5}$ exposure and cardiovascular effects are not artifacts due to confounding by another air pollutant (2019 PM ISA, Section 6.1.14.1). These epidemiologic studies reduce a key uncertainty identified in the 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular effects relationship.

The independence of $PM_{2.5}$ effects is further addressed by findings of controlled human exposure and animal toxicological studies evaluated in the 2019 PM ISA. The most consistent evidence from controlled human exposure studies was for a $PM_{2.5}$ effect on endothelial function (2019 PM ISA, Section 6.1.13). Multiple recent controlled human exposure studies reported that $PM_{2.5}$ impaired some measure of vessel dilation following reactive hyperemia or pharmacological challenge relative to filtered air. Given the relationship between endothelial function and BP, these results were coherent with multiple controlled human exposure studies that reported changes in BP following short-term $PM_{2.5}$ concentrated ambient particles (CAPs) exposure (2019 PM ISA, Section 6.1.6.3). However, these results were inconsistent with some controlled human exposure studies from previous reviews that did not find changes in endothelial function or BP. The results of controlled human exposure studies evaluated in the 2019 PM ISA are also coherent with evidence from animal toxicological studies demonstrating endothelial dysfunction and changes in BP or the renin angiotensin system following short-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.1.13.3 and Section 6.1.6.4). Moreover, changes in endothelial function and BP reported in recent experimental studies were consistent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and IHD, as well as with limited epidemiologic panel study evidence of associations with BP. In addition, animal toxicological studies demonstrating that short-term $PM_{2.5}$ exposure results in decreased cardiac contractility and changes in left ventricular

pressure were coherent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF.

Collectively, the evidence from controlled human exposure, animal toxicological, and epidemiologic panel studies provided a biologically plausible pathway by which short-term $PM_{2.5}$ exposure could result in cardiovascular effects such as those leading to an ED visit, hospital admission, or mortality. This proposed pathway (2019 PM ISA, Section 6.1.1) begins with pulmonary inflammation and/or activation of sensory nerves in the respiratory track and progresses to autonomic nervous system imbalance and/or systemic inflammation that can potentially affect cardiovascular endpoints such as endothelial function, heart rate variability (HRV), hemostasis, and/or BP. Changes in the aforementioned cardiovascular endpoints may then lead to the development of arrhythmia, thrombosis, and/or acute myocardial ischemia, potentially resulting in outcomes such as myocardial infarction, IHD, HF, and possibly death.

Overall, across the scientific disciplines, recent studies extended and supported the previous evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects range from relatively modest increases in biomarkers related to inflammation, to subclinical cardiovascular endpoints such as endothelial dysfunction, the overt outcomes of ED visits and hospital admissions, specifically for IHD and HF, and ultimately cardiovascular-related mortality.

2.1.1.2.2. Cardiovascular Effects Associated with Long-Term $PM_{2.5}$ Exposure

Multiple epidemiologic studies evaluated in the 2019 PM ISA and previous assessments that extensively control for potential confounders provided strong evidence of positive associations with cardiovascular mortality, which in combination with supporting evidence from recent studies examining cardiovascular morbidity reaffirmed the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and cardiovascular effects in the 2009 PM ISA (Table 2-2). This conclusion was based on U.S. and Canadian cohort studies evaluated in the 2019 PM ISA that demonstrated consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality, with more limited evidence from studies examining long-term $PM_{2.5}$ exposure and cardiovascular morbidity.

Epidemiologic studies consisting of U.S.-based cohorts and subsequent analyses of these cohorts, provided the basis of the conclusions in the 2009 PM ISA. These studies, in combination with cohort studies evaluated in the 2019 PM ISA, continued to demonstrate consistent, positive associations and support a strong relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality. The results of these cohort studies are consistent across various spatial extents, exposure assessment techniques, and statistical techniques in locations where mean annual average concentrations are near or below 12 micrograms per cubic meter ($\mu g/m^3$) (2019 PM ISA, Section 6.2.10).

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity has greatly expanded since the 2009 PM ISA. Epidemiologic studies evaluated in the 2019 PM ISA examining cardiovascular morbidity endpoints consisted of several large U.S. cohort studies each focusing on populations with distinct demographic characteristics (e.g., postmenopausal women, male doctors) and extensive consideration of potential confounders. These studies have reported heterogeneous results, with several studies that adjusted for important confounders, including socioeconomic status (SES), reporting positive associations for cardiovascular morbidity endpoints. The strong associations reported between long-term $PM_{2.5}$ exposure and coronary events (e.g., coronary heart disease [CHD] and stroke) among postmenopausal women in the Women's Health Initiative (WHI) cohort, highlighted in 2009 PM ISA, were strengthened in an extended analysis that considered individual and neighborhood-level SES (2019 PM ISA, Section 6.2.3; Section 6.2.10). Recent analyses of other cohorts of women (i.e., Nurses' Health Study [NHS], California Teachers Study [CTS]) that were comparable to WHI in that they considered menopausal status or hormone replacement therapy did not show consistent positive associations with CHD, myocardial infarction, or stroke. Longitudinal studies demonstrated that changes in the progression of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ were variable across cohorts and found to depend, in part, on the vascular bed in which atherosclerosis was evaluated (2019 PM ISA, Section 6.2.4.1). However, within a study focusing on the progression of atherosclerosis in a healthy population, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA-Air), an association was observed between long-term $PM_{2.5}$ exposure and coronary artery calcification (CAC), which is a strong predictor of CHD (2019 PM ISA, Section 6.2.4). A small number of studies reported positive associations between long-term $PM_{2.5}$ exposure and HF, BP changes, and hypertension. Longitudinal epidemiologic analyses also supported the observation of positive associations with markers of systemic inflammation, coagulation, and endothelial dysfunction. These HF studies were coherent with animal toxicological studies demonstrating decreased contractility and cardiac output and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.2.4.2). Moreover, animal toxicological studies finding a relationship between long-term exposure to $PM_{2.5}$ and changes in BP in rats and mice were coherent with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension. Similarly, evidence of atherosclerotic plaque progression in a genetically susceptible mouse model was consistent with epidemiologic studies reporting associations between atherosclerosis and long-term $PM_{2.5}$ exposure.

The body of evidence evaluated in the 2019 PM ISA also reduced uncertainties identified in the 2009 PM ISA related to potential copollutant confounding and the shape of the concentration-response (C-R) relationship for cardiovascular disease (CVD) effects following long-term $PM_{2.5}$ exposure. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure to cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for O_3, NO_2, SO_2, and $PM_{10–2.5}$ (2019 PM ISA, Section 6.2.15). In addition, most of the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at mean annual $PM_{2.5}$ concentrations ≤ 12 $\mu g/m^3$ (2019 PM ISA, Section 6.2.10). Some studies reported that the slope of the C-R curve tended to be steeper at lower concentrations,

especially for IHD mortality, suggesting a supralinear C-R relationship. A limited number of cardiovascular morbidity studies examined the shape of the C-R relationship and generally reported a steeper C-R curve at lower concentrations (starting at ~10 $\mu g/m^3$) with the slope of the C-R curve decreasing at higher $PM_{2.5}$ concentrations (2019 PM ISA, Section 6.2.16).

Evidence from animal toxicological and epidemiologic studies also provided biologically plausible pathways by which long-term $PM_{2.5}$ exposure could lead to cardiovascular effects such as CHD, stroke, and CVD-related mortality (2019 PM ISA, Section 6.2.1). These pathways initially involve autonomic nervous system changes and/or systemic inflammation that can potentially affect endpoints related to vascular function, altered hemostasis, hypertension, atherosclerotic plaque progression, and arrhythmia. Changes in cardiovascular endpoints such as these may then lead to IHD, HF, and possibly death.

Overall, there was consistent evidence from multiple epidemiologic studies that long-term exposure to $PM_{2.5}$ is associated with cardiovascular mortality. Associations with CHD, stroke, and atherosclerosis progression were observed in several recent epidemiologic studies providing coherence for $PM_{2.5}$-related cardiovascular mortality. Results from copollutant models generally support the independence of $PM_{2.5}$ associations. Additional evidence of the direct effect of $PM_{2.5}$ on the cardiovascular system was provided by experimental studies in animals demonstrating effects including atherosclerosis plaque progression and changes in cardiac contractility and BP.

2.1.1.3. Nervous System Effects

2.1.1.3.1. Nervous System Effects Associated with Long-Term $PM_{2.5}$ Exposure

The 2009 PM ISA evaluated a small number of animal toxicological studies pertaining to the effects of long-term exposures to $PM_{2.5}$ on the nervous system. Since the 2009 PM ISA, the literature base has greatly expanded with studies evaluated in the 2019 PM ISA providing new information that strengthens the lines of evidence indicating that long-term $PM_{2.5}$ exposure may lead to effects on the brain that are associated with neurodegeneration (i.e., neuroinflammation and reductions in brain volume), as well as cognitive effects in older adults (Table 2-2). Animal toxicological studies provided evidence for a range of nervous system effects including neuroinflammation and oxidative stress, neurodegeneration, cognitive effects, and effects on neurodevelopment. Although the epidemiologic evidence was more limited in terms of the number of studies conducted, multiple studies generally supported associations between long-term $PM_{2.5}$ exposure and changes in brain morphology, cognitive decrements, and dementia in adult populations. The consistency and coherence of the evidence across disciplines as it relates to region-specific brain inflammation, morphologic changes in the brain, cognitive effects, and dementia in adult populations supported that there is a *likely to be causal relationship* between long-term $PM_{2.5}$

exposure and nervous system effects. Thus, the expanded evidence base allowed for the first-time, a causality determination for long-term $PM_{2.5}$ exposure and nervous system effects.

There was strong evidence for biologically plausible pathways that may underlie nervous system effects resulting from long-term exposure to $PM_{2.5}$. Studies demonstrated modulation of the autonomic nervous system leading to downstream consequences including cardiovascular effects (2019 PM ISA, Section 6.2.1). In addition, the pathway involving neuroinflammation in specific regions of the brain (i.e., the hippocampus, cerebral cortex, and hypothalamus) and morphologic changes in the brain indicative of neurodegeneration, is well substantiated and coherent across animal toxicological and epidemiologic studies (2019 PM ISA, Section 8.2.3 and Section 8.2.4). Specifically, morphologic changes induced in the hippocampus of animals were accompanied by impaired learning and memory and there was consistent evidence from multiple epidemiologic studies that long-term $PM_{2.5}$ exposure is associated with reduced cognitive function (2019 PM ISA, Section 8.2.5). Further, the presence of early markers of Alzheimer's disease pathology was demonstrated in animals following long-term exposure to $PM_{2.5}$ CAPs, which was consistent with a small number of epidemiologic studies that reported positive associations with neurodegenerative changes in the brain (i.e., decreased brain volume) and Alzheimer's disease or all-cause dementia (2019 PM ISA, Section 8.2.6). Although the loss of dopaminergic neurons in the substantia nigra, which is a hallmark of Parkinson's disease, was demonstrated in animals (2019 PM ISA, Section 8.2.4), epidemiologic studies did not report associations with Parkinson's disease (2019 PM ISA, Section 8.2.6). Overall, the lack of consideration of copollutant confounding introduces some uncertainty in the interpretation of the epidemiologic studies but this uncertainty was addressed, in part, by the direct evidence of effects provided by animal toxicological studies.

In addition to the findings described above, which are mostly relevant to adults, several recent studies of neurodevelopmental effects in children have also been conducted. Positive associations between long-term exposure to $PM_{2.5}$ during the prenatal period and autism spectrum disorder (ASD) were consistently observed across multiple epidemiologic studies (2019 PM ISA, Section 8.2.7.2). However, several studies of performance on tests of cognitive function provided little support for an association. Overall, these epidemiologic studies of developmental effects were limited due to their lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows. A study in animals that found inflammatory and morphologic changes in the corpus collosum and hippocampus, as well as ventriculomegaly in young animals following prenatal exposure to $PM_{2.5}$ CAPs provided initial evidence indicating a potential biologically plausible pathway for a relationship between $PM_{2.5}$ and ASD.

2.1.1.4. Cancer

2.1.1.4.1. Cancer Associated with Long-Term $PM_{2.5}$ Exposure

Experimental and epidemiologic evidence indicating genotoxicity, epigenetic effects (e.g., DNA methylation), and increased carcinogenic potential due to $PM_{2.5}$ exposure, along with strong epidemiologic evidence for increases in lung cancer incidence and mortality, supported a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and cancer (Table 2-2). This causality determination represented a change from the *suggestive of a causal relationship*[11] determination reported in the 2009 PM ISA. The evidence base underlying this conclusion encompasses the decades of research on whole PM exposures and research evaluated in the 2019 PM ISA focusing specifically on $PM_{2.5}$.

$PM_{2.5}$ exhibits various characteristics of carcinogens, as shown in studies demonstrating genotoxic effects (e.g., DNA damage), epigenetic alterations, oxidative stress, and electrophilicity. The examination of the role of $PM_{2.5}$ in cancer development has often focused on whether whole PM, not specific size fractions, has mutagenic properties and whether exposure to whole PM results in genotoxicity or carcinogenicity. Additionally, it has been well characterized that some components of $PM_{2.5}$, specifically hexavalent chromium, nickel, arsenic, and polycyclic aromatic hydrocarbons are known human carcinogens. Extensive analyses of $PM_{2.5}$ and $PM_{2.5}$ extracts in the Ames *Salmonella*/mammalian-microsome mutagenicity assay demonstrated that $PM_{2.5}$ contains mutagenic agents (2019 PM ISA, Section 10.2.2.1). Additional in vitro and in vivo toxicological studies indicated the potential for $PM_{2.5}$ exposure to result in DNA damage, which was supported by limited human evidence (2019 PM ISA, Section 10.2.2.2). Some studies have also demonstrated that $PM_{2.5}$ exposure can result in cytogenetic effects, specifically micronuclei formation and chromosomal aberrations (2019 PM ISA, Section 10.2.2.3), as well as differential expression of genes potentially relevant to genotoxicity or other aspects of cancer pathogenesis (2019 PM ISA, Section 10.2.2.4). Although inconsistently examined across studies, changes in cellular and molecular markers of genotoxicity and epigenetic alterations, which may lead to genomic instability, are demonstrated in response to $PM_{2.5}$ exposure. Further, the carcinogenic potential of $PM_{2.5}$ was demonstrated in an animal toxicological study in which chronic inhalation enhanced tumor formation that was initiated by exposure to urethane (2019 PM ISA, Section 10.2.4). Additionally, epidemiologic studies evaluated in the 2019 PM ISA encompassing multiple cohorts that are diverse in terms of both geographic coverage and population characteristics have provided evidence of primarily consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, particularly in never smokers (2019 PM ISA, Section 10.2.5.1). Experimental and epidemiologic evidence of genotoxicity, epigenetic effects, and carcinogenic potential provides biological plausibility for epidemiologic results of lung cancer incidence and mortality. Although evaluated in a limited number of studies, the assessment of potential copollutant confounding,

[11]Since the 2009 PM ISA, the causality determination language has been updated and this category is now stated as *suggestive of, but not sufficient to infer, a causal relationship.*

particularly with O_3, indicated that $PM_{2.5}$ associations with lung cancer incidence and mortality are relatively unchanged in copollutant models (2019 PM ISA, Section 10.2.5.1.3). There was limited evidence that long-term $PM_{2.5}$ exposure is associated with cancers in other organ systems; however, there was initial evidence that $PM_{2.5}$ exposure may reduce survival in individuals with cancer.

2.1.1.5. Mortality

Consistent with the conclusions of the 2009 PM ISA, evidence from studies evaluated in the 2019 PM ISA reaffirmed and further strengthened that there is a *causal relationship* between both short- and long-term $PM_{2.5}$ exposure and total mortality. These causality determinations were based on the consistency of findings across a large body of epidemiologic studies. Evidence from controlled human exposure, epidemiologic, and animal toxicological studies of respiratory and cardiovascular morbidity also provided coherence, as well as biological plausibility. Together, the consistency and coherence in the evidence collectively supported a continuum of effects by which short- and long-term $PM_{2.5}$ exposure could result in mortality.

2.1.1.5.1. Mortality Associated with Short-Term $PM_{2.5}$ Exposure

Strong epidemiologic evidence from studies evaluated in the 2019 PM ISA, as well as in previous assessments, that examined total (nonaccidental) mortality in combination with evidence for cause-specific respiratory and cardiovascular mortality continued to support the conclusion of the 2009 PM ISA that there is a *causal relationship* between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality (Table 2-2). This conclusion was based on multiple recent multicity studies conducted in the U.S., Canada, Europe, and Asia that continued to provide evidence of consistent, positive associations between short-term $PM_{2.5}$ and total mortality, across studies that used different approaches to control for the potential confounding effects of weather (e.g., temperature). In addition, there was evidence of biological plausibility for cause-specific mortality and ultimately total mortality as demonstrated by the consistent and coherent evidence across scientific disciplines for cardiovascular morbidity, particularly ischemic events and HF (2019 PM ISA, Chapter 6), and respiratory morbidity, with the strongest evidence coming from studies of exacerbations of COPD and asthma (2019 PM ISA, Chapter 5).

Multicity studies evaluated in the 2019 PM ISA added to the body of evidence evaluated in the 2009 PM ISA and continued to support a positive association between short-term $PM_{2.5}$ exposure and total mortality with percentage increases in mortality ranging from 0.19% to 2.80% at lags of 0 to 1 day in studies in which mean 24-hour avg concentrations were primarily < 20 $\mu g/m^3$ (2019 PM ISA,

Figure 11-1; Table 11-1).[12] The positive associations observed across studies reflected traditional analyses using ambient monitors as well as analyses conducted in both urban and rural locations that used new exposure assignment techniques and relied on multiple sources of $PM_{2.5}$ data (e.g., ambient monitors, statistical models, and satellite data). Whereas the analysis of potential copollutant confounding was limited to single-city studies and studies of PM_{10} in the 2009 PM ISA, recent multicity studies conducted in Europe and Asia indicated that $PM_{2.5}$-mortality associations were relatively unchanged in copollutant models with gaseous pollutants and $PM_{10–2.5}$ (2019 PM ISA, Section 11.1.4). These results from copollutant models further supported an independent effect of $PM_{2.5}$ on mortality. The associations reported for total mortality were also supported by analyses demonstrating increases in cause-specific mortality, specifically for cardiovascular and respiratory mortality which comprise ~33% and ~9%, respectively, of total mortality [NHLBI (2017); 2019 PM ISA, Figure 11-2]. The consistent and coherent evidence across scientific disciplines for cardiovascular morbidity, particularly ischemic events and HF (2019 PM ISA, Chapter 6), and to a lesser degree for respiratory morbidity, with the strongest evidence for exacerbations of COPD and asthma (2019 PM ISA, Chapter 5), provided biological plausibility for cause-specific mortality and ultimately total mortality. The relationship between short-term $PM_{2.5}$ exposure and total mortality was additionally supported by analyses of the concentration-response (C-R) relationship. Although alternatives to linearity have not been systematically evaluated, mortality studies evaluated in the 2019 PM ISA continued to support a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.1.10).

2.1.1.5.2. Mortality Associated with Long-Term $PM_{2.5}$ Exposure

Strong epidemiologic evidence from cohorts in the U.S., Canada, and Europe evaluated in the 2019 PM ISA, as well as in previous assessments, continued to support the conclusion of the 2009 PM ISA that there is a *causal relationship* between long-term $PM_{2.5}$ exposure and total mortality (Table 2-2). This conclusion was based on the evaluation of multiple cohorts that continued to provide evidence of consistent, positive associations, across studies that controlled for a range of individual- and ecological covariates, such as smoking status and SES. Additional evidence indicated coherence of effects across scientific disciplines for cardiovascular and respiratory morbidity and metabolic disease, which provided biological plausibility for cause-specific mortality and supported a *causal relationship* with total mortality.

Additional reanalyses and extensions of the American Cancer Society (ACS) and Harvard Six Cities (HSC) cohorts as well as new cohorts consisting of Medicare participants, people that live in Canada, or people employed in a specific job (e.g., teacher, nurse) provided further evidence of positive associations between long-term $PM_{2.5}$ exposure and total mortality, particularly in areas with annual mean

[12]Throughout this Supplement, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations and long-term exposures are for a 5 $\mu g/m^3$ increase in annual concentrations, unless otherwise noted.

concentrations < 20 μg/m^3, and in some cases below 12 μg/m^3 (2019 PM ISA, Figure 11-17 and Figure 11-18). Across studies, positive associations were consistently observed regardless of the exposure assignment approach employed, with some studies relying on ambient monitors while others using modeled or remote sensing data or hybrid methods that combine two or more data sources. Recent studies have conducted analyses to examine potential copollutant confounding and indicated that associations between long-term $PM_{2.5}$ exposure and total mortality are relatively unchanged in copollutant models, particularly for O_3, with fewer studies examining NO_2, and $PM_{10–2.5}$ (2019 PM ISA, Section 11.2.3; Figure 11-20, Figure 11-21). The evidence for total mortality was further supported by analyses of cause-specific mortality, which reported positive associations with cardiovascular, respiratory, and lung cancer mortality. Biological plausibility for mortality due to long-term $PM_{2.5}$ exposure was provided by the coherence of effects across scientific disciplines for cardiovascular morbidity, particularly for CHD, stroke, and atherosclerosis, and for respiratory morbidity, particularly for the development of COPD. Recent studies extensively examined the C-R relationship between long-term $PM_{2.5}$ exposure and total mortality, specifically in several U.S. and Canadian cohorts, and collectively continued to support a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.2.4; Table 11-7).

A series of studies evaluated in the 2019 PM ISA, examined the relationship between long-term exposure to $PM_{2.5}$ and mortality by examining the temporal trends in $PM_{2.5}$ concentrations to test the hypothesis that decreases in $PM_{2.5}$ concentrations are associated with increases in life expectancy (2019 PM ISA, Section 11.2.2.5). These studies reported that decreases in long-term $PM_{2.5}$ concentrations were associated with an increase in life expectancy across the U.S. for the multiple time periods examined.

Table 2-2 Key evidence contributing to *causal* and *likely to be causal* causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Respiratory Effects and Short-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 5.1): Likely to Be Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 5.1.12 Table 5-18	Epidemiologic evidence, consisting mainly of ED visits and hospital admissions, strongly supported a relationship with asthma exacerbation, COPD exacerbation, and combinations of respiratory-related diseases. Evidence for associations with respiratory symptoms and medication use are coherent with other findings for asthma and COPD exacerbation. Some epidemiologic studies examined copollutant confounding and reported that results are robust in models with gaseous pollutants (i.e., O_3, NO_2, SO_2, and with more limited evidence for CO) and other particle sizes (i.e., $PM_{10-2.5}$), especially for asthma exacerbation, combinations of respiratory-related ED visits and hospital admissions, and respiratory mortality. There was a large body of experimental evidence demonstrating respiratory effects due to short-term $PM_{2.5}$ exposure. These experimental studies provided evidence for biologically plausible pathways by which $PM_{2.5}$ exposure could cause a respiratory effect. Specifically, animal toxicological studies provided biological plausibility for asthma exacerbation, COPD exacerbation, and respiratory infection with some evidence of an independent effect of $PM_{2.5}$ on respiratory endpoints. Controlled human exposure studies provided minimal evidence of respiratory effects such as altered lung function and pulmonary inflammation. Consistent positive associations with respiratory mortality provide evidence of a continuum of effects.	Mean ambient concentrations from epidemiologic studies for: *Hospital admissions and ED visits for asthma, COPD, respiratory infections, and combinations of respiratory-related diseases:* U.S. and Canada: 4.7−24. 6 µg/m³ Europe: 8.8−27.7 µg/m³ Asia: 11.8−69.9 µg/m³ *Respiratory mortality:* U.S. and Canada: 7.9−19.9 µg/m³ Europe: 8.0−27.7 µg/m³ Asia: 11.8−69.9 µg/m³ Concentrations from animal toxicological studies for: *Allergic airway disease:* 442−596 µg/m³ *COPD:* 171−1,200 µg/m³ *Altered host defense:* 100−350 µg/m³

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Respiratory Effects and Long-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 5.2): Likely to Be Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 5.2.13 Table 5-27	Epidemiologic evidence strongly supported a relationship with decrements in lung function growth in children. Additional epidemiologic evidence supported a relationship with asthma development in children, increased bronchitic symptoms in children with asthma, acceleration of lung function decline in adults, and respiratory mortality, including cause-specific respiratory mortality for COPD and respiratory infection. Some epidemiologic studies examined copollutant confounding and reported that results are robust in models with O_3, NO_2, and CO, especially for respiratory mortality. There was limited experimental evidence for respiratory effects from long-term $PM_{2.5}$ exposure. However, animal toxicological studies provided biological plausibility for decrements in lung function and asthma development in children, and they reduced the uncertainty regarding the independent effect of $PM_{2.5}$ for these endpoints. Animal toxicological studies also provided evidence for a wide variety of other subclinical effects, such as oxidative stress, inflammation, and morphologic changes. Epidemiologic studies examining the effects of declining $PM_{2.5}$ concentrations strengthened the relationship between long-term $PM_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and reduced bronchitic symptoms in children and improved lung function in adults as a result of lower $PM_{2.5}$ concentrations. However, these studies have a limited examination of copollutant confounding, which was a notable uncertainty because concentrations of other pollutants have also declined.	Mean ambient concentrations from epidemiologic studies for: *Decrement in lung function growth:* 6−28 µg/m^3 *Asthma development in children:* 5.2−16.5 µg/m^3 *Bronchitic symptoms in children with asthma:* 9.9−13.8 µg/m^3 *Accelerated lung function decline in adults:* 9.5−17.8 µg/m^3 *Respiratory mortality:* 6.3−23.6 µg/m^3 Concentrations from animal toxicological studies for: *Impaired lung development:* 16.8 µg/m^3 *Development of allergic airway disease:* 100 µg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Cardiovascular Effects and Short-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 6.1): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 6.1.16 Table 6-34	There was strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure. Consistent epidemiologic evidence from multiple studies at relevant $PM_{2.5}$ concentrations provided evidence of increases in ED visits and hospital admissions for IHD and HF, as well as cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. These associations remained positive, but in some cases were reduced with larger uncertainty estimates, in copollutant models with gaseous pollutants. Controlled human exposure studies provided coherence and consistent evidence for changes in various measures of endothelial dysfunction and generally consistent evidence of changes in BP. These controlled human exposure studies were consistent with animal toxicological studies also demonstrating endothelial dysfunction, as well as changes in BP and the renin-angiotensin system. In addition, animal toxicological studies demonstrating that short-term $PM_{2.5}$ exposure results in decreased cardiac contractility and left ventricular pressure were coherent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF.	Mean ambient concentrations from epidemiologic studies for: *IHD:* 5.8−18.6 μg/m³ *HF:* 5.8−18.0 μg/m^3 Concentrations from controlled human exposure studies: 24−325 μg/m^3 for 2 h Concentrations from animal toxicological studies: 178−190 μg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Cardiovascular Effects and Long-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 6.2): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 6.2.18 Table 6-54	Multiple epidemiologic studies continued to provide evidence of consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality at lower ambient concentrations. The cardiovascular mortality associations were observed across different exposure assignment and statistical methods and were relatively unchanged in copollutant models with both gaseous (i.e., O_3, NO_2, SO_2) and particulate (i.e., $PM_{10-2.5}$) pollutants. The evidence for cardiovascular mortality was supported by a smaller body of epidemiologic studies that further explored associations between long-term $PM_{2.5}$ exposure and cardiovascular morbidity. These studies reported some evidence for increased risk of $PM_{2.5}$-related MI and stroke, specifically in individuals with a preexisting cardiovascular disease or diabetes. Recent epidemiologic studies also presented evidence for an effect of long-term $PM_{2.5}$ exposure on subclinical features of cardiovascular morbidity, particularly progression of atherosclerosis as reflected by associations with CAC, with more limited evidence for other measures, such as cIMT. Key evidence from animal toxicological studies included consistent evidence for changes in BP, as well as some evidence for decreases in measures of heart function (e.g., contractility and cardiac output) and cardiac remodeling. Moreover, as in the previous review, there was also some additional evidence for atherosclerotic plaque progression in a genetically susceptible mouse model.	Mean ambient concentrations from epidemiologic studies for: *Cardiovascular mortality*: 4.1−17.9 μg/m^3 *Coronary events*: 13.4 μg/m^3 *CAC*: 14.2 μg/m^3 *CHD and stroke (in those with preexisting disease)*: 13.4−23.9 μg/m^3 Concentrations from animal toxicological studies for: *BP*: 85−375 μg/m^3 (up to 15 weeks)

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Nervous System Effects and Long-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 8.2): Likely to Be Causal Relationship *Not Evaluated in the 2009 PM ISA; New Evidence Showing Brain Inflammation and Oxidative Stress, Neurodegeneration, Cognitive Effects, and Neurodevelopmental Effects.*		
Section 8.2.9 Table 8-20	There was evidence that long-term exposure to $PM_{2.5}$ can modulate the autonomic nervous system leading to downstream consequences, including cardiovascular effects (2019 PM ISA, Section 6.2.1). A second pathway involving neuroinflammation and morphologic changes in the brain indicative of neurodegeneration is well substantiated and coherent across animal toxicological and epidemiologic studies. This combination of evidence supported $PM_{2.5}$-related reductions in brain volume and cognitive effects in older adults. The evidence relating to Parkinson's disease, and neurodevelopmental effects was more limited. Consideration of copollutant confounding was generally lacking in the epidemiologic studies, but the uncertainty in interpreting the study findings was partly addressed by the direct evidence of effects provided by animal toxicological studies.	Mean annual concentrations from epidemiologic studies for: *Brain volume:* 11.1−12.2 µg/m^3 *Cognition:* 8.5 (5-yr avg)−14.9 µg/m^3 *Autism:* 14.0−19.6 µg/m^3 Concentrations from animal toxicological studies for: *Brain inflammation/oxidative stress:* 65.7−441.7 µg/m^3 *Neurodegenerative changes:* 94.4 µg/m^3 *Neurodevelopment:* 92.7 µg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Cancer and Long-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 10.2): Likely to Be Causal Relationship *Change in Causality Determination from the 2009 PM ISA (Suggestive of a Causal Relationship) Due to Increased Evidence of Genotoxicity, Carcinogenicity, and Epigenetic Effects for $PM_{2.5}$ and Lung Cancer Incidence and Mortality.*		
Section 10.2.7 Table 10-8	Primarily positive associations from multiple epidemiologic studies reported increases in the risk of lung cancer incidence and mortality. This evidence was supported by analyses focusing on never smokers and limited evidence of associations with histological subtypes of lung cancer found in never smokers. Across studies that examined lung cancer incidence and mortality, potential confounding by smoking status and exposure to SHS was adequately controlled. A limited number of studies examined potential copollutant confounding, but associations were relatively unchanged in models with O_3 with more limited assessment of other gaseous pollutants and particle size fractions. Experimental and epidemiologic studies provided evidence for a relationship between $PM_{2.5}$ exposure and genotoxicity, epigenetic effects, and carcinogenic potential. Uncertainties exist due to the lack of consistency in specific cancer-related biomarkers associated with $PM_{2.5}$ exposure across both experimental and epidemiologic studies; however, $PM_{2.5}$ exhibits several characteristics of carcinogens, which provided biological plausibility for $PM_{2.5}$ exposure contributing to cancer development. Additionally, there was limited evidence of cancer occurring in other organ systems, but there was some evidence that $PM_{2.5}$ exposure may detrimentally affect survival from any type of cancer.	Mean annual concentrations from epidemiologic studies for: *Lung cancer incidence and mortality*: U.S. and Canada: 6.3−23.6 μg/m^3 Europe: 6.6−31.0 μg/m^3 Asia: 33.7 μg/m^3 Concentrations from animal toxicological studies for: *Carcinogenic potential:* 17.66 μg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Total Mortality and Short-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 11.1): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 11.1.12 Table 11-4	There was consistent epidemiologic evidence from multiple multicity studies conducted in the U.S., Canada, Europe, and Asia for increases in total (nonaccidental) mortality at ambient concentrations, often below 20 μg/m^3. The associations observed were relatively unchanged in copollutant models with gaseous pollutants and $PM_{10-2.5}$, which was consistent with copollutant analyses for cardiovascular and respiratory mortality, but copollutant analyses were limited to studies conducted in Europe and Asia. Biological plausibility for the epidemiologic evidence for total mortality was provided by the strong cardiovascular morbidity evidence, particularly for ischemic events and HF, while support for biological plausibility was more limited from the respiratory morbidity evidence, with the strongest evidence for exacerbations of COPD and asthma. Although alternatives to linearity have not been systematically evaluated, recent mortality studies continued to support a linear, no-threshold C-R relationship.	Mean 24-h avg concentrations from epidemiologic studies for: *Total mortality*: U.S. and Canada: 4.37−17.97 μg/m^3 Europe: 13−27.7 μg/m^3 Asia: 11.8−69.9 μg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Total Mortality and Long-Term $PM_{2.5}$ Exposure (2019 PM ISA, Section 11.2): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 11.2.7 Table 11-8	There was consistent epidemiologic evidence from multiple studies reporting increases in the risk of total (nonaccidental) mortality from extended follow-ups of the ACS cohort and HSC cohort, as well as multiple studies focusing on a Medicare cohort, Canadian cohorts, and North American employment cohorts. The consistent increases in total mortality were observed across different exposure metrics based on ambient measurements, models, remote sensing, or hybrid methods that combine two or more of these methods, providing additional support for the mortality associations due to long-term $PM_{2.5}$ exposure reported in the 2009 PM ISA that relied on exposure metrics from ambient monitors. The consistent epidemiologic evidence for total mortality was supported by positive associations for cardiovascular, respiratory, and lung cancer mortality. Biological plausibility for total mortality was provided by the strong cardiovascular morbidity evidence, particularly for CHD, stroke, and atherosclerosis, while there is more limited evidence for biological plausibility from the respiratory morbidity evidence, with some evidence for development of COPD. Extensive epidemiologic evidence provides additional support for a linear, no-threshold C-R relationship. A series of studies demonstrated that decreases in long-term $PM_{2.5}$ concentrations were associated with an increase in life expectancy across the U.S. for multiple time periods examined.	Mean annual concentrations from epidemiologic studies for: *Total mortality*: ACS/HSC cohorts: 11.4−23.6 $\mu g/m^3$ Medicare cohort: 8.12−12.0 $\mu g/m^3$ Canadian cohorts: 8.7−9.1 $\mu g/m^3$ Employment cohorts: 12.7−17.0 $\mu g/m^3$

ACS = American Cancer Society; avg = average; BP = blood pressure; CAC = coronary artery calcification; CHD = coronary heart disease; cIMT = carotid intima-media thickness; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; C-R = concentration-response; h = hour; HF = high frequency; HSC = Harvard Six Cities; IHD = ischemic heart disease; $\mu g/m^3$ = micrograms per cubic meter; MI = myocardial infarction; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm; SHS = second-hand smoke; SO_2 = sulfur dioxide.

[a]A large spectrum of outcomes is evaluated as part of a broad health effect category including physiological measures (e.g., airway responsiveness, lung function), clinical outcomes (e.g., respiratory symptoms, hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by the nature of the evidence for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced in the 2019 PM ISA include a detailed discussion of the available evidence that informed the causality determinations.

2.2. Policy-Relevant Considerations

In the process of evaluating the current state of the science with respect to the effect of short- and long-term PM exposure on health, studies were identified and evaluated within the 2019 PM ISA that conducted analyses focused on addressing some of the main policy-relevant questions of this review, as detailed in the *Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter* (U.S. EPA, 2016), such as:

- Is there new evidence aimed at disentangling the effect of PM from the complex air pollution mixture to inform a direct effect of PM on health, specifically the assessment of potential copollutant confounding?
- Is there new evidence to inform the current indicators (i.e., $PM_{2.5}$ for fine particles and PM_{10} for thoracic coarse particles), averaging times (i.e., 24-hour avg, annual average), and levels of the PM NAAQS?
- Is there new evidence on the shape of the C-R relationship and whether a threshold exists between PM exposure and various health outcomes (e.g., mortality, hospital admissions), especially for concentrations near or below the levels of the current PM NAAQS?
- Is there new evidence that individual PM component(s) or source(s) (e.g., industrial facilities, roads, atmospheric formation), are more strongly associated with health effects than PM mass, particularly for health effects for which there is sufficient evidence of a strong relationship (e.g., cardiovascular effects, mortality) with PM exposure?
- Is there new evidence indicating that specific populations or lifestages are at increased risk of a PM-related health effect compared with a referent population?

The following sections summarize the evidence that can inform consideration of these policy-relevant questions, specifically: potential copollutant confounding (Section 2.2.1), timing of effects (Section 2.2.2), C-R relationship (Section 2.2.3), PM components and sources (Section 2.2.4), and populations potentially at increased risk of a PM-related health effect (Section 2.2.5).

2.2.1. Potential Copollutant Confounding

Studies evaluated in the 2019 PM ISA further examined the potential confounding effects of copollutants, both gaseous and particulate, on the relationship between short- and long-term $PM_{2.5}$ exposure and health effects. These studies built upon the evidence detailed in the 2009 PM ISA and continued to provide evidence indicating that associations with $PM_{2.5}$ are relatively unchanged in copollutant models. Evidence from epidemiologic studies, in combination with experimental studies detailed in multiple chapters of the 2019 PM ISA (i.e., "Respiratory Effects"—Chapter 5 and "Cardiovascular Effects"—Chapter 6 within the 2019 PM ISA) that examined exposure to PM

(e.g., CAPs, resuspended PM, and whole mixtures in the presence and absence of a particle trap), demonstrate a direct effect of PM on health.

2.2.1.1. Short-Term $PM_{2.5}$ Exposure

Building upon the studies evaluated in the 2009 PM ISA, epidemiologic studies evaluated in the 2019 PM ISA have further examined whether copollutants confound associations between short-term $PM_{2.5}$ exposure and respiratory and cardiovascular effects and mortality. These studies continued to demonstrate that $PM_{2.5}$-associations are relatively unchanged in copollutant models with both gaseous (i.e., O_3, NO_2, SO_2, and CO) and particulate (i.e., $PM_{10–2.5}$) pollutants.

The examination of potential copollutant confounding on the relationship between short-term $PM_{2.5}$ exposure and respiratory effects has been assessed most extensively through studies examining respiratory-related ED visits and hospital admissions, particularly for asthma, with more limited assessments of COPD and respiratory infection, and studies examining respiratory mortality (Section 5.1.10.1). Correlations between $PM_{2.5}$ and gaseous and particulate pollutants varied across studies, with low to moderate correlations (i.e., $r < 0.7$) observed for NO_2, SO_2, CO, and $PM_{10–2.5}$, and correlations spanning from low to high for O_3. Across the studies that assessed copollutant confounding, O_3 was most examined, followed by NO_2 and $PM_{2.5}$. Within these studies results were relatively unchanged in copollutant models. Although fewer studies focused on SO_2 and CO, the results from copollutant analyses were consistent with studies evaluated in the 2009 PM ISA, indicating that results are relatively unchanged in copollutant models. Studies evaluated in the 2019 PM ISA that examined $PM_{10–2.5}$ further expanded upon the initial results detailed in the 2009 PM ISA, and although results are consistent with observations from analyses of gaseous pollutants, there is greater uncertainty in these results due to the different methods employed across studies to estimate $PM_{10–2.5}$ concentrations.

For cardiovascular effects, moderate to strong correlations were reported for NO_2 and CO, with low to moderate correlations for O_3, SO_2, and $PM_{10–2.5}$. Across studies of various cardiovascular-related ED visits and hospital admissions and cardiovascular mortality, results were relatively unchanged in copollutant models, but there were some instances of attenuation of the $PM_{2.5}$ association in models with NO_2 and CO (2019 PM ISA, Section 6.1.14.1). Overall, there was no observed difference in the trend or pattern of copollutant model results across cardiovascular endpoints (e.g., aggregate CVD endpoints, IHD, HF, cardiovascular mortality). However, the few instances of attenuation were with traffic-related pollutants (i.e., NO_2, CO), which generally had higher correlations with $PM_{2.5}$ than the other copollutants. As a result, it was difficult to distinguish whether the instances of observed attenuation in $PM_{2.5}$ associations were due to confounding or collinearity with other pollutants.

Most epidemiologic studies evaluated in the 2019 PM ISA that examined the potential confounding effects of copollutants focused on respiratory and cardiovascular effects; only a few focused on mortality (2019 PM ISA, Section 11.1.4). Recent multicity studies conducted in Europe and Asia

supported the results from single- and multicity studies examined in the 2004 PM AQCD and 2009 PM ISA that reported limited evidence of confounding by copollutants. Across studies that examined both gaseous and particulate (i.e., $PM_{10–2.5}$) pollutants, low to moderate correlations were reported with $PM_{2.5}$. Associations with $PM_{2.5}$ were relatively unchanged in copollutant models across the various study locations examined.

In addition to conducting traditional copollutant analyses, epidemiologic studies of respiratory (2019 PM ISA, Section 5.1.10.1.1) and cardiovascular (2019 PM ISA, Section 6.1.14.1.1) effects have also examined the role of PM within the broader air pollution mixture. These studies do not inform whether PM is independently associated with a respiratory effect, but they can assess whether days with higher $PM_{2.5}$ concentrations are more closely related to health effects. Studies of respiratory effects demonstrated that days when the air pollution mixture has high $PM_{2.5}$ concentrations often represented the days with the largest associations (in terms of magnitude) with a respiratory effect. Additionally, results indicated that risk estimates for a mixture were often similar, but in some cases larger, than those reported for $PM_{2.5}$ alone. However, for cardiovascular effects in general, the evidence neither consistently nor coherently indicated a stronger or weaker effect of combined exposure to $PM_{2.5}$ and another pollutant compared with exposure to $PM_{2.5}$ and other pollutants alone.

2.2.1.2. Long-Term $PM_{2.5}$ Exposure

Epidemiologic studies focusing on long-term $PM_{2.5}$ exposure and health effects have traditionally provided a more limited assessment of the potential confounding effects of copollutants on $PM_{2.5}$ associations. Studies evaluated in the 2019 PM ISA that provided an assessment of copollutant confounding directly addressed a previously identified uncertainty in the scientific evidence.

Across the health effects evaluated within the 2019 PM ISA, relatively few studies examined the potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and respiratory (2019 PM ISA, Section 5.2.13), cardiovascular (2019 PM ISA, Section 6.2.18), and cancer (2019 PM ISA, Section 10.2.7), with a general lack of studies assessing the role of copollutant confounding on observed associations with nervous system effects (2019 PM ISA, Section 8.2.9). These studies often did not examine the full suite of gaseous pollutants but tended to focus on traffic-related pollutants (i.e., NO_2, NO_X, and CO) and O_3, with some studies also examining $PM_{10–2.5}$. Across studies, low to moderate correlations (i.e., $r < 0.7$) were often observed between copollutants and $PM_{2.5}$. Collectively, studies that examined the potential confounding effects of copollutants on the $PM_{2.5}$ association with respiratory (i.e., lung function and asthma development) and cardiovascular effects (i.e., cardiovascular mortality), along with lung cancer incidence and mortality, reported associations that were relatively unchanged in copollutant models, but these assessments were conducted in a limited number of studies.

Several studies of long-term $PM_{2.5}$ exposure and mortality examined potential copollutant confounding. Within studies that examined the potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and mortality, the most extensive analyses occurred for O_3, with a limited number of studies examining NO_2, SO_2, $PM_{10–2.5}$, and benzene. Studies that examined O_3 reported correlations that were generally moderate (ranging from $r = 0.49$ to 0.73), with a few studies reporting weak correlations ($r < 0.4$). Overall, associations remained relatively unchanged in copollutant models for total (nonaccidental) mortality, cardiovascular, and respiratory mortality (2019 PM ISA, Figure 11-18). Studies focusing on copollutant models with NO_2, $PM_{10–2.5}$, SO_2, and benzene were examined in individual studies, and across these studies the $PM_{2.5}$-mortality association was relatively unchanged (2019 PM ISA, Figure 11-19).

2.2.2. Timing of Effects

An important question to address when evaluating the scientific evidence demonstrating health effects due to short-term $PM_{2.5}$ exposure is the timing of observed effects. Studies have attempted to address this question through two primary avenues: (1) examining various averaging times of the exposure metric used to represent short-term $PM_{2.5}$ exposure to determine whether $PM_{2.5}$ concentrations averaged over time periods other than 24 hours are more closely associated with health effects and (2) assessing whether the relationship between exposure and effect is biologically plausible by examining the lag days over which associations are observed.

2.2.2.1. Averaging Time

Most epidemiologic studies evaluated in the 2019 PM ISA that examined the relationship between short-term $PM_{2.5}$ exposures and health effects relied primarily on an exposure metric averaged over 24-hours. Some recent studies, focusing on respiratory and cardiovascular effects and mortality, have examined whether there is evidence that subdaily exposure metrics are more closely related to health effects than the traditional 24-hour avg metric.

Epidemiologic studies that examined both respiratory-related ED visits and hospital admissions, as well as subclinical markers of respiratory effects, explored associations with subdaily exposure metrics (2019 PM ISA, Section 5.1.10.5). In studies of respiratory-related ED visits and hospital admissions, positive associations were not consistently observed with subdaily exposure metrics, and often there was no information on spatiotemporal variability of the subdaily metrics. Additionally, in a study that examined multiple subdaily averaging times and compared them with the 24-hour avg exposure metric, there was no difference in associations across metrics, but this result was limited to a single study location. Panel studies also examined subdaily exposure metrics through personal monitoring, but

associations were not consistently observed at shorter averaging times for markers of pulmonary inflammation and changes in lung function.

A more limited number of studies examined subdaily exposure metrics and cardiovascular effects (2019 PM ISA, Section 6.1.14.3). Studies of ST elevation, myocardial infarction, out-of-hospital cardiac arrest, and cerebrovascular disease ED visits and hospital admissions reported positive associations with subdaily exposure metrics, but the magnitude of the association tended to be larger when averaging over multiple hours up to 1 day (i.e., 24-hour avg). These studies provided evidence that continues to support the use of a 24-hour avg exposure metric.

A few studies examined subdaily $PM_{2.5}$ exposure metrics and associations with mortality, focusing on comparisons between the 24-hour avg and an hourly peak exposure metric (2019 PM ISA, Section 11.1.8.2). In these studies, positive associations were reported for both the 24-hour avg and hourly peak exposure metric, with the association often slightly larger in magnitude for the 24-hour avg metric. Collectively, the available evidence did not indicate that subdaily averaging periods for $PM_{2.5}$ were more closely associated with health effects than the 24-hour avg exposure metric.

2.2.2.2. Lag Structure of Associations

Often epidemiologic studies examined associations between short-term $PM_{2.5}$ exposure and health effects over a series of single-day lags, multiday lags, or by selecting lags a priori. Studies evaluated in the 2019 PM ISA have expanded the assessment of the timing of effects by systematically examining lag days by focusing on whether there is evidence of an immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days) effect of PM on health.

Epidemiologic studies of respiratory effects have primarily focused on examining the lag structure of associations for respiratory-related ED visits and hospital admissions, with most studies examining asthma exacerbation with a more limited assessment for COPD exacerbation and respiratory infection (2019 PM ISA, Section 5.1.10.3). Across the studies that examined asthma, COPD, respiratory infections, and combinations of respiratory-related diseases, the strongest association reported, in terms of magnitude and precision, was generally within a few days after exposure, but there was some evidence demonstrating the potential for a prolonged effect of $PM_{2.5}$ (i.e., lags ranging from 0 to 5 days). Recent studies of respiratory mortality provided additional insight on the lag structure of associations for respiratory-related effects due to short-term $PM_{2.5}$ exposure. Studies of respiratory mortality tended to support more immediate $PM_{2.5}$ effects (i.e., lags of 0 to 2 days), but with initial evidence of stronger associations, in terms of magnitude and precision, at lags of 0−5 days. Collectively, the studies of respiratory morbidity and mortality that conducted systematic evaluations of $PM_{2.5}$ associations across a range of lags provided evidence of effects within the range of 0−5 days after exposure.

As with respiratory effects, the majority of epidemiologic studies examining the lag structure of associations for cardiovascular effects focused on ED visits and hospital admissions. Studies of ED visits and hospital admissions for IHD, MI, and cardiovascular-related outcomes reported stronger associations for multiday lags, but these effects tended to be in the range of 0−1 or 0−2 days. When examining cerebrovascular disease, there was no evidence of an association at any of the lag days examined; however, when focusing on specific stroke types, particularly ischemic stroke, there was evidence of immediate effects at lags of 0 and 1 day, which was consistent with other cardiovascular outcomes. The immediate effects of $PM_{2.5}$ on cardiovascular morbidity outcomes, specifically those related to ischemic events, were consistent with the lag structure of associations observed in studies of cardiovascular mortality that reported immediate effects (i.e., lag 0−1 day). There was some evidence indicating $PM_{2.5}$-cardviovascular mortality associations with exposures over longer durations, but this was not supported by studies examining single-day lags that encompassed the same number of days.

An evaluation of epidemiologic studies of short-term $PM_{2.5}$ exposure and mortality found that studies either conducted analyses of single-day lags over many days or various iterations of multiday lags (e.g., 0−1, 0−2, 0−3; 2019 PM ISA, Section 11.1.8.1). Across studies, associations were largest in terms of magnitude and precision for total (nonaccidental) mortality at lags of 0 to 1 day, but there was some evidence that associations remained positive at multiday lags up to 0−4 days. The combination of the multi- and single-day lag analyses provided further support of an immediate effect of short-term $PM_{2.5}$ exposure on mortality.

2.2.3. Concentration-Response Relationship

In assessing the relationship between short- and long-term PM exposure and health effects, an important consideration is whether the relationship is linear across the full range of ambient concentrations and whether a threshold concentration exists below which there is no evidence of an effect. As detailed in the 2004 AQCD and 2009 PM ISA, conducting C-R and threshold analyses is challenging because of the "(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of (at-risk) populations (between cities); and (3) influence of measurement error" (U.S. EPA, 2004). Studies evaluated in the 2019 PM ISA that focused on the shape of the C-R curve expanded upon the health effects evaluated in previous reviews and continued to provide evidence of a linear, no-threshold relationship between both short- and long-term $PM_{2.5}$ exposure and several respiratory and cardiovascular effects, and mortality. Some evidence indicated a steeper slope (i.e., supralinear curve) at lower concentrations for some outcomes (i.e., long-term $PM_{2.5}$ exposure and mortality). Cutpoint analyses that focused on whether risk changed at different concentration ranges provided some evidence of nonlinearity, specifically in the relationship between short-term $PM_{2.5}$ exposure and respiratory-related ED visits and hospital admissions. Although studies evaluated in the 2019 PM ISA have used many different statistical methods to examine the shape of the C-R relationship

and generally provided evidence for a linear, no-threshold relationship, many of these studies have not systematically evaluated alternatives to a linear relationship.

2.2.3.1. Short-Term Exposure

Epidemiologic studies evaluated in the 2019 PM ISA that examined the C-R relationship between short-term $PM_{2.5}$ exposure and health were limited to studies of respiratory-related ED visits and hospital admissions (2019 PM ISA, Section 5.1.10.6) and mortality (2019 PM ISA, Section 11.1.10). Across studies that examined respiratory effects, different analytical methods have been employed to examine the C-R relationship, either explicitly examining the shape of the C-R curve and whether there was evidence of linearity across the full range of $PM_{2.5}$ concentrations, or through cutpoint analyses that examine whether the risk of a $PM_{2.5}$-related respiratory effect changed within specified ranges of $PM_{2.5}$ concentrations. These studies primarily focused on asthma ED visits and hospital admissions, with some studies examining combinations of respiratory-related ED visits and hospital admissions. Studies that focused on the shape of the C-R curve provided initial evidence of a linear relationship for short-term $PM_{2.5}$ exposure and both respiratory disease and asthma ED visits and hospital admissions, with less certainty at concentrations below 10 $\mu g/m^3$. However, cutpoint analyses provided some initial evidence indicating nonlinearity in the relationship (i.e., larger risk estimates at various quintiles when compared with the lowest quintile) between short-term $PM_{2.5}$ exposure and asthma ED visits and hospital admissions.

Studies that examined the C-R relationship for short-term PM exposure and mortality were initially limited to those focusing on PM_{10}. Recent epidemiologic studies focused on $PM_{2.5}$ and specifically the shape of the C-R curve at the low end of the $PM_{2.5}$ concentration distribution. Evidence from U.S. studies conducted at lower $PM_{2.5}$ concentrations compared with other countries, provided evidence indicating a linear relationship at concentrations as low as 5 $\mu g/m^3$. The observations from C-R analyses were further supported by cutpoint analyses examining associations at different $PM_{2.5}$ concentrations, as well as analyses that reported no evidence of a threshold. Overall, studies evaluated in the 2019 PM ISA focusing on short-term $PM_{2.5}$ exposure and mortality supported a linear, no-threshold relationship at ambient $PM_{2.5}$ concentrations lower than those evaluated in the 2009 PM ISA.

2.2.3.2. Long-Term Exposure

The most extensive analyses of the C-R relationship between long-term PM exposure and a health effect have generally been for $PM_{2.5}$ and mortality. Recent studies further expanded and provided new insights on the relationship between long-term $PM_{2.5}$ exposure and mortality. In addition, these studies provided initial examinations of the C-R relationship for respiratory and cardiovascular effects, as well as for lung cancer incidence and mortality.

Although the C-R relationship for long-term $PM_{2.5}$ exposure has not been assessed for most health effects, it has been extensively examined in studies of mortality (2019 PM ISA, Section 11.2.4). Across studies, a variety of statistical methods have been used to assess whether there is evidence of deviations in linearity. Studies have also conducted cutpoint analyses that focus on examining risk at specific ambient concentrations (2019 PM ISA, Table 11-7). These studies reported results that generally support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at lower ambient $PM_{2.5}$ concentrations, with confidence in the linear relationship as low as 5−8 $\mu g/m^3$ in some studies. Additionally, there was initial evidence indicating that the slope of the C-R curve may be steeper (supralinear) at lower concentrations for cardiovascular mortality.

Few epidemiologic studies have examined the C-R relationship for long-term $PM_{2.5}$ exposure and respiratory effects (2019 PM ISA, Section 5.2.3.1.2), but the ones that have focused on asthma incidence and childhood wheeze. Studies of asthma incidence that examined the shape of the C-R curve and whether risk changes at different quartiles of $PM_{2.5}$ concentrations did not find any evidence of deviations in linearity and monotonically increasing risk, respectively. In an initial study of childhood wheeze, specifically repeated wheeze events, there was evidence of a linear C-R relationship with confidence in the linear relationship at long-term $PM_{2.5}$ concentrations as low as 10 to 12 $\mu g/m^3$.

A limited number of studies reported initial assessments of the C-R relationship for long-term $PM_{2.5}$ concentrations and cardiovascular effects, specifically IHD incidence, CAC, and hypertension (2019 PM ISA, Section 6.2.16). For IHD incidence, there was evidence of a linear C-R relationship at concentrations below 15 $\mu g/m^3$, which was consistent with the shape of the curve when compared with the full range of $PM_{2.5}$ concentrations. Analyses of the relationship between long-term $PM_{2.5}$ exposure and CAC indicated both linear and nonlinear relationships, while there is preliminary evidence of a linear relationship between long-term $PM_{2.5}$ exposure and incidence of hypertension. A few studies that examined the relationship between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality also examined the shape of the C-R curve by assessing its linearity and conducting cutpoint and threshold analyses (2019 PM ISA, Section 10.2.5.1.4). These collective assessments provided initial evidence supporting a no-threshold, linear relationship across the range of $PM_{2.5}$ concentrations observed in the U.S., with confidence in a linear relationship as low as 5−10 $\mu g/m^3$ in some studies.

2.2.4. PM Components and Sources

Building on the initial evaluation conducted in the 2004 PM AQCD, the 2009 PM ISA formally evaluated the relationship between exposures to PM components and sources and health effects. This evaluation found that many components and sources representative of combustion-related activities (e.g., motor vehicle emissions, coal combustion, oil burning, vegetative burning) were associated with a range of health effects. The 2009 PM ISA, therefore, concluded that "many [components] of PM can be

linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those components or sources that are more closely related to specific health outcomes."

Building upon the evaluation of PM sources and components in the 2009 PM ISA, and as detailed in the Preface of the 2019 PM ISA, the 2019 PM ISA systematically evaluated whether specific PM components or sources were more strongly associated with health effects than PM mass by focusing on those studies that: (1) included a composite metric of PM (e.g., mass of $PM_{2.5}$ and/or $PM_{10–2.5}$, or in the case of ultrafine particles [UFP] mass, particle number) and PM components; (2) applied some approach to assess the particle effect (e.g., particle trap) of a mixture; or (3) conducted formal statistical analyses to identify source-based exposures (see 2019 PM ISA, Preface). Overall, these criteria allowed for a thorough evaluation of whether there was evidence that an individual component(s) and/or source(s) was more closely related to health effects than PM mass. Across the health effects categories evaluated in the 2019 PM ISA, most studies that examined PM sources and components focused on $PM_{2.5}$. Thus, the following sections summarize the state of the science on $PM_{2.5}$ components and sources for those health effects categories for which it was concluded within the 2019 PM ISA that there was a *causal* or *likely to be causal relationship*. Details on the $PM_{2.5}$ components and sources evidence relevant to other health effects categories (e.g., Reproductive and Developmental Effects) are covered in the health chapters of the 2019 PM ISA.

Overall, recent studies continued to demonstrate that many $PM_{2.5}$ components and sources were associated with health effects ranging from subclinical (e.g., changes in heart function, such as HRV, or circulating biomarkers) to the more overt (i.e., ED visits, hospital admissions, and mortality). The results of these studies confirmed and further supported the conclusion of the 2009 PM ISA that many $PM_{2.5}$ components and sources are associated with many health effects and that the evidence does not indicate that any one source or component is consistently more strongly related with health effects than $PM_{2.5}$ mass.

2.2.4.1. Respiratory Effects

The examination of $PM_{2.5}$ components and sources and respiratory effects was limited to epidemiologic studies (2019 PM ISA, Section 5.1.11). Epidemiologic studies that examined the relationship between respiratory health effects and short-term exposure to both $PM_{2.5}$ mass (n = 113) and $PM_{2.5}$ components, primarily focused on the components nitrate (n = 29), sulfate (n = 40), OC (n = 50), and EC/BC (n = 95). Across these studies, the health effects examined range from inflammation and changes in lung function to respiratory-related ED visits and hospital admissions. When examining the pattern of associations for individual $PM_{2.5}$ components with those observed for $PM_{2.5}$ mass, all the components examined (i.e., evaluated in at least three studies) were positively associated with a respiratory effect in at least a few studies (2019 PM ISA, Section 5.1.11.7). For EC/BC, the most extensively examined $PM_{2.5}$ component, many studies reported positive associations, but some studies

also reported results indicating no association, which was consistent with the pattern of associations for $PM_{2.5}$ mass.

A more limited number of studies examined associations between long-term $PM_{2.5}$ components exposure and respiratory effects (2019 PM ISA, Section 5.2.12). Similar to short-term exposure studies, most long-term exposure studies focused on EC/BC and did not observe a pattern of associations with respiratory effects different from that observed for $PM_{2.5}$ mass. Collectively, positive associations were observed in studies examining short- and long-term $PM_{2.5}$ component exposure and respiratory effects, but there was no evidence that any one component was more strongly associated with respiratory effects than $PM_{2.5}$ mass.

Few studies examined the relationship between $PM_{2.5}$ sources and respiratory health effects. Through analyses in which $PM_{2.5}$ components were apportioned into source factors, positive associations were reported for several respiratory effects, particularly asthma exacerbation, and sources representative of combustion-related activities, such as traffic and biomass burning. No studies evaluated in the 2019 PM ISA examined long-term exposure to $PM_{2.5}$ sources and respiratory effects.

2.2.4.2. Cardiovascular Effects

Both epidemiologic and experimental studies examined the relationship between exposure to $PM_{2.5}$ component and sources and cardiovascular effects (2019 PM ISA, Section 6.1.15). In short-term exposure studies, the epidemiologic evidence focused on studies examining cardiovascular-related ED visits and hospital admissions, with only a few studies examining other cardiovascular effects. Similar to respiratory effects studies, the cardiovascular effects studies that examined both $PM_{2.5}$ mass and components (n = 14) focused most extensively on EC (n = 12), OC (n = 10), sulfate (n = 9), and nitrate (n = 9). Across all components examined, most were positively associated with cardiovascular-related ED visits and hospital admissions in at least one study (2019 PM ISA, Section 6.1.15). Although EC was positively associated with cardiovascular-related ED visits and hospital admissions in many of the studies evaluated, it was not possible to tell whether EC was independently associated or a marker of exposure to $PM_{2.5}$ mass.

Few studies examined long-term exposure to $PM_{2.5}$ components and cardiovascular effects, and those that did were consistent with the long-term exposure and respiratory effects studies that primarily focused on EC/BC (2019 PM ISA, Section 6.2.17). These studies did not provide evidence that any one component was more strongly associated with a cardiovascular effect. Collectively, studies examining short- and long-term $PM_{2.5}$ components exposure continue to support that there is no evidence that any one component is more strongly associated with a cardiovascular effect than $PM_{2.5}$ mass.

Epidemiologic and animal toxicological studies conducted source-based analyses using mathematical methods to apportion $PM_{2.5}$ components into source factors (2019 PM ISA, Section 6.1.15.6

and Section 6.1.15.8). Epidemiologic studies focused on cardiovascular-related ED visits and hospital admissions and reported positive associations with sources representative of combustion-related activities (e.g., industrial combustion, traffic), with more limited evidence for wildfires. Animal toxicological studies, which focused on markers of heart function (e.g., HR, HRV), reported associations with a variety of source categories, but the associations were dependent on the location of the study (i.e., where the $PM_{2.5}$ CAPs were collected). Additional studies focusing on long-term exposures to $PM_{2.5}$ sources were fewer, with epidemiologic studies only examining traffic sources and animal toxicological studies reporting associations between a number of sources and various cardiovascular effects.

2.2.4.3. Mortality

Epidemiologic studies that examined associations with $PM_{2.5}$ components and sources and mortality have primarily focused on examining short- and long-term exposures to components (2019 PM ISA, Section 11.1.11 and Section 11.2.6). Both short- and long-term exposure studies reported consistent, positive associations with $PM_{2.5}$ mass across all studies that also examined a $PM_{2.5}$ component. Although the respiratory and cardiovascular effects studies focused mainly on EC/BC, the studies of mortality did not examine any one component disproportionately over the others. Of the $PM_{2.5}$ components examined, each were found to be positively associated with mortality in at least a few studies, but overall, one component was not found to be as consistently associated with mortality as $PM_{2.5}$ mass.

Compared with the 2009 PM ISA, in which most epidemiologic studies of mortality conducted formal source apportionment analyses, studies evaluated in the 2019 PM ISA have focused more exclusively on $PM_{2.5}$ components. Of the limited number of studies that examined associations between short- and long-term source exposures and mortality, positive associations were observed for those sources representative of combustion-related activities, including traffic, coal, and vegetative fires.

2.2.5. Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect

An important consideration in evaluating the scientific evidence for PM, and in determining the extent to which the NAAQS provides public health protection, is whether specific populations or lifestages are at increased risk of a PM-related health effect. As detailed in the preceding sections of this chapter and in health effects chapters of the 2019 PM ISA, a large body of evidence shows that health effects related to PM exposure, particularly $PM_{2.5}$ exposure, occur across populations with diverse characteristics (e.g., children, older adults, people with preexisting cardiovascular diseases). Although this larger body of evidence provided information on the causal nature of the relationship between PM exposure and health effects, this section focuses on answering the following question:

Are there specific populations and lifestages at increased risk of a PM-related health effect, compared to a reference population? That is, is the magnitude of effect or exposure greater for some populations or lifestages compared to a reference population, where applicable?

The evaluation of populations and lifestages potentially at increased risk builds off the approach used in the 2009 PM ISA and involved application of a framework detailed in the 2013 O_3 ISA to characterize the evidence informing whether a population or lifestage is at increased risk (U.S. EPA, 2013). The focus of this evaluation was on determining the extent to which specific factors may increase the risk of a PM-related health effect in a population or lifestage relative to a reference population, where applicable. Importantly, this evaluation builds on the conclusions drawn elsewhere in the 2019 PM ISA, taking into consideration the relationship between exposure to PM and health effects. As detailed in the Preamble to the ISAs (U.S. EPA, 2015), the evaluation of the evidence includes (1) epidemiologic studies that conducted stratified analyses, (2) evidence from animal toxicological studies using animal models of disease and epidemiologic or controlled human exposure studies conducted in specific populations (e.g., lung function growth in children, people with mild asthma), (3) information on the dosimetry of PM within the body, and (4) consideration of information on differential exposure to PM within a population or lifestage. Overall, the framework allows for a transparent characterization of the collective body of evidence to draw conclusions on the degree to which the scientific evidence indicates that a specific population or lifestage is at increased risk of a PM-related health effect (2019 PM ISA, Table 12-1).

The causality determinations briefly summarized within this section, which are more fully detailed in the health effects chapters of the 2019 PM ISA, suggest that the strongest evidence indicating an effect of short- and long-term PM exposure on health is for $PM_{2.5}$ and the broad health categories of respiratory and cardiovascular effects, nervous system effects, cancer, and mortality. Thus, the assessment of populations and lifestages potentially at increased risk of a $PM_{2.5}$-related health effect primarily focused on studies that form the basis of these causality determinations that also conducted analyses to inform whether there is differential risk in a specific population or lifestage. In evaluating studies, several factors can influence the ability to observe an association, including, but not limited to, publication bias (i.e., not reporting null findings when examining evidence of differential risk), variability in how indicators or metrics are defined across studies (e.g., socioeconomic status, obesity, age), and variability in the population as a whole, particularly with respect to behavioral differences, biological differences (e.g., obese versus nonobese), and adherence to treatment for preexisting diseases.

Of the factors evaluated (2019 PM ISA, Table 12-3 for a full list), children and race were the only factors for which it was concluded that *"adequate evidence"* was available, indicating that people of a specific lifestage and race are at increased risk of $PM_{2.5}$-related health effects (2019 PM ISA, Section 12.5.1.1 and Section 12.5.4). Although stratified analyses do not indicate a difference in the risk of PM-related health effects between children and adults, there was strong evidence from studies focusing on children that demonstrated health effects only observable in growing children that were attributed to $PM_{2.5}$ exposure. Specifically, epidemiologic studies evaluated in the 2019 PM ISA of long-term $PM_{2.5}$

exposure provided strong evidence of impaired lung function growth with additional evidence of decrements in lung function and the development of asthma. The results of these longitudinal epidemiologic studies were consistent with and extended the evidence that was available in the 2009 PM ISA demonstrating health effects in children due to long-term $PM_{2.5}$ exposure. The conclusion of *"adequate evidence"* for race was based on studies that examined whether there was evidence of increased risk for $PM_{2.5}$-related health effects as well as studies that examined differential exposure by race. Multiple studies reported that minority populations (often defined as non-White populations within individual studies) across different geographical regions are exposed to higher $PM_{2.5}$ concentrations and were at increased risk for $PM_{2.5}$-related mortality, particularly due to long-term exposure. Collectively, the combination of evidence demonstrated that minority populations are at greater risk for both $PM_{2.5}$-related health effects and $PM_{2.5}$ exposure than are Whites.

There was *"suggestive evidence"* that populations with preexisting cardiovascular (2019 PM ISA, Section 12.3.1) or respiratory (2019 PM ISA, Section 12.3.5) disease, those who are overweight or obese (2019 PM ISA, Section 12.3.3), those with particular genetic variants (2019 PM ISA, Section 12.4), those who are of low SES (2019 PM ISA, Section 12.5.3), and those who are current or former smokers (2019 PM ISA, Section 12.6.1) are at increased risk for $PM_{2.5}$-related health effects. Epidemiologic studies that conducted analyses stratified by preexisting cardiovascular disease tended to focus on hypertension, one of the most easily measurable cardiovascular conditions, and did not consistently indicate increased risk for several outcomes examined (e.g., mortality, stroke, BP). However, the strong evidence supporting a *causal relationship* between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects, which included cardiovascular-related mortality and ischemic heart disease (2019 PM ISA, Section 6.1.16 and Section 6.2.18) indicated that individuals with underlying cardiovascular conditions related to these serious outcomes may be at increased risk of a $PM_{2.5}$-related health effect. Similarly, there were few studies that evaluated whether there is evidence of increased risk of a $PM_{2.5}$-related health effect between people with preexisting asthma (2019 PM ISA, Section 12.3.5) and COPD (2019 PM ISA, Section 12.3.5) compared with people that do not have a preexisting respiratory disease. However, epidemiologic studies, particularly those studies examining short-term $PM_{2.5}$ exposure and asthma or COPD ED visits and hospital admissions reported generally consistent positive associations (2019 PM ISA, Section 5.1.2.1 and Section 5.1.4.1), which represent exacerbations that are only possible in people with asthma or COPD. Therefore, there was limited evidence to support that people with preexisting respiratory diseases, specifically asthma or COPD, are at increased risk for a $PM_{2.5}$-related health effect, but there was generally consistent evidence demonstrating these populations experience health effects due to a $PM_{2.5}$ exposure.

Studies that examined whether being obese or overweight increased the risk of a $PM_{2.5}$-related health effect, reported evidence of increased risk for mortality associated with long-term exposures to $PM_{2.5}$, but inconsistent evidence was found for subclinical cardiovascular outcomes, when comparing obese or overweight individuals with normal weight individuals. However, the evaluation of studies

focusing on differences in risk by weight were complicated by the different definitions of obesity used across studies.

The examination of whether specific genetic characteristics dictate increased risk of a $PM_{2.5}$-related health effect involved studies of genetic variants. Across the large number of genetic variants examined there was a consistent trend for increased risk of respiratory and cardiovascular effects associated with $PM_{2.5}$ exposure across gene variants involved in the glutathione transferase pathway. These results were consistent with underlying mechanisms that provided biological plausibility for $PM_{2.5}$-related health effects and have shown that oxidative stress is an early response to $PM_{2.5}$ exposure.

Epidemiologic studies have examined several measures of SES (e.g., income level, educational attainment) in assessing whether populations are at increased risk of a $PM_{2.5}$-related health effect. In studies examining both differential exposure and increased risk of health effects, there was some evidence that low SES populations are more likely to have higher $PM_{2.5}$ exposures and that low SES populations, as measured by metrics for income, are at increased risk of $PM_{2.5}$-related mortality when compared with populations defined as higher SES. Finally, there was some epidemiologic evidence from studies examining long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, as well as total mortality, that people who currently smoke or were former smokers may be at increased risk of a $PM_{2.5}$-related health effect compared with never smokers.

For the remaining factors evaluated, "*inadequate evidence*" exists to determine whether having diabetes (2019 PM ISA, Section 12.3.2), being in an older lifestage (i.e., older adults; 2019 PM ISA, Section 12.5.1.2), residential location (including proximity to source and urban residence; 2019 PM ISA, Section 12.5.5), sex (2019 PM ISA, Section 12.5.2), or diet (2019 PM ISA, Section 12.6.2) increase the risk of $PM_{2.5}$-related health effects. Across these factors there was either limited assessment of differential risk or exposure (i.e., residential location, diet), or inconsistency in results across studies to support evidence of increased risk of a $PM_{2.5}$-related health effect (i.e., diabetes and sex). Instead, the inconsistency in the evidence makes the determination of disproportionately increased risk more difficult. For example, for older adults (2019 PM ISA, Section 12.5.1.2) there was a relatively small number of studies that examined whether there is evidence of differential risk between age groups. In the evaluation of these studies there was limited evidence indicating that older adults are at increased risk of $PM_{2.5}$-related health effects compared with other age ranges; however, epidemiologic studies focusing only on older adults demonstrated associations with respiratory-related ED visits and hospital admissions with additional, but more limited, evidence of subclinical cardiovascular effects from epidemiologic panel studies and controlled human exposure studies.

2.3. Welfare Effects

Whereas the evaluation of the evidence for PM exposures and health effects was specific to exposure duration (i.e., short- and long-term) and PM size fraction (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFP), the

evaluation of the evidence for welfare effects focused generally on whether there was a *causal relationship* between PM and visibility impairment, climate effects, and effects on materials. As detailed below, the evidence continued to support a *causal relationship* between PM and visibility impairment (2019 PM ISA, Section 1.6.1), climate effects (2019 PM ISA, Section 1.6.2), and materials effects (2019 PM ISA, Section 1.6.3).

2.3.1. Visibility Impairment

It is well known that light extinction from pollution is primarily due to $PM_{2.5}$, resulting in the 2019 PM ISA concluding there is a *causal relationship* between PM and visibility impairment, which was consistent with the conclusions of the 2009 PM ISA (Table 2-3). This conclusion was based on additional characterization of the effect of PM size and composition on light extinction.

The relationship between PM and light extinction has been well documented (2019 PM ISA, Section 13.2.2). Although reconstruction of light extinction is best achieved with detailed information on the size and composition of PM measurements, empirical relationships between light extinction of PM components are more practical and have been successfully evaluated and widely used (2019 PM ISA, Section 13.2.3). Light extinction has been found to vary depending on the available PM species monitoring data, with light extinction efficiencies varying by a factor of 10 between species. Additionally, the variation in PM species by region and season, as well as urban and rural location, can affect light extinction. The steep decline in $PM_{2.5}$ sulfate of −4.6% per year in rural areas and −6.2% per year in urban areas from 2002 to 2012 (2019 PM ISA, Section 1.2.1) has affected the apportionment of light extinction among $PM_{2.5}$ species. Although $PM_{2.5}$ sulfate is still a major contributor to light extinction, visibility in many areas has improved, and a smaller and less seasonally variable fraction of light extinction can be attributed to $PM_{2.5}$ sulfate, with an increasing share due to nitrate and organic matter (2019 PM ISA, Section 13.2.4).

2.3.2. Climate Effects

Substantial evidence indicates that PM affects the radiative forcing of the climate system, both through direct scattering and absorption of radiation, and indirectly, by altering cloud properties, resulting in the conclusion that there is a *causal relationship* between PM and climate effects, which was consistent with the conclusions of the 2009 PM ISA (2019 PM ISA, Table 1-3). This conclusion was based on multiple studies evaluated in the 2019 PM ISA that have strengthened the evidence for the effects of PM on radiative forcing and have improved the characterization of major sources of uncertainty in estimating PM climate effects, including the indirect radiative forcing effects associated with PM-cloud interactions, and the additional climate effects and feedbacks involving atmospheric circulation and the hydrologic cycle resulting from PM effects on radiative forcing.

Because of these radiative effects, the net effect of PM has been to cool the planet over the last century, masking some of the effects of greenhouse gases on warming (2019 PM ISA, Section 13.3.3). The decrease in PM concentrations in many developed countries over the last few decades has likely contributed to the recent shift toward "global brightening," which may in turn have helped drive rapid warming in North America and Europe because this greenhouse-gas warming was unmasked (2019 PM ISA, Section 13.3.6). In developing countries in Asia, by contrast, PM concentrations have increased over the last several decades, but the associated radiative forcing effects are highly uncertain, due to uncertainties in emissions estimates and the lack of accurate information on the proportion of reflecting versus absorbing species. Although uncertainties in the relationship between PM and climate effects have been further studied and characterized since the 2009 PM ISA, there are still substantial uncertainties with respect to key processes linking PM and climate, specifically the interaction between clouds and aerosols. This is because of the small scale of PM-relevant cloud microphysical processes compared with the coarse resolution of state-of-the-art models, and because of the complex cascade of indirect effects and feedbacks in the climate system that result from a given initial radiative perturbation caused by PM.

2.3.3. Materials Effects

Multiple studies evaluated in the 2019 PM ISA further characterized soiling and corrosion processes associated with PM and add to the body of evidence of PM damage to materials. Approaches to quantify pollutant exposure corresponding to perceived soiling and damage continue to indicate that deposition can result in increased cleaning and maintenance costs and reduced usefulness of soiled material. The combination of this evidence resulted in the conclusion that there is a *causal relationship* between PM and effects on materials, which was consistent with the conclusions of the 2009 PM ISA (Table 2-3).

Assessments of the relationship between PM and effects on materials have often focused on quantitative assessments including the development of dose-response relationships and application of damage functions to stone used for historic monuments and buildings. Recent studies provided additional information on understanding soiling and corrosion process for glass and metals and have allowed for the development of new dose-response curves (2019 PM ISA, Section 13.4.3), particularly for glass, as well as new damage functions for materials (2019 PM ISA, Section 13.4.4). Additional evidence demonstrated that atmospheric soiling can affect energy costs and climate control, energy consumption of large buildings, and the efficiency of photovoltaic systems (2019 PM ISA, Section 13.4.2).

Table 2-3 Key evidence contributing to *causal* causality determinations for PM exposure and welfare effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Welfare Effect Category[a] and Causality Determination
Visibility Impairment and PM Exposure (2019 PM ISA, Section 13.2): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*	
Section 13.2.6	Visibility impairment by atmospheric PM, with the strongest effects in the size range from 0.1 to 1.0 μm, was supported by numerous studies summarized in the 1969 PM AQCD (NAPCA, 1969), although the relationship between PM and atmospheric visibility impairment was well established decades earlier. Additional studies supporting the relationship have been described in subsequent documents, and additional new evidence is based on extensive simultaneous network measurements of $PM_{2.5}$ and light extinction.
Climate Effects and PM Exposure (2019 PM ISA, Section 13.3): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*	
Section 13.3.9	Effects of PM on radiative forcing of the climate system through both absorption and scattering of radiation directly, as well as through indirect effects involving interactions between PM and cloud droplets, with corresponding effects on temperature, precipitation, and atmospheric circulation, was supported by numerous observational and modeling studies. Research since the 2009 PM ISA (U.S. EPA, 2009) has improved understanding of climate-relevant aerosol properties and processes, as well as characterized key sources of uncertainty in estimating PM climate effects, particularly with respect to PM-cloud interactions.
Materials Effects and PM Exposure (2019 PM ISA, Section 13.4): Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*	
Section 13.4.5	Both soiling and corrosion associated with PM contribute to materials damage (U.S. EPA, 2009, 2004, 1982). Deposition of PM can physically affect materials by promoting or accelerating the corrosion of metals, by degrading paints, and by deteriorating building materials such as stone, concrete, and marble. Further characterization of PM effects on glass and metals, along with quantitative dose-response relationships and damage functions for stone and other materials lend additional support to the causal relationship in the 2009 PM ISA. Studies evaluated in the 2019 PM ISA showed that deposition of PM reduces energy efficiency of photovoltaic systems.

AQCD = Air Quality Criteria Document; PM = particulate matter.

[a]The sections referenced in the 2019 PM ISA include a detailed discussion of the available evidence that informed the causality determinations.

3. EVALUATION OF RECENT HEALTH EFFECTS EVIDENCE

The following section focuses on the evaluation of recent health effects studies that fall within the scope of this Supplement as detailed in Section 1.2.2. Within this section the evaluation of recent studies is performed in the context of the studies evaluated and scientific conclusions presented in the Integrated Science Assessment for Particulate Matter (2019 PM ISA). As a result, within each of the following sections, the summary and causality determination from the 2019 PM ISA is presented prior to the evaluation of recent studies published since the literature cutoff date of the 2019 PM ISA that examine the relationship between short-term (i.e., hours up to 1 month) and long-term (i.e., over 1 month to years) $PM_{2.5}$ exposure and cardiovascular effects (Section 3.1) and mortality (Section 3.2).[13] This approach allows for a full accounting of the evidence that formed the basis of the key scientific conclusions in the 2019 PM ISA and the identification of specific sections of the 2019 PM ISA that provide additional details on the total evidence base being considered in the process of reconsidering the 2020 PM NAAQS.

In addition to the evaluation of recent U.S. and Canadian epidemiologic studies that examine the relationship between short-term and long-term $PM_{2.5}$ exposure cardiovascular effects and mortality, this section also evaluates studies that address key scientific topics for which the literature has evolved since the 2020 PM NAAQS review was completed, specifically since the literature cutoff date for the 2019 PM ISA (Section 3.3). These topics that further inform the health effects attributed to $PM_{2.5}$ exposure include experimental studies conducted at near-ambient concentrations (Section 3.3.1), studies that examine the role of $PM_{2.5}$ exposure on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) death (Section 3.3.2), and studies that examine whether there are disparities in exposure to $PM_{2.5}$ or the risk of $PM_{2.5}$-related health effects by race/ethnicity or socioeconomic status (SES).

The studies evaluated in the following sections represent only those studies most informative in considering potential revisions to the PM NAAQS as defined by the scope of this Supplement (Section 1.2.2), that is, U.S. and Canadian epidemiologic studies and other studies that address key scientific topics. Therefore, the scientific information presented in this section does not represent the full multidisciplinary evaluation presented within the 2019 PM ISA, which would lead to the formation of a causality determination. As a result, the summary sections for each health effects category convey how the evidence from recent studies fits within the scientific conclusions of the 2019 PM ISA, and indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with and

[13]Throughout this Supplement, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations and long-term exposures are for a 5 $\mu g/m^3$ increase in annual concentrations, unless otherwise noted.

reduces uncertainties), or does not support (is not consistent with) the causality determinations in the 2019 PM ISA.

3.1. Cardiovascular Effects

3.1.1. Short-Term $PM_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for short-term $PM_{2.5}$ exposure and cardiovascular effects presented in the 2019 PM ISA (Section 3.1.1.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.1.1.2). [14] In addition, with the expansion of epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.1.1.3), which can further inform the relationship between short-term $PM_{2.5}$ exposure and cardiovascular morbidity. Finally, a summary of the results of recent studies evaluated in the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.1.1.4). The evaluation of recent studies presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.1.1.1. Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

A large body of evidence evaluated in the 2019 PM ISA confirmed and extended the evidence from the 2009 PM ISA (U.S. EPA, 2009) indicating a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. The strongest evidence in the 2009 PM ISA was from epidemiologic studies of emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD) and heart failure, with supporting evidence from epidemiologic studies of cardiovascular mortality. Changes in various measures of cardiovascular function in controlled human exposure studies provided some biological plausibility for these associations. In addition, animal toxicological studies reporting some evidence of reduced myocardial blood flow during ischemia, altered vascular reactivity, and ST segment depression provided additional biological plausibility.

In addition to evaluating evidence across scientific disciplines that examined the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects, discussed below, the 2019 PM ISA

[14] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations, unless otherwise noted.

characterized whether evidence supported biologically plausible mechanisms by which short-term $PM_{2.5}$ exposure could lead to cardiovascular effects. This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies that examined a range of cardiovascular effects (2019 PM ISA, Section 6.1.1). Plausible mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to apical events reported in epidemiologic studies (2019 PM ISA, Figure 6-1). The first proposed pathway identified begins as respiratory tract inflammation leading to systemic inflammation. The second proposed pathway identified involves activation of sensory nerve pathways in the respiratory tract that lead to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as ED visits and hospital admissions for IHD and heart failure, and ultimately mortality (2019 PM ISA, Figure 6-1).

In the 2019 PM ISA, evidence supporting the causality determination included generally positive associations from epidemiologic studies of hospital admissions and ED visits for cardiovascular-related effects, and in particular, for IHD and heart failure. Results from these observational studies were supported by experimental evidence from controlled human exposure and animal toxicological studies of endothelial dysfunction, as well as endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in heart rate variability (HRV), increases in blood pressure (BP), and increases in indicators of systemic inflammation, oxidative stress, and coagulation. Additional results from observational panel studies, although not entirely consistent, provided at least some evidence of increased risk of arrhythmia, decreases in HRV, increases in BP, and ST segment depression. Thus, epidemiologic panel studies also provided some support to the causality determination and to biological plausibility. Finally, epidemiologic studies of cardiovascular-related mortality provided additional evidence that demonstrated a continuum of effects from biomarkers of inflammation and coagulation, subclinical endpoints (e.g., HRV, BP, endothelial dysfunction), ED visits and hospital admissions, and eventually death. The evidence evaluated in the 2019 PM ISA also reduced uncertainties from the previous review related to potential copollutant confounding and limited biological plausibility for cardiovascular effects following short-term $PM_{2.5}$ exposure. Evidence supporting the causality determination for short-term $PM_{2.5}$ exposure and cardiovascular effects reached in the 2019 PM ISA is discussed below and summarized in Table 3-1, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 3-1 Summary of evidence for a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects from the 2019 Integrated Science Assessment for Particulate Matter.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects[c] ($\mu g/m^3$)
Consistent epidemiologic evidence from multiple studies at relevant $PM_{2.5}$ concentrations	Increases in ED visits and hospital admissions for IHD and heart failure in multicity studies conducted in the U.S., Canada, Europe, and Asia Increases in cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 6.1.2.1 Section 6.1.3.1 Section 6.1.9	5.8−18.6 5.8−18.0
Evidence from controlled human exposure studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of endothelial dysfunction Generally consistent recent evidence for small increases in measures of blood pressure following CAPs exposure Although not entirely consistent, there is additional evidence of conduction abnormalities, heart rate variability, impaired heart function, systemic inflammation/oxidative stress.	Section 6.1.13.2 Section 6.1.6.3 Section 6.1.4.3 Section 6.1.3.2 Section 6.1.10.2 Section 6.1.11.2	24−325 See Tables in identified sections
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in indicators of endothelial dysfunction. Additional evidence of changes in impaired heart function, conduction abnormalities/arrhythmia, heart rate variability, blood pressure, systemic inflammation/oxidative stress.	Section 6.1.13.3 Section 6.1.6.4 Section 6.1.4.4 Section 6.1.3.3 Section 6.1.11.3	168.7−510 See Tables in identified sections
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants. Further support from copollutant analyses indicates positive associations for cardiovascular mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 6.1.14.1	

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects[c] ($\mu g/m^3$)
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and CVD ED visits and hospital admissions across exposure measurement metrics	Positive associations consistently observed across studies that used ground-based (i.e., monitors), model (e.g., CMAQ, dispersion models), and remote sensing (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more of these methods.	Kloog et al. (2014)	
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure. Includes evidence for reduced myocardial blood flow, altered vascular reactivity, and ST segment depression.	Section 6.1.1 Figure 6-1	
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-cardiovascular ED visit and hospital admission associations. Evidence supports the supposition that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.	Section 6.1.2.1 Section 6.1.3.1	

Note: This table corresponds to Table 6-34 in the 2019 PM ISA.

AOD = aerosol optical depth; CMAQ = Community Multiscale Air Quality model; CVD = cardiovascular disease; ED = emergency department; IHD = ischemic heart disease; $\mu g/m^3$ = micrograms per cubic meter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; ST = beginning of S wave to end of T wave.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

The generally consistent, positive associations observed in numerous epidemiologic studies of ED visits and hospital admissions for IHD, heart failure, and combined cardiovascular-related endpoints contributed to the evidence supporting a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular disease (CVD). Among this body of evidence, nationwide studies of older adults using Medicare reported positive associations between $PM_{2.5}$ concentrations and heart failure hospital admissions (2019 PM ISA, Section 6.1.3.1). Consistent with the results of these large Medicare studies, additional multicity studies conducted in the Northeast U.S. reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits or hospital admissions for IHD (2019 PM ISA, Section 6.1.2.1), whereas studies conducted in the U.S. and Canada reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits for heart failure. Results from epidemiologic studies conducted in single cities contributed additional support to the causality determination but are less consistent and reported both positive and null associations between $PM_{2.5}$ concentrations and these endpoints (2019 PM ISA, Section 6.1.2 and Section 6.1.3). Overall, the body of IHD and heart failure epidemiologic evidence evaluated in the 2019 PM ISA agreed with the evidence from previous ISAs reporting mainly positive associations between short-term $PM_{2.5}$ concentrations and ED visits and hospital admissions. In addition, several controlled human exposure, animal toxicological, and epidemiologic panel studies provided biologically plausible evidence that $PM_{2.5}$ exposure could result in IHD or heart failure through pathways that include endothelial dysfunction, arterial thrombosis, and arrhythmia (2019 PM ISA, Section 6.1.1). Epidemiologic panel studies evaluated in the 2019 PM ISA also supported biological plausibility for IHD and heart failure endpoints by reporting some evidence of ST segment depression (2019 PM ISA, Section 6.1.2.2), with a controlled human exposure study and animal toxicological study showing decreased cardiac function following short-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.1.3.2 and Section 6.1.3.3).

Results from additional controlled human exposure studies published since the 2009 PM ISA also support a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. The most consistent evidence from these studies is for endothelial dysfunction as measured by changes in brachial artery diameter (BAD) or flow-mediated dilatation (FMD). More specifically, and in contrast to the 2009 PM ISA for which a couple of studies did not find changes in endothelial function, multiple studies evaluated in the 2019 PM ISA that examined the potential for endothelial dysfunction reported an effect of $PM_{2.5}$ on measures of blood flow (2019 PM ISA, Section 6.1.13.2) relative to filtered air (FA) exposure. Nevertheless, all studies were not in agreement with respect to the timing of the effect or the mechanism by which reduced blood flow occurred (i.e., endothelial-independent versus endothelial-dependent mechanisms). In addition to endothelial dysfunction, controlled human exposure studies evaluated in the 2019 PM ISA that used CAPs, but not filtered diesel exhaust (DE), generally reported evidence for small increases in blood pressure, although there were inconsistencies across studies with respect to changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP). It is notable however, that CAPs studies evaluated in the 2019 PM ISA that reported increases in one measure of BP (e.g., SBP), but not the other (e.g., DBP) was found to be statistically significant, that other measure of

BP usually changed as well, but the change was not found to be statistically significant (2019 PM ISA, Section 6.1.6.3). That said, the results of studies evaluated in the 2019 PM ISA are not in agreement with a couple of older controlled human exposure studies that reported no appreciable changes in blood pressure following short-term $PM_{2.5}$ exposure. In addition, although not entirely consistent, there is further evidence from controlled human exposure studies evaluated in the 2019 PM ISA for conduction abnormalities/arrhythmia (2019 PM ISA, Section 6.1.4.3), changes in HRV (2019 PM ISA, Section 6.1.10.2), changes in hemostasis that could promote clot formation (2019 PM ISA, Section 6.1.12.2), and increases in inflammatory cells and markers (2019 PM ISA, Section 6.1.11.2). Thus, although uncertainties remain, controlled human exposure studies are in coherence with epidemiologic studies by demonstrating that short-term exposure to $PM_{2.5}$ may result in the types of cardiovascular endpoints that could lead to ED visits and hospital admissions.

Animal toxicological studies published since the 2009 PM ISA also support a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. A study evaluated in the 2019 PM ISA demonstrated decreased cardiac contractility and left ventricular pressure in mice which was coherent with the results of epidemiologic studies that reported associations between short-term $PM_{2.5}$ exposure and heart failure (2019 PM ISA, Section 6.1.3.3). In addition, like in the controlled human exposure studies, there was generally consistent evidence in animal toxicological studies for indicators of endothelial dysfunction (2019 PM ISA, Section 6.1.13.3). Studies in animals also provided evidence for changes in several other cardiovascular endpoints following short-term $PM_{2.5}$ exposure. Although not entirely consistent, these studies provided at least some evidence of conduction abnormalities and arrhythmia (2019 PM ISA, Section 6.1.4.4), changes in HRV (2019 PM ISA, Section 6.1.10.3), changes in BP (2019 PM ISA, Section 6.1.6.4), and evidence for systemic inflammation and oxidative stress (2019 PM ISA, Section 6.1.11.3). Finally, these toxicological studies also provided evidence indicating that genetic background, diet, and PM composition may influence the effect of short-term $PM_{2.5}$ exposure on some of these health endpoints.

As outlined above, across the scientific disciplines, there is evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects ranged from relatively modest increases in biomarkers related to inflammation and coagulation, to subclinical CVD endpoints such as endothelial dysfunction, to ED visits and hospital admissions for outcomes such as IHD and heart failure. This continuum of effects is supported by epidemiologic studies that reported a relatively consistent relationship between short-term $PM_{2.5}$ exposure and CVD-related mortality. These epidemiologic studies also reduced a key uncertainty from the 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular mortality relationship.

Taken together, the evidence described within the 2019 PM ISA extends the consistency and coherence of the evidence base reported in the 2009 PM ISA and 2004 AQCD. Direct evidence for $PM_{2.5}$ exposure-related cardiovascular effects can be found in several controlled human exposure and animal toxicological studies. In coherence with these results are epidemiologic panel studies also finding that

$PM_{2.5}$ exposure is associated with some of the same cardiovascular endpoints reported in controlled human exposure and animal toxicological studies. The number of studies is limited that evaluate these endpoints, and there are some inconsistencies in results across some animal toxicological, controlled human exposure, and epidemiologic panel studies—although this may be due to substantial differences in study design, study populations, or differences in PM composition across air sheds. Nonetheless, the results from these epidemiologic panel, controlled human exposure, and animal toxicological studies, in particular those related to endothelial dysfunction, impaired cardiac function, ST segment depression, thrombosis, conduction abnormalities, and BP, provide coherence and biological plausibility for the consistent results from epidemiologic studies that reported positive associations between short-term $PM_{2.5}$ concentrations and IHD and heart failure, and ultimately cardiovascular mortality. **Overall, considering the entire evidence base, the evidence continues to be sufficient to conclude that a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects.**

3.1.1.2. Recent U.S. and Canadian Epidemiologic Studies

Recent epidemiologic studies conducted in the U.S. and Canada build on the strong epidemiologic evidence base evaluated in the 2019 PM ISA, as well as in previous assessments, which provided the scientific rationale supporting a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects (Section 3.1.1.1). In addition to examining the relationship between short-term $PM_{2.5}$ exposure and specific cardiovascular outcomes (i.e., IHD and myocardial infarction [Section 3.1.1.2.1], cerebrovascular disease and stroke [Section 3.1.1.2.2], heart failure [Section 3.1.1.2.3], arrhythmia [Section 3.1.1.2.4], combined cardiovascular effects [Section 3.1.1.2.5], and cardiovascular mortality [Section 3.1.1.2.6]), analyses within these recent studies also further examined issues relevant to expanding the overall understanding of the effect of short-term $PM_{2.5}$ exposure on cardiovascular outcomes. Specifically, recent studies assessed potential copollutant confounding (Section 3.1.1.2.7) and the lag structure of associations (Section 3.1.1.2.8). The following sections present an evaluation of recent epidemiologic studies conducted in the U.S. and Canada that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-1).

3.1.1.2.1. Ischemic Heart Disease and Myocardial Infarction

IHD is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart. Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death occurs that is secondary to prolonged ischemia. The effect of short-term $PM_{2.5}$ exposure on acute MI, complications from recent MI, and other acute or chronic IHD are generally evaluated using International

Classification of Diseases (ICD) codes recorded when a patient is admitted or discharged from the hospital or ED (ICD-Ninth Revision [ICD-9]: 410−414 or ICD-Tenth Revision [ICD-10]: I20−I25). In experimental or epidemiologic panel studies, indicators of MI include ST segment depression as measured by an electrocardiograph (ECG). The ST segment of an electrocardiogram recorded by surface electrodes corresponds to the electrical activity of the heart registered between ventricular depolarization and repolarization and is normally isoelectric.

The epidemiologic studies reviewed in the 2019 PM ISA (U.S. EPA, 2019) strengthened the evidence characterized in the previous ISA (U.S. EPA, 2009). Most of the evidence for IHD and MI in the 2009 PM ISA was from multicity epidemiologic studies of ED visits and hospital admissions [i.e., the U.S. Medicare Cohort Air Pollution Study (MCAPS) (Dominici et al., 2006), a four-city study in Australia (Barnett et al., 2006), and a study among older adults in several French cities (Host et al., 2008)]. The positive associations reported in these studies were an important line of evidence in the 2009 PM ISA concluding a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. Uncertainties noted in the 2009 PM ISA with respect to exposure measurement error for those not living near a $PM_{2.5}$ monitor were reduced in the 2019 PM ISA with the consideration of studies that applied hybrid exposure assessment techniques that combine land use regression data with satellite aerosol optical depth (AOD) measurements and $PM_{2.5}$ concentrations measured at fixed-site monitors to estimate $PM_{2.5}$ concentrations. Further, compared with the 2009 PM ISA, the evidence in the 2019 PM ISA was expanded to include studies examining the association of short-term $PM_{2.5}$ exposure ST segment depression in addition to ED visits and hospital admissions for MI.

A recent study extends the evidence presented in the 2019 PM ISA through its examination of the association between short-term $PM_{2.5}$ exposure with hospital admissions for MI among the low-income and/or disabled Americans comprising the Medicaid population (deSouza et al., 2021). deSouza et al. (2021) reported a positive association between $PM_{2.5}$ concentration (0−1 day average) and acute MI (OR: 1.1 [95% CI: 1.03, 1.7]). Recent studies have also addressed methodological challenges. Specifically, Krall et al. (2018) conducted an analysis to elucidate the interpretation of potentially uncertain single-city estimates. These authors used Poisson time-series regression to estimate the associations of 24-hour average $PM_{2.5}$ concentration (lag Day 0) with ED visits for IHD and other cardiovascular outcomes for each of the five cities included in their study. To estimate the association across all cities and the posterior city-specific associations, they fit both traditional Bayesian hierarchical models in which associations were estimated for each outcome separately, and multi-cause multicity (MCM) Bayesian hierarchical models in which multiple cardiovascular outcomes were included in the model simultaneously so that a shared between-city variation could be estimated. The authors also performed analyses to determine whether their results were sensitive to the choice of exposure lag (Section 3.1.1.2.8) or the specification of time trends. The associations between 24-hour $PM_{2.5}$ concentration and IHD ED visits in the traditional multicity model was 1.009 (95% Posterior Interval [PI]: 0.993, 1.025). The comparable association (1.009 [95% PI: 0.998, 1.022]) using MCM was more precise (i.e., narrower confidence intervals). As expected, the city specific estimates were relatively uncertain and heterogeneous across cities when there were a

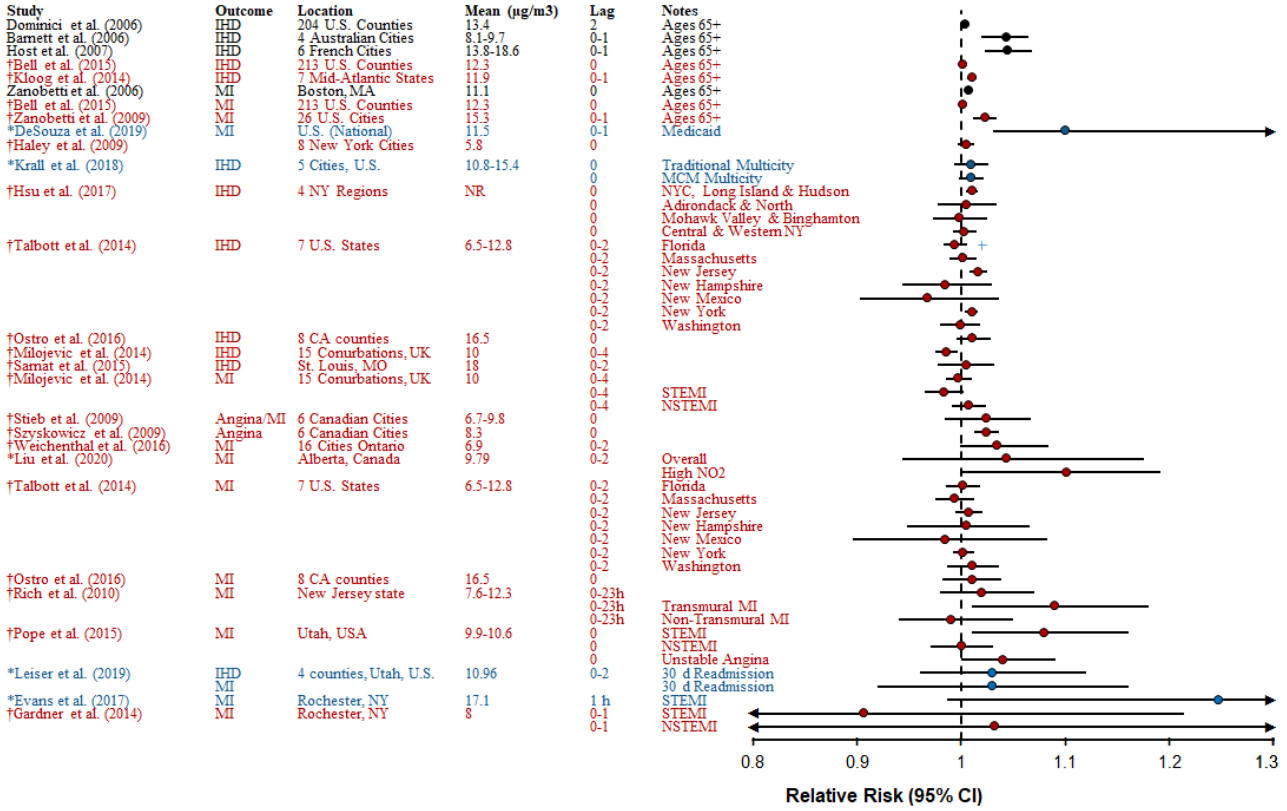
small number of daily ED visits. In another recent study, Leiser et al. (2019) designed an analysis to examine the association between short-term $PM_{2.5}$ exposure and IHD and MI hospital admissions in which the competing risk of mortality was controlled and differences across sex and age categories were examined. These authors used Medicare data for residents, 65 years and older, of the contiguous counties of the Wasatch Front in Utah to examine the association between $PM_{2.5}$ concentration and cardiac hospital re-admissions within 30 days of an index hospitalization, controlling for competing mortality risk. These authors found an association of 3-day average $PM_{2.5}$ concentration (lag 0−2 day) with IHD (HR: 1.03 [95% CI: 0.96, 1.12]) and MI (HR: 1.03 [95% CI: 0.92, 1.16]). Confidence intervals for the age- and sex-stratified results, which were conducted to evaluate potential modification of the association, were generally overlapping.

In another analysis of older adults using Medicare data, Wei et al. (2019) estimated the association of short-term $PM_{2.5}$ exposure with MI hospital admissions and a range of other health conditions, including some diseases that are rarely studied in relationship to $PM_{2.5}$ exposure. Hospital admission data were ascertained using discharge data recorded for Medicare inpatient hospital claims in the continental U.S. (2000−2012). Rather than report a relative risk (RR) estimate, the authors reported the absolute risk per 10 million person-days associated with each 1 unit increase in lag 0−1 $PM_{2.5}$ concentration (i.e., 0.29 [95% CI: 0.17, 0.40]).

Recent single city studies also add to the evidence base presented in the 2019 PM ISA. Liu et al. (2020) examined the modification of the association between short-term $PM_{2.5}$ exposure and MI hospital admissions by long-term NO_2 exposure. These authors performed a case-crossover study to estimate the association of short-term exposure to $PM_{2.5}$ among individuals living in Calgary neighborhoods with higher long-term NO2 exposure (2004−2012). No association between 0−2-day average $PM_{2.5}$ concentration with hospital admissions for MI among the entire population was observed [OR: 1.03 (95% CI: 0.96, 1.12)]. The association was null in the lowest tertile of long-term NO_2 concentration (OR: 0.94 [95% CI: 0.86, 1.18]), but the association strengthened in terms of magnitude and precision with increasing NO_2 concentration tertile (tertile 2, OR: 1.04 [95% CI: 0.94, 1.18]) and (tertile 3, OR: 1.10 [95% CI: 1.00, 1.19]). In addition, an extended analysis of a study reviewed in the 2019 PM ISA supports previous results that found a positive association between short-term $PM_{2.5}$ exposure and ST elevation myocardial infarction (STEMI) (Evans et al., 2017). Specifically, Evans et al. (2017) performed a case-crossover analysis to examine the relationship between short-term $PM_{2.5}$ concentration and STEMI in acute coronary syndrome or unstable angina patients (n = 362) in Monroe County, NY (2007−2012). The association between previous 1-hour $PM_{2.5}$ concentration and STEMI reported by these authors (OR: 1.25 [95% CI: 0.99, 1.59]) was virtually identical to the association (OR: 1.26 [95% CI: 1.01, 1.57]) reported in a previous analysis of this population conducted by Gardner et al. (2014) that reported fewer patients (n = 338) and a shorter follow-up time (2007−2010).

Results of studies of IHD and MI included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff date of the 2019 PM ISA are summarized in Figure 3-1.

Overall, recent studies support and extend the findings of the 2019 PM ISA with additional studies reporting positive associations between short-term $PM_{2.5}$ exposure and both IHD and MI hospital admissions and ED visits.



Source: Update of Figure 6-2, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. IHD = ischemic heart disease, MCM = multi-cause multicity; MI = myocardial infarction, NR = not reported; NSTEMI = non-ST segment elevation MI, STEMI = ST- elevation MI. Risk estimates are standardized to a 10 µg/m^3 increase in $PM_{2.5}$ concentrations.

Figure 3-1 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for ischemic heart disease.

3.1.1.2.2. Cerebrovascular Disease and Stroke

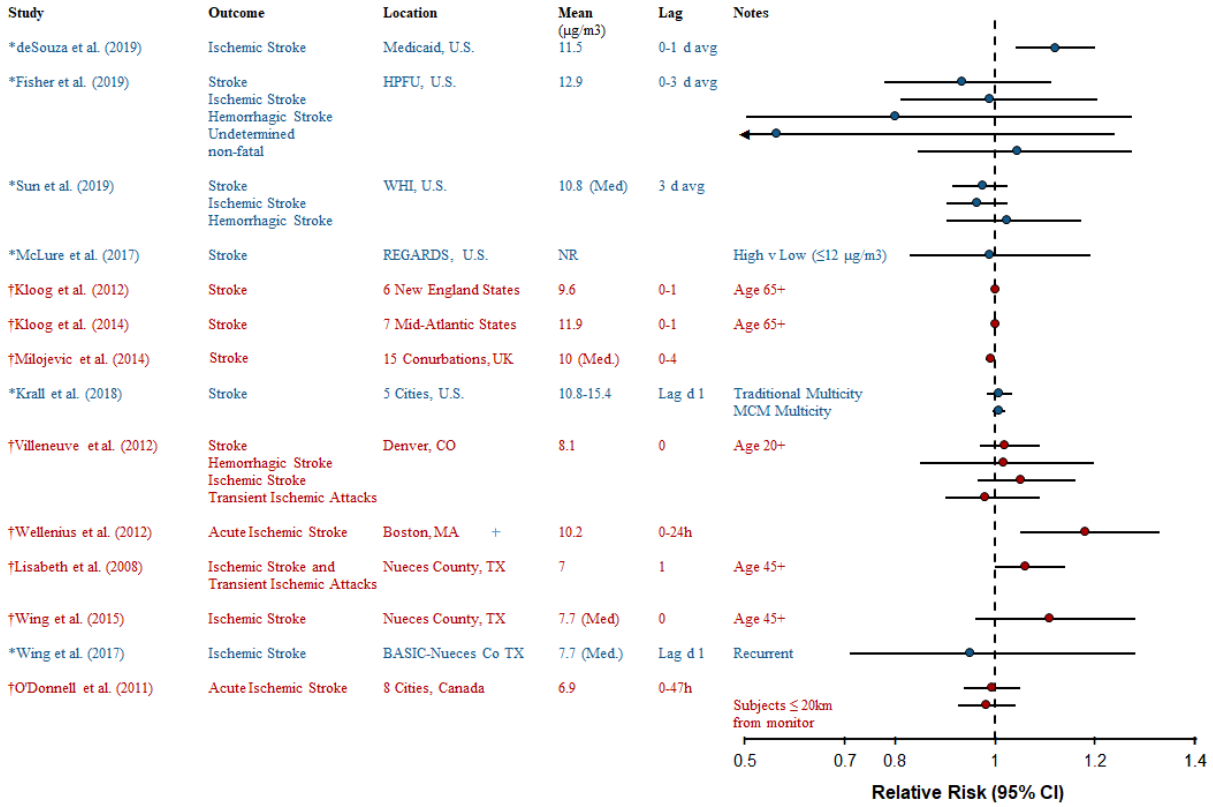
Cerebrovascular disease (CBVD) typically includes conditions classified under ICD-10 codes I60−I69 (ICD-9: 430−438) such as hemorrhagic stroke (HS), cerebral infarction (i.e., ischemic stroke [IS]) and occlusion of the precerebral and cerebral arteries. IS results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction, and accounts for 87% of all strokes (Goldberger et al., 2008). Hemorrhagic stroke is less common but results in a disproportionate number of fatalities. The HS subtype results from a brain aneurysm or leaking vessel in the brain and can be further categorized by brain region (e.g., intracerebral, or subarachnoid). Comorbidities that increase stroke risk but may also be associated with $PM_{2.5}$ exposure include hypertension, diabetes, CHD, and atrial fibrillation. The 2009 PM ISA and the 2019 PM ISA described inconsistent results across epidemiologic studies that considered the relationship between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for CBVD, with most studies reporting a lack of an association. Evidence relating to various stroke subtypes was also inconsistent. Results from recent studies of the association between short-term $PM_{2.5}$ concentration and stroke expand the evidence but remain inconsistent overall. Specifically, a study of Medicaid recipients found a large magnitude positive association, while several analyses of established cohorts (Health Professionals Follow-Up [HPFU] study, Women's Health Initiative [WHI], REasons for Geographic and Racial Differences in Stroke [REGARDS]) report null or inverse associations with stroke regardless of subtype.

Recent studies that analyze data from participants enrolled in several established cohort studies expand the evidence pertaining to stroke subtype. Fisher et al. (2019) estimated the associations of short-term $PM_{2.5}$ exposure with several stroke types, which were ascertained through self-report and expert medical record review, among men enrolled in the HPFU study. The authors reported no evidence of positive associations between lag 0 to 3-day average $PM_{2.5}$ concentration and total stroke (OR: 0.93 [95% CI: 0.78, 1.11]), ischemic (OR: 0.99 [95% CI: 0.81, 1.20]), hemorrhagic (OR: 0.80 [95% CI: 0.50, 1.27]), undetermined type (OR: 0.56 [95% CI: 0.26, 1.24]), and nonfatal stroke (OR: 1.05 [95% CI: 0.84, 1.27]). The authors also evaluated whether factors including age, BMI, smoking status, diabetes mellitus, hypertension, hypercholesterolemia, and current aspirin use potentially modified the associations with IS or HS; however, the number of stroke events within each strata was small and no statistical evidence of heterogeneity between stratified estimates was reported based on chi-square tests of model homogeneity. Sun et al. (2019) also estimated the association of short-term $PM_{2.5}$ with total, hemorrhagic, and ischemic stroke but studied a different population (i.e., post-menopausal women enrolled in the WHI study). Stroke was ascertained through self-report and physician adjudication. Three-day average $PM_{2.5}$ concentration (lag 0−2) was not associated with total (OR: 0.98 [95% CI: 0.92, 1.02]), ischemic (OR: 0.96 [95% CI: 0.90, 1.02]), or hemorrhagic stroke (OR: 1.02 [95% CI: 0.90, 1.17]) in this study. The authors also conducted stratified analysis to examine whether associations varied across categories of age at stroke onset, U.S. census region, smoking status, body mass index, and prior history of diabetes mellitus, hypertension, heart or circulation problems, or arterial fibrillation at enrollment. Across these different

stratified analyses, only when examining the stratum for obese women was there some evidence that the association of total stroke with $PM_{2.5}$ may be increased. Finally, McClure et al. (2017) performed a case-cross over analysis among participants in the REGARDS study to determine the association between $PM_{2.5}$ exposure at single-day lags (1, 2, and 3 day lags) and stroke ascertained through self-report followed by a medical record. The REGARDS study oversampled participants in several southern states where stroke risk is high among Black residents in order to study geographic and racial differences in stroke. $PM_{2.5}$ concentration was dichotomized ($\leq$ 12 $\mu g/m^3$ versus 12 to 150.4 $\mu g/m^3$) and the odds of stroke in the higher category was compared with the odds of stroke in the lower category. After adjustment for temperature and relative humidity, no association was reported between $PM_{2.5}$ exposure and stroke, regardless of the lag examined (OR: 0.99 [95% CI: 0.83, 1.19], lag 1). This finding persisted regardless of stroke subtype or exposure lag. Overall, analyses from three established and diverse cohorts did not present evidence of an association between short-term $PM_{2.5}$ exposure and stroke.

Unlike the analyses described above, deSouza et al. (2021) examined the relationship between $PM_{2.5}$ concentration (0−1 day average) and hospital admissions for IS among the low-income and/or disabled Americans comprising the Medicaid population. The OR for the association between $PM_{2.5}$ (lag 0−1 day average) and IS was 1.12 (95% CI: 1.04, 1.20). In a study designed to gain an understanding of the heterogeneity in results across single-city studies, Krall et al. (2018) examined the associations of 24-hour $PM_{2.5}$ concentration (lag 0) with ED visits for stroke. These authors estimated the associations across five cities using a traditional Bayesian hierarchical approach and a MCM Bayesian hierarchical model in which all outcomes were modeled simultaneously. The association of 24-hour $PM_{2.5}$ concentration (lag 0) with ED visits for stroke was 1.008 (95% CI: 0.984, 1.034) in the traditional multicity model and more precise (i.e., narrower confidence intervals) 1.008 (95% PI: 0.995, 1.021) in the MCM model. However, in a single city study of recurrent IS in Nueces county Texas, Wing et al. (2017) did not report evidence of an association between $PM_{2.5}$ concentration during the previous day (lag 1), and the odds of recurrent stroke (OR: 0.95 (95% CI: 0.71−1.28]).

Results of studies of short-term exposure to $PM_{2.5}$ and ED visits or hospital admissions for stroke included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff date of the 2019 PM ISA are summarized in Figure 3-2. The epidemiologic evidence for an association between short-term $PM_{2.5}$ and various stroke subtypes assessed in the 2019 PM ISA was characterized as inconsistent and limited. Some recent studies report evidence of a positive association with stroke while others report null or inverse associations. Therefore, the evidence pertaining to the effect of short-term $PM_{2.5}$ exposure and stroke remains inconsistent overall.



Source: Update of Figure 6-5, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. NR = not reported. Risk estimates are standardized to a 10 µg/m^3 increase in $PM_{2.5}$ concentrations.

Figure 3-2 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for stroke.

3.1.1.2.3. Heart Failure

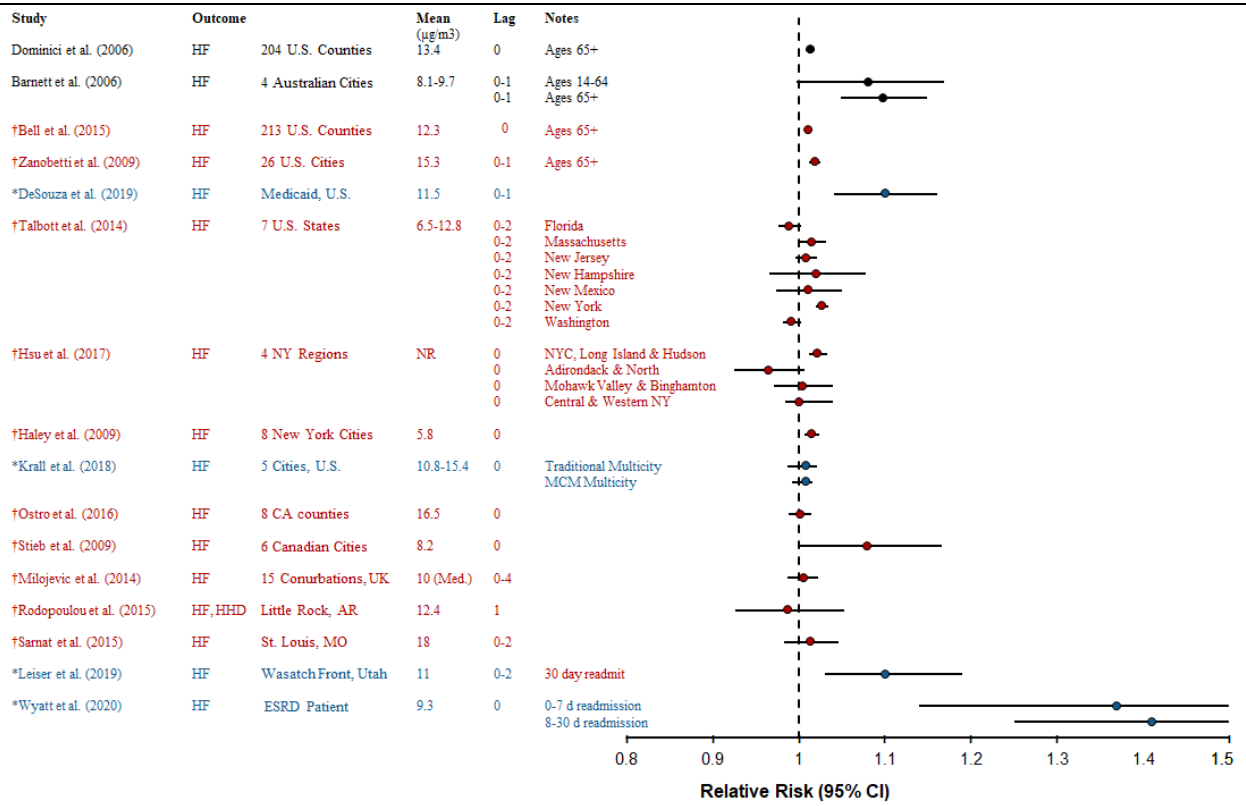
Heart failure (HF) refers to a set of conditions in which pumping action of the heart is weakened. In congestive heart failure (CHF), the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). The effect of short-term $PM_{2.5}$ exposure on people with CHF—which is a chronic condition—is generally evaluated using ICD codes recorded when a patient is admitted or discharged from the hospital or ED. The relevant diagnostic codes for heart failure are ICD-9 428 and ICD-10 I50. These codes encompass left, systolic, diastolic, and combined heart failure. Similar to the other cardiovascular outcomes, the majority of the evidence in the 2009 PM ISA was from epidemiologic studies of hospital admissions and ED visits [i.e., multicity studies in the U.S.(Dominici et al., 2006) and Australia (Barnett et al., 2006)]. Studies evaluated in the 2019 PM ISA strengthened this line of evidence with additional multicity epidemiologic studies conducted in the U.S., Canada, and Europe generally reporting positive associations between short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for HF. Results from single-city studies tended to be less consistent. Several recent studies add to the body of evidence providing additional support for a positive association between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for exacerbations of HF.

Recent studies conducted examined the association of short-term $PM_{2.5}$ exposure with readmission to the hospital for HF within 30 days of an index hospitalization. Leiser et al. (2019) used Medicare data to examine the association of short-term $PM_{2.5}$ exposure and cardiac hospital re-admissions among older adults within 30 days of the index hospitalization. These authors reported an association of 3-day average $PM_{2.5}$ concentration (lag 0−2 day) with readmission for HF (HR: 1.10 [95% CI: 1.03, 1.19]). Confidence intervals of the age and sex stratified results were generally overlapping. In another study of 30-day hospital readmission, Wyatt et al. (2020c) characterized the association of short-term $PM_{2.5}$ exposure with CHF among end-stage renal disease patients (i.e., those undergoing hemodialysis). Both readmission within 1 to 7 days and readmission between 8 to 30 days was evaluated. The RR for the association of 24-hour $PM_{2.5}$ concentration (lag 0) with HF readmission within 1−7 days was 1.37 (95% CI: 1.14, 1.60). The association with late readmission (8−30 days) was 1.41 (95% CI: 1.25, 1.58). In another unique population, deSouza et al. (2021) estimated the association of $PM_{2.5}$ concentration (0−1 day average) with CHF hospital admissions among the low-income and/or disabled Americans comprising the Medicaid population. The OR for the association between $PM_{2.5}$ (lag 0−1 day average) and CHF was 1.10 (95% CI: 1.04, 1.16).

In addition to the studies described above that focus on 30-day hospital readmission, Krall et al. (2018) examined the association of 24-hour $PM_{2.5}$ concentration (lag Day 0) with ED visits for CHF in an analysis in five cites that was designed to compare methods used for multicity studies. These authors estimated the multicity associations using a traditional Bayesian hierarchical approach and a MCM Bayesian hierarchical model in which all outcomes were modeled simultaneously. The association of 24-hour $PM_{2.5}$ concentration (lag 0) with CHF was 1.003 (95% CI: 0.986, 1.021) in the traditional

multicity model and 1.003 (95% PI: 0.992, 1.016) in the MCM model. In another study, Wei et al. (2019) used Medicare data (i.e., inpatient hospital claims) to estimate the association of short-term $PM_{2.5}$ exposure with CHF hospital admissions in the continental U.S. between 2000 and 2012. Rather than report a RR estimate, the authors reported the absolute increase in risk of admission to hospital per 10 million person-days associated with each 1 $\mu g/m^3$ increase in lag 0−1 $PM_{2.5}$ (i.e., 0.68 [95% CI: 0.52 to 0.84]).

Results of studies of HF included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff date of the 2019 PM ISA are summarized in Figure 3-3. Overall, these studies support and extend the limited evidence in the 2019 PM ISA, reporting positive associations between short-term $PM_{2.5}$ exposure and HF.



Source: Update of Figure 6-3, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. ESRD = end-stage renal disease; HF = heart failure, HHD = hypertensive heart disease, NR = not reported; re-HA = readmission to the hospital for heart failure. Risk estimates are standardized to a 10 µg/m^3 increase in $PM_{2.5}$ concentrations.

Figure 3-3 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for heart failure.

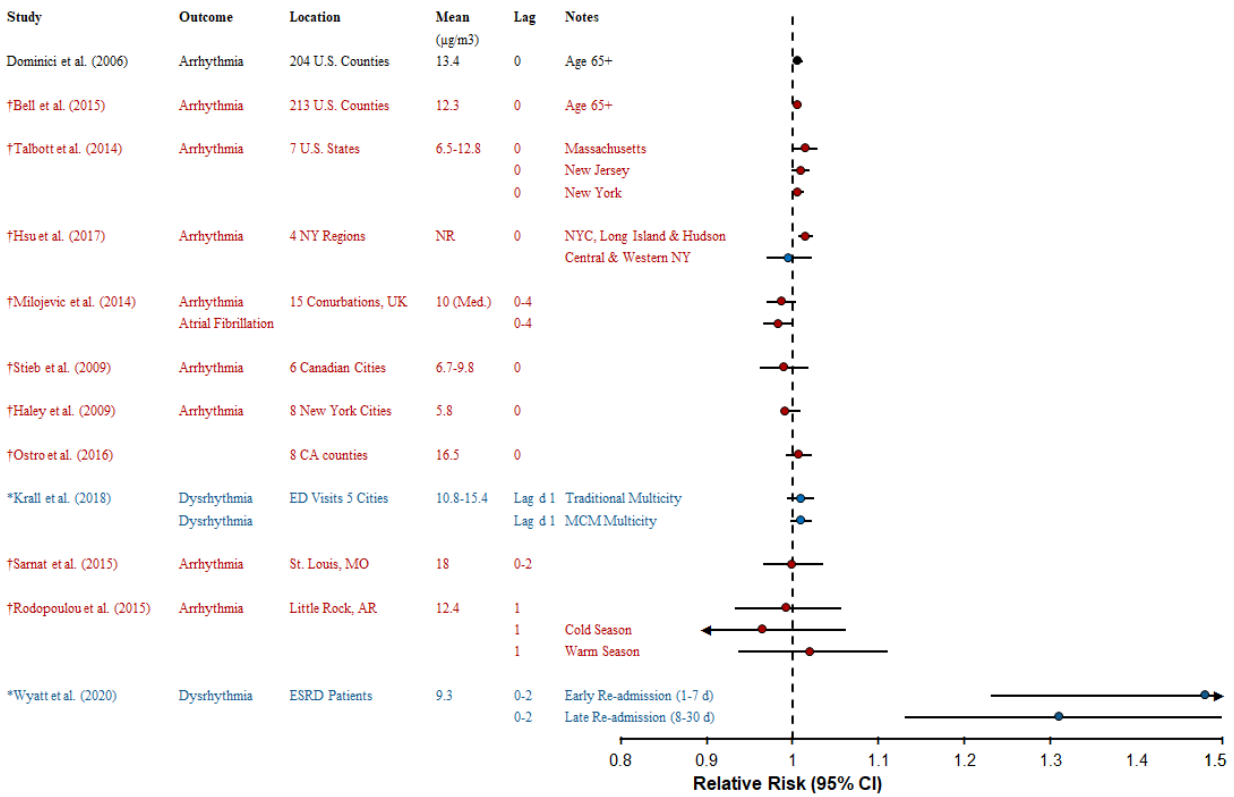
3.1.1.2.4. Arrhythmia

In epidemiologic studies, the association between short-term $PM_{2.5}$ exposure and arrhythmia is generally evaluated using ICD codes (ICD-9 427 or ICD-10 149.9) for hospital admissions and ED visits. Out-of-hospital cardiac arrests (OHCA) that typically result from ventricular arrhythmia were evaluated with the body of evidence pertaining to arrhythmia. Overall, the evidence evaluated in the 2009 PM ISA and the 2019 PM ISA was limited. However, in the 2019 PM ISA, some evidence from epidemiologic panel studies indicated an association between short-term $PM_{2.5}$ exposure and potential indicators of arrhythmia (e.g., ectopic beats and tachycardia). The small number of recent studies support a positive association of short-term $PM_{2.5}$ exposure with arrythmias.

Recent studies examined the association of short-term exposure to $PM_{2.5}$ and dysrhythmia adding to the limited evidence evaluated in the 2019 PM ISA. Wyatt et al. (2020c) examined 30-day hospital re-admission among end-stage renal disease patients (i.e., those undergoing hemodialysis). Both early re-admission within 1 to 7 days and later readmission after 8 to 30 days was evaluated. The RR for the association of 24-hour $PM_{2.5}$ concentration (lag 0) with dysrhythmia and conduction disorder readmissions within 1−7 days was 1.48 (95% CI: 1.23, 1.74). The association with late re-admission (8−30 days) was 1.31 (95% CI: 1.13, 1.50). In another study of 30-day hospital re-admission, Leiser et al. (2019) estimated the association of $PM_{2.5}$ concentration and cardiac arrhythmia among Medicare beneficiaries who survived a cardiovascular event, and examined differences across sex and age in models that adjusted for the competing risk of readmission due to a non-cardiovascular cause or death. These authors reported an inverse association of 3-day average $PM_{2.5}$ concentration (lag 0−2 days) with re-admission for dysrhythmia or arrhythmia (HR: 0.88 [95% CI: 0.75, 1.02]). Confidence intervals of the age and sex stratified results were generally overlapping and did not provide evidence of effect modification. Krall et al. (2018) examined the association of 24-hour $PM_{2.5}$ concentration (lag Day 0) with CVD ED visits in an analysis designed to compare methods for multicity analyses. These authors estimated the associations with CVD ED visits including visit for dysrhythmia across five cities using a traditional Bayesian hierarchical approach and a MCM Bayesian hierarchical model in which all outcomes were modeled simultaneously. The association between 24-hour $PM_{2.5}$ concentration (lag 0) with ED visits for dysrhythmia was 1.009 (95% CI: 0.993, 1.023) in the traditional Bayesian hierarchical model and 1.009 (95% PI: 0.998, 1.022) in the MCM Bayesian hierarchical model. Finally, Wei et al. (2019) estimated the association of short-term $PM_{2.5}$ exposure with arrhythmia hospital admissions in a study using discharge data recorded for Medicare inpatient hospital claims in the continental the U.S. (2000−2012). Rather than report a RR estimate, the authors reported the absolute increase in risk of admission to hospital per 10 million person-days associated with each 1 $\mu g/m^3$ increase in lag 0−1 $PM_{2.5}$ concentration (i.e., 0.26 [95% CI: 0.13 to 0.38]).

Results of studies of arrythmia included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the 2019 PM ISA are summarized in Figure 3-4. Overall, these studies extend the limited evidence evaluated in the 2019 PM ISA as they report positive associations between short-term $PM_{2.5}$

exposure and arrhythmia in most studies. However, an analysis of Medicare recipients in Utah that adjusted for the competing risk of readmission for a non-cardiovascular cause or death reported an inverse association.



Source: Update of Figure 6-4, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. HF = heart failure, HHD = hypertensive heart disease, NR = not reported. Risk estimates are standardized to a 10 µg/m^3 increase in $PM_{2.5}$ concentrations.

Figure 3-4 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for arrhythmia.

3.1.1.2.5. Combinations of Cardiovascular-Related Outcomes

In addition to analyses of individual CVDs (e.g., MI, stroke, and HF), epidemiologic studies examined CVDs in aggregate (i.e., specific combination of cardiovascular diseases). The 2009 PM ISA and the 2019 PM ISA reviewed multicity studies of adults ages 65 years and older that provided strong evidence of an association [(Bell et al., 2008; Host et al., 2008; Barnett et al., 2006); Table 6-19 of the 2019 PM ISA]. Studies of aggregate CVD have larger case counts than studies of specific CVDs, potentially providing statistical power needed to detect associations. Several recent studies examine the association between short-term exposure to $PM_{2.5}$ and CVD hospital admissions and ED visits, and report results that are generally consistent with studies evaluated in the 2019 PM ISA.

In a study of low-income and/or disabled Americans enrolled in Medicaid deSouza et al. (2021) estimated the association of $PM_{2.5}$ concentration (0−1 day average) with cardiovascular hospital admissions. The association of $PM_{2.5}$ concentration (0−1 day average) with all CVD hospital admissions was 1.09 (95% CI: 1.06, 1.11). In addition, the authors reported that the association with all CVD hospital admissions was larger in magnitude when restricting the analysis to $PM_{2.5}$ concentrations less than 25 micrograms per cubic meter ($\mu g/m^3$) (OR: 1.13 [95% CI: 1.09, 1.16]). The association was similar among older and younger adults (OR: 1.09 [95% CI: 1.06, 1.13]) among those < 65 years old 1.08 (95% CI: 1.06, 1.09) versus among those ≥ 65 years old. In another study, Wyatt et al. (2020c) examined hospital admissions among end-stage renal disease patients (i.e., those undergoing hemodialysis). Same-day $PM_{2.5}$ concentration (lag 0) was associated with an increase in the risk of CVD hospital admissions in this population (RR: 1.09 [95% CI: 1.02, 1.17]).

Some recent studies of ED visits report null associations between short-term $PM_{2.5}$ concentration and aggregated CVD outcomes in adjusted models. Krall et al. (2018) examined the associations of 24-hour $PM_{2.5}$ concentration (lag Day 0) with CVD ED visits, estimating the association across five cities using a traditional Bayesian hierarchical approach. A null association between 24-hour $PM_{2.5}$ concentration (lag 0) with CVD ED visits was observed (1.0 [95% CI: 0.992, 1.009]) while positive associations were reported for specific cardiovascular outcomes evaluated. Ye et al. (2018) performed a study to estimate the association between short-term exposure to $PM_{2.5}$ components that are not routinely measured, including water-soluble metals, and CVD ED visits for a five-county area of Atlanta during the period 1998 to 2013. In a single-pollutant model, these authors reported a positive association of 24-hour $PM_{2.5}$ concentration (lag 0) with CVD ED visits; however, the association was null after adjustment for water-soluble iron (WS Fe), which may be an indicator for certain aspects of traffic pollution.

Evidence assessed in the 2019 PM ISA from multicity studies reported consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related ED visits and hospital admissions. Recent studies, including one in renal disease patients and another in the Medicaid population, support the conclusion of the 2019 PM ISA and extend the evidence base.

3.1.1.2.6. Cardiovascular Mortality

As noted in the 2019 PM ISA, "studies that examine the association between short-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for $PM_{2.5}$-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects" (2019 PM ISA, Section 6.1.9). Epidemiologic studies evaluated in the 2019 PM ISA, expanded upon the evidence presented in the 2009 PM ISA indicating consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular mortality (2019 PM ISA, Section 6.1.9). Experimental evidence (i.e., both animal toxicological and controlled human exposure studies) presented within both the 2009 PM ISA and 2019 PM ISA provided coherence and biological plausibility for the $PM_{2.5}$-related cardiovascular mortality associations reported in epidemiologic studies. A recent multicity study conducted by Lavigne et al. (2018) in addition to examining short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality also examined cause-specific mortality and provided evidence that continues to support a relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality (Section 3.2.1.2.2).

3.1.1.2.7. Consideration of Copollutant Exposures

In the examination of potential confounding of the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects by exposure to copollutants, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. As noted in the Appendix (Table A-1) to the 2019 PM ISA, copollutant models are not without their limitations, such as instances for which correlations are high between pollutants resulting in greater bias in results. However, a change in the $PM_{2.5}$ risk estimate, after adjustment for a copollutant may indicate the potential for confounding. The evidence reviewed in the 2019 PM ISA represented an expanded set of studies that performed analyses using two-pollutant, also referred to as copollutant, models. These studies addressed a data gap, generally supporting an association of $PM_{2.5}$ with cardiovascular-related health effects that persisted after adjustment for copollutant exposures (i.e., O_3, NO_2, SO_2, CO, and $PM_{10–2.5}$). In addition to copollutant models, a limited number of studies that examined the joint effects of multiple pollutants provided information on the role of $PM_{2.5}$ within the complex air pollution mixture. Overall, the evidence and the available statistical methods were limited with respect to characterizing the multipollutant effects of air pollution on cardiovascular disease. This limited evidence neither consistently nor coherently indicated a stronger or weaker effect of combined exposure to $PM_{2.5}$ and another pollutant compared with exposure to a single pollutant alone (Luben et al., 2018).

Recent studies that examine the potential confounding of the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects by copollutants are limited; however, the results of available studies are consistent with the evidence evaluated in the 2019 PM ISA. deSouza et al. (2021) found that the positive single-pollutant association (OR: 1.09 [95% CI: 1.06, 1.11]) between all CVD and short-term $PM_{2.5}$ observed among Medicaid recipients persisted in a two-pollutant model adjusted for ozone (OR: 1.10 [95% CI: 1.07, 1.12]). In another recent study, Wing et al. (2017) reported no association between

short-term $PM_{2.5}$ exposure and recurrent stroke in both single- and two-pollutant model that were adjusted for ozone. This study does not alter the conclusion of the 2019 PM ISA with respect to copollutant confounding because associations between $PM_{2.5}$ exposure and stroke were not consistently reported.

3.1.1.2.8. Lag Structure of Associations

An examination of the association between short-term $PM_{2.5}$ exposure and cardiovascular effects across different lag days can inform whether $PM_{2.5}$ elicits an immediate (e.g., lag 0–1 days), delayed (e.g., lag 2–5 days), or prolonged (e.g., lag 0–5 days) effect on these endpoints, and whether the effect of $PM_{2.5}$ is consistent across cardiovascular endpoints. The evidence reviewed in the 2019 PM ISA supported an immediate effect of short-term $PM_{2.5}$ exposure on hospital admissions and ED visits for aggregate CVD outcomes, IHD, HF, and OHCA, as well as for cardiovascular mortality. This evidence came from the evaluation of both single-day and multiday lags, as well as studies that evaluated subdaily lag periods. By contrast, the studies evaluated in the 2019 PM ISA did not provide evidence of a consistent lag period for the association of short-term $PM_{2.5}$ exposure with CBVD and arrhythmia. Overall, stronger associations in terms of magnitude and precision were reported for immediate lags for most cardiovascular-related outcomes, and the associations tended to be stronger for immediate multiday lag periods (i.e., 0−1, 0−2) compared with immediate single-day lag periods (i.e., 0, 1).

Several recent studies conducted analyses to determine whether results were sensitive to the choice of exposure lag. Overall, the available studies continue to support an immediate effect of short-term $PM_{2.5}$ exposure on MI. In a case-crossover analysis of STEMI among unstable angina patients, Evans et al. (2017) found that the association between previous 1-hour $PM_{2.5}$ concentration and STEMI became less precise (i.e., wider confidence intervals) at exposure lags up to 24 or 48 hours and null with an exposure lag of 72 hours. In a multicity analysis of ED visits for a number of cardiovascular outcomes (i.e., IHD, CHF, Dysrhythmia), Krall et al. (2018) found that lags longer than their a priori choice (i.e., same-day exposure [lag 0]) did not produce substantially different results. Studies that examined the lag structure of associations in relation to stroke reported null associations that were unchanged regardless of the choice of lag (Fisher et al., 2019; McClure et al., 2017). In a study of recurrent IS in Nueces county Texas, Wing et al. (2017) reported null associations with short-term $PM_{2.5}$ concentrations on lag Day 1, 2, and 3 and an inverse association with same day exposures.

3.1.1.3. Recent Epidemiologic Studies Examining the $PM_{2.5}$-Cardiovascular Effects Relationship through Accountability Analyses and Alternative Methods for Confounder Control

As discussed in Section 3.1.1.1, the 2019 PM ISA reported that there was sufficient evidence to conclude that a *causal relationship* exists between short-term $PM_{2.5}$ exposure and cardiovascular effects. However, the body of evidence that supported this causality determination did not include any

epidemiologic studies that conducted accountability analyses or employed alternative methods for confounder control because no such studies were published prior to the literature cutoff date for the 2019 PM ISA. Studies that conduct accountability analyses can provide insight on whether the implementation of environmental policies or air quality interventions result in changes/reductions in air pollution concentrations and the corresponding effect on health outcomes. Additionally, accountability studies can reduce uncertainties related to residual confounding of temporal and spatial factors. Alternative methods for confounder control seek to mimic randomized experiments through the use of study design and advanced statistical methods to reduce the potential bias of effects due to confounding more than traditional regression model approaches. Examples of alternative methods for confounder control are general propensity scores and inverse probability weighting models. Since the literature cutoff date for the 2019 PM ISA, several studies that conducted accountability analyses or implemented alternative methods for confounder control have been published, which further inform the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects, specifically cardiovascular hospital admissions (Table A-2). The cardiovascular-related hospital admissions examined ranged from specific cardiovascular endpoints such cardiac arrhythmia, hypertension, ST segment elevation myocardial infarction to a broader assessment of all cardiovascular diseases.

Zhang et al. (2018) and Wang et al. (2019) both conducted accountability analyses that evaluated whether associations between short-term $PM_{2.5}$ exposures and cardiovascular hospital admissions differed before, during, and/or after the implementation of environmental policies to improve air quality in cities in New York. Zhang et al. (2018) estimated the rate of cardiovascular hospital admissions associated with short-term $PM_{2.5}$ concentrations, and whether the rates differed before (2005−2007), during (2008−2013), or after (2014−2016) the implementation of multiple national and state policies aimed at improving air quality in multiple cities in New York. Using a time-stratified, case-crossover design, the authors employed conditional logistic regression models to estimate the rate ratio for cardiovascular hospital admissions, examining associations with$PM_{2.5}$ at lag 0 or averaged over the previous 1–7 days (lag 0–1, 0–2, 0–3, 0–4, 0–5, 0−6), adjusting for temperature and relative humidity. The excess rate of hospital admissions decreased over the entire time period for total cardiovascular disease (before: 1.4% [95% CI: 1.0, 1.8]; during: 1.1% [95% CI: 0.7, 1.5]; after: 1.0% [95% CI: 0.3, 1.17]), with the largest association, in terms of magnitude, observed in the “before” implementation period and weaker associations observed in the “after” implementation period for the 0–6 day lag average. Similar results were reported for cerebrovascular disease, ischemic stroke, chronic rheumatic heart disease, hypertension, ischemic heart disease, and myocardial infarction. The incidence rates of all disease categories decreased across the study period. However, there was no difference in the excess rate of most cardiovascular disease subgroups associated with each interquartile range increase in $PM_{2.5}$ concentration “after” the implementation of environmental policies and actions (2014–2016) compared with “before” (2005–2007) or “during” (2008–2013) implementation. Conversely, there were increases in the excess rate of hospital admissions for cardiac arrhythmia and congestive heart failure in the “after” period compared with the “before” and “during” periods. Although the change in the excess rates for cause-specific cardiovascular hospital admissions was relatively small in magnitude and varied by lag period and location, overall,

short-term increases in ambient $PM_{2.5}$ concentrations were associated with increased rates of hospital admissions for total cardiovascular disease, cardiac arrhythmias, heart failure ischemic stroke, ischemic heart disease, and myocardial infarction.

Wang et al. (2019) also used a time-stratified case-crossover study design to examine whether the rate of ST segment elevation myocardial infarction (STEMI) is associated with $PM_{2.5}$ concentrations in the previous few hours or days, and whether these associations were modified by periods in which there were changes in environmental policies in Rochester, NY. The authors hypothesized that increases in the rate of STEMI associated with short-term $PM_{2.5}$ exposures would be smaller after the changes were implemented (2014−2016), compared with the periods before (2005−2007) and during (2008−2013) implementation. Within this study, referent days were selected as the same hour of the event on the same day earlier and later than the case event within the same month and calendar year. The analyses examined hourly exposures of 1 hour (lag hour 1), 3-hour avg (lag hours 0−2), 12-hour average (lag hours 0−11), 24-hour average (lag hours 0−23), 48-hour average (lag hours 0−47), and 72-hour average (lag hours 0−71) prior to the onset of STEMI symptoms. To examine whether the rate of STEMI was associated with different hourly average concentrations of $PM_{2.5}$ and were modified by the period of when changes were implemented, two interaction terms for the "period" (a categorical variable to distinguish periods of before, during, and after implementation) and $PM_{2.5}$ concentrations of the time period were included in the conditional logistic regression model. Over the entire study period, there was a decrease of approximately 30% in $PM_{2.5}$ concentrations. Across the three periods, there was a decrease in the rate of STEMI for an interquartile range (7.59 $\mu g/m^3$) increase in $PM_{2.5}$ concentration in the previous hour (lag hour 0) (before: OR = 1.03 [95% CI: 0.91, 1.17]; during: OR = 1.07 [95% CI: 0.92, 1.24]; after: OR = 0.99[95% CI: 0.81, 1.21]). However, in the previous 72-hour (lag hours 0−71) period, the rate of STEMI increased with an IQR increase in $PM_{2.5}$ concentration across the three periods from 0.91 (95% CI: 0.79, 1.05) before, 0.98 (95% CI: 0.82, 1.18) during, and 1.11 (95% CI: 0.88, 1.41) after implementation. Although the results of this accountability analysis are small in magnitude or null across the time periods, this study provides support that implementation of air quality policies can lead to reductions in $PM_{2.5}$ concentrations and subsequently may affect health effects associated with $PM_{2.5}$ exposures.

The use of alternative methods for confounder control can further inform the causal nature of the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects through the use of advanced statistical methods to reduce uncertainties with respect to confounding. Recent epidemiologic studies that use these alternative methods have primarily focused on examining cardiovascular hospital admission rates. Inverse probability weighting (IPW) is an alternative method for confounder control that analyzes observational data in a way that approximates conducting a randomized experiment to make exposure independent of all potential confounders, rather than to control for the confounders in the outcome regression (Qiu et al., 2020). To explore the relationship between short-term $PM_{2.5}$ exposure and cardiovascular disease hospital admissions, Qiu et al. (2020) used IPW propensity score methods in a case-crossover study design to examine an unconstrained distributed lag (lag 0−5) for acute myocardial

infarction (AMI), CHF, and IS hospital admissions among New England Medicare participants between 2000 and 2012. In the first step, a linear regression model was fitted with the exposure lag of interest against the other five lags of $PM_{2.5}$ exposure and six lags of ozone along with linear and quadratic terms for temperature (lag 0 and 1) and linear terms for relative humidity (lag 0 and 1) to control for potential confounding by meteorological conditions. In the second step, under the assumptions that no important confounders are omitted and correct specification of the propensity score models, for each of the six lags the outcome was regressed against $PM_{2.5}$ at each individual lag with weights specific to each individual lag. After using the weights generated from propensity score models to predict the exposure at each lag of interest, copollutant exposure and meteorological variables were used to create a pseudo-randomized population. The pseudo-randomized population was subsequently used in conditional logistic regression models to regress cardiovascular hospital admissions against each exposure lag, estimating the marginal effect of each lag of exposure independent of covariates.

Using the IPW method, Qiu et al. (2020) reported an increase of 4.3% (95% CI: 2.2, 6.4) in AMI hospital admission rate, 3.9% (95% CI: 2.4, 5.5) in CHF rate, and 2.6% (95% CI: 0.4, 4.7) in IS hospital admission rate for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ concentrations. While Qiu et al. (2020) reported associations using alternative methods for confounder control that further confirm an association between short-term $PM_{2.5}$ exposure and cardiovascular-related hospital admissions, several assumptions were used by the authors when applying the IPW methods that are important to recognize. First, the authors assumed exchangeability, meaning that there was no unmeasured confounding, with the caveat that the authors did not have the resources to obtain all the potential unmeasured confounders. This assumption was tested through a series sensitivity analyses, testing the most critical confounder of temperature by including more lags of temperature and spline adjustments. Because the results from the sensitivity analyses involving temperature did not deviate from the estimates in the main analysis, it can be inferred that the most important confounders with available data were adjusted for and that the time-invariant variables are not potential confounders due to the case-crossover study design. The second assumption was positivity, which was guaranteed in the analysis through the positivity exclusion. Qiu et al. (2020) note that the positivity assumption means there are both exposed and non-exposed individuals at every level of the confounders. The last assumption is consistency, or that the observed outcome is exactly the same as the potential outcome the individual will have under the exposure assigned; however, this assumption is difficult to prove. Overall, the inverse probability weighted distributed lag model employed by Qiu et al. (2020) provides unconstrained, less conditional effect estimates that are less influenced by highly correlated covariates and reduces uncertainties regarding unmeasured confounders.

The recent studies that utilized accountability approaches and alternative methods for confounder control evaluated in this section provide additional support for a relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. These studies reported consistent associations between cardiovascular hospital admissions with short-term $PM_{2.5}$ exposures across different statistical methods and study designs, which reduce uncertainties related to potential confounder bias, and further supports the conclusions of the 2019 PM ISA.

3.1.1.4. Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Short-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

Recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects in the 2019 PM ISA. Multicity analyses of the relationship between short-term exposure to $PM_{2.5}$ and cardiovascular ED visits and hospital admissions were an important consideration in this causality determination. Recent studies support the evidence characterized in the 2019 PM ISA, extending the evidence relating to hospital admissions and ED visits for specific outcomes (i.e., IHD, MI, HF, and arrhythmia) with positive association observed across diverse populations (i.e., older adults enrolled in Medicare, Medicaid recipients, and patient populations). With respect to stroke, the evidence in the 2019 PM ISA was characterized as inconsistent. Recent studies of established cohorts (i.e., WHI, REGARDS, and HPFU) extend this evidence with observations of null or inverse associations between short-term $PM_{2.5}$ exposure and stroke, regardless of stroke subtype. However, an association between short-term $PM_{2.5}$ exposure and IS was observed in the Medicaid population.

Multiple studies included in the 2019 PM ISA applied hybrid exposure assessment techniques that combined land use regression with satellite AOD measurements and $PM_{2.5}$ concentrations measured at fixed site monitors. Most recent studies also rely on exposure assessment strategies that characterize the temporal and spatial variability of short-term $PM_{2.5}$ concentrations. Recent studies also performed analyses to address methodological challenges, including applying techniques to elucidate uncertainties related to the observation of variable results across single-city studies and controlling for competing mortality risks in studies of ED visits and hospital admissions.

The evidence in the 2019 PM ISA indicated that the associations between short-term $PM_{2.5}$ exposure and cardiovascular effects generally persisted in models that were adjusted for copollutants. A recent study that reports copollutant model results supports the evidence characterized in the 2019 PM ISA that the effect of short-term $PM_{2.5}$ exposure on the cardiovascular system is independent of ozone exposure. Recent studies continue to support an immediate effect of short-term $PM_{2.5}$ exposure on the cardiovascular system that was described in the 2019 PM ISA. Finally, recent studies that employed alternative methods for confounder control or conducted accountability analyses when examining short-term $PM_{2.5}$ exposure and cardiovascular-related hospital admissions provide additional support for a relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects while reducing uncertainties related to potential confounder bias.

3.1.2. Long-Term $PM_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for long-term $PM_{2.5}$ exposure and cardiovascular morbidity presented within the 2019 PM

ISA (Section 3.1.2.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.1.2.2). [15] In addition, with the expansion of epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.1.2.3), which can further inform the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity. Finally, a summary of the results of recent studies evaluated within the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.1.2.4). The evaluation of recent studies presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.1.2.1. Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

The evidence reviewed in the 2009 PM ISA provided the rationale to conclude that there is a "causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects" (U.S. EPA, 2009). Studies of mortality from cardiovascular causes provided the strongest evidence in support of this conclusion. While several studies included in the 2009 PM ISA reported associations between long-term PM_{10} exposure and morbidity outcomes such as post-MI CHF and deep vein thrombosis (DVT), studies of $PM_{2.5}$ were limited. One large prospective study of postmenopausal women reported an increased risk of cardiovascular events, including CHD and stroke, in association with long-term exposure to $PM_{2.5}$ (Miller et al., 2007). Cross-sectional analyses provided supporting evidence and experimental studies demonstrating enhanced atherosclerotic plaque development and inflammation following long-term exposures to $PM_{2.5}$ CAPs provided biological plausibility for the epidemiologic findings. In addition, evidence from the limited number of toxicological studies reporting CAPs-induced effects on hypertension and vascular reactivity were drawn upon to support the causality determination.

In addition to evaluating evidence across scientific disciplines that examined the relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects, the 2019 PM ISA characterized whether evidence supported biologically plausible mechanisms by which long-term $PM_{2.5}$ exposure could lead to cardiovascular effects. This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies that examined a range of cardiovascular effects (2019 PM ISA, Section 6.2.1). Plausible biological mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to apical events reported in epidemiologic studies (2019 PM ISA, Figure 6-2). The first proposed pathway begins as respiratory tract inflammation leading to systemic

[15] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining long-term exposures are for a 5 $\mu g/m^3$ increase in annual concentrations, unless otherwise noted.

inflammation. The second proposed pathway involves modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that long-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as IHD and heart failure (2019 PM ISA, Figure 6-1).

The evidence for the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects as characterized in the 2019 PM ISA is described below and summarized in Table 3-2, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 3-2 Summary of evidence for a *causal relationship* between long-term $PM_{2.5}$ exposure and cardiovascular effects from the 2019 Integrated Science Assessment for Particulate Matter.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects[c] ($\mu g/m^3$)
Consistent epidemiologic evidence from multiple studies at relevant $PM_{2.5}$ concentrations	Positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in U.S. and Canadian cohorts; positive associations persisted after adjustment for common confounders.	Section 6.2.10 Figure 6-19	Mean concentrations ranged from 4.08 (CCHS)−17.9 CA Teachers
	Positive associations observed in studies examining varying spatial scales and across different exposure assessment and statistical methods.	Section 6.2.10	
Evidence from copollutant models generally supports an independent $PM_{2.5}$ association	Positive associations observed between long-term $PM_{2.5}$ exposure and cardiovascular mortality remain relatively unchanged after adjustment for copollutants. Correlations with ozone were generally moderate to high (0.49−0.73). When reported, correlations with SO_2, NO_2, and $PM_{10-2.5}$ ranged from weak to moderate (r = 0.25−0.55).	Section 6.2.15 Figure 6-21 Figure 6-22	
Epidemiologic evidence supports a linear no-threshold C-R relationship	Most analyses support a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$. Confidence in C-R relationship extends to 8 $\mu g/m^3$ in Harvard Six Cities study.	Section 6.2.16 Lepeule et al. (2012)	
Inconsistent evidence from epidemiologic studies of CHD or stroke	Association with coronary events, CHD, and stroke (mortality and morbidity combined) that persist after adjustment for SES reported in the WHI study. Association with stroke but not CHD in the CA Teachers cohort. No association with CHD or stroke in the NHS or HPFU.	Section 6.2.2 Section 6.2.3	Range: 13.4−17.8
Generally consistent evidence of an association with CHD or stroke among those with preexisting disease	Consistent associations with MI in patient populations. Association among women with diabetes in NHS.	Hartiala et al. (2016) Tonne et al. (2015) Koton et al. (2013) Hart et al. (2015b)	Mean: 15.5 Mean: 14.6 Mean: 23.9 Mean: 13.4

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects[c] ($\mu g/m^3$)
Some, but not all, epidemiologic studies provide evidence for effect of long-term $PM_{2.5}$ on CAC	Longitudinal change in CAC observed in MESA but not in Framingham Heart Offspring study.	Section 6.2.4 Kaufman et al. (2016) Dorans et al. (2016)	Mean: 14.2 Median: 9.8
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of impaired heart function and blood pressure. Additional evidence of atherosclerosis, systemic inflammation, changes in endothelial function.	Section 6.2.5.2 Section 6.2.7.2 Section 6.2.4.2 Section 6.2.12.2 Section 6.2.14.2	~85−30 See Tables in identified sections
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to long-term $PM_{2.5}$ exposure. Includes evidence for impaired heart function, atherosclerosis, and increased blood pressure.	Section 6.2.1	

Note: This table corresponds to Table 6-54 in the 2019 PM ISA.

CAC = coronary artery calcification; CCHS = Canadian Community Health Survey; C-R = concentration-response; CHD = coronary heart disease; HPFU = Health Professionals Follow-Up; MESA = Multi-Ethnic Study of Atherosclerosis; $\mu g/m^3$ = micrograms per cubic meter; NHS = Nurses' Health Study; NO_2 = nitrogen dioxide; $PM_{2.5}$ = 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; $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm; *r* = correlation coefficient; SES = socioeconomic status; SO_2 = sulfur dioxide.

[a] Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015).

[b] Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c] Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

The studies of long-term exposure to $PM_{2.5}$ and cardiovascular mortality evaluated in the 2019 PM ISA continue to provide strong evidence of a *causal relationship* between long-term exposure to $PM_{2.5}$ and cardiovascular effects. Results from U.S. and Canadian cohort studies demonstrated consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (2019 PM ISA, Figure 6-19). Overall, the studies reporting positive associations examined the relationship at varying spatial scales and employed different exposure assessment and statistical methods (2019 PM ISA, Section 6.2.10). The studies were conducted in locations where mean annual average concentrations ranged from 4.08 to 17.9 $\mu g/m^3$. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2. In addition, most of the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$.

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity evaluated in the 2019 PM ISA had greatly expanded since the 2009 PM ISA, with positive associations reported in several cohorts. The findings from the WHI cohort of postmenopausal women (Miller et al., 2007), reporting associations of long-term $PM_{2.5}$ and coronary events, were strengthened through a subsequent analysis, which considered potential confounding and modification by SES and applied enhanced exposure assessment methods (Chi et al., 2016). However, analyses of the Nurses' Health Study (NHS) and California Teachers Study (CTS), both of which are cohorts of women and include extensive data on covariates (i.e., hormone use, menopausal status, and SES), were not entirely consistent with the WHI findings. Although the NHS cohort is comparable to WHI in that it is made of predominantly postmenopausal women, no associations with CHD or stroke were observed in this population (Hart et al., 2015b). An association with stroke, but not CHD, that was stronger among postmenopausal women was observed in the CTS (Lipsett et al., 2011). Several studies conducted among cardiovascular disease patient populations generally reported positive associations with MI (Hartiala et al., 2016; Tonne et al., 2015; Koton et al., 2013), and a sensitivity analysis of the NHS restricted to women with diabetes detected a positive association with CHD. Although the evidence is not consistent across the populations studied, heterogeneity is expected when the methods, or the underlying distribution of covariates vary across studies (Higgins, 2008).

Longitudinal change in measures of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ add to the collective evidence base (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). Findings were somewhat variable across cohorts and depended, in part, on the vascular bed in which atherosclerosis was evaluated. Kaufman et al. (2016) reported an association of $PM_{2.5}$ with coronary artery calcification (CAC) among middle to older aged adults in the MESA study, while Dorans et al. (2016) reported no association in the Framingham Heart Study. Associations of long-term exposure to $PM_{2.5}$ with carotid intima media thickness (cIMT) were not consistently observed across cohorts or between analyses of the same cohort with variable methods. Relationships between $PM_{2.5}$ and cIMT at

younger ages were not observed. However, a toxicological study supported similar evidence from the 2009 PM ISA by demonstrating increased plaque progression in ApoE$^{-/-}$ mice following long-term exposure to $PM_{2.5}$ collected from multiple locations across the U.S. (Lippmann et al., 2013a). Thus, this study provided direct evidence that long-term exposure to $PM_{2.5}$ may result in atherosclerotic plaque progression. This study was also coherent with the epidemiologic studies discussed above reporting positive associations between long-term exposure to $PM_{2.5}$ and indicators of atherosclerosis.

A small number of epidemiologic studies also reported positive associations between long-term $PM_{2.5}$ exposure and heart failure (2019 PM ISA, Section 6.2.5), blood pressure, and hypertension (2019 PM ISA, Section 6.2.7). These heart failure studies are in agreement with animal toxicological studies that demonstrated decreased cardiac contractility and function and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.2.5.2). Similarly, a limited number of animal toxicological studies demonstrated a relationship between long-term exposure to $PM_{2.5}$ and consistent increases in BP in rats and mice are coherent with epidemiologic studies that reported positive associations between long-term exposure to $PM_{2.5}$ and hypertension.

Longitudinal epidemiologic analyses also supported the observation of positive associations with markers of systemic inflammation (2019 PM ISA, Section 6.2.12), coagulation (2019 PM ISA, Section 6.2.13), and endothelial dysfunction (2019 PM ISA, Section 6.2.14). These results were in coherence with animal toxicological studies generally reporting increased markers of systemic inflammation and oxidative stress (2019 PM ISA, Section 6.2.12.2), as well as with toxicological studies that generally demonstrated endothelial dysfunction as evidenced by reduced vasodilation in response to acetylcholine (2019 PM ISA, Section 6.2.14).

There was also consistent evidence from multiple epidemiologic studies that long-term exposure to $PM_{2.5}$ was associated with mortality from cardiovascular causes. Associations with CHD, stroke, and atherosclerosis progression were observed in several additional epidemiologic studies, providing coherence with the mortality findings. Results from copollutant models generally supported the independence of the $PM_{2.5}$ associations. Additional evidence of the direct effect of $PM_{2.5}$ on the cardiovascular system was provided by experimental studies in animals, which in part, demonstrate biologically plausible pathways by which long-term inhalation exposure to $PM_{2.5}$ could potentially result in outcomes such as CHD, stroke, CHF, and cardiovascular mortality. **Together, these epidemiologic and experimental studies constitute strong evidence that a causal relationship exists between long-term exposure to $PM_{2.5}$ and cardiovascular effects.**

3.1.2.2. Recent U.S. and Canadian Epidemiologic Studies

Recent epidemiologic studies conducted in the U.S. and Canada build upon the strong epidemiologic evidence base evaluated in the 2019 PM ISA, as well as in previous assessments, which provided the scientific rationale supporting a *causal relationship* between long-term $PM_{2.5}$ exposure and

cardiovascular effects (Section 3.1.1.1). In addition to examining the relationship between long-term $PM_{2.5}$ exposure and specific cardiovascular outcomes (i.e., IHD and myocardial infarction [Section 3.1.2.2.1], cerebrovascular disease and stroke [Section 3.1.2.2.2], atherosclerosis [Section 3.1.2.2.3], heart failure and impaired heart function [Section 3.1.2.2.4], cardiac electrophysiology and arrhythmia [Section 3.1.2.2.5], blood pressure and hypertension [Section 3.1.2.2.6], and cardiovascular mortality [Section 3.1.2.2.7]), analyses within these recent studies also further examined issues relevant to expanding the overall understanding the effect of long-term $PM_{2.5}$ exposure on cardiovascular outcomes. Specifically, recent studies assessed potential copollutant confounding (Section 3.1.2.2.8) and the shape of the concentration-response (C-R) relationship (Section 3.1.2.2.9). The following sections present an evaluation of recent epidemiologic studies conducted in the U.S. and Canada that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-3).

3.1.2.2.1. Ischemic Heart Disease and Myocardial Infarction

The terms ischemic heart disease (IHD), coronary artery disease (CAD), and coronary heart disease (CHD) are generally interchangeable as they appear in the epidemiologic literature on the effects of air pollution. Most IHD is caused by atherosclerosis, which can result in the blockage of the coronary arteries and restriction of blood flow to the heart muscle. A myocardial infarction (MI) or heart attack is an acute event that results in heart muscle tissue death secondary to coronary artery occlusion. The epidemiologic studies included in the 2019 PM ISA represented a substantial expansion of the literature compared with the few studies available for review in the 2009 PM ISA. Overall, findings from these studies were not entirely consistent. The strongest evidence of an association with IHD was found in populations with preexisting diseases such as diabetes or cardiac patients that are followed after an acute event or procedure. Recent studies examine the association between long-term $PM_{2.5}$ exposure and MI with most reporting results that are consistent with those studies evaluated in the 2019 PM ISA.

Recent analyses of the Canadian Ontario Population Health and Environment Cohort (ONPHEC) also add to the available evidence on the relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects. ONPHEC includes more than 5 million Canadian-born adults (35−85 years old at enrollment in 1996) who were registered with the provincial health service and had resided in Ontario for ≥ 5 years. In a prospective analysis, Bai et al. (2019) estimated the association between 3-year average $PM_{2.5}$ concentrations and incident cases of acute MI. The study reported a positive association (HR: 1.07 [95% CI: 1.06, 1.09]). In addition, stratified analyses showed patterns of associations that indicated stronger effect estimates in the youngest (35−44 years) and oldest (75−85 years) age groups. Bai et al. (2019) also examined effect modification by oxidant gases, which was estimated as the redox weighted average of NO_2 and O_3 (O_x). A stronger association, in terms of magnitude, with acute MI was observed

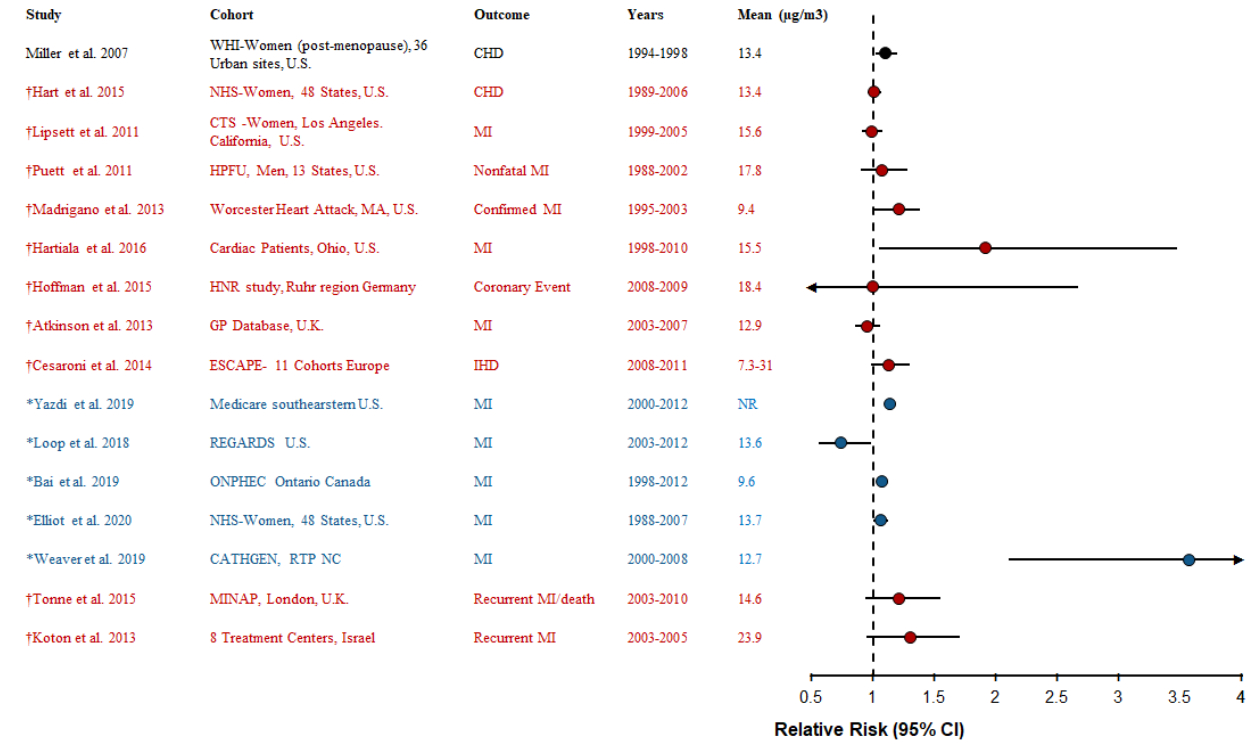
in the highest tertile of (> 38.97 ppm) O_x concentrations (HR: 1.12 [95% CI: 1.09, 1.15]) compared with the lowest (HR: 1.04 [95%CI: 1.01, 1.06]) and middle tertiles (HR: 1.06 [95% CI: 1.00, 1.12]).

Chen et al. (2020) also analyzed data from the ONPHEC study but examined the association of annual average $PM_{2.5}$ in the previous year with the incidence of acute MI. The authors conducted single pollutant analyses using both a traditional Cox proportional hazards model where $PM_{2.5}$ is fit as a linear term and a Cox proportional hazards model where $PM_{2.5}$ was fit as a nonlinear term. Model fit, which was assessed based on the Akaike information criterion (AIC) value, did not vary across models. The risk estimates were also virtually the same across models (i.e., HR = 1.14 [95% CI: 1.12, 1.16] in both models). In addition to conducting single-pollutant analyses, the authors introduced a new approach to assess whether the association of $PM_{2.5}$ with acute MI varied depending on the proportion of $PM_{2.5}$ attributed to selected components (i.e., sulfate, nitrate, ammonium, black carbon, organic matter, mineral dust, and sea salt). The study found that the model that adjusted for the proportion of each of the seven selected components was a better predictor of acute MI based on lower AIC values. In addition, Chen et al. (2020) reported that acute MI associations increased by an average of 10% when compared with single-pollutant results across each of the five regions of Ontario when using the component proportion adjusted approach. Overall, the component adjusted model provided some support that variability in the proportion of individual components that comprise $PM_{2.5}$, could explain regional variability in risk estimates.

While the studies above focus on examining the relationship between long-term $PM_{2.5}$ exposure and MI in cohorts of diverse populations, some recent studies have analyzed data from a cohort of women and cardiac catheterization patients. Elliott et al. (2020) examined the interaction between 24-month $PM_{2.5}$ concentration and physical activity in association with MI among women enrolled in the NHS. Unlike an earlier analysis of this cohort that examined IHD (Hart et al., 2015b), the authors found a positive association of $PM_{2.5}$ with MI (HR: 1.06 [95% CI: 1.00, 1.12]), although no statistical evidence of an interaction with physical activity was observed. In the previous analysis of the NHS cohort, Hart et al. (2015b) reported no association between long-term $PM_{2.5}$ exposure and incident CHD (HR: 1.01 [95% CI: 0.96, 1.07]), although a positive association with IHD was observed among women with diabetes (HR: 1.10 [95% CI: 0.99, 1.21]). Weaver et al. (2019) studied cardiac catheterization patients residing in three counties in NC to determine the association of annual average $PM_{2.5}$ concentration with MI, CAD, and hypertension. Among the objectives of this study was to understand the effect of sociodemographic characteristics on associations by assigning study participants to clusters based on the census block group of their residence that indicated specific sets of sociodemographic characteristics. Positive associations of annual average $PM_{2.5}$ concentration with both CAD and MI were observed. The association with MI was observed across all sociodemographic clusters (OR for all clusters: 3.57 [95% CI: 2.10, 5.77]). The association with CAD was also observed across all clusters (OR: 1.40 [95% CI: 0.90, 2.19]) but was largely driven by one cluster (OR: 2.01 [95% CI: 1.00, 3.86]), which was urban and characterized by low poverty, low unemployment, and composed of relatively highly educated residents with managerial jobs.

In another study, Loop et al. (2018) conducted an analysis of the REGARDS cohort, a nationwide study which oversampled participants from states in the southern U.S. where there is known to be an increased risk of stroke. Participants who were free from CHD at baseline were followed for an average of 6 years. Loop et al. (2018) reported an inverse association between annual average $PM_{2.5}$ concentration at baseline and nonfatal MI (HR: 0.74 [95% CI: 0.56, 0.98]). Loop et al. (2018) also examined associations for total CHD (i.e., CHD deaths and nonfatal MI cases combined) and reported no evidence of an association (HR: 0.89 [95% CI: 0.71, 1.11]).

The evidence informing the relationship between long-term exposure to $PM_{2.5}$ and IHD, including the recent studies of MI, is summarized in Figure 3-5. Recent studies do not all report positive associations; however, the strongest evidence of a relationship continues to be for those with preexisting diseases or patient populations that are followed after a cardiac event or procedure such as catheterization.



Source: Update of Figure 6-17, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent evidence considered in 2019 PM ISAs; and blue text and circles represent recent studies published since the 2019 ISA. Mean concentrations in $\mu g/m^3$. Hazard ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. CATHGEN = Catheterization Genetics Study; CHD = Coronary Heart Disease; CTS = California Teachers Study; ESCAPE = European Study of Cohorts for Air Pollution; HNR = Heinz Nixdorf Recall study; HPFU = Health Professionals Follow-up Study; IHD = Ischemic Heart Disease; MI = myocardial infarction; MINAP = Myocardial Ischemia National Audit Project; NHS = Nurses' Health Study; ONPHEC = Ontario Population Health and Environmental Cohort; REGARDS = REasons for Geographic and Racial Differences in Stroke; WHI = Women's Health Initiative.

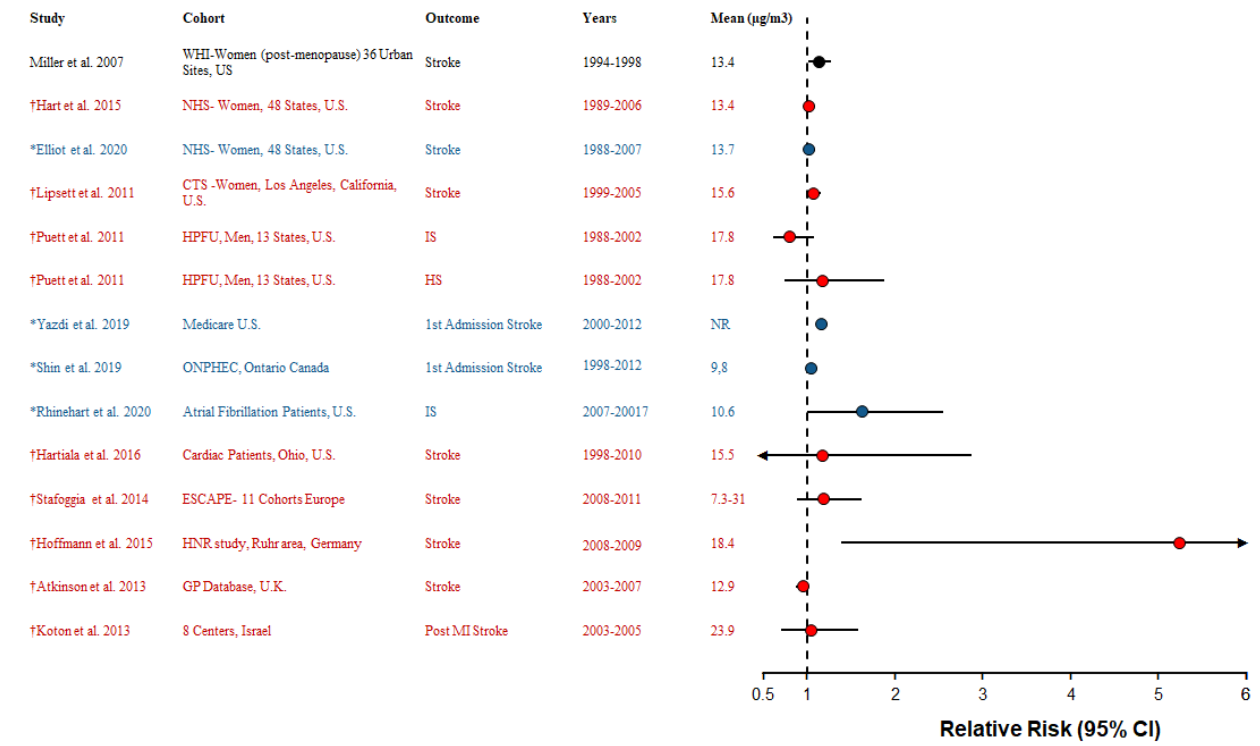
Figure 3-5 Associations between long-term $PM_{2.5}$ exposure and ischemic heart disease or myocardial infarction.

3.1.2.2.2. Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes the conditions hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke), and occlusion of the precerebral and cerebral arteries. The 2009 PM ISA identified one study that indicated a positive association between $PM_{2.5}$ and cerebrovascular morbidity and mortality (HR: 1.16 [95%CI: 1.04, 1.30]) in post-menopausal women (Miller et al., 2007). Although the results were not entirely consistent across studies or stroke subtype, some studies reviewed in the 2019 PM ISA provided evidence to support a positive association between long-term exposure to $PM_{2.5}$ and stroke. Several recent studies that observe positive associations add to this evidence base (Figure 3-6).

Several studies examined the association between long-term $PM_{2.5}$ concentration and stroke as discussed below. In a study of women enrolled in the NHS cohort, Elliott et al. (2020) reported an imprecise (i.e., wide confidence intervals relative to the size of the HR) association between 24 month average $PM_{2.5}$ concentration and stroke that overlapped the null value (HR: 1.02 [95% CI: 0.96, 1.09]). An earlier analysis examining the association with annual average $PM_{2.5}$ concentration in the NHS, reported an increased risk among women with diabetes (HR: 1.29 [95% CI: 1.14, 1.45]) but not in the population, overall (HR: 1.01 [95% CI: 0.96, 1.05]) (Hart et al., 2015b). Rhinehart et al. (2020) estimated the association of annual average $PM_{2.5}$ concentration within 300 meters of the residence with stroke in a prospective analysis of residents of Allegheny County, PA, who were diagnosed with atrial fibrillation but had no history of stroke. This study reported a positive association (HR: 1.62 [95% CI: 1.00, 2.55]). As opposed to examining annual or 24-month average $PM_{2.5}$ exposures, Shin et al. (2019) estimated the association between 5-year $PM_{2.5}$ concentration and incident cases of stroke in a prospective analysis of the Canadian ONPHEC study and reported a positive association (HR: 1.05 [95% CI: 1.03, 1.07]).

Studies that examined the relationship of long-term $PM_{2.5}$ exposure with CBVD and stroke are summarized in Figure 3-6. Recent studies support the evidence in the 2019 PM ISA and extend the evidence relating to the observation of associations among patients that are followed after a cardiac event or procedure.



Source: Update of Figure 6-18, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent evidence included in the 2019 PM ISA; blue text and circles represent evidence not included in the 2019 PM ISA. Mean concentrations in $\mu g/m^3$. Hazard ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. (U.S. EPA, 2018). ESCAPE = European Study of Cohorts for Air Pollution; GP = general practitioner; HNR = Heinz Nixdorf Recall; HPFU = Health Professional's Follow-up; HS = hemorrhagic stroke; IS = ischemic stroke; MI = myocardial infarction; NHS = Nurses' Health Study; ONPHEC = Ontario Population Health and Environment Cohort; WHI = Women's Health Initiative.

Figure 3-6 Associations between long-term $PM_{2.5}$ exposure and the incidence of stroke.

3.1.2.2.3. Atherosclerosis

Atherosclerosis is the process of plaque buildup that forms lesions on the walls of the coronary arteries, which can lead to narrowing of the vessel, reduced blood flow to the heart and IHD. Atherosclerosis can be assessed within large arterial vascular beds in distinct regions of the body i.e., carotid intima-media thickness (cIMT), coronary artery calcification (CAC), ankle-brachial index (ABI), and the presence of plaques. Findings from studies reviewed in the 2009 PM ISA were inconsistent, reporting null or positive, but imprecise associations with cIMT, CAC, and ABI. Similarly, findings from studies reviewed in the 2019 PM ISA were not entirely consistent across populations, exposure assessment methods, and measures of atherosclerosis. Notably, an extended MESA analysis reported a longitudinal increase in CAC (4.1 Agatston unit increase per year [95% CI: 1.4, 6.8]) in association with annual average $PM_{2.5}$ exposure, but no association (β: -0.90 µm per year [95%CI: -3.00,

1.30]) with cIMT (Kaufman et al., 2016). Exposure measurement error, variation in baseline measures of atherosclerosis as well as statistical power were noted as possible explanations for the lack of association observed in these studies. Consideration of copollutant confounding was generally limited across the evidence base reviewed in the 2019 PM ISA.

Several recent studies expand the evidence available to consider the association of long-term $PM_{2.5}$ exposure with atherosclerosis. Following the analysis by Kaufman et al. (2016), Keller et al. (2018) estimated the association of $PM_{2.5}$ concentration (i.e., multi-year average during the study period 2000−2012) with CAC progression among participants in MESA air residing in Baltimore, MD. The authors also assessed whether this association was modified by membership in clusters with different traffic-related air pollution (TRAP) component profiles. The authors reported a 23.0 Agatston unit per year increase (95% CI :14.2, 31.7) among participants overall. Keller et al. (2018) also reported a larger magnitude association with CAC progression (42.6 Agatston unit per year increase [95% CI: 25.7, 59.4]) in the cold season among those belonging to a cluster that was characterized as downtown with above average ratios of ultrafine and accumulation mode particles relative to NO_X.

Among women enrolled in the Study of Women's Health Across the Nation (SWAN), a cohort of U.S. women transitioning through menopause, Duan et al. (2019a) estimated the association of 5-year average $PM_{2.5}$ concentration with cIMT. The study reported a 27.95 μm (95% CI: −2.90, 58.75) thicker mean cIMT in association with 5-year mean $PM_{2.5}$ concentration in adjusted models. $PM_{2.5}$ was also associated with an increase in increased mean inter-adventitial diameter (IAD), which is a marker of vascular remodeling and aging as well as a predictor of cardiovascular events, of 105.90 (95% CI: −63.00, 274.80). No association was reported with plaque presence (OR: 0.90 [95% CI: 0.50, 1.61]) or plaque severity index (plaque index 0−2, OR: 1.05 [95% CI: 0.53, 8.95] and plaque index > 2, OR: 0.62 [95% CI: 0.25, 1.47]) in the SWAN study. In an analysis of a subset of SWAN participants (Pittsburgh and Chicago only), Duan et al. (2019b) estimated the association of the same measures of atherosclerosis as Duan et al. (2019a) with annual average $PM_{2.5}$ concentration reporting a 11.25 μm per year increase (95% CI: −3.05, 25.60) in mean cIMT. The authors also reported associations with plaque presence (OR: 2.10 [95% CI: 0.66, 6.63]) and plaque index progression (OR: 2.70 [95% CI: 0.77, 9.24]).

Recent studies support and extend the evidence characterized in the 2019 PM ISA with observations of associations with cIMT among women transitioning into menopause and potential effect modification by TRAP in the MESA study.

3.1.2.2.4. Heart Failure and Impaired Heart Function

HF refers to a set of conditions including CHF in which the heart's pumping action is weakened. With CHF the blood flow from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). Risk factors for HF include IHD, high blood pressure, atrial fibrillation, and diabetes. The

small number of epidemiologic studies reviewed in the 2019 PM ISA provided evidence supporting a possible relationship between heart failure and long-term exposure to $PM_{2.5}$. In addition, an association with increased right ventricular (RV) mass was observed among MESA participants (Aaron et al., 2016). Right sided HF is typically a consequence of left-sided HF but can also result from damage to the pulmonary vasculature, which can result in increased RV mass, reduced flow to the left ventricle, and reduced left ventricular (LV) mass.

A recent study examining the association between long-term $PM_{2.5}$ exposure and HF was conducted among participants in the Canadian ONPHEC study. In this prospective analysis, Bai et al. (2019) examined the relationship between 3-year moving average $PM_{2.5}$ concentration with new cases of CHF. A positive association was reported, overall (HR: 1.07 [95% CI: 1.06, 1.07]), and a larger magnitude association was reported in the highest tertile of O_x concentrations in a stratified analysis examining potential effect modification (HR: 1.12 [95% CI: 1.10, 1.13]). The hazard ratios in the lowest and middle O_x tertiles were 1.04 (95% CI: 1.03, 1.06) and 1.06 (95% CI: 1.03, 1.07), respectively. This study supports the evidence in the 2019 PM ISA that indicates a positive association between long-term $PM_{2.5}$ and HF; however, the evidence remains limited overall.

3.1.2.2.5. Cardiac Electrophysiology and Arrhythmia

Electrical activity in the heart is typically measured using surface electrocardiography (ECG). ECGs measure electrical activity in the heart due to depolarization and repolarization of the atria and ventricles. Atrial fibrillation (AF) is the most common type of arrhythmia. Despite being common, clinical and subclinical forms of AF are associated with reduced functional status and quality of life and are associated with downstream consequences such as ischemic stroke (Prystowsky et al., 1996; Laupacis et al., 1994) and CHF (Roy et al., 2009), contributing to both CVD and all-cause mortality (Kannel et al., 1983). Ventricular fibrillation is a well-known cause of sudden cardiac death and commonly associated with MI, HF, cardiomyopathy, and other forms of structural (e.g., valvular) heart disease.

In an analysis of the WHI, which was reviewed in the 2009 PM ISA, Liao et al. (2009) found no association of long-term $PM_{2.5}$ concentrations with supraventricular or ventricular ectopy, which are the most frequent forms of arrhythmia in the general population. A limited number of studies reviewed in the 2019 PM ISA found associations of long-term $PM_{2.5}$ exposure with premature atrial contractions and ventricular conduction abnormalities, but not arrhythmias recorded on implantable cardioverter defibrillators. In a recent prospective analysis of the Canadian OPHEC study, Shin et al. (2019) estimated the association between 5-year average $PM_{2.5}$ concentration and incident cases of AF and reported a positive association (HR: 1.03 [95% CI: 1.01, 1.04]). Overall, the evidence pertaining to the association between long-term $PM_{2.5}$ exposure and various types of arrythmias remains limited.

3.1.2.2.6. Blood Pressure and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg (U.S. EPA, 2019). Hypertension, the clinically relevant consequence of chronically high blood pressure, typically develops over years. The body of literature reviewed in the 2019 PM ISA was substantially larger than in the 2009 PM ISA with longitudinal analyses generally showing small magnitude increases in SBP, pulse pressure (PP), and mean arterial pressure (MAP) in association with long-term exposure to $PM_{2.5}$. In addition, the expanded body of literature provided evidence of associations between long-term $PM_{2.5}$ exposure and hypertension. Recent studies add to the evidence providing support for positive associations among post-menopausal women enrolled in the WHI study and in cardiac catheterization patients, but not among Black women enrolled in the Jackson Heart Study (JHS).

Honda et al. (2017) estimated the association of $PM_{2.5}$ concentration with incident hypertension among post-menopausal women enrolled in the WHI. Annual average $PM_{2.5}$ concentration was associated with incident hypertension. (HR: 1.17 [95% CI 1.10, 1.22]). The association with $PM_{2.5}$ concentration increased among minority participants (i.e., Black, Asian/Pacific Islander, Hispanic/Latino race/ethnicity, which were characterized as non-White in the study) participants and those who lived in the Northeast U.S. By contrast, no association of 1-year or 3-year average $PM_{2.5}$ concentration with hypertension was observed in a recent prospective analysis conducted by Weaver et al. (2021) of African American women enrolled in the JHS (1-year, RR: 1.00 [95% CI: 0.52, 2.03] and 3-year, RR: 1.10 [95% CI: 0.39, 2.84]). Further adjustment for diabetes did not change these findings. A cross-sectional analysis of $PM_{2.5}$ concentration and prevalent hypertension conducted by Weaver et al. (2021) yielded similar results.

An association between long-term $PM_{2.5}$ exposure and hypertension was also observed among cardiac catheterization patients in three counties in North Carolina (Weaver et al., 2019). In this study Weaver et al. (2019) estimated the association of annual average $PM_{2.5}$ concentration with hypertension. No association between long-term $PM_{2.5}$ exposure and hypertension was observed in the study population overall (OR: 0.90 [95% CI: 0.59, 1.34). The pattern of associations between long-term $PM_{2.5}$ concentration and hypertension indicated larger magnitude associations among study participants who lived in two sociodemographic clusters, the first characterized as urban, having a high proportion of Black individuals and individuals in non-managerial occupations (denoted as Cluster 1) and the second characterized as urban, impoverished, having a high proportion of individuals who are unemployed, work in non-managerial occupations, are Black, and live in single parent homes (Cluster 2). The OR for Cluster 1 was 2.70 (95% CI: 0.95, 7.59) and the OR for Cluster 2 was 11.86 (95% CI: 2.10, 67.21).

The literature assessed in the 2019 PM ISA provided evidence of associations between long-term $PM_{2.5}$ exposure and hypertension. Recent studies are generally consistent with this assessment, reporting positive associations among post-menopausal women enrolled in the WHI study and in cardiac catheterization patients. However, no association between long-term $PM_{2.5}$ exposure and hypertension was observed among Black women enrolled in the JHS.

3.1.2.2.7. Cardiovascular Mortality

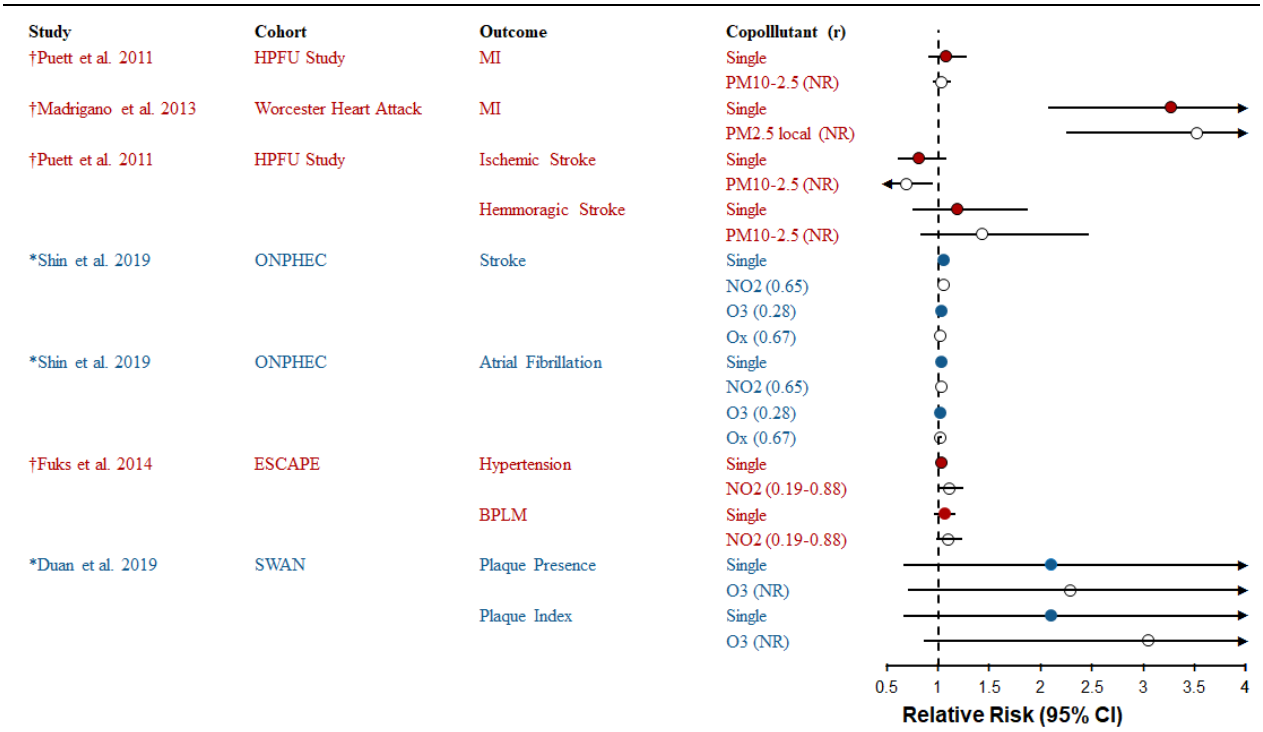
Multiple epidemiologic studies (Section 3.2.2.2.2) reviewed in the 2009 PM ISA and in the 2019 PM ISA reported consistent positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality. Generally, these studies had extensive control for a wide range of potential confounders and the observed effect estimates remained relatively unchanged or increased in copollutant models adjusted for ozone, NO_2, $PM_{10–2.5}$, or SO_2. Recent cohort studies, which are reviewed in detail in Section 3.2.2.2.2 provide additional evidence for associations with cardiovascular mortality outcomes across the distribution of $PM_{2.5}$ concentrations (Hayes et al., 2020), the potential implications of a comorbidity on the $PM_{2.5}$-cardiovascular mortality relationship (Pinault et al., 2018), and associations with individual cardiovascular mortality outcomes including IHD (Crouse et al., 2020; Wang et al., 2020; Cakmak et al., 2018; Pinault et al., 2017) and stroke (Crouse et al., 2020; Hayes et al., 2020; Wang et al., 2020; Pope et al., 2019; Pinault et al., 2017). Overall, these recent studies support the conclusions in the 2019 PM ISA of consistent positive associations of long-term $PM_{2.5}$ exposure with cardiovascular mortality, and specifically with IHD- and stroke-related mortality. Although Pope et al. (2014) reported positive associations of long-term $PM_{2.5}$ exposure with CHF mortality in a study of the ACS cohort evaluated in the 2019 PM ISA, a recent analysis of the Medicare cohort Wang et al. (2020) reported a null association. Recent studies also indicate that the combination of cardiovascular disease and diabetes together has a greater mortality risk than cardiovascular mortality alone and that cardiovascular diseases such as heart failure or previous MI may increase the risk of $PM_{2.5}$-related all-cause mortality (Ward-Caviness et al., 2020; Malik et al., 2019).

3.1.2.2.8. Copollutant Confounding

One approach to assessing the independence of the association between exposure to $PM_{2.5}$ and a health effect, such as long-term exposure to $PM_{2.5}$ and cardiovascular health effects is through the use of copollutant models. As noted in the Appendix (Table A-3) to the 2019 PM ISA, copollutant models are not without their limitations, such as instances when correlations are high between pollutants resulting in greater bias in results. However, in assessing the results from copollutant models, a change in the $PM_{2.5}$ risk estimates, after adjusting for copollutants, may indicate the potential for confounding. A limited number of studies were available in the 2019 PM ISA to assess copollutant confounding of the association between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity. Considering these few available studies, risk estimates remained largely unchanged after adjustment for $PM_{10–2.5}$, NO_2, and $PM_{2.5}$ from traffic sources. The limited number of recent analyses report some attenuation of risk estimates in models adjusted for O_3 and NO_2.

Several recent analyses of the ONPHEC study add to the evidence pertaining to copollutant confounding (Figure 3-7). Shin et al. (2019) reported that the association of long-term $PM_{2.5}$ exposure with stroke (HR: 1.03 [95%CI: 1.01, 1.04]) persisted after adjustment for NO_2 but was attenuated in the

models with O_3 and oxidant gases (O_x) represented by the redox weighted average of NO_2 and O_3 (HR: 1.05 [95% CI: 1.03, 1.06] and HR: 1.03 [95% CI:1.02, 1.04], and HR: 1.02 [95% CI:1.00, 1.05], respectively). In an analysis of AF, these authors found that the association was slightly attenuated, but remained positive, in two-pollutant models that adjusted for NO_2, O_3 and redox weighted average of NO_2 and O_3 (O_x) (HR: 1.03 [95% CI: 1.02, 1.04] and HR: 1.02 [95% CI: 1.01, 1.03], and HR: 1.02 [95% CI: 1.01, 1.03], respectively). In addition, a study of atherosclerosis in the SWAN cohort, Duan et al. (2019a) reported that the estimate for the association of long-term $PM_{2.5}$ exposure with cIMT was slightly attenuated in a two-pollutant model that adjusted for O_3 (24.45 µm [95% CI: −18.35, 67.25]). In a separate analysis of a subset of this cohort, however, Duan et al. (2019b) reported that associations with plaque presence and plaque index progression persisted in models adjusted for ozone (OR: 2.29 [95% CI: 0.70, 7.59]) for plaque presence and (OR 3.05 [95% CI: 0.86, 10.82] for plaque index progression). Overall, the limited evidence indicates that associations between $PM_{2.5}$ and cardiovascular health effects persist, but may be slightly attenuated, in models that are adjusted for copollutants.



Source: Update of Figure 6-20, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for 2019 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Solid circles represent single pollutant results and open circles represent copollutant results. Hazard ratios are standardized to a 5 µg/m^3 increase in $PM_{2.5}$ concentrations.

Figure 3-7 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity in single pollutant models and models adjusted for copollutants.

3.1.2.2.9. Examination of the Concentration-Response (C-R) Relationship between Long-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and cardiovascular effects is whether the C-R relationship is linear across the full concentration range that is encountered, or whether there are concentration ranges that exhibit departures from linearity. A limited number of studies evaluated in the 2019 PM ISA examined the shape of the C-R relationships for cardiovascular morbidity outcomes with the majority of studies lacking thorough evaluations of alternatives to linearity (2019 PM ISA, Table 6-51). Several recent studies expand the evidence pertaining to the shape of the C-R relationship for the incidence of MI, AF, stroke, and CHF. A number of these studies use statistical techniques that allow for departures from linearity (Table 3-3) generally supporting and extending the evidence characterized in the 2019 PM ISA showing linear, no-threshold C-R relationship for most CVD outcomes. However, there is some evidence for a sublinear or supralinear C-R relationship for some outcomes.

Table 3-3 Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular morbidity.

Study Location—Cohort (Table/Figure from Reference)	Outcome	Exposure $PM_{2.5}$ Mean: (Range) in $\mu g/m^3$	Statistical Analysis Summary
Bai et al. (2019) Figure 3-8 Ontario, Canada ONPHEC	Acute MI incidence	Mean (IQR):9.6 (3.5)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF** (Nasari et al., 2016). A linear concentration-response relationship between acute MI and $PM_{2.5}$ concentration was observed.
Chen et al. (2020) Figure 3-9 Ontario, Canada ONPHEC	Acute MI Incidence	Mean: 8.61	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF** (Nasari et al., 2016). Restricted cubic splines with 4 df to assess linearity used in sensitivity analysis. Approximately linear relationship observed with both methods.
Danesh Yazdi et al. (2019) Figure 3-10 Medicare Southeastern, U.S.	First hospital admission for MI	NR	Penalized spline to estimate the shape of the C-R relationship, with degrees of freedom chosen based on corrected AIC values.

Table 3-3 (Continued): Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular morbidity.

Study Location—Cohort (Table/Figure from Reference)	Outcome	Exposure $PM_{2.5}$ Mean: (Range) in $\mu g/m^3$	Statistical Analysis Summary
			C-R relationship continued down to low-exposure levels and persisted when the data set was restricted <12 $\mu g/m^3$. The relationship was generally linear at concentrations below 14 $\mu g/m^3$.
Loop et al. (2018) Figure 3-11 U.S. Nationwide REGARDS	Nonfatal MI incidence	Median (IQR): 13.6 (2.7)	Predicted log hazard modeled as a linear function (nonlinear relationship tested using restricted cubic splines). Sensitivity analyses to test for interactions of $PM_{2.5}$ with gender, race, and urbanicity were conducted to elucidate discrepant findings (i.e., inverse relationship). No statistically significant interactions observed (p = 0.05 level). Inverse relationship between annual average $PM_{2.5}$ exposure and nonfatal MI.
Shin et al. (2019) ONPHEC Ontario, Canada	Atrial Fibrillation	Mean (IQR): 9.8 (4.0)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF (Nasari et al., 2016). Sublinear relationship observed with some evidence of potential threshold at $PM_{2.5}$ concentrations < 6 $\mu g/m^3$.
Shin et al. (2019) ONPHEC Ontario, Canada	Stroke	Mean (IQR): 9.8 (4.0)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF (Nasari et al., 2016). Linear association was observed with no evidence of a threshold.
Danesh Yazdi et al. (2019) Medicare Southeastern, U.S.	First hospital admission for stroke	NR	Penalized spline to estimate the shape of the C-R relationship, with degrees of freedom chosen based on corrected AIC values. C-R relationship continued down to low-exposure levels and persisted when the data set was restricted <12 $\mu g/m^3$. The relationship was generally linear at concentrations below 14 $\mu g/m^3$.

Table 3-3 (Continued): Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular morbidity.

Study Location—Cohort (Table/Figure from Reference)	Outcome	Exposure $PM_{2.5}$ Mean: (Range) in $\mu g/m^3$	Statistical Analysis Summary
Bai et al. (2019) Ontario, Canada ONPHEC	CHF	Mean (IQR):9.6 (3.5)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF (Nasari et al., 2016). A supralinear concentration-response relationship between CHF and $PM_{2.5}$ concentration was observed.

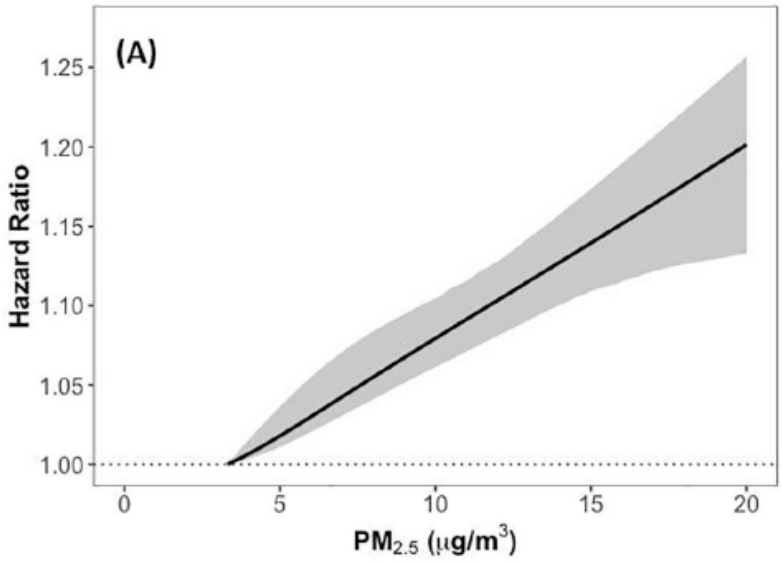
AIC = Akaike information criterion; C-R = concentration-response; CAC = coronary artery calcification; CHF = congestive heart failure; df = degrees of freedom; ESCAPE = European Study of Cohorts for Air Pollution Effects, HR = hazard ratio, IHD = ischemic heart disease, IQR = interquartile range; MI = myocardial infarction; REGARDS = REasons for Geographic and Racial Differences in Stroke; SCHIF = Shape Constrained Health Impact Function.

Note: **SCHIF models various shapes including supra-linear, near-linear, and sublinear forms and permits different shapes of the pollutant−outcome association in a monotonically nondecreasing manner but limits the amount of curvature in the shape.

†Studies included in the 2019 Integrated Science Assessment for Particulate Matter.

*Recent studies published since the literature cutoff date (~January 2018) for the 2019 Integrated Science Assessment for Particulate Matter.

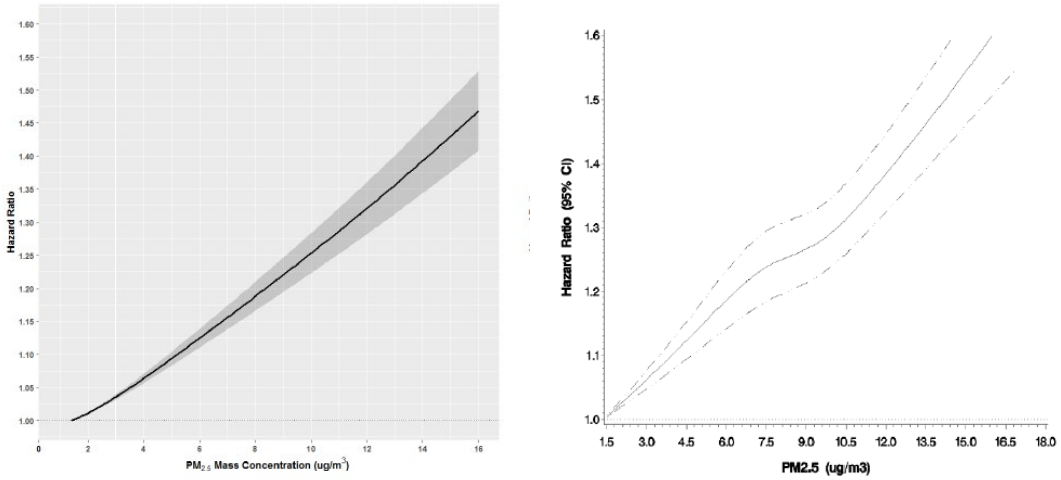
Several studies evaluated the shape of the C-R function for the relationship between long-term $PM_{2.5}$ exposure and MI, including two analyses of the ONPHEC study (Figure 3-8 and Figure 3-9), an analysis of the U.S. Medicare population (Figure 3-10), and an analysis of the REGARDS cohort (Figure 3-11). Approximately linear relationships were observed in the ONPHEC analyses (Chen et al., 2020; Bai et al., 2019) using Shape Constrained Health Impact Function (SCHIF) method (Nasari et al., 2016), which is described as a new class of variable coefficient risk functions that can capture potentially nonlinear associations, and in the Medicare analysis using penalized splines, which is described in Section 3.1.2.1 (Danesh Yazdi et al., 2019). Both methods allow for deviations from linearity. By contrast, Loop et al. (2018) found an inverse relationship between annual average $PM_{2.5}$ exposure and nonfatal MI.



Source: Bai et al. (2019)

Note: The gray shaded area represents the 95% confidence interval.

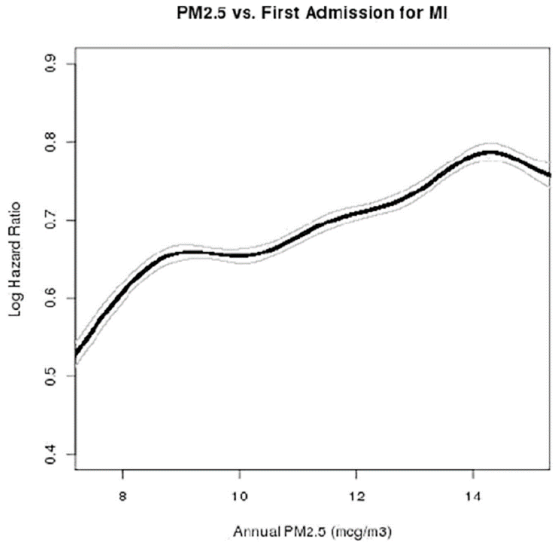
Figure 3-8 Concentration-response relationship for the association of $PM_{2.5}$ concentration with acute myocardial infarction.



Source: Chen et al. (2020)

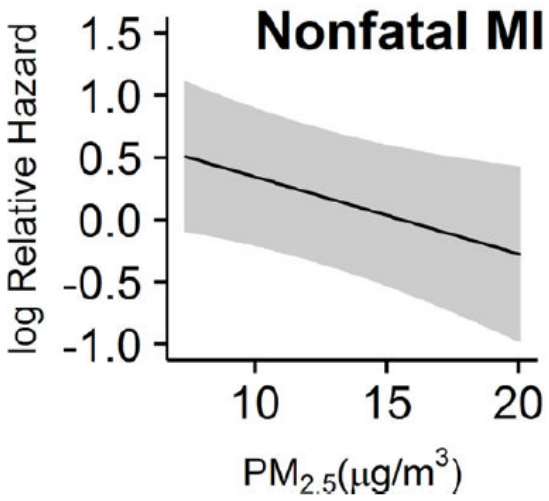
Note: The gray shaded area represents the 95% confidence interval.

Figure 3-9 Concentration-response relationship for the association of $PM_{2.5}$ concentration with acute myocardial infarction using SCHIF (A) and penalized splines (B) with 4 degrees of freedom.



Source: Danesh Yazdi et al. (2019)
Note: The gray shaded area represents the 95% confidence interval.

Figure 3-10 Concentration-response relationship for the association of $PM_{2.5}$ concentration with first admissions for myocardial infarction.



Source: Loop et al. (2018)
Note: Gray bands are 95% prediction intervals.

Figure 3-11 Predicted log hazard for incident nonfatal myocardial infarction versus previous 1-year mean ambient $PM_{2.5}$ concentration.

Several additional analyses evaluated the shape of the C-R relationship for atrial fibrillation and stroke. In analyses of ONPHEC using SCHIF, a sublinear relationship was observed for atrial fibrillation with some evidence of potential threshold at $PM_{2.5}$ concentrations < 6 μg/m^3 (Shin et al., 2019), and a linear relationship with no evidence of a threshold was observed for stroke. Danesh Yazdi et al. (2019) also found a C-R relationship that was generally linear (i.e., at $PM_{2.5}$ concentrations < 14 μg/m^3) among Medicare recipients. One study assessed the shape of the C-R function for CHF, which was observed to be supralinear, flattening at higher concentrations at approximately 14 μg/m^3 (Bai et al., 2019).

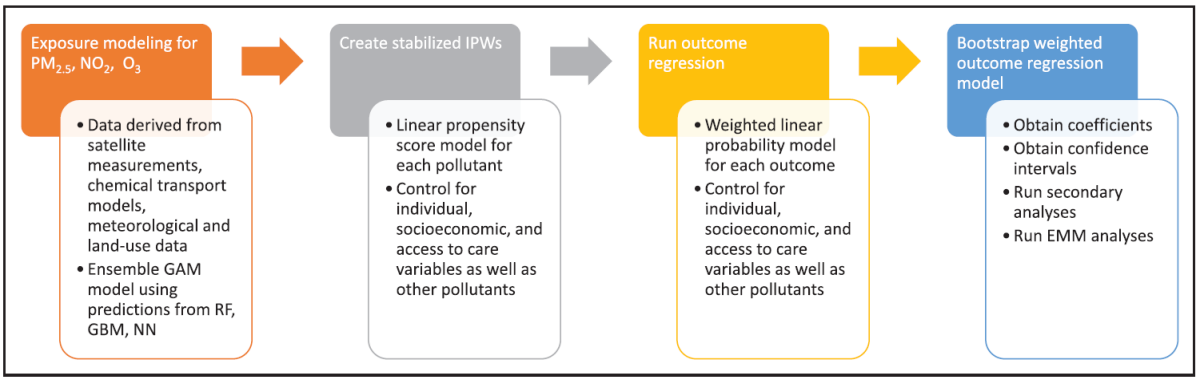
3.1.2.3. Recent Epidemiologic Studies Examining the $PM_{2.5}$-Cardiovascular Effects Relationship through Accountability Analyses and Alternative Methods for Confounder Control

Several studies in the 2019 PM ISA were assessed and in general, supported an association between long-term $PM_{2.5}$ exposure and a variety of cardiovascular hospital admissions (2019 PM ISA, Section 6.2). However, the assessment of this outcome did not include any epidemiologic studies that conducted accountability analyses or employed alternative methods for confounder control because no such studies were prior to the literature cutoff date for the 2019 PM ISA. Since the literature cutoff date of the 2019 PM ISA, a few recent studies conducted accountability analyses or employed alternative methods for confounder control to evaluate the relationship of long-term $PM_{2.5}$ exposure and cardiovascular hospital admissions (Table A-4).

Henneman et al. (2019) utilized a difference-in-difference (DID) approach to conduct an accountability analysis of emissions reductions from coal-fueled power plants in the U.S. between 2005 and 2012 on cardiovascular hospital admission rates for acute myocardial infarction, cardiovascular stroke, heart failure, heart rhythm disorders, ischemic heart disease, peripheral vascular disease, and all cardiovascular diseases among Medicare beneficiaries. DID methods are used to estimate the effect of a specific treatment or intervention, such as reductions in coal-fueled power plant emissions, by comparing the changes in outcomes over time prior to the treatment/intervention and after. For each 1 μg/m^3 decrease in $PM_{2.5}$ concentrations, the authors reported the change in hospital admissions per 10,000 person-years and found overall reductions for all cardiovascular diseases of −8.4 (95% CI: −12.67, −4.14), −0.01 (95% CI: −0.93, 0.91) for acute myocardial infarction, −1.95 (95% CI: −3.20, −0.70) for stroke, −4.26 (95% CI: −6.09, −2.43) for heart failure, and −3.87 (95% CI: −5.67, −2.08) for ischemic heart disease. However, an increase was reported for heart rhythm disorders 0.96 (95% CI: −0.21, 2.12). Overall, Henneman et al. (2019) found that reductions in annual $PM_{2.5}$ concentrations from coal-fueled power plants resulted in corresponding reductions in a number of cardiovascular-related hospital admissions.

To examine the relationship between annual average $PM_{2.5}$ concentrations and cardiovascular-related hospital admissions including myocardial infarction, stroke, and atrial fibrillation and flutter among Medicare beneficiaries, Danesh Yazdi et al. (2021) used a doubly robust additive model

(DRAM). The steps for the approach used by Danesh Yazdi et al. (2021) is depicted in Figure 3-12. $PM_{2.5}$ concentrations were derived from a spatiotemporal ensemble model. To control for potential confounding from individual, socioeconomic, access to care variables, and copollutants (ozone and NO_2), an inverse probability weighting approach was applied through linear propensity score models to generate weights. The weights were then stabilized by taking the probability of the exposure as the numerator and the denominator as the probability density of the exposure as defined on the basis of the linear regression with $PM_{2.5}$ as the outcome and covariates and other pollutants (ozone and NO_2) as the predictors. If the inverse probability weights for the exposure and the adjustment for the weights in the outcome regression are correctly specified, it can be assumed that the estimated coefficient is unbiased. A weighted linear probability model showed that long-term exposure to $PM_{2.5}$ was associated with increased admissions across all cardiovascular hospitalization outcomes. For each 1 $\mu g/m^3$ increase in annual average $PM_{2.5}$ concentrations, the authors estimated 2,536 (95% CI: 2,383, 2,691) additional admissions for ischemic stroke, 637 (95% CI: 483, 814) additional admissions for myocardial infarction, and 1,575 (95% CI: 1,426, 1,691) additional admissions for atrial fibrillation and flutter.



Source: Danesh Yazdi et al. (2021)

Figure 3-12 Analysis steps used by Danesh Yazdi et al. (2021) to examine long-term $PM_{2.5}$ exposure and cardiovascular-related hospital admissions.

Zigler et al. (2018) used a hybrid approach of integrating an accountability analysis with an alternative method for confounder control to examine whether attainment status for the 1997 NAAQS led to an improvement in $PM_{2.5}$ concentrations and subsequently health. By focusing on nonattainment designations, the authors are able to examine the role of local control strategies in reducing $PM_{2.5}$ concentrations that occurred above and beyond reductions due to regional strategies. Within this study, Zigler et al. (2018) employed propensity scores, within a spatial hierarchical regression model to examine whether designation of nonattainment in 2005 for the 1997 PM NAAQS, for either the annual standard of 15 $\mu g/m^3$ or the daily standard of 65 $\mu g/m^3$, led to a corresponding reduction in ambient $PM_{2.5}$

concentrations and hospitalization admission rates for cardiovascular-related outcomes (i.e., cardiovascular stroke, heart failure, heart rhythm disorders, ischemic heart disease, and peripheral vascular disease) among Medicare beneficiaries in the eastern U.S. from 2009 to 2012. Using publicly available date sources for the analysis, Zigler et al. (2018) compared average annual $PM_{2.5}$ concentrations and selected cardiovascular hospital admission rates in nonattainment areas against those in attainment areas using a two-step approach and adjusting for confounding factors that differed between the areas.

In the first step, propensity scores were used to adjust for confounders by grouping attainment and nonattainment areas based on similarities in baseline characteristics, which are detailed in Appendix A (Table A-4). Under the assumption that these baseline factors comprise all factors that differ between locations in attainment and nonattainment areas and that the factors are correlated with both the exposure (ambient $PM_{2.5}$ concentration) and each outcome (cardiovascular-related hospital admission rates), there should be no unmeasured confounders. To ensure that nonattainment areas are compared only with attainment areas with similar baseline factors, (1) propensity scores were estimated based on the probability that a monitoring location is in a nonattainment area, conditional on the baseline factors; (2) areas with features that are not comparable to other areas in the comparison group were identified and omitted (propensity score pruning); and (3) the remaining locations were grouped into quartiles, where attainment and nonattainment areas have similar baseline factors (e.g., population, $PM_{2.5}$ concentrations, demographics) within each subgroup.

In the second step, a spatial hierarchical regression model was used to predict the potential annual ambient $PM_{2.5}$ concentration in 2010–2012 that would have occurred in nonattainment areas if the designations had never occurred. For this part of the analysis, the spatial hierarchical model is estimated jointly with a log-linear model using the same confounding adjustment for propensity score group and additional covariates for each type of cardiovascular hospital admission. In addition to estimating the effect estimates for the overall average effects, a principal stratification approach was used to estimate "associative effects" and "dissociative effects." Within this study, Zigler et al. (2018) define effect estimates for the "associative effects" as the effects of the nonattainment designations on cardiovascular-related hospital admissions among areas where the nonattainment designations are estimated to reduce ambient $PM_{2.5}$ concentrations by at least 1 $\mu g/m^3$, and "dissociative effects" as the effects of the nonattainment designations estimated to not affect $PM_{2.5}$ concentrations by more than ± 1 $\mu g/m^3$.

Zigler et al. (2018) reported a slight reduction in the overall average effect for hospital admission rates for cardiovascular stroke, heart failure, and ischemic heart disease and an increase in the overall effect for hospital admission rates for peripheral vascular disease; however, 95% CIs were wide and included zero. There was no evidence of a reduction in hospital admission rates for heart rhythm disorders or peripheral vascular disease. When examining the average "associative effects," the authors reported an average reduction of −2.38 (95% CI: −4.35, -0.44) and −2.60 (95% CI: −4.24, −1.14) for only heart failure and ischemic heart disease hospital admissions per 1,000 person-years, respectively. The authors reported a similar pattern of associations for the average "dissociative effects," that is, slight reductions in

hospital admission rates for only cardiovascular stroke and heart failure with wide 95% CIs that included the null. Overall, the results of Zigler et al. (2018) provide evidence that reductions in ambient $PM_{2.5}$ concentrations and the selected cardiovascular hospital admissions could not be conclusively attributed to nonattainment designations against the backdrop of other regional strategies that impacted the eastern U.S.

The addition of these recent studies further supports the findings from the studies of the 2019 PM ISA. Overall, these studies reported consistent findings that long-term $PM_{2.5}$ exposure is associated with increased hospital admissions for a variety of cardiovascular disease outcomes among large nationally representative study populations. The addition of studies that use methods to reduce uncertainties related to potential confounding bias with statistical methods and/or study design approaches, like DRAM used by Danesh Yazdi et al. (2021) or the DID approach used by Henneman et al. (2019), further increase confidence in the relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects.

3.1.2.4. Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Long-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

Recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and cardiovascular effects. Numerous U.S. and Canadian cohort studies conducted in locations where the long-term $PM_{2.5}$ concentration are less than 13 $\mu g/m^3$ add to the strong evidence base that was characterized in the 2019 PM ISA describing the relationship between long-term $PM_{2.5}$ and cardiovascular mortality, and specifically IHD- and stroke-related mortality. Overall, these recent cardiovascular mortality studies reported positive associations at varying spatial scales and across different exposure assessment and statistical methods. The associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality generally persisted in models that were adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2, and most analyses of the C-R function supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$ (Section 3.2.2.2.2).

Although results were not entirely consistent, evidence of positive associations between long-term $PM_{2.5}$ exposure and cardiovascular morbidity (i.e., CHD, stroke, and atherosclerosis progression) were observed in epidemiologic studies reviewed in the 2019 PM ISA, providing coherence with the mortality findings described above. Recent studies support and the extend findings characterized in the 2019 PM ISA, providing additional evidence of positive associations between long-term $PM_{2.5}$ exposure and cardiovascular outcomes including MI, stroke, arrhythmias, atherosclerosis, HF, and hypertension. Although positive associations are not reported in all studies, these recent studies also support and extend the most consistent evidence of cardiovascular effects reviewed in the 2019 PM ISA, which described positive associations among those with preexisting diseases and among patients that are followed after a cardiac event or procedure (Rhinehart et al., 2020; Ward-Caviness et al., 2020; Malik et

al., 2019; Weaver et al., 2019). Recent studies also support and extend the evidence in the 2019 PM ISA regarding effect measure modification by income and SES (Section 3.3.3). Together these recent studies examining effect measure modification may explain inconsistency observed across cardiovascular morbidity studies by identifying factors that determine the heterogeneity.

The limited number of studies reviewed in the 2019 PM ISA found that risk estimates remained largely unchanged after adjustment for $PM_{10-2.5}$, NO_2, and $PM_{2.5}$ from traffic sources. The few recent analyses report some attenuation of risk estimates in models adjusted for O_3 and NO_2. Recent studies also support and extend the evidence in the 2019 PM ISA pertaining to the joint effects of multiple pollutants indicating that associations may be modified by oxidant gases, $PM_{2.5}$ composition and long-term exposure to NO_2. Further, recent studies support and extend the evidence in the 2019 PM ISA pertaining to the shape of the C-R function for cardiovascular morbidity effects. Although still limited in number, recent studies characterizing the C-R relationship provide a more thorough examination of potential for departures from linearity. Evidence from these studies is generally consistent with that presented in the 2019 PM ISA, and shows a linear, no-threshold C-R relationship for most CVD outcomes. However, there is some evidence for a sublinear or supralinear C-R relationship for specific outcome (i.e., CHF and AF). Finally, a few recent epidemiologic studies that employed alternative methods for confounder control to reduce uncertainties related to potential confounding bias provide additional support for a relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects.

3.2. Mortality

3.2.1. Short-Term $PM_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for short-term $PM_{2.5}$ exposure and mortality presented within the 2019 PM ISA (Section 3.2.1.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.2.1.2). [16] In addition, with the expansion of epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.2.1.3), which can further inform the relationship between short-term $PM_{2.5}$ exposure and mortality. Finally, a summary of the results of recent studies evaluated within the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.2.1.4). The evaluation of recent studies on short-term $PM_{2.5}$ exposure and mortality

[16] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations, unless otherwise noted.

presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.2.1.1. Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

Multicity studies evaluated since the completion of the 2009 PM ISA continue to provide evidence of primarily positive associations between short-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mostly in urban areas using traditional exposure assignment approaches (i.e., average of all available monitors) as well as studies with a larger spatial coverage (i.e., urban and rural areas) employing new methods using multiple types of $PM_{2.5}$ data (i.e., combination of monitoring, satellite, and land use regression [LUR]). Additionally, the evidence from studies evaluated in the 2019 PM ISA further substantiated the relationship between short-term $PM_{2.5}$ exposure and mortality by providing additional information on potential copollutant confounding; effect modification (e.g., stressors, pollutants, season); geographic heterogeneity in associations; and the shape of the C-R relationship, which collectively reaffirmed that a *causal relationship* exists between short-term $PM_{2.5}$ exposure and mortality. The body of evidence for total mortality was supported by generally consistent positive associations with cardiovascular and respiratory mortality.

In addition to evaluating epidemiologic studies that examined the relationship between short-term $PM_{2.5}$ exposure and mortality, the 2019 PM ISA characterized whether evidence supported biologically plausible mechanisms by which short-term $PM_{2.5}$ exposure could lead to mortality (2019 PM ISA, Section 11.1.1). This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies of morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically, cardiovascular and respiratory morbidity (2019 PM ISA, Section 6.1.1 and Section 5.1.1, respectively). Plausible mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as ED visits and hospital admissions due to cardiovascular disease, particularly ischemic heart disease and congestive heart failure (2019 PM ISA, Section 6.1.1). Similarly, available evidence was characterized by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system (2019 PM ISA, Section 5.1.1). However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions, in particular for chronic obstructive pulmonary disease (COPD) and asthma was limited. In summary, although there was coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) and biological plausibility for $PM_{2.5}$-related cardiovascular (2019 PM ISA, Chapter 6) and respiratory (2019 PM ISA, Chapter 5) morbidity, there was strong evidence indicating biological plausibility for $PM_{2.5}$-related cardiovascular mortality with more limited evidence for respiratory mortality.

This section describes the evaluation of evidence for total (nonaccidental) mortality conducted in the 2019 PM ISA, with respect to the causality determination for short-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 3-4.

Table 3-4 Summary of evidence for a *causal relationship* between short-term $PM_{2.5}$ exposure and total mortality from the 2019 Integrated Science Assessment for Particulate Matter.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects ($\mu g/m^3$)[c]
Consistent epidemiologic evidence from multiple studies at relevant $PM_{2.5}$ concentrations	Increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. Total mortality associations, further supported by increases in cardiovascular and respiratory mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 11.1.2 Figure 11-1 Figure 11-2 Section 5.1.9 Section 6.1.9	Mean 24-h avg: U.S. and Canada: 4.37−17.97 Europe: 13−27.7d Asia: 11.8−69.9 Table 11-1
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants and $PM_{10-2.5}$, supporting the limited evidence from the 2009 PM ISA. Further support comes from copollutant analyses indicating positive associations for cardiovascular and respiratory mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low ($r < 0.4$) to moderate ($r \geq 0.4$ or < 0.8) range.	Section 11.1.4 Figure 11-3 Section 5.1.10.1 Section 6.1.14.1	
Epidemiologic evidence supports a linear, no-threshold C-R relationship	Recent multicity studies conducted in the U.S. and Europe provide direct evidence of a linear, no-threshold C-R relationship at lower $PM_{2.5}$ concentrations with initial evidence of a steeper slope, but extensive systematic evaluations of alternatives to linearity have not been conducted.	Section 11.1.10 Shi et al. (2015) Lee et al. (2015) Di et al. (2017a)	

Table 3-4 (Continued): Summary of evidence for a *causal relationship* between short-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects ($\mu g/m^3$)[c]
Biological plausibility from cardiovascular morbidity evidence	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure, specifically for ischemic events and heart failure, which is supported by experimental evidence and epidemiologic studies examining hospital admissions and ED visits. The collective body of cardiovascular morbidity evidence provides biological plausibility for a relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality, which comprises ~33% of total mortality.	Section 6.1.16 Table 6-33	
Limited biological plausibility from respiratory morbidity evidence	Limited evidence for coherence of effects across scientific disciplines and biological plausibility, with the strongest evidence for exacerbations of COPD and asthma. The collective body of respiratory morbidity evidence provides limited biological plausibility for a relationship between short-term $PM_{2.5}$ exposure and respiratory mortality, which comprises ~9% of total mortality.	Section 5.1.12 Table 5-18	
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-mortality associations. Evidence supports that a combination of factors, including composition and exposure factors may contribute to the observed heterogeneity.	Section 11.1.6.3	

Note: This table corresponds to Table 11-4 in the 2019 PM ISA.

avg = average; COPD = chronic obstructive pulmonary disease; C-R = concentration-response; ED = emergency department; h = hour; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm; *r* = correlation coefficient.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs U.S. EPA (2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

[d]Median concentration from Samoli et al. (2013).

[e]Statistics taken from NHLBI (2017).

Collectively, the evidence from multicity studies of short-term $PM_{2.5}$ exposures and mortality evaluated in the 2019 PM ISA generally demonstrated positive associations with total (nonaccidental) mortality, with increases ranging from 0.19% (Lippmann et al., 2013b) to 2.80% (Kloog et al., 2013) at lags of 0 to 1 days in single-pollutant models. These results were further supported by initial studies employing causal inference and quasi-experimental statistical approaches (2019 PM ISA, Section 11.1.2.1). Whereas most studies relied on assigning exposure using data from ambient monitors, some of the studies evaluated also employed hybrid modeling methods, which use additional sources of $PM_{2.5}$ data (i.e., monitor, satellite, and LUR) to estimate $PM_{2.5}$ concentrations and assign exposure, allowing for the inclusion of less urban and rural locations in analyses (Lee et al., 2015; Shi et al., 2015; Kloog et al., 2013). The studies evaluated expanded the assessment of potential copollutant confounding on the $PM_{2.5}$-mortality relationship, and provided additional evidence supporting the conclusion that $PM_{2.5}$ associations remain positive and relatively unchanged in copollutant models with both gaseous pollutants and $PM_{10–2.5}$, but this conclusion was based on a limited number of multicity studies conducted in Europe and Asia where mean 24-hour avg $PM_{2.5}$ concentrations are higher (2019 PM ISA, Table 3-1). However, the low ($r < 0.4$) to moderate correlations ($r = 0.4 < 0.7$) between $PM_{2.5}$ and gaseous pollutants and $PM_{10–2.5}$ increased the confidence in $PM_{2.5}$ having an independent effect on mortality.

The positive associations for total (nonaccidental) mortality reported across the majority of studies evaluated was further supported by analyses focusing on cause-specific mortality that continue to provide evidence of generally consistent positive associations with both cardiovascular and respiratory mortality, except in the case of a multicity study conducted in Europe (Lanzinger et al., 2016). Risk estimates for cardiovascular mortality ranged from 0.09% (Lippmann et al., 2013b) to 2.32% (Lee et al., 2015), while those for respiratory mortality ranged from 0.09% (Lee et al., 2015) to 2.30% (Janssen et al., 2013), but overall associations tended to be larger in magnitude for respiratory mortality. For both cardiovascular and respiratory mortality there was a limited assessment of potential copollutant confounding, but for both outcomes, initial evidence indicated that associations remained positive and relatively unchanged in models with gaseous pollutants and $PM_{10–2.5}$, which further supported the copollutant analyses conducted for total (nonaccidental) mortality. The strong evidence for ischemic events and heart failure detailed in the assessment of cardiovascular morbidity (2019 PM ISA, Chapter 6), provided strong biological plausibility for $PM_{2.5}$-related cardiovascular mortality, which comprises the largest percent of total mortality [i.e., ~33%; NHLBI (2017)]. Although there was evidence for exacerbations of COPD and asthma, the collective body of respiratory morbidity evidence provided limited biological plausibility for $PM_{2.5}$-related respiratory mortality (2019 PM ISA, Chapter 5).

In addition to examining potential copollutant confounding, a number of studies evaluated in the 2019 PM ISA also assessed whether statistical models adequately accounted for temporal trends and weather covariates. Across studies that evaluated model specification, $PM_{2.5}$-mortality, associations remained positive, although in some cases were attenuated, when using different approaches to account for temporal trends or weather covariates (2019 PM ISA, Section 11.1.5). Seasonal analyses continued to

provide evidence that associations were larger in magnitude during warmer months, but it remained unclear whether copollutants confound the associations observed. In addition to seasonal analyses, some studies also examined whether temperature modified the $PM_{2.5}$-mortality relationship. Initial evidence indicated that the $PM_{2.5}$-mortality association may be larger in magnitude at lower and higher temperatures, but this observation has not been substantiated by studies conducted in the U.S. (2019 PM ISA, Section 11.1.6.2).

At the completion of the 2009 PM ISA, one of the main uncertainties identified was the regional and city-to-city heterogeneity in $PM_{2.5}$-mortality associations observed in multicity studies. Studies evaluated in the 2019 PM ISA examined both city specific as well as regional characteristics to identify the underlying factors that contribute to this heterogeneity (2019 PM ISA, Section 11.1.6.3). Analyses focusing on effect modification of the $PM_{2.5}$-mortality relationship by $PM_{2.5}$ components, regional patterns in $PM_{2.5}$ components, and city-specific differences in composition and sources indicated some differences in the $PM_{2.5}$ composition and sources across cities and regions, but these differences did not fully explain the heterogeneity observed. Additional studies examined whether exposure factors play a role in explaining the heterogeneity in $PM_{2.5}$-mortality associations and found that some factors related to housing stock and commuting, as well as city-specific factors (e.g., land use, port volume, and traffic information), also explain some of the observed heterogeneity. Collectively, the studies evaluated indicated that the heterogeneity in $PM_{2.5}$-mortality risk estimates cannot be attributed to one factor, but instead to a combination of factors, including, but not limited to, compositional and source differences, as well as exposure differences.

A number of studies evaluated conducted systematic evaluations of the lag structure of associations for the $PM_{2.5}$-mortality relationship by examining either multiday lags or a series of single-day lags, and these studies continued to support an immediate effect (i.e., lag 0 to 1 days) of short-term $PM_{2.5}$ exposures on mortality (2019 PM ISA, Section 11.1.8.1). Studies also conducted analyses comparing the traditional 24-hour avg exposure metric with a subdaily metric (i.e., 1-hour max). These initial studies provided evidence of a similar pattern of associations for both the 24-hour avg and 1-hour max metric, with a larger association for the 24-hour avg metric. Additionally, some studies examined alternative exposure metrics representing size fractions smaller than $PM_{2.5}$ and reflecting number concentration (NC) and surface-area concentration (SC). The generally positive associations reported with mortality for these smaller PM size fractions supported the larger body of $PM_{2.5}$-mortality evidence, but it is difficult to compare NC and SC metrics with the traditional mass-based metric.

Building off the initial analysis of the C-R relationship between short-term PM exposure and mortality that focused on PM_{10}, multicity studies conducted in the U.S. and Europe examined the shape of the C-R relationship and whether a threshold exists specifically for $PM_{2.5}$ (2019 PM ISA, Section 11.1.10). These studies used different statistical approaches and consistently demonstrated a linear relationship with no evidence of a threshold. Additionally, recent analyses conducted at lower $PM_{2.5}$ concentrations (i.e., 24-hour avg $PM_{2.5}$ concentrations < 30 $\mu g/m^3$) provided initial evidence

indicating that $PM_{2.5}$-mortality associations persist and may be stronger (i.e., a steeper slope) at lower concentrations. However, to date, extensive analyses have not been conducted to systematically explore alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship.

Overall, epidemiologic studies evaluated in the 2019 PM ISA built upon and further reaffirm the conclusions of the 2009 PM ISA for total mortality. The evidence particularly from the assessment of $PM_{2.5}$-related cardiovascular morbidity, with more limited evidence from respiratory morbidity, provided biological plausibility for mortality from short-term $PM_{2.5}$ exposures. In conclusion, the primarily positive associations observed across studies conducted in various locations was further supported by the results from copollutant analyses that indicated robust associations, along with evidence from analyses of the C-R relationship. **Collectively, this body of evidence is sufficient to conclude that a causal relationship exists between short-term $PM_{2.5}$ exposure and total mortality.**

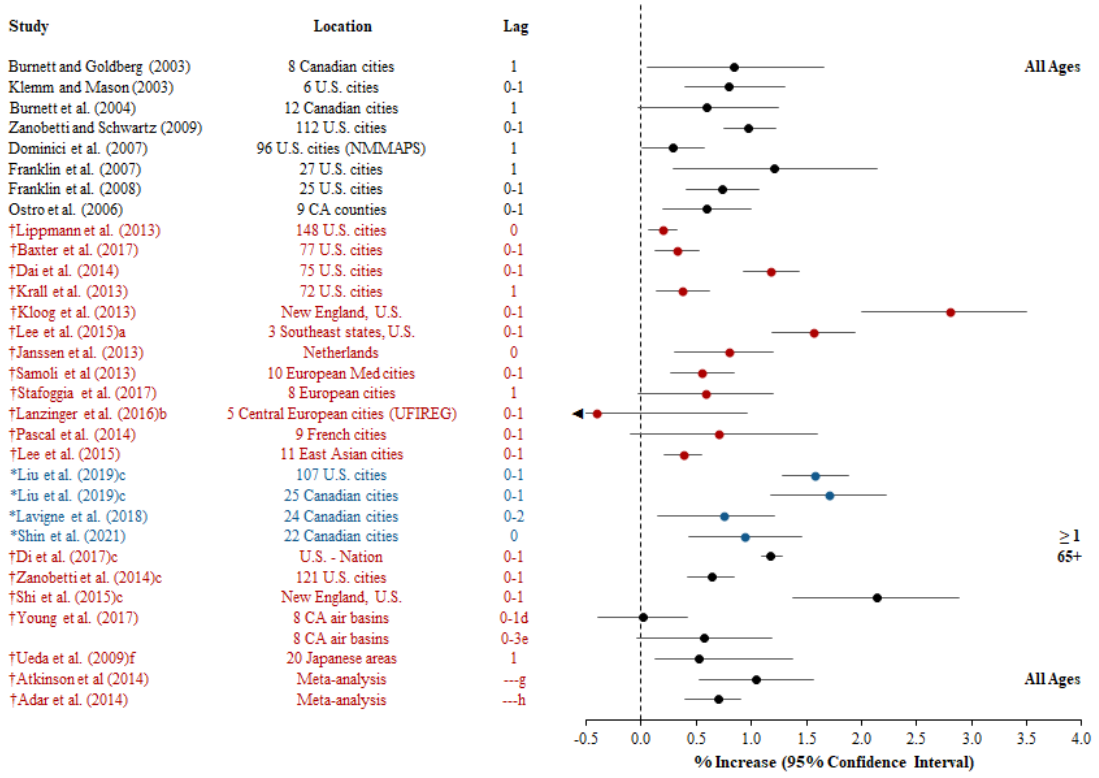
3.2.1.2. Recent U.S. and Canadian Epidemiologic Studies

The few recent multicity studies conducted in the U.S. and Canada build upon the strong epidemiologic evidence base evaluated in the 2019 PM ISA, as well as in previous assessments, which provided the scientific rationale supporting a *causal relationship* between short-term $PM_{2.5}$ exposure and mortality (Section 3.1.1.1). In addition to examining the relationship between short-term $PM_{2.5}$ exposure and all-cause or nonaccidental mortality (Section 3.1.1.2.1) and cause-specific mortality (Section 3.1.1.2.2), additional analyses within these recent studies also further examined issues relevant to expanding the overall understanding of the effect of short-term $PM_{2.5}$ exposure on mortality. Specifically, recent studies have assessed potential copollutant confounding (Section 3.1.1.2.3), examined effect modification of the $PM_{2.5}$-mortality relationship (Section 3.1.1.2.4), the lag structure of associations (Section 3.1.1.2.5), and assessed the shape of the concentration-response (C-R) relationship (Section 3.1.1.2.6). The following sections present an evaluation of recent multicity studies that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-5).

3.2.1.2.1. All-Cause and Total (Nonaccidental) Mortality

Since the literature cutoff date for the 2019 PM ISA, a limited number of multicity studies have been conducted within the U.S. and Canada (Shin et al., 2021a; Liu et al., 2019; Lavigne et al., 2018). Although few in number, these recent studies add to the extensive number of multicity studies evaluated in the 2019 PM ISA that were conducted globally, specifically in locations where mean 24-hour concentrations were generally < 20 $\mu g/m^3$ (2019 PM ISA, Section P.3.1). Taken together, these studies

provide consistent evidence of positive associations between short-term $PM_{2.5}$ exposure and mortality across diverse geographic locations; in populations with a wide range of demographic characteristics; and using a variety of statistical models, approaches to confounder adjustment, and exposure assessment approaches (Figure 3-13).



Source: Update of Figure 11-1, 2019 PM ISA.

avg = average; $\mu g/m^3$ = microgram per cubic meter; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; UFIREG = Ultrafine Particles—An Evidence-Based Contribution to the Development of Regional and European Environmental and Health Policy.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) 2019 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Blue circles = multicity U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA. Risk estimates are standardized to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations.

[a]Results are from modeled $PM_{2.5}$ analysis, analysis focusing on measured $PM_{2.5}$ reported 1.21% (95% CI: 0.94, 1.47).

[b]Only four of the five cities measured $PM_{2.5}$.

[c]Shi et al. (2015), Zanobetti et al. (2014), and Liu et al. (2019) only had data for all-cause mortality including accidental mortalities.

[d]Main model used in Young et al. (2017) included current and average of 3 previous days daily maximum temperature, daily minimum temperature, and maximum daily relative humidity.

[e]Sensitivity analysis in Young et al. (2017) focusing on only the San Francisco Bay air basin, dropping out the maximum daily relative humidity term, where the shortest duration of lag days examined was 0−3 days.

[f]Ueda et al. (2009) presented results for three different modeling approaches, which are presented here: generalized additive model (GAM), generalized linear model (GLM), and case-crossover.

[g]Atkinson et al. (2014) primarily focused on single-day lag results.

[h]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Figure 3-13 Summary of associations between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality in multicity studies.

Recent studies that conducted multicity analyses in the U.S. and Canada include a large international study that performed a global multicity analysis (Liu et al., 2019) and a few studies in Canada that relied on data from over 20 cities (Shin et al., 2021a; Lavigne et al., 2018). Using the Multi-City Multi-Country (MCC) Collaborative Research Network, Liu et al. (2019) was able to collect data globally, resulting in a data set consisting of air pollution and mortality data from 652 urban areas in 24 countries from 1986 to 2015. Although the goal of the study was to estimate a global estimate of the association between short-term $PM_{2.5}$ exposure and mortality, the authors presented country specific estimates as well, including for the U.S. and Canada. The authors applied a uniform statistical model across all of the cities within the study consisting of a quasi-Poisson general additive model that controlled for temporal trends and weather covariates. In a second-stage analysis, the authors used a random-effects model to pool city-specific estimates into a country-specific estimate. All analyses relied on $PM_{2.5}$ data for which the highest and lowest 5% of data was trimmed to remove outliers. In analyses of 25 Canadian cities from 1986 to 2011 and 107 U.S. cities from 1987 to 2006, the authors reported a 1.70% (95% CI: 1.17, 2.23) and 1.58% (95% CI: 1.28, 1.88) increase in mortality, respectively, at lag 0−1 days.

Recent studies conducted in Canada by Lavigne et al. (2018) and Shin et al. (2021a) focused on more recent years of data, 1998−2011 and 2001−2012, respectively, in comparison to Liu et al. (2019). Lavigne et al. (2018) focused on examining whether oxidant gases modified the association between short-term $PM_{2.5}$ exposure and mortality in 24 Canadian cities (discussed in more detail in Section 3.2.1.2.4). In a time-stratified case-crossover analysis that adjusted for both mean temperature and location-specific temperature distributions and relative humidity, the authors reported a 0.76% (95% CI: 0.15, 1.21) increase in mortality at lag 0−2 days. The results of Lavigne et al. (2018) are consistent with those reported by Shin et al. (2021a) in a time-series study of 22 Canadian cities. The authors examined single-day lags ranging from 0 to 2 days using a two-stage hierarchical model consisting of a Poisson model in the first stage to examine city-specific associations and a Bayesian random effects model in the second stage to combine city-specific effects into a national estimate. Shin et al. (2021a) reported associations with mortality similar in magnitude at lag 0 (0.94% [0.43, 1.46]) and 1 day (0.90% [95% CI: 0.33, 1.41]) with no evidence of an association at lag 2. Although it is unclear as to why the magnitude of associations reported in Lavigne et al. (2018) and Shin et al. (2021a) differ from those reported by Liu et al. (2019), even though both are using a similar subset of cities, it could be attributed to the more recent years of data used in Lavigne et al. (2018) and Shin et al. (2021a) where there has been a decreasing trend in $PM_{2.5}$ concentrations (Shin et al., 2021a).

Sudden Nonaccidental Mortality

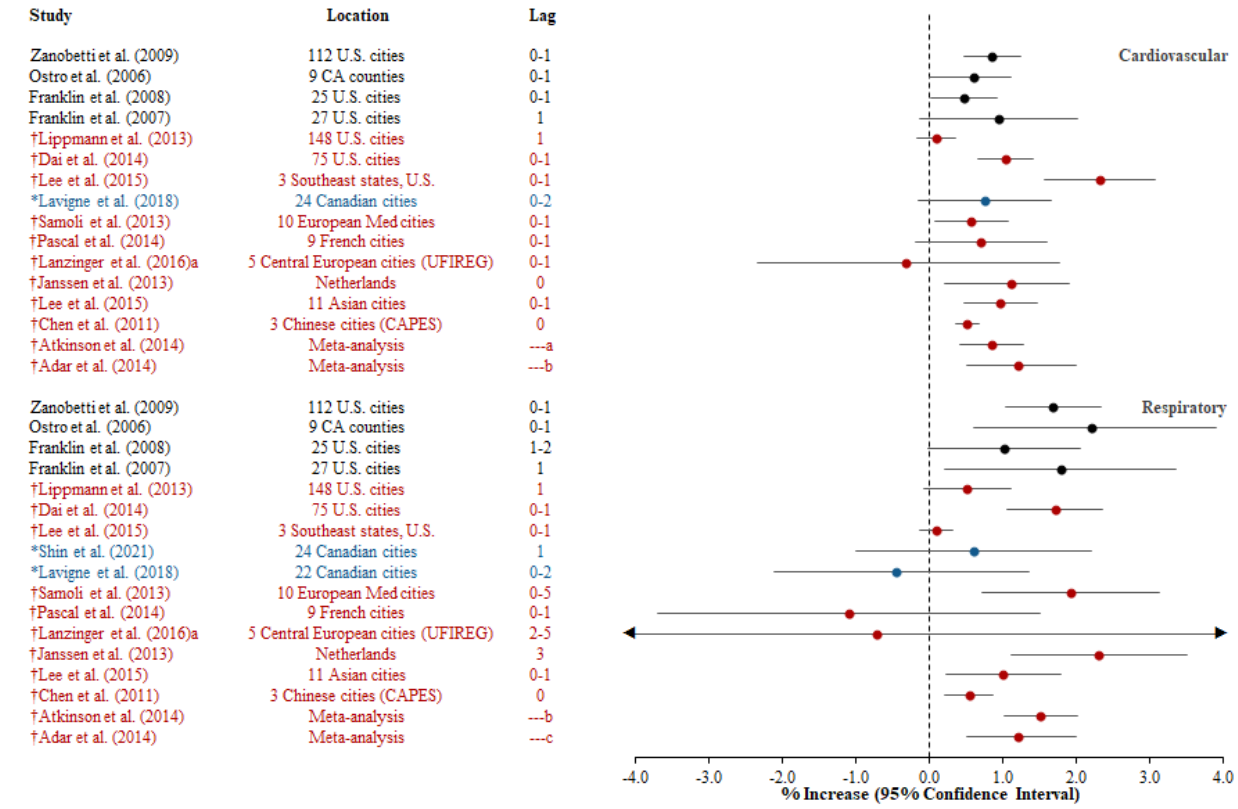
The 2009 PM ISA reviewed a handful of small studies examining the association between $PM_{2.5}$ exposure and out-of-hospital cardiac arrest (OHCA). No evidence of an association was reported. Section 6.1.4.1 of the 2019 PM ISA evaluated studies published since the 2009 PM ISA, which provided evidence for an association between short-term $PM_{2.5}$ exposure and OHCA. This association was typically

observed with $PM_{2.5}$ concentrations averaged over the past 0 to 2 days, although associations with $PM_{2.5}$ concentrations as far back as 4 days before the event have been reported. Additionally, all of the studies assessed in the 2009 and 2019 ISAs relied on a single monitor or an average of fixed-site monitors to estimate $PM_{2.5}$ exposure, which restricts the study population to people living near monitors. While the previously evaluated studies focused on a cardiovascular outcome (i.e., OHCA) and as a result were discussed within the evidence for short-term $PM_{2.5}$ exposure and cardiovascular effects, the results of these previous studies are summarized here as they can inform a recent study by Rappazzo et al. (2019) that examined out-of-hospital sudden unexpected deaths.

Rappazzo et al. (2019) conducted a time-stratified case-crossover analysis to examine the relationship between short-term $PM_{2.5}$ exposure and out-of-hospital nonaccidental sudden unexpected deaths in a small population of individuals (n = 399) over a 2-year period that resided in Wake County, NC. In analyses examining both single-day lags ranging from 0 to 3 days and a 0−1 day lag, the authors reported a positive association at lag 1 (OR = 1.39 [95% CI: 0.96, 1.99]) that was smaller in magnitude when using a 0−1 day lag (OR = 1.18 [95% CI: 0.79, 1.78]). However, due to the small sample size within this study confidence intervals are large. In addition to single-pollutant models, the authors examined copollutant models across the single-day lags and reported that $PM_{2.5}$ associations are relatively unchanged in models with NO_2, SO_2, ozone, and CO. This initial study focusing out-of-hospital sudden unexpected deaths from all nonaccidental causes, provides evidence consistent with the relatively limited number of previous studies examining OHCA.

3.2.1.2.2. Cause-specific Mortality

Single and multicity studies evaluated in the 2009 PM ISA that examined cause-specific mortality reported consistent positive associations with both cardiovascular and respiratory mortality. The magnitude of the association was larger for respiratory mortality, but these associations also had wider confidence intervals due to the smaller number of respiratory-related deaths than cardiovascular-related deaths. Studies evaluated in the 2019 PM ISA added to this body of evidence but provided more consistent evidence of associations for cardiovascular mortality compared with respiratory mortality. Recent multicity studies conducted in Canada provide additional support for an association with cardiovascular mortality (Lavigne et al., 2018). Consistent with the evidence assessed in previous ISAs, recent studies report more variable results with wider confidence intervals for respiratory mortality (Shin et al., 2021b; Lavigne et al., 2018).



Source: Update of Figure 11-2, 2019 PM ISA.

avg = average; μg/m^3 = microgram per cubic meter; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; UFIREG = Ultrafine Particles—An Evidence-Based Contribution to the Development of Regional and European Environmental and Health Policy.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Studies organized by lag structure, therefore, cardiovascular and respiratory mortality results are not in the same order. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = multicity studies and meta-analyses published since the literature cutoff date of the 2009 PM ISA. Risk estimates are standardized to a 10 μg/m^3 increase in $PM_{2.5}$ concentrations. All ages examined for all studies except Lanzinger et al. (2016) and Shin et al. (2021b) which focused on ages ≥ 1 year old.

[a]Only four of the five cities measured $PM_{2.5}$.

[b]Atkinson et al. (2014) primarily focused on single-day lag results.

[c]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Figure 3-14 Summary of associations between short-term $PM_{2.5}$ exposure and cardiovascular and respiratory mortality in multicity studies.

3.2.1.2.3. Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

As discussed in Section 3.1.2.2.8, one approach to assessing the independence of the association between exposure to $PM_{2.5}$ and a health effect, such as short-term $PM_{2.5}$ exposure and mortality, can be examined is through the use of copollutant models. Appendix (Table A-1) to the 2019 PM ISA notes that copollutant models are not without their limitations, such as instances where correlations are high between pollutants resulting in greater bias in results. However, in assessing the results from copollutant

models a change in the $PM_{2.5}$ risk estimate, after adjustment for a copollutant, may indicate the potential for confounding.

At the time of the 2009 ISA, only a few studies had assessed the potential for confounding of the $PM_{2.5}$-mortality association by co-occurring pollutants. In contrast, the 2019 ISA included a number of multicity studies that used copollutant models to evaluate this issue, including studies that examined both gaseous pollutants and other particle size fractions. These studies reported that associations were relatively unchanged in copollutant models, albeit with wider confidence intervals than single pollutant models (2019 PM ISA, Figure 11-3).

Of the recent multicity studies conducted in the U.S. and Canada, only Lavigne et al. (2018) conducted an assessment of copollutant confounding, with a focus on oxidant gases. Within this study, oxidant gases were defined as the daily combined oxidant capacity of ozone and NO_2 based on the redox-weighted averages of both pollutants. In a copollutant model with oxidant gases, the association between short-term $PM_{2.5}$ exposure and mortality is unchanged compared with the single pollutant model with both reporting a 0.76% increase in mortality at lag 0−2 days.

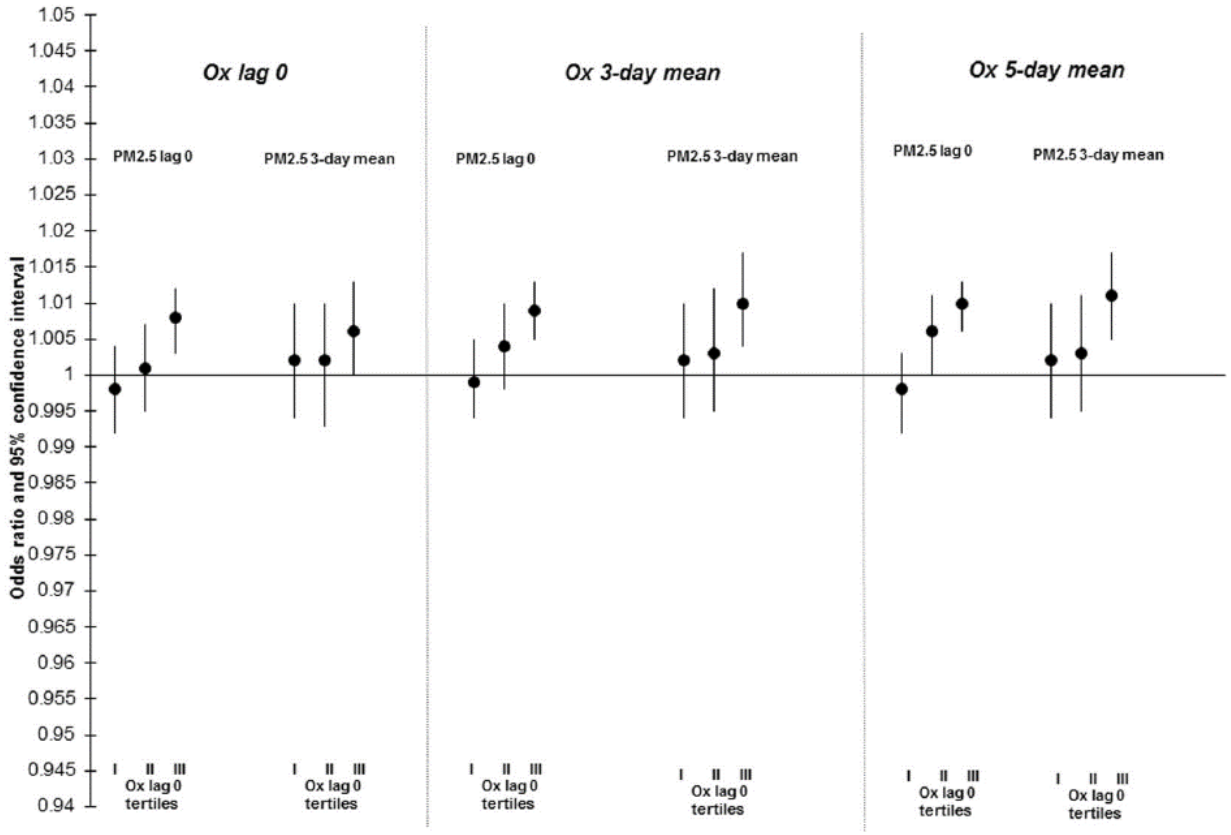
3.2.1.2.4. Effect Modification of the $PM_{2.5}$-Mortality Relationship

Multicity epidemiologic studies evaluated in the 2009 PM ISA and 2019 PM ISA provided evidence of city-to-city and regional heterogeneity in $PM_{2.5}$-mortality associations. Within the 2019 PM ISA, studies were evaluated that examined factors that could modify the $PM_{2.5}$-mortality association and potentially explain some of the observed heterogeneity in associations, including season (2019 PM ISA, Section 11.1.6.1), temperature (2019 PM ISA, Section 11.1.6.2), city and regional characteristics (Section 11.1.6.3) such as composition/mixtures (2019 PM ISA, Section 11.1.6.3.1), and exposure factors (i.e., residential infiltration factors and commuting factors) (2019 PM ISA, Section 11.1.6.3.2). Recent multicity studies provide additional insight into some of these factors that could modify the $PM_{2.5}$-mortality association.

The 2009 PM ISA reported some evidence that $PM_{2.5}$-mortality associations are larger in magnitude during the warm season, specifically the spring, with the majority of this evidence coming from U.S. multicity studies (Zanobetti and Schwartz, 2009; Franklin et al., 2008). As discussed in Section 11.1.6.1 of the 2019 PM ISA, across recent multicity studies, there was general agreement that $PM_{2.5}$-mortality associations were larger in magnitude during warmer months. However, it remained unclear whether copollutants confound the seasonal patterns in the associations observed. Across most studies, the pattern of seasonal associations persisted using different methods to examine whether there was evidence of seasonal differences in associations, with some studies relying on stratified analyses (Dai et al., 2014; Samoli et al., 2013) and others incorporating interaction terms between $PM_{2.5}$ and season (Pascal et al., 2014; Lippmann et al., 2013b). The recent studies conducted by Shin et al. (2021a) and Shin et al. (2021b) further inform seasonal analyses, but do not address the uncertainties identified in the 2019

PM ISA. Both studies assessed associations by season through stratified analyses in which the warm season is defined as April−September and the cold season as October−March. In Shin et al. (2021a), when focusing on lag 0, which had the largest magnitude of an association in all-year analyses, there is a clear pattern of the warm season driving the overall association; however, the reverse pattern is reported when focusing on lag 1, complicating the overall interpretation of results from this study. However, in Shin et al. (2021b), which focused on respiratory mortality a slight larger association, with wide confidence intervals, is reported for the warm season (1.0% [95% CI: −1.6, 3.5]) compared with the cold season (0.6% [95% CI: −2.2, 4.1]) at lag 1, the main lag examined for $PM_{2.5}$ and mortality within the study. Across these recent studies there continues to be some evidence indicating larger associations during the warm season, but there are inconsistencies across the individual lags examined.

Within the 2019 PM ISA, an assessment of composition and mixtures (2019 PM ISA, Section 11.1.6.3.1) focused on whether differences in the pollutant mixture across cities could explain heterogeneity in the $PM_{2.5}$-mortality association across cities and regions of the U.S. In the process of examining the association between short-term $PM_{2.5}$ exposure and mortality across 24 Canadian cities, Lavigne et al. (2018) did not focus on whether effect modification by other pollutants could explain heterogeneity, but broadly whether oxidant gases, defined as the redox-weighted average of O_3 and NO_2, modify the $PM_{2.5}$-mortality association. The authors examined the role of oxidant gases on the $PM_{2.5}$-mortality relationship because previous studies have shown that oxidant gases can deplete antioxidants in the lung and increase permeability of the lung epithelium, and that oxidant gases may accelerate photochemical aging of $PM_{2.5}$, potentially changing its toxicity (Lavigne et al., 2018). To assess whether there is evidence of effect modification of the $PM_{2.5}$-mortality relationship by oxidant gases, the authors conducted stratified analyses across tertiles of oxidant gases based on the distribution of oxidant gases across all cities. For nonaccidental mortality, in analyses examining both lag 0 and lag 0−2 days for $PM_{2.5}$, there was a consistent pattern of the $PM_{2.5}$-mortality association being larger in magnitude for the third tertile of oxidant gases. However, there is some variability in the $PM_{2.5}$-mortality association depending on the lag structure used to represent oxidant gases, with some evidence indicating that as the exposure for oxidant gases increased in length, there are larger $PM_{2.5}$-mortality associations for both the second and third tertiles (Figure 3-15). The pattern of associations for nonaccidental mortality is similar for cardiovascular mortality, but there is no evidence of effect modification for respiratory mortality.



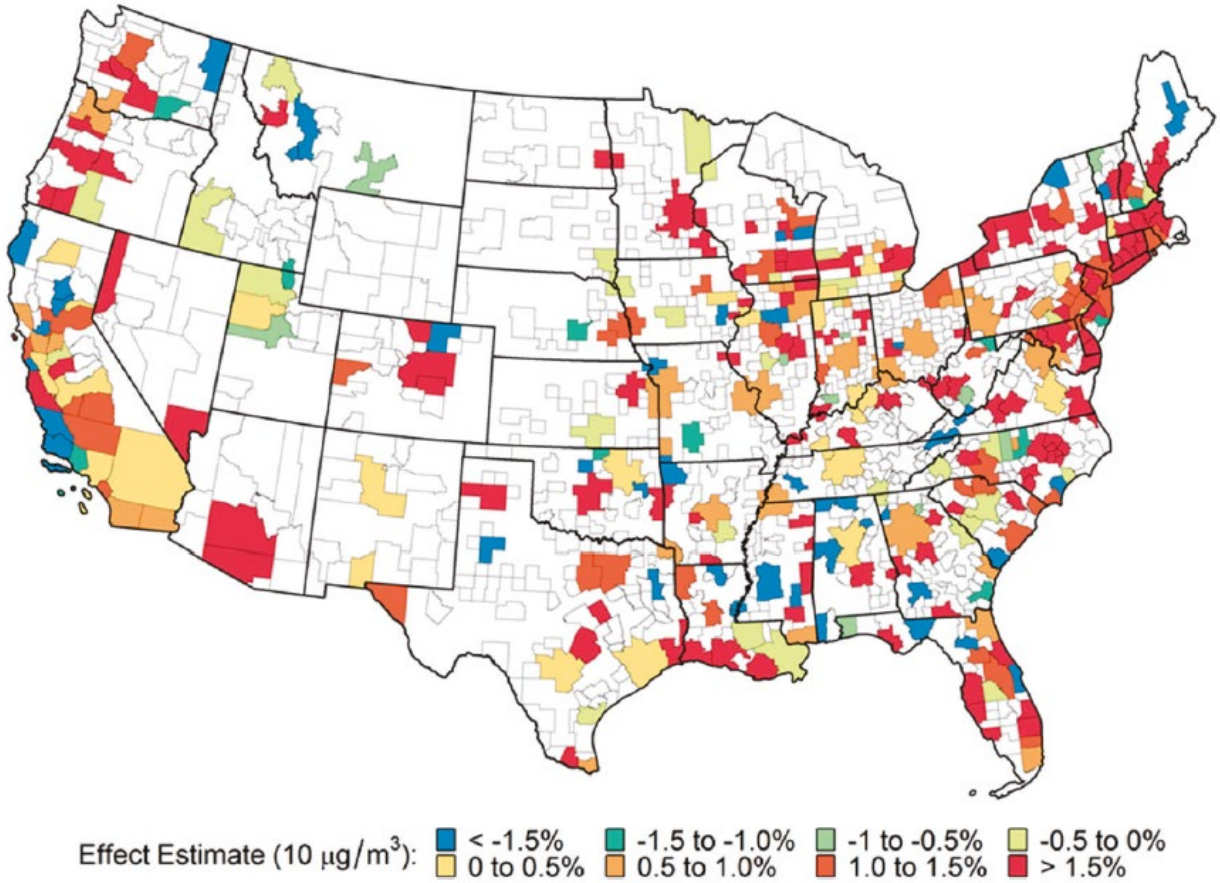
Source: Lavigne et al. (2018)

Figure 3-15 Odds ratio and 95% confidence intervals for lag 0 and lag 0−2 days of nonaccidental mortality across tertiles of lag 0, lag 0−2, and lag 0−4 oxidant gases across 24 Canadian cities.

A recent study by Baxter et al. (2019) expands upon studies evaluated in the 2019 PM ISA (Baxter et al., 2017; Baxter and Sacks, 2014), which provided evidence indicating that combinations of exposure factors representative of residential infiltration (i.e., prevalence of central AC, mean year home was built, and mean size of home) explained some of the heterogeneity in the $PM_{2.5}$-mortality association. As discussed in the 2019 PM ISA (Section 3.4, 2019 PM ISA), examining these exposure factors is important in the context of interpreting health effects associations reported in epidemiologic studies because they can affect the relationship between indoor and outdoor ambient PM concentrations and between personal exposure to ambient PM and ambient PM concentrations.

In a time-series analysis, Baxter et al. (2019) examined the association between short-term $PM_{2.5}$ exposure and nonaccidental mortality in 312 core-based statistical areas (CBSAs) within the U.S. from 1999−2005. In a two-stage analysis, the authors first examined associations with mortality in each CBSA in a time-series analysis and then conducted a meta-regression using a fixed-effects inverse variance weighted linear regression to examine whether individual exposure factors or combinations of exposure factors explained observed heterogeneity. The variables examined within the meta-regression fall within

five categories representative of housing characteristics, commuting, household heating, meteorological factors, and poverty measures. In the first-stage analysis, Baxter et al. (2019) reported a 0.95% (IQR of 2.25)[17] increase in mortality across all CBSAs, but as depicted in Figure 3-16 there is extensive city-to-city variability in associations across the U.S.



Source: Baxter et al. (2019)

Figure 3-16 Associations between short-term $PM_{2.5}$ exposure and nonaccidental mortality at lag 1 for the 312 core-based statistical areas examined in Baxter et al. (2019).

In the second-stage analysis, the authors conducted both a univariate and multivariate meta-regression. In the univariate regression, mortality associations larger in magnitude were observed for CBSAs with larger homes, more heating degree days, and a higher percentage of homes heating with oil, while cities with more gas heating had smaller associations. Across all univariate analyses, no

[17] 95% CIs were not presented in this study.

individual factor explained much of the heterogeneity as reflected by $R^2 < 1\%$. For the multivariate model, a backward selection approach was used to develop the final model that included variables for gas heating use, heating degree days, cooling degree days, and variables for home size and age. Compared with the univariate models, the multivariate models explained a larger amount of the heterogeneity in mortality associations across the CBSAs examined, ranging from 11% to 13%. Overall, the results of Baxter et al. (2019) further support studies evaluated in the 2019 PM ISA, which indicated that a combination of factors that influence exposure to $PM_{2.5}$, not an individual factor, explains some of the observed city-to-city and regional heterogeneity reported in multicity epidemiologic studies.

3.2.1.2.5. Lag Structure of Associations

Within the 2009 PM ISA, the studies evaluated indicated that the effect of short-term $PM_{2.5}$ exposure on mortality was immediate, occurring within the first few days after exposure, with the strongest evidence, in terms of magnitude and precision of the associations, in the range of 0 to 1 day. However, these studies defined the lags to examine a priori, often in accordance with the 1-in-3 or 1-in-6-day sampling schedule of ambient $PM_{2.5}$ monitors. As detailed in Section 11.1.8.1 of the 2019 PM ISA, some studies published since the completion of the 2009 PM ISA conducted more extensive examinations of the lag structure of associations for short-term $PM_{2.5}$ exposures and mortality and continue to support associations being largest in terms of magnitude and precision primarily within the first few days of exposure (i.e., lags of 0 to 1 day) as depicted in Figure 3-14.

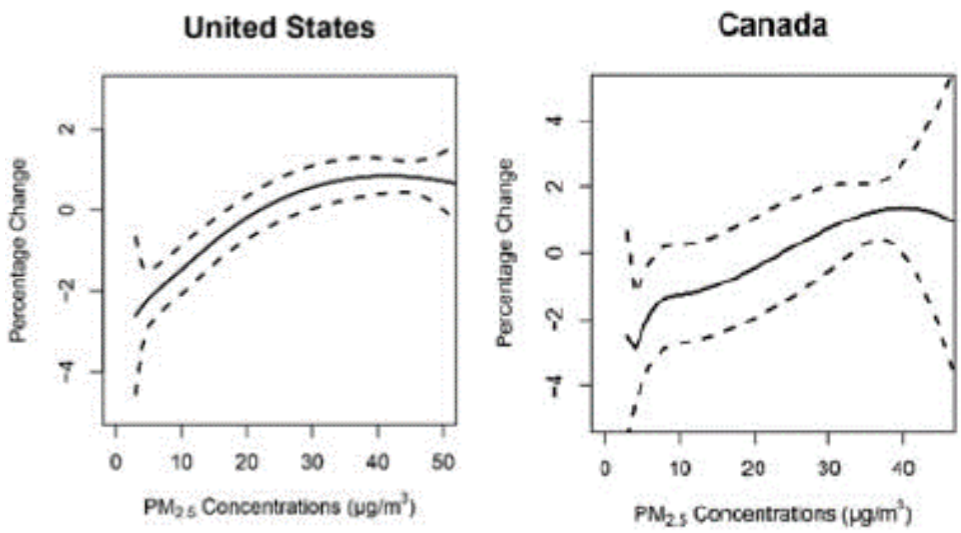
Of the recent studies evaluated, Lavigne et al. (2018) and Shin et al. (2021a) in multi-city studies conducted in Canada examined the lag structure of associations primarily through examining single-day lags ranging from 0 to 2 days, with Lavigne et al. (2018) also examining a multi-day lag of 0−1 days. In the single-day lag analyses, Lavigne et al. (2018) and Shin et al. (2021a) both reported positive associations relatively similar in magnitude at lag 0 and 1 with no evidence of an association at lag 2. In the multi-day lag analysis focusing on lag 0−1 day, Lavigne et al. (2018) reported results similar in magnitude to the single-day lag analysis of lag 0 and 1 day. The single-day lag analyses in combination with the multi-day lag analysis conducted by Lavigne et al. (2018) supports the conclusions of previously evaluated studies in the 2009 and 2019 PM ISA that indicated associations largest in magnitude at lags of 0 to 1 day.

3.2.1.2.6. Examination of the Concentration-Response (C-R) Relationship between Short-Term $PM_{2.5}$ Exposure and Mortality

In the 2009 PM ISA, the examination of the PM-mortality C-R relationship was limited to studies of PM_{10}. Within the multicity studies examined, there was evidence of a linear, no-threshold C-R relationship between short-term PM exposures and mortality with some evidence of differences in the shape of the C-R curve across cities. Studies evaluated in the 2019 PM ISA, focused specifically on

examining the C-R relationship between short-term $PM_{2.5}$ exposure and mortality. Although difficulties remain in assessing the shape of the $PM_{2.5}$-mortality C-R relationship, as identified in the 2009 PM ISA, and studies had not conducted systematic evaluations of alternatives to linearity, the studies evaluated in the 2019 PM ISA continued to provide evidence of a no-threshold linear relationship, with less confidence at concentrations lower than 5 $\mu g/m^3$. Additionally, those studies that conducted analyses focused on examining associations at lower $PM_{2.5}$ concentrations provided initial evidence indicating that associations persist and may be larger (i.e., have a steeper slope) at lower $PM_{2.5}$ concentrations.

Liu et al. (2019) in the global analysis examining the association between short-term $PM_{2.5}$ exposure and mortality in 652 cities, also examined country-specific C-R relationships. For each country, a linear term for $PM_{2.5}$ was added to the main model with a B-spline function with knots at the 25th and 75th percentiles of the mean $PM_{2.5}$ concentration across all cities. In C-R analyses consisting of 107 U.S. cities (Figure 3-17a) and 25 Canadian cities (Figure 3-17b), analyses indicated a linear, no-threshold relationship at concentrations often experienced within the U.S. and Canada, with less certainty in the shape of the curve at concentrations less than approximately 8 $\mu g/m^3$ and greater than 30 $\mu g/m^3$.



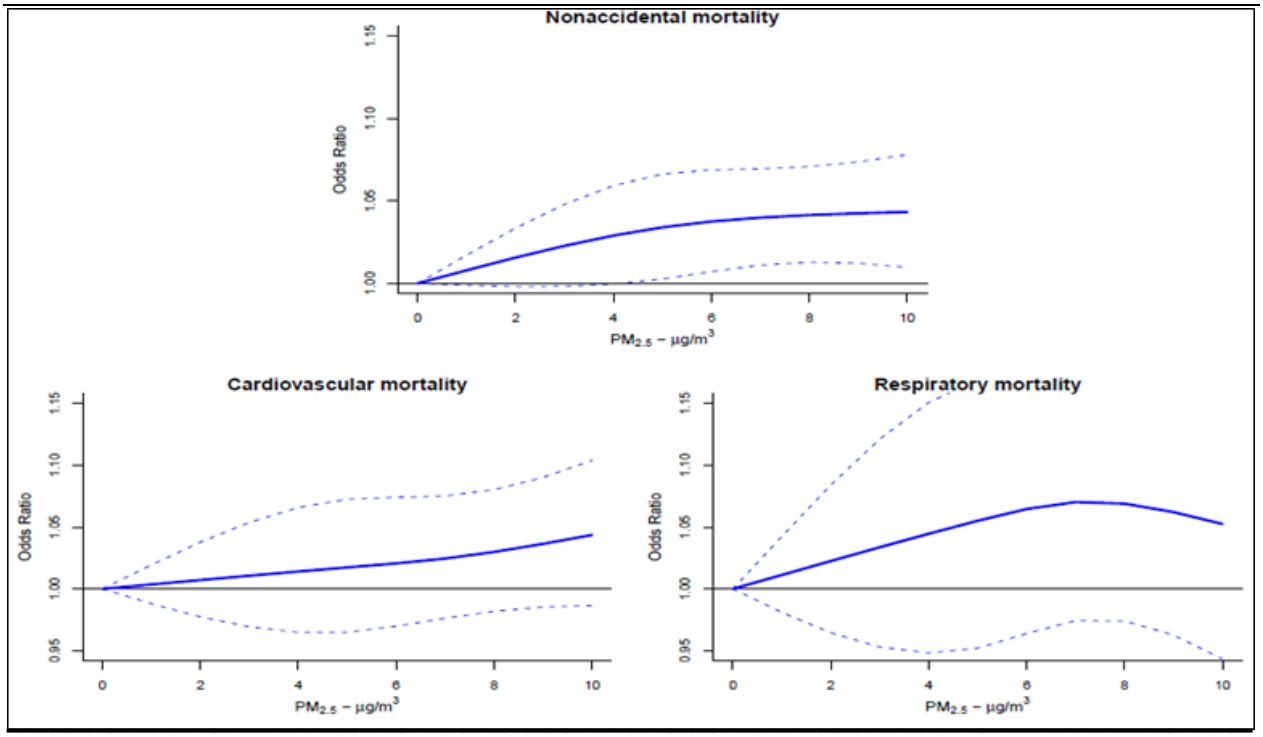
Source: Adapted from Liu et al. (2019)..

Note: As noted in Liu et al. (2019), the "y-axis can be interpreted as the relative change from the mean effect of $PM_{2.5}$ on mortality; the fraction of the curve below zero denotes a smaller estimate compared with the mean effect."

Figure 3-17 Concentration-response curves for the United States (A) and Canada (B) using a B-spline function with knots at the 25th and 75th percentiles of $PM_{2.5}$ concentrations across all cities in each location.

While Liu et al. (2019) focused on nonaccidental mortality, Lavigne et al. (2018) examined the C-R relationship for nonaccidental mortality as well as cardiovascular- and respiratory-related mortality

in an analysis of 24 Canadian cities. The authors used the same model for each mortality outcome, consisting of natural cubic splines with 3 df focusing on 0−2-day $PM_{2.5}$ exposures. Across mortality outcomes examined in Lavigne et al. (2018), C-R curves support a linear relationship at $PM_{2.5}$ concentrations often experienced in the U.S. and Canada, with less certainty in the shape of the curve for nonaccidental mortality at concentrations below approximately 5 µg/m^3 as reflected by the lower bound of the 95% confidence interval (CI) going below the null and some evidence of nonlinearity in the respiratory mortality C-R relationship as reflected by the inflection point occurring around 7 µg/m^3 (Figure 3-18). However, compared with nonaccidental mortality, for both cardiovascular and respiratory mortality, the lower bound of the 95% confidence interval was wider and below the null resulting in less confidence in the overall shape of the C-R curve for both mortality outcomes.



Source: Lavigne et al. (2018)

Figure 3-18 Concentration-response curves for nonaccidental, cardiovascular, and respiratory mortality using natural cubic splines with 3 degrees of freedom for associations with 0−2-day $PM_{2.5}$ across 24 Canadian cities.

Overall, recent studies, although limited in number continue to provide evidence of a linear, no-threshold relationship between short-term $PM_{2.5}$ exposure and mortality. Additionally, analyses of nonaccidental mortality support previous studies evaluated that indicated confidence in the shape of the C-R relationship down to concentrations in the range of 5−8 µg/m^3. However, consistent with studies

evaluated in previous assessments, neither study conducted systematic evaluations of alternatives to linearity.

3.2.1.3. Recent Epidemiologic Studies Examining the $PM_{2.5}$-Mortality Relationship through Accountability Analyses and Alternative Methods for Confounder Control

Within the 2019 PM ISA, in assessing the relationship between short-term $PM_{2.5}$ exposure and mortality several epidemiologic studies were evaluated that employed alternative methods for confounder control (referred to as causal modeling methods in the 2019 PM ISA, Section 11.1.2.1). These studies, which were limited to single-city analyses and used different statistical approaches provided evidence that further confirmed the consistent positive association between short-term $PM_{2.5}$ exposure and mortality reported in numerous multi-city studies and further supported the conclusion of a causal relationship. Since the literature cutoff date of the 2019 PM ISA, additional epidemiologic studies have been identified that implemented alternative methods for confounder control, which further inform the relationship between short-term $PM_{2.5}$ exposure and mortality (Table A-6).

Epidemiologic studies that use alternative methods for confounder control seek to mimic randomized experiments through the use of study design and statistical methods, which reduce the potential bias of effects due to confounding. One such method, generalized propensity score (GPS), estimates the conditional probability of an individual being exposed to the observed ambient concentration, accounting for all measured potential confounders. To assess the associations between short-term $PM_{2.5}$ exposure and mortality, recent studies by Wei et al. (2020) and Wei et al. (2021b) used different GPS approaches.

Wei et al. (2020) evaluated the association between short-term $PM_{2.5}$ exposure and all-cause mortality among Medicare beneficiaries residing in Massachusetts during 2000−2012. In the design stage, to construct the GPS, an ordinary least squares model was used to regress $PM_{2.5}$ against a linear combination of covariates including the copollutants ozone and NO_2 (Wei et al., 2020). In the analysis stage, an ordinary least squares regression was used to fit a linear probability model relating the outcome (death) with the observed exposures and the estimated GPS. Wei et al. (2020) reported 3.04 (95% CI: 2.17, 3.94) excess deaths per 10 million person-days for each 1 $\mu g/m^3$ increase in short-term $PM_{2.5}$ exposure. When the analysis was restricted to a range of $PM_{2.5}$ concentrations, the number of excess deaths associated with a 1 $\mu g/m^3$ increase in short-term $PM_{2.5}$ exposure increased from 3.33 ($PM_{2.5}$ concentrations < 35 ug/m^3; 95% CI: 2.41, 4.11) to 14.56 ($PM_{2.5}$ concentrations < 5 ug/m^3; 95% CI: 3.96, 24.59), per 10 million person-days.

In a subsequent study, Wei et al. (2021b) used three GPS approaches (linear probability model, weighted least squares, and m-out-of-n random forests [moonRF]), for assessing additive effects of short-term exposures to $PM_{2.5}$ and the copollutants O_3, and NO_2 on mortality rates among Medicare

beneficiaries residing in Massachusetts between 2000 and 2012. To reduce the computational burden of the linear probability model GPS approach, weighted least squares and moonRF GPS approaches were proposed as alternatives. Consistent with Wei et al. (2020), for the linear probability model, the authors had both a design stage and an analysis stage. In the design stage, the GPS for $PM_{2.5}$ concentrations was constructed by fitting a linear regression of the predicted $PM_{2.5}$ concentration against a column vector of covariates. In the analysis stage, a linear probability model was fitted with the outcome of death, against the predicted $PM_{2.5}$ concentration and the GPS.

For the weighted least squares method, there was also a design stage and an analysis stage. In the design stage, the person-days that had the same sex, race, age, Medicaid eligibility, ZIP code of residence, and date were aggregated as a single record and assigned the numbers of person-days for that record as weight. The GPS was constructed by fitting a weighted linear regression of the predicted $PM_{2.5}$ concentration against all the covariates from this aggregated data set, with continuous covariates modeled with cubic polynomials. The average outcome for each aggregated person-day group was calculated and assigned to the person-day in the aggregated data set. A weighted linear regression was then fitted for the averaged outcome against the predicted $PM_{2.5}$ concentration and the estimated GPS.

The moonRF method is based on the random forest method, which is a non-parametric machine learning approach of classification for possible nonlinear relationships and interactions through building individual decision trees through resampling. The m-out-of-n bootstrapping method resamples the m observations out of an original data set (1,…,n) without replacement, where $m << n$ (Wei et al., 2021b). In the design stage, the number of person-days aggregated for each record in the aggregated data set was used as the frequency weight and sampled 62,000 person-days without replacement. With this sample, trees were built for $PM_{2.5}$ to make predictions of the exposure for each person-day in the aggregated data set, which was repeated 100 times. The final predicted $PM_{2.5}$ concentration for each person-day was obtained by averaging the predictions of the 100 trees. The GPS was constructed by using the averaged predictions of the 100 trees as the predicted $PM_{2.5}$ concentration and covariates for each person-day in the aggregated data set. In the analysis stage, the authors fit a weighted regression of the averaged outcome against the predicted $PM_{2.5}$ concentration and the estimated GPS using the aggregated data set to obtain the estimate for the additive effect of short-term $PM_{2.5}$ exposure on mortality rate.

Wei et al. (2021b) reported that the linear probability model and the weighted least squares model produced identical results with the estimated annual number of early deaths associated with a 1 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations being 92 (95% CI: 67, 117). However, the moonRF approach estimated a smaller number of annual deaths 69 (95% CI: 44, 95). When restricting the analysis to person-days with 24-hour average $PM_{2.5}$ concentrations below < 35 $\mu g/m^3$, the authors estimated a larger annual number of early deaths for each method (101 [95% CI: 74, 127] for the linear probability model and weighted least squares approaches and 78 [95% CI: 52, 105] for the moonRF approach).

In another recent study that employed alternative methods for confounder control, using data from the National Center for Health Statistics in 135 U.S. cities, Schwartz et al. (2018a) utilized three

statistical methods: instrumental variable analysis, a negative exposure control, and marginal structural models to estimate the association between local pollution, including $PM_{2.5}$, and daily deaths. Instrumental variable analysis constructs a single or set of instrument variables that represent variations in the exposure that are randomized with respect to both measured and unmeasured confounders. The instrument variables considered were planetary boundary layer, wind speed, and sea level pressure. Negative exposure control identifies a negative exposure variable, which is likely to be correlated with unmeasured potential confounders but could not be a cause of the outcome of interest. Negative exposure controls serve as instruments for the unmeasured confounders. If such confounders exist, control for the negative exposure would be expected to reduce or eliminate the estimated effect of the exposure of interest. If no such confounders exist, then control for the negative exposure would be expected to have no change in the association between the exposure and outcome, which indicates no confounding by any measured or unmeasured variables. Marginal structural models estimate the marginal effects of exposure by using inverse probability weights of time-varying exposures to render the exposure independent of the measured covariates. If the exposure is independent of covariates, its effect on the outcome cannot be confounded by them and resulting estimates do not depend on the distributions of confounders. The instrumental variable approach estimated that mortality increased by 1.54% (95% CI: 1.12, 1.97) at lag 0−1 for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations. When restricted to days with 24-hour average $PM_{2.5}$ concentrations below 25 $\mu g/m^3$, the instrument for $PM_{2.5}$ was associated with an increase of 1.70% (95% CI: 1.11, 2.29). With the negative control exposure method, there was −0:1% (95% CI: −0.5, 0.3) change in mortality. For the marginal structural models, there was an estimated 0.75% (95% CI: 0.35, 1.15) increase in mortality. When restricted to days with 24-hour average $PM_{2.5}$ concentrations below 25 $\mu g/m^3$, the marginal structural model also reported a 0.83% (95% CI: 0.39, 1.27) increase in mortality, albeit smaller in magnitude than the instrumental variable approach. Overall, the results of Schwartz et al. (2018a) continue to support a relationship between short-term $PM_{2.5}$ exposure and mortality.

Recent epidemiologic studies that employed alternative methods for confounder control to examine the association between short-term $PM_{2.5}$ exposure and mortality reported consistent positive associations within large cohorts across multiple cities in the U.S. Furthermore, the use of alternative methods for confounder control within these studies aims to reduce the uncertainties related to potential confounders that may bias reported associations. Overall, these recent studies further support the conclusions of the 2019 PM ISA with respect to short-term $PM_{2.5}$ exposure and mortality.

3.2.1.4. Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Short-Term $PM_{2.5}$ Exposure and Mortality

The few multicity epidemiologic studies conducted since the literature cutoff date of the 2019 PM ISA, provide additional support to the evidence base that contributed to the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and mortality. Recent U.S. and Canadian studies in

combination with previously evaluated multicity studies provide evidence of consistent positive associations with all-cause and nonaccidental mortality, primarily within the first few days after exposure (i.e., lag 0 and 1 day), across studies conducted in different geographic locations and in populations with different demographic characteristics. Additionally, these positive associations persist across studies that used different statistical models, exposure assessment approaches, and methods for confounder control. Overall, recent studies continue to support a relationship between short-term $PM_{2.5}$ exposure and mortality at lower mean 24-hour average concentrations, generally below 12 $\mu g/m^3$, as detailed in the 2019 PM ISA.

The limited assessment of cause-specific mortality in recent studies provides similar results to previously evaluated studies demonstrating a consistent relationship with cardiovascular mortality and more variability in the magnitude and precision of associations with respiratory mortality. Consistent with studies evaluated in the 2019 PM ISA, recent studies indicate that associations between short-term $PM_{2.5}$ exposure and mortality are relatively unchanged in copollutant models but may be larger in magnitude in the presence of some co-occurring pollutants (i.e., oxidant gases). In addition, factors that have been shown to vary between cities and regions of the U.S., such as housing characteristics, have been shown to explain some of the city-to-city and regional variability observed in $PM_{2.5}$-mortality associations in multi-city epidemiologic studies. The continued assessment of the C-R relationship between short-term $PM_{2.5}$ exposure and mortality further supports a linear, no-threshold relationship, with less confidence in the shape at concentrations below 5 $\mu g/m^3$. Additionally, recent studies that employed alternative methods for confounder control provide additional support for a relationship between short-term $PM_{2.5}$ exposure and mortality.

3.2.2. Long-Term $PM_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for long-term $PM_{2.5}$ exposure and mortality presented within the 2019 PM ISA (Section 3.2.2.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.2.2.2). [18] In addition, with the expansion of in epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.2.2.3), which can further inform the relationship between long-term $PM_{2.5}$ exposure and mortality. Finally, a summary of the results of recent studies evaluated within the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.2.2.4). The evaluation of recent studies on long-term $PM_{2.5}$ exposure and

[18] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining long-term exposures are for a 5 $\mu g/m^3$ increase in annual concentrations, unless otherwise noted.

mortality presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.2.2.1. Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

Cohort studies evaluated in the 2019 PM ISA provided consistent evidence of positive associations between long-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mainly in North America and Europe. Many analyses further evaluated the association between long-term $PM_{2.5}$ exposures and the risk of mortality based on the original American Cancer Society (ACS) study (Pope et al., 1995), added new details about deaths due to cardiovascular disease (including IHD) and respiratory disease (including COPD), and extended the follow-up period of the ACS to 22 years (1982−2004). Adding to this evidence, U.S. and Canadian cohort studies demonstrated consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, and statistical techniques, and locations, where mean annual average concentrations are ≤ 12 μg/m^3 (2019 PM ISA, Section 11.2.2.2). Additionally, the evidence from these studies reduced uncertainties related to potential copollutant confounding (2019 PM ISA, Section 11.2.3) and continued to provide strong support for a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.2.4). The body of evidence for total mortality was supported by generally consistent, positive associations with cardiovascular and respiratory mortality.

In addition to evaluating epidemiologic studies that examined the relationship between long-term $PM_{2.5}$ exposure and mortality, the 2019 PM ISA characterized whether evidence supported biologically plausible mechanisms by which long-term $PM_{2.5}$ exposure could lead to mortality (2019 PM ISA, Section 11.2.1). This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies of morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically, cardiovascular and respiratory morbidity and metabolic disease (2019 PM ISA, Section 6.2.1, Section 5.2.1, and Section 7.2.1, respectively). Plausible mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as IHD, stroke and atherosclerosis (2019 PM ISA, Section 6.2.1). Similarly, available evidence was characterized by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system and to population outcomes such as exacerbation of COPD (2019 PM ISA, Section 5.2.1). In addition, there was evidence for plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from initial events (e.g., pulmonary inflammation, autonomic nervous system activation) to intermediate endpoints (e.g., insulin resistance, increased blood glucose and lipids) and result in population outcomes such as metabolic disease and diabetes. In summary, there was coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure, and epidemiologic studies) and biological plausibility for $PM_{2.5}$-related cardiovascular (2019 PM ISA, Chapter 6), respiratory (2019 PM

ISA, Chapter 5), and metabolic (2019 PM ISA, Chapter 7) disease, which supports the $PM_{2.5}$-mortality relationship.

This section describes the evaluation of evidence included in the 2019 PM ISA for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 3-5.

Table 3-5 Summary of evidence for a *causal relationship* between long-term $PM_{2.5}$ exposure and total mortality from the 2019 Integrated Science Assessment for Particulate Matter.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects ($\mu g/m^3$)[c]
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of the ACS and HSC cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.1	Mean across studies: 11.4−23.6
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of the Medicare cohort, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean across studies: 8.12−12.0
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of Canadian cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean across studies: 8.7−9.1
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple North American occupational cohorts, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean across studies: 12.7−17.0
	Positive associations with cardiovascular, respiratory, and lung cancer mortality.	Section 6.3.10.1	Mean across studies: 4.1−17.9
		Section 5.2.10	Mean across studies: 4.1−17.9
		Section 10.2.5.1	Mean across studies: 6.1−33.7
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	Positive associations observed between long-term $PM_{2.5}$ exposure and total mortality remain relatively unchanged after adjustment for O_3, NO_2, and $PM_{10-2.5}$. When reported, correlations with copollutants were highly variable (low to high).	Section 11.2.3; Figure 11-20; Figure 11-21	

Table 3-5 (Continued): Summary of evidence for a *causal relationship* between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	$PM_{2.5}$ Concentrations Associated with Effects ($\mu g/m^3$)[c]
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and total mortality across exposure measurement metrics	Positive associations consistently observed across studies that used fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models), and satellite-based (e.g., AOD observations from satellites) methods, including hybrid methods that combine two or more of these methods.	Section 11.2.2.5; Jerrett et al. (2016)	
Epidemiologic evidence supports a linear, no-threshold C-R relationship	No evidence for deviation from linearity in several U.S. and Canadian cohorts.	Section 11.2.2.3	
Biological plausibility from studies of cardiovascular and respiratory morbidity and lung cancer incidence and mortality	Cardiovascular morbidity studies provide expanded body of evidence for associations between long-term $PM_{2.5}$ exposure and CHD, stroke, and atherosclerosis, providing biological plausibility for a relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality.	Section 6.3 Miller et al. (2007) Chi et al. (2016)	Mean across studies: 10.7−13.4
	Respiratory morbidity studies provide some evidence for an association between long-term $PM_{2.5}$ exposure and development of COPD, providing limited biological plausibility for a relationship between long-term $PM_{2.5}$ exposure and respiratory mortality.	Section 5.2.5	
	Consistent epidemiologic evidence for associations between $PM_{2.5}$ exposure and lung cancer incidence and mortality in cohort studies conducted in the U.S., Canada, Europe, and Asia.	Section 10.2.5.1 Figure 10-3	Mean across U.S. and Canadian studies: 6.3−23.6

Note: This table corresponds to Table 11-8 in the 2019 PM ISA.

ACS = American Cancer Society; AOD = aerosol optical depth; CHD = coronary heart disease; CMAQ = Community Multiscale Air Quality; COPD = chronic obstructive pulmonary disease; C-R = concentration-response; HSC = Harvard Six Cities; $\mu g/m^3$ = microgram per cubic meter; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

The strongest evidence supporting the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and total mortality in the 2009 PM ISA was derived from analyses of the ACS and Harvard Six Cities (HSC) cohorts. Extended analyses and reanalysis of these cohorts included in the 2019 PM ISA continued to support this relationship, demonstrating consistent positive associations for total (nonaccidental mortality) and across different cause-specific mortality outcomes. A series of analyses of the Medicare cohort of U.S. individuals provided additional support, culminating with the largest cohort study of nearly 61 million U.S. Medicare enrollees that reported positive associations with increases in $PM_{2.5}$ concentrations and stronger associations in areas where the mean annual $PM_{2.5}$ concentrations were ≤ 12 $\mu g/m^3$ (Di et al., 2017b). Another series of studies conducted in Canada provided results consistent with those of the Medicare cohort (i.e., positive associations between long-term $PM_{2.5}$ exposure and total mortality in areas where mean annual $PM_{2.5}$ concentrations are ≤ 12 $\mu g/m^3$). One difference between these studies was that the Canadian cohorts include all adults (age 25+ years) and the Medicare cohort only included adults age 65+ years, demonstrating that these effects are not specific to one lifestage, but affect all adults. Also, an additional line of evidence was available that includes results from a number of cohorts that recruited subjects based on their place of employment, including female nurses, female teachers, male health professionals, and male truck drivers, which show consistent, positive associations between long-term $PM_{2.5}$ exposure and total mortality.

Evidence included in the 2019 PM ISA helped to reduce uncertainties related to potential copollutant confounding of the relationship between long-term $PM_{2.5}$ exposure and mortality. Multiple studies evaluated ozone (2019 PM ISA, Figure 11-20) and NO_2 (2019 PM ISA, Figure 11-21) in copollutant models and observed similar hazard ratios for $PM_{2.5}$ regardless of whether ozone or NO_2 were included in the model. This supports an independent effect of long-term $PM_{2.5}$ exposure on mortality. Evidence for other potential copollutants (e.g., SO_2, CO) was limited.

Studies evaluated in the 2019 PM ISA used a variety of both fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models), and satellite-based (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more fixed-site, model, and/or satellite-based techniques to measure, estimate, or predict $PM_{2.5}$ concentrations for use in assigning long-term $PM_{2.5}$ exposure in epidemiologic studies. Overall, the exposure assessment technique had little influence on study results, with consistently positive associations of similar magnitude observed across studies using a variety of exposure assessment techniques. Notably, Jerrett et al. (2016) applied fixed-site measurements and satellite-based observations of AOD to a common data set, the ACS cohort, and calculated effect estimates for circulatory and IHD mortality associated with $PM_{2.5}$ using both methods. They observed consistently positive associations between long-term $PM_{2.5}$ exposure and mortality, regardless of the exposure assessment technique used to assign exposure. Additionally, Jerrett et al. (2016) combined multiple exposure assessment techniques into an ensemble model, weighted by model fit, and continued to observe similar positive associations with mortality. These results support an independent effect of

long-term $PM_{2.5}$ exposure on mortality that is not overtly influenced by or is a residual of the exposure assessment technique used in the study.

The number of studies that examined the shape of the C-R function for long-term $PM_{2.5}$ exposure and mortality substantially increased between the 2009 PM ISA and the 2019 PM ISA. These studies used a number of different statistical techniques to evaluate the shape of the C-R function, including natural cubic splines, restricted cubic splines, penalized splines, thin-plate splines, and cutpoint analyses (2019 PM ISA, Table 11-7), and generally observed linear, no-threshold relationships down to 4−8 $\mu g/m^3$. Few studies have conducted extensive analyses exploring alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship. Among these studies, there was some emerging evidence for a supralinear C-R function, with steeper slopes observed at lower $PM_{2.5}$ concentrations. Although few, such supralinear C-R functions were most commonly observed for cardiovascular mortality compared with total (nonaccidental) or respiratory mortality.

The 2009 PM ISA concluded that there is not sufficient evidence to differentiate the components or sources more closely related to health outcomes when compared with $PM_{2.5}$ mass, although the evidence for long-term exposure and mortality was limited. Several studies included in the 2019 PM ISA examined the relationship between long-term exposure to PM components and mortality (2019 PM ISA, Figure 11-24). Collectively, these studies continued to demonstrate that no individual $PM_{2.5}$ component or source was a better predictor of mortality than $PM_{2.5}$ mass.

Overall, epidemiologic studies examined in the 2019 PM ISA built upon and further reaffirmed the conclusions of the 2009 PM ISA for total mortality. The evidence, particularly from the assessment of $PM_{2.5}$-related cardiovascular and metabolic diseases, with more limited evidence from respiratory morbidity, provided biological plausibility for mortality due to long-term $PM_{2.5}$ exposures. In conclusion, the consistent positive associations observed across cohort studies conducted in various locations across North America were further supported by the results from copollutant analyses indicating robust associations independent of O_3 and NO_2. **Collectively, this body of evidence was sufficient to conclude that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.**

3.2.2.2. Recent U.S. and Canadian Cohort Studies

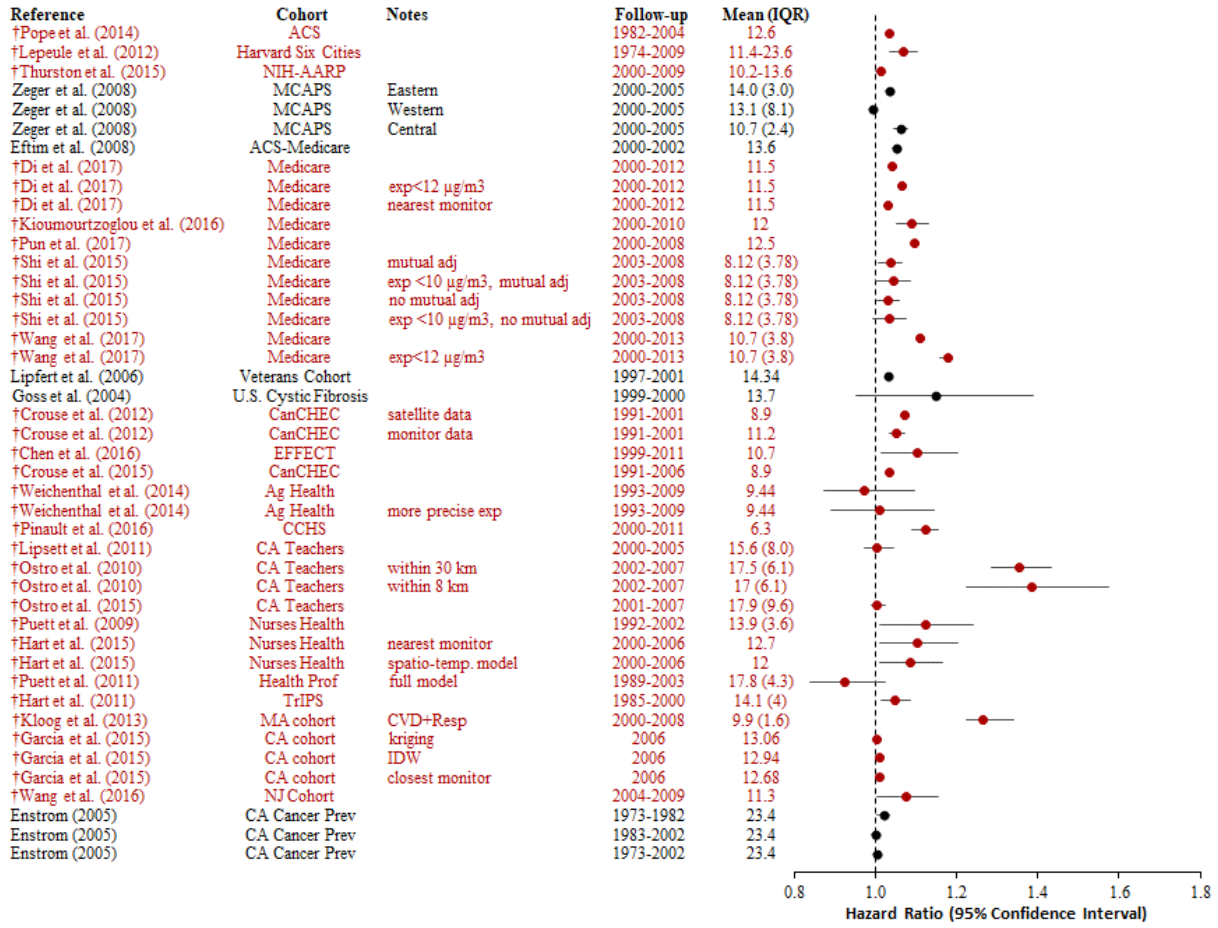
Recent cohort studies conducted in the U.S. and Canada build upon the strong evidence base evaluated in the 2019 PM ISA, as well as previous in assessments, which provided the scientific rationale supporting a *causal relationship* between long-term $PM_{2.5}$ exposure and mortality (Section 3.2.2.1). In addition to examining the relationship between long-term $PM_{2.5}$ exposure and all-cause or nonaccidental mortality (Section 3.2.2.2.1) and cause-specific mortality (Section 3.2.2.2.2), some studies also further examined issues relevant to expanding the overall understanding of the effect of long-term $PM_{2.5}$ exposure on mortality. Specifically, recent studies have assessed the effect of long-term $PM_{2.5}$ exposure on mortality in populations with underlying health conditions (Section 3.2.2.2.3), examined the role of

long-term $PM_{2.5}$ exposure on life expectancy (Section 3.2.2.2.4), examined potential copollutant confounding (Section 3.2.2.2.5), explored new and innovative methods for assessing confounding (Section 3.2.2.2.6), and assessed the shape of the concentration-response (C-R) relationship (Section 3.2.2.2.7). The following sections present an evaluation of recent cohort studies that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-7).

3.2.2.2.1. All-Cause and Total (Nonaccidental) Mortality

Recent North American cohort studies that examined the relationship between long-term $PM_{2.5}$ exposure and mortality support and expand upon the cohort studies evaluated in the 2019 PM ISA that spanned diverse geographical areas and study populations. These recent studies build upon the studies evaluated in the 2019 PM ISA that addressed key uncertainties identified in the 2009 PM ISA (e.g., $PM_{2.5}$-mortality associations at low concentrations, shape of the concentration-response [C-R] relationship).

Consistent with the North American cohort studies evaluated in the 2019 PM ISA (Figure 3-19), recent studies representing cohorts in the U.S. and Canada report a similar pattern of associations between long-term $PM_{2.5}$ exposure and all-cause or nonaccidental mortality in locations with generally low mean annual $PM_{2.5}$ concentrations (Figure 3-20). Whereas the use of hybrid exposure models, which includes some combination of monitoring, modeled, and satellite data, represented an advancement in methods in the 2019 PM ISA, recent studies primarily relied on these exposure assessment methods demonstrating the growth in their application and utility. Study-specific information for each of the recent studies evaluated in this section including information on the cohort, exposure assessment methodology, and $PM_{2.5}$ concentrations over the study duration are detailed in Table A-7.

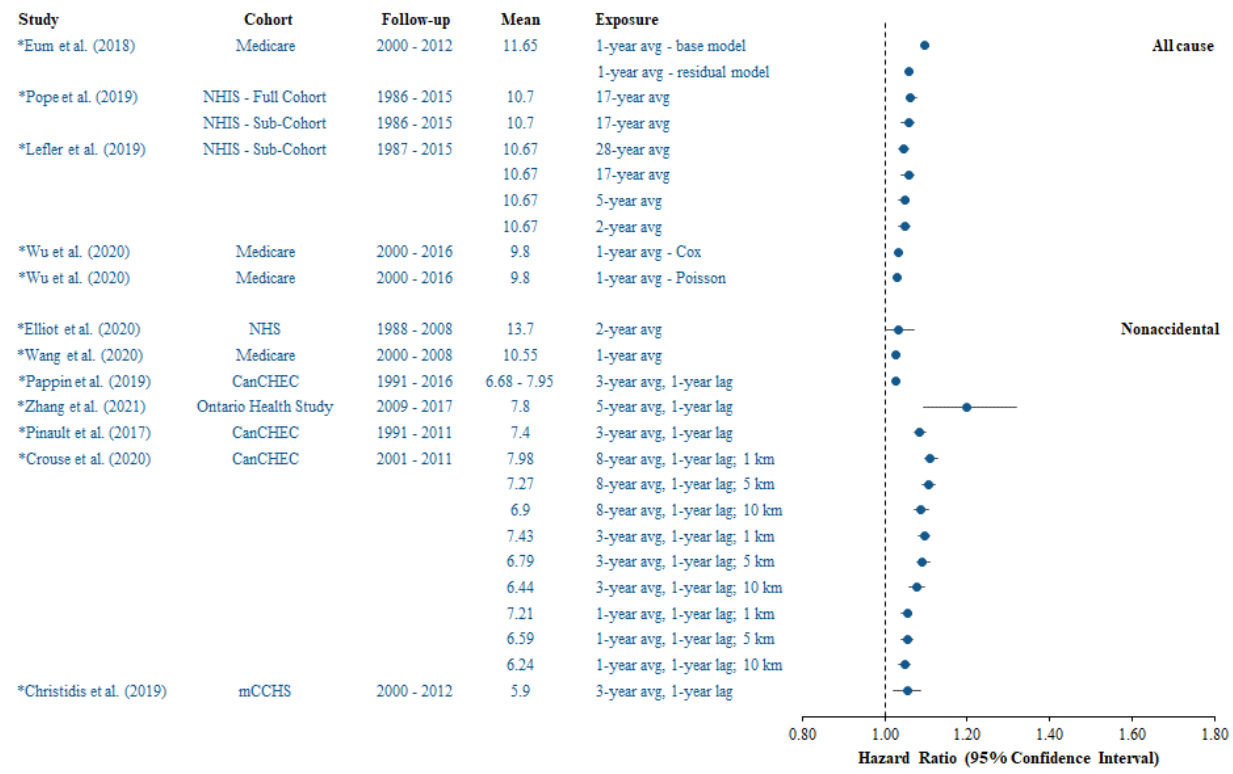


Source: Figure 11-18, 2019 PM ISA.

ACS = American Cancer Society; adj = adjustment; Ag Health = Agricultural Health Study; Cancer Prev = Cancer Prevention; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CVD = cardiovascular; EFFECT = Enhanced Feedback for Effective Cardiac Treatment; exp = exposure; Health Prof = health professionals; IDW = inverse-distance weighting; IQR = interquartile range; km = kilometer; µg/m^3 = microgram per cubic meter; MCAPS = Medicare Cohort Air Pollution Study; NIH-AARP = National Institutes of Health—American Association of Retired Persons; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; Resp = respiratory; TrIPS = Trucking Industry Particle Study.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 µg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Due to precise confidence intervals for estimates from some studies, the lines representing the confidence intervals cannot be viewed behind the point representing the effect estimate. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Study results from Pope et al. (2014) are representative of the results from the American Cancer Society cohort.

Figure 3-19 Associations between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality in recent North American cohorts.



avg = average; CanCHEC = Canadian Census Health and Environment Cohort; mCCHS = Canadian Community Health Survey—mortality cohort; km = kilometer; μg/m^3 = microgram per cubic meter; NHIS = National Health Interview Survey; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm.

Note: *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Due to precise confidence intervals for estimates from some studies, the lines representing the confidence intervals cannot be viewed behind the point representing the effect estimate. Blue text and circles represent U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA.

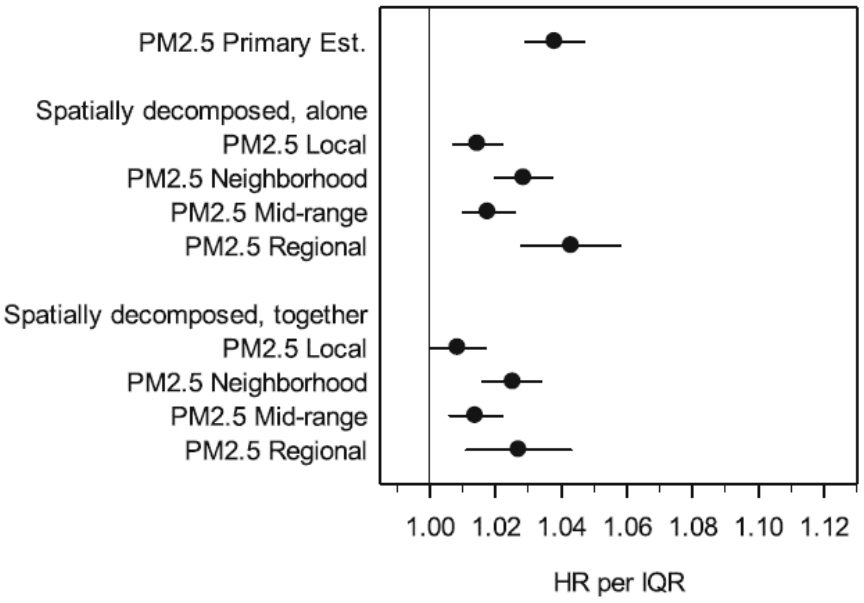
Figure 3-20 Associations between long-term $PM_{2.5}$ exposure and all-cause and total (nonaccidental) mortality in cohort studies in the United States and Canada published since the 2019 Integrated Science Assessment for Particulate Matter.

In the continuous evolution of studies aimed at assessing the relationship between long-term $PM_{2.5}$ exposure and mortality, recent research efforts focus on identifying increasingly larger and more diverse cohorts, including the National Health Interview Survey (NHIS) cohort and the Medicare cohort. Pope et al. (2019) formed the NHIS cohort by linking participants from the NHIS from 1986 to 2014 with mortality data through 2015 resulting in approximately 1.5 million participants. The authors also formed a subcohort comprising over 650,000 participants that had individual-level data on smoking status and body mass index (BMI). In analyses of both the full cohort and subcohort, Pope et al. (2019) uses a combination of monitored and modeled $PM_{2.5}$ data (see Table A-7) to estimate population-weighted 17-year average $PM_{2.5}$ concentrations at the census tract centroid of each participant. In fully adjusted Cox regression models, the authors report associations with all-cause mortality similar in magnitude for both the full cohort (HR = 1.06 [95% CI: 1.05, 1.08]) and subcohort (HR = 1.06 [95% CI: 1.04, 1.07]). In

a sensitivity analysis, back-casted $PM_{2.5}$ concentrations were imputed from 1988 to 1998, allowing for the use of a 28-year average $PM_{2.5}$ exposure window. In both the full cohort and subcohort, associations were attenuated, but remained positive when using the 28-year average exposure window, in comparison to the main analyses using the 17-year average exposure window (quantitative results not presented).

Lefler et al. (2019) expands upon the analyses initially conducted by Pope et al. (2019) by focusing on the NHIS subcohort with a primary focus being to examine potential sensitivity of $PM_{2.5}$-mortality associations to spatially and temporally decomposed $PM_{2.5}$. However, it is important to note that the spatial and temporal decomposition approaches employed by Lefler et al. (2019) attempt to examine the effect of distance to source and the sensitivity of exposure window on associations, respectively, and are not analogous to the decomposition methods discussed in Section 3.1.2.2.5, where the focus is on examining whether there is confounding due to unmeasured variables. To assess the temporal aspect, the authors employed two approaches to examine the sensitivity of associations to different exposure windows. In the first approach, they recreated cohorts for each year starting in 1992 that were then assigned either 2- or 5-year average $PM_{2.5}$ concentrations with an overall effect across the entire study duration estimated through a fixed effects meta-analysis. In the second approach, the authors applied the same exposure windows used in Pope et al. (2019) (i.e., 17-year or 28-year average $PM_{2.5}$ concentrations) as a comparison. Lefler et al. (2019) reported associations consistent in magnitude, regardless of the exposure windows used (HRs: 17-year: 1.06; 28-year: 1.04; 2-year: 1.05; 5-year: 1.05).

In the spatial decomposition approach, the authors developed exposure indicators indicative of $PM_{2.5}$ emanating from different sources and defined them as local (< 1 km); neighborhood (1−10 km); mid-range (10−100 km); and regional (> 100 km). In developing each exposure indicator, Lefler et al. (2019) subtracted the minimum $PM_{2.5}$ concentration identified within the defined circular buffers around each census tract for each year from 2000 to 2015. When focusing on results presented for an IQR increase in $PM_{2.5}$ concentrations, positive associations were reported for each exposure indicator; however, there was some variability across each of the exposure indicators examined with the regional indicator being closer in magnitude to the primary $PM_{2.5}$ exposure indicator (Figure 3-21). Overall, these results indicate that the mortality risk attributed to $PM_{2.5}$ is not due solely to regionally or locally derived $PM_{2.5}$.



Source: Lefler et al. (2019)

Figure 3-21 Hazard ratios for spatially decomposed analyses for an interquartile range increase in $PM_{2.5}$ concentrations for all-cause mortality.

Although the majority of cohort studies focus primarily on adults, generally over the age of 20, a number of recent studies focus on only individuals 65 years of age and older that are Medicare beneficiaries. Wang et al. (2020) used a hybrid spatiotemporal exposure model (see Table A-7) to estimate exposures at each Medicare participant's ZIP code centroid to examine nonaccidental mortality from 2000 to 2008. Using an exposure that represented the 12-month average $PM_{2.5}$ concentration prior to death, the authors reported a HR of 1.03 (95% CI: 1.02, 1.03) in a Cox proportional hazards model that adjusted for state-level SES to account for urbanicity and annual mean gross adjusted income.

Recent cohort studies published since the 2019 PM ISA focus primarily on examining the relationship between long-term $PM_{2.5}$ exposure and mortality in demographically diverse populations that are generally representative of the entire population in both the U.S. and Canada. Elliott et al. (2020) differs from those studies by focusing on an occupation-based cohort of female registered nurses (i.e., the NHS). Elliott et al. (2020) represents an updated and extended analysis of Hart et al. (2015a), which was evaluated in the 2019 PM ISA. Although the focus of Elliott et al. (2020) is on examining the interaction between long-term $PM_{2.5}$ exposure and physical activity, and the risk of cardiovascular disease and mortality, the authors used a 24-month exposure window and more years of data (i.e., 1988−2008) in the overall analysis of the association between long-term $PM_{2.5}$ exposure and mortality, which differs from Hart et al. (2015a), which used a 12-month exposure window for the years 2000−2008. In the fully adjusted Cox proportional hazards model the authors reported a HR of 1.07 (95% CI: 1.00, 1.15), which is consistent with previous studies of the NHS cohort (Figure 3-19).

While the studies discussed above add to the total body of evidence supporting a relationship between long-term $PM_{2.5}$ exposure and mortality, key questions that often arise in the assessment of the evidence are (1) Do associations persist at low concentrations? and (2) Is there a point below which there is less confidence in that relationship? This led to two recent research efforts with a main focus on examining the relationship between long-term $PM_{2.5}$ exposure and mortality at low concentrations. One of these studies conducted in the U.S., referred to as the Harvard Medicare study, focused on using a cohort of Medicare beneficiaries 65 years of age or older (Dominici et al., 2019), while another study conducted in Canada, referred to as the Mortality-Air Pollution Associations in Low Exposure Environments (MAPLE) study, relied on respondents from multiple years of the long-form Canadian Census Health & Environment Cohorts (CanCHEC) and/or participants from multiple years of the Canadian Community Health Survey (CCHS) (Brauer et al., 2019). A third study was conducted in Europe, using data from the European Study of Cohorts for Air Pollution Effects (ESCAPE) but is beyond the scope of this Supplement. Both of these research efforts conducted extensive analyses to further inform the $PM_{2.5}$-mortality relationship in a series of studies, with a focus on examining associations at low $PM_{2.5}$ concentrations, which are often considered as below the level of the current annual PM NAAQS of 12.0 $\mu g/m^3$.

As detailed in the 2019 PM ISA (Section 11.2.2.1), the initial publication from the Harvard Medicare study applied a hybrid exposure model at a refined spatial resolution (i.e., 1 km^2 grid cells) to assign $PM_{2.5}$ exposures at the ZIP code level to all Medicare beneficiaries age 65 and older in the continental U.S. between 2000 and 2012 to examine long-term $PM_{2.5}$ exposure and all-cause mortality (Di et al., 2017b). Di et al. (2017b) reported a HR of 1.041 (95% CI: 1.039, 1.042) for the relationship between $PM_{2.5}$ and all-cause mortality (Figure 3-20) with associations remaining relatively unchanged in copollutant models with ozone estimated from the nearest monitor. The majority of recent studies that fall under the Harvard Medicare study primarily focus on examining alternative methods for confounder control and are evaluated in Section 3.1.2.3. However, a recent study by Wu et al. (2020a) builds on the original study by Di et al. (2017b) of the Medicare cohort, by including additional years of data up to 2016. Within this study, the authors focused on examining associations with all-cause mortality using both traditional and alternative methods for confounder control (Section 3.1.2.3), and the sensitivity of associations to different confounder adjustment (Section 3.1.2.2.5). In the main analysis, the authors reported a HR of 1.03 using both a Poisson and Cox model that adjusted for calendar year and meteorological variables including season, maximum daily temperature, and relative humidity. Although the regression models used by Wu et al. (2020a) include additional covariates not included in the models used in Di et al. (2017b), similar results were reported by both studies.

Recent studies that fall under the umbrella of the MAPLE study instituted various advancements in exposure assessment. Similar to the Harvard Medicare study (Dominici et al., 2019), MAPLE studies rely on a hybrid exposure model that is a combination of monitored, modeled, and satellite data. Within the MAPLE studies, as detailed in Table A-7, an exposure model was used that predicts $PM_{2.5}$ concentrations at a 1 km^2 grid cell through a combination of satellite-derived $PM_{2.5}$ concentration

estimates, and model predictions in GEOS-Chem that are calibrated using monitor data. The 1 km^2 resolution $PM_{2.5}$ concentrations are then aggregated to the postal code of residence. In the process of assigning exposures to cohort participants, the majority of epidemiologic studies examining long-term $PM_{2.5}$ exposure and mortality tend to use exposure windows that consist of average $PM_{2.5}$ concentrations for a single year or all years that $PM_{2.5}$ data are available, which does not account for potential temporal changes in $PM_{2.5}$ concentrations [U.S. EPA (2019), Table A-7]. In addition, the exposure assigned often includes the year of death which could result in exposure misalignment if the death occurred early in the year. In an attempt to address both issues, MAPLE studies use a primary exposure representing a 3-year average with a 1-year lag prior to death to ensure that the exposure window for each individual within the cohort occurs prior to death (Pinault et al., 2017). Finally, building on Crouse et al. (2015), which accounted for residential mobility during the course of the study, MAPLE studies, instead of assigning exposure based on residential address at baseline or excluding individuals from the cohort when residential location information was missing, developed a new method in which postal codes were imputed if missing to maintain the size of the cohort.

While the MAPLE studies discussed below employ the 3-year average, 1-year lag approach to assigning exposure, it remained unclear how the combination of temporal and spatial scale of exposure assessment impacted the association with nonaccidental mortality. Crouse et al. (2020), within the 2001 census cycle of CanCHEC, examined whether HRs varied depending on the combination of years of $PM_{2.5}$ data used to assign exposure (i.e., 1-year avg, 3-year avg, or 8-year avg) and the spatial resolution of the exposure model (i.e., 1, 5, or 10 km). As depicted in Figure 3-20, across each temporal and spatial combination, associations are consistently positive, with the magnitude of the association being smallest when using the 1-year average. Additionally, the authors showed that the magnitude of the association declined as the spatial scale increased regardless of the temporal scale assigned. Although associations are larger in magnitude when using the 8-year average, they are relatively similar to the 3-year average (e.g., 1 km spatial scale: 8-year avg HR = 1.11 [95% CI: 1.10, 1.13]; 3-year avg HR = 1.10 [95% CI: 1.08, 1.11]). It is worth noting that the difference in results based on the exposure window used by Crouse et al. (2020) are not consistent with the results of Lefler et al. (2019), discussed above, that reported associations similar in magnitude when using shorter and longer duration exposure windows. However, because different cohorts and exposure assessment methods are used in each study it is not clear why these differences are observed. Overall, the results of Crouse et al. (2020) provide additional support for the use of the 3-year average, 1-year lag approach to assigning exposure predicted at the 1 km^2 spatial scale within the MAPLE studies.

Of the MAPLE studies, Pinault et al. (2017) was the first to institute the series of exposure assessment advancements discussed above. Pinault et al. (2017) expands upon the initial analyses of the CanCHEC cohort conducted by Crouse et al. (2012) and Crouse et al. (2015), which focused on the 1991 CanCHEC [see U.S. EPA (2019), Section 11.2.2.1; Figure 3-19]. In addition to using the 2001 CanCHEC, which allowed for an updated analysis using a larger and more recent cohort, Pinault et al. (2017) was able to address some of the limitations of the original CanCHEC studies. Specifically, Pinault

et al. (2017), used a hybrid exposure model that predicted concentrations at the 1 km^2 spatial scale versus the 10 km^2 spatial scale as was done in Crouse et al. (2012) and Crouse et al. (2015), potentially allowing for a better representation of spatial gradients in $PM_{2.5}$ concentrations. In addition, Pinault et al. (2017) used a 3-year average, 1-year lag $PM_{2.5}$ exposure instead of assigning exposure based on the average of all years of available $PM_{2.5}$ data as was done for each previous CanCHEC study, and employed the new approach to capture missing data on residential location. In a Cox proportional hazards model that was stratified by age, sex, airshed, population center size, and included all available individual and ecological covariates the authors reported a hazard ratio (HR) with nonaccidental mortality of 1.08 (95% CI: 1.07, 1.10).

Most of the studies examining the CanCHEC cohort, such as Pinault et al. (2017), focused on an individual census year, but Pappin et al. (2019) examined all three census cycles (i.e., 1991, 1996, and 2001) individually and in a pooled analysis. Although, the main focus of Pappin et al. (2019) was to examine the C-R relationship across the different census cycles (Section 3.2.2.2.7), in examining the relationship between long-term $PM_{2.5}$ exposure and mortality the authors expanded upon the regression model used in Pinault et al. (2017) and Crouse et al. (2016). This resulted in a regression model that included a variable to account for population size of a participant's community (Pinault et al., 2017), a covariate to account for airshed of residence (Crouse et al., 2016), and a variable of neighborhood marginalization based on the Canadian Marginalization Index (CAN-Marg). In the pooled analysis, the authors reported a HR = 1.03 (95% CI: 1.02, 1.03) in the fully adjusted model.

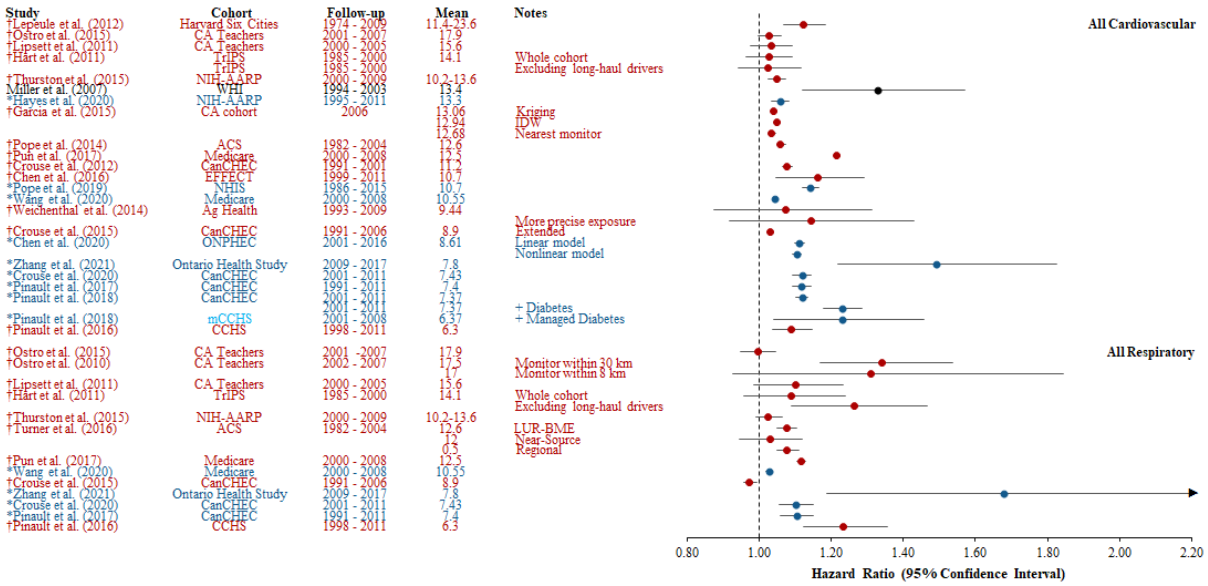
In addition to the MAPLE studies focusing on the larger CanCHEC cohort, other studies either focused solely on the CCHS-mortality (mCCHS) cohort (Christidis et al., 2019) or relied on data from it due to its extensive individual-level data [Pinault et al. (2018) in Section 3.1.2.2.2 and Erickson et al. (2019) in Section 3.1.2.2.4]. Christidis et al. (2019) represents an extended analysis of Pinault et al. (2016), detailed in the 2019 PM ISA (Section 11.2.2.1), which increased the year of analysis by 1 year to 2012. While both Christidis et al. (2019) and Pinault et al. (2016) relied on the same cohort, there were fundamental differences between the two studies, including different contextual variables included in statistical models and different criteria around the inclusion of immigrants in the cohort, that resulted in a difference in the magnitude of the association in both studies even though both relied on a 3-year average, 1-year lag exposure [i.e., HR = 1.12 (95% CI: 1.09, 1.16) in Pinault et al. (2016) and HR = 1.05 (95% CI: 1.02, 1.09) in Christidis et al. (2019)]. Overall, the primary driver of the difference in the magnitude of the association in both studies can be attributed to Christidis et al. (2019) including immigrants that have resided in Canada for 10 or more years, who have substantially lower HRs of mortality compared with the non-immigrant population. This differs from Pinault et al. (2016) where only immigrants that resided in Canada for 20 or more years were included in the analysis. However, this difference due to years of residence in Canada may be specific to the mCCHS cohort. For example, Erickson et al. (2020) in an analysis focusing on immigrants within the 2001 CanCHEC, reported larger risk estimates for immigrants that resided in Canada for ≤ 10 years and 11−20 years (HRs of 1.09 and 1.11, respectively), compared

with established immigrants (> 30 years residence) and non-immigrants (HR of 1.05 and 1.04, respectively).

An additional study conducted in Canada, the Ontario Health Study, that was not part of MAPLE, but used the same exposure model and a similar exposure assignment approach, provides continued support for a relationship between long-term $PM_{2.5}$ exposure and mortality (Zhang et al., 2021). Whereas the CanCHEC cohort lacked information on some individual-level risk factors, the Ontario Health Study collected individual-level data on socio-demographics, medical history, lifestyle factors, and health care utilization from 2009 to 2017. In fully adjusted Cox models that included all individual-level and contextual variables, Zhang et al. (2021) used a 5-year average exposure with a 1-year lag and reported a HR of 1.20 (95% CI: 1.09, 1.32) for nonaccidental mortality. In a sensitivity analysis comparing the 5-year average exposure metric to alternative exposure windows of 4- and 3-year averages, the authors reported an increase in the magnitude of the association as the number of years increased, which is consistent with Crouse et al. (2020) discussed above.

3.2.2.2.2. Cause-Specific Mortality

Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, including cardiovascular and respiratory mortality, can provide additional support for $PM_{2.5}$-related cardiovascular and respiratory effects, specifically whether there is evidence of an overall continuum of effects. Some of the studies evaluated in Section 3.1.2.2.1, in addition to examining all-cause or nonaccidental mortality, conducted analyses of cardiovascular and respiratory mortality, which builds on the evidence detailed in the 2019 PM ISA (respiratory mortality, Section 5.2.10 and Section 11.2.2.3; cardiovascular mortality, Section 6.2.10 and Section 11.2.2.2). As detailed in Figure 3-22, recent cohort studies provide evidence of consistent positive associations in analyses of both cardiovascular and respiratory mortality. In addition to examining all cardiovascular and respiratory mortality outcomes, some studies also examined individual cardiovascular and respiratory mortality outcomes, as well as mortality in individuals with preexisting cardiovascular-related disease. The following sections provide an overview of the evidence presented in recent cohort studies with respect to cause-specific mortality.



Source: Update of Figure 11-19, 2019 PM ISA.

ACS = American Cancer Society; Ag Health = Agricultural Health Study; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CVD = cardiovascular disease; EFFECT = Enhanced Feedback for Effective Cardiac Treatment; IDW = inverse distance weighting; km = kilometer; LUR-BME = land use regression—Bayesian maximum entropy; mCCHS = Canadian Community Health Survey—mortality cohort; μg/m^3 = microgram per cubic meter; NHIS = National Health Interview Survey; NIH-AARP = National Institutes of Health—American Association of Retired Persons; ONPHEC = Ontario Population Health and Environment Cohort; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; TrIPS = Trucking Industry Particle Study; WHI = Women's Health Initiative.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates, closed published before 2009 PM ISA, and open published after 2019 PM ISA; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Due to precise confidence intervals for estimates from some studies, the lines representing the confidence intervals cannot be viewed behind the point representing the effect estimate. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs; and blue text and circles represent recent U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA. Results from Crouse et al. (2020) are for 3-year average, 1-year lag $PM_{2.5}$ concentrations at 1 km resolution.

Figure 3-22 Associations between long-term $PM_{2.5}$ exposure and all cardiovascular disease and all respiratory disease mortality in recent North American cohorts.

Cardiovascular Mortality

Studies investigating cardiovascular mortality provided some of the strongest evidence for a cardiovascular effect related to long-term $PM_{2.5}$ exposure in the 2009 PM ISA, which was further supported by studies evaluated in the 2019 PM ISA (Figure 3-22). Generally, across the cohort studies evaluated in the 2019 PM ISA, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in magnitude in copollutant models adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2. The results of recent cohort studies provide additional evidence for associations with cardiovascular mortality outcomes across the distribution of $PM_{2.5}$ concentrations, the potential implications of comorbidity on the $PM_{2.5}$-cardiovascular mortality relationship, and associations with individual cardiovascular mortality outcomes.

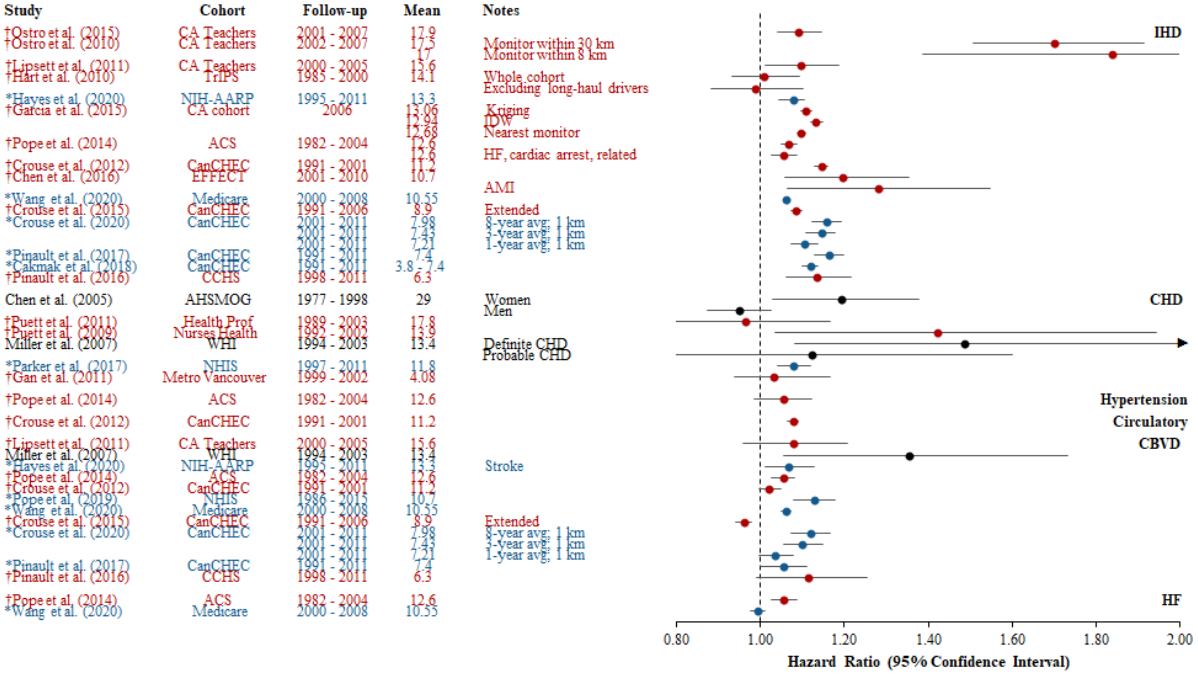
In a study of the NIH-AARP cohort, which consists of participants ranging from 50 to 71 years of age, Hayes et al. (2020) examined not only the overall relationship between long-term $PM_{2.5}$ exposure and cardiovascular-related mortality, but whether associations changed over different ranges of $PM_{2.5}$ concentrations. In the main analysis, the authors applied a spatiotemporal model that predicted $PM_{2.5}$ concentrations at the census tract and reported a HR of 1.06 (95% CI: 1.03, 1.08) for all cardiovascular mortality. This result was consistent with a sensitivity analysis that assigned exposure based on distance to monitor from participant residence when focusing on monitors 0−25 km away (HR = 1.07 [95% CI: 1.03, 1.10]), with more variability and less precision for greater distances (i.e., 25−50 km and 50−100 km) due to the smaller sample size and the increased exposure error that can occur as distance to monitor increases.

The results of Hayes et al. (2020) are consistent with another study focusing exclusively on cardiovascular mortality conducted by Chen et al. (2020) using the ONPHEC. Within ONPHEC, Chen et al. (2020) examined associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in individuals 35−85 years of age using an exposure model similar to the one used in the MAPLE studies (Table A-7). In analyses using 1-year average $PM_{2.5}$ exposures with a 1-year lag prior to death, the authors conducted single pollutant analyses using a traditional Cox proportional hazards model where $PM_{2.5}$ is fit as a linear term and then a Cox proportional hazards where $PM_{2.5}$ could be nonlinearly associated with cardiovascular mortality using the SCHIF detailed in Nasari et al. (2016). The authors reported that the nonlinear model is a better predictor of cardiovascular mortality through an assessment of model fit based on AIC. However, relatively similar HRs were reported for both the linear (HR = 1.11 [95% CI: 1.10, 1.12]) and nonlinear (HR = 1.10 [95% CI: 1.09, 1.12]) models, which are consistent with the results presented in other studies of cardiovascular mortality (Figure 3-22). In addition to conducting single-pollutant analyses, the authors introduced a new approach to assess whether the $PM_{2.5}$-cardiovascular mortality association varies depending on the proportion of $PM_{2.5}$ attributed to selected components (i.e., sulfate, nitrate, ammonium, black carbon, organic matter, mineral dust, and sea salt). In a Cox proportional hazards model that adjusted for the proportion of each of the seven selected components Chen et al. (2020) reported that cardiovascular mortality associations increased on average by 27% when compared with single-pollutant results across each of the five regions of Ontario. These results provide some evidence that variability in the proportion of individual components that comprise $PM_{2.5}$, could explain regional variability in mortality risk estimates.

While there is evidence of consistent positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (Figure 3-22), it is plausible that comorbidities may increase the overall risk of cardiovascular mortality. As a result, Pinault et al. (2018) examined both the CanCHEC and mCCHS cohorts to assess whether the combination of cardiovascular disease and diabetes together yielded larger $PM_{2.5}$-mortality risk estimates than cardiovascular disease alone. Within CanCHEC, the authors identified all participants for whom, in addition to having cardiovascular disease as the primary cause of death, diabetes was mentioned on the death certificate, whereas for the mCCHS, which consisted of individual-level data, participants self-reported diabetes status by noting insulin or medication use to

manage diabetes at baseline. In both analyses, the authors applied the same base hybrid exposure model used in the MAPLE studies, which ultimately resulted in a 3-year average $PM_{2.5}$ concentration assigned to each participant, lagged 1-year prior to death (Table A-7). In both cohorts, there was an almost doubling of the HR for mortality for the combination of cardiovascular disease and diabetes compared with cardiovascular disease alone (CanCHEC: CVD, HR = 1.12 [95% CI: 1.10, 1.14], CVD+diabetes, HR = 1.23 [95% CI: 1.18, 1.28]; mCCHS: CVD, HR = 1.14 [95% CI: 1.08, 1.21], CVD+managed diabetes, HR = 1.23 [95% CI: 1.04, 1.46]).

In addition to the studies that examined all cardiovascular mortality outcomes, a number of studies also examined specific cardiovascular mortality outcomes (Figure 3-23). As described in Section 6.2.10 of the 2019 PM ISA, there were generally positive associations across studies for IHD mortality with a more limited assessment of other outcomes (e.g., cerebrovascular, heart failure, hypertensive disorders). Recent studies within the Medicare cohort (Wang et al., 2020), the CanCHEC cohort (Crouse et al., 2020; Cakmak et al., 2018; Pinault et al., 2017), and NIH-AARP cohort (Hayes et al., 2020) report positive associations with IHD, supporting the results of studies evaluated in the 2019 PM ISA. However, Cakmak et al. (2018) conducted a slightly different analysis of the CanCHEC cohort than Pinault et al. (2017) by using the 1991 CanCHEC and a 7-year average exposure instead of the 3-year average, 1-year lag exposure of the studies within MAPLE. Although Crouse et al. (2020) also examined the 2001 CanCHEC, as noted previously, the study focused on examining different temporal (1-, 3-, and 8-year average) and spatial (1, 5, and 10 km) scales of exposure assignment. Across each temporal scale the authors reported consistent positive associations regardless of spatial scale, but overall, the magnitude of the $PM_{2.5}$-IHD association was smaller when using 1-year average $PM_{2.5}$ concentrations. Of the studies that included an assessment of IHD mortality, only Cakmak et al. (2018) examined copollutant models and reported that IHD associations, although attenuated, remained positive in models with ozone ($PM_{2.5}$: HR = 1.12 [95% CI: 1.10, 1.14]; $PM_{2.5}$ + ozone: HR = 1.06 [95% CI: 1.04, 1.09]).



Source: Update of Figure 6-19, 2019 PM ISA

ACS = American Cancer Society; AHSMOG = Adventist Health Study and Smog; AMI = acute myocardial infarction; AQCD = Air Quality Criteria Document; CA = California; CanCHEC = Canadian Census Health and Environment Cohort; CBVD = cerebrovascular disease; CCHS = Canadian Community Health Survey; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EFFECT = Enhanced Feedback for Effective Cardiac Treatment; HF = heart failure; IDW = inverse-distance weighting; IHD = ischemic heart disease; km = kilometer; NHIS = National Health Interview Survey; NIH-AARP = National Institutes of Health–American Association of Retired Persons; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; WHI = Women's Health Initiative.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Due to precise confidence intervals for estimates from some studies, the lines representing the confidence intervals cannot be viewed behind the point representing the effect estimate. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs, with open red circles representing studies published since the 2019 PM ISA; and blue text and circles representing U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA. Study results from Pope et al. (2014) are representative of the results from the American Cancer Society cohort.

Figure 3-23 Associations between long-term $PM_{2.5}$ exposure and cause-specific cardiovascular mortality in recent North American cohorts.

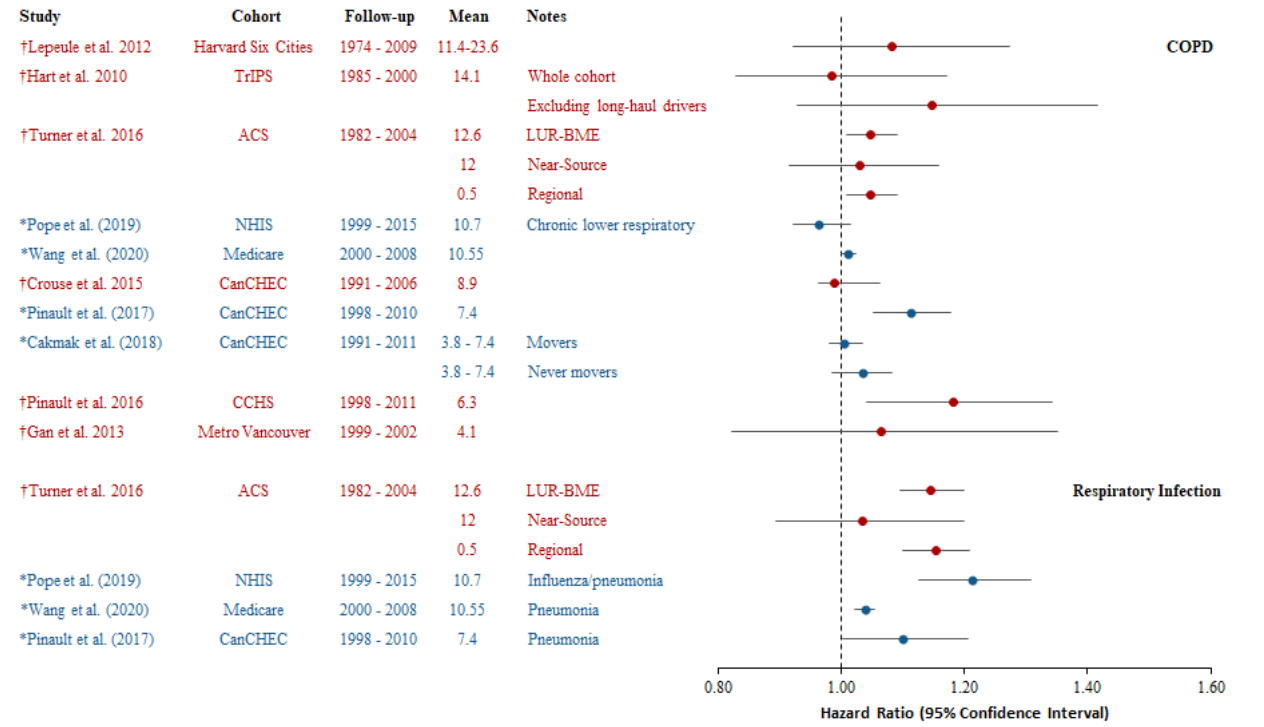
Few studies to date have examined associations between long-term $PM_{2.5}$ exposure and cerebrovascular disease or stroke mortality, but studies by Wang et al. (2020), Pinault et al. (2017), Crouse et al. (2020), and Hayes et al. (2020) along with a study within the NHIS cohort by Pope et al. (2019) add to the growing body of evidence indicating a positive relationship. Although Pope et al. (2014) in a study of the ACS cohort, evaluated in the 2019 PM ISA indicated a positive association with CHF mortality, in a recent study of the Medicare cohort Wang et al. (2020) reported a null association. Finally, a few studies using the CanCHEC cohort (Crouse et al., 2020; Pinault et al., 2017) examined the combination of cardiovascular mortality with either metabolic-related or diabetes mortality, and found that associations were similar in magnitude to cardiovascular mortality alone [e.g., within Pinault et al.

(2017) all cardiovascular: HR = 1.12 (95% CI: 1.09, 1.14); all cardiovascular + diabetes: HR = 1.13 (95% CI: 1.10, 1.15)].

Respiratory Mortality

Evidence from studies investigating respiratory-related mortality provided limited and inconsistent evidence for a respiratory effect related to long-term $PM_{2.5}$ exposure in the 2009 PM ISA (U.S. EPA, 2009). Studies evaluated in the 2019 PM ISA (Section 5.2.10; Figure 5-34) primarily focused on all respiratory mortality with a more limited assessment of COPD and respiratory infection. Across studies there was evidence of generally consistent, positive associations. Recent cohort studies provide an additional assessment of the relationship between long-term $PM_{2.5}$ exposure and COPD and respiratory infection mortality.

Studies conducted within the NHIS (Pope et al., 2019) and Medicare (Wang et al., 2020) cohorts provided limited evidence of an association with chronic lower respiratory and COPD mortality, respectively (Figure 3-24). However, in a study of the CanCHEC cohort Pinault et al. (2017) reported a HR for COPD mortality of 1.11 (95% CI: 1.05, 1.18), which is similar in magnitude to the association reported in Pinault et al. (2016) within the CCHS cohort as detailed in the 2019 PM ISA. In another study of the CanCHEC cohort, which as noted earlier used a different exposure assessment approach compared with Pinault et al. (2017), Cakmak et al. (2018) reported evidence of a positive association between long-term $PM_{2.5}$ exposure and COPD mortality in analyses of never movers. In addition, Cakmak et al. (2018) alone examined potential copollutant confounding of the $PM_{2.5}$-COPD mortality relationship, but in analyses focused on movers and never movers, not the entire cohort. In models with O_3, in both movers and never movers the authors reported larger HRs, albeit with wide confidence intervals, with ozone in the model, which was substantially larger for movers (movers: HR = 1.08 [95% CI: 1.03, 1.12]; never movers: HR = 1.05 [95% CI: 0.88, 1.26]).



Source: Modification of Figure 5-34, 2019 PM ISA.

ACS = American Cancer Society; AQCD = Air Quality Criteria Document; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CI = confidence interval; LUR-BME = Land Use Regression—Bayesian Maximum Entropy; μg/m^3 = micrograms per cubic meter; NHIS = National Health Interview Survey; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; TrIPS = Trucking Industry Particle Study.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs, with blue text and circles representing U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA. Study results from Pope et al. (2014) are representative of the results from the American Cancer Society cohort.

Figure 3-24 Associations between long-term $PM_{2.5}$ exposure and cause-specific respiratory mortality in recent North American cohorts.

The examination of respiratory infection mortality is more limited, with recent cohort studies examining either pneumonia alone (Wang et al., 2020; Pinault et al., 2017) or the combination of influenza and pneumonia (Pope et al., 2019). Across the studies, which employed different approaches to assign $PM_{2.5}$ exposures including a 1-year average in the Medicare cohort (Wang et al., 2020), a 3-year average with a 1-year lag in the CanCHEC cohort (Pinault et al., 2017), and a 17-year average in the NHIS cohort (Pope et al., 2019), each reported positive associations with the magnitude of the association increasing as the length of the exposure window increased.

Other Mortality Outcomes

While cardiovascular- and respiratory-related mortality comprise the majority of mortality outcomes examined, as noted in the 2019 PM ISA, additional mortality outcomes are also associated with

long-term $PM_{2.5}$ exposure, including cardiopulmonary, diabetes, and lung cancer (2019 PM ISA, Section 10.2.5 and Section 11.2.2). Recent cohort studies published since the 2019 PM ISA also provide evidence of positive associations with cardiopulmonary (Lefler et al., 2019; Pope et al., 2019), diabetes/cardiometabolic disease (Crouse et al., 2020; Erickson et al., 2020; Lim et al., 2018; Pinault et al., 2017), and lung cancer (Crouse et al., 2020; Erickson et al., 2020; Erickson et al., 2019; Pope et al., 2019; Cakmak et al., 2018; Pinault et al., 2017) mortality.

3.2.2.2.3. Long-Term $PM_{2.5}$ Exposure and Mortality in Populations with Preexisting Conditions

In addition to recent studies examining cause-specific mortality, a few studies focused on examining the overall risk of mortality in individuals with preexisting cardiovascular conditions, specifically HF (Ward-Caviness et al., 2020) and previous MI (Malik et al., 2019). To date, relatively few studies have been conducted with the sole focus being on examining associations between long-term $PM_{2.5}$ exposure and mortality within a cohort of individuals with a preexisting cardiovascular condition. Instead, studies have traditionally relied on the examination of effect modification, through stratified analyses, of the $PM_{2.5}$-mortality association by specific cardiovascular conditions.

Ward-Caviness et al. (2020) examined associations between annual average $PM_{2.5}$ exposure at the time of initial HF diagnosis with all-cause mortality in a hospital-based cohort within North Carolina developed from electronic health records of individuals diagnosed with heart failure. The authors assigned annual average $PM_{2.5}$ exposures to each participant based on their residential address at the time of HF diagnosis. Exposures were assigned based on the nearest $PM_{2.5}$ monitor and using the hybrid exposure model used in the Medicare studies discussed previously that estimated concentrations at 1 km^2 (Table A-7). Over 10,000 of the 35,000 patients within the cohort died less than 1 year after diagnosis, which does not follow the traditional pattern of HF mortality. As a result, the authors excluded the year after diagnosis as a time at risk in the model. In a Cox proportional hazards model that controlled for individual-level covariates, distance to monitor, and neighborhood-level socioeconomic variables, Ward-Caviness et al. (2020) reported a HR for all-cause mortality of 1.84 (95% CI: 1.61, 2.01). In sensitivity analyses, associations were similar in magnitude to the main analysis when restricting it to participants <30 km from a $PM_{2.5}$ monitor and larger in magnitude when applying the hybrid exposure model.

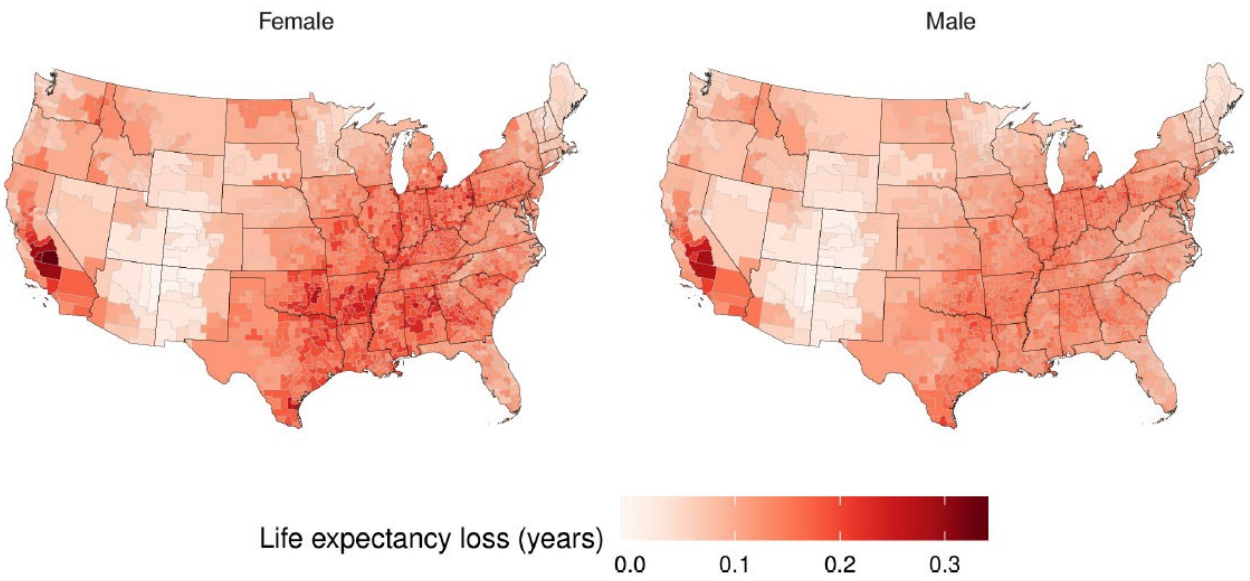
Whereas Ward-Caviness et al. (2020) examined the risk of mortality attributed to long-term $PM_{2.5}$ exposure in the years following HF diagnosis over the entire study duration, Malik et al. (2019) focused on examining the 5-year survival for all-cause mortality following an MI event. A total of 5,650 patients with clinically diagnosed MI as defined by having biomarker evidence of myocardial necrosis and additional clinical evidence of MI, including prolonged ischemic signs/symptoms or electrocardiographic criteria of ST-segment changes, were enrolled in the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction (TRIUMPH) and Prospective Registry Evaluating Myocardial Infraction: Events and Recovery (PREMIER) studies. Using U.S. EPA's downscaler Community

Multi-Scale Air Quality Model (CMAQ), $PM_{2.5}$ concentrations were estimated at the census tract centroid of each participants residence. Exposures assigned to each participant consisted of the 12-month average $PM_{2.5}$ concentration prior to MI, which allowed for the examination of the association between $PM_{2.5}$ exposure and survival after an MI. In a Cox regression model that controlled for numerous individual-level covariates as well as ozone, Malik et al. (2019) reported a HR of 1.34 (95% CI: 1.17, 1.54) for 5-year all-cause mortality.

Overall, the studies conducted by Ward-Caviness et al. (2020) and Malik et al. (2019) indicate that preexisting cardiovascular conditions substantially increase the risk of all-cause mortality. This is further reflected when comparing the magnitude of associations between these studies and the numerous cohort studies spanning diverse populations summarized in Section 3.1.2.2.1 and Figure 3-19.

3.2.2.2.4. Studies of Life Expectancy

The 2019 PM ISA characterized a recent series of studies evaluating the relationship between long-term exposure to $PM_{2.5}$ and mortality by examining the temporal trends in $PM_{2.5}$ concentrations and changes in life expectancy. These studies generally observed that decreases in $PM_{2.5}$ concentrations are associated with increases in life expectancy. A few recent studies add to this evidence base. Bennett et al. (2019) reported that $PM_{2.5}$ concentrations in excess of the lowest observed concentration (2.8 $\mu g/m^3$) were associated with a lower national life expectancy by an estimated 0.15 years for women and 0.13 years for men (Figure 3-25). Using a different approach, Ward-Caviness et al. (2020) compared participants residing in areas with $PM_{2.5}$ concentrations > 12 $\mu g/m^3$ to participants living in areas with $PM_{2.5}$ concentrations < 12 $\mu g/m^3$ and estimated that the years of life lost due to living in areas with higher $PM_{2.5}$ concentrations was 0.84 years (95% CI, 0.73−0.95) over a 5-year period.



Source: Bennett et al. (2019)

Figure 3-25 Estimated loss in life expectancy by county for females and males for $PM_{2.5}$ concentrations in excess of the lowest observed $PM_{2.5}$ concentration of 2.8 µg/m^3.

3.2.2.2.5. Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

As discussed in Section 3.1.2.2.8, one approach to assessing the independence of the association between exposure to $PM_{2.5}$ and a health effect, such as long-term $PM_{2.5}$ exposure and mortality, can be examined is through the use of copollutant models. The Appendix (Table A-1) to the 2019 PM ISA notes that copollutant models are not without their limitations, such as instances where correlations are high between pollutants resulting in greater bias in results. However, in assessing the results from copollutant models a change in the $PM_{2.5}$ risk estimate, after adjustment for a copollutant, may indicate the potential for confounding.

At the completion of the 2009 PM ISA there was limited assessment of potential confounding of the relationship between long-term $PM_{2.5}$ exposure and mortality by co-occurring pollutants. Studies evaluated in the 2019 PM ISA (Section 11.2.3) examined the potential for copollutant confounding by evaluating copollutant models that included O_3 (Figure 11-20), NO_2, $PM_{10–2.5}$, SO_2, and benzene (Figure 11-21). These studies addressed a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of coexposure to correlated copollutants in long-term analyses. Overall, $PM_{2.5}$ effects to remained relatively unchanged in copollutant models adjusted for NO_2, $PM_{10–2.5}$, SO_2, or benzene. Recent North American cohort studies conducted additional analyses that further inform whether the relationship between long-term $PM_{2.5}$ exposure and mortality is confounded by gaseous pollutants or other particle size fractions (i.e., $PM_{10–2.5}$).

In an analysis of the NHIS subcohort, Lefler et al. (2019) reported that the $PM_{2.5}$-mortality association was relatively unchanged in copollutant analyses with SO_2, NO_2, O_3, CO, and $PM_{10-2.5}$. In addition to Lefler et al. (2019), within the Medicare cohort, Wang et al. (2020) also conducted an analysis of potential confounding of the $PM_{2.5}$-mortality association with a focus on ozone and traffic-related pollution. The ozone analysis was conducted in a subset of the cohort that resided in ZIP codes within 6 miles of an ozone AQS monitor. To control for traffic-related pollution, instead of including NO_2 in a copollutant model, Wang et al. (2020) regressed 12-month $PM_{2.5}$ on NO_2 and used the residuals as the exposure metric to estimate the $PM_{2.5}$ association that is unrelated to traffic. The authors reported associations similar in magnitude in both a single (HR = 1.03 [95% CI: 1.02, 1.03]) and copollutant model with ozone (HR = 1.03 [95% CI: 1.02, 1.03]). Positive associations were also reported for the non-traffic $PM_{2.5}$ analyses, and although the association was smaller in magnitude to the total $PM_{2.5}$ analysis, this result provides evidence that the $PM_{2.5}$-mortality association persists independent of traffic-related pollutants (HR = 1.01 [95% CI: 1.00, 1.01]).

A few studies within the MAPLE study also conducted analyses to assess potential copollutant confounding by gaseous pollutants. Within CanCHEC, Crouse et al. (2020) assessed potential copollutant confounding by ozone, NO_2, and oxidant gases in sensitivity analyses using both 3-year and 8-year average $PM_{2.5}$ concentrations at 1 km^2 resolution. Associations between $PM_{2.5}$ and mortality were found to be slightly attenuated but remained positive in copollutant models with each of the gaseous pollutants when using either 3-year or 8-year average $PM_{2.5}$ exposures.

While there was no evidence of copollutant confounding in the analysis of CanCHEC by Crouse et al. (2020), there was some evidence in the pooled analysis of CanCHEC by Pappin et al. (2019). In the single-pollutant analysis, the authors reported a HR of 1.03 (95% CI: 1.02, 1.03) in the fully adjusted model, which is consistent with the copollutant model including NO_2 (HR = 1.02 [95% CI: 1.01, 1.03]). However, there was no evidence of a $PM_{2.5}$-mortality association in copollutant models with ozone (HR = 0.99 [95% CI: 0.98, 1.00]) and oxidants (HR = 0.98 [95% CI: 0.97, 0.98]). The ozone and oxidants results of Pappin et al. (2019) are consistent with those of Christidis et al. (2019) within the mCCHS cohort. However, Christidis et al. (2019) reported evidence of potential confounding by NO_2. In a single-pollutant analysis, the authors reported a HR of 1.05 (95% CI: 1.02, 1.09). In copollutant models, $PM_{2.5}$-mortality associations are null in models with ozone (HR = 1.00 [95% CI: 1.00, 1.01]) and oxidants (HR = 1.00 [95% CI: 0.99, 1.01]), and attenuated in a model with NO_2 (HR = 1.01 [95% CI: 1.00, 1.02]).

Zhang et al. (2021) also conducted copollutant analyses when examining associations between long-term $PM_{2.5}$ exposure and mortality in the Ontario Health Study. The authors reported that the $PM_{2.5}$-mortality association in a single-pollutant model (HR = 1.20 [95% CI: 1.09, 1.32]) is relatively unchanged in a model with NO_2 (HR = 1.18 [95% CI: 1.08, 1.30]), which is consistent with Lefler et al. (2019) in the NHIS cohort and Pappin et al. (2019) within CanCHEC. However, it is inconsistent with the results from the mCCHS cohort where Christidis et al. (2019) reported evidence of attenuation of the $PM_{2.5}$-mortality association.

While there is some evidence from recent studies that $PM_{2.5}$-mortality associations remain relatively unchanged in copollutant models, there are some differences in results across studies, particularly for copollutant analyses including ozone. This difference in results is most evident between MAPLE studies and other studies that previously examined copollutant confounding by ozone as summarized in Figure 11-20 of the 2019 PM ISA. This difference between studies could be attributed to the MAPLE studies using different spatial resolutions in estimating air pollutant concentrations, 1 km^2 for $PM_{2.5}$ and 21 km^2 for ozone, potentially resulting in some degree of exposure error.

3.2.2.2.6. Studies That Address the Potential Implications of Unmeasured Confounders on $PM_{2.5}$-Mortality Associations

As discussed in Section 11.2.2.4 of the 2019 PM ISA, some recent studies used statistical techniques to reduce uncertainties related to potential unmeasured confounders that can further inform the relationship between long-term $PM_{2.5}$ exposure and mortality. An initial study conducted by Janes et al. (2007) and then followed up by Greven et al. (2011) attempted to assess whether there is evidence of unmeasured confounding in the relationship between long-term $PM_{2.5}$ exposure and mortality using data from the Medicare cohort from 2000 to 2006. In both studies the authors decomposed the association between $PM_{2.5}$ and mortality into two components: (1) the association between the "national" trend in the monthly $PM_{2.5}$ concentrations averaged over the previous 12 months and the national average trend in monthly mortality rates (purely temporal association); and (2) the association between the "local" trend in the deviation in the community-specific trend from the national average trend of monthly averages of $PM_{2.5}$ and the deviation of the community-specific trends from the national average trend of mortality rates (residual spatiotemporal association). The authors concluded that differences in effect estimates at these two spatiotemporal scales raise concerns about confounding bias in these analyses, with the association for the national trend more likely to be confounded than the association for the local trend. However, in the process of decomposing the data, it eliminated all spatial variation in air pollution and mortality. Thus, while the results of the papers themselves provide evidence for an association between exposure to $PM_{2.5}$ and mortality, it is not possible to directly compare the results of these studies to the results of other cohort studies investigating the relationship between long-term exposure to $PM_{2.5}$ and mortality, which make use of spatial variability in air pollution and mortality data.

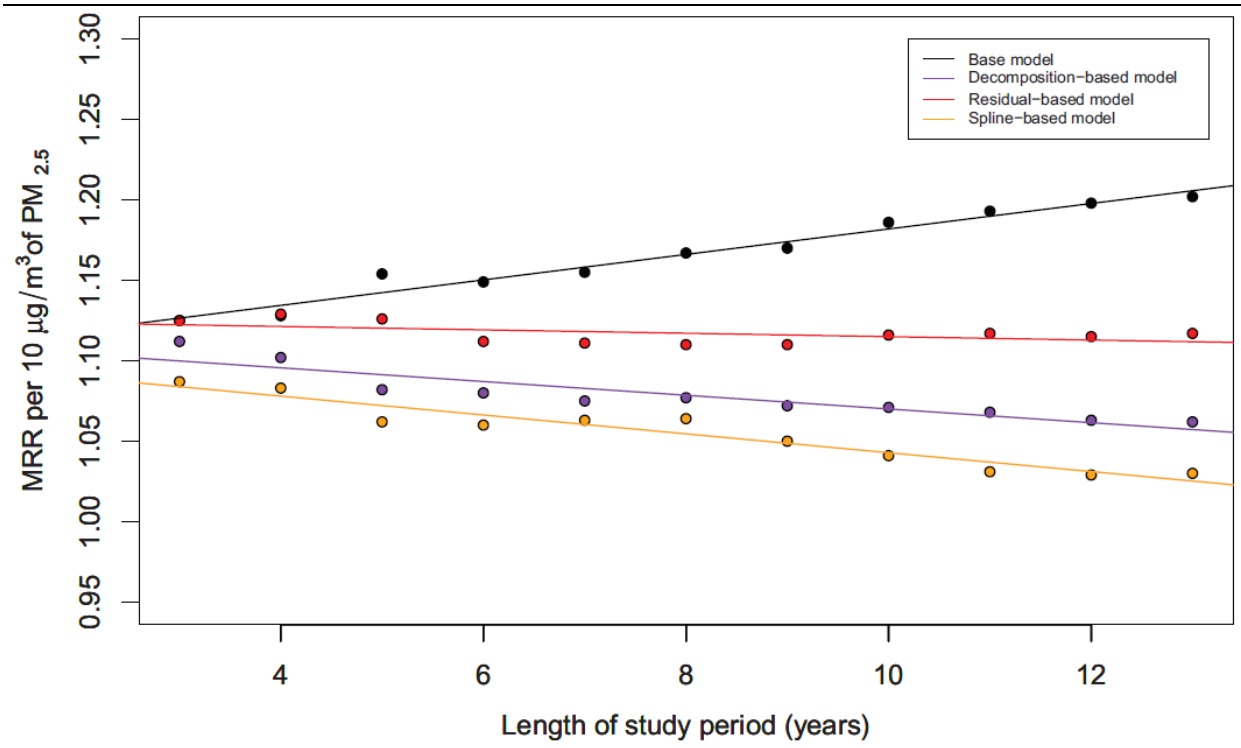
Similarly, Pun et al. (2017) completed a sensitivity analyses as part of their Medicare cohort study for the years 2000−2008 in which they decomposed $PM_{2.5}$ into "temporal" and "spatiotemporal" variation, which is analogous to "national" and "local" respectively in Greven et al. (2011). The purpose of this sensitivity analysis was to determine the presence or absence of bias due to unmeasured confounding. Pun et al. (2017) observed positive associations for the "temporal" variation model and approximately null associations for the "spatiotemporal" variation model for all causes of death except for COPD mortality. The difference in the results of these two models for most causes of death suggests the presence of unmeasured confounding, though the authors do not indicate anything about the direction or

magnitude of this bias. It is important to note that the "temporal" and "spatiotemporal" coefficients are not directly comparable to the results of other epidemiologic studies when examined individually and can only be used in comparison with one another to evaluate the potential for unmeasured confounding bias.

As a result of the studies noted above suggesting the presence of unmeasured confounders, including long-term time trends, Eum et al. (2018) focused specifically on whether temporal confounding exists in the $PM_{2.5}$-mortality relationship using the Medicare cohort from 2000 to 2012. In a base model that did not account for temporal confounding the authors used the exact methods of Greven et al. (2011) to decompose $PM_{2.5}$ into "temporal" and "spatiotemporal" components, with and without the inclusion of behavioral covariates from the Behavioral Risk Factor Surveillance System (BRFSS), to identify whether there was evidence of unmeasured confounding. Consistent with the previous studies larger associations were reported for the "temporal" compared with the "spatiotemporal" component, with results being positive for both components. As a result of the magnitude of associations between these two components being different, Eum et al. (2018) attempted to assess whether temporal confounding of the $PM_{2.5}$-mortality relationship could explain the observed difference in results. The authors developed a base model that used data for the entire 13 year period and shorter periods ranging from 3 to 12 years (e.g., 2001−2012, 2009−2012) as well as three additional models: (1) residual-base model: calculated the residuals of a linear regression of $PM_{2.5}$ on time in 4-year intervals (i.e., 2000−2004, 2005−2008, and 2009−2012), for which the residuals were then used as the exposure in the base model; (2) spline-based model: added a penalized spline with two knots per year to the base model; and (3) decomposition-based model: added the temporal component of decomposed $PM_{2.5}$ to the base model based on the approach described in Greven et al. (2011). In analyses of the base model, the authors observed that as the years of data included in the analysis increased so did the magnitude of the mortality risk ratio (MRR) (Figure 3-26). Contrary to the base model, as depicted in Figure 3-26, there was a steady decline in the MRR for both the spline-based and decomposition-based models while MRRs remained relatively stable using the residual-based model. These results provide some evidence indicating that long-term temporal trends in $PM_{2.5}$ concentrations may be one source of unmeasured confounding to consider in long-term exposure studies lasting many years, and that a residual-based approach could potentially account for those trends.

The results of Eum et al. (2018) are consistent with a confounder analysis of temporal trends conducted by Wu et al. (2020a), originally discussed in Section 3.1.2.2.1. In the main analysis, the authors controlled for temporal trends by adjusting for calendar year and also included meteorological variables to account for season (i.e., summer and winter), maximum daily temperature, and relative humidity. In Cox and Poisson models that did not adjust for calendar year, HRs increased in analyses of both the entire cohort (Cox, main analysis, HR = 1.03 [95% CI: 1.03, 1.04]; Cox, minus calendar year, HR = 1.08 [95% CI: 1.08, 1.09]) and those limited to individuals living in locations where $PM_{2.5}$ concentrations were ≤ 12 $\mu g/m^3$ for the entire study duration (main analysis, HR = 1.17 [95% CI: 1.16, 1.18]; minus calendar year, HR = 1.25 [95% CI: 1.24, 1.27]), indicating that not accounting for temporal trends may overestimate associations. In addition, in analyses that excluded meteorological variables,

HRs were relatively unchanged compared with the main analysis (Cox, HR = 1.03 [95% CI: 1.02, 1.03]), indicating they are not a source of residual confounding in long-term exposure studies.



Source: Eum et al. (2018)

Figure 3-26 Mortality risk ratios for a 10 µg/m³ increase in $PM_{2.5}$ by length of study for the base model and temporal adjusted models in Eum et al. (2018).

Although there is extensive evidence of a relationship between long-term $PM_{2.5}$ exposure and mortality provided by numerous cohort studies discussed throughout this section, potential residual confounding remains a concern as reflected in the studies discussed above. Of these studies, only Eum et al. (2018) and Wu et al. (2020a) attempted to address a specific potential source of confounding (i.e., long-term trends). Erickson et al. (2019) also examined the potential implications of unmeasured confounders on the $PM_{2.5}$-mortality relationship by using an approach that indirectly adjusts for missing covariates via partitioned regression, based on an approach developed by Shin et al. (2014). This approach controls for unmeasured potential confounders that are not available in the primary data set for an individual cohort by using data from an ancillary matching data set. Shin et al. (2014) suggested that in applying indirect adjustment it is important for the primary data set and ancillary data set to have a similar distribution of the primary exposure (i.e., $PM_{2.5}$) among subjects across demographic characteristics, and to conduct a "gold-standard" evaluation to assess the magnitude of bias correction by excluding and

indirectly adjusting for specific variables in both data sets. Erickson et al. (2019) applied both of these suggestions by using three cohorts from the MAPLE studies. Specifically, the 2001 CanCHEC, which represented the main data set, and the CCHS as the ancillary matching data set were used for validation analyses, while the assessment of the direction and magnitude of bias of this approach was conducted using the mCCHS cohort as the ancillary data set that contained information, missing in CanCHEC, on cigarettes/day, alcohol use, fruit and vegetable intake, and leisure exercise.

A multi-step process was used to conduct this analysis that consisted of the following: (1) assess the representativeness of the primary data set (i.e., CanCHEC) to the ancillary data set (CCHS) to compare absolute and proportional differences in the distribution of $PM_{2.5}$ concentrations within the two populations; (2) conduct an internal validation to assess the degree of bias in HRs when applying the indirect adjustment; and (3) conduct an external validation to assess bias of using CCHS as the ancillary data set to indirectly adjust CanCHEC. In (1), Erickson et al. (2019) applied sampling weights to the CCHS to ensure the distribution of $PM_{2.5}$ concentrations was the same across demographic and socioeconomic characteristics at baseline. For (2), the authors used a "gold-standard" that consisted of removing and indirectly adjusting for variables available within the CanCHEC cohort (i.e., education and income). The results of this adjustment were then compared with a "True Model" that adjusted for education, income, and all other individual-level covariates. To conduct the internal validation, a "Partial Model" was developed that excluded education and income. The coefficient and variance terms for education and income were derived from the "True Model" with $PM_{2.5}$ excluded. The coefficient and variance terms for education and income were used to indirectly adjust for each covariate in the "Partial Model" resulting in the "Internal (validation) Model." A comparison of the "True Model" and "Internal (validation) Model" allows for an assessment of the indirect adjustment approach. In (3), the authors used a similar approach to the internal validation for conducting the external validation using variables available in both CanCHEC and CCHS (i.e., education and income) instead of using only the CanCHEC data. Finally, after going through each of the aforementioned steps to validate the indirect adjustment approach, Erickson et al. (2019) used the data from mCCHS on cigarettes/day, alcohol use, fruit and vegetable intake, and leisure exercise to indirectly adjust for the covariates within CanCHEC. For all analyses both time-varying and static $PM_{2.5}$ concentrations were evaluated, but for comparison with the exposure assignment approach used within the MAPLE studies, the results below primarily focus on the time-varying exposure.

In the internal and external validations, which focused on the educational and income variables, in analyses of nonaccidental, cardiovascular, IHD, and lung cancer mortality, the authors reported an overall reduction (i.e., bias) in the HRs compared with the "True Model" when indirectly adjusting for the covariates. There was a 3%−5.6% bias across mortality outcomes for the "Partial Model," which did not control for either covariate, which was reduced to 1.7%−2.9% and 1.3%−2.3% in the internal and external validation analyses, respectively. The results of the validation analyses were further confirmed in the main analysis using the mCCHS cohort as the ancillary data set, where there was an approximately 1.5% increase in the HR when indirectly adjusting for missing covariates in the CanCHEC cohort.

Additionally, the results using the ancillary data set within the CanCHEC cohort for nonaccidental, cardiovascular, and IHD mortality were consistent in magnitude to those reported in mCCHS.

The methods detailed by Erickson et al. (2019) provide an approach to address the issue of unmeasured confounders, but this method is limited by the availability of an ancillary data set. In addition, the direction and magnitude of the bias is dependent upon the direction and magnitude of the correlation between air pollution and the missing covariates within the population of interest. However, the direction of the bias can vary when using this confounder adjustment approach, with an underestimation of the HR observed when using a time-varying exposure and an overestimation observed when using a static exposure when compared with the "True Model." Overall, the results of Erickson et al. (2019) indicate that the lack of data for some covariates leads to an underestimation, not an overestimation, of the $PM_{2.5}$-mortality association.

In conclusion, recent studies that further evaluate the potential implications of unmeasured confounders on the association between long-term $PM_{2.5}$ exposure and mortality indicate that bias can occur in either direction. However, across the studies evaluated, the control for unmeasured confounders as detailed in Eum et al. (2018), Wu et al. (2020a), and Erickson et al. (2019) do not result in the elimination of the association, but instead provide additional confirmation that an association between long-term $PM_{2.5}$ exposure and mortality exists when accounting for additional confounders.

3.2.2.2.7. Examination of the Concentration-Response (C-R) Relationship between Long-Term $PM_{2.5}$ Exposure and Mortality

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response (C-R) relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. The 2009 PM ISA characterized the results of an analysis by Schwartz et al. (2008) that demonstrated that the shape of the C-R curve was generally linear. A substantially larger number of studies was evaluated in the 2019 PM ISA, which provided strong evidence for a linear, no-threshold concentration-response relationship for long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality [U.S. EPA (2019); Section 11.2.4]. Although analyses of the Harvard Six Cities study (Lepeule et al., 2012) and the U.S. Medicare cohort (Di et al., 2017b; Shi et al., 2015) reported linear, no-threshold C-R relationships down to 8, 6 and 5 $\mu g/m^3$, respectively, evidence presented in the 2019 PM ISA demonstrated less certainty in the shape of the C-R curve at mean annual $PM_{2.5}$ concentrations generally below 8 $\mu g/m^3$, though some studies characterized the C-R relationship with certainty down to 4 $\mu g/m^3$ (e.g., analyses of the CanCHEC (Pinault et al., 2016)).

A number of recent studies conducted analyses that further inform the shape of the C-R relationship for the association between long-term $PM_{2.5}$ exposure and mortality and are summarized in Table 3-6. Generally, the results of these analyses continue to support a linear, no-threshold relationship

for total (nonaccidental) mortality, though there is some evidence for a sublinear (shallower slope at lower concentrations and steeper slope at higher concentrations) (Zhang et al., 2021; Pope et al., 2019) or supralinear (steeper slope at lower concentrations and shallower slope at higher concentrations) (Christidis et al., 2019; Pappin et al., 2019; Pinault et al., 2017) relationship at lower ambient $PM_{2.5}$ concentrations. Many of the recent studies that conducted C-R analyses include concentration ranges that extend below the level of the current annual $PM_{2.5}$ NAAQS of 12 $\mu g/m^3$.

Table 3-6 Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term $PM_{2.5}$ exposure and mortality.

Study Location—Cohort Table/Figure from Reference	Exposure; $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
Christidis et al. (2019) mCCHS (Figure 2)	$PM_{2.5}$ estimates at 1 km^2 over 3-yr average (3-yr/1-km model) with single-yr lag assigned to postal code of residence 5.9 (0.4-17.2)	C-R: SCHIF fits a class of flexible, but monotonically nondecreasing functions to select best fitting model Supralinear at lower concentrations (< 5 $\mu g/m^3$)
Elliott et al. (2020) Nurses' Health Study (Table 2)	24-mo average ambient $PM_{2.5}$ exposures were estimated at residential addresses using a spatiotemporal prediction model 13.7; (NR)	Exposure categories (quintiles) Monotonic (linear) relationship demonstrated by HRs remaining generally consistent and statistically significant. P for trend = 0.07
Pappin et al. (2019) CanCHEC (Figure 2)	$PM_{2.5}$ estimates at 1 km over 3-yr average (3-yr/1-km model) with single-yr lag assigned to postal code of residence 6.68−7.95 (0.37−20.0)	C-R analysis, three-step approach: (1) restricted cubic splines (RCS) with a large number of knots; (2) smooth potential erratic predictions from the large number of knots using monotonically increasing smoothing splines (MISS); and (3) fit the SCHIF to the MISS predictions Supralinear at lower concentrations (< 5 $\mu g/m^3$)

Table 3-6 (Continued): Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long term $PM_{2.5}$ exposure and mortality.

Study Location—Cohort Table/Figure from Reference	Exposure; $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
Pinault et al. (2017) CanCHEC (Figure 2; Table S4)	$PM_{2.5}$ estimates at 1 km over 3-yr average (3-yr/1-km model) with single-yr lag assigned to postal code of residence 7.37 (0.37−20.0)	C-R: SCHIF fits a class of flexible, but monotonically nondecreasing functions to select best fitting model (counterfactual is 0 $\mu g/m^3$); cutpoint analyses: 0−5, 5−10, > 10 $\mu g/m^3$
		Supralinear at lower concentrations (< 5 $\mu g/m^3$); HRs remained positive and statistically significant in the two lowest cutpoint categories with highest HRs for the 0−5 $\mu g/m^3$ category, consistent with the supralinear C-R function
Pope et al. (2019) NHIS Cohort (Figure 4)	Population-weighted annual $PM_{2.5}$ concentrations averaged for census-tract centroids. 10.7; (2.5−19.2)	C-R: Integrated model that fit a class of flexible, but monotonically nondecreasing functions to select best fitting model.
		Generally linear, though some evidence of a shallower slope at lower concentrations (< 8 $\mu g/m^3$)
Wang et al. (2020) Medicare Cohort (Figure 1; Table S4)	Daily $PM_{2.5}$ was estimated on a 6-km grid using a spatiotemporal model 10.3 (NR)	C-R: RCS model with 3 knots; Threshold: $PM_{2.5}$ < 8, < 10, < 12 $\mu g/m^3$
		C-R: Linear across distribution of exposure concentrations with no evidence of a threshold; HRs remained positive and statistically significant when only participants with exposure concentrations below 8, 10, or 12 $\mu g/m^3$ were included
Ward-Caviness et al. (2020) HF Patient Cohort (Table 2; Figure 3)	Nearest monitor (Threshold model) or Harvard's 1 km × 1 km modeled $PM_{2.5}$ surface (C-R figure); 10.3; (8−14)	Threshold model ($PM_{2.5}$ < 12 $\mu g/m^3$); C-R: limited to $PM_{2.5}$ concentration within inner 95% of distribution (8−14 $\mu g/m^3$)
		HRs remained positive and statistically significant when only participants with exposure concentrations below 12 $\mu g/m^3$ were included; linear C-R curve, with greatest certainty between 9 and 13 $\mu g/m^3$

Table 3-6 (Continued): Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long term $PM_{2.5}$ exposure and mortality.

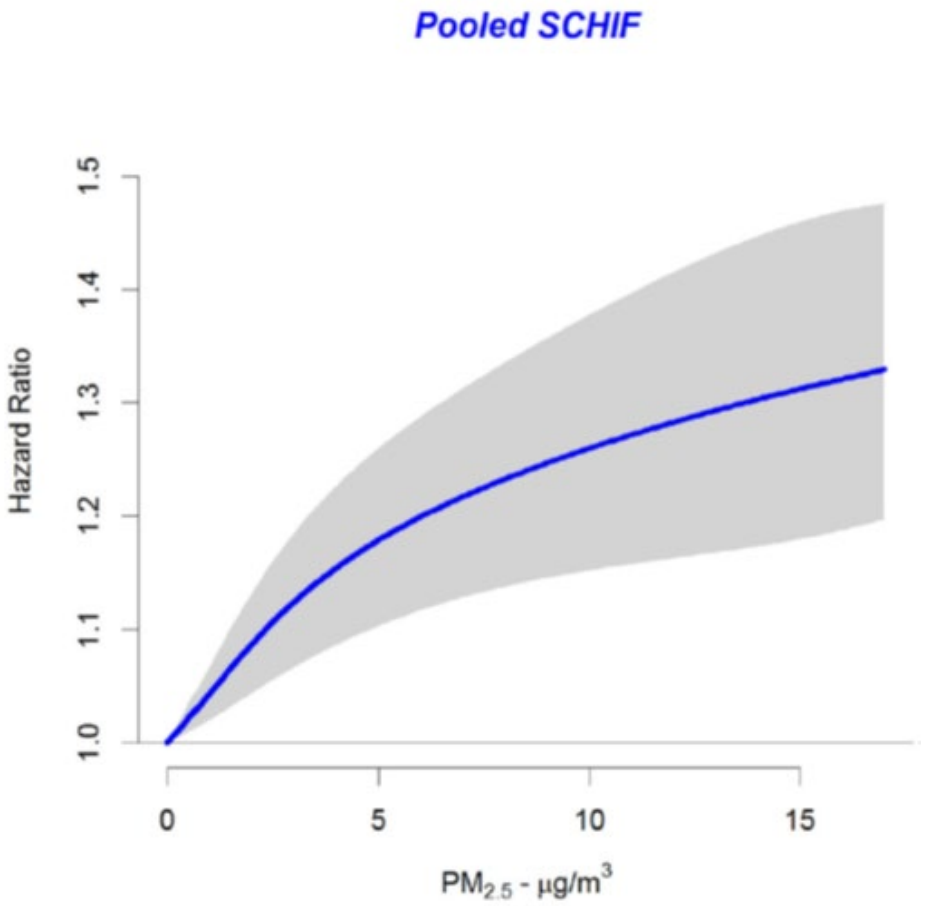
Study Location—Cohort Table/Figure from Reference	Exposure; $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
Wu et al. (2020a) Medicare Cohort (Figure 3)	An ensemble-based prediction model was used to estimate daily $PM_{2.5}$ concentrations for a 1-km^2 grid network across the contiguous U.S. 9.8 (NR)	Threshold model ($PM_{2.5}$ <12 $\mu g/m^3$)
		HRs remained positive and statistically significant when only participants with exposure concentrations below 12 $\mu g/m^3$ were included
Zhang et al. (2021) Ontario Health Study (Figure 2; Tables S3, S8)	$PM_{2.5}$ estimates at 1 km^2 over 3-yr average (5-yr/1-km model) with single-yr lag assigned to postal code of residence 7.8 (NR)	C-R: SCHIF fits a class of flexible, but monotonically nondecreasing functions to select best fitting model; threshold model ($PM_{2.5}$ < 10 and < 8.8 $\mu g/m^3$); Categorical exposure (quartiles)
		Sublinear relationship with shallower slope at lower concentrations and steeper slope at mid-range concentrations; HRs remained positive and statistically significant when only participants with exposure concentrations below 10 $\mu g/m^3$ were included. Results were positive but attenuated and no longer statistically significant below 8.8 $\mu g/m^3$; categorical exposure results demonstrate sublinear relationship, similar to C-R function with strongest association for concentrations > 8.5 $\mu g/m^3$

CanCHEC = Canadian Census Health and Environment Cohort; HF = heart failure; HR = hazard ratio; km = kilometer; mCCHS = Canadian Community Health Survey—mortality cohort; NHIS = National Health Interview Survey; NR = not reported; SCHIF = Shape Constrained Health Impact Function.

Wang et al. (2020) and Ward-Caviness et al. (2020) observed linear, no-threshold concentration-response relationships for total (nonaccidental) mortality, with confidence in the relationship down to a concentration of 5 and 9 $\mu g/m^3$, respectively. Using exposure categories (i.e., quintiles of exposure) to estimate the shape of the concentration-response relationship, Elliott et al. (2020) report evidence that supports a monotonic (linear) function.

Studies that relied on data from Canadian cohorts evaluated the shape of the concentration-response relationship using a SCHIF approach to model the function (Zhang et al., 2021; Christidis et al., 2019; Pappin et al., 2019; Pinault et al., 2017). The SCHIF approach, developed by Nasari et al. (2016), fits a class of flexible, but monotonically nondecreasing functions to select the best fitting model of the concentration-response relationship. Most of the studies that used the SCHIF approach (Christidis et al., 2019; Pappin et al., 2019; Pinault et al., 2017) identified a supralinear

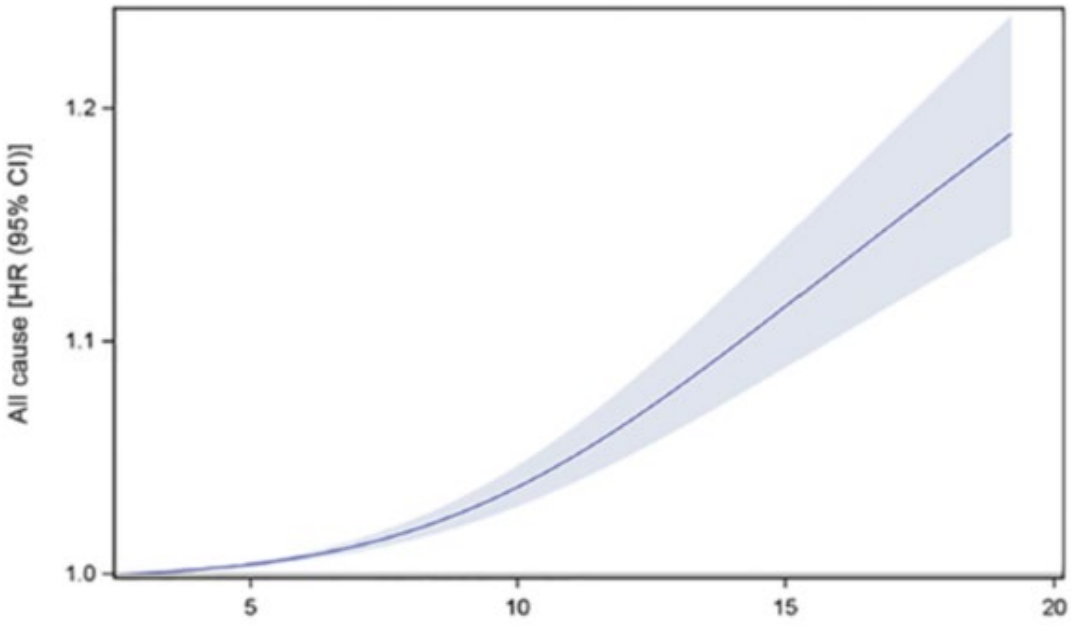
concentration-response relationship at relatively low $PM_{2.5}$ concentrations (< 5 µg/m^3) (for example, see Figure 3-27). In contrast, Zhang et al. (2021) applied the SCHIF approach to their analysis of the Ontario Health Study and identified a sublinear concentration-response relationship, with a more shallow slope observed for $PM_{2.5}$ concentrations < 8 µg/m^3. Analyses of exposure categories (i.e., quartiles) by Zhang et al. (2021) provides additional support for a sublinear concentration-response relationship. A similar sublinear relationship was reported by Pope et al. (2019) for a U.S. cohort (Figure 3-28).



Source: Pappin et al. (2019)

Note: Uncertainty bounds are displayed as gray shaded area. The uncertainty bounds are anchored at zero because the logarithm of the hazard ratio is fixed at zero and its associated standard error is also set at zero.

Figure 3-27 Shape Constrained Health Impact Function predictions by $PM_{2.5}$ concentration for the pooled CanCHEC cohort.



Source: Pope et al. (2019)
Note: Shaded area represents the 95% uncertainty bounds.

Figure 3-28 Estimated concentration-response associations between $PM_{2.5}$ and all-cause mortality with a flexible modeling approach within the NHIS cohort.

In addition to statistical analyses of the concentration-response relationship, several studies conducted threshold analyses to estimate associations between all-cause mortality and $PM_{2.5}$ concentrations below a certain concentration. Pinault et al. (2017) reported that HRs remained positive and statistically significant when examining cut-point categories of 0−5 and 5−10 μg/m^3, with the highest HRs for the 0−5 μg/m^3 category, consistent with the supralinear concentration-response function estimated by the SCHIF analysis. Wang et al. (2020) observed that HRs remained positive and statistically significant when restricting analyses to participants with exposure concentrations below 8, 10, or 12 μg/m^3. Similarly, Ward-Caviness et al. (2020) and Wu et al. (2020a) reported that HRs remained positive and statistically significant when restricting analyses to participants with exposure concentrations below 12 μg/m^3. Zhang et al. (2021) noted that HRs remained positive and statistically significant when only participants with exposure concentrations below 10 μg/m^3 were included, though the results were positive, but attenuated, and no longer statistically significant when restricting to exposure concentrations below 8.8 μg/m^3.

In addition to examining the C-R relationship between long-term $PM_{2.5}$ exposure and all-cause mortality, a limited number of studies evaluated the C-R relationship with cause-specific mortality. Wang et al. (2020) reported a linear, no-threshold C-R relationship for both cardiovascular and respiratory mortality. When the authors adjusted for ozone, the C-R relationship remained the same for

cardiovascular mortality, but the C-R relationship for respiratory mortality became supralinear below 10 μg/m^3. In threshold analyses, Wang et al. (2020) observed that HRs remained positive and statistically significant when restricting analyses to participants with exposure concentrations below 8, 10, or 12 μg/m^3. In analyses stratified by $PM_{2.5}$ concentration, Hayes et al. (2020) reported evidence of positive associations with cardiovascular mortality that increased in magnitude and decreased in precision as the range of $PM_{2.5}$ concentrations examined increased from 8−12, to 12−20, and finally to over 20 μg/m^3. When evaluating deaths due to diabetes, Lim et al. (2018) observed a linear C-R relationship, with the greatest confidence between 10 and 15 μg/m^3. Overall, recent studies that evaluated the C-R relationship for long-term $PM_{2.5}$ exposure and cause-specific mortality are consistent with those that examined all-cause mortality.

Consistent with the conclusions of the 2019 PM ISA, recent studies provide evidence that continues to support a linear, no-threshold C-R relationship for long-term $PM_{2.5}$ exposure and all-cause or cause-specific mortality across the range of exposure concentrations observed in North American cohort studies, with some studies characterizing the C-R relationship with certainty down to 4 μg/m^3 (i.e., the confidence intervals become relatively wide and in some instances the lower 95% CI crosses the null at this concentration). Generally, the evidence remains consistent in supporting a no-threshold relationship, and in supporting a linear relationship for $PM_{2.5}$ concentrations > 8 μg/m^3. However, uncertainties remain about the shape of the C-R curve at $PM_{2.5}$ concentrations < 8 μg/m^3, with some recent studies providing evidence for either a sublinear, linear, or supralinear relationship at these lower concentrations.

3.2.2.3. Recent Epidemiologic Studies Examining the $PM_{2.5}$-Mortality Relationship through Accountability Analyses and Alternative Methods for Confounder Control

Within the 2019 PM ISA, a few studies were evaluated that conducted analyses that further informed the relationship between long-term $PM_{2.5}$ exposure and mortality through the use of alternative methods for confounder control (2019 PM ISA, Section 11.2.2.4). These initial studies provided additional support for a causal relationship between long-term $PM_{2.5}$ exposure and mortality. Since the literature cutoff date of the 2019 PM ISA, additional epidemiologic studies have been identified consisting of accountability analyses as well as studies that implemented alternative methods for confounder control that have the ability to reduce uncertainties related to confounding bias in the examination of the relationship between long-term $PM_{2.5}$ exposure and mortality (Table A-8). Study-specific details of the methods implemented in these recent studies can be found in Table 3-7.

Table 3-7 Description of methods from epidemiologic studies using accountability analyses or alternative methods for confounder control to examine long-term exposure to $PM_{2.5}$ and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wei et al. (2020) Massachusetts Medicare 2000−2012	Generalized Propensity Score (GPS): estimates the conditional probability of an individual being exposed to the observed concentration level, accounting for all measured potential confounders In the design stage, an ordinary least squares (OLS) model regressed predicted $PM_{2.5}$ concentrations against a linear combination of covariates, including the other pollutants (Table A-8). In the analysis stage, an ordinary least squares regression was used to fit a linear probability model relating mortality with the predicted $PM_{2.5}$ concentration and the estimated GPS.	35.4 (95% CI: 33.4, 37.6) excess deaths per 10 million person-days for each 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wei et al. (2021b) Massachusetts Medicare 2000−2012	Three GPS approaches were used: Linear Probability Model: In the design stage, GPS was constructed by fitting a linear regression of predicted $PM_{2.5}$ concentration against a column vector of covariates including copollutants (Table A-8) In the analysis stage, a linear probability model was fitted with the outcome of death, against the predicted $PM_{2.5}$ concentration and the GPS. Weighted Least Squares: In the design stage, the person-days that had the same sex, race, age, Medicaid eligibility, ZIP code of residence, and date were aggregated as a single record and assigned the numbers of person-days for that record as a weight. The GPS was constructed by fitting a weighted linear regression of predicted $PM_{2.5}$ concentrations against all the covariates from this aggregated data set, with continuous covariates modeled with cubic polynomials. The average outcome for each aggregated person-day group was calculated and assigned to the person-day in the aggregated data set. A weighted linear regression was fitted for the averaged outcome against the predicted $PM_{2.5}$ concentration and the estimated GPS. MoonRF: In the design stage, the number of person-days aggregated for each record was used as the frequency weight and sampled 62,000 person-days without replacement. With this sample, trees were built for $PM_{2.5}$ to make predictions of the exposure for each person-day, which was repeated 100 times. The final predicted $PM_{2.5}$ concentration for each person-day was obtained by averaging the predictions of the 100 trees. The GPS was constructed by using the averaged predictions of the 100 trees as the predicted $PM_{2.5}$ concentrations and covariates for each person-day in the aggregated data set. In the analysis stage, weighted regression of the averaged outcome was fitted against the predicted $PM_{2.5}$ concentration and the estimated GPS to obtain the effect estimate.	Linear Probability Model and Weighted Least Squares: 1053 (95% CI: 984, 1,122) annual early deaths for a 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations MoonRF: 1,058 (95% CI: 988, 1,127) annual early deaths for a 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wu et al. (2020a) U.S. Medicare 2000−2016	Three GPS approaches were used that required GPS estimation as the first step. The conditional density of predicted annual average $PM_{2.5}$ concentration on the 14 ZIP code or county-level covariates, with dummy variables for region and calendar year, were modeled using gradient boosting machine with normal residuals. GPS matching: a matched pseudo-population was constructed. Once the covariate balance was achieved, a univariate Poisson regression model was fit to regress the death counts, with an offset of person-time term, on $PM_{2.5}$ exposure, stratifying by the individual-level covariates and the same follow-up year. GPS weighting: a weighted pseudo-population was constructed. Once the covariate balance of the weighted pseudo-population was achieved, a weighted univariate Poisson regression was fitted, regressing the death count, with an offset term of person-time, on $PM_{2.5}$ exposure incorporating the assigned weights and stratifying by the individual-level covariates and the same follow-up year. GPS adjustment: the conditional expectation of the death counts given the exposure and estimated GPS was modeled as a stratified Poisson regression with flexible formulation of bivariate variables, with the corresponding offset term of person-time. A univariate linear regression regressed the counterfactual mean hazard rates for each $PM_{2.5}$ concentration, stratified by the individual-level covariates and the same follow-up year.	For a 10 μg/m^3 increase in annual $PM_{2.5}$ concentrations GPS matching: HR = 1.068 (95% CI: 1.054, 1.083) GPS weighting: HR = 1.076 (95% CI: 1.065, 1.088) GPS adjustment: HR = 1.072 (95% CI: 1.061, 1.082)

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wu et al. (2019) New England (Vermont, New Hampshire, Connecticut, Massachusetts, Rhode Island, and Maine) Medicare 2000−2012	GPS: Regression calibration-GPS approach. The RC step of this approach adjusts for measurement error in a continuous exposure. The adjustment relies on two assumptions: transportability and nondifferential measurement error. Transportability assumes that the relationship between continuous exposure (X), the error-prone continuous exposure (W), and the error-free covariates associated with the measurement error (D) would be the same in the validation study where X is observed and the main study in which it is not. The nondifferential measurement error assumption is equivalent to the surrogacy assumption and means the conditional distribution of outcome given X, W, D depends only on X and D. The relationship between true exposures X and error-prone exposures W, conditional on other covariates D, was modeled using a regression model, specified by mean and variance. More specifically in the RC stage, Wu et al. (2019) obtained the $PM_{2.5}$ exposure at each grid cell in New England and then fit the regression model to include 14 meteorological variables as predictors. In the second step, the GPS is implemented. The authors define the GPS as the conditional probability of receiving each category of the exposure given other pre-exposed covariates (C) (Table A-8). There are two assumptions for the GPS implementation: overlap/positivity and weak unconfoundedness. The overlap/positivity assumption guarantees that for all possible values of C, the average treatment effect can be estimated for each category of the exposure without relying on extrapolation (Wu et al., 2019). Weak unconfoundedness assumes that the assignment mechanism is weakly unconfounded (Wu et al., 2019). Three GPS approaches were considered: Subclassification GPS: individuals were classified into groups based on the GPS elements, with each group containing the observations having similar values of the corresponding estimated GPS elements. Inverse Probability of Treatment Weighting GPS: weights each individual by the inverse of their GPS. GPS matching: involves matching individuals who receive one category of exposure to individuals who received another category of exposure based on the estimated GPS. For each of the three GPS approaches, Wu et al. (2019) used multinomial logistic regression with 16 area-level covariates as confounders to construct the GPS. After constructing GPS for each approach, a stratified log-linear outcome model with a person-time offset estimated the IRR of the effect of long-term $PM_{2.5}$ exposure on all-cause mortality. The stratification variables were the individual-level covariates (age, as 5-yr age categories; race; sex; and Medicare eligibility).	Subclassification GPS: IRR = 1.03 (95% CI: 1.01, 1.05) IPTW GPS: IRR = 1.02 (95% CI: 1.01, 1.04) Matching GPS: IRR = 1.03 (95% CI: 1.01, 1.05)

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Schwartz et al. (2018b) Northeastern and mid-Atlantic States (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Delaware, Pennsylvania, Maryland, Washington, DC, Virginia, and West Virginia) Medicare 2000−2013	Inverse Probability Weights (IPW): A GPS was fitted with a linear regression of continuous predicted $PM_{2.5}$ concentrations against the measured covariates. The IPW is constructed as the marginal probability density of exposure as the numerator and the probability density of each observation receiving the predicted $PM_{2.5}$ concentration in a year given the covariates in that year as the denominator. Separate logistic regression models were fitted to estimate the risk of dying at that age given the annual average $PM_{2.5}$ concentration at each subject's residential ZIP code and age-specific IPW weights to allow the influence of potential confounders to change with age.	The estimated mean age at death for a population with an annual average $PM_{2.5}$ concentration of 12 μg/m^3 was 0.89 (95% CI: 0.88, 0.91) less years
Awad et al. (2019) U.S. Medicare 2000−2012	IPW: Constructed from a GPS model in which the weights were the inverse conditional probabilities of the continuous exposure given the covariates (Table A-8). The weights were then stabilized using the marginal probability of exposure as the numerator and the denominator was the conditional density function of change in exposure where the vector of covariates evaluated at observed covariate values for each participant. The Cox proportional model estimated the effect of change in annual $PM_{2.5}$ concentrations on the risk of all-cause mortality, stratified by ZIP code before moving, with the IPW to account for confounding after moving and follow-up time.	For a 10 μg/m^3 increase in annual $PM_{2.5}$ concentrations: HR = 1.21 (95% CI = 1.20, 1.22) among White individuals HR = 1.12 (95% CI = 1.08, 1.15) among Black individuals
Higbee et al. (2020) U.S. National Center for Health Statistics 1986−2015	IPW: Constructed by taking the inverse of the conditional probability of the exposure to a given value from a continuous scale of $PM_{2.5}$ concentrations and stabilized by multiplying the weights by the marginal probability of the $PM_{2.5}$ concentration. The Cox proportional hazard models estimated the hazard ratios associated with a 10 μg/m^3 increase in $PM_{2.5}$ concentration. Each of the covariates (Table A-8) were included as confounders while constructing the IPW for weighting the estimated model.	For a 10 μg/m^3 increase in annual $PM_{2.5}$ concentrations: All-cause mortality HR = 1.12 (95% CI: 1.08, 1.15) Cardiopulmonary mortality HR = 1.23 (95% CI: 1.17, 1.29)

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wei et al. (2021a) U.S. Medicare 2000−2016	IPW: Proposed a decile binning, which divided $PM_{2.5}$ concentrations by deciles and predicted the inverse probability of being assigned to the observed group for each observation, adjusting for copollutants (ozone and NO_2), personal characteristics, meteorological, socioeconomic, behavioral, and medical access variables, and long-term time trend (Table A-8). The IPW was constructed in two stages—a design stage and an analysis stage. In the design stage, a randomized pseudo-population was constructed by weighting the observed population by the inverse probability of the exposure given all the measured confounders. In the analysis stage, the treatment effect was estimated among the constructed pseudo-population. The IPW for each $PM_{2.5}$ decile was stabilized by using the probability of any observed exposure being within the decile as the numerator. The denominator was the inverse logistic link function of a gradient boosting machine model with logistic loss function for predicting the probability of the observed binned exposure given the set of confounders, weighted by the number of person-years aggregated in the stratum. A log-linear regression model was then fitted to estimate the number of deaths and $PM_{2.5}$ decile category, weighted by the stabilized inverse probabilities.	2nd decile group (mean annual $PM_{2.5}$ concentration of 6.60 μg/m^3): RR = 1.02 (95% CI: 1.02, 1.03) 10th decile group (mean annual $PM_{2.5}$ concentration of 15.47 μg/m^3): RR = 1.21 (95% CI: 1.20, 1.21)
Corrigan et al. (2018) U.S. National Center for Health Statistics 2000−2010	Difference-in-Difference (DID): A linear regression model was used to estimate the association between the change in cardiovascular mortality rate and the change in $PM_{2.5}$ across U.S. counties, adjusted for potential confounders.	1.10 (95% CI: 0.37, 1.82) fewer cardiovascular deaths per year per 100,000 people for each 1 μg/m^3 decrease in annual $PM_{2.5}$ concentrations
Sanders et al. (2020) U.S. Medicare 2000−2013	DID: Examined if policy actions reduced $PM_{2.5}$ concentrations and mortality in treatment counties relative to control counties. DID flexibly captures the effects of treatment over time by using separate dummy variables for each year. With the event study design in the DID models, nearest neighbor matching based on propensity score was used as an estimate of probability of attainment status. The independent variables used to estimate the propensity score were the mortality counts and the population for each year from 2000 to 2005 and were sampled without replacement. An instrumental variable analysis was applied by dividing the mortality coefficient by the $PM_{2.5}$ coefficient to obtain the estimate of the effect of $PM_{2.5}$ on mortality, which is equivalent to a Wald instrument variable estimator, where the standard errors of the estimates were calculated.	After the regulatory changes in 2005, $PM_{2.5}$ concentrations decreased 1.59 μg/m^3 (95% CI: 1.39, 1.80) and mortality rates among those 65 years and older also decreased by 0.93% (95% CI: 0.10, 1.77).

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Henneman et al. (2019) U.S. Medicare 2005−2012	DID: Estimated changes in each morality associated with changes in annual $PM_{2.5}$ concentrations. The differences between 2012 and 2005 mortality rates (per 10,000 beneficiaries) were estimated from a linear model that included the difference in $PM_{2.5}$ concentrations from 2012 and 2005, controlled for changes in census and meteorological variables.	Reduction in all-cause mortality of −0.38 (95% CI: −2.76, 2.01) per 10,000 person-days for each 1 $\mu g/m^3$ decrease in annual $PM_{2.5}$ concentrations during the time period
Fan and Wang (2020) U.S. Medicare 1999−2013	DID: Treatment counties based on the location of the power plant and wind direction. For each treatment county, covariate matching was used, with matching based on county characteristics to select controls. After constructing a set of treatment and control counties, the effect of annual $PM_{2.5}$ on monthly age-adjusted mortality was estimated using an instrument variable (IV) approach to compare the before and after the retirement of coal plants between the treated and control counties. The instrumental variables were weather variables and time-varying socioeconomic variables. DID approach was also used to estimate the effect of coal plant retirements on $PM_{2.5}$ and mortality among populations older than 65.	IV: a 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations led to 7.17 fewer deaths per 100,000 people per month, or a 1.7% lower monthly mortality rate among people older than 65 yr of age DID: power plant retirement decreased both monthly $PM_{2.5}$ concentrations by 2.1 $\mu g/m^3$, and the monthly age-adjusted mortality by approximately 15 people per 100,000 people (or 3.6%) in treated counties, relative to control counties

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Yitshak-Sade et al. (2019b) Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Delaware, Pennsylvania, Maryland, Washington, DC, Virginia, and West Virginia Medicare 2000−2013	DID: Used a Poisson survival analysis using the Anderson-Gill formulation with time-varying covariates. The data were randomly split into subsets due to computational limitations. The effect estimates were then pooled using a fixed-effect meta-analysis.	4.04% (95% CI: 3.49, 4.59) increase in mortality rates for an IQR (3 μg/m^3) increase in annual $PM_{2.5}$ concentrations
Schwartz et al. (2021) U.S. Medicare 2000−2016	DID: Applied the standard approach for continuous predictors. The mortality rate in a ZIP code given the demographic group (age, sex, race, Medicaid coverage) was associated with annual $PM_{2.5}$ concentrations, given the time-invariant or slowly changing confounders in a ZIP code, and the time-varying confounders that are common across ZIP codes. The time-invariant confounders were controlled by fitting individual intercepts for each ZIP code, while the time-varying confounders were removed by fitting nonlinear time trend using a natural spine function of year with three degrees of freedom. An additive model was used to estimate the additive effect of $PM_{2.5}$ on the probability of dying.	Probability of dying in each year increased by 3.85×10^{-4} (95% CI 1.95×10^{-4}, 5.76×10^{-4}) for each 1 μg/m^3 increase in annual $PM_{2.5}$ concentrations

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied alternative methods for confounder control in examining long-term $PM_{2.5}$ exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Peterson et al. (2020) U.S. National Center for Health Statistics 1990−2010	Accountability: To determine the portion of the temporal change in cardiovascular mortality attributable to the temporal change in the annual $PM_{2.5}$ concentrations, linear models were fitted, adjusted for time variant covariates (age-standardized annual COPD mortality rates) and time-invariant covariates (median household income, percent of non-White population, and population). The authors first estimated the overall national temporal trend in annual cardiovascular mortality, which accounted for the temporal changes in the cardiovascular mortality adjusted for the time variant and time-invariant covariates, but not adjusted by $PM_{2.5}$. Second, the national temporal trend in the annual $PM_{2.5}$ concentrations was estimated, while adjusting for the time variant and time-invariant covariates. Then, the association between $PM_{2.5}$ concentrations and cardiovascular mortality was estimated, assuming that this association was consistent nationally after adjusting for the covariates set and for other time-varying changes in cardiovascular morality unrelated to $PM_{2.5}$ concentrations. The $PM_{2.5}$-related cardiovascular mortality association was calculated as a product of the risk to cardiovascular mortality for each unit change in $PM_{2.5}$ concentration. A county-level random intercept term was included in the models to account for variation due to repeated measures from the same county and difference in baseline cardiovascular morality rates.	3.88 (95% CI: 3.56, 4.21) fewer deaths per 100,000 persons for each 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations
Zigler et al. (2018) Eastern U.S. Medicare 2000-2012	Accountability and Propensity Score: To examine whether attainment status for the 1997 NAAQS led to an improvement in $PM_{2.5}$ concentrations and subsequently health, the authors employed propensity scores, within a spatial hierarchical regression model to examine whether designation of nonattainment, for either the annual standard of 15 $\mu g/m^3$ or the daily standard of 65 $\mu g/m^3$, made in 2005 for the 1997 PM NAAQS led to a corresponding reduction in ambient $PM_{2.5}$ concentrations and all-cause mortality. In the first step, propensity scores were used to adjust for confounders by grouping attainment and nonattainment locations based on similarities of baseline characteristics, including air pollution monitoring data, population demographics, meteorological data, baseline Medicare characteristics, and $PM_{2.5}$ and mortality. In the second step, a spatial hierarchical regression model was used to predict the potential ambient $PM_{2.5}$ concentration in 2010–2012 that would have occurred in nonattainment areas if the designations had never occurred. The model used in this step specifies linear adjustment terms for propensity score group indicators and several specific covariates, each including an interaction with the indicator of attainment status, while including a spatial random effect that accounts for the similarity of ambient air quality at nearby locations. For the analysis, the spatial hierarchical model is estimated jointly with a log-linear model for all-cause mortality, with the same confounding adjustment for propensity score group and additional covariates. In addition to estimating the effect estimates for the overall average effects, a principal stratification approach was used to estimate “associative effects” and “dissociative effects.”	Overall average effect: a reduction in the all-cause mortality rate by 1.25 (95% CI: -2.63, 0.11) deaths per 1000 beneficiaries Average associative effects: a reduction in the all-cause mortality rate of 3.16 (95% CI: -5.19, -1.21) deaths per 1000 beneficiaries Average disassociative effects: Quantitative results not presented

DID = difference-in-difference; GPS = generalized propensity score; HR = hazard ratio; IPTW = inverse probability treatment weighting; IPW = inverse probability weighting; IRR = incidence rate ratio; IV = instrument variable; moonRF = m-out-of-n random forests.

Wei et al. (2020), Wei et al. (2021b), and Wu et al. (2020a) implemented different GPS modeling approaches to assess associations between long-term $PM_{2.5}$ concentrations and mortality among Medicare beneficiaries. GPS statistical approaches were developed as an extension of propensity score methods for continuous exposures and represent the relative likelihood of being exposed to the observed pollutant concentration and all measured confounders (Wei et al., 2020). The GPS approach estimates the conditional probability of an individual being exposed to the observed pollutant concentration, accounting for all measured potential confounders (Table A-8).

Wei et al. (2020) evaluated the association of long-term $PM_{2.5}$ concentrations and all-cause mortality among Medicare beneficiaries residing in Massachusetts during 2000−2012 using a GPS approach. The authors define long-term exposure as a 1-year moving average of the $PM_{2.5}$ concentration. Wei et al. (2020) reported that each 1 $\mu g/m^3$ increase in long-term $PM_{2.5}$ concentrations was associated with 35.4 (95% CI: 33.4, 37.6) excess deaths per 10 million person-days. When the analysis was restricted to different low-level concentrations, the number of excess deaths associated with a 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations increased to 35.5 per 10 million person-days (95% CI: 33.4, 37.7) when restricting to $PM_{2.5}$ concentrations $\leq$ 14 $\mu g/m^3$ and to 60.7 per 10 million person-days (95% CI: 47.9, 73.9) when restricting to $PM_{2.5}$ concentrations $\leq$ 7 $\mu g/m^3$.

Whereas Wei et al. (2020) focused on a single GPS approach, Wei et al. (2021b) presented three GPS-based approaches in examining long-term $PM_{2.5}$ concentrations and mortality including a linear probability model, weighted least squares, and m-out-of-n random forests (moonRF), for assessing the effect of long-term $PM_{2.5}$ exposures on mortality rates among Medicare beneficiaries residing in Massachusetts between 2000 and 2012. The moonRF method is based on the random forest method, which is a non-parametric machine learning approach of classification for possible nonlinear relationships and interactions through building individual decision trees through resampling. To reduce the computational burden of the linear probability model GPS approach, weighted least squares and moonRF GPS approaches were proposed as alternatives. Wei et al. (2021b) showed that the linear probability model and the weighted least squares model produced nearly identical results. The annual number of early deaths associated with 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations was 1,053 (95% CI: 984, 1,122) using linear probability model and weighted least squares approaches and was 1,058 (95% CI: 988, 1,127) using moonRF. When restricting the analysis to annual $PM_{2.5}$ concentrations below < 12 $\mu g/m^3$, 1,203 (95% CI: 1,126, 1,280) annual early deaths were associated with a 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations when using both the linear probability model and weighted least squares approaches with a slightly higher number of early deaths with the moonRF approach (1,214 [95% CI: 1,137, 1,292]).

Similar to Wei et al. (2021b), Wu et al. (2020a) also assessed the association between long-term $PM_{2.5}$ concentrations and mortality among Medicare beneficiaries between 2000 and 2016 using multiple GPS approaches including: (1) matching by GPS; (2) weighting by GPS; and (3) adjustment by GPS, meaning the GPS was included as a covariate in the health outcome model. Wu et al. (2020a) reported that the three GPS approaches yielded similar results with a 10 $\mu g/m^3$ increase in annual $PM_{2.5}$

concentrations corresponding to a reduction in mortality rate ranging from 6% to 7% (matching by GPS: HR = 1.07 [95% CI: 1.05, 1.08]; weighting by GPS: HR = 1.08 [95% CI: 1.07, 1.09]; and adjustment by GPS: HR = 1.07 (95% CI: 1.06, 1.08]). The estimated hazard ratios were even larger when restricting the cohort of Medicare enrollees to only those that lived in locations where annual $PM_{2.5}$ concentrations were lower than 12 $\mu g/m^3$: matching by GPS: HR = 1.26 (95% CI: 1.23, 1.29); weighting by GPS: HR = 1.27 (95% CI: 1.24, 1.30); and adjustment by GPS: HR = 1.23 (95% CI: 1.18, 1.28).

Whereas Wei et al. (2020), Wei et al. (2021b), and Wu et al. (2020a) used different GPS approaches to examine the association between long-term exposure to $PM_{2.5}$ and mortality, Wu et al. (2019) developed a new two-stage GPS approach consisting of a regression calibration-GPS (RC-GPS) based adjustment for continuous error-prone exposure combined with GPS to adjust for potential confounding. The new proposed method provides a correction for measurement error in the exposure for both the design and analysis stages with GPS, allows the GPS implementation to be paired with any generalized linear model, and shows how standardized bias can be used to assess fit in the context of GPS analysis for categorical exposures. The RC approach was applied in conjunction with three GPS approaches: subclassification, inverse probability of treatment weighting (IPTW), and matching. After constructing GPS for each approach, a stratified log-linear outcome model with a person-time offset estimated the incidence rate ratio (IRR) of the effect of long-term exposure to $PM_{2.5}$ on all-cause mortality. When applying the RC-GPS based adjustment, the authors reported IRRs that were consistent across the three GPS approaches: RC-GPS subclassification approach: IRR was 1.03 (95% CI: 1.01, 1.05); 1.02 (95% CI: 1.01, 1.04) for the IPTW GPS approach, and 1.03 (95% CI: 1.01, 1.05) for the GPS matching approach, when comparing moderate levels of $PM_{2.5}$ concentrations ($8 < PM_{2.5} \leq 10$ $\mu g/m^3$) to low concentration ($PM_{2.5} \leq 8$ $\mu g/m^3$). When comparing high levels of $PM_{2.5}$ concentrations ($PM_{2.5} >$ 10 $\mu g/m^3$) to low concentrations ($PM_{2.5} \leq 8$ $\mu g/m^3$), the IRRs were 1.04 (95% CI: 1.00, 1.07) for subclassification, 1.03 (95% CI: 1.01, 1.06) for IPTW, and 1.04 (95% CI: 1.02, 1.06) for matching.

In addition to GPS, other alternative methods for confounder control have been employed in epidemiologic studies including inverse probability weighting (IPW). IPW generates weights by taking the inverse of the conditional probability of the exposure of a pollutant concentration. The weight is then stabilized by multiplying the weights by the marginal probability of the level of exposure, meaning that by applying weights the exposure is no longer associated with the confounders (Higbee et al., 2020; Awad et al., 2019).

Schwartz et al. (2018b) and Awad et al. (2019) both applied IPW methods to estimate the effect of long-term exposure to $PM_{2.5}$ on mortality among Medicare beneficiaries, while controlling for similar confounders (Table A-8). Schwartz et al. (2018b) estimated the marginal effect of annual $PM_{2.5}$ concentrations on the distribution of life expectancy among Medicare beneficiaries residing in the northeastern and mid-Atlantic region of the U.S. between 2000 and 2013 by applying an IPW survival model. The estimated mean age at death for a population with an annual average $PM_{2.5}$ concentration of 12 $\mu g/m^3$ was 0.89 (95% CI: 0.88, 0.91) years less than estimated for a counterfactual $PM_{2.5}$

concentrations of 7.5 μg/m^3. Schwartz et al. (2018b) estimated that 23.5% of the Medicare population would die before 76 years of age if they were exposed to an annual $PM_{2.5}$ concentration of 12 μg/m^3 compared with 20.1% if the Medicare population was exposed to an annual average $PM_{2.5}$ concentration of 7.5 μg/m^3. Furthermore, the authors estimated that 40.8% of Medicare recipients would live past 85 years of age if exposed to an annual $PM_{2.5}$ concentration of 12 μg/m^3 $PM_{2.5}$ compared with 44.5% at 7.5 μg/m^3.

Awad et al. (2019) estimated the effect of a change in annual $PM_{2.5}$ concentrations due to moving on the risk of mortality among Medicare beneficiaries from 2000 to 2012 in the U.S. from Cox proportional hazards using an IPW approach to control for potential confounding (Table A-8). The Cox proportional model estimated the effect of change in $PM_{2.5}$ concentrations on the risk of all-cause mortality, stratified by ZIP code before moving, with the IPW to account for confounding after moving and follow-up time. Awad et al. (2019) estimated a HR of 1.21 (95% CI: 1.20, 1.22) among White individuals and 1.12 (95% CI: 1.08, 1.15) among Black individuals for a 10 μg/m^3 increase in annual $PM_{2.5}$ concentrations for all-cause mortality. When restricting the analysis to movers with $PM_{2.5}$ concentration ≤ 12 μg/m^3, the hazard ratio was 1.25 (95% CI: 1.24, 1.27) for White individuals and 1.08 (95% CI: 1.01, 1.14) for Black individuals for all-cause mortality.

Wei et al. (2021a) used an IPW approach to emulate a dose-response between $PM_{2.5}$ and all-cause mortality from Medicare beneficiaries between 2000 and 2016. This newer IPW approach used decile binning, which divided $PM_{2.5}$ concentrations into 10 equally sized deciles and predicted the inverse probability of being assigned to the observed group for each observation, adjusting for copollutants (i.e., ozone and NO_2) and other covariates (Table A-8). The lowest decile group is treated as the reference with effects estimated for the other decile groups compared with the reference. The RR of all-cause mortality associated with long-term exposure to $PM_{2.5}$ ranged from 1.02 (95% CI: 1.02, 1.03) at 6.60 μg/m^3 (2nd decile group) to 1.21 (95% CI: 1.20, 1.21) at 15.47 μg/m^3 (10th decile group). Assuming that the IPW models were correctly specified with the adjustment of copollutants and confounders, the dose-response curves demonstrated that in general, higher concentrations of $PM_{2.5}$ are associated with a greater risk of all-cause mortality (Wei et al., 2021a). While the previous studies all used the IPW approach in analyses of Medicare beneficiaries, Higbee et al. (2020) examined the association between long-term exposure to $PM_{2.5}$ and all-cause and cardiopulmonary mortality from the National Health Interview Survey from 1986 to 2015. Within this study the authors applied a series of Cox proportional hazards models, adjusted using IPW. The hazard ratio for all-cause mortality was 1.12 (95% CI: 1.08, 1.15) per 10 μg/m^3 increase in $PM_{2.5}$ concentration and for cardiopulmonary mortality, it was 1.23 (95% CI: 1.17, 1.29) per 10 μg/m^3 increase in $PM_{2.5}$ concentration.

In addition to GPS and IPW, additional epidemiologic studies used a difference-in-difference (DID) approach to control for unmeasured confounders. In this method, the mean exposure is calculated for exposed and non-exposed groups between two time periods, such as pre- and post-intervention (Schwartz et al., 2021; Yitshak-Sade et al., 2019b). The predictors of the outcome, such as socioeconomic

status, education, and smoking status, are the same in each group in both time periods, therefore, theoretically the difference between outcomes in the two time periods in the exposed group cannot be confounded by those predictors (Schwartz et al., 2021).

To account for changes in $PM_{2.5}$ concentrations due to policy or the implementation of an intervention, Corrigan et al. (2018), Sanders et al. (2020), Henneman et al. (2019), and Fan and Wang (2020) used DID methods to assess whether there was evidence of changes in associations with mortality due to changes in annual $PM_{2.5}$ concentrations. Corrigan et al. (2018) examined whether there was a change in the cardiovascular mortality rate before (2000−2004) and after (2005−2010) implementation of the first annual $PM_{2.5}$ NAAQS in 2005 based on mortality data from the National Center for Health Statistics (Table A-8). The authors reported 1.10 (95% CI: 0.37, 1.82) fewer cardiovascular deaths per year per 100,000 people for each 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations. When comparing whether counties achieved NAAQS compliance (attainment) or not (non-attainment), there were 1.96 (95% CI: 0.77, 3.15) fewer cardiovascular deaths for each 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations between the two periods for attainment counties, whereas for non-attainment counties, there were 0.59 (95% CI: −0.54, 1.71) fewer cardiovascular deaths between the two periods. Sanders et al. (2020) conducted a similar study as Corrigan et al. (2018) by attempting to isolate the relationship between regulation of and reductions in $PM_{2.5}$ concentrations and associated mortality from Medicare beneficiaries between 2000 and 2013 (Table A-8). After the release of the first annual $PM_{2.5}$ NAAQS implementation in 2005, annual $PM_{2.5}$ concentrations decreased by 1.59 $\mu g/m^3$ (95% CI: 1.39, 1.80), which corresponded to a reduction in mortality rates among individuals 65 years and older of 0.93% (95% CI: 0.10, 1.77).

While Corrigan et al. (2018) and Sanders et al. (2020) used DID to examine the relationship between changes in annual $PM_{2.5}$ concentrations and mortality due to the $PM_{2.5}$ NAAQS, Henneman et al. (2019) and Fan and Wang (2020), applied DID methods to explore the changes in $PM_{2.5}$ concentrations following retirement of coal-fueled power plants and mortality. Henneman et al. (2019) conducted an accountability analysis of emissions reductions from coal-fueled power plants in the U.S. between 2005 and 2012 and whether there were corresponding reductions in all-cause mortality using Medicare data (Table A-8). The authors reported a reduction in all-cause mortality of −0.38 (95% CI: −2.76, 2.01) deaths per 10,000 person-days for each 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations during the time period. Fan and Wang (2020) also used Medicare data from 1999 to 2013 to estimate the relationship between mortality and low $PM_{2.5}$ concentrations in response to the retirement of five large coal plants by applying both instrumental variable and DID approaches (Table A-8). The instrumental variable represents variations in the exposure (e.g., $PM_{2.5}$) that are randomized with respect to both measured and unmeasured confounders and can therefore provide an estimate of the effect of the exposure (Schwartz et al., 2018a). The authors reported that a 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations corresponded to 7.17 fewer deaths per 100,000 people per month, or a 1.7% lower monthly mortality rate among people older than 65 years of age when applying an instrument variable approach. The power plant retirement decreased both monthly $PM_{2.5}$ concentrations by 2.1 $\mu g/m^3$, and the monthly age-adjusted mortality by

approximately 15 people per 100,000 people (or 3.6%) in treated counties, relative to control counties, based on the DID approach.

Yitshak-Sade et al. (2019b) and Schwartz et al. (2021) also used DID approaches to evaluate the changes in long-term exposure to $PM_{2.5}$ over time on mortality rates among Medicare beneficiaries. Yitshak-Sade et al. (2019b) applied a DID approach to the Medicare population of the northeastern and mid-Atlantic states to incorporate individual covariates and assess the effect of annual $PM_{2.5}$ concentrations on all-cause mortality rates from 2000 to 2013 (Table A-8). For an IQR (3 $\mu g/m^3$) increase in annual $PM_{2.5}$ concentrations, the authors reported a 4.04% (95% CI: 3.49, 4.59) increase in mortality rates. In a sensitivity analysis, the mortality effect was modified by eligibility to Medicaid insurance and race, with larger associations among people who are eligible to receive Medicaid services (5.99% [95% CI: 4.38, 7.62] and among Black individuals (10.10% [95% CI: 8.56, 11.67]. Whereas Yitshak-Sade et al. (2019b) applied DID to a portion of Medicare beneficiaries, Schwartz et al. (2021) applied two DID approaches to assess whether changes in $PM_{2.5}$ are associated with changes in mortality rates nationally among Medicare participants between 2000 and 2016 (Table A-8). The authors reported that the probability of dying in each year increased by 3.85×10^{-4} (95% CI: 1.95×10^{-4}, 5.76×10^{-4}) for each 1 $\mu g/m^3$ increase in $PM_{2.5}$ in that year. When the analysis was restricted to those beneficiaries residing in locations where $PM_{2.5}$ concentrations are below 12 $\mu g/m^3$ during the follow-up period, the probability of dying in each year increased to 4.26×10^{-4} (95% CI 1.43×10^{-4}, 7.09×10^{-4}) for 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations.

Peterson et al. (2020) conducted an accountability analysis to examine which portion of the observed declining trend in cardiovascular mortality from the National Center for Health Statistics between 1990 and 2010 was associated with changes in ambient $PM_{2.5}$. To determine the portion of the temporal change in cardiovascular mortality attributable to the temporal change in the ambient concentration of $PM_{2.5}$, Peterson et al. (2020) fit linear models, and adjusted for time-variant covariates (age-standardized annual COPD mortality rates) and time-invariant covariates (median household income, percent of non-White population, and population). On average, each 1 $\mu g/m^3$ reduction in annual $PM_{2.5}$ concentrations was associated with 3.88 (95% CI: 3.56, 4.21) fewer deaths per 100,000 persons. When combined with the annual decline in $PM_{2.5}$ concentrations, the $PM_{2.5}$-trend accounted for 0.52 (95% CI: 0.48, 0.57) fewer deaths per 100,000 persons each year, for a total change of 10.44 (95% CI: 9.56, 11.32) fewer deaths per 100,000 persons over the entire study period.

Zigler et al. (2018) used a hybrid approach of integrating an accountability analysis with an alternative method for confounder control to examine whether attainment status for the 1997 NAAQS led to an improvement in $PM_{2.5}$ concentrations and subsequently health, as previously discussed in Section 3.1.2.3. By focusing on nonattainment designations, the authors are able to examine the role of local control strategies in reducing $PM_{2.5}$ concentrations that occurred above and beyond reductions due to regional strategies. Within this study, Zigler et al. (2018) employed propensity scores, within a spatial hierarchical regression model to examine whether designation of nonattainment in 2005 for the 1997 PM

NAAQS (see Table 3-7), for either the annual standard of 15 μg/m^3 or the daily standard of 65 μg/m^3, led to a corresponding reduction in ambient $PM_{2.5}$ concentrations and all-cause mortality rates among Medicare beneficiaries in the eastern U.S. from 2009 to 2012. Zigler et al. (2018) reported a reduction in the overall average effect for all-cause mortality across the nonattainment areas of 1.25 (95% CI: −2.63, 0.11) deaths per 1000 beneficiaries, which is similar in magnitude and precision to the average "dissociative effect" (i.e., the effects of the nonattainment designations estimated to not affect $PM_{2.5}$ concentrations by more than ±1 μg/m^3). When examining the average "associative effect" (i.e., the effects of the nonattainment designations on mortality rates among areas where the nonattainment designations are estimated to reduce ambient $PM_{2.5}$ concentrations by at least 1 μg/m^3), the authors reported a reduction in the all-cause mortality rate that was larger than the "dissociative effect" (−3.16 [95% CI: −5.19, −1.21] deaths per 1000 beneficiaries). Collectively, the results of Zigler et al. (2018) provide evidence that reductions in ambient $PM_{2.5}$ concentrations and all-cause mortality could not be conclusively attributed to nonattainment designations against the backdrop of other regional strategies that impacted the eastern U.S.

Overall, recent epidemiologic studies employed a variety of alternative methods for confounder control such as GPS, IPW, and DID and reported consistent results among large study populations across the U.S. These alternative methods for confounder control in combination with accountability analyses reduce uncertainties related to confounder bias and further informs the relationship between long-term $PM_{2.5}$ exposure and total mortality and supports the conclusions of the 2019 PM ISA.

3.2.2.4. Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Long-Term $PM_{2.5}$ Exposure and Mortality

Recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence base that contributed to the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and mortality. Numerous cohort studies conducted in the U.S. and Canada in locations with mean annual concentrations that, in many instances, are lower than those reported in studies evaluated in the 2019 PM ISA, add to the large evidence base indicating consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality. These positive associations were reported across studies using different: cohorts, exposure windows, approaches for confounder adjustment, and exposure assessment methods that used different sources of data and were conducted at different spatial resolutions. In addition, studies examining cause-specific mortality further expand upon the studies that reported consistent, positive associations with cardiovascular- and respiratory-related mortality as well as other mortality outcomes. Recent studies also provide some of the initial evidence demonstrating that individuals with preexisting health conditions (i.e., heart failure and diabetes) are at increased risk of mortality overall, which, until recently, was primarily examined in studies using stratified analyses, rather than a cohort of individuals with an underlying health condition.

Additional support for a relationship between long-term $PM_{2.5}$ exposure and mortality stems from studies that examined the influence of potential confounding bias. While there is some evidence of potential confounding of the $PM_{2.5}$-mortality association by copollutants within the MAPLE studies, this is not consistent with other recent studies evaluated in the U.S. and Canada that reported associations consistent in magnitude in both single and copollutant models or with the studies evaluated in the 2019 PM ISA. In addition to copollutants, a few studies examined whether additional potential confounders, such as temporal trends and meteorological variables, could explain the $PM_{2.5}$-mortality association. Analyses examining these additional covariates, which have previously been hypothesized to be confounders of the association, further confirm that the relationship between long-term $PM_{2.5}$ exposure and mortality is unlikely to be biased by these factors.

Consistent with the conclusions of the 2019 PM ISA, recent studies provide evidence that continues to support a generally linear, no-threshold C-R relationship for long-term $PM_{2.5}$ exposure and all-cause or cause-specific mortality. Recent studies extend the evidence base by using novel statistical techniques for estimating the C-R relationship, by examining the C-R relationship among populations with relatively low $PM_{2.5}$ concentrations, and by evaluating cause-specific mortality in addition to all-cause mortality. A limited number of recent studies add to and support the evidence from the 2019 PM ISA by examining the temporal trends in $PM_{2.5}$ concentrations and changes in life expectancy. These studies generally observed that higher exposures to $PM_{2.5}$ concentrations are associated with decreases in life expectancy.

Finally, a number of recent studies employed alternative methods for confounder control or conducted accountability analyses in the process of examining the relationship between long-term $PM_{2.5}$ exposure and mortality. These studies, which used different statistical approaches for confounder control in combination with accountability analyses that examined the effect of policies or interventions on $PM_{2.5}$ concentrations and mortality, collectively provide additional support for the consistent positive associations between long-term $PM_{2.5}$ exposure and mortality reported in cohort studies spanning diverse geographic locations and populations.

3.3. Key Scientific Topics that Further Inform the Health Effects of $PM_{2.5}$

This section evaluates recent studies that address specific scientific topics that further inform the relationship between $PM_{2.5}$ exposure and health and are relevant to consider in the process of reconsidering the PM NAAQS. The topics covered in this section include recent experimental studies conducted at near-ambient concentrations, which can further inform the biological plausibility of health effects at the ambient concentrations reported in epidemiologic studies (Section 3.3.1); the role of $PM_{2.5}$ exposure on COVID-19 infection and death (Section 3.3.2); and an evaluation of studies that examine $PM_{2.5}$ exposure and health risk disparities among racial and ethnic groups and SES (Section 3.3.3).

3.3.1. Recent Experimental Studies at Near-Ambient Concentrations

Few controlled human exposure studies have investigated the effects of exposure to near ambient concentrations of $PM_{2.5}$ (i.e., at or below the 24-hour NAAQS $PM_{2.5}$ standard of 35 $\mu g/m^3$). As discussed in Sections 6.1.10 and 6.1.13 of the 2019 PM ISA, one such study was conducted in Copenhagen (Hemmingsen et al., 2015b; Hemmingsen et al., 2015a). In this study, older (55−83 years) overweight study participants (n = 60) were exposed for 5 hours to urban street air that had an average $PM_{2.5}$ concentration of 24 $\mu g/m^3$ or particle-filtered urban street air while at rest. Notably, 27 of these participants had never smoked, while 33 former smokers had not smoked on average 20 years prior to study participation. The study was a randomized, repeated measures, single blinded cross-over study. Decreased vasomotor function was reported immediately (within 1 hour) after exposure when comparing nonfiltered with particle-filtered air. The decrease in nitroglycerin-mediated vasodilation was statistically significant, while the decrease in reactive hyperemia-induced vasodilation was not. These two responses represent endothelium-independent and endothelium-dependent mechanisms, respectively. In the companion study, Hemmingsen et al. (2015a) (2019 PM ISA, Section 6.1.11) observed no changes in blood biomarkers of oxidative stress or inflammation. Similarly, blood pressure, blood lipids, and metabolic biomarkers were unaffected by exposure. With respect to HRV, Hemmingsen et al. (2015b) found the high frequency domain was statistically significantly decreased and the low frequency domain was statistically significantly increased when nonfiltered street air was compared with particle-filtered street air. In addition, the standard deviation of NN intervals (SDNN) was statistically significantly reduced after first entering the nonfiltered chamber, but this effect did not persist. In addition, (Hemmingsen et al., 2015a) (2019 PM ISA, Section 10.2.2.2) found no evidence of oxidative stress or DNA damage in peripheral blood monocytes of participants exposed to unfiltered street air.

A recent study conducted at near ambient $PM_{2.5}$ concentrations by Wyatt et al. (2020a) adds to this limited evidence base of controlled human exposure studies conducted at near ambient concentrations. This study was a randomized double-blind crossover study in healthy young participants (18−35 years, n = 21) who were subject to intermittent moderate exercise. Study participants were exposed for 4 hours to clean air or to an average concentration of 37.8 $\mu g/m^3$ $PM_{2.5}$ CAPs in Chapel Hill, NC. Ventilation rate was monitored, and workload adjusted so that participants achieved a ventilation rate of 20 $L/min/m^2$ body surface area. Thus, dose was approximately the same among participants. When comparing mean values from the exposed and unexposed groups, changes in lung function were observed in $PM_{2.5}$ exposed participants, including a statistically significant decrease in forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio of 1.2% at 1-hour postexposure that returned to baseline by 20 hours postexposure. Decreases in peak expiratory flow (PEF) (1.8%) and FEV1 (0.8%) were also observed when comparing mean values from the exposed and unexposed groups at 1-hour postexposure, but they did not achieve statistical significance. Furthermore, when comparing mean values from the exposed and unexposed groups, markers of the acute phase response—serum amyloid A and C reactive protein—were increased at both 1 and 20 hours postexposure. Serum amyloid A was increased by 8.7% at 1-hour postexposure and by 34.6% at 20 hours postexposure. C reactive protein was increased

by 9.1% at 1-hour postexposure and by 22.8% at 20 hours postexposure. These changes, except for C reactive protein at 20 hours postexposure, were statistically significant. Other statistically significant changes observed when comparing differences in mean values were increases in markers of vascular inflammation, soluble intercellular adhesion molecule 1 (sICAM) (10.7%) and soluble vascular cell adhesion molecule 1 (sVCAM) (6.6%), at 1-hour postexposure, decreases in percent blood neutrophils (5.7%) at 20 hours postexposure and decreases in blood LDH levels of 6.9% and 11.2% at 1 and 20 hours postexposure, respectively. The percentage of white blood cells other than neutrophils were unchanged by exposure, as were cytokines, red blood cells, and measures of blood chemistry. Hematocrit levels were decreased, but this change failed to reach statistical significance. No statistically significant changes were found in time domain measures of HRV in the study population as a whole, but SDNN was statistically significantly decreased in men and increased in women. No statistically significant results with respect to frequency domains were reported. P-wave duration, a measure of cardiac repolarization, was increased by 10.5% at 1-hour postexposure, a statistically significant change. Another measure of cardiac repolarization, QRS complex, was altered by $PM_{2.5}$ exposure, but this change did not reach statistical significance. Some sex-related changes that reached statistical significance were found in HRV measures, cardiac repolarization parameters, FEV1 and PEF, however the small sample size precludes any conclusions.

The higher ventilation rate and longer exposure duration of Wyatt et al. (2020a) compared with most controlled human exposure studies of PM, is roughly equivalent to a 2-hour exposure of 75−150 $\mu g/m^3$ $PM_{2.5}$. Thus, dosimetric considerations may explain the observed changes in lung function and inflammation in this population of young healthy individuals exposed to near-ambient concentrations of $PM_{2.5}$. While Wyatt et al. (2020a) provides evidence of some effects at lower $PM_{2.5}$ concentrations, overall there is inconsistent evidence for changes in lung function (2019 PM ISA, Section 5.1.7.2 and Section 5.1.2.3.3) and inflammation (2019 PM ISA, Section 6.1.11.2.1) in other controlled human exposure studies conducted at higher $PM_{2.5}$ concentrations evaluated in the 2019 PM ISA. Strengths of Wyatt et al. (2020a) include power calculations made based on the primary endpoints, normalization of results, and good diurnal control (i.e., all exposures occurred within a half hour of the same time—9:30 a.m.). However, a limitation of this study is that no Bonferroni corrections were made to account for the multiple comparisons made in the study; this limitation was acknowledged by the study authors.

3.3.2. $PM_{2.5}$ Exposure and SARS-CoV-2 Infection and COVID-19 Death

With the advent of the global COVID-19 pandemic, several studies have emerged that evaluate the relationship between ambient air pollution, specifically $PM_{2.5}$, on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the virus responsible for COVID-19 disease) infections and COVID-19 deaths, including a few studies with locations in the U.S. and Canada. The following sections present an evaluation of studies that examined the relationship between short-term (Section 3.3.2.1) and long-term (Section 3.3.2.2) $PM_{2.5}$ exposure and outcomes including SARS-CoV-2 infection and replication rate as

well as COVID-19 hospital admissions and deaths. While there is no exact corollary within the 2019 PM ISA for these types of studies, there is evidence presented in the 2019 PM ISA that evaluates the potential relationship between short-term and long-term $PM_{2.5}$ exposure and respiratory infection (2019 PM ISA, Section 5.1.5 and Section 5.2.6). Briefly, studies outlined in the 2019 PM ISA reported some evidence of positive associations between short-term $PM_{2.5}$-exposure and ED visits and hospital admissions for respiratory infections, but interpretation of these results was complicated by the variability in the type of respiratory infection outcome examined (2019 PM ISA, Figure 5-7). Studies of long-term $PM_{2.5}$ exposure were limited in number and although some positive associations were reported there was minimal overlap in respiratory infection outcomes examined across studies. As detailed in Section 5.1.1 and 5.1.5 of the 2019 PM ISA, exposure to $PM_{2.5}$ has been shown to impair host defense, specifically altering macrophage function, providing a biologically plausible pathway by which $PM_{2.5}$ exposure could lead to respiratory infection. Additionally, there is some evidence that exposure to $PM_{2.5}$ can lead to decreases in an individual's immune response and can subsequently facilitate replication of respiratory viruses (Bourdrel et al., 2021).

3.3.2.1. Short-Term $PM_{2.5}$ Exposure

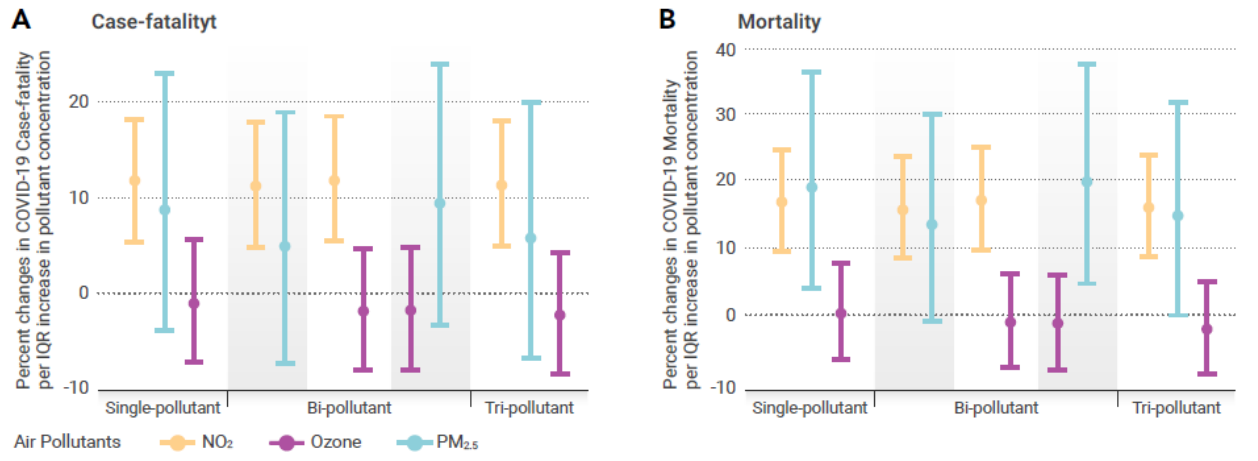
Since the onset of the COVID-19 pandemic, studies have evaluated the relationship between short-term $PM_{2.5}$ exposure and COVID-19 outcomes (Table A-9). Specifically, these studies examine whether or not daily-changes in $PM_{2.5}$ can influence COVID-19 outcomes. A recent study conducted in Queens County, NY, evaluated the relationship between short-term $PM_{2.5}$-exposure and incident SARS-CoV-2 infections and COVID-19 deaths between March 1, 2020 and April 20, 2020 (Adhikari and Yin, 2020). This time frame corresponds to the timing of the first wave of the pandemic in Queens County, NY (NYC, 2022). This study used negative binomial regression to independently model $PM_{2.5}$ collected from stationary monitors, as well as several other meteorological factors to predict new SARS-CoV-2 infections and COVID-19 deaths, controlling for the lagged outcome (to account for potential autocorrelation of the time-series and new cases) and a trend for day. Using a 21-day moving average of $PM_{2.5}$ exposure, the authors identified a null association between $PM_{2.5}$ concentrations and increased risk of SARS-CoV-2 infection (IRR: 0.02 [95% CI: 0.01, 0.02] or COVID-19 death [IRR: 0.32 (95% CI: 0.10, 0.97)]).

3.3.2.2. Long-Term $PM_{2.5}$ Exposure

Several recent studies have evaluated long-term $PM_{2.5}$-exposure and COVID-19 outcomes in North America (Chakrabarty et al., 2021; Mendy et al., 2021; Liang et al., 2020; Stieb et al., 2020; Wu et al., 2020b). These studies evaluated whether chronic $PM_{2.5}$ exposure is related to increased susceptibility to COVID-19 outcomes. When considered together, these studies that examined the relationship between long-term $PM_{2.5}$ exposure and the global COVID-19 pandemic have several methodological limitations

(e.g., studies conducted during an ongoing pandemic) and as a result caution is warranted when interpreting results (Table A-10).

Two large ecological studies (Liang et al., 2020; Wu et al., 2020b) evaluated the association between long-term $PM_{2.5}$ concentrations and county-level COVID-19 deaths in the U.S. The study by Wu et al. (2020b) evaluated COVID-19 death rates (ratio of COVID-19 deaths to county-level population) in 3,089 U.S. counties through June 18, 2020. At that point in the COVID-19 pandemic, over 40% of U.S. counties had zero cases. The MRR was predicted using a negative binomial regression using the 17-year average (2000−2016) of $PM_{2.5}$ as the main exposure and controlling for 20 covariates (19 count-level, 1 state-level). Overall, the authors reported an increased risk of COVID-19 mortality (MMR: 1.69 [95% CI: 1.34, 2.19]). This result was validated by the use of over 80 sensitivity analyses. These sensitivity analyses included alternative methods by which to estimate $PM_{2.5}$ exposure, model specifications, transformation of confounding variables, and repeating the analysis daily between April 18, 2020 and June 18, 2020 to evaluate temporal changes. Another ecological study by Liang et al. (2020), evaluated the mortality ratio (MR) (COVID-19 deaths per 1 million population) and the case fatality rate (CFR) (ratio of COVID-19 deaths to COVID-19 cases) within 3,122 U.S. counties between January 22, 2020 and July 17, 2020. At that point in the pandemic, many areas of the U.S. were still reporting zero cases (USAFacts, 2022). This study also relied on negative binomial regression and used 7-year average (2010−2016) $PM_{2.5}$ as the main exposure of interest while controlling for county-level characteristics and meteorology. The authors estimated the MR to be 1.40 (95% CI: 1.08, 1.83), and CFR was estimated to be 1.18 (95% CI: 0.92, 1.49). When including either NO_2 or O_3 in the model, the results remained consistent (Figure 3-29).



Source: Liang et al. (2020)

Figure 3-29 Percent change in county-level COVID-19 case fatality rate and mortality rate in single and multipollutant models (January 22, 2020−July 17, 2020).

In contrast, a Canadian ecological study by Stieb et al. (2020) evaluated SARS-CoV-2 infections within 111 Canadian Health Regions through May 18, 2020. These data were used to estimate the IRR of SARS-CoV-2 infections and the 17-year average (2000−2016) of $PM_{2.5}$. This analysis used negative binomial regression and controlled for several health region-specific demographics and descriptors as well as meteorology. The authors reported null associations between long-term $PM_{2.5}$ exposure and SARS-CoV-2 infections (IRR: 1.40 [95% CI: 0.86, 2.29]).

A small U.S. study conducted by Mendy et al. (2021) examined the relationship between COVID-19 hospitalizations, among individuals with a SARS-CoV-2 infection, and 10-year average (2008−2017) $PM_{2.5}$ exposure, measured at the ZIP code level. This cross-sectional study within the University of Cincinnati Hospital System considered several different individual-level factors, such as self-reported age, race/ethnicity, and smoking status, along with other co-morbidities abstracted from medical records. However, this study did not consider community-based factors, such as population density. Mendy et al. (2021) observed that among individuals with a SARS-CoV-2 infection, those with COPD or asthma had increased odds of hospitalization associated with long-term $PM_{2.5}$ exposure (OR: 11.16 [95% CI: 1.00, 128.24]) compared with those without COPD or asthma (OR: 0.42 [95% CI: 0.12, 1.54]).

In a departure from examining solely SARS-CoV-2 infections, deaths, or COVID-19 hospitalizations, another recent study evaluated the association between 6-year average $PM_{2.5}$ concentrations (2012−2017) and the COVID-19 reproduction ratio (R0) for each state (Chakrabarty et al., 2021). The R0 refers to the approximate number of individuals that an infected individual would infect in a completely susceptible population. The R0 was calculated for the time between March 2, 2020 and April 30, 2020, which coincided with nationwide stay-at-home orders. Using a susceptible-exposed-infected-recovered (SEIR) model, confirmed COVID-19 cases were recorded by state and R0 was predicted, while controlling for over 40 different state-level variables. This study showed that long-term $PM_{2.5}$ exposure was associated with increases in the R_0 (ΔR0: 1.25 [95% CI: 0.24, 2.24]).

3.3.2.3. Summary of Recent Epidemiologic Studies Examining $PM_{2.5}$ Exposure and COVID-19 Infection and Death

The body of evidence that examined associations between long- and short-term $PM_{2.5}$-exposure and COVID-19 outcomes consists mostly of studies employing an ecological study design. While some of these studies exploring the relationship between $PM_{2.5}$ concentrations and SARS-CoV-2 infections and COVID-19 deaths reported positive associations, a number of methodological issues could influence results. Specifically, all of these studies were conducted in the midst of an ongoing pandemic before COVID-19 had reached many parts of the country and at that time the etiology of COVID-19 was still not well understood. In addition, recent investigations have noted important differences in COVID-19-related

health outcomes based on occupation, race, socioeconomic status, and health insurance status, among others.

While all the included studies account for population density, with the exception of Mendy et al. (2021), they mostly do not consider other crucial factors that may strongly influence the spread of COVID-19. In particular, factors such as social distancing, stay-at-home orders, use of N95 masks, as well as other preventive measures are important for slowing the spread of SARS-CoV-2. Two critiques of the $PM_{2.5}$ exposure and COVID-19 literature conducted by Bourdrel et al. (2021) and Villeneuve and Goldberg (2020) highlight the importance of control for race/ethnicity and other sociodemographic factors, which may strongly influence exposure or susceptibility to SARS-CoV-2. Additionally, they indicate the potential for exposure misclassification and the likelihood of underreporting of cases and deaths, particularly in the early stages of the pandemic. Taken together, there is limited evidence at this point in the COVID-19 pandemic to determine whether short- or long-term exposure to air pollutants, such as $PM_{2.5}$, influence the spread or susceptibility of SARS-CoV-2 in the population.

3.3.3. Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect

As discussed in the 2019 PM ISA in Chapter 12, the NAAQS are intended to protect public health with an adequate margin of safety, which includes protection for the population as a whole and for those groups potentially at increased risk for health effects from exposure to a criteria air pollutant [e.g., PM; see Preamble to the ISA (U.S. EPA, 2015)]. While there is strong evidence for PM-related health effects occurring in the exposed general population and in some specific populations or lifestages, it is also important to evaluate and characterize the evidence to determine whether there are populations or lifestages potentially at increased risk of a PM-related health effect, with specific emphasis placed on studies that compare responses to a reference population, where appropriate [see Preamble to the ISA (U.S. EPA, 2015)].

As discussed in the Preamble to the ISAs (U.S. EPA, 2015), the risk of health effects from exposure to an ambient air pollutant, including PM, may be modified as a result of intrinsic (e.g., preexisting disease, genetic factors) or extrinsic factors (e.g., sociodemographic or behavioral factors), differences in internal dose (e.g., due to variability in ventilation rates or exercise behaviors), or differences in exposure to air pollutant concentrations (e.g., more time spent in areas with higher ambient concentrations). Taking into consideration each of these factors, Chapter 12 of the 2019 PM ISA documented a full evaluation and characterization of the evidence and conveyed the overall confidence (i.e., adequate evidence, suggestive evidence, inadequate evidence, or evidence of no effect) as to whether specific populations or lifestages are at increased risk of a PM-related health effect (see Section 2.2.5) using a framework detailed in Table 12-1 of the 2019 PM ISA. As a result, this Supplement does not include a full evaluation and characterization of all studies published since the literature cutoff date of the

2019 PM ISA that provided evidence as to whether specific populations and lifestages are at increased risk of a PM-related health effect. Instead, given recent Agency guidance addressing environmental justice [e.g., U.S. EPA (2021)] and the expansion of studies examining the role of $PM_{2.5}$ on populations with environmental justice concerns, the focus in this section is on recent studies that examine disparities in exposure or risk to PM by socioeconomic status (Section 3.3.3.1) and race and ethnicity (Section 3.3.3.2).

3.3.3.1. Socioeconomic Status

The 2019 PM ISA noted that SES—a composite measure that can include metrics such as income, education, or occupation—plays a role in access to healthy environments and access to health care in the U.S., therefore indicating that SES may underlie differential risk for $PM_{2.5}$-related health effects. Measures of SES can be examined on the individual level (e.g., personal income, education, occupation, etc.), at a community-level (e.g., median household income per census tract, percent of population with bachelor's degrees), or as a "composite" metric incorporating several different SES measurements into one single score or metric. Additionally, some evidence demonstrated that having low income or residing in low-income areas results in stronger associations (i.e., larger in magnitude) between mortality and long-term $PM_{2.5}$ exposures, when compared with their higher income counterparts. When considering educational attainment, as an indicator for SES, there was no clear pattern of differential risk when comparing those with low educational attainment and those with higher educational attainment. Taken together, the 2019 PM ISA concluded that the combination of exposure disparities and health evidence was suggestive that lower SES populations are at increased risk for $PM_{2.5}$-related health effects compared with higher SES populations. The following sections present an evaluation of recent studies pertaining to both $PM_{2.5}$ exposure among different SES groups (Section 3.3.3.1.1) and $PM_{2.5}$-related health risks among different SES groups (Section 3.3.3.1.2).

3.3.3.1.1. Exposure Disparity

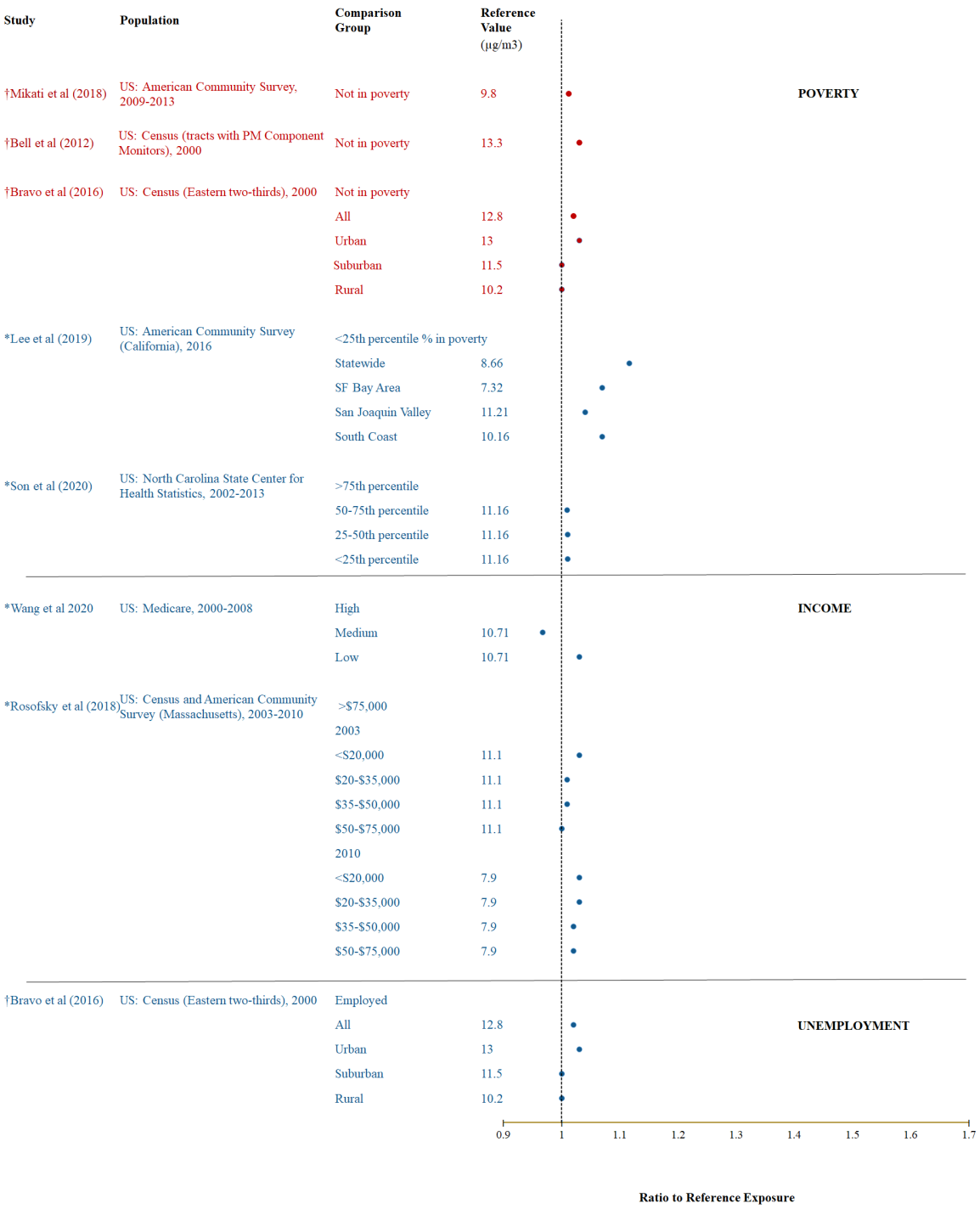
Several recent studies within the U.S. and Canada evaluated the relationship between $PM_{2.5}$ exposure and community-level SES since the completion of the 2019 ISA (Lee and Park, 2020; Richmond-Bryant et al., 2020; Son et al., 2020; Lee, 2019; Tanzer et al., 2019; Weaver et al., 2019; Rosofsky et al., 2018; Han et al., 2017). These recent studies add to the initial conclusions drawn within the 2019 ISA, which include that there is disparate $PM_{2.5}$ exposure among lower SES communities. When considered together, on average, these additional studies provide further evidence that lower SES communities are exposed to higher concentrations of $PM_{2.5}$ compared with higher SES communities (Figure 3-30a, Figure 3-30b—SES exposure, Table A-11). Specifically, Figure 3-30a and Figure 3-30b compare the mean exposure of low SES populations with that of higher SES populations, with a ratio value > 1 indicative of higher $PM_{2.5}$ exposure among the group with lower SES.

Educational attainment is a common metric with which to assess the SES of a community. A study by Lee (2019) in the state of California observed that in 2016, census block-groups with a high percent (≥ 75th percentile) of low educational attainment had a higher exposure to $PM_{2.5}$ (9.90 μg/m^3) compared with those with a low percent (< 25th percentile) of low educational attainment (8.46 μg/m^3). Rosofsky et al. (2018) conducted a study in Massachusetts that examined exposure differences by community-level educational attainment for both 2003 and 2010 but did not find as substantial of an exposure difference by educational attainment. Specifically, census block groups with more individuals with less than a high school education were exposed to $PM_{2.5}$ concentrations of 11.3 μg/m^3 in 2003 and 2010: 8.2 μg/m^3 in 2010; whereas those with a master's degree or higher were exposed to 11.2 μg/m^3 in 2003 and 8.0 μg/m^3 in 2010. Additionally, those with a high school education, post-secondary education, or bachelor's degree were exposed to slightly lower $PM_{2.5}$ concentrations ranging from 11.1 to 11.2 μg/m^3 in 2003 and 7.9 to 8.0 μg/m^3 in 2010 (Rosofsky et al., 2018).

Measures of poverty or household income are other indicators that can be used to assess SES in a community. Median household income was also evaluated in assessing potential exposure disparities in different communities in the study conducted by Rosofsky et al. (2018) noted above. Within this study it was observed that mutually exclusive census block groups with median household income categories with ranges < $75,000 ($50,000−$75,000; $35,000−$50,000; $20,000−$35,000; < $20,000) were exposed to slightly higher $PM_{2.5}$ concentrations of $PM_{2.5}$ in 2003 (11.2−11.4 μg/m^3) and 2010 (8.0−8.2 μg/m^3) compared with block groups with median household income ≥ $75,000 (11.1 μg/m^3 in 2003 and 7.9 μg/m^3 in 2010). Another study evaluating income differential in North Carolina provided some evidence that those living in census tracts with a median household income ≥ $52,269 (75th percentile) (11.3 μg/m^3) are exposed to slightly higher concentrations of $PM_{2.5}$ compared with census tracts above the 75th percentile (11.2 μg/m^3) for median household income (Son et al., 2020). Instead of examining specific household income cut points, Lee (2019) specifically evaluated the percent living in poverty (defined as those living two times below the poverty line in the state of California). In 2016, those living in census block groups in poverty (9.7 μg/m^3) were shown to be exposed to higher concentrations of $PM_{2.5}$ compared with block groups not in poverty (8.7 μg/m^3).

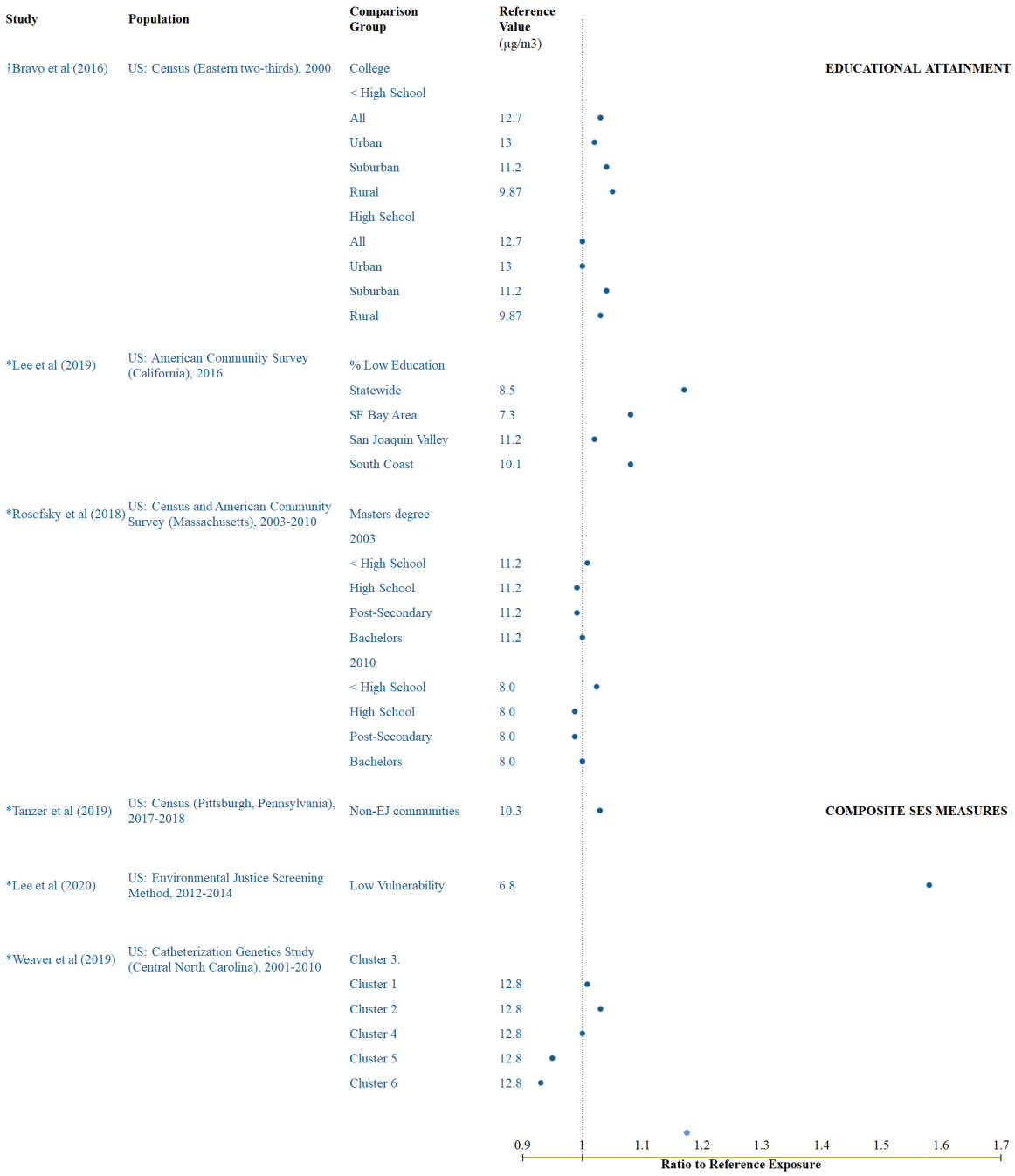
A study by Richmond-Bryant et al. (2020) using data from the National Emissions Inventory (NEI), evaluated potential changes in $PM_{2.5}$ burden due to the closure of 92 coal-fired electricity generating units (EGUcf) facilities in the U.S. This study was an extension of the study presented in the 2019 PM ISA by Mikati et al. (2018). The authors demonstrated that census tracts below the poverty line were subject to a slightly greater decrease (8.8%) in EGUcf $PM_{2.5}$ emissions compared with census tracts not below the poverty line (8.5%). However, when evaluating proportional burden, or the ratio of burden among each subgroup to the burden among the entire population, there was less than a 1% change for those above versus. below the poverty line. This study, while not including all sources of ambient $PM_{2.5}$, generally indicates that census tracts below the poverty line experience a greater burden of exposure to $PM_{2.5}$.

Several recent studies evaluated more complex measurements of community-level SES. These measurements, or "composite" characteristics incorporated several different SES measurements into one single score or metric and were applied in assessing potential disparities in $PM_{2.5}$ exposure. A study conducted in Houston, TX, observed higher $PM_{2.5}$ concentrations obtained from stationary monitors, in a single ZIP code with low SES characteristics (lower median household income, low percentage of non-Hispanic (NH)-White populations, and high percentages of NH-Black and Hispanic populations) (11.3 $\mu g/m^3$) compared with ZIP codes with high SES characteristics (9.6 $\mu g/m^3$) (Han et al., 2017). Similarly, a study by Lee and Park (2020) in the state of California, compared vulnerable with less vulnerable communities based on the Social and Health Vulnerability (SHV) metric within the Environmental Justice Screening Method. The SHV score is on a scale between 1 and 5 and is a composite of: percent residents of color, percent of residents twice below the national poverty line, home ownership, housing value, educational attainment, biological vulnerability (percent of residents < 5 and > 60 and birth outcomes), and civic engagement (linguistic isolation and voter turnout). Low vulnerability communities (SHV score 1−2) (6.8 $\mu g/m^3$) had lower $PM_{2.5}$ exposure, compared with communities with higher vulnerability (SHV score 4−5) (10.8 $\mu g/m^3$). Additionally, Tanzer et al. (2019) reported that environmental justice (EJ) communities, as defined by the state of Pennsylvania as census tracts with ≥ 20% of the population living below the poverty line and/or ≥ 30% of the populations belonging to a minority group, had a slightly greater exposure to $PM_{2.5}$ (10.6 $\mu g/m^3$) compared with non-EJ communities (10.3 $\mu g/m^3$). A study by Weaver et al. (2019) evaluated certain neighborhood clusters located within three counties (Durham, Orange, and Wake) in Central North Carolina. In this study, six clusters were derived using Ward's hierarchical clustering for 11 sociodemographic factors at the census block group level including percent of the population: with at least a bachelor's degree, in owner occupied housing, with income below the poverty level, on public assistance, who identify as Black, who identify as "other" race (neither Black nor White), unemployed, in nonmanagerial positions, of households with a single parent, and of vacant housing, and urban environment (Weaver et al., 2019). Cluster 1 was defined as urban and having a high percent of Black residents and nonmanagerial occupations. Cluster 2 was defined as urban and having a high percent of: poverty, Black residents, public assistance, single-parent homes, unemployment, and nonmanagerial occupations. Cluster 3 was defined as urban, high percent with bachelor's degrees, and low percentages of: nonmanagerial occupations, poverty, and unemployment. Cluster 4 was defined as urban, and a high percentage of: other race, bachelor's degrees, poverty, and owner-occupied housing. Cluster 5 was the only highly rural cluster and had a high percent of owner occupied housing, and low percentages of: poverty, Black individuals, and unemployment. Finally, Cluster 6 was similar to Cluster 5 but was more urban. When compared with Cluster 3 (urban, high bachelor's degrees) (12.8 $\mu g/m^3$), Cluster 2 (urban, high poverty, Black race) (13.2 $\mu g/m^3$) and Cluster 1 (urban, high Black race) (12.9 $\mu g/m^3$) were exposed to slightly higher concentration of $PM_{2.5}$. Additionally, Clusters 4 and 5 either had the same level of exposure, or slightly lower levels of exposure compared with Cluster 3 (11.9−12.8 $\mu g/m^3$). Overall, areas (clusters) with high relative SES disadvantage were exposed to higher concentrations of $PM_{2.5}$, compared with areas with high relative SES advantage.



Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent ratio of each SES group to the reference group; red text and circles represent evidence included in the 2019 PM ISA; blue text and circles represent evidence not included in the 2019 PM ISA. Reference concentrations in µg/m^3. This figure builds on Figure 12-1 in the 2019 PM ISA.

Figure 3-30a Differences in $PM_{2.5}$ exposure by socioeconomic status.



Note: *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent ratio of each SES group to the reference group; red text and circles represent evidence included in the 2019 PM ISA; blue text and circles represent evidence not included in the 2019 PM ISA. Reference concentrations in µg/m^3. This figure builds on Figure 12-1 in the 2019 PM ISA.

Figure 3-30b Differences in $PM_{2.5}$ exposure by socioeconomic status (continued).

3.3.3.1.2. Health Risk Disparity

Since the literature cutoff date of the 2019 PM ISA, several additional studies evaluated health disparities and short- and long-term $PM_{2.5}$ exposure, stratified by individual and community-level SES. The 2009 PM ISA, summarized evidence that indicated an increased risk between mortality and long-term exposure to $PM_{2.5}$ among groups with lower SES, which was further extended within the 2019 PM ISA. However, there was little evidence of any SES differences among studies assessing health outcomes, such as cardiovascular disease. Recent evidence is consistent with an increase in the risk of $PM_{2.5}$-related health effects by SES as detailed in the 2019 PM ISA. Overall, there was minimal evidence of differential health risks by SES within studies assessing $PM_{2.5}$-related all-cause or nonaccidental mortality. However, stronger associations in lower SES groups were often observed in studies assessing certain cause-specific mortality outcomes or other health endpoints. The following sections describe recent literature pertaining to short-term (Table A-12) and long-term (Table A-13) $PM_{2.5}$ exposure and health risks among different SES groups.

Short-Term $PM_{2.5}$ Exposure

Individual-Level SES

A recent time-stratified case-crossover analysis in North Carolina conducted by Son et al. (2020) evaluated the association between total mortality and $PM_{2.5}$ exposure, stratified by individual median household income. The authors reported null associations for total mortality (excluding external causes) when stratified at the median household income (< $41,500) as well as by educational attainment.

Community-Level SES

Another time-stratified case-crossover by Yitshak-Sade et al. (2019a) examined the intersection of greenspace, cardiovascular mortality, $PM_{2.5}$ exposure, and community-level educational attainment. This study showed that among census block groups with a low percentage of those without a high school diploma, there was a 1.42% (95% CI: −0.72, 3.62) increase in cardiovascular mortality in less green areas, and a 2.64% (95% CI: 0.46, 4.68) increase in cardiovascular mortality in more green areas associated with 2-day average (lag 0−1) $PM_{2.5}$ exposure. However, in census block groups with a high percentage of those without a high school diploma, less greenspace was associated with a 3.31% (95% CI: 1.26, 5.41) increase, in cardiovascular mortality, while more greenspace was associated with a 2.64% (95% CI: 0.60, 4.72) increase in cardiovascular mortality. These results indicate that the association between $PM_{2.5}$ and cardiovascular mortality was attenuated by greenspace only in census block groups with lower SES. Additionally, in a time-stratified case-crossover analysis in North Carolina, Son et al. (2020) reported null associations for total mortality (excluding external causes) when stratified at the median household income (< $41,500), or by educational attainment.

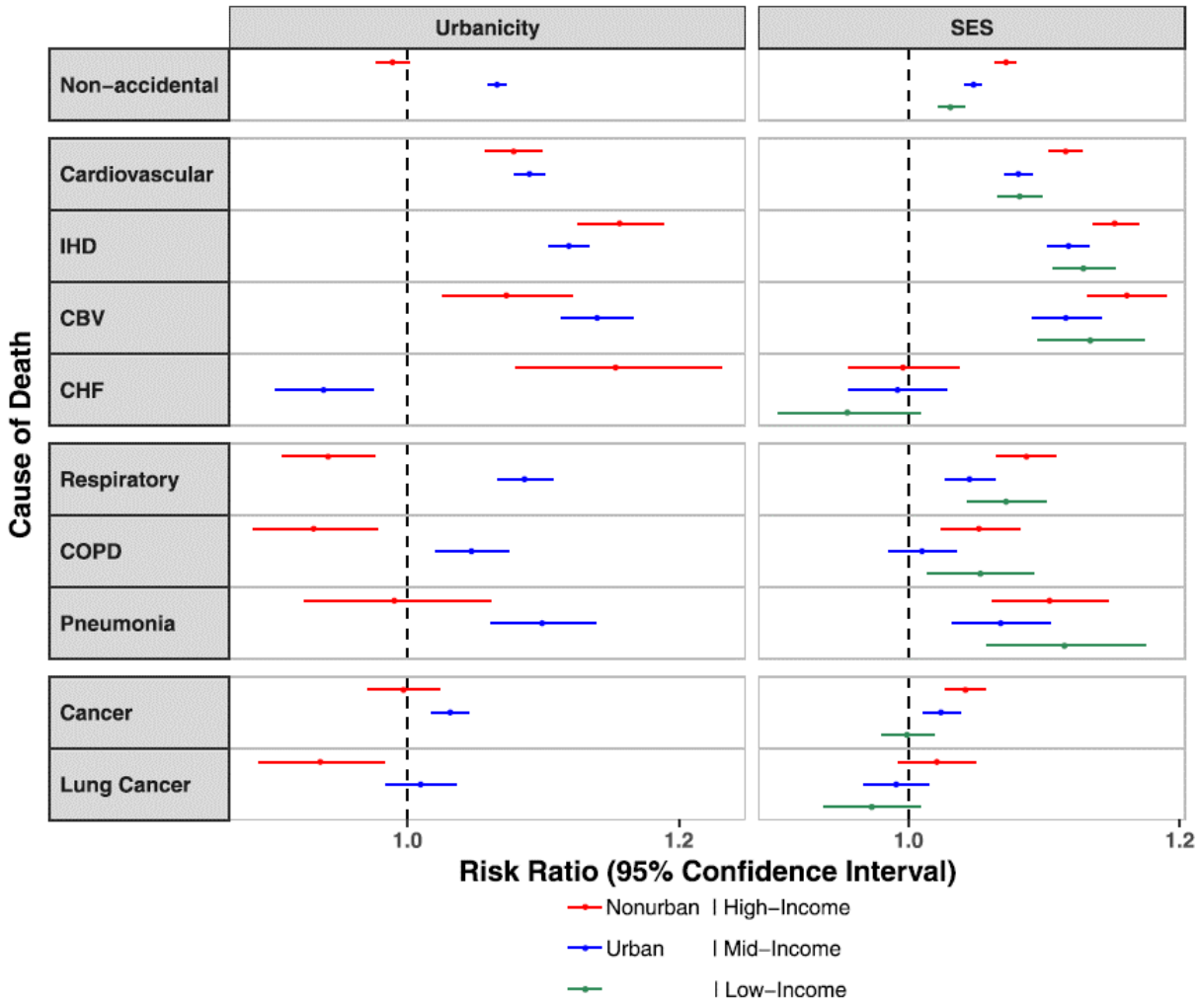
Long-Term $PM_{2.5}$ Exposure

Individual-Level SES

Individual-level SES characteristics were evaluated within some recent studies. Specifically, a Canadian study evaluating individual-level household income and $PM_{2.5}$-related nonaccidental mortality at the six-character postal code (equivalent to a street block or single large building in urban areas) level, reported the greatest magnitude of association in the lowest income category (< $25,000CAD HR: 1.61 [95% CI: 1.23, 2.12]) (Zhang et al., 2021). The overall magnitude of the association was reduced with each increasing income category. Additionally, this study also showed that risk of $PM_{2.5}$-related cardiovascular and respiratory mortality were influenced by household income, with the strongest association noted among those in the lowest individual income category for cardiovascular mortality (< 25,000CAD HR: 4.58 [95% CI: 2.48, 8.47]) compared with the highest income category (≥ $100,000CAD HR: 1.46 [95% CI: 0.94, 2.25]). Fewer differences were noted between the lowest (< 25,000CAD HR: 3.20 [95% CI: 1.40, 7.34]) and the highest (≥ $100,000CAD HR: 4.48 [95% CI: 1.69, 11.83]) individual income categories and respiratory mortality.

Community-Level SES

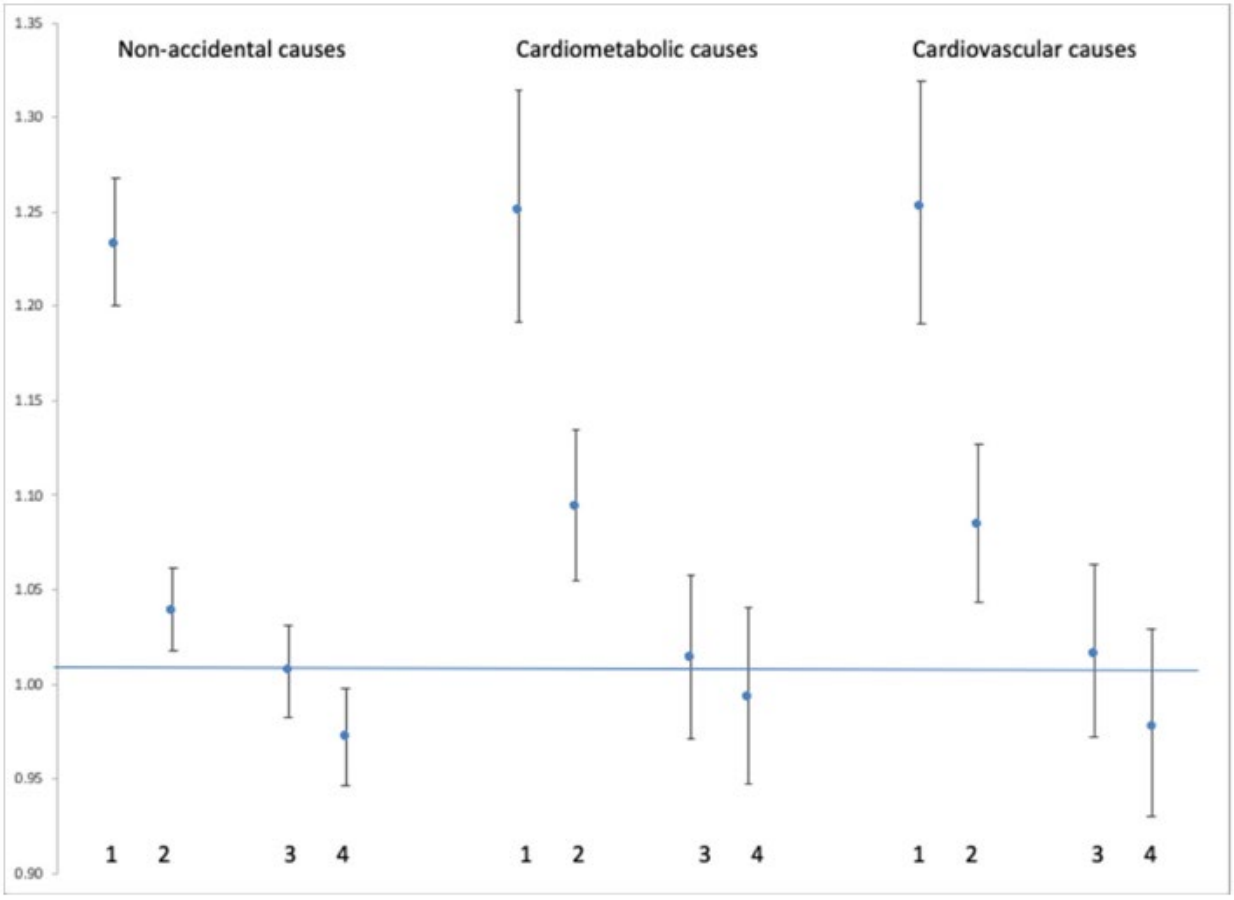
The majority of recent studies focusing on SES evaluate the relationship between $PM_{2.5}$ and health effects, stratified by community-level measures of SES. Specifically, some studies explore whether SES modifies the relationship between exposure to $PM_{2.5}$ and total or all-cause mortality. Similarly, a study by Wang et al. (2020) evaluated over 53 million Medicare beneficiaries using a combination of hybrid machine learning and Cox proportional hazards to assess long-term $PM_{2.5}$ exposure and mortality at the ZIP code level, but also showed null associations for $PM_{2.5}$-related nonaccidental mortality by ZIP code level income (high, medium, low) (Figure 3-31).



Source: Wang et al. (2020)
SES = socioeconomic status.

Figure 3-31 Risk ratio of association between $PM_{2.5}$ and mortality, stratified by socioeconomic status.

Using a more comprehensive method of assessing community-level SES, another Canadian study evaluated if a combination of greenspace and social deprivation modified the relationship between long-term $PM_{2.5}$ exposure and total nonaccidental mortality (Crouse et al., 2019). Community-level deprivation was assessed using the Canadian Marginalization Index, which incorporates measures such as community-level material deprivation, residential instability, dependency, and ethnic concentration. Crouse et al. (2019) found that the group with the lowest deprivation and lowest amount of greenspace had a stronger association, in terms of magnitude, with nonaccidental mortality compared with groups with high deprivation and low greenspace. However, there was little difference in the association comparing high to low deprivation in areas with high greenspace (Figure 3-32).

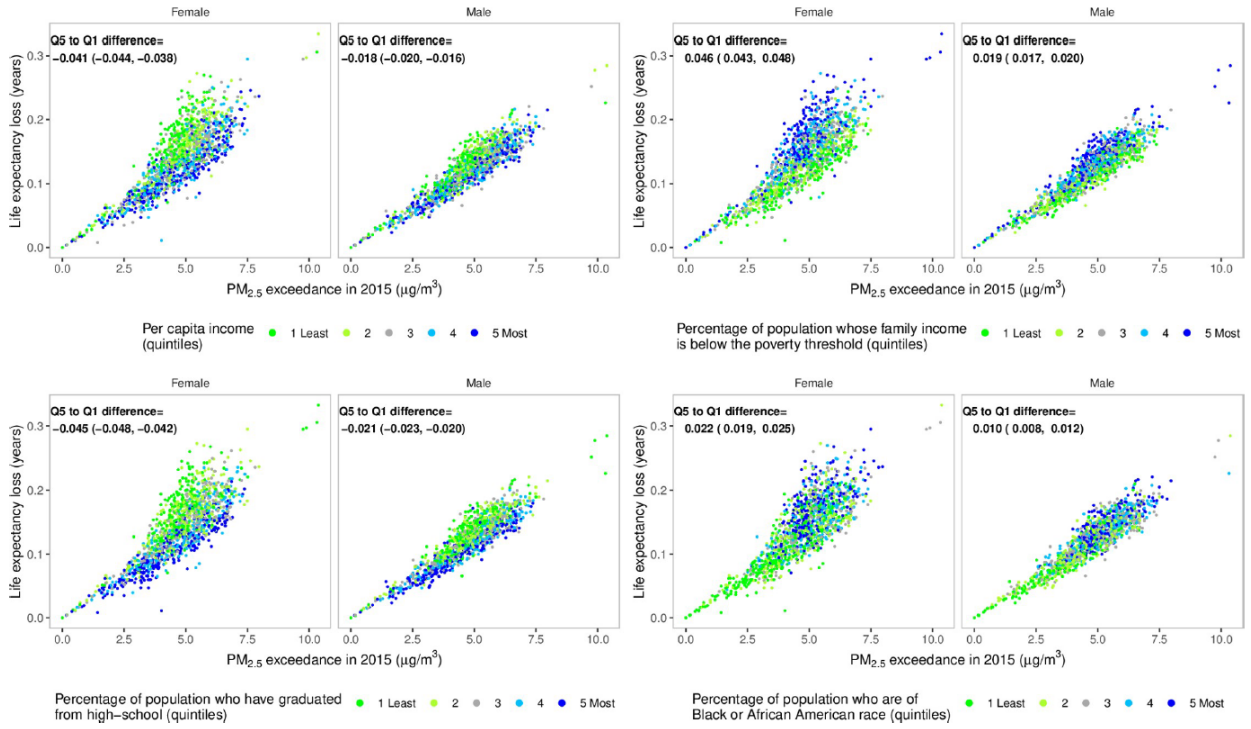


Source: Crouse et al. (2019)

1 = low greenness and low deprivation; 2 = low greenness and high deprivation; 3 = high greenness and low deprivation; 4 = high greenness and high deprivation.

Figure 3-32 Hazard ratios for the association between $PM_{2.5}$ and mortality, by greenspace and community-level material deprivation.

A study by Bennett et al. (2019) evaluated life-expectancy changes and $PM_{2.5}$ among differing SES groups in the U.S., using data from the National Center for Health Statistics. In this study, $PM_{2.5}$ concentrations that were greater than the lowest observed concentration of 2.8 $\mu g/m^3$ were associated with lower life expectancy among counties with: lower income, higher percent poverty, and those with a low percent of the population who graduated from high school. These differences were greater among females compared with males (Figure 3-33). In another study examining life expectancy, Jorgenson et al. (2020) evaluated the relationship between $PM_{2.5}$ exposure, Black race, and income inequality. This study observed that $PM_{2.5}$ had a stronger effect on life expectancy at birth in states with high income inequality. Black race further exacerbated the effect of $PM_{2.5}$ exposure on life expectancy at birth.



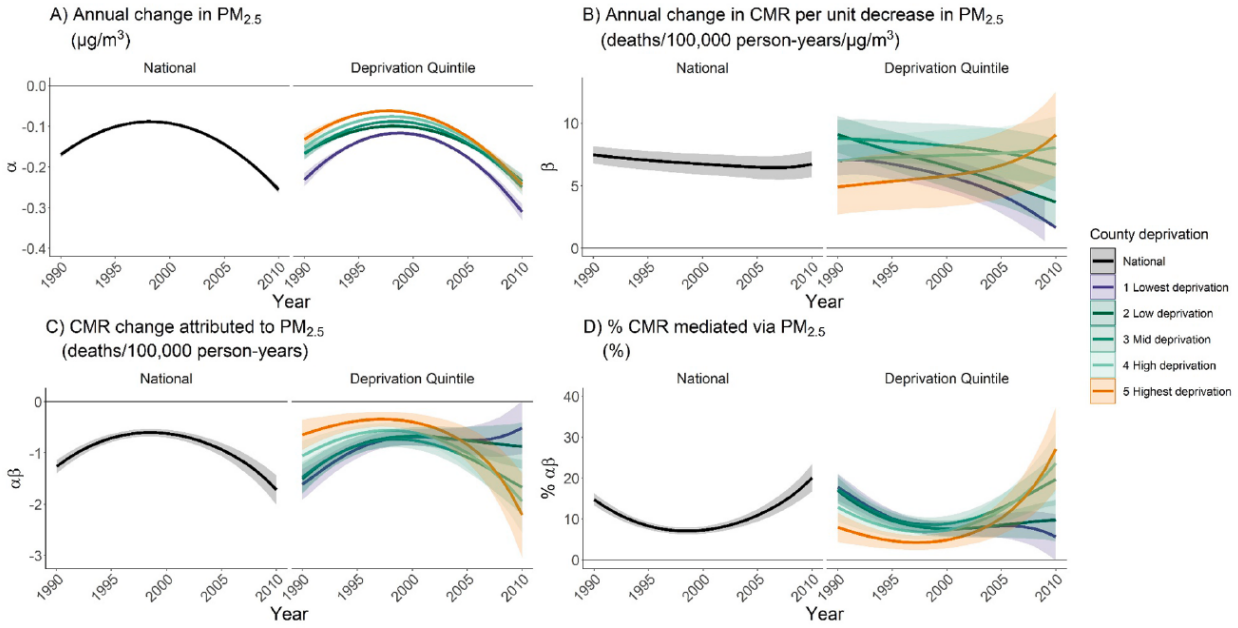
Source: Bennett et al. (2019)

Q5 to Q1 difference = estimated difference in life expectancy loss between quintile 5 ($34,200−$114,000) and quintile 1 ($17,400−$24,900).

Figure 3-33 County-level life expectancy losses due to $PM_{2.5}$ exceeding 2.8 µg/m³.

Numerous recent studies also evaluated whether the association between $PM_{2.5}$ exposure and certain causes of death (i.e., cause-specific mortality) is modified by community-level SES. The study by Wang et al. (2020) using data on Medicare beneficiaries, consistently reported null associations in any cause-specific mortality by income (low, medium, high) (Figure 3-31). However, a cross-sectional study by Bevan et al. (2021) evaluated the association between $PM_{2.5}$ exposure and age-adjusted cardiovascular mortality, modified by the 2015 Social Deprivation Index (SDI). The SDI is generated from a factor analysis using information collected from the American Community Survey, including county-level descriptors of race/ethnicity, income, housing, and education. The SDI ranges between 1 (least deprived) and 100 (most deprived). Bevan et al. (2021) demonstrated that when examining the annual average $PM_{2.5}$ and age-adjusted cardiovascular mortality, stratified by SDI, there is increased risk of cardiovascular mortality in counties with higher social deprivation (SDI 1−25: 39.1 deaths/100,000 persons [95% CI: 32.1, 46.1]; SDI 26−50: 48.2 deaths/100,000 persons [95% CI: 38.5, 57.9]; SDI 51−75: 71.0 deaths/100,000 persons [95% CI: 57.6, 84.4]; SDI 76−100: 52.0 deaths/100,000 persons [95% CI: 30.9, 73.1]). In another study focusing on social deprivation, Wyatt et al. (2020b) estimated the change in $PM_{2.5}$ concentration between 1990 and 2010 and the associated annual change in the age-adjusted cardiovascular mortality rate (CMR) in the U.S. A social deprivation variable was created using 1990

U.S. Census measures including: percent of households below the poverty line, median household income, percent of those ≥ with at least a high school education, civilian unemployment rate, percent female households with no spouse, percent vacant housing units, and percent owner occupied housing units. Overall, in the earliest years, the counties with the highest social deprivation benefited the least by the reduction in $PM_{2.5}$. However, as time progressed through to 2010, reductions in CMR were the largest in the most deprived counties (Figure 3-34).



Source: Wyatt et al. (2020b)

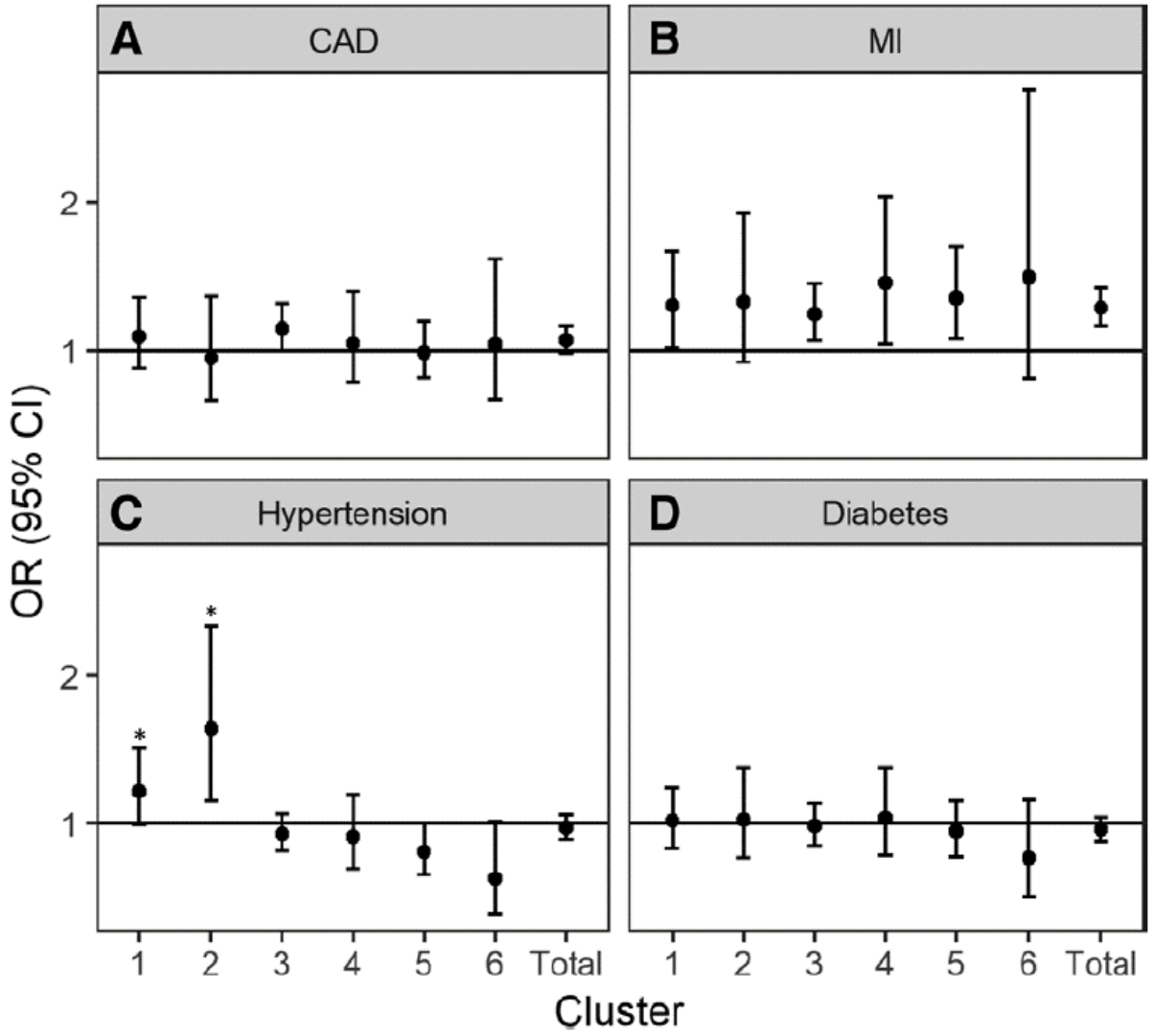
Note: Estimated national and socioeconomic deprivation (SED) quintile specific annual rates (95% confidence intervals). (A) depicts the change in $PM_{2.5}$ (α); (B) depicts the change in cardiovascular mortality rate (CMR) per 1 μg/m^3 change in $PM_{2.5}$ (β); (C) depicts $PM_{2.5}$-related change in CMR (αβ); and (D) depicts the $PM_{2.5}$-related change in CMR as a portion of the overall CMR. A negative sign for α indicates a decrease in ambient $PM_{2.5}$ concentrations, while a positive sign indicates an increase. A positive sign for β indicates an increase in CMR per unit increase in $PM_{2.5}$, while a negative sign indicates a decrease. A negative sign for αβ indicates a net reduction in CMR related to $PM_{2.5}$ change, whereas a positive sign indicates a net increase.

Figure 3-34 Estimated national and socioeconomic deprivation quintile-specific mortality rates.

Schulz et al. (2018) evaluated cardiopulmonary mortality and $PM_{2.5}$ in the Detroit metropolitan area in 2013, stratified by area-level vulnerability. The census-tract level vulnerability index developed by the authors incorporated percent of households below the poverty index, median home value (reversed), percent of homes occupied by renters, percent of population > 24 with less than a high school education, linguistic isolation, percent people of color, and the percent of the population < 5 and ≥ 60 years of age. Hierarchical linear models, with a logit link independently evaluated $PM_{2.5}$ and cardiopulmonary, cardiovascular, and IHD mortality associated with $PM_{2.5}$ exposure and increased vulnerability. Both $PM_{2.5}$ and vulnerability were independently associated with cardiopulmonary, cardiovascular, and IHD mortality, and the associations remained, when both PM and vulnerability were included. Additionally, the Canadian study on greenspace and social deprivation by Crouse et al. (2019) estimated that

greenspace protected against $PM_{2.5}$ attributable cardiovascular and cardiometabolic (defined as the combination of circulatory and diabetes) mortality, but demonstrated a stronger association in areas with low greenness and low deprivation (Figure 3-32).

A prospective analysis by Bai et al. (2019) evaluated the association between $PM_{2.5}$ and either CHF or AMI, using the Canadian ONPHEC, by neighborhood-level income categories. The authors observed the strongest association for both CHF (HR: 1.12 [95% CI: 1.10, 1.13]) and AMI (HR: 1.12 [95% CI: 1.09, 1.15]) among those in the lowest income groups, compared with the uppermost income groups (CHF HR: 1.01 [95% CI: 1.00, 1.04], AMI HR: 1.03 [95% CI: 1.00, 1.06]). A study based on the same cohort also showed stronger associations for atrial fibrillation (HR: 1.06 [1.04, 1.08]) and stroke (HR: 1.08 [1.04, 1.13]) among the lowest income groups (Shin et al., 2019). The central North Carolina study by Weaver et al. (2019) evaluated the relationship between certain health outcomes, such as: coronary artery disease, MI, hypertension, and diabetes, among cardiac catheterization patients. When compared with Cluster 3 (urban, high percent with bachelor's degrees, and low percentages of: nonmanagerial occupations, poverty, and unemployment) (OR: 0.70 [95% CI: 0.86, 1.07], per 5 $\mu g/m^3$), there was a greater association between $PM_{2.5}$ and hypertension in Cluster 1 (urban and having a high percent of Black residents and nonmanagerial occupations) (OR = 2.70, [95% CI: 0.95, 7.59], per 5 $\mu g/m^3$) and 2 (urban and having a high percent of: poverty, Black residents, public assistance, single-parent homes, unemployment, and nonmanagerial occupations) (OR = 11.86, 95% [95% CI: 2.10, 67.21], per 5 $\mu g/m^3$). While $PM_{2.5}$ was associated with MI, the associations did not vary by cluster, and there were null associations noted for diabetes. However, the strongest association observed among CAD outcomes was in Cluster 3 (OR = 1.15 [95% CI: 1.00, 1.31], per 5 $\mu g/m^3$) (Figure 3-35). Overall, this study concluded that areas with a relatively greater amount of social disadvantage had stronger associations in magnitude between $PM_{2.5}$ and hypertension compared with areas with lower social disadvantage.



Source: Weaver et al. (2019)
CAD = Coronary Artery Disease, MI = Myocardial Infarction. Results resented for 1 μg/m_3 increase in $PM_{2.5}$ concentrations.

Figure 3-35 Odds ratios for the association between $PM_{2.5}$ and cardiovascular outcomes and diabetes by neighborhood cluster.

3.3.3.2. Race/Ethnicity

The 2019 PM ISA provided evidence indicating that people of different racial and ethnic backgrounds experience disparities in the risk of $PM_{2.5}$-related health effects. When the 2009 PM ISA was finalized, there were relatively few studies evaluating whether race/ethnicity modifies the relationship between $PM_{2.5}$ exposure and health effects. As a result, the 2009 PM ISA observed little evidence for increased $PM_{2.5}$-related risk by race and some evidence of increased risk by Hispanic ethnicity. However, the 2019 PM ISA demonstrated evidence that there are consistent racial and ethnic disparities in $PM_{2.5}$

exposure across the U.S., particularly for Black/African Americans, compared with non-Hispanic White individuals. Additionally, some studies provided evidence of increased $PM_{2.5}$-related mortality and other health effects from long-term exposure to $PM_{2.5}$ among Black individuals. Taken together, the 2019 PM ISA concluded that the evidence was adequate to conclude that race and ethnicity modify $PM_{2.5}$-related risk, and that minority populations, particularly Black populations, are at increased risk for $PM_{2.5}$-related health effects, in part due to disparities in exposure. The following sections present an evaluation of recent studies pertaining to both $PM_{2.5}$ exposure among different racial and ethnic groups (Section 3.3.3.2.1) and $PM_{2.5}$-related health risks among different racial and ethnic groups (Section 3.3.3.2.2).

3.3.3.2.1. Exposure Disparity

Several recent studies conducted within the U.S. and Canada evaluated the relationship between $PM_{2.5}$ exposure and racial and ethnic disparities since the literature cutoff date of the 2019 ISA. These recent studies add to the conclusions of the 2019 ISA, which included that there are disparities in $PM_{2.5}$ exposure by race and ethnicity. When considered together, these additional studies provide further evidence that minority communities are exposed to higher concentrations of $PM_{2.5}$, compared with predominantly White communities (Figure 3-38—Race exposure, Table A-14—Race exposure). Specifically, Figure 3-38 and compares the mean exposure of minority populations with that of nonminority populations, with a ratio value > 1 indicative of higher $PM_{2.5}$ exposure among the minority group.

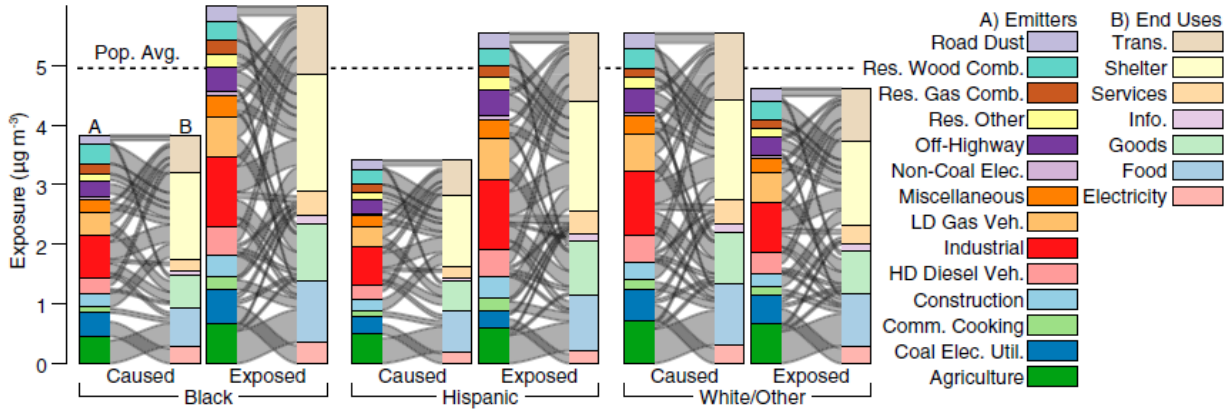
Recent evidence further indicates that disparities in exposure persist by race and ethnicity. Several multi-year cohort studies evaluated the potential disparity in long-term $PM_{2.5}$ exposure by race/ethnicity. The Heart Strategies Concentration on Risk Evaluation (HeartSCORE) study, conducted in Pittsburg, PA, between 2001 and 2014, observed that Black participants (16.1 $\mu g/m^3$) were exposed to slightly higher concentrations of $PM_{2.5}$ compared with White participants (15.7 $\mu g/m^3$) (Erqou et al., 2018). Similarly, the Veterans Cohort Study, conducted between 1976 and 2001 also showed that Black participants (15.7 $\mu g/m^3$) were exposed to a substantially higher concentration of $PM_{2.5}$ compared with White participants (13.9 $\mu g/m^3$) (Lipfert and Wyzga, 2020). The NIH-AARP Diet and Health Study, conducted between 1995 and 2011, also identified disparities in $PM_{2.5}$ exposure by race and ethnicity. When compared with White race (10.9 $\mu g/m^3$), those of Black race (12.3 $\mu g/m^3$) experience higher exposures to $PM_{2.5}$, followed by Asian, Pacific Islander, or American Indian/Alaska Native (11.9 $\mu g/m^3$) and Hispanic (11.4 $\mu g/m^3$) individuals Lim et al. (2018). A study conducted among the Medicare population that moved outside of their original ZIP code between 2000 and 2012 observed that while post-move $PM_{2.5}$ concentrations were lower among Black (pre-move: 13.02 $\mu g/m^3$, post-move: 12.12 $\mu g/m^3$) and White (pre-move: 11.88 $\mu g/m^3$, post-move: 11.15 $\mu g/m^3$) beneficiaries, a disparity in exposure was still present, with Black populations being exposed to elevated concentrations of $PM_{2.5}$ compared with White populations (Awad et al., 2019). A study by Parker et al. (2018) using the Health

Interview Survey also showed that a greater number (37.2%) of non-Hispanic Black and Hispanic (33.3%) individuals lived in the highest $PM_{2.5}$ quartile, compared with White individuals (21.3%). Additionally, most White (26.1%) and Hispanic (34.7%) individuals lived in the lowest $PM_{2.5}$ quartile, compared with only 10.5% of non-Hispanic Black individuals.

Other recent studies used data from the U.S. Census or American Community Survey to gather area-level measures of race and ethnicity. A study by Rosofsky et al. (2018) observed that despite declines in the $PM_{2.5}$ concentrations during the study period, between 2003 and 2010 in Massachusetts, the relative disparity in $PM_{2.5}$ exposure by race/ethnicity remained, with non-Hispanic Black (2003: 11.7 $\mu g/m^3$, 2010: 8.4 $\mu g/m^3$), non-Hispanic Asian (2003: 11.6 $\mu g/m^3$, 2010: 8.2 $\mu g/m^3$), and Hispanic (2003: 11.6 $\mu g/m^3$, 2010: 8.4 $\mu g/m^3$), populations experiencing higher $PM_{2.5}$ exposures compared with non-Hispanic White (2003: 11.1 $\mu g/m^3$, 2010: 7.8 $\mu g/m^3$) populations. (Kelly et al., 2020) evaluated racial and ethnic disparities using nine different exposure models. Despite differences in the absolute concentrations estimated from each method, all exposure models demonstrated that areas of the U.S. with a high percentage of Black individuals experienced higher $PM_{2.5}$ exposures compared with areas with a higher percentage of White individuals. Additionally, compared with areas with a predominant population of White individuals, areas with a predominant population of those classified as "other" race and Hispanic populations were also more highly exposed to $PM_{2.5}$. The result of (Kelly et al., 2020) was supported in a study by Yitshak-Sade et al. (2020) using data collected from the Massachusetts Department of Public Health showed that only 6.0% of Black individuals were in the lowest quartile of $PM_{2.5}$ exposure, while 8.1% were in the highest quartile. Additionally, Lee (2019) in a study conducted in the state of California, demonstrated that block-groups with a high percent ($\geq$ 75th percentile) of people of color (9.98 $\mu g/m^3$) compared with those with a low percent (< 25th percentile) of people of color (7.90 $\mu g/m^3$) were exposed to higher concentrations of $PM_{2.5}$.

Several recent studies used data from the NEI to evaluate racial and ethnic disparities in $PM_{2.5}$ exposure. Richmond-Bryant et al. (2020) evaluated changes in burden due to the closure of 92 coal-fired electricity generating units (EGUcf). Estimated from the American Community Survey, the omission of the facilities resulted in an 11% reduction in absolute burden in census tracts with a majority of White individuals. However, census tracks with a majority of Black (6.6%) or Hispanic (4.4%) populations experienced less of a decrease in absolute burden. When considering the proportional burden—the ratio of absolute burden in a racial subgroup to the absolute burden of the total population—White census tracts had an overall decrease of 2.4%, while predominantly Hispanic and Black census tracts had an increase in proportional burden of 4.5 and 2.2%, respectively. A study by Tessum et al. (2019) estimated the disparities between the consumption of goods and services by each racial and ethnic group that produce $PM_{2.5}$ and the amount of $PM_{2.5}$ each racial and ethnic group is exposed to in order to estimate pollution inequity. Overall, the authors indicate that Black individuals are exposed to the highest concentration of $PM_{2.5}$ (6.0 $\mu g/m^3$), while only consuming 3.8 $\mu g/m^3$, meaning that their estimated pollution inequity is 56%. Hispanic individuals were estimated to have a pollution inequity of 63% (exposed to 5.5 $\mu g/m^3$, consuming 3.4 $\mu g/m^3$), while White individuals have an estimated pollution

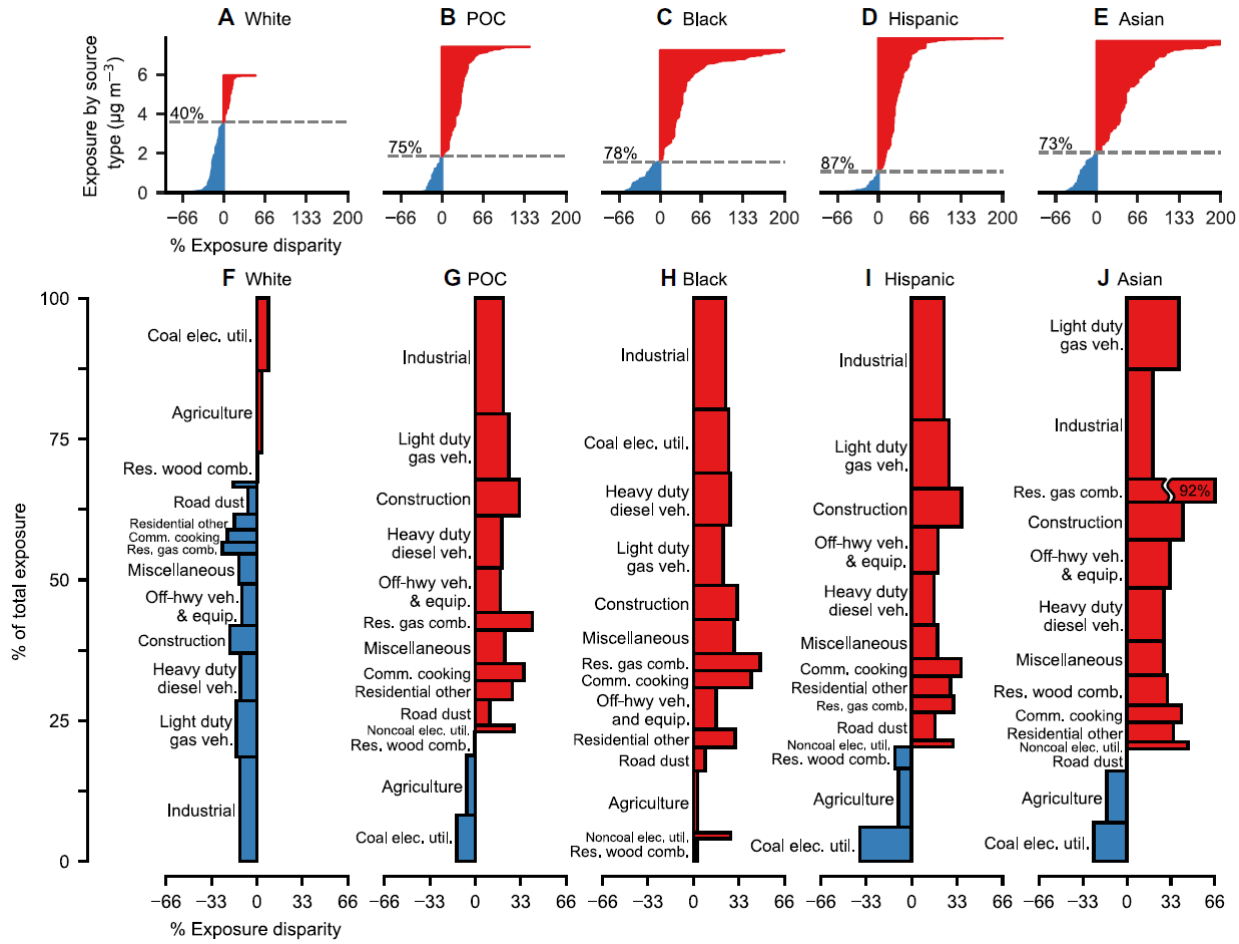
inequity of −17% (exposed to 4.6 µg/m^3, consume 5.5 µg/m^3) (Figure 3-36). Another similar study by Tessum et al. (2021) showed that people of color are consistently exposed to $PM_{2.5}$ caused by each emitter type in the U.S. The authors estimated Black (7.9 µg/m^3), Asian (7.7 µg/m^3), Hispanic (7.2 µg/m^3) individuals are exposed to greater proportions of $PM_{2.5}$ compared with White (5.9 µg/m^3) individuals (Figure 3-37).



Source: Tessum et al. (2019)

Note: In this figure, pollution inequity is the percent difference between a group's "exposed" and "caused" bars. Within each group of bars, the emitters (A) and end uses (B) responsible for the exposure are depicted with gray lines showing relationships among emitters and end uses.

Figure 3-36 Racial and ethnic inequities in $PM_{2.5}$ exposure caused by population-adjusted group consumption ("caused") and total personal consumption ("exposed").



Source: Tessum et al. (2021)

Note: Individual source type contributions to exposure presented on the y-axis and % exposure disparity presented on the x-axis. Positive values are shaded red and negative values shaded blue. Dashed lines denote percent exposure caused by sources with positive exposure disparity.

Figure 3-37 Source contributions to racial-ethnic disparity in $PM_{2.5}$ exposure.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent ratio of each racial or ethnic group to the reference group (White individuals). Red text and circles represent evidence included in the 2019 PM ISA; blue text and circles represent evidence not included in the 2019 PM ISA. Reference concentrations in µg/m^3. NH: non-Hispanic. This figure builds on Figure 12-2 in the 2019 PM ISA.

Figure 3-38 Difference in $PM_{2.5}$ exposure by race.

3.3.3.2.2. Health Risk Disparity

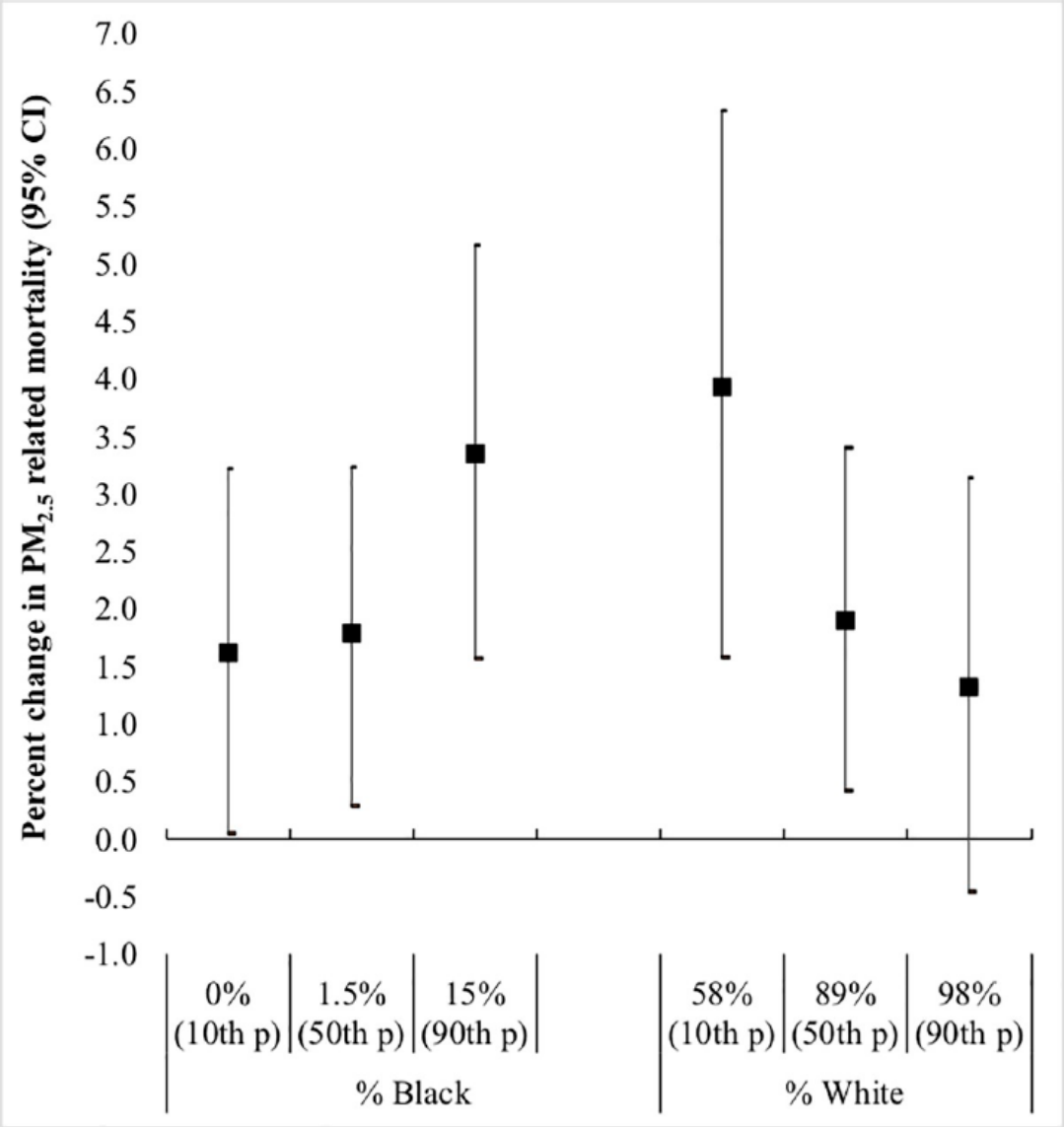
Since the literature cutoff date of the 2019 ISA, several additional studies evaluated disparities in the risk of $PM_{2.5}$-related health effects, stratified by race and ethnicity. A small number of studies were included in the 2009 PM ISA that summarized racial and ethnic disparities in $PM_{2.5}$ mortality risk. The 2019 PM ISA further identified several studies which provided evidence for an increased association between mortality and long-term exposure to $PM_{2.5}$ among minority groups. However, evidence of any racial or ethnic disparities and $PM_{2.5}$-related health outcomes was inconsistent. The most recent evidence is consistent with differences in the risk of $PM_{2.5}$-related health effects by race and ethnicity, as detailed in the 2019 PM ISA. While the studies that evaluated all-cause or total (nonaccidental) mortality were inconsistent, there was stronger evidence to indicate a greater risk of cause-specific mortality and some other health endpoints among people of color. In particular, individuals of Black race consistently were shown to have a greater risk for health outcomes associated with $PM_{2.5}$ exposure. The following sections present an evaluation of recent studies pertaining to short-term (Table A-15) and long-term (Table A-16) $PM_{2.5}$ exposure and $PM_{2.5}$-related health risks among different racial groups.

Short-Term $PM_{2.5}$ Exposure

In a time-stratified case-crossover analysis, Yitshak-Sade et al. (2019a) examined the intersection of greenspace, cardiovascular mortality, and $PM_{2.5}$ exposure in Massachusetts. This study demonstrated that among census block groups with a low percentage of White individuals, there was a 3.55% (95% CI: 1.49, 5.65) increase in cardiovascular mortality in less green areas, and a 2.47% (95% CI: 0.43, 4.56) increase in cardiovascular mortality in more green areas associated with two-day average (lag 0−1) $PM_{2.5}$ exposure. However, in census block groups with a high percentage of White individuals, less greenspace was associated with a 1.14% (95% CI: −1.00, 3.33) increase, in cardiovascular mortality, while more greenspace was associated with a 2.8% (95% CI: 0.62, 5.02) increase in cardiovascular mortality (Figure 3-39). These results indicate that regard less of greenspace, census block groups with low percentage of White individuals have a higher risk of $PM_{2.5}$-related cardiovascular mortality. Additionally, the North Carolina case-crossover study by Son et al. (2020) also reported very little racial and ethnic differences in the magnitude of the association between short-term $PM_{2.5}$ exposure and total mortality when stratified by race/ethnicity (non-Hispanic White OR: 1.01 [1.01, 1.01]; non-Hispanic Black OR: 1.01 [1.00, 1.02]; Hispanic OR: 0.97 [0.93, 1.02]; non-Hispanic Asian OR: 1.01 [0.97, 1.02]; non-Hispanic Other OR: 1.01 [0.97, 1.04]).

Another study examining short-term $PM_{2.5}$ exposure and cardiovascular mortality conducted in Massachusetts used four different metrics in which to evaluate race and ethnicity within the state (Yitshak-Sade et al., 2020). There was a higher percent change in cardiovascular mortality among Black (4.78% [95% CI: −1.99, 12.02]) individuals compared with White (2.25% [95% CI: 0.80, 3.23]) associated with the two-day moving average (lag 0−1) of $PM_{2.5}$. When evaluating the racial composition by census block group, there was a 1.62% (95% CI: 0.05, 3.22) increase in cardiovascular mortality in census block groups with 0% Black (10th percentile) compared with a 3.35% (95% CI: 1.57, 5.16)

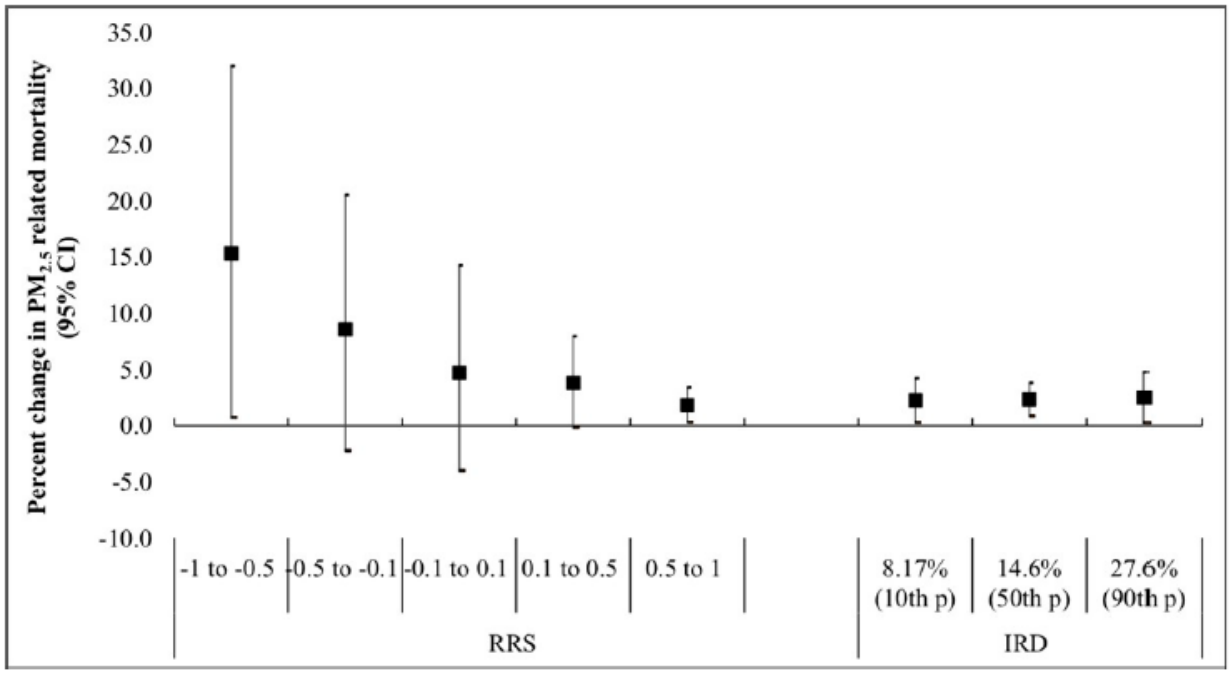
increase in cardiovascular mortality in census block groups with more than a 15% Black population (90th percentile) (see Figure 3-39). This study also evaluated two novel measures of racial segregation. The first was the Racial Residential Segregation (RRS) metric, which quantified the concentration of non-Hispanic Black and non-Hispanic White individuals in each census block group and could range between −1 (more Black individuals) to 1 (more White individuals). In census block groups with more White individuals (RRS 0.5 to 1) there was a 1.84% (95% CI: 0.31, 3.40) increase in cardiovascular mortality, whereas in census block groups with more Black individuals (RRS −1 to −0.5) there was a 15.37% (95% CI: 0.76, 31.99) increase in cardiovascular mortality. The second indicator examined was the Index of Racial Dissimilarity (IRD), which measured the dissimilarity between the distribution of non-Hispanic Black and non-Hispanic White individuals within the census block group to the larger census tract. A higher IRD is indicative of greater dissimilarity in the proportion of Black residents between the census block group and the census tract. There was no evidence of differences in cardiovascular mortality risk attributed to short-term $PM_{2.5}$ exposure among any of the groups (Figure 3-40).



Source: Yitshak-Sade et al. (2020)

Note: Results presented for a 10 μg/m^3 increase in $PM_{2.5}$.

Figure 3-39 Percent change in cardiovascular disease mortality by $PM_{2.5}$ exposure, stratified by census block group racial composition in Massachusetts (2001−2011).



Source: Yitshak-Sade et al. (2020)
Note: Results presented for a 10 μg/m^3 increase in $PM_{2.5}$.
RRS = racial residential segregation, IRD = Index of Racial Dissimilarity.

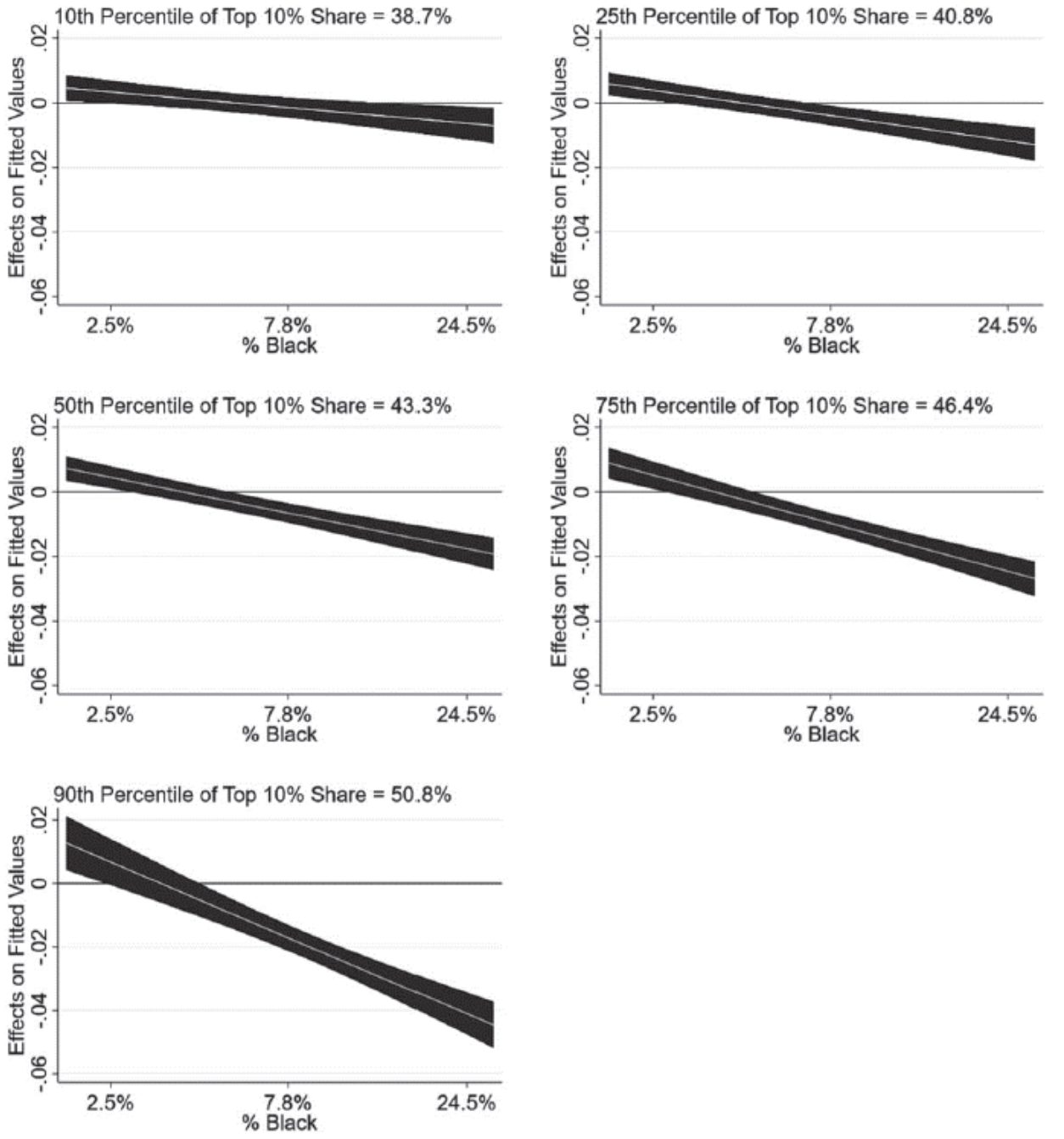
Figure 3-40 Percent change in cardiovascular disease mortality by $PM_{2.5}$ exposure, stratified by the Racial Residential Segregation (RSS) metric and Index of Racial Dissimilarity in Massachusetts (2001−2011).

Long-Term $PM_{2.5}$ Exposure

A number of recent epidemiologic studies further evaluated whether race and ethnicity modify the association between all-cause (nonaccidental) mortality and long-term $PM_{2.5}$ exposure. A study by Parker et al. (2018) using NHIS data evaluated all-cause mortality (excluding unintentional injuries) and $PM_{2.5}$ by race and ethnicity. This study reported a larger association, in terms of magnitude, among Black (HR: 1.05 [95% CI: 1.03, 1.09]) and White (HR: 1.02 [95% CI: 1.00, 1.05]) individuals and a null association among Hispanic individuals (HR: 0.98 [95% CI: 0.94, 1.03]). However, Awad et al. (2019) in a study of Medicare beneficiaries who moved out of their ZIP code did not report results consistent with Parker et al. (2018). By utilizing data from the subpopulation of Medicare enrollees that moved, the authors were able to examine changes in $PM_{2.5}$ exposure, thus creating a natural experiment that essentially randomized an individual's exposure. Inverse probability weights were used to control for several select covariates. Among Black movers, the HR for all-cause mortality was lower (HR: 1.06 [95% CI: 1.04, 1.07]), compared with White movers (HR: 1.10 [95% CI: 1.10, 1.10]). Similarly, a recent study using data from the Veterans Cohort Mortality Study from 1976 to 2001 evaluated mortality risk among Black and White veterans. The RR were expressed in terms of the difference in the annual average and

the minimum concentration of $PM_{2.5}$, and the results are interpreted as the change in mortality that would result if all cohort members were exposed to the minimum concentration of $PM_{2.5}$. The mortality rate using years 1976−2001 and $PM_{2.5}$ measured between 1999−2001 was higher among White veterans (RR:1.05 [95% CI: 1.01, 1.10]) compared with Black veterans (RR: 0.82 [95% CI: 0.75, 0.89]). This effect was less pronounced when only examining the cohort between 1997 and 2001 (White RR: 1.03 [95% CI: 0.91, 1.17], Black RR: 0.96 [95% CI: 0.76, 1.21]) (Lipfert and Wyzga, 2020). Another study that examined the association between long-term $PM_{2.5}$ exposure and nonaccidental mortality among Medicare beneficiaries by Wang et al. (2020) observed positive, but equal, RR among Black (RR: 1.02 [95% CI: 1.02, 1.02]) and White (RR: 1.03 [95% CI: 1.02, 1.03]) beneficiaries.

Bennett et al. (2019) evaluated life-expectancy changes and $PM_{2.5}$ among differing racial groups in the U.S. In this study, counties with $PM_{2.5}$ concentrations that exceeded 2.8 $\mu g/m^3$ and had a high proportion of Black or African Americans were associated with lower life expectancy. This difference was also greater among females compared with males (Figure 3-33). The study by Jorgenson et al. (2020) that assessed the intersection between $PM_{2.5}$ exposure, Black race, and income inequality also demonstrated that states with a high percentage of Black populations had worse life expectancy at birth associated with $PM_{2.5}$. When including a three-way interaction between $PM_{2.5}$, Black race, and income inequality, the slope for $PM_{2.5}$ and life expectancy becomes more negative as the percent of the population that is Black and the income inequality increase. Overall, this study states that $PM_{2.5}$ appears to have the largest effect on life expectancy in states with a high level of income inequality and a larger percentage of people of Black race (Figure 3-41).



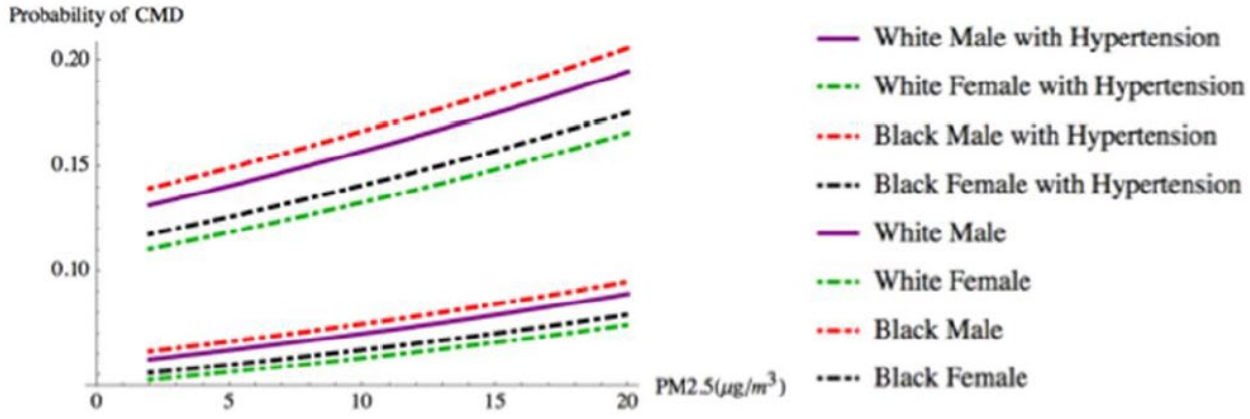
Source: Jorgenson et al. (2020)

Figure 3-41 Relationship between life expectancy and $PM_{2.5}$ exposure by income inequality and percent Black.

Recent epidemiologic studies also evaluated specific causes of death attributable to $PM_{2.5}$ stratified by race and ethnicity. In an analysis of the NIH-AARP Diet and Health Study (1995−2011), Lim et al. (2018) evaluated diabetes mortality. Minority participants (i.e., Non-Hispanic Black, Hispanic, Asian, Pacific Islander, or American Indian/Alaskan Native, or unknown race/ethnicity, referred to as

"Other" in the study) had an association larger in magnitude between annual $PM_{2.5}$ exposure and diabetes mortality (HR: 1.27 [95% CI: 1.02, 1.58]), compared with White participants (HR: 1.05 [95% CI: 0.96, 1.14]). However, other studies that examined whether there are disparities in $PM_{2.5}$-related cause-specific mortality did not report results consistent with Lim et al. (2018). The study by Parker et al. (2018) that used data from the NHIS between 1997 and 2001 to evaluate heart disease mortality and annual $PM_{2.5}$ exposure reported the largest association among White individuals (HR: 1.10 [95% CI: 1.05, 1.15]), with associations smaller in magnitude for Black (HR: 1.04 [95% CI: 0.94, 1.15] and Hispanic (HR: 1.03 [95% CI: 0.95, 1.12] individuals, and no evidence of an association for individuals of "other" races (HR: 0.90 [95% CI: 0.75, 1.07]). Finally, the study by Wang et al. (2020) evaluating over 53 million Medicare beneficiaries showed associations between $PM_{2.5}$ and cause-specific mortality that were larger in magnitude among White beneficiaries compared with minority beneficiaries (i.e., Black, Asian, Hispanic race/ethnicity, referred to as "non-White" in the study) for cardiovascular mortality (White RR: 1.05 [95% CI: 1.05, 1.06], minority RR 1.03 [95% CI: 1.02, 1.03]), heart disease mortality (White RR: 1.07 [95% CI: 1.07, 1.08], minority RR 1.03 [95% CI: 1.02, 1.04]), and vascular disease mortality (White RR: 1.07 [95% CI: 1.06, 1.08], minority RR 1.05 [95% CI: 1.04, 1.06]).

In a study of post-menopausal women enrolled in the WHI, Honda et al. (2017) estimated the association between long-term exposure to $PM_{2.5}$ and incident hypertension by individual race/ethnicity, and also by dichotomizing (White versus minority participants [i.e., Black, Asian/Pacific Islander, Hispanic/Latino, referred to as "non-White" in the study]). This study indicated that the association between $PM_{2.5}$ and incident hypertension was larger in magnitude among Asian/Pacific Islander (HR: 1.34 [95% CI: 1.00, 1.64]), minority (i.e., non-White in the study) (HR: 1.27 [95% CI: 1.17, 1.38]), and Black participants (HR: 1.26 [95% CI: 1.06, 1.44]) compared with White participants (HR: 1.15 [95% CI: 0.99, 1.35]). However, a cross-sectional study evaluating a cohort of community center health patients located in 12 southeastern U.S. states evaluated self-reported cardiometabolic disease (defined as cardiovascular disease, stroke, and diabetes) and long-term $PM_{2.5}$ exposure reported no differences in the association by race (Juarez et al., 2020) (Figure 3-42).



Source: Juarez et al. (2020)

Figure 3-42 Probability of cardiometabolic disease and $PM_{2.5}$ exposure, stratified by race, gender, and hypertension status.

3.3.3.3. Summary of Recent Evidence on At-Risk Populations in the Context of Conclusions of the 2019 Integrated Science Assessment for Particulate Matter

Within the 2019 PM ISA, evidence was evaluated that indicated some populations and lifestages are at increased risk of a $PM_{2.5}$-related health effect (2019 PM ISA, Chapter 12). These disparities between populations and lifestages were in some cases found to be attributed to differences in health risks as well as to exposure. When considering indicators for SES, such as income or educational attainment, having low income, or residing in a low-income area, studies were evaluated that reported associations larger in magnitude between mortality and long-term $PM_{2.5}$ exposure, compared with populations with higher income or living in higher income neighborhoods. However, there was inconsistent evidence of differential risk when comparing across populations with low and high educational attainment. Studies evaluating composite metrics, including a combination of SES factors and even some measures of race/ethnicity, generally demonstrated associations larger in magnitude between various health outcomes and long-term $PM_{2.5}$ exposure, thus demonstrating the complexity of SES indicators. Additionally, evidence was presented in the 2019 PM ISA that indicated a consistent disparity in $PM_{2.5}$ exposure among different racial and ethnic groups. This disparity also translated to PM-related health risks, specifically demonstrating that Black populations were at higher risk for $PM_{2.5}$-related health outcomes, such as mortality. Taken together, the 2019 PM ISA determined that the evidence was suggestive that people of low SES and adequate to indicate that race and ethnicity, specifically minority populations including Black populations, are at increased risk of $PM_{2.5}$-related health effects, in part due to disparities in exposure. Overall, the recent studies support the conclusions of the 2019 PM ISA.

Recent epidemiologic studies published since the 2019 PM ISA supports the evidence that SES may modify the association between $PM_{2.5}$ exposure and $PM_{2.5}$-related health risk. Studies

evaluating $PM_{2.5}$-related health risks by SES add to the growing evidence presented in the 2019 PM ISA. In addition to the indicator-SES metrics (e.g., income, educational attainment), several recent studies explored composite measures of neighborhood SES, which consistently demonstrated a disparity in both $PM_{2.5}$ exposure and the risk of $PM_{2.5}$-related health outcomes. Additionally, the recent evidence supported the conclusions that lower SES is associated with cause-specific mortality and certain health endpoints (i.e., MI and CHF), but less so for all-cause or total (nonaccidental) mortality (Section 3.3.3.1).

Consistent with the evidence presented in the 2019 PM ISA, recent studies continue to support and extend the evidence that disparities in $PM_{2.5}$ exposure and health risk exist among different racial and ethnic groups. Those of Black race, or who live in predominantly Black neighborhoods, are consistently subjected to the higher $PM_{2.5}$ exposures, especially when compared with non-Hispanic White groups. Recent studies also continue to support racial and ethnic disparities in the association between $PM_{2.5}$ exposure and cause-specific mortality or certain health endpoints (i.e., incident hypertension), especially when comparing Hispanic and non-Hispanic Black populations with non-Hispanic White populations. However, similar to SES, there was less consistency when evaluating $PM_{2.5}$ exposure and all-cause or total (nonaccidental) (Section 3.3.3.2).

4. EVALUATION OF RECENT WELFARE EFFECTS EVIDENCE

The Integrated Science Assessment for Particulate Matter (2019 PM ISA) concluded a *causal relationship* for each of the three nonecological welfare effects categories evaluated: visibility effects, climate effects, and materials effects. However, the welfare effects studies evaluated within this chapter represent only those studies most informative in considering potential revisions to the PM NAAQS as defined by the scope of this Supplement (Section 1.2.2), specifically studies that inform the relationship between PM and visibility impairment. Within this section the evaluation of recent studies is performed in the context of the studies evaluated and scientific conclusions presented in the 2019 PM ISA. As a result, within the following section, the summary and causality determination from the 2019 PM ISA is presented prior to the evaluation of recent studies published since the literature cutoff date of the 2019 PM ISA that examine the relationship between PM and visibility impairment (Section 4.2). This approach allows for a full accounting of the evidence that formed the basis of the key scientific conclusions in the 2019 PM ISA with respect to visibility impairment and the identification of specific sections of the 2019 PM ISA that provide additional details on the total evidence base being considered in the process of reconsidering the PM NAAQS.

The studies evaluated in the following sections represent only those studies most informative in considering potential revisions to the PM NAAQS (i.e., that provide new information on public preferences and/or methodologies or quantitative analyses of visibility impairment). As a result, the summary section (Section 4.3) for visibility effects conveys how the evidence from recent studies fits within the scientific conclusions of the 2019 PM ISA, and indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with and reduces uncertainties), or does not support (is not consistent with) the causality determination for visibility effects in the 2019 PM ISA.

4.1. Summary of Evidence for Visibility Effects from 2019 Integrated Science Assessment for Particulate Matter

Overall, visibility in most regions of the U.S. has improved since the 2009 PM ISA, as indicated by lower estimates of light extinction. The greatest improvements have occurred in the eastern half of the country, in regions with the poorest visibility. This has likely occurred because of a reduction in SO_2 emissions, resulting in lower ammonium sulfate concentrations, because ammonium sulfate has historically accounted for a large fraction of $PM_{2.5}$ mass in the eastern U.S., and also because ammonium sulfate is more effective than other $PM_{2.5}$ components at scattering light. The resulting decrease in $PM_{2.5}$ in the eastern part of the country has resulted in better visibility.

Rural visibility impairment is greatest in eastern U.S. regions, including the Southeast, East Coast, Mid-South, Central Great Plains, and Appalachian regions. In contrast, visibility is better, on average, in most regions of the western U.S. Urban visibility is also generally better in the western part of the country than in the east, except for urban areas in California and Alaska. In part, this reflects the difference in $PM_{2.5}$ composition between the east and west, with a greater fraction being made up of ammonium sulfate in the eastern U.S. and of particulate organic matter in the west. The effectiveness of light extinction by $PM_{2.5}$ depends on composition and relative humidity, with low scattering efficiency from $PM_{10-2.5}$, moderate scattering efficiency by organic mass and sea salt, high scattering efficiency by ammonium sulfate and ammonium nitrate, and high total light extinction (scattering + absorption) by light-absorbing carbon. However, the difference in light extinction between the eastern and western U.S. also reflects considerably higher $PM_{2.5}$ concentrations in the eastern U.S. and California than in the rest of the western U.S.

Altogether, new results and observations discussed in the 2019 PM ISA regarding atmospheric visibility provide evidence that atmospheric visibility has improved as PM concentrations have decreased, that regional and seasonal differences in atmospheric visibility parallel regional and seasonal PM concentration patterns, and that regional differences in the relationship between PM and visibility are due to differences in PM composition characteristics, rather than any factors beyond PM. These results confirm a well-established relationship between PM and visibility summarized in the 2009 PM ISA and earlier assessments. **Overall, the evidence is sufficient to conclude that a causal relationship exists between PM and visibility impairment.**

4.2. Recent Studies That Inform the Relationship between PM and Visibility Effects

Within the 2019 PM ISA (Section 13.2), studies that assessed the relationship between PM and visibility impairment were evaluated. These included preference studies to assess acceptability of visual air quality (Section 4.2.1), as well as field studies and computational methods to evaluate trends in visual air quality (Section 4.2.2). Some studies published since the literature cutoff date for the 2019 PM ISA provide additional insight into the PM-visibility impairment relationship.

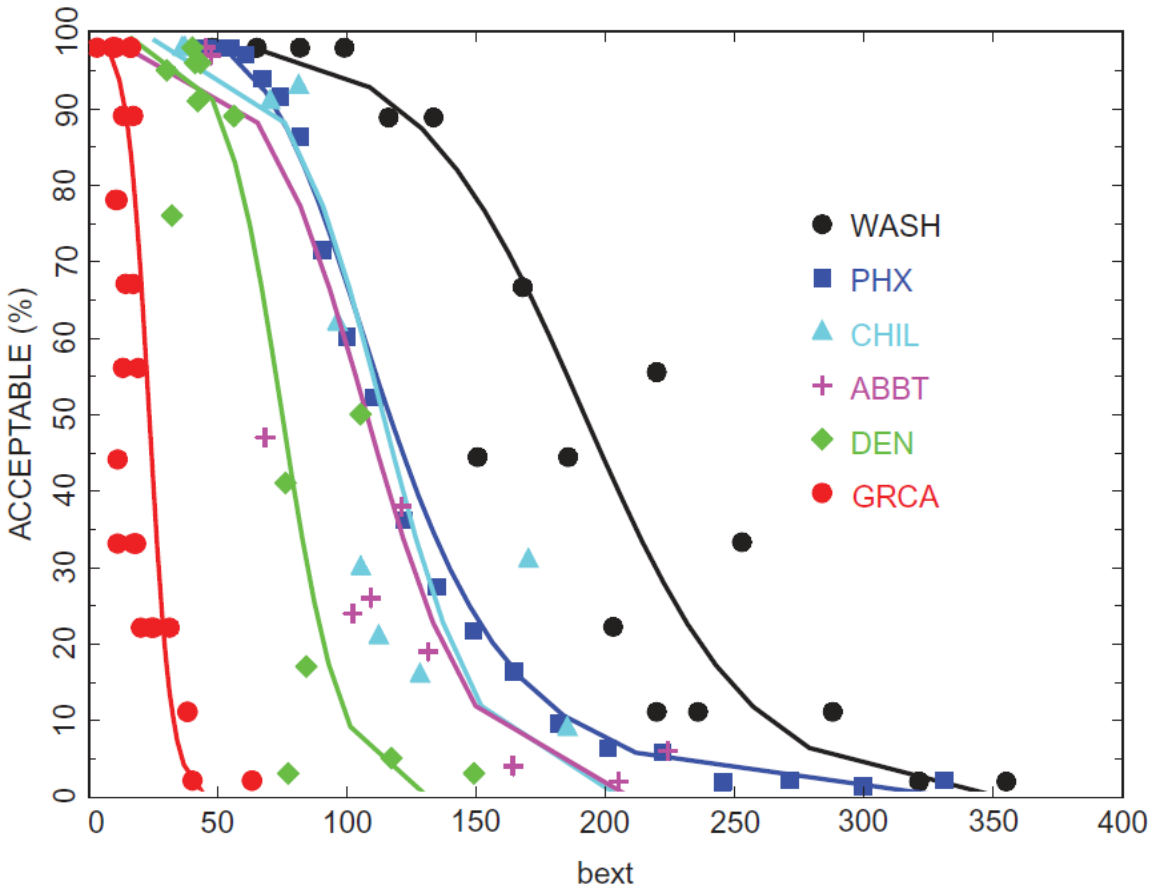
4.2.1. Visibility Preference and Light Extinction

A recent study by Malm et al. (2019) reported results from a new visibility preference study and evaluated the consistency between previous visibility preference studies. The main conclusion of this study was that the level of acceptable visual air quality is more consistent across studies using metrics that evaluate the distinction of an object from a background than using metrics that evaluate the greatest distance at which an object can be observed. As described in the 2019 PM ISA, two fundamental

characteristics of atmospheric visibility impairment are (1) a reduction in visual range, the greatest distance through the atmosphere at which a prominent object can be identified, and (2) a reduction in contrast, the sharpness with which an object can be distinguished from another object or background (Malm, 2016). Both of these concepts can be expressed in terms of an *extinction coefficient* (b_{ext}), which relates the distance of an observed object to light extinction following the Beer-Lambert Law (U.S. EPA, 2019). In practice, assessment of visibility impairment typically involves estimating the amount of light extinction (b_{ext}) from measurements of PM species concentrations (Section 4.2.2).

The demand for good visual air quality has been evaluated in multiple diverse locations using visibility preference studies with similar protocols. In these studies, respondents are shown photographic slides or hard copy photographs of a single scene under various visibility conditions and asked to (1) rate the visual air quality for each photograph on a scale from 1 (poor) to 7 (excellent) and (2) judge whether the visual air quality depicted in the image was considered to be acceptable or unacceptable. Visibility preference results from eight locations have been published between 1991 and 2019 using this approach (Malm et al., 2019), including five urban and two non-urban locations in the U.S. or Canada. Results from the five urban locations were all reported before publication of the 2009 PM ISA (U.S. EPA, 2009), where they are reviewed in detail. Results to these studies were generally reported in terms of light extinction (b_{ext}), or related metrics concerned with the distance at which an object can be seen, like visual range. When results were compared between different locations, a wide range in acceptable values was observed for these metrics. For example, median acceptable visual range values ranged from 20 km in Washington, DC to 59 km in Denver (U.S. EPA, 2009).

Although no new visibility preference studies in the U.S. had been reported between the publication of the 2009 PM ISA and the 2019 PM ISA (U.S. EPA, 2019), an additional U.S. study of the Grand Canyon was published since that time, and previous studies that were summarized in the 2009 ISA were reanalyzed using alternative visibility metrics that reduced the variability in acceptability between settings and locations (Malm et al., 2019). Figure 4-1 (Malm et al., 2019) shows the percentage of observers that indicated acceptable visual air quality, labeled acceptable (%) on the y-axis, as a function of light extinction, labeled b_{ext} on the x-axis. Data are based on rankings of photographic images from six visibility preference studies conducted in Phoenix, AZ (ADEQ, 2003); Chilliwack and Abbotsford, BC (Pryor, 1996), Denver, CO (Ely et al., 1991), Washington, DC (Abt, 2001), and the Grand Canyon, AZ (Malm et al., 2019).



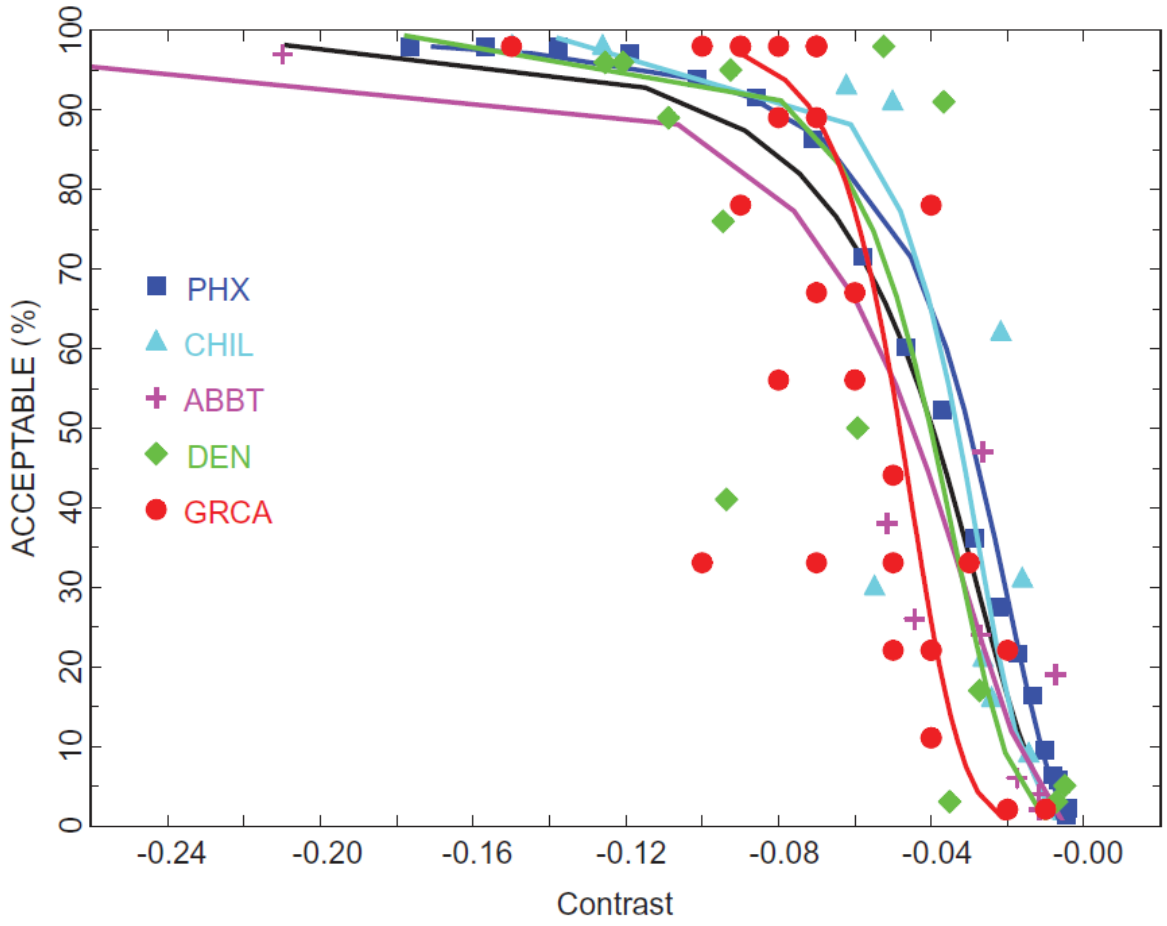
Source: Malm et al. (2019)

Figure 4-1 Percent acceptability levels plotted against light extinction (b_{ext}) for each of the images used in studies for Washington, DC (WASH), Phoenix, AZ (PHX), Chilliwack, BC (CHIL), Abbotsford, BC (ABBT), Denver, CO (DEN), and the Grand Canyon, AZ (GRCA).

These results clearly demonstrate a large range in light extinction (b_{ext}) across different locations considered acceptable by 50% of observers, indicating that metrics based on light extinction are not universal indicators of visibility preference levels. For example, considerably more light extinction was regarded as acceptable by 50% of observers for the Washington, DC scene (192 Mm^{-1}) than for the Grand Canyon, AZ scene (23 Mm^{-1}) (Malm et al., 2019). For other locations the amount of light extinction considered acceptable by 50% of observers was intermediate between Washington, DC and the Grand Canyon, AZ (Malm et al., 2019). For context, urban monthly average b_{ext} derived from 2011 to 2014 Chemical Speciation Network (CSN) data presented in the 2019 PM ISA was within this range for at least 1 month in all 31 U.S. regions analyzed (U.S. EPA, 2019).

Ideally, the relationship between the acceptability rating and the metric used for visibility impairment would be independent of the scene being observed (Malm et al., 2019). However, Figure 4-1 shows that when using light extinction or any universal haze metric, the response was highly dependent on the scene. Malm et al. (1981) showed that visual air quality judgments like those applied in visibility preference studies are related to contrast of landscape features and thus are dependent on the integration of haze over the sight paths between the observer and landscape features. Based on these results, Malm et al. (2019) suggested that scene-dependent metrics like contrast, which integrate the effects of b_{ext} along the sight paths between observers and landscape features, are better predictors of preference levels than universal metrics like light extinction. The explanation for this is that light extinction alone is not a measure of haze (Malm et al., 2019), but of light attenuation per unit distance, and visible haze is dependent on both light extinction and distance to a landscape feature. As a result, more haze is required to affect a nearby feature than more distant features, and landscape features at different distances from an observer each have a unique sensitivity to changes in light extinction, and consequently to PM mass concentration (Malm et al., 2019).

Figure 4-2 shows acceptability levels for the same studies in Figure 4-1 plotted against apparent contrast of the distant feature most sensitive to haze. When the features reach the visual range, corresponding to a contrast between approximately −0.03 and −0.05, about 50% of observers rated the image as not acceptable. When acceptability is expressed as a function of contrast in Figure 4-2, the response is less dependent on scene, as indicated by a smaller difference between average acceptability between studies than when acceptability is expressed as a function of light extinction in Figure 4-1. This is because most features in the Grand Canyon, AZ scene were more than 10 km distant, while landscape elements in the other studies were closer (Malm et al., 2019).



Source: Malm et al. (2019)

Figure 4-2 Percent acceptability levels plotted against apparent contrast of distant landscape features for each of the images used in studies for Phoenix, AZ (PHX), Chilliwack, BC (CHIL), Abbotsford, BC (ABBT), Denver, CO (DEN), and the Grand Canyon, AZ (GRCA).

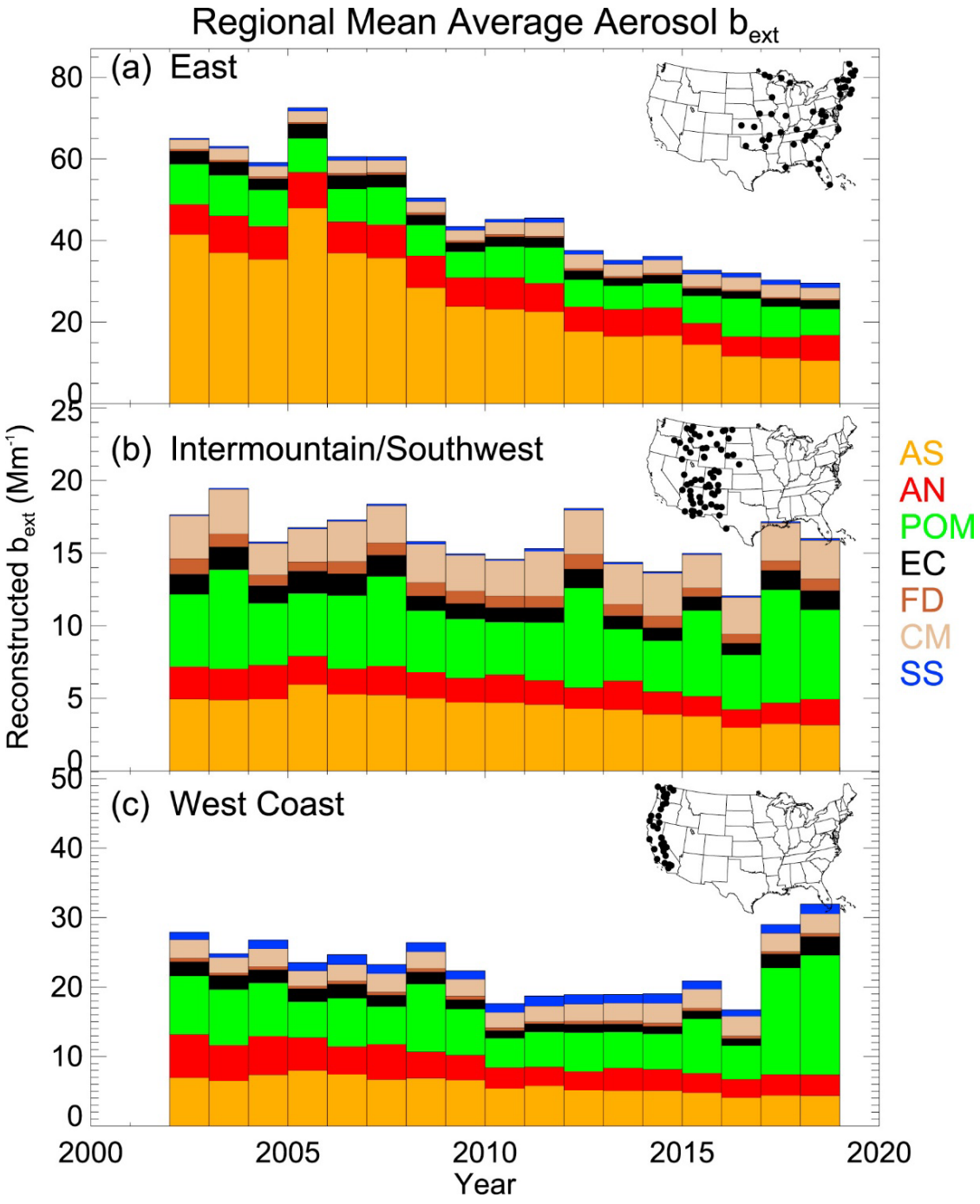
Malm et al. (2019) concluded that visibility preference studies suggest that about 50% of individuals would find visibility unacceptable if at any time the more distant landscape features nearly disappear, and that this occurs when these features are near the visual range and have contrast levels of approximately −0.03 to −0.05. Further, an acceptability level of 90% would require contrast levels to remain above a level of about −0.01.

4.2.2. Recent Estimates of Light Extinction Trends

The 2019 PM ISA reported that light extinction by PM was decreasing in most regions of the U.S. and that the greatest improvements had occurred in the eastern half of the country, in regions with

the poorest visibility based on the analysis of Interagency Monitoring of Protected Visual Environments (IMPROVE) network (U.S. EPA, 2019). Analysis of IMPROVE network data since the publication of the 2019 PM ISA show that the trends of decreasing light extinction and decreasing contribution of ammonium sulfate to total light extinction have continued in the eastern U.S., but that in the western part of the country, changes in total light extinction were smaller, and the contribution of particulate organic matter to atmospheric light extinction was increasing due to increasing wildfire emissions (Hand et al., 2020). On average, light extinction decreased by 1.8% per year from 1990 to 2018 and by 2.8% per year from 2002 to 2018. In the eastern U.S., the light extinction coefficient decreased by 4.3% per year from 2002 to 2018 and was associated with major reductions of SO_2 and NO_X emissions (Hand et al., 2020). The reduction in light extinction reported by Hand et al. (2020) is supported by the declining trend in sulfate concentrations detailed in the 2019 PM ISA (U.S. EPA, 2019).

The trend in light extinction is depicted in Figure 4-3, which shows regional time-series plots of estimated annual mean b_{ext} for major aerosol species aggregated from individual remote and rural monitors for the eastern U.S. (east of 100º W), the Intermountain West and Southwest (between 100º W and 116º W), and the West Coast (west of 116º W) from 2002 to 2018 as reported by Hand et al. (2020). The greatest declines in b_{ext} were observed in the eastern U.S., where annual mean total b_{ext} declined by 74% from 2002 through 2018 and light extinction by ammonium sulfate, which was estimated to account for 72% of total light extinction in 2002-2004, decreased by 148% (Hand et al., 2020). The annual mean b_{ext} was also significantly highly correlated ($r = 0.096$) with combined $SO_2 + NO_x$ total emissions in the eastern U.S. (Hand et al., 2020). During the period 2016–2018, the average contribution to total reconstructed light extinction in the eastern U.S. was 55% from ammonium sulfate and ammonium nitrate combined, 31% from carbonaceous aerosols, and 14% from fine dust, coarse particulate matter, and fine sea salt combined. Compared with 2016–2018, average contributions during 2002–2004 of 72% from ammonium sulfate and ammonium nitrate combined, 21% from carbonaceous aerosols, and 5% from fine dust, coarse particulate matter, and fine sea salt combined. Hand et al. (2020) also observed that the highest b_{ext} value had shifted westward from the Ohio Valley and Appalachians to the agricultural regions of the central U.S.



Source: Hand et al. (2020)

Figure 4-3 **Annual mean reconstructed light extinction (b_{ext}) for the a) East, b) Intermountain West/Southwest, c) West Coast by species, including ammonium sulfate (AS), ammonium nitrate (AN), particulate organic matter (POM), fine dust (FD), coarse mass (CM), and sea salt (SS). Map insets show individual sites aggregated into regional means.**

In the western regions of the U.S., the reduction of total reconstructed b_{ext} was smaller, decreasing by 15% in the Intermountain West and Southwest and 25% along the West Coast (Hand et al., 2020). In these regions, the contribution of ammonium sulfate and nitrate had been roughly equal to the contribution of carbonaceous aerosols (i.e., organic mass and elemental carbon) during 2002–2004 in both regions, but in 2016–2018, light extinction became dominated by carbonaceous aerosols, which accounted for 45% of reconstructed total light extinction in the Intermountain/Southwest and 51% in the West Coast region. Although some of this change occurred because ammonium sulfate and nitrate also decreased in these regions, an increase in wildfire emissions was also a likely contributor (Hand et al., 2020). Therefore, the analysis conducted by Hand et al. (2020) indicates that the composition of haze has shifted away from being dominated by sulfate to having greater contributions from carbonaceous and crustal aerosols. Additionally, as emissions of SO_2 and NO_X continue to decline, contributions to haze from unregulated sources including oil and gas extraction, agricultural activities, international sources, wildfires, and windblown dust seem to be increasing.

4.2.3. Recent Advancements in Visibility Monitoring and Assessment

The changing PM concentrations and composition in the U.S. have also resulted in an increasing bias in b_{ext} estimates (Prenni et al., 2019). An artifact of the method used to estimate light extinction from national monitoring network data could be contributing up to 1% per year in the eastern U.S. and 0.5% per year in the western U.S. to apparent long-term trends Hand et al. (2020). Research is progressing to address these concerns about increasing bias in light extinction estimates, and an alternative approach to estimating the split of component mass between large and small size modes reduced the bias (Prenni et al., 2019). A more detailed explanation of this approach in the context of the evolution of the IMPROVE algorithm used to estimate light extinction from the IMPROVE network is presented in the Appendix A, Section A.1.

Other recent research has addressed the effects of relative humidity on light extinction, the effect of increasing wildfires and atmospheric dust, and development of new instrumentation and measurement methods. A 25% underprediction was reported when reconstructed light extinction was compared with open-path cavity ringdown spectrometry measurements of light extinction in the Great Smoky Mountains National Park during the summer of 2016 by Gordon et al. (2018). The authors concluded that the accuracy of light extinction estimates from both the original and revised IMPROVE equations (Equations A-1 and A-2 in Appendix A, Section A.1) was reasonable at average relative humidity, but substantially lower at both higher and lower humidity

The importance of including relative humidity in estimating light extinction in urban areas of the eastern U.S. was demonstrated in the Baltimore, MD-Washington, DC area (Beyersdorf et al., 2016). On days when PM was transported from the north, $PM_{2.5}$ concentrations averaged 5.4 micrograms per cubic meter ($\mu g/m^3$) and the variability of light extinction was controlled primarily by differences in PM

concentrations. However, substantially higher concentrations, averaging 18.4 $\mu g/m^3$, were observed for westerly PM transport from the Ohio River Valley, PM was more hygroscopic, and the variability of light extinction was controlled by both $PM_{2.5}$ concentration and relative humidity (Beyersdorf et al., 2016).

Recent decreases in SO_2 and NO_X emissions have coincided with increasing PM emissions from wildland fires (U.S. EPA, 2019) as well as dust in some regions of the U.S. (Lambert et al., 2020). As a result, recent studies have focused on visibility impairment specifically from fire-related PM. Recent estimates of mass scattering efficiencies for wildland fire smoke ranged from 2.50 to 4.76 m^2/g, and increased with particle median diameter, as expected from theoretical predictions (Laing et al., 2016). Mass scattering efficiencies of fire-related PM were observed to increase by 56% during the first 2−3 hours after emission, at least in part due to increasing particle size during atmospheric aging (Kleinman et al., 2020). The large and rapid change in mass scattering efficiencies during atmospheric aging presents a challenge for accurately estimating light extinction based on constant mass scattering coefficients, as in Equations A-1 through A-4 in Appendix A, Section A.1.

Recent studies have also introduced new instrumentation and measurement methods that could help to reduce uncertainties in light extinction. Multi-wavelength light attenuation methods used as a part of thermal/optical carbon analysis in the IMPROVE and Chemical Speciation Networks (2019 PM ISA, Section 2.4 and Section 13.2.4) were initiated in 2016 and are used to estimate brown carbon, which in turn can be used to estimate biomass burning contributions to atmospheric light absorption (Chow et al., 2021). Application of a paired-wavelength method to estimate light absorption by brown carbon resulted in a factor of two increase in the estimate of the contribution of brown carbon to light absorption in CSN network samples from 2016 to 2017 (Chow et al., 2021). These results suggest a considerably greater contribution of organic PM to light absorption by PM than could be estimated using network thermal/optical methods in place before 2016. This is a highly relevant result given that organic matter has recently overtaken sulfate as the most abundant $PM_{2.5}$ component in many locations, and that wildland fire emissions are an increasing source of PM (U.S. EPA, 2019).

Capabilities for estimating light extinction from photographic images have also progressed. In the 2019 PM ISA photography is identified as one of several methods of measuring light extinction (U.S. EPA, 2019), and results from image processing techniques had been shown to be highly correlated with measured light extinction under hazy conditions. Additionally, a recent study demonstrated that light extinction could also be estimated quantitatively from photographic images under more pristine conditions from webcams that are routinely operated at the Grand Canyon and Great Smoky Mountains National Parks (Malm et al., 2018).

4.3. Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Visibility Effects

Recent studies published since the 2019 PM ISA have addressed several existing research gaps and emerging trends identified in the 2019 PM ISA. Analyzing visibility preference study results using contrast as a metric greatly reduced the variability in acceptability between studies that reported results in terms of light extinction or related metrics. Evaluation of uncertainties and development of alternative approaches to estimating light extinction using the IMPROVE algorithm as well as alternative methods for analyzing both light extinction and PM species have helped to meet new needs introduced by rapidly decreasing sulfate and increasing fire-related contributions to PM. New measurements of physical and optical properties of wildfire smoke also provide useful new data for understanding PM sources responsible for light extinction.

Some recent studies evaluated in this section provide the following new insights:

- The wide range in response to the level of acceptable visibility observed across different settings was reduced by accounting for the distances of 20–59 km between observer and landscape feature as a part of a visibility metric. This reduction was demonstrated by observation of a smaller variation across different settings using apparent contrast than light extinction.
- Impacts of the rapidly decreasing sulfate and increasing fire-related contributions to PM have been evaluated in recognition that the changing nature of PM composition in the U.S. is changing the relationship between PM and visibility impairment.
- The changing relationship between PM and visibility impairment has led to increased bias and spurred alternate approaches that have reduced bias in the IMPROVE algorithm used to estimate light extinction.

Additional recent studies further support the conclusions in the 2019 PM ISA, specifically:

- In polluted environments most of the light extinction (b_{ext}) is due to mainly to scattering by $PM_{2.5}$; although absorption by elemental carbon and some crustal materials, as well as scattering by coarse PM, are important in some locations.
- Light extinction (b_{ext}) is generally elevated in urban centers compared with surrounding rural areas, particularly in the western U.S.
- In practice, b_{ext} is estimated with reasonable accuracy using routinely available PM species monitoring data using data on dry mass extinction efficiency and hygroscopicity growth functions for major species. Mass extinction efficiencies can vary by a factor of 10 or more between particulate species, which vary by region and season as well as by urban versus rural settings.
- Mass extinction efficiencies for sulfates, nitrates, and organics in rural areas tend to increase with increasing concentrations due to shifts in the size distributions and more recent studies have shown a similar dependency on concentration in urban and polluted environments.

5. SUMMARY AND CONCLUSIONS

The 2019 Integrated Science Assessment for Particulate Matter (2019 PM ISA) is a comprehensive, systematic evaluation of the state of the science with respect to the health and welfare effects of PM that built upon previous assessments conducted in support of the National Ambient Air Quality Standards (NAAQS) for PM (U.S. EPA, 2019). While the 2019 PM ISA presented key scientific conclusions that informed many policy-relevant questions, as detailed in Section 2, a subset of these conclusions was most informative in the process of establishing the 2020 PM NAAQS (as discussed in Section 1.2), which is under reconsideration. Specifically, extensive evidence spanning scientific disciplines supported the conclusion of a *causal relationship* between both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality. In addition, an assessment of those populations potentially at increased risk of a PM-related health effect identified many populations and lifestages that experience both health risk and/or exposure disparities with some of the strongest evidence being for minority populations, with more limited evidence for people of low socioeconomic status (SES). Finally, in the assessment of welfare effects, there is extensive evidence indicating a *causal relationship* between PM and visibility effects, specifically visibility impairment. These topics are the basis of the scientific evaluation conducted in this Supplement.

Recent studies published in the U.S. and Canada provide additional support for the conclusions of the 2019 PM ISA. Overall: (a) recent studies support, and in some instances strengthen, the evidence presented in the 2019 PM ISA; (b) many of the recent epidemiologic studies evaluated report positive associations in areas with annual average or mean 24-hour avg $PM_{2.5}$ concentrations similar to, or in many cases lower, than those studies evaluated in the 2019 PM ISA; (c) some recent studies address key scientific topics for which the literature has evolved since the 2020 PM NAAQS review was completed, specifically since the literature cutoff date for the 2019 PM ISA, including examining health effects at near-ambient $PM_{2.5}$ concentrations in experimental settings, and examining the association between $PM_{2.5}$ exposure and COVID-19 infection and death, both of which provide preliminary evidence to further inform the $PM_{2.5}$-health effects relationship; (d) recent studies support, and in some instances extend, the evidence base indicating that minority populations, specifically Black individuals, and low SES individuals, experience disparities in both $PM_{2.5}$-related health risks and exposures compared with non-Hispanic White populations; and (e) recent studies further inform the role of PM on light extinction and visibility impairment. In conclusion, the results of recent studies evaluated in this Supplement to the 2019 PM ISA support, and in some instances extend, the evidence base that informed the scientific conclusions of the 2019 PM ISA.

Overall, this Supplement to the 2019 PM ISA found the following:

Cardiovascular Effects

Short-Term $PM_{2.5}$ Exposure

- Recent U.S. and Canadian multicity studies conducted within populations with diverse demographic characteristics continue to report positive associations between short-term $PM_{2.5}$ exposure and emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD), myocardial infarction (MI), and heart failure (HF) in studies with mean 24-hour avg $PM_{2.5}$ concentrations ranging from 7.1 to 15.4 $\mu g/m^3$. Consistent with the evidence in the 2019 PM ISA, most recent studies report no evidence of an association with stroke, regardless of stroke subtype. Further, recent epidemiologic studies like those evaluated in the 2019 PM ISA often employed hybrid exposure assessment models that allowed for a broader inclusion of geographic locations outside of the traditional urban centers where ambient monitors are located. In addition, these studies report evidence that continues to indicate an immediate effect of $PM_{2.5}$ on cardiovascular-related outcomes primarily within the first few days after exposure, and that associations generally persisted in models adjusted for copollutants. Furthermore, recent epidemiologic studies that conducted accountability analyses or employed alternative methods for confounder control also report positive associations across a number of statistical approaches, which further supports a relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. Overall, recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects.

Long-Term $PM_{2.5}$ Exposure

- Consistent with studies evaluated in the 2019 PM ISA, some of the strongest evidence for long-term $PM_{2.5}$ exposure and cardiovascular effects comes from epidemiologic studies examining cardiovascular mortality. Recent studies report consistent, positive associations for cardiovascular mortality, specifically IHD and stroke mortality, across different cohorts at varying spatial scales and across different exposure assessment and statistical methods with the majority having annual $PM_{2.5}$ concentrations ranging from 8.6 to 13.7 $\mu g/m^3$. In addition, recent studies of cardiovascular morbidity, specifically coronary heart disease (CHD), stroke, and atherosclerosis progression, most consistently report positive associations when focusing on individuals with preexisting diseases and among patients followed after a cardiac event or procedure, and not among the general population, which supports and extends the evidence presented in the 2019 PM ISA. Recent studies of cardiovascular mortality and morbidity also indicate that associations are relatively unchanged in copollutant models and that most assessments indicate a linear, no-threshold concentration-response (C-R) relationship with initial evidence of nonlinearity at lower concentrations for some outcomes. Finally, a few recent epidemiologic studies that employed alternative methods for confounder control, reduce some uncertainties related to potential confounding bias and further support a relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects. Overall, recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and cardiovascular effects.

Mortality

Short-Term $PM_{2.5}$ Exposure

- Since the literature cutoff date for the 2019 PM ISA, relatively few multicity studies have been conducted in the U.S. and Canada; however, these studies add to the extensive evidence base evaluated in the 2019 PM ISA and in previous assessments that reported consistent positive

associations across studies using different statistical models, exposure assessment approaches, and methods for confounder control. These recent studies continue to report associations at mean 24-hour average concentrations ranging from 8.8 to 12.4 μg/m^3; support an immediate effect of $PM_{2.5}$ on mortality (i.e., at lag 0 to 1 day); and report that associations remain relatively unchanged in copollutant models. Additionally, evidence continues to build that the heterogeneity in city-to-city $PM_{2.5}$-mortality risk estimates can be attributed partly to exposure differences, such as housing characteristics. The assessment of the C-R relationship continues to support a linear, no-threshold relationship with confidence in the shape at concentrations as low as 5 μg/m^3. The relationship between short-term $PM_{2.5}$ exposure and mortality is further supported by recent epidemiologic studies that employed alternative methods for confounder control and report consistent, positive associations. Overall, recent epidemiologic studies published since the 2019 PM ISA provide additional support to the evidence base that contributed to the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and mortality.

Long-Term $PM_{2.5}$ Exposure

- Recent epidemiologic studies conducted in the U.S. and Canada consisting of cohorts with mean annual $PM_{2.5}$ concentrations mostly below 12 μg/m^3, with the majority ranging from 5.9 to 11.65 μg/m^3, add to the large evidence base indicating consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality detailed in the 2019 PM ISA. The reporting of consistent, positive associations across studies examining various exposure windows, approaches for confounder adjustment, and exposure assessment methods that used different sources of data and were conducted at different spatial resolutions increases confidence in the relationship between long-term $PM_{2.5}$ exposure and mortality. In addition, recent studies further inform whether there is evidence of copollutant confounding; although there were some differences across studies, generally, associations persisted in copollutant models. The assessment of the C-R relationship continues to support a linear, no-threshold relationship at $PM_{2.5}$ concentrations > 8 μg/m^3. However, uncertainties remain about the shape of the C-R curve at lower $PM_{2.5}$ concentrations (< 8 μg/m^3), with some recent studies providing evidence for a sublinear, linear, or supralinear relationship at these lower concentrations. Finally, an extensive number of epidemiologic studies that conducted accountability analyses or employed alternative methods for confounder control have been conducted since the literature cutoff date of the 2019 PM ISA. Collectively, these studies that used different statistical approaches and cohorts spanning diverse geographic locations and populations provide additional support for the $PM_{2.5}$-mortality relationship. Overall, recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and mortality.

Additional Considerations Regarding the Health Effects of $PM_{2.5}$

Experimental Studies at Near-Ambient $PM_{2.5}$ Concentrations

- At the completion of the 2019 PM ISA, only a few controlled human exposure studies were identified that had been conducted in Europe and examined health effects with near-ambient $PM_{2.5}$ concentrations (i.e., at concentrations around the 24-hour PM NAAQS of 35 μg/m^3). These studies conducted in a population of older (55 years of age and older) overweight individuals provided initial evidence for vascular changes and reductions in heart rate variability (HRV) at low concentrations. A recent study in young, healthy participants also adds to the evidence base indicating effects at near-ambient $PM_{2.5}$ concentrations, specifically changes in lung function, cardiac function, and inflammation. However, these results are inconsistent with the evidence for both lung function and inflammation examined in controlled human exposure studies evaluated in

the 2019 PM ISA, which could be attributed to the higher ventilation rate and longer exposure duration used compared with other studies.

SARS-CoV-2 Infection and COVID-19 Death

- With the onset of the COVID-19 pandemic, recent epidemiologic studies examined whether both short-term and long-term $PM_{2.5}$ exposure is associated with SARS-CoV-2 infection and COVID-19 death. While some of these studies reported positive associations, these studies overall were subject to methodological issues that may influence results. Specifically, many consisted of an ecological study design, studies were conducted during on ongoing pandemic while the etiology of COVID-19 was still not understood (e.g., there are important differences in COVID-19-related health outcomes, such as by race and SES), and studies did not account for crucial factors that could influence results (e.g., stay-at-home orders, social distancing, use of masks, and testing capacity). While there is initial evidence of positive associations with SARS-CoV-R infection and COVID-19 death, uncertainties remain due to methodological issues.

Populations at Potentially Increased Risk of a PM-Related Health Effect

Socioeconomic Status

- Recent studies that use a variety of metrics to represent SES, including educational attainment and income, along with studies that used composite metrics to represent neighborhood SES, provide additional support indicating there may be disparities in $PM_{2.5}$ exposure and health risk by SES. These studies indicate that the strongest evidence of a health risk disparity for low SES is for cause-specific mortality and certain health endpoints (i.e., MI and CHF) when compared with higher SES groups.

Race and Ethnicity

- Building upon the conclusions of the 2019 PM ISA, recent studies continue to support disparities in $PM_{2.5}$ exposure and health risks by race and ethnicity, with the strongest evidence for minority populations, specifically Black populations. Black populations or individuals that live in predominantly Black neighborhoods experience higher $PM_{2.5}$ exposures, in comparison with non-Hispanic White populations. Additionally, there is evidence of health risk disparities for both Hispanic and non-Hispanic Black populations compared with non-Hispanic White populations for cause-specific mortality and incident hypertension.

Visibility Effects

- Recent studies indicate that using contrast instead of light extinction as a metric greatly reduced the variability in results in visibility preference studies. In addition, rapidly decreasing sulfate and increasing fire-related contributions to PM have led to a changing relationship between PM and visibility impairment, likely affecting estimates of light extinction. In response, alternate approaches to the application of the traditional IMPROVE algorithm for estimating light extinction have been developed that reduce the bias in light extinction estimates. Parallel efforts have better characterized light extinction by major contributors to PM, particularly for biomass burning. Overall, recent studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between PM and visibility.

Appendix A

Table A-1 Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu g/m^3$)[a]	Outcome	Confounders Considered	Copollutant Examination
Wei et al. (2019) Continental U.S. 2000−2012	Medicare ≥ 65 yr	Daily concentration for 1 × 1 km grid cells using validated satellite based neural network model calibrated using data from monitors (n = 1,928), C-V R2 = 0.83 overall, 0.78−0.88 by region (Di et al., 2016) Lag 0−1-day avg assigned based on ZIP code of residence.	NR	HA discharge data recorded on Medicare claims	Age, race, sex, MI, diet, time-invariant behavior factors, ZIP code-level SES, population density, ethnicity, access to parks, food, drug stores, day of week, seasonality, long-term trends. Temperature controlled using cubic spline with up to 9 df.	Correlation (*r*): NA Copollutant models with: NA
Leiser et al. (2019) Wasatch Front, UT (4 counties) 1999−2009	Medicare n = 19,602 (2,032 cardiac events) ≥ 65 yr	Daily average for ZIP code centroids (n = 123) using inverse distance weighting. Lags 0, 1, 0−2, and 0−6 days.	Lag 0: 10.96 Lag 1: 10.95 3-day avg: 10.96 7-day avg: 10.79	Hospital re-admission for IHD, MI (ICD-9 410), HF (ICD-9 428), dysrhythmia/ arrhythmia (ICD 427)	Maximum daily temperature, ZIP code- level median house-hold income, Charlson Comorbidity Index, enrollment in Medicare part A and B.	Correlation (*r*): NA Copollutant models with: NA

Table A-1 (Continued): Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu g/m^3$)[a]	Outcome	Confounders Considered	Copollutant Examination
Wing et al. (2017) Nueces county, TX 2000−2012	BASIC n = 317 events ≥ 65 yr	Daily $PM_{2.5}$ concentration from centrally located monitor. Lag 1 day.	Median: 7.7 IQR: 5.6 to 10.7	Passive and active surveillance of IS (i.e., acute onset neurologic lasting > 24 h)	Temperature and relative humidity, individual-level characteristics and time trends controlled by design	Correlation (*r*): NA Copollutant models with: Ozone Results did not change after co-adjustment
Evans et al. (2017) Monroe County, NY 2007−2012	Coronary syndrome/ unstable angina patients (n = 362) Mean age: 62.3 ± 12.9	Hourly average concentrations, one monitor, east side of Rochester adjacent to two major highways, patients reside within 15 miles of monitor. 1 h avg.	Mean (IQR): 7.1 (7.62) all year; 8.18 (5.96) Nov−Apr; 7.08 (7.80) May−Oct Upper (75th): 10.30 all year; 10.60 Nov−Apr 9.80 May−Oct Upper (Max): 79.2 all year; 79.20 Nov−Apr; 64.01 May−Oct	Physician-diagnosed STEMI (> 1 mm in ≥ 2 contiguous precordial leads, or ≥ 2 adjacent limb leads, or new or presumed-new left bundle branch block with angina)	3 h avg temp, RH	Copollutant models with: NA Correlation (*r*): Delta-C: 0.31 BC: 0.57 NO_2: 0.38 SO_2: −0.01 Ozone: 0.11 CO: 0.29

Table A-1 (Continued): Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu g/m^3$)[a]	Outcome	Confounders Considered	Copollutant Examination
Liu et al. (2020) Calgary, Alberta Canada 2004−2012	APPROACH n = 6,142 HAs among patients admitted to cardiology services	Hourly concentrations from three monitors positioned to represent background used to compute daily average $PM_{2.5}$ concentration. Long-term NO_2 concentrations at ZIP code of residential address estimated using LUR (Bertazzon et al., 2015). Lag 0, 1, 2 day and 3-, 5-day avgs.	Mean (SD): 9.79 (5.91) Median: 7.00 IQR: 6.17 Upper: NR	MI HAs captured in registry of cardiac catheterization patients	Temperature, RH	Copollutant models with: NA Correlation (*r*): O_3: −0.2 O_3 max: 0.08 NO: 0.08 CO: 0.07 PM_{10}: 0.43
Krall et al. (2018) Atlanta, GA (20 counties) 2002−2008 Birmingham, AL (7 counties) 2004−2008 Dallas, TX (12 counties) 2006−2008 Pittsburgh, PA (3 counties) 2002−2008 St. Louis, MO, and IL (16 counties) 2002−2007	Electronic billing databases of ED visits	Population-weighted average estimates estimated using 24 h avg from ambient monitors within each metropolitan area with CMAQ predictions (Friberg et al., 2017; Friberg et al., 2016). A priori lag 0 with sensitivity analyses for 2-day avg.	Mean (SD): Atlanta: 15.4 (7.1) Birmingham: 14.5 (7.1) Dallas: 10.8 (4.7) Pittsburgh: 15 (8.6) St. Louis: 13.8 (6.7) IQR: 8.71	ED visits: CHF (ICD-9 428); Cardiac dysrhythmia (ICD-9 427); IHD (ICD-9 410−414); Stroke (ICD-9 433−437)	Weekday, season, holidays, meteorology (lag Day 0 maximum temperature, lag Day 0−2 dew-point temperature), the hospitals reporting data for each day, cubic splines with 1 df for long-term trends	Correlation (*r*): Ozone; 0.47 EC: 0.5 OC: 0.68 SO_4: 0.81 NH_4: 0.77 (Correlations only reported when > 0.4) Copollutant models with: NA

Table A-1 (Continued): Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu g/m^3$)[a]	Outcome	Confounders Considered	Copollutant Examination
Ye et al. (2018) Atlanta, GA (5 counties) Aug 14, 1998−Dec 15, 2013		24 h avg from one monitor (Jefferson Street). A priori lag 0.	Mean (SD): 14.46 (7.69) IQR: 9.28 75th: 18.21	CVD ED visits (i.e., IHD, Dysrhythmia, and CHF)	Temporal trends and meteorology (maximum temperature, cubic function of minimum and dew point temperature, day of week, holiday, season, hospital participation period)	Correlation (*r*): CO: 0.47 NO_2: 0.50 SO_2: 0.24 Ozone: 0.44 WS Fe: 0.65 Copollutant models with: water-soluble Fe
Fisher et al. (2019) Contiguous U.S. 1999−2010	HPFS Men 40−75 yr in 1986 n = 51,529	Validated kriging models to estimate daily $PM_{2.5}$ concentration (Liao et al., 2006) Data from > 1,000 monitors used in model. Lags up to 3 days prior to stroke event and 4-day avg.	Mean (SD): 12.9 (7.4)	Self-reported stroke adjudicated by physician medical record review Multiple strokes at least 1 yr apart included OR Total Stroke Lag 0−3 (avg): 0.94 (0.80, 1.10) Lag 0: 1.01 (0.90, 1.14) Lag 1: 0.92 (0.82, 1.03) Lag 2: 0.93 (0.82, 1.04) Lag 3: 1.00 (0.89, 1.12)	Temperature controlled as a linear term (restricted cubic splines in sensitivity analysis) with individual-level covariates and time trends controlled by design	Correlation (*r*): NR Copollutant models with: NR

Table A-1 (Continued): Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu g/m^3$)[a]	Outcome	Confounders Considered	Copollutant Examination
Sun et al. (2019) U.S. 1993−2012	WHI n = 5,417 confirmed events Post-menopausal women aged 50−79 at enrollment	Daily $PM_{2.5}$ concentrations estimated using Kriging model (Liao et al., 2006) and assigned to residential address of participant. PEs 0-0.27; SPEs: −0.11−0.04; RMSSs~1.Lag 0, 0−1, and 0−2-day averages. Sensitivity analyses to evaluate 4, 5, and 6-day moving averages.	Median: 10.8 75th: 15.3 95th: 26.1 IQR: 8.2	Self-reported stroke (i.e., rapid onset of persistent neurologic deficit lasting > 24 h). Stroke type adjudicated by trained neurologists	Temperature and RH, individual-level characteristics and time trends controlled by design	Correlation (*r*): PM_{10}: 0.57 NO_2: 0.44 NO_X: 0.35 SO_2: 0.30 Ozone: 0.20 Copollutant models with: NR
Wyatt et al. (2020c) U.S. nationwide 2008−2014	USRDS Hemodialysis patients n = 351,294	Satellite derived $PM_{2.5}$ concentration estimates (AOD) integrated with chemical transport model predictions, meteorology, land use variables for 1 km grid cells (Di et al., 2016). Lag 0 and examination using unconstrained distributive lag model.	Mean: 9.3 Range: 0.05−155.16	CVD, dysrhythmia, HF 30-day hospital readmissions (ICD-9 codes: 401−405, 410−411, 413, 426−27, 428)	Temperature and RH. Individual-level characteristics, county characteristics (i.e., population size, risk Characteristics) day of the week, seasonal and long-term time trends controlled by design.	Correlation (*r*): NR Copollutant models with: NR

Table A-1 (Continued): Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu g/m^3$)[a]	Outcome	Confounders Considered	Copollutant Examination
deSouza et al. (2021) Continental U.S. 2000−2012	Medicaid adults (low-income and/or disabled) n = 3,666,657 CVD HAs	Daily average at ZIP code of residence. Predictions for 1 km^2 grid cells integrated remote sensing, chemical transport model outputs, meteorological and land-use variables. Ensemble model integrated machine learning algorithms. C-V R2 = 0.86 (Di et al., 2019). Lag Day 0−1 used in all analyses.	Mean (SD) 11.5 (7.3)	First HA for CVD (ICD-9 390−495); IHD (ICD-9 410−414); CHF (ICD-9 428); AMI 410.9; IS: (ICD-9 434.91)	Air and dew-point temperature (daily mean for 32 km^2 grid cells in U.S); individual-level factors, seasonality and long-term trends controlled by design.	Copollutant correlation (*r*): NR Copollutant models with: Ozone
McClure et al. (2017) Continental U.S. Exposure: 2003−2011 Outcome: 2003−2007 to 2011	REGARDS n = 30,239 n = 746 events	Integrated measurements from monitors and satellite derived $PM_{2.5}$ concentrations (AOD) estimated for 10 × 10 km grid cells across the U.S. (Al-Hamdan et al., 2014). Exposure assigned based on residential address. Lags 0, 1, 2 days.	≤ 12: n = 403 (53%) 12−150.4: n = 343 (47%)	Stroke (i.e., rapid onset of persistent neurologic deficit lasting > 24 h) defined by WHO criteria (WHO, 1989) ascertained by self-report and medical record review	Temperature and RH with individual characteristics and time trends controlled by design	Copollutant correlation (*r*): NR Copollutant models with: NR

AMI = acute myocardial infarction; APPROACH = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; Avg = average; BASIC = Brain Attack Surveillance in Corpus Christi: BC = black carbon; CHF = congestive heart disease; CMAQ = Community Multi-Scale Air Quality; C-V = cross-validation; CVD = cardiovascular disease(s); ED = emergency department; h = hour; HA = hospital admission; HF = heart failure; HPFU = Health Professionals Follow-up Study; ICD-9 = International Classification of Disease 9th revision; IHD = ischemic heart disease; IQR = interquartile range; km = kilometer(s); LUR = land use regression; MI = myocardial infarction; NA = not applicable; NR = not reported; PE = prediction error; PM_{10} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10; *r* = correlation coefficient; REGARDS = REasons for Geographic and Racial Differences in Stroke; RH = relative humidity; RMSS = root mean square standardized; SD = standard deviation; SPE = standardized prediction error; STEMI = ST segment elevation myocardial infarction; USRDS = U.S. Renal Data System; WHO = World Health Organization; WS Fe = water-soluble iron.

Table A-2 Study-specific details for epidemiologic studies using accountability analyses or alternative methods for confounder control to examine short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentration ($\mu g/m^3$)	Confounders	Copollutant Examination
Zhang et al. (2018) Albany, Bronx, Buffalo, Manhattan, Queens, and Rochester, NY 2005−2016	New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS) n = 1,922,918	Total cardiovascular disease; cardiac arrhythmia; cerebrovascular disease; chromic rheumatic heart disease; congestive heart disease; hypertension; ischemic heart disease; myocardial infarction; ischemic stroke	U.S. EPA Air Quality System for each of the six sites: Buffalo, Rochester, Albany, and New York City (Bronx, Manhattan, Queens). Hourly $PM_{2.5}$ concentrations were measured using tapered element oscillating microbalance monitors and 24-h daily averages were computed for each site and each day for which measurements of at least 75% of the hours that day in that site were available (18 h).	Case Period Median (25th, 75th Percentile): Albany: 7.2 (4.4, 11.4) Bronx: 8.8 (5.7, 13.8) Buffalo: 8.5 (5.6, 12.6) Manhattan: 10.5 (7.2, 15.3) Queens: 8.0 (5.2, 12.5) Rochester: 7.2 (4.5, 11.0) Control Period Median (25th, 75th Percentile): Albany: 7.2 (4.4, 11.3) Bronx: 8.8 (5.7, 13.8) Buffalo: 8.5 (5.6, 12.6) Manhattan: 10.5 (7.2, 15.3) Queens: 7.9 (5.2, 12.5) Rochester: 7.1 (4.5, 10.9)	Temperature; relative humidity	Correlation (*r*): NA Copollutant models with: NA

Table A-2 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine short-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentration ($\mu g/m^3$)	Confounders	Copollutant Examination
Qiu et al. (2020) Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont 2000−2012	Medicare Acute myocardial infarction n = 156,717 Congestive heart failure n = 207,774 Ischemic stroke n = 170,663	Acute myocardial infarction; congestive heart failure; ischemic stroke	Daily ambient levels of $PM_{2.5}$ (24 h averaged, $\mu g/m^3$) and ozone (8-h maximum, ppb) were predicted at a spatial resolution of 1 km from a machine learning algorithm that combined satellite remote censoring data, chemical transport models, land use, and meteorology, using a neural network. Daily averaged values were constructed by averaging the exposure levels of all grid cells within each individual ZIP code	Mean (SD): Acute myocardial infarction: 10.13 (6.48) Congestive heart failure: 10.08 (6.42) Ischemic stroke: 10.10 (6.47)	Temperature, relative humidity Age, sex, race, smoking history, cholesterol, BMI, preexisting medical conditions	Correlation (*r*): NA Copollutant models with: O_3
Wang et al. (2019) Rochester, NY 2005−2016	University of Rochester Medical Center Cardiac Catherization Laboratory n = 921	ST segment elevation myocardial infarction (STEMI)	New York State Department of Environmental Conservation air quality monitoring site, where $PM_{2.5}$, SO_2, O_3, CO, and black carbon were measured continuously throughout the study period (2005−2016) for patients residing within 15 miles of the monitoring station	Mean (SD) for All Years (2005−2016): 8.32 (7.17) Mean (SD) for Before (2005−2007): 10.37 (8.74) Mean (SD) for During (2008−2013): 8.31 (6.83) Mean (SD) for After (2014−2016): 6.67 (5.55)	Temperature and relative humidity	Correlation (*r*): NA Copollutant models with: SO_2, O_3, CO, BC

BC = black carbon; BMI = body mass index; EPA = Environmental Protection Agency; NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SD = standard deviation; SPARCS = New York State Department of Health Statewide Planning and Research Cooperative System; STEMI = ST segment elevated myocardial infarction.

Table A-3 Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration ($\mu g/m^3$)	Confounders Considered	Copollutant Examination
Rhinehart et al. (2020) Allegheny County, PA Jan 1, 2007 Rhinehart et al. (2020) Dec 1, 2017	Resident of Allegheny County, PA, and diagnosed with AF (ECG, ablation, cardioversion [ICD-10 427.31]). Excluded those <18 yr, reporting history of stroke, cardiothoracic surgery or with no record of follow-up. n = 31,414	Diagnosis of ischemic stroke on uniform electronic health record	Exposure: 1-yr avg assigned across entire study period Spatial saturation monitoring campaign (June−July 2012 and Jan−Mar 2013) and LUR to estimate 1-yr avg concentration within a 300 m buffer of participants geocoded address.	Mean: 10.6 Q4 (range): 11.11−15.74	Age, sex, race, neighborhood-level income and education	Correlation (*r*): NA Copollutant models with: NA

Table A-3 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration ($\mu g/m^3$)	Confounders Considered	Copollutant Examination
Chen et al. (2020) Ontario Canada Outcome: 2001−2016 Exposure: 2000−2016	ONPHEC (adults 35−85 yr residing ≥5 yr in Ontario Canada). Excluded prevalent cases of AMI	AMI ascertained using hospital discharge records (validation study: 89% sensitivity/93% specificity)	Annual $PM_{2.5}$ concentration assigned at centroid of postal code of residence reported for each year. AOD and $PM_{2.5}$ simulated by the GEOS-Chem chemical transport model. $PM_{2.5}$ measurements incorporated via geographically weighted regression. Final surface with 1 × 1 km resolution for Ontario (R square = 0.76 with ground level measurements)	Mean: 8.61 See Figure 1 (Chen et al., 2020)	Age, sex, income, education attainment, percentage of recent immigrants, unemployment rate, urban/rural residency, indicators for Greater Toronto Area and north/south	Correlation (*r*): BC: 0.97 Mineral Dust: 0.94 See salt: 0.87 NO_3: −0.87 Ammonium: 0.85 OM: 0.62 SO_4: 0.73
Weaver et al. (2021) Jackson, MS 2000−2004 to 2005−2008	JHS n = 5,306 African American adults 20−95 yr at baseline (2000−2004)	Hypertension (BP ≥ 140 diastolic BP ≥ 90 mmHg) or self-report of hypertensive medication use	Annual and 3-yr avg $PM_{2.5}$ concentration estimated for geocoded address. U.S. EPA Bayesian space−time downscaling fusion model to estimate census tract level $PM_{2.5}$ concentration (Berrocal et al., 2012, 2010a, b).	Visit 1: Annual average: 12.2 (IQR: 0.8) 3-yr avg: 12.4 (IQR: 0.4) Visit 2: 12.1 (IQR: 0.8) 3-yr avg: 12.4 (IQR: 0.4)	Education, smoking status, nutritional status, physical activity, NSAID use, date of measurement, sex, BMI, neighborhood SES, age, and food environment within 1.5 miles	Correlation (*r*): O_3 Visit 1: $PM_{2.5}$ (1-yr); $PM_{2.5}$ (3-yr) 1-yr: 0.12; 0.05 3-yr avg: −0.06; −0.03 Visit 2: 1-yr: 0.07; 0.19 3-yr avg: −0.32; −0.36 Copollutant models with: O_3

Table A-3 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration ($\mu g/m^3$)	Confounders Considered	Copollutant Examination
Weaver et al. (2019) Durham, Wake, or Orange counties, NC Exposure: 2000−2010 Outcome: 2001−2010	CATHGEN n = 2,254 cardiac catheterization patients residing in 3 NC counties.	CAD index > 23 (indicating 75% coronary vessel occlusion) MI ascertained using medical records	Annual average $PM_{2.5}$ concentration prior to index case. Daily mean $PM_{2.4}$ estimated at 1 km spatial resolution using AOD with chemical transport model, land use variables and meteorology (Di et al., 2016)	Annual average: 12.7 (SD: 1.1)	Age, sex, BMI, race, and smoking status	Correlation (*r*): NR Copollutant models with: NR
Loop et al. (2018) U.S. Nationwide 2003−2007 (baseline) to 2012	REGARDS n = 17,126 Black and White adults (≥ 45 yr old)	Total CHD (deaths and nonfatal MI combined), nonfatal MI	Annual average $PM_{2.5}$ concentration linked to geocoded residential address at baseline. Daily $PM_{2.5}$ concentration estimated for 10 × 10 km grid using ground-level monitoring data, satellite measurements of AOD.	Median: 13.6 75th: 14.8	1-yr mean temperature, season, race, region, urbanicity, income, education, age, gender, pack-years, BMI, alcohol use, physical activity, and calendar year	Correlation (*r*): NR Copollutant models with: NR

Table A-3 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration ($\mu g/m^3$)	Confounders Considered	Copollutant Examination
Honda et al. (2017) Exposure: 1980−2010 Outcome: 1993−1998 (recruitment) to 2010	WHI n = 44,255 post-menopausal women (average age 62 yr)	First self-report of medication for hypertension (SBP ≥140 mm Hg, or DBP ≥ 90 mm Hg)	Annual moving average $PM_{2.5}$ concentration estimated with daily concentrations from the AQS and IMPROVE networks using a universal kriging model (CV R2 = 0.88)	Mean: 13.2	Age, BMI, education, ethnicity, smoking status, physical activity, sodium intake, neighborhood SES, household income, employment status, insurance status, history of high cholesterol, history of cardiovascular disease, history of diabetes, clinical trial study arm, and WHI clinical site	Correlation (*r*): PM10: 0.56; $PM_{10-2.5}$: 0.03 Copollutant models with: NR
Duan et al. (2019b) Pittsburgh and Chicago, U.S.	SWAN n = 417 Black and White women (mean age 51 yr at baseline)	cIMT by ultrasound and plaque burden (i.e., four levels, with 0 for no plaque to 3 for a plaque taking up > 50% diameter of the artery)	Annual average 360 days prior to clinic visit calculated from monitors located within 20 km of residential address Daily $PM_{2.5}$ values retrieved from U.S. AQS (Green et al., 2016; Ostro et al., 2014)	Mean: 16.5 (baseline) 75th: 17.1 (baseline)	Age, race, education, SES, BMI, and CVD risk factors (i.e., smoking, total cholesterol, HDL-c, triglyceride, menopause status, hormone use, fasting glucose, antidiabetic medication, and antihypertensive medication)	Correlation (*r*): O_3: Copollutant models: with O_3

Table A-3 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration ($\mu g/m^3$)	Confounders Considered	Copollutant Examination
Duan et al. (2019a) Detroit, MI; Oakland, CA; Pittsburgh, PA; Chicago, IL; and Newark, NJ Exposure: 1999−2005 Outcome: 2009−2013	SWAN n = 1,188 women Mean age 59.6 yr	Mean cIMT, max cIMT, IAD and plaque presence or severity (i.e., four levels, with 0 for no plaque to 3 for a plaque taking up > 50% diameter of the artery)	5-yr avg 360 days prior to each clinic visit calculated from monitors located within 20 km of residential address Daily $PM_{2.5}$ values retrieved from U.S. AQS (Green et al., 2016; Ostro et al., 2014)	Mean (SD): 14.9 (1.9) 75th: 16.1 Figure 2	Age, race, education, SES, BMI, and CVD risk factors (i.e., smoking, total cholesterol, HDL-c, triglyceride, menopause status, hormone use, fasting glucose, antidiabetic medication, and antihypertensive medication)	Correlation (*r*): O_3: 0.56 Copollutant models : with O_3
Keller et al. (2018) Baltimore, MD Jul 2000−Aug 2002 through 2012 Exposure: Feb and Jun 2012	MESA Air n = 1,005	CAC progression (Agatston units)	Spatiotemporal prediction models used to long-term average $PM_{2.5}$ concentration from recruitment to exam based on each participants residential history (Keller et al., 2015). C-V R2 = 0.84.	Mean (SD): 15.9 (0.80)	Age, sex, race/ethnicity, site, scanner type, adiposity, physical activity, smoking, employment, total cholesterol, high-density lipoprotein level, triglyceride level, statin use, an index of neighborhood SES, education, and income	Correlation (*r*): NR Copollutant models: NR

Table A-3 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration ($\mu g/m^3$)	Confounders Considered	Copollutant Examination
Shin et al. (2019) Ontario Canada Exposure: 1998−2012 Outcome: Apr 2001−Mar 2015	ONPHEC Ontario residents (adults 35−85 yr) n = 5,071,956 (those with history of AF and stroke excluded)	AF and Stroke (first hospital admission for ischemic or hemorrhagic stroke) ascertained using administrative databases	5-yr moving average $PM_{2.5}$ concentrations estimated at residence using AOD and $PM_{2.5}$ simulated by the GEOS-Chem chemical transport model. Final surface with 1 × 1 km resolution for Ontario (R square = 0.82 for 2004×2008 5-yr mean)	Mean: 9.8 (SD: 2.9) IQR: 4.0 75th: 11.9 Max: 20	Age, sex, area level risk factors including SES, and geographic indicator variables to distinguish whether a participant's residence was located in the north or south of Ontario and whether it was urban or rural	Correlation (*r*): NO_2: 0.65 O_3 0.275 Ox: 0.668 Copollutant models: with NO_2, O_3, Ox
Bai et al. (2019) Exposure: 1998−2012 Outcome: Apr 2001−Mar 2015	ONPHEC Ontario residents (adults 35−85 yr) n = 5,062,146 CHF n = 5,141,172 AMI (those with history of CHF and MI excluded)	CHF and AMI ascertained using registries based on hospital discharge data	3-yr moving concentrations assigned to postal code participant residence estimated using AOD and $PM_{2.5}$ simulated by the GEOS-Chem chemical transport model. Final surface with 1 × 1 km resolution for Ontario	Mean: 9.6 (2.8) IQR: 3.5 75th: 11.4 Max: 20	Age, sex, area level risk factors including SES, and geographic indicator variables that distinguished participants based on the location of their residence, i.e., north or south of Ontario and urban vs. rural	Correlation (*r*): NO_2: 0.4 O_3 0.2 Ox: 0.4 Copollutant models: NR

Table A-3 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (μg/m^3)	Confounders Considered	Copollutant Examination
Elliott et al. (2020) Contiguous U.S. Exposure:1988−2007 Outcome: 1988−2008	NHS n = 104,990 Women (35−55 at baseline in 1976)	MI (ICD-9 410) and Stroke (ICD-9 430−437) Self-reported physician diagnosed confirmed by medical record review	24-mo moving average $PM_{2.5}$ at residence using spatiotemporal prediction models for contiguous U.S. (C-V R^2: 0.77) (Yanosky et al., 2014b).	13.7 (1988−2008) 80th: 16.5	Preexisting health conditions, smoking status, healthy eating, alcohol use, income, and education	Correlation (*r*): NR Copollutant models: NR
Danesh Yazdi et al. (2019) Southeastern U.S. (Florida, Alabama, Mississippi, Georgia, North Carolina, South Carolina, and Tennessee) 2000−2012	Medicare data n = 11,084,660 Older adults (65 plus yr)	First hospital admission for MI (ICD-9: 410), CHF (ICD-9 428) and Stroke (ICD-9 430−438), ascertained using Medicare data	Annual average $PM_{2.5}$ concentrations predicted using AOD from satellites, land use, and chemical transport models to assign daily exposure in 1 ×1 km grid cells (C-V R^2 = 0.86) (Di et al., 2016)		State, sex, race, year, eligibility for Medicaid, and census measures of SES	Correlation (*r*): NR Copollutant models: NR

AF = atrial fibrillation; AMI = acute myocardial infarction; AOD = aerosol optical depth; AQS = Air Quality System; BMI = body mass index; CAC = coronary artery calcium; CATHGEN = Catheterization Genetics study; CHF = congestive heart failure; cIMT = carotid intimal-medial thickness; C-V = cross-validation; DBP = diastolic blood pressure; ECG = electrocardiogram; GEOS-Chem = Goddard Earth Observing System with global chemical transport model; HDL = high-density lipoprotein; IAD = inter-adventitial diameter; ICD = International Classification of Disease; IMPROVE = Interagency Monitoring of Protected Visual Environments; JHS = Jackson Heart Study; km = kilometer(s); MESA = Multi-Ethnic Study of Atherosclerosis and Air Pollution; MI = myocardial infarction; NHS = Nurses' Health Study; ONPHEC = Ontario Population Health and Environment Cohort; Ox = redox weighted average of NO2 and O3; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; PM10 = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10; $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 and less than or equal to 10; *r* = correlation coefficient; REGARDS = REasons for Geographic and Racial Differences in Stroke; SBP = systolic blood pressure SD = standard deviation; SES = socioeconomic states; SWAN = Study of Women's Health Across the Nation; yr = year(s).

Table A-4 Study-specific details for epidemiologic studies using accountability analyses or alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentration ($\mu g/m^3$)	Confounders	Copollutant Examination
Danesh Yazdi et al. (2021) U.S. 2000−2016	Medicare n = 63,006,793	Myocardial infarction; ischemic stroke; atrial fibrillation, and flutter	High-resolution spatiotemporal ensemble models, each of which combined estimates from three different machine learning algorithms, including a neural network, a gradient boosting machine, and a random forest. The models used hundreds of predictors including land use terms, chemical transport model predictions, meteorologic variables, and satellite measurements to estimate daily levels of the pollutants on a scale of 1 km × 1 km.	Mean: 10.21 Median: 10.05 Range: 0.01−30.92	Individual: sex, race, age, Medicaid eligibility ZIP code level: proportion of the population > 65 yr of age living below the poverty line; population density; median value of owner occupied properties; proportion of the population listed as Black; median household income; proportion of housing units occupied by the owner; proportion of the population identified as Hispanic; proportion of the population > 65 yr of age who had not graduated from high school; lung cancer hospitalization rate; mean BMI; smoking rate; proportion of Medicare beneficiaries with at least one hemoglobin A1c test in a year; proportion of elderly diabetic beneficiaries who had a lipid panel test in a year; proportion of beneficiaries who had an eye examination in a year; proportion of beneficiaries with at least one ambulatory doctor visit in a year; and proportion of female beneficiaries who had a mammogram during a 2-yr period; region of residence	Correlation (*r*): NA Copollutant models with: O_3, NO_2

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentration ($\mu g/m^3$)	Confounders	Copollutant Examination
Henneman et al. (2019) U.S. 2005−2012	Medicare	Acute myocardial infarction; cardiovascular stroke; heart failure; heart rhythm disorders; ischemic heart disease; all cardiovascular disease	Modeled national $PM_{2.5}$ concentrations estimated by combining GEOS-Chem chemical transport model-simulated $PM_{2.5}$, satellite-retrieved aerosol optical depth, and observed $PM_{2.5}$ concentrations. Estimated monthly 0.1 longitude × 0.1 latitude $PM_{2.5}$ concentrations were averaged to annual concentrations and spatially overlayed on U.S. ZIP codes. Coal exposure: HYSLPLIT air parcel trajectory and dispersion model	Mean (IQR): 2005: 10.0 (4.5) 2012: 7.2 (2.6) Difference between 2012 and 2005: −3.2 (2.4)	Median age; median household income; per-capita income; sex; race; fraction of population by county that smoked in 2000; temperature; specific humidity	Correlation (r): NA Copollutant models with: NA
Zigler et al. (2018) Eastern U.S. 2000-2012	Medicare N=3,892,984 Medicare fee-for-service beneficiaries and N=1,620,778 Medicare managed-care beneficiaries	Cardiovascular stroke, heart failure, heart rhythm disorders, ischemic heart disease, peripheral vascular disease	U.S. EPA Air Quality System: Ambient $PM_{2.5}$ measurements in operation between 1997 and 2012 and enumerated which were in areas designated as nonattainment for $PM_{2.5}$ in 2005. Monitors were only included each year if the annual percentage of valid measurements for that year was at least 67%.	Mean (SD) for 2002-2004 in attainment areas: 11.59 (1.88) Mean (SD) for 2002-2004 in non-attainment areas: 14.48 (1.39) Mean (SD) for 2010-2012 in attainment areas: 9.39 (1.65) Mean (SD) for 2010-2012 in non-attainment areas: 11.13 (1.35)	Temperature, relative humidity, dew point, which were measured from climate monitors located within 150 km of the monitoring site Age, sex, race, rural/urban, education, income, occupied housing, migration rate, house value among zip codes with controls located within 6 miles of the monitoring station Smoking rate from the surrounding county	Correlation (r): NA Copollutant models with: NA

EPA = Environmental Protection Agency; GEOS-Chem = Goddard Earth Observing System with global chemical transport model; HYSLPLIT = HYbrid Single-Particle Lagrangian Integrated Trajectory; IQR = interquartile range; km = kilometer(s); NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; r = correlation coefficient; SD = standard deviation.

Table A-5 Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Study Population	Mortality Outcome	Exposure Assessment	Confounders in Statistical Model	Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Copollutant Examination
Liu et al. (2019) 652 cities globally; 107 cities in the U.S.; 25 cities in Canada (U.S.: 1987−2006; Canada: 1986−2011)	All ages	All cause	Available $PM_{2.5}$ data in the MCC database. Measurements for air pollutants from fixed-site monitoring networks operated by local authorities for each country.	DOW RH Temperature Year	U.S.: 12.4 Canada: 9.3	Correlation (*r*): NA Copollutant models with: NA
Lavigne et al. (2018) U.S. Canada (24 cities) 1998−2011	All ages Nonaccidental: n = 1,179,491 Cardiovascular: n = 401,719 Respiratory: n = 105,980	Nonaccidental Cardiovascular Respiratory	Daily (24-h) average $PM_{2.5}$ concentrations from monitors in Canada's NAPS network were used to estimate exposures. Exposure estimates were assigned to each study participant based on the monitoring station(s) located in participants' city of residence. If $PM_{2.5}$ measurements were available from multiple monitors in a single city, daily concentrations were averaged across monitors.	RH (lag 0−2) Temperature (lag 0−2)	Mean: 8.8 Max: 98.2	Correlation (*r*): NO_2: 0.53 O_3: 0.03 O_X: 0.28 Copollutant models with: O_X
Shin et al. (2021b) Canada (24 cities)2001−2012	> 1 yr of age 65+	Respiratory	Daily (24-h) average $PM_{2.5}$ concentrations were calculated for each study city using ambient monitoring data available from Canada's NAPS. Daily $PM_{2.5}$ concentrations were averaged across monitors within a city when multiple monitoring sites were present.	DOW Temperature (lag 0) Year	Mean: Warm (April−September): 8 Cold (October−March): 6	Correlation ®: NA Copollutant models with: NA

Table A-5 (Continued): Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Study Population	Mortality Outcome	Exposure Assessment	Confounders in Statistical Model	Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Copollutant Examination
Shin et al. (2021a) Canada (22 cities) 2001−2012	> 1 yr of age 65+	All cause	Daily (24-h) average $PM_{2.5}$ concentrations were calculated for each study city using ambient monitoring data available from Canada's NAPS. Daily $PM_{2.5}$ concentrations were averaged across monitors within a city when multiple monitoring sites were present.	DOW Temperature (lag 0) Year	Mean Warm (April−September): 8 Cold (October−March): 6	Correlation (*r*): O_3 warm: 0.4 O_3 cold: −0.3 Copollutant models with: NA
Rappazzo et al. (2019) North Carolina Mar 2013−Feb 2015	18−64 yr of age n = 399	Nonaccidental out-of-hospital sudden unexpected deaths	Hourly $PM_{2.5}$ measurements from the Wake County central site monitor were obtained though EPA's AQS data mart. Daily concentrations were calculated by averaging hourly measurements over 24-h (midnight to midnight).	Temperature (lag 0) RH (lag 0)	Mean: 10.93 75th: 13.22 Max: 31.14	Correlation (*r*): CO: 0.45 NO_2: 0.36 O_3: 0.22 SO_2: 0.18 Copollutant models with: CO, NO_2, O_3, SO_2
Baxter et al. (2019) U.S. (312 CBSAs) 1999−2005	All ages	Nonaccidental	Daily (24-h) mean $PM_{2.5}$ concentrations from population-based monitors were obtained from EPA's AQS. Concentrations were averaged across monitors within a CBSA/MD when multiple monitoring sites were present as detailed in Baxter et al. (2017).	DOW Dew Point Temperature (lag 0) Temperature (lag 0; lag 1, 2, 3) Year	---	Correlation (*r*): NA Copollutant models with: NA

AQS = Air Quality System; CBSA = core-based statistical area; DOW = day of week; EPA = Environmental Protection Agency; h = hour; MCC = Multi-City Multi-Country Collaborative Research Network; MD = metropolitan division; NA = not applicable; NAPS = National Air Pollution Surveillance System; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; RH = relative humidity; yr = year(s).

Table A-6 Study-specific details for epidemiologic studies using alternative methods for confounder control to examine short-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Wei et al. (2020) Massachusetts 2000−2012	Medicare n = 1,503,572	All-cause mortality	Predicted daily ambient $PM_{2.5}$, ozone, and nitrogen dioxide levels in each 1-km × 1-km grid cell across the contiguous U.S. using well-validated ensemble models	Mean (SD): 8.9 (5.4) Range: 0.1−65.3	Temperature−air and dew point Individual: sex; race/ethnicity; age; Medicaid eligibility ZIP code level: annual median household income; median value of owner-occupied housing units; percentage of population living in poverty; percentage of the population with less than a high school education; population density; home ownership rate County level: annual percentage of ever smokers; percentage of obese people	Correlation (*r*): NA Copollutant models with: O_3, NO_2

Table A-6 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine short-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Wei et al. (2021b) Massachusetts 2000−2012	Medicare n = 1,503,572	All-cause mortality	Daily concentrations of ambient $PM_{2.5}$, ozone, and nitrogen dioxide at 1 km × 1 km grid cells were predicted using geographically weighted regressions that ensembled predictions from ensemble methods	Mean (SD): 8.9 (5.4) Range: 0.1−65.3	Air surface temperature, dew point temperature, and relative humidity Individual: sex, race, age, Medicaid eligibility ZIP code level: median household income, median house value, percent of owner-occupied homes, percent of population living in poverty, percent of population below high school education, population density, percent of Black population and percent of Hispanic population, percent of persons over age 65 with an annual hemoglobin A1c test, an annual low-density lipoprotein test, and an annual eye exam in each hospital catchment area County level: percent of ever smokers, lung cancer rate, and average BMI	Correlation (*r*): NA Copollutant models with: O_3, NO_2
Schwartz et al. (2018a) U.S. (135 cities) 1999−2010	National Center for Health Statistics n = 7,277,274	Mortality (daily deaths)	Obtained $PM_{2.5}$ and NO_2 from U.S. EPA's Air Quality System Technology Transfer Network	Mean: 12.8 25th Percentile: 7.5 75th Percentile: 16.1	Meteorologic: Daily mean temperature, wind speed, and sea-level pressure data	Correlation (*r*): NA Copollutant models with: NO_2

BMI = body mass index; EPA = Environmental Protection Agency; km = kilometer(s); NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SD = standard deviation.

Table A-7 Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Pope et al. (2019) Contiguous U.S $PM_{2.5}$: 1999−2015 (1988−2015 in sensitivity analyses) Follow-up: 1986−2015	NHIS n = 1,599,329 deaths = 267,204 18−84 yr of age	All cause Cardiopulmonary Cardiovascular Cerebrovascular Chronic lower respiratory Influenza/ pneumonia Cancers Influenza/ pneumonia Lung cancer Other/unknown	Primary analyses: Population-weighted annual $PM_{2.5}$ concentrations averaged over the years 1999 to 2015 for census-tract centroids. $PM_{2.5}$ concentrations were estimated from regulatory monitoring data and constructed in a universal kriging framework relying on information from geographic variables, including land use, population, and satellite-derived estimates of land use and air pollution as described in Kim et al. (2020). This method was shown to have good model performance, R2 = 0.78−0.90. Sensitivity analyses: Census-tract mean $PM_{2.5}$ concentrations for the years 1988 to 2015 were estimated using imputed data from 1988 to 1998, based on the relationship between monitored PM_{10} and $PM_{2.5}$ concentrations, and primary modeled data from 1999 to 2015. Approach is described in Kim et al. (2020).	Age, sex, race-ethnicity using 104 variables for all interactive combinations of 13 age ranges, sex, and race-ethnicity; income (inflation-adjusted to 2015); education level; marital status; rural versus urban; U.S. census region; survey years Subcohort analysis also included smoking status; BMI	Mean: 10.7 SD: 2.4 Range: 2.5−19.2	Correlation (*r*): NA Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Lefler et al. (2019) U.S. $PM_{2.5}$: 1988−2015 Follow-up: 1987−2015	NHIS—Subset n = 635,539 deaths = 106,385 18−84 yr of age	All cause Cardiopulmonary	Annual average $PM_{2.5}$ was modeled using regulatory monitors and land use data as described in Kim et al. (2020). Exposure estimates were assigned to home census tracts as either 2-yr (i.e., cohort year and previous year) or 5-yr (i.e., cohort year and previous 4 yr) average $PM_{2.5}$ concentrations, 17-yr average $PM_{2.5}$ concentrations (1999−2015), or 28-yr average $PM_{2.5}$ concentrations (1988−2015).	Variables for all interactive combinations of 13 age ranges, sex, and race-ethnicity; marital status; inflation-adjusted household income; education; smoking status; BMI; U.S. census region; rural vs. urban; survey year	Mean: 10.67 SD: 2.37 IQR: 3.12	Correlation (*r*): CO: 0.42 SO_2: 0.41 $PM_{10-2.5}$: 0.19 NO_2: 0.56 O_3: 0.33 Copollutant models with: CO, $PM_{10-2.5}$, SO_2, O_3, NO_2
Wang et al. (2020) U.S. $PM_{2.5}$: 2000−2008 Follow-up: 2000−2008	Medicare n = 52,954,845 deaths = 15,843,982 65−120 yr of age	Nonaccidental Cardiovascular IHD Cerebrovascular CHF Respiratory COPD Pneumonia	Daily $PM_{2.5}$ was estimated on a 6-km grid using a spatiotemporal model described in Yanosky et al. (2014a). Model inputs included monitored $PM_{2.5}$, meteorological and geospatial covariates, and traffic-related PM estimated using a Gaussian line-source dispersion model. Medicare beneficiaries were matched to the grid point closest to their ZIP code centroid and $PM_{2.5}$ concentrations were averaged for the 12-mo period prior to death.	Strata for age, race, sex, and ZIP code; ZIP code, and state SES	Mean: 10.3 SD: 3.2	Correlation (*r*): NO_2: 0.59 O_3: 0.24 Copollutant models with: O_3

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Elliott et al. (2020) U.S. $PM_{2.5}$: 1988−2007 Follow-up: 1988−2008	Nurses' Health Study n = 104,990 female participants deaths = 9,827 Average age 63.1 yr	Nonaccidental	24-mo average ambient $PM_{2.5}$ exposures were estimated at residential addresses using the spatiotemporal prediction model described in Yanosky et al. (2014a). Model predictions used publicly available monitoring data, geospatial predictors (road network data, residential and urban land use, density of $PM_{2.5}$ and PM_{10} point-sources, elevation data) and monthly average meteorological data (windspeed, temperature, precipitation).	Age; race; incident cancer; family history of MI; smoking status; pack-years; overall diet quality; alcohol consumption; multivitamin use; individual-level SES	Mean: 13.7 SD: 3.5	Correlation (*r*): NA Copollutant models with: NA
Wu et al. (2020a) U.S. $PM_{2.5}$: 2000−2016 Follow-up: 2000−2016	Medicare n = 68,503,979 person-years = 573,370,257 deaths = 27,106,639 65+ yr of age	All cause	An ensemble-based prediction model was used to estimate daily $PM_{2.5}$ concentrations for a 1-km2 grid network across the contiguous U.S. [discussed in Di et al. (2019)]. Grid cell predictions were aggregated to ZIP codes, and annual averages for each ZIP code were calculated by averaging daily concentrations. Annual average $PM_{2.5}$ concentrations in each ZIP code were then assigned to individuals who resided in that ZIP code for each calendar year.	Age; race/ethnicity; sex; Medicaid eligibility County-level: average BMI; smoking rate ZIP code level: proportion of Hispanic and Black residents; median household income and home value; proportion of residents in poverty, with high school diploma, and own their house; population density; summer/winter average max daily temperature and RH Geographic region of U.S.; calendar year	Entire Cohort: Mean: 9.8 SD: 3.2 Subset of cohort ≤ 12.0: Mean: 8.4 SD: 2.3	Correlation (*r*): NA Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Eum et al. (2018) U.S. $PM_{2.5}$: 2000−2012 Follow-up: Dec 2000−Dec 2012	Medicare n = 20,744,214 deaths = 5,484,947 65+ yr of age	All cause	U.S. EPA Air Quality System (AQS) monitors. Included monitors with at least 8 calendar years of data, having 9+ months with 4+ measurements, which equaled 798 monitors. For each site, smoothed time-series using linear regression with thin plate splines with 4 df per year. Gaps longer than 90 days smoothed $PM_{2.5}$ before and after each gap separately. Predicted values used to calculate moving averages for $PM_{2.5}$ for each month. Yearly averages considered valid if 350+ days of data available. Exposure assigned to individuals that lived in ZIP codes with centroids within 6 miles of a valid monitor.	County-level proportion of non-Whites, current smokers, diabetes, asthma, individuals possessing health care plans, mean income, and mean BMI	Mean: 11.65 SD: 3.09	Correlation (*r*): NA Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Crouse et al. (2020) Canada $PM_{2.5}$: 1998−2010 Follow-up: 2001−2011	CanCHEC (2001) n = 2,452,665 deaths = 191,555 25−89 yr of age	Nonaccidental Cardiovascular Cardiometabolic IHD Cerebrovascular Respiratory Lung cancer	Base model: $PM_{2.5}$ estimates at 1 km over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. Sensitivity analyses: Examined 1, 5, and 10 km spatial scales and 1, 3, and 8-yr temporal scales.	Age, sex Community-level: time-varying indicator of size of each subject's home community from most recent census; CAN-Marg Index; geographic airshed of subject's residence Individual-level: Aboriginal identity, visible minority status, marital status, highest level of education, employment status, and household income adequacy quintiles	1-yr (Mean, Range) 1 km: 7.21 (0.0−20.0) 5 km: 6.59 (0.05−20.0) 10 km: 6.24 (0.21−20.0) 3-yr (Mean, Range) 1 km: 7.43 (0.00−20.0) 5 km: 6.79 (0.40−18.50) 10 km: 6.44 (0.60−18.16) 8-yr (Mean, Range) 1 km: 7.98 (0.35−18.36) 5 km: 7.27 (0.92−16.83) 10 km: 6.90 (0.79−16.40)	Correlation (r): NO_2: 0.49−0.62 O_3: 0.44−0.58 O_x: 0.60−0.68 Copollutant models with: O_3, NO_2, O_x

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Pinault et al. (2017) U.S. $PM_{2.5}$:1998−2010 Follow-up: May 15, 1991− Dec 31, 2011	CanCHEC (2001) n = 2,448,500 deaths = 233,300 person-years = 25,484,400 25−89 yr of age	Nonaccidental Cardiometabolic Cardiovascular IHD Cerebrovascular Respiratory COPD Pneumonia Lung Cancer	$PM_{2.5}$ estimates at 1 km over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence for years 1998−2012. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. $PM_{2.5}$ concentrations extended back to 1998 by applying interannual variation of a published $PM_{2.5}$ data set (Boys et al., 2014). Over North America R2 = 0.82 in locations where $PM_{2.5} < 20\ \mu g/m^3$.	Age, sex Individual-level: Aboriginal identity, visible minority status, marital status, educational attainment, income adequacy quintile, labor force status Population center size, airshed Contextual: proportion of persons 25 or older who were unemployed, proportion that had not graduated from high school, proportion of persons in low-income families	Mean (SD): 7.37 (2.60) 75th: 9.07 95th: 11.97 Max: 20.00	Correlation (*r*): NA Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Pappin et al. (2019) Canada $PM_{2.5}$: 1988−2015 Follow-up: 1991−2016	CanCHEC (1991, 1996, and 2001) n = 8.5 million deaths = 1.5 million person-years = 150,996,500 25−89 yr of age	Nonaccidental	$PM_{2.5}$ estimates at 1 km over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence for years 1998−2012. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. For $PM_{2.5}$ concentrations prior to 1998, back casting method employed that applied observed trends in ground monitoring data for $PM_{2.5}$ to adjust pre-gridded $PM_{2.5}$ estimates (Meng et al., 2019).	Age, sex, immigrant status Contextual: CAN-Marg Index, population size of home community/city, urban form, regional airshed Individual-level: income, education, occupational class, Indigenous status, visible minority status, employment status, marital status	Mean (SD): 1991: 7.95 (3.28) 1996: 7.18 (2.70) 2001: 6.68 (2.24) 99th Percentile: 1991: 17.26 1996: 15.00 2001: 12.30 Range (min−max): 1991: 0.37−20.00 1996: 0.37−20.00 2001: 0.37−18.50	Correlation (*r*): NA Copollutant models with: O_3, NO_2, O_x
Christidis et al. (2019) Canada $PM_{2.5}$: 1998−2015 Follow-up: 2000−2012 (linked to postal code history 1981−2016)	mCCHS n = 452,700 deaths = 50,700 person-years = 4,452,700	Nonaccidental	$PM_{2.5}$ estimates at 1 km^2 over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. Spatial variation from modeled surface used with simulate $PM_{2.5}$ and constrained with local ground-based monitors to estimate $PM_{2.5}$ concentrations through 2015 as detailed in Meng et al. (2019).	Age, sex, immigrant status, visible minority identity, Indigenous identity, marital status, educational attainment, employment status, income quintile, alcohol consumption, smoking behavior, fruit and vegetable consumption, leisure exercise frequency, BMI, CAN-Marg Index, ethnic concentration, community/city size, urban form, airshed	Mean (SD): 5.9 (2.0) 75th: 7.1 95th: 9.7 Max: 17.2	Correlation (*r*): NA Copollutant models with: O_3, NO_2, O_x

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Erickson et al. (2020) Canada $PM_{2.5}$: 1998−2106 Follow-up: May 15, 2001−Dec 31, 2016	CanCHEC (2001) n = 3,101,605 immigrants (n) = 684,400 deaths (non-immigrants) = 323,430 deaths (immigrants) = 87,775	Nonaccidental Cardiovascular Cardiometabolic IHD Cerebrovascular Respiratory COPD Lung cancer	$PM_{2.5}$ estimates at 1 km^2 over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence for years 1998−2012. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. Spatial variation from modeled surface used with simulate $PM_{2.5}$ and constrained with local ground-based monitors to estimate $PM_{2.5}$ concentrations through 2015 as detailed in Meng et al. (2019). $PM_{2.5}$ concentrations extended back to 1998 by applying interannual variation of a published $PM_{2.5}$ data set (Boys et al., 2014).	Age, sex, visible minority status, Aboriginal identity, marital status, educational attainment, income adequacy quintiles, employment status, occupational classification, age at immigration, geographic region of birth, CAN-Marg Index, community size, urban form, regional airshed	Mean (SD) Non-immigrant: 7.53 (2.65) Immigrant: Pre-1971: 9.13 (2.53) 1971−1980: 9.28 (2.28) 1981−1990: 9.54 (2.13) 1991−2001: 9.69 (2.02)	Correlation (*r*): NA Copollutant models with: NA
Erickson et al. (2019) Canada $PM_{2.5}$: 1998−2012 Follow-up: 2001−2011	CanCHEC (2001) n = 2,468,190 CCHS n = 80,630	Nonaccidental Cardiovascular IHD Lung cancer	$PM_{2.5}$ estimates at 1 km over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence for years 1998−2012. As detailed in van Donkelaar et al. (2015). $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR.	Age, sex, visible minority status, Aboriginal status, marital status, educational attainment, income quintile, labor force status, CMA-size, airshed, CAN-Marg Index	CanCHEC Mean: 8.40 CCHS: Mean: 6.70	Correlation (*r*): NA Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Zhang et al. (2021) Ontario, Canada $PM_{2.5}$: 2000−2016 Follow-up: 2009−2017	Ontario Health Study n = 88,615 deaths = 7,488 30+ yr of age	Nonaccidental Cardiovascular Respiratory	$PM_{2.5}$ estimates at 1 km^2 over 3-yr average (5-yr/1-km model) with single-year lag assigned to postal code of residence. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. Additional methodological changes including treating topographical changes and urban land cover as separate predictors improved R2 to 0.80.	Age, sex, ethnicity, place of birth, educational level, marital status, annual household income, BMI, daily intake of fruits and vegetables, physical activity, smoking habit, drinking habit, environmental exposure to smoke, urban residency, percentage of recent immigrants, percentage of population ≥ 15 with educational attainment lower than high school, and percentage of population ≥ 15 unemployed and income quintile	Mean (SD): 7.8 (1.5) 75th: 8.8	Correlation (*r*): NO_2 = 0.63 Copollutant models with: NO_2
Cakmak et al. (2018) Canada $PM_{2.5}$:1998−2011 Follow-up: 1991−2011	CanCHEC (1991) n = 2,291,250 deaths = 522,305 ≥25 yr of age	IHD COPD Lung cancer	$PM_{2.5}$ estimates from median satellite-derived concentrations from 1998 to 2011 at 10 km × 10 km resolution as detailed in van Donkelaar et al. (2010). Changes in $PM_{2.5}$ from 1998 to 2005 inferred from MISR and SeaWiFS satellites (Boys et al., 2014). Seven-year average exposures applied to each participant.	Age, sex, Aboriginal ancestry, visible minority status, marital status, education level, occupational level, immigrant status, income quintile Smoking data and BMI from CCHS	Mean (Range) (SD): 3.8 (1.2)−7.4 (2.2)	Correlation (*r*): O_3: −0.007 to 0.698 Copollutant models with: O_3

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Hayes et al. (2020) U.S. $PM_{2.5}$: 1980−2010 Follow-up: 1995−2011	NIH-AARP Diet and Health Study n = 565,477 deaths = 135,289 50−71 yr of age	Nonaccidental Cardiovascular Respiratory	Spatiotemporal prediction model detailed in Kim et al. (2017) that provided mean annual estimates of $PM_{2.5}$ for each census tract. $PM_{2.5}$ data prior to 1999 estimated using extrapolation based on $PM_{2.5}$ data in FRM/IMPROVE; $PM_{2.5}$ sulfate data in Clean Air Status and Trends Network; and visibility data across the Weather-Bureau-Army-Navy network. Annual average $PM_{2.5}$ concentrations assigned at census tract level lagged by 1 yr in time-dependent manner. Sensitivity analyses: (1) Follow-up period starting in 2000; and (2) distance to residence from AQS $PM_{2.5}$ monitoring site.	Age, race/ethnicity, education level, marital status, BMI, alcohol consumption, smoking status, city/state, characteristics of census tract at enrollment (median income, percentage not completing high school)	Median: 13.3 Range: 2.9−28.0	Correlation (*r*): NA Copollutant models with: NA
Chen et al. (2020) Ontario, Canada $PM_{2.5}$: 2000−2016 Follow-up: 2001−2016	ONPHEC n = 5,264,985 deaths = 305,335 35−85 yr of age	Cardiovascular	Annual average $PM_{2.5}$ estimated at 1 km2 from multiple satellite retrievals of AOD combined with geophysical relationship between AOD and $PM_{2.5}$ simulated by GEOS-Chem, which were then calibrated with surface measurements by GWR as detailed in van Donkelaar et al. (2019). Annual estimates closely agree with ground measurements across North America (R2 = 0.76).	Age, sex, urban/rural residency, north/south, percentage of population ≥ 15 with educational attainment lower than high school, percentage of recent immigrants, unemployment rate, income quintile, urban vs. other areas	Mean: 8.61	Correlation (*r*): Organic mass: 0.62 Sulfate: 0.73 Ammonium: 0.85 Nitrate: 0.9 Sea salt: 0.87 Mineral dust: 0.92 Black carbon: 0.97 Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Pinault et al. (2018) Canada CanCHEC $PM_{2.5}$:1998−2012 Follow-up: May 15, 2001− Dec 31, 2011 mCCHS $PM_{2.5}$:1998−2012 Follow-up: 2001−2008	CanCHEC (2001) n = 2,448,500 CVD deaths = 123,500 mCCHS n = 270,600 CVD deaths = 12,400	Cardiovascular	$PM_{2.5}$ estimates at 1 km2 over 3-yr average (3-yr/1-km model) with single-year lag assigned to postal code of residence for years 1998 – 2012. As detailed in van Donkelaar et al. (2015) $PM_{2.5}$ exposures derived from AOD retrievals using GEOS-Chem calibrated to surface measurements by GWR. $PM_{2.5}$ concentrations extended back to 1998 by applying interannual variation of a publishing $PM_{2.5}$ data set (Boys et al., 2014). Estimates were correlated with ground measurements, R2 = 0.82.	Age, sex, population center size, airshed, Aboriginal identity, visible minority status, educational attainment, labor force status, income adequacy quintile, percentage of persons ≥ 25 unemployed or had not graduated from high school, overall percentage of people in low-income families	2001 CanCHEC Mean (SE): 7.37 (2.60) mCCHS Mean (SE): 6.37 (2.65)	Correlation (*r*): NA Copollutant models with: NA
Lim et al. (2018) U.S. $PM_{2.5}$: 2002−2010 Follow-up: 1995−2011	NIH-AARP Diet and Health Study n = 549,735 Diabetes deaths = 3,597 50−71 yr of age	Diabetes	Long-term exposure to $PM_{2.5}$ was estimated using annual average concentrations for the Years 2002 to 2010 from a spatiotemporal prediction model as described in Kim et al. (2017). Average $PM_{2.5}$ concentrations were assigned based on residential census tract centroids.	Age, sex, region, race/ethnicity, education level, marital status, BMI, alcohol consumption, smoking status, diet, median census tract household income, percent of census tract population less than high school education	Mean (SD): 11.0 (2.7) Range: 2.8−21.2	Correlation (R2): NO_2: 0.6 O_3: 0.01 Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Ward-Caviness et al. (2020) North Carolina, U.S. $PM_{2.5}$: 2003−2016 Follow-up: Jul 2004−Dec 2016	North Carolina hospital-based cohort of individuals diagnosed with heart failure; using electronic health records n = 23,302 contributed to analyses (out of total of 35, 084 HF patients) Deaths = 4,496 Mean age = 66.9 yr (SD = 15.2 years; IQR = 22.2 yr)	All cause	Exposures are estimated using nearest $PM_{2.5}$ monitor and using Harvard's 1 km × 1 km modeled $PM_{2.5}$ surface. Monitors: Daily $PM_{2.5}$ values were obtained from EPA National Ambient Air Quality Standards (NAAQS) ground-based monitoring network (July 1, 2003−December 31, 2016). Annual average $PM_{2.5}$ concentration assigned to nearest monitor of geocoded address for the 365 days preceding the time of initial heart failure, based on the patient's electronic health records. Sensitivity analyses were restricted to participants < 30 km from a monitor. Modeled: An ensemble-based prediction model was used to estimate daily $PM_{2.5}$ concentrations for a 1-km^2 grid network across the contiguous U.S.; (model validation: r2 = 0.89 for Middle Atlantic region of U.S. for 2000−2015) [discussed in Di et al. (2019)]. Daily $PM_{2.5}$ estimates for North Carolina were extracted for the years 2003−2016 and annual averages were calculated.	Age, sex, race, distance to nearest monitor, neighborhood-level socioeconomic variables (household below federal poverty line, median home value, median household income, urbanicity, households receiving public assistance)	Monitors: Mean: 10.2 SD: 2.11 IQR: 3.36 Modeled: Mean: 10.3 SD: 1.70 IQR: 2.45	Correlation (*r*): NA Copollutant models with: NA

Table A-7 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Copollutant Examination
Malik et al. (2019) U.S. (31 hospitals) $PM_{2.5}$: 2002−2007 Follow-up: 2003−2013	TRIUMPH and PREMIER cohorts n = 5,640 deaths = NA Mean age = 59.9 (SD = 12.7)	All cause	Daily average $PM_{2.5}$ concentration estimated at census tract centroid of patient using U.S. EPA's downscaled CMAQ, which is a Bayesian space-time fusion model that bias corrects modeled output data with monitored data as detailed in (Berrocal et al., 2012). Annual average $PM_{2.5}$ concentrations estimated for year prior to myocardial infarction.	Age, sex, race, smoking status, date of enrollment, SES (patients' education, insurance status, history of avoiding care because of costs, end-of-the-month financial resources)	Mean: 11.96 SD: 2.11 Range: 4.3−20.5	Correlation (r): O_3: −0.02 Copollutant models with: O_3
Bennett et al. (2019) U.S. (1,339 county units) $PM_{2.5}$: 1999−2015 Follow-up: NA	Vital Registration data from NCHS Deaths = 41.9 million	All cause	Annual average $PM_{2.5}$ estimated from integrated geographic model described in Kim et al. (2020). $PM_{2.5}$ modeled through application of universal kriging approach to monitoring data and geographic variables, and satellite-derived estimates of $PM_{2.5}$. $PM_{2.5}$ concentrations predicted to 2010 census block centroids in contiguous U.S. and aggregated by population-weighting to county level.	Per capita income; percentage of population Black/African American, graduated from high school, live in urban areas, unemployed; proxy for cumulative smoking, mean temperature and RH	1999 Median: 12.7 75th: 14.6 99th: 19.7 2015 Median: 7.7 75th: 8.5 99th: 10.1	Correlation (r): NO_2: 0.50 O_3: 0.55 Copollutant models with: NA

AOD = aerosol optical depth; AQS = Air Quality System; BMI = body mass index; CanCHEC = Canadian Census Health and Environment Cohort; CAN-Marg = Canadian Marginalization Index; CCHEC = Canadian Census Health and Environment Cohort; CMA = census metropolitan area size; CMAQ = Community Multiscale Air Quality model; EPA = Environmental Protection Agency; FRM = Federal Reference Method; GEOS-Chem = Goddard Earth Observing System-Chem; GWR = geographically weighted regression; HF = heart failure; IMPROVE = Interagency Monitoring of Protected Visual Environments; IQR = interquartile range; mCCHS = Canadian Community Health Survey—Mortality cohort; NA = not applicable; NAAQS = National Ambient Air Quality Standards; NCHS = National Center for Health Statistics; NHIS = National Health Interview Survey; ONPHEC = Ontario Population Health and Environment Cohort; Ox = redox weighted average of NO2 and O3; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; PM_{10} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10; PREMIER = Prospective Registry Evaluating Myocardial Infarction: Events and Recovery; r = correlation coefficient; RH = relative humidity; SD = standard deviation; SE = standard error; SES = socioeconomic status; TRIUMPH = Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction; yr = year(s).

Table A-8 Study-specific details for epidemiologic studies using accountability analyses or alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Peterson et al. (2020) U.S. 1990−2010	National Center for Health Statistics n = 2,132 counties	Cardiovascular mortality	Estimated annual average $PM_{2.5}$-total and component concentrations (sulfates, nitrates, elemental carbon, and organic carbon) between 1990 and 2010 from CMAQ	Weighted annual trend mass concentration (standard error): 0.134 (0.001)	County: median household income, percent of non-White population, and population; age-standardized annual COPD mortality rates (to account for the cumulative burden of smoking and annual smoking rates)	Correlation (*r*): NA Copollutant models with: NA
Wei et al. (2020) Massachusetts 2000−2012	Medicare n = 1,503,572	All-cause mortality	Used predicted daily ambient $PM_{2.5}$, ozone, and nitrogen dioxide levels in each 1-km × 1-km grid cell across the contiguous U.S. using well-validated ensemble models	Mean (SD): 9.0 (1.9) Range: 3.3−16.4	Temperature—air and dew point Individual: sex; race/ethnicity; age; Medicaid eligibility ZIP code level: annual median household income; median value of owner-occupied housing units; percentage of population living in poverty; percentage of the population with less than a high school education; population density; home ownership rate County level: annual percentage of ever smokers; percentage of obese people	Correlation (*r*): NA Copollutant models with: O_3, NO_2

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Wei et al. (2021b) Massachusetts 2000−2012	Medicare n = 1,503,572	All-cause mortality	Daily concentrations of ambient $PM_{2.5}$, ozone, and nitrogen dioxide levels at 1 km × 1 km grid cells were predicted using geographically weighted regressions that ensembled predictions from ensemble methods	Mean (SD): 9.0 (1.9) Range: 3.3−16.4	Air surface temperature, dew point temperature, and relative humidity Individual: sex, race, age, Medicaid eligibility ZIP code level: median household income, median house value, percent of owner-occupied homes, percent of population living in poverty, percent of population below high school education, population density, percent of Blacks, and percent of Hispanics, percent of persons over age 65 with an annual hemoglobin A1c test, an annual low-density lipoprotein test, and an annual eye exam in each hospital catchment area County level: percent of ever smokers, lung cancer rate, and average BMI	Correlation (*r*): NA Copollutant models with: O_3, NO_2

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Wu et al. (2020a) U.S. 2000−2016	Medicare n = 68,503,979	Mortality	Estimated daily $PM_{2.5}$ levels at a high spatiotemporal resolution using a 1-km^2 grid network across the contiguous U.S. and a well-validated ensemble-based prediction model	Mean (SD): 9.8 (3.2)	Meteorologic variables: ZIP code level summer and winter averages of maximum daily temperatures; relative humidity Individual: age, race/ethnicity, sex, Medicare eligibility ZIP code level: proportion of Hispanic residents; proportion of Black resident; median household income; median home value; proportion of residents in poverty; proportion of residents with a high school diploma; population density; proportion of residents that own their house County level: average BMI and smoking rate Indicator variables: four census geographic regions (Northeast, South, Midwest, and West); calendar years (2000−2016)	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Wu et al. (2019) New England (Vermont, New Hampshire, Connecticut, Massachusetts, Rhode Island, and Maine) 2000−2012	Medicare n = 3,300,000	All-cause mortality	$PM_{2.5}$ exposures are determined at each 1 km × 1 km grid cell using a spatiotemporal prediction model which uses multiple different sources as input	Mean: 9.35	Individual: Age, sex, race, and Medicare eligibility Area-level: BMI; percent ever smoke; percent Hispanic population; percent Black population; median household income; median value of housing; percent below poverty level; percent below high school education; percent of owner-occupied housing; population density; percent with LDL-c test; percent with one ambulatory visit; percent with hemoglobin A1c test; temperature; relative humidity	Correlation (*r*): NA Copollutant models with: O_3
Corrigan et al. (2018) U.S. 2000−2010	National Center for Health Statistics n = 619 counties (total) n = 486 counties (attainment) n = 133 counties (non-attainment)	Cardiovascular mortality	U.S. EPA's Air Quality System (AQS) monitoring sites—calculated annual average $PM_{2.5}$ concentrations at each monitoring site for each year between 2000 and 2010; then averaged the annual means across the monitors located in the same county to calculate annual averages for counties	Before (2000−2004) Mean (IQR): 12.0 (3.9) After (2005−2010) Mean (IQR): 10.8 (3.3)	Temperature County: total income, percent with at least a high school diploma (of population 25 yr and older), percent Hispanic (of total population), and percent Black (of total population)	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Yitshak-Sade et al. (2019b) Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Delaware, Pennsylvania, Maryland, Washington, DC, Virginia, and West Virginia 2000−2013	Medicare n = 15,401,064	Mortality	Highly spatially resolved $PM_{2.5}$ data (1 × 1 km spatial resolution) from a hybrid satellite-based model incorporating daily satellite remote sensing Aerosol Optic Depth data and classic land-use regression methodologies	Range of Mean Annual $PM_{2.5}$ Concentrations: 6.5−14.5	Temperature Individual: age, race/ethnicity, sex, Medicare eligibility	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Henneman et al. (2019) U.S. 2005−2012	Medicare	All-cause mortality	Modeled national $PM_{2.5}$ concentrations estimated by combining GEOS-Chem chemical transport model-simulated $PM_{2.5}$, satellite-retrieved aerosol optical depth, and observed $PM_{2.5}$ concentrations. Estimated monthly 0.1 longitude × 0.1 latitude $PM_{2.5}$ concentrations were averaged to annual concentrations and spatially overlayed on U.S. ZIP codes Coal exposure: HYSLPLIT air parcel trajectory and dispersion model	Mean (IQR): 2005: 10.0 (4.5) 2012: 7.2 (2.6) Difference between 2012 and 2005: −3.2 (2.4)	Median age; median household income; per-capita income; sex; race; fraction of population by county that smoked in 2000; temperature; specific humidity	Correlation (*r*): NA Copollutant models with: NA
Sanders et al. (2020) U.S. 2000−2013	Medicare n = 137 counties (non-attainment) n = 467 counites (attainment)	Mortality	Daily 24-h average $PM_{2.5}$ was calculated for each county as a simple average of all monitors within a county (if multiple monitors exist)	Mean (SD): 10.84 (3.06) Mean for Non-attainment < 2006: 15.29 Attainment < 2006: 10.99 Mean for Non-attainment ≥ 2006: 11.96 Attainment ≥ 2006: 9.33	Temperature (daily minimum and maximum) Total precipitation Income per capita, share of population employed, migration	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Fan and Wang (2020) U.S. 1999−2013	Medicare n = 770 county-month observation for treated n = 7504 county-month observation for controls	Mortality	Ambient $PM_{2.5}$ monitoring data from EPA AQS and power plants were selected from a list of coal-fired power plants from Clean Air Watch	Mean (SD): 12.04 (3.78)	Temperature, dew point, barometric pressure County: median household income, poverty rate, percentage of non-Hispanic Whites in the population, and percentage of population with college degree	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Schwartz et al. (2021) U.S. 2000−2016	Medicare n = 623,036,820 person-years of follow-up	Mortality	Used a validated prediction model calibrated to measurements at almost 2000 U.S. EPA AQS monitoring stations using an ensemble of machine learners that provided daily estimates for a 1 km grid of the contiguous U.S.	Mean (SD): 10.3 (3.1) Median: 9.8 IQR: 7.9, 12.0	Individual: age, sex, ZIP code, Medicaid eligibility ZIP code: percent of people ≥ 65 living in poverty, median household income, median house value, percent of owner occupied homes, percent Black, percent Hispanic, population density, and education, percentage of Medicare participants who had a hemoglobin A1c test, a low-density lipoprotein cholesterol (LDL-c) test, a mammogram, an eye exam, and a visit to an annual checkup for each year in each hospital catchment area, distance from each ZIP code centroid to the nearest hospital, hospitalization rate for lung cancer (proxy for long-term smoking) County: percentage of people who ever smoked and BMI Meteorologic: average temperature in the warm months (April−September) and in the cold months (October−March)	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Schwartz et al. (2018b) Northeastern and mid-Atlantic States (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Delaware, Pennsylvania, Maryland, Washington, DC, Virginia, and West Virginia) 2000−2013	Medicare n = 129,341,959 person-years n = 6,334,905 deaths	Life expectancy	Estimate annual average concentrations of $PM_{2.5}$ at each ZIP code, which uses a hybrid model that integrates land use, meteorological, and satellite remote sensing data	Mean: 10.3 Median: 10.4 25th Percentile: 9.2 75th Percentile: 11.4	Individual: age, sex, race, ZIP code of residence for that year, Medicaid eligibility ZIP code: percentage of the population that was Black, Hispanic, ≥ 65 yr of age living in poverty, living in owner-occupied housing, and with less than a high school education as well as median household income, median value of owner-occupied housing, and population density; hospitalization rate for lung cancer (to capture long-term smoking); percentage of Medicare participants who had a hemoglobin A1c test, a low-density lipoprotein cholesterol (LDL-c) test, a mammogram, and a visit to a primary care physician for each year in each hospital catchment area County: percentage of people who ever smoked and BMI scores	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Awad et al. (2019) U.S. 2000−2012	Medicare n = 12,095,504	Mortality	Mean annual exposure to $PM_{2.5}$ for each enrollee at his/her residential ZIP code for each year between 2000 and 2012 was estimated using a neural network-based hybrid prediction mode. Daily predictions were generated and then averaged over the calendar year for the four grids closest to the centroid of the ZIP code of residence	Mean in the year of move: 11.88 for Whites and 13.02 for Blacks Mean in second year after move: 11.15 for Whites and 12.12 for Blacks	Individual: age, sex, race, ZIP code of residence, Medicaid eligibility; hospitalizations for Alzheimer's disease, acute myocardial infarction, diabetes Mellitus, heart failure, Parkinson's disease, pneumonia, other respiratory diseases, ischemic stroke, unstable angina, vascular dementia, chronic obstructive pulmonary disease, and lung cancer ZIP code: median household income, population density, percentage Black, percentage of owner-occupied housing units, median value of owner-occupied housing, percentage above age 65 living below the poverty level, and percentage above age of 65 with less than high school education	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Zigler et al. (2018) Eastern U.S. 2000-2012	Medicare N=3,892,984 Medicare fee-for-service beneficiaries and N=1,620,778 Medicare managed-care beneficiaries	All-cause mortality	U.S. EPA Air Quality System: Ambient $PM_{2.5}$ measurements in operation between 1997 and 2012 and enumerated which were in areas designated as nonattainment for $PM_{2.5}$ in 2005. Monitors were only included each year if the annual percentage of valid measurements for that year was at least 67%.	Mean (SD) for 2002-2004 in attainment areas: 11.59 (1.88) Mean (SD) for 2002-2004 in non-attainment areas: 14.48 (1.39) Mean (SD) for 2010-2012 in attainment areas: 9.39 (1.65) Mean (SD) for 2010-2012 in non-attainment areas: 11.13 (1.35)	Temperature, relative humidity, dew point, which were measured from climate monitors located within 150 km of the monitoring site Age, sex, race, rural/urban, education, income, occupied housing, migration rate, house value among zip codes with controls located within 6 miles of the monitoring station Smoking rate from the surrounding county	Correlation (*r*): NA Copollutant models with: NA
Higbee et al. (2020) U.S. 1986−2015	National Center for Health Statistics n = 635,539	All-cause mortality Cardiopulmonary mortality	Annual pollution exposures were estimated for each census block using national regulatory monitoring data from 1999 to 2015 within a universal kriging model employing land use regression methods and hundreds of variables	Mean (SD): 10.7 (2.4) Range: 2.5−19.2	Individual: age, sex, race/ethnicity, educational attainment, marital status, income level, urban–rural designation, census tract, interview date, mortality status, smoking status, BMI, and date of death	Correlation (*r*): NA Copollutant models with: NA

Table A-8 (Continued): Study-specific details for epidemiologic studies using alternative methods for confounder control to examine long-term $PM_{2.5}$ exposure and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	$PM_{2.5}$ Concentrations ($\mu g/m^3$)	Confounders	Copollutant Examination
Wei et al. (2021a) U.S. 2000−2016	Medicare n = 74,537,533	All-cause mortality	The daily concentrations of ambient $PM_{2.5}$, O_3, and NO_2 at 1 km × 1 km grid cells across the contiguous U.S. were predicted and validated using hybrid models that ensembled predictions from random forest, gradient boosting, and neural network	Mean (SD): 9.85 (3.17)	Meteorologic: Air temperature, humidity, average temperature in warm (April−September) and cold seasons (January−March, plus October−December) Individual: sex, race, age, Medicaid eligibility ZIP code: percentage of Blacks, percentage of Hispanics, median household income, median value of owner occupied housing, percentage of Americans aged 65 and older living below the poverty threshold, percentage of Americans with less than high school education, percentage of owner occupied housing units, and population density; percentage of Medicare participants who had a hemoglobin A1c test, a low-density lipoprotein cholesterol (LDL-c) test, a mammogram, and an eye exam to a primary care physician for each year in each hospital catchment area County: BMI and percentage of ever smokers	Correlation (*r*): NA Copollutant models with: O_3 and NO_2

AQS = Air Quality System; BMI = body mass index; EPA = Environmental Protection Agency; GEOS-Chem = Goddard Earth Observing System with global chemical transport model; HYSLPLIT = HYbrid Single-Particle Lagrangian Integrated Trajectory; IQR = interquartile range; km = kilometer; NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SD = standard deviation; yr = year(s).

Table A-9 Study-specific details for epidemiologic studies of short-term $PM_{2.5}$ exposure and COVID-19 outcomes.

Study/Location Years	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations (µg/m^3)	Covariates in Statistical Model	Copollutant Examination
Adhikari and Yin (2020) Queens County, NY Mar 1, 2020−Apr 20, 2020	Daily confirmed COVID-19 cases and deaths	Daily average $PM_{2.5}$ collected and averaged from two stationary monitors. Mean (SD): 4.73 (2.39) Median: 4.1 Range: 0.65 to 11.15	Lagged outcome and day trend	Correlation (*r*): O_3 = −0.82 Copollutant models with: NA

AQS = Air Quality System; BMI = body mass index; EPA = Environmental Protection Agency; GEOS-Chem = Goddard Earth Observing System with global chemical transport model; HYSLPLIT = HYbrid Single-Particle Lagrangian Integrated Trajectory; IQR = interquartile range; km = kilometer(s); LDL = low-density lipoprotein; NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SD = standard deviation.

Table A-10 Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and COVID-19 outcomes.

Study/Location Years	Outcome	Exposure Assessment	Covariates in Statistical Model	Copollutant Examination
Chakrabarty et al. (2021) U.S.	R0	$PM_{2.5}$ concentrations were aggregated at the state-level using monthly estimates based on stationary monitors, model inputs, and satellite observations between the years 2012−2017.	population, population density, % of population ≤ 9, % of population 10−19, % of population 20−29 % of population 30−39, % of population 40−49, % of population 50−59, % of population 60−69, % of population 70−79, % of population ≥ 80, number of people tested, hospital beds, Intensive Care Unit beds, liquid asset poverty rate, total health care and social services workers, total essential workers, fraction of total health care and social services workers, fraction of total essential workers, average household size, average family size, number of households, number of family, households with elderly resident, renter-occupied housing units, lapse in states issuance of stay-at-home order, residents in two or more unit structures, median income for single earner household, median income for working age individuals, % White, % African American, % Asian, % Native American Indian, % Pacific Islander, % Other race, ozone, NO_2, relative humidity, SO_2.	Correlation (*r*): NA Copollutant models with: NA

Table A-10 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and COVID-19.

Study/Location Years	Outcome	Exposure Assessment	Covariates in Statistical Model	Copollutant Examination
Liang et al. (2020) U.S. (3,122 U.S. counties) Jan 22, 2020 to Jul 17, 2020	U.S. COVID-19 deaths n = 138,552	Daily ambient $PM_{2.5}$ concentrations estimated using an ensemble machine learning model at the 1 km × 1 km grid level for 2010−2016. Annual mean concentrations were aggregated to county level. 5th percentile: 3.8 95th percentile: 10.4	County-level number of cases per 1,000 people, social deprivation index, population density, % of residents > 60, % males, % race and ethnicity, body mass index, smoking rate, number of regular hospital beds per 1,000 people, number of intensive unit beds per 1,000 people, number of medical doctors per 1,000 people, average mobility (March and July 17, 2020), average temperature and humidity, state-level COVID-19 test positive rate as of July 17, 2020, and spatial smoother with 5 degrees of freedom for both latitude and longitude.	Correlation (*r*): NA Copollutant models with: NO_2, O_3
Mendy et al. (2021) University of Cincinnati Hospital System Mar 13, 2020−Jul 5, 2020	COVID-19 hospitalizations n =1,128 COVID cases n = 310 hospitalizations	10-yr average and 10-yr maximum concentrations of $PM_{2.5}$ were aggregated for each ZIP code between 2008 and 2017 within the study area. Average Mean ± SD: 11.34 ± 0.70 Maximal Mean ± SD: 13.83 ± 1.03	Age, race, sex, median household income, smoking status, obesity, diabetes, asthma, COPD, cardiovascular disease, chronic kidney disease, neoplasm/history of neoplasm	Correlation (*r*): NA Copollutant models with: NA
Stieb et al. (2020) Canada (111 health regions) Up to May 13, 2020	SARS-CoV-2 infections n = 73,390	Annual $PM_{2.5}$ concentrations estimated using satellite imagery, chemical transport models, and ground observations for years 2000−2016 on a 0.01° × 0.01° grid. Concentrations were aggregated to 2018 health region boundaries. Mean (SD): 6.1 (2.1)	Temperature (minimum, maximum), population density, % ≥ 65, % with income < lowest income cutoff, % Black, % asthma, % COPD, % hypertension, % diabetes, % physically active, % overweight, % obese, % smokers, days since first case, days since peak incidence, greenspace	Correlation (*r*): NA Copollutant models with: NA

Table A-10 (Continued): Study-specific details for epidemiologic studies of long-term $PM_{2.5}$ exposure and COVID-19.

Study/Location Years	Outcome	Exposure Assessment	Covariates in Statistical Model	Copollutant Examination
Wu et al. (2020b) U.S. (3,089 counties Up to Jun 18, 2020	COVID-19 deaths n = 116,747	Daily $PM_{2.5}$ concentrations estimated using atmospheric chemistry and machine learning models for the years 2000−2016 on 0.01° × 0.01° grid. Daily concentrations were aggregated to county level and averaged. Mean (SD): 8.4 (2.5)	Days since first COVID-19 case reported, population density, % of population ≥ 65, % of population 45−64, % of population 15−44, % of population in poverty, median household income, % Black residents, % Hispanic residents, % of adult population with < high school education, median house value, % owner-occupied housing, % of population with obesity, % current smokers, number of hospital beds per unit population, average daily temperature, relative humidity for summer (June to September) and winter (December to February) for each county, days since issuance of stay-at-home order for each state.	Correlation (*r*): NA Copollutant models with: NA

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Table A-11 Study-specific details for epidemiologic studies examining socioeconomic status and $PM_{2.5}$ exposure.

Study/Location Years	Exposure Assessment	Mean Concentration (µg/m^3)	Copollutant Examination
Han et al. (2017) Houston, TX Jun 2013−Nov 2013	$PM_{2.5}$ concentrations collected from two stationary monitors placed in a single Low SES community, and a High SES community.	Mean (SD): Low SES: 11.3 (2.90) High SES: 9.6 (2.93)	Correlation (*r*): NA Copollutant models with: NA
Lee (2019) California 2016	$PM_{2.5}$ concentrations estimated from both stationary monitors and satellite	Statewide Mean (SD): 8.09 (3.25) Poverty: High: 9.7, Low: 8.7 Education: High: 9.9, Low: 8.5	Correlation (*r*): NA Copollutant models with: NA
Lee and Park (2020) California 2012−2014	$PM_{2.5}$ concentrations estimated from stationary monitors	Mean (SD): Overall: 9.4 (8.0) High Vulnerability: 10.8 (8.0) Low Vulnerability: 6.8 (5.5)	Correlation (*r*): NA Copollutant models with: NA
Richmond-Bryant et al. (2020) U.S. 2008, 2011, 2014	$PM_{2.5}$ emissions from fossil-fuel Electricity Generating Units obtained from the National Emissions Inventory	NR	Correlation (*r*): NA Copollutant models with: NA

Table A-11 (Continued): Study-specific details for epidemiologic studies examining socioeconomic status and $PM_{2.5}$ exposure.

Study/Location Years	Exposure Assessment	Mean Concentration (µg/m^3)	Copollutant Examination
Rosofsky et al. (2018) Massachusetts 2003−2010	$PM_{2.5}$ concentrations estimated at 1 km × 1 km grid using a modeling approach which incorporated satellite, land use, and meteorological data aggregated to yearly averages.	Population-weighted annual average $PM_{2.5}$ range: Education: Masters: 2003:11.2, 2010: 8,0 Bachelors: 2003: 11.2, 2010: 8.0 High School-Post Secondary: 2003: 11.1, 2010: 7.9 < High School: 2003: 11.3, 2010: 8.2 Household Income: > $75,000: 2003:11.1, 2010:7.9 $50−$75,000: 2003: 11.1, 2010: 8.0 $35−$50,000: 2003: 11.2, 2010: 8.0 $20−$35,000: 2003: 11.2, 2010: 8.1 < $20,000: 2003: 11.4, 2010: 8.2	Correlation (*r*): NA Copollutant models with: NA
Tanzer et al. (2019) Pittsburgh, PA Apr 2017−May 2018	$PM_{2.5}$ measured using Met-One Neighborhood PM Monitors (NPMs) and small subset measured using PurpleAir PA-II, as part of a Real-time Affordable Multi-Pollutant (RAMP) package	Annual average range: 7.5 to 25.8 EJ Communities: 10.6 (1.0) Non-EJ Communities: 10.3 (1.5)	Correlation (*r*): 0.32 (0.16−0.56) SO_2 Copollutant models with: NA
Weaver et al. (2019) 2001−2010 Duke University Medical Center Wake, Durham, and Orange Counties in NC	Daily average $PM_{2.5}$ concentrations were estimated using a hybrid model on a 1 × 1 km grid	Mean (SD): 12.7 (1.1) Cluster 1: 12.9 (1.1) Cluster 2: 13.2 (1.0) Cluster 3: 12.8 (1.1) Cluster 4: 12.8 (1.1) Cluster 5: 12.2 (1.2) Cluster 6: 11.9 (1.0)	Correlation (*r*): NA Copollutant models with: NA

EJ = environmental justice; km = kilometer(s); NA = not applicable; NR = nor reported; NPMs = Neighborhood PM Monitors; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; RAMP = Real-time Affordable Multi-Pollutant; SD = standard deviation; SES = socioeconomic status.

Table A-12 Study-specific details for epidemiologic studies examining short-term $PM_{2.5}$ exposure and health risk disparity by socioeconomic status.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment and Mean Concentration (µg/m³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Yitshak-Sade et al. (2019a) Massachusetts 2001−2011 Case-crossover	Massa-chusetts Department of Public Health n = 179,986	Cardio-vascular mortality	Daily average $PM_{2.5}$ estimated from a model incorporating aerosol optical depth and monitored $PM_{2.5}$ at a 1 × 1 km grid Mean: 10.2 Max: 17.4	Change in CV Mortality High % High School Educated Green: 2.64% (0.46, 4.68) Less Green: 1.42% (0.72, 3.62) High % without high school diploma Green: 2.64% [0.60, 4.72] Less Green: 3.31% [1.26, 5.41] High % White Green: 2.80% (0.62, 5.02) Less Green: 1.14% (−1.00, 3.33) Low % White Green: 2.47% (0.43, 4.56) Less Green: 3.55% (1.49, 5.65)	Temperature and day of the week	Correlation (*r*): NA Copollutant models with: NA
Son et al. (2020) North Carolina 2002−2013	Death Records n = 775,338	Total Mortality	Daily average $PM_{2.5}$ concentrations estimated from the CMAQ downscaler model on a 12 × 12 grid Mean (SD): 11.4 (5.7) Max: 70.8	OR (95% CI): Income < $41,500: 1.01 (1.01, 1.01) ≥ $41,500: 1.01 (1.00, 1.01) Education < 12 yr: 1.01 (1.01, 1.02) High School: 1.01 (1.00, 1.01) 1−4 yr of college: 1.01 (1.00, 1.01) ≥ 5 yr of college: 1.01 (0.99, 1.02) Unknown: 1.00 (0.98, 1.03)	Residential greenness, proximity to water bodies, median household income, and classification of urbanicity	Correlation (*r*): O_3: 0.48 Copollutant models with: NA

CI = confidence interval; CMAQ = Community Multi-Scale Air Quality; CV = cardiovascular; km = kilometer(s); NA = not applicable; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SD = standard deviation.

Table A-13 Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by socioeconomic status.

Study/ Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Select Results	Covariates in Statistical Model	Copollutant Examination
Bai et al. (2019) Ontario, Canada 2001-2015	Canadian Ontario Population and Health Cohort	Congestive Heart Failure (n = 5,062,146) Acute Myocardial Infarction (n = 5,141,172)	Annual average $PM_{2.5}$ concentrations estimated using the GEOS-Chem CTM model and a geographically weighted regression model Mean (SD): 9.6 (2.8) Max: 20.0	Income HR (95% CI) CHF Lowest: 1.12 (1.10, 1.13) Lower: 1.09 (1.06, 1.10) Middle: 1.03 (1.01, 1.04) Upper: 1.04 (1.03, 1.06) Uppermost: 1.01 (1.00, 1.04) AMI Lowest: 1.12 (1.09, 1.15) Lower: 1.09 (1.06, 1.12) Middle: 1.04 (1.03, 1.07) Upper: 1.03 (1.01, 1.06) Uppermost: 1.03 (1.00, 1.06)	Age, sex, area level risk factors including SES, and geographic indicator variables that distinguished participants based on whether their residence in the north or south of Ontario and whether it was urban or rural	Correlation (*r*): NA Copollutant models with: NA
Bennett et al. (2019) U.S. 2015	National Center for Health Statistics n = 41.9 million	Life expectancy loss	Annual average $PM_{2.5}$ concentrations estimated using an integrated geographic regression model Median: 7.7 99th percentile: 10.1	$PM_{2.5}$ associated with lower life expectancy among counties with lower income, higher percent poverty, and those with a low % who graduated from high school.	Income, % in poverty, Black race, ≥ high school, urbanization, unemployment, cumulative smoking, mean temperature, relative humidity, county-specific random intercepts	Correlation (*r*): NA Copollutant models with: NA

Table A-13 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by socioeconomic status.

Study/ Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations (µg/m³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Bevan et al. (2021) U.S. 2000−2016	National Center for Health and Statistics n = 5,769,315	Cardiovascular Mortality	Annual zip-level average $PM_{2.5}$ concentrations estimated using aerosol optical depth calibrated to ground-based observations Mean (SD): 6.51 (1.54)	Social Deprivation Index (SDI) (1−100) No. deaths/100,000 (95% CI) SDI 1−25: 39.1 (32.1, 46.1) SDI 26−50: 48.2 (38.5, 57.9) SDI 51−75: 71.0 (57.6, 84.4) SDI 76−100: 52.0 (30.9, 73.1)	Smoking, diabetes obesity, physical inactivity, and urbanization	Correlation (*r*): NA Copollutant models with: NA
Crouse et al. (2019) Canada 2001−2011	Canadian Census Health Environment Cohort	Nonaccidental Mortality Cardio-metabolic Mortality Cardiovascular Mortality	Annual average $PM_{2.5}$ concentrations estimated from satellite derived annual estimates on a 1 × 1 km grid Mean (SD): 8.4 (2.7) 95th percentile: 13.3	For all mortality outcomes, the strongest associations were among the group with the lowest amount of deprivation and the lowest amount of greenspace.	Aboriginal identity, visible minority status, marital status, highest level of education, employment status, and household income adequacy quintiles	Correlation (*r*): NA Copollutant models with: O_3
Jorgenson et al. (2020) U.S. 2000−2014	U.S. Mortality Database	Life expectancy at birth	$PM_{2.5}$ concentrations estimated from stationary monitors, averaged at the state level Mean: 10.55 Max: 19.02	$PM_{2.5}$ more detrimental in states with high percent of income inequality.	Income share of top 10%, % Black, total population, median household income, median age, % college degree or higher	Correlation (*r*): NA Copollutant models with: NA
Schulz et al. (2018) Detroit Metropolitan Area 2013	n = 171,000	Cardio-pulmonary Mortality	Annual average $PM_{2.5}$ concentrations estimated from downscaler and CMAQ by census tract Mean: 9.6 Max: 10	Both $PM_{2.5}$ and social vulnerability were independently related to CV mortality in the same model.	Age, gender, race/ethnicity, educational attainment, death attributable to smoking, and marital status	Correlation (*r*): NA Copollutant models with: NA

Table A-13 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by socioeconomic status.

Study/ Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations (µg/m³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Shin et al. (2019) Ontario, Canada April 1, 2001 – March 31, 2015	Canadian Ontario Population and Health Cohort n = 5,071,956	Atrial Fibrillation Stroke	Annual average $PM_{2.5}$ concentrations estimated using AOD and $PM_{2.5}$ simulated by the GEOS-Chem CTM at a 1 × 1 km grid Mean (SD): 9.8 (2.9) IQR: 4.0 Max: 20	Income HR (95% CI) Atrial Fibrillation Lowest: 1.06 (1.04, 1.08) Lower: 1.05 (1.03, 1.07) Middle: 1.02 (1.00, 1.04) Upper: 1.02 (1.01, 1.04) Uppermost: 0.99 (0.97, 1.02) Stroke Lowest: 1.08 (1.04, 1.13) Lower: 1.08 (1.05, 1.11) Middle: 1.04 (1.00, 1.08) Upper: 1.01 (0.99, 1.04) Uppermost: 1.01 (0.99, 1.04)	Age, sex, area-level SES (education, recent immigrants, unemployment rate, and income quintile), urban/rural area, and northern/southern Ontario	Correlation (*r*): NO_2: 0.65 O_3 0.275 Ox: 0.668 Copollutant models : with NO_2, O_3, Ox
Wang et al. (2020) U.S. 2000−2008	Medicare, ≥ 65 n = 52,954,845	Mortality	Daily average $PM_{2.5}$ concentrations estimated from a validated spatiotemporal generalized additive model on a 6 km grid Mean (SD): 10.32 (3.15)	Associations were null by income.	Age, sex, race, and ZIP code with additional control for ZIP code and state SES	Correlation (*r*): NO_2: 0.59, O_3: 0.24 Copollutant models with: O_3

Table A-13 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by socioeconomic status.

Study/ Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Select Results	Covariates in Statistical Model	Copollutant Examination
Weaver et al. (2019) NC, U.S. Duke University Medical Center Wake, Durham, and Orange Counties 2001−2010	Catheterization Genetics (CATHGEN) study	Coronary Artery Disease, Myocardial Infarction, hypertension, Diabetes Mellitus	Daily average $PM_{2.5}$ concentrations were estimated using a hybrid model on a 1 × 1 km grid Mean (SD): 12.7 (1.1)	Hypertension OR (95% CI) Cluster 1: 2.70 (0.95, 7.59) Cluster 2: 11.86 (2.10, 67.21) Cluster 3: 0.70 (0.86, 1.07)	Odds ratios were adjusted for age, sex, BMI, race, and smoking status	Correlation (*r*): NA Copollutant models with: NA
Wyatt et al. (2020b) U.S. 3,132 counties 1990−2010	National Center for Health Statistics	Cardiovascular mortality	Annual average $PM_{2.5}$ concentrations were estimated using CMAQNR	In the 1990s, counties with highest social deprivation benefited least, but by 2010, counties with highest social deprivation benefited the most by a reduction in $PM_{2.5}$.	Age, baseline year $PM_{2.5}$ and CMR for each county	Correlation (*r*): NA Copollutant models with: NA

Table A-13 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by socioeconomic status.

Study/ Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations (µg/m³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Zhang et al. (2021) Ontario, Canada 2009−2017	Ontario Health Study n = 88,615	Total nonaccidental mortality, cardiovascular mortality, respiratory mortality	Annual average $PM_{2.5}$ estimated from model incorporating satellite, chemical transport, and ground-level observation data at a 1 × 1 km grid Mean: 7.8 75th percentile: 8.8	Household Income Hazard Ratio (95% CI) Nonaccidental < $25,000: 1.61 (1.23, 2.12) $25,000−$49,999: 1.42 (1.18, 1.72) $50,000−$74,999: 1.14 (0.94, 1.38) $75,000−$99,999: 1.24 (0.97, 1.60) ≥ $100,000: 1.00 (0.82, 1.21) Cardiovascular < $25,000: 4.58 (2.48, 8.47) $25,000−$49,999: 1.34 (0.91, 1.97) $50,000−$74,999: 1.10 (0.73, 1.68) $75,000−$99,999: 1.11 (0.63, 1.98) ≥ $100,000: 1.46 (0.94, 2.25) Respiratory < $25,000: 3.20 (1.40, 7.34) $25,000−$49,999: 0.84 (0.45, 1.57) $50,000−$74,999: 1.33 (0.63, 2.79) $75,000−$99,999: 1.47 (0.45, 4.74) ≥ $100,000: 4.48 (1.69, 11.83)	Age, sex, ethnicity, survey year, Canadian born, educational level, marital status, BMI, fruit and vegetable intake, smoking, alcohol drinking, physical activity, environmental exposure to tobacco smoke at home or in the workplace, urban/rural, south/north, and neighborhood SES characteristics (percent recent immigrants, percent population ≥ 15 unemployed, percent population ≥ 15 with educational level lower than high school, and income quintile)	Correlation (*r*): NA Copollutant models with: NO_2

AMI = acute myocardial infarction; AOD = aerosol optical depth; BMI = body mass index; CATHGEN = Catheterization Genetics study; CHF = congestive heart disease; CI = confidence interval; CMAQ = Community Multi-Scale Air Quality; CTM = chemical transport model; GEOS-Chem = Goddard Earth Observing System with global chemical transport model; hr = hazard ratio; IQR = interquartile range; km = kilometer(s); $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; *r* = correlation coefficient; SD = standard deviation; SDI = social deprivation index; SES = socioeconomic status.

Table A-14 Study-specific details for epidemiologic studies examining race/ethnicity and $PM_{2.5}$ exposure.

Study/Location Years	Exposure Assessment	Mean Concentration (μg/m^3)	Copollutant Examination
Awad et al. (2019) U.S. 2000−2012	Annual average $PM_{2.5}$ concentrations estimated using a neural network-based hybrid model between 2000 and 2012 on a 1 × 1 km grid	White Mean: pre-move: 11.88, post-move: 11.15 99th Percentile: pre-move: 20.24, post-move: 18.08 Black Pre-move: 13.02, post-move: 12.12 99th Percentile: pre-move: 20.68, post-move: 18.95	Correlation (*r*): NA Copollutant models with: NA
Erqou et al. (2018) Pittsburg, PA 2001−2014	$PM_{2.5}$ concentrations estimated using land use regression models for the 300 m buffer surrounding an individual's residence for the year prior to enrollment in the study	Mean (SE) Overall: 15.7 (0.77) Black: 16.1 (0.75) White: 15.7 (0.73)	Correlation (*r*): NA Copollutant models with: NA
Kelly et al. (2020) U.S. 2011	$PM_{2.5}$ concentrations estimated from nine different exposure models which can be described as either geophysical process, interpolation-based, Bayesian statistical regression, satellite-AOD-based, or machine learning models	Population-weighted average (range from models) NH-White: 9−10.3 Hispanic: 9.8−11.4 NH-Other: 9.4−11.5 NH-Black: 10.1−12.1	Correlation (*r*): NA Copollutant models with: NA
Lee (2019) California 2016	$PM_{2.5}$ concentrations estimated from both stationary monitors and satellite	Mean (SD): 8.09 (3.25) 25th−75th percentiles = 5.77−9.76	Correlation (*r*): NA Copollutant models with: NA

Table A-14 (Continued): Study-specific details for epidemiologic studies examining race/ethnicity and $PM_{2.5}$ exposure.

Study/Location Years	Exposure Assessment	Mean Concentration (µg/m^3)	Copollutant Examination
Liévanos (2019) California 2009−2011	$PM_{2.5}$ concentrations estimated from stationary monitors for each census tract centroid using kriging	Annual mean concentrations percentile ranges: ≤ 20th: 2.30−7.71 20−40th: 7.71−9.11 40−60th: 9.11−10.86 60−80th: 10.86−12.52 > 80th: 12.54−17.04	Correlation (*r*): NA Copollutant models with: NA
Lim et al. (2018) U.S. 1995−2011	Annual average $PM_{2.5}$ concentrations estimated using a spatiotemporal prediction model at the census tract	Mean (SD) Overall: 11.0 (2.7) White: 10.9 (2.7) Black: 12.3 (2.4) Hispanic: 11.4 (3.5) Asian, Pacific Islander, or American Indian/Alaska Native: 11.9 (3.0) Max: 21.2	Correlation (*r*): NO_2 = 0.60, O_3 = 0.01 Copollutant models with: NA
Lipfert and Wyzga (2020) U.S. 1976−2001	Average $PM_{2.5}$ concentrations estimated from stationary monitors, averaged at the county level	Mean at cohort entry: White: 13.9 Black: 15.7	Correlation (*r*): White: SO_4^{2}: 0.68, NO_2: 0.55, peak CO: −0.19, peak O_3: 0.57, peak SO_2: 0.20, PM_{10}: 0.45 Black: SO_4^{2}: 0.50, NO_2: 0.58, peak CO: 0.16, peak O_3: 0.19, peak SO_2: 0.43, PM_{10}: 0.49 Copollutant models with: NA
Parker et al. (2018) U.S. 1997−2011	Annual average $PM_{2.5}$ concentrations estimated from stationary monitors	Median:11.8 90th percentile: 14.7	Correlation (r): NA Copollutant models with: NA

Table A-14 (Continued): Study-specific details for epidemiologic studies examining race/ethnicity and $PM_{2.5}$ exposure.

Study/Location Years	Exposure Assessment	Mean Concentration (µg/m^3)	Copollutant Examination
Richmond-Bryant et al. (2020) U.S. 2008, 2011, 2014	$PM_{2.5}$ emissions from fossil-fuel Electricity Generating Units obtained from the National Emissions Inventory	NR	Correlation (*r*): NA Copollutant models with: NA
Rosofsky et al. (2018) Massachusetts 2003−2010	$PM_{2.5}$ concentrations estimated at 1 km x 1 km grid using a modeling approach which incorporated satellite, land use, and meteorological data aggregated to yearly averages	Population-weighted annual average $PM_{2.5}$ range: 2003: 11.1 to 11.7 2010: 7.8 to 8.4	Correlation (*r*): NA Copollutant models with: NA
Tessum et al. (2019) U.S. 2002−2015	$PM_{2.5}$ concentrations estimated using a modeling approach based on the InMAP model and incorporating 2014 National Emissions Inventory data as well as biogenic and wildfire emission sources	Average Exposure: Black: 6.0 Hispanic: 5.5 White: 4.6	Correlation (*r*): NA Copollutant models with: NA
Tessum et al. (2021) U.S. 2014	$PM_{2.5}$ concentrations estimated using a modeling approach based on the InMAP model and incorporating 2014 National Emissions Inventory data	Population average exposure from all domestic anthropogenic sources People of Color: 7.4 Black: 7.9 Hispanic: 7.2 Asian: 7.7 White: 5.9	Correlation (*r*): NA Copollutant models with: NA
Yitshak-Sade et al. (2020) Massachusetts 2001−2011	Daily average $PM_{2.5}$ estimated from a model incorporating aerosol optical depth and monitored $PM_{2.5}$ at a 1 x 1 km grid	NR	Correlation (*r*): NA Copollutant models with: NA

AOD = aerosol optical depth; inMAP = Intervention Model for Air Pollution; km = kilometer(s); NA = not applicable; NR = not reported; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; PM_{10} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10; *r* = correlation coefficient; SD = standard deviation.

Table A-15 Study-specific details for epidemiologic studies examining short-term $PM_{2.5}$ exposure and health risk disparity by race/ethnicity.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment Short-term Mean Concentration ($\mu g/m^3$)	Select Results	Covariates in Statistical Model	Copollutant Examination
Yitshak-Sade et al. (2019a) Massachusetts 2001−2011	Massachusetts Department of Public Health n = 179,986	Cardiovascular mortality	Daily average $PM_{2.5}$ estimated from a model incorporating aerosol optical depth and monitored $PM_{2.5}$ at a 1 x 1 km grid Mean: 10.2 Max: 17.4	Change in CV mortality High % White Green: 2.80% (0.62, 5.02) Less green: 1.14% (−1.00, 3.33) Low % White Green: 2.47% (0.43, 4.56) Less green: 3.55% (1.49, 5.65)	Temperature and day of the week	Correlation (*r*): NA Copollutant models with: NA
Yitshak-Sade et al. (2020) Massachusetts 2001−2011	Massachusetts Department of Public Health n = 130,863	Cardiovascular mortality	Daily average $PM_{2.5}$ estimated from a model incorporating aerosol optical depth and monitored $PM_{2.5}$ at a 1 × 1 km grid NR	Change in CV mortality Individual Black: 4.78% (−1.99, 12.02) White: 2.25% (0.80, 3.23) Block group Low % Black: 1.62% (0.05, 3.22) High % Black: 3.35% (1.57, 5.16) Racial Residential Segregation (RRS) More White (RRS 0.5, 1): 1.84% (0.31, 3.40) More Black (RRS −1, −0.5): 15.37% (0.76, 31.99) Index of Racial Dissimilarity (IRD) No difference	Temperature and day of the week	Correlation (*r*): NA Copollutant models with: NA

CV = cardiovascular; km = kilometer(s); IRD = Index of Racial Dissimilarity; NA = not applicable; NR = not reported; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; RRS = racial residential segregation.

Table A-16 Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by race/ethnicity.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Select Results	Covariates	Copollutant Examination
Awad et al. (2019) U.S. 2000−2012	Medicare n = 12,095,504	All-cause mortality	Annual average $PM_{2.5}$ concentrations estimated using a neural network-based hybrid model between 2000 and 2012 on a 1 x 1 km grid White Mean: pre-move: 11.88, post-move: 11.15 99th percentile: pre-move: 20.24, post-move: 18.08 Black Pre-move: 13.02, post-move: 12.12 99th percentile: pre-move: 20.68, post-move: 18.95	HR (95% CI) Black movers: 1.06 (1.04, 1.07) White movers: 1.10 (1.10, 1.10)	Age, race, sex, Medicaid eligibility, calendar year, hospitalization before move for: Alzheimer's disease, AMI, COPD, CV disease, diabetes, heart failure, lung cancer, Parkinson's Disease, pneumonia, any respiratory illness, stroke, unstable angina, vascular dementia and ZIP code level variables for the new ZIP code including: median household income, % Black, % Hispanic, % of owner-occupied housing units, population density, and median value of owner occupied housing	Correlation (*r*): NA Copollutant models with: NA
Bennett et al. (2019) U.S. 2015	National Center for Health Statistics n = 41.9 million	Life expectancy loss	Annual average $PM_{2.5}$ concentrations estimated using an integrated geographic regression model Median: 7.7 99th percentile: 10.1	$PM_{2.5}$ associated with lower life expectancy among counties with, higher percent of Black or African Americans.	Income, % in poverty, Black race, ≥ high school, urbanization, unemployment, cumulative smoking, mean temperature, relative humidity, county-specific random intercepts	Correlation (*r*): NA Copollutant models with: NA
Jorgenson et al. (2020) U.S. 2000−2014	U.S. Mortality Database	Life expectancy at birth	$PM_{2.5}$ concentrations estimated from stationary monitors, averaged at the state level Mean: 10.55 Max: 19.02	$PM_{2.5}$ more detrimental in states with high percent of population of Black race.	Income share of top 10%, % Black, total population, median household income, median age, % college degree or higher	Correlation (*r*): NA Copollutant models with: NA

Table A-16 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by race/ethnicity.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Select Results	Covariates	Copollutant Examination
Juarez et al. (2020) Southeastern U.S. 2002−2009	Southern Community Cohort Study n = 72,215	Cardio-metabolic disease	Annual average $PM_{2.5}$ concentrations estimated from a continuous, spatial surface model using ground-level ambient air measures and satellite-derived measurements Mean: 13.5 90th percentile: 15.8	Race did not modify the relationship between $PM_{2.5}$ and CMD.	Age, history of tobacco use/smoking status, air quality outdoors, educational level, household income, marital status, gender, residence location, race	Correlation (*r*): NA Copollutant models with: NA
Honda et al. (2017) U.S. 1993−2010	Women's Health Initiative n = 23,656	Hypertension	Mean (SD): 13.2 (3.0)	HR (95% CI) White:1.15 (0.99, 1.35) Black: 1.26 (1.06, 1.44) Non-White: 1.27 (1.17, 1.38) Asian/Pacific Islander: 1.34 (1.00, 1.64) Hispanic/Latino: 1.18 (0.99, 1.38)	Age, BMI, education, ethnicity, smoking status, physical activity, sodium intake, neighborhood SES, household income, employment status, insurance status, history of high cholesterol, history of cardiovascular disease, history of diabetes, clinical trial study arm and WHI clinical site	Correlation (*r*): PM_{10}: 0.56 $PM_{10-2.5}$: 0.03 Copollutant models with: NA
Lim et al. (2018) U.S. 1995−2011	NIH-AARP Diet and Health Study n = 549,735	Diabetes Mortality	Annual average $PM_{2.5}$ concentrations estimated using a spatiotemporal prediction model at the census tract Mean (SD): 11.0 (2.7) Max: 21.2	HR (95% CI) Black: 1.27 (1.02, 1.58) White: 1.05 (0.96, 1.14)	Age sex, region, race, or ethnic group, level of education, marital status, BMI, alcohol consumption, smoking status, diet, median census tract household income, % of census tract population with < a high school education	Correlation (*r*): NO_2 = 0.60, O_3 = 0.01 Copollutant models with: NA

Table A-16 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by race/ethnicity.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Select Results	Covariates	Copollutant Examination
Lipfert and Wyzga (2020) U.S. 1976−2001	Veterans Cohort Mortality Study n = 70,000	Mortality	Average $PM_{2.5}$ concentrations estimated from stationary monitors, averaged at the county level White: 13.9 Black: 15.7	RR (95% CI) 1976−2001 White: 1.05 (1.01, 1.10) Black: 0.82 (0.75, 0.89) 1997−2001 White: 1.03 (0.91, 1.17) Black: 0.96 (0.76, 1.21)	individual age, race, smoking, height, body mass index, blood pressure, county-wide climate and ZIP code level socioeconomic indicators	Correlation (*r*): White: SO_4^{2}: 0.68, NO_2:0.55, peak CO: −0.19, peak O_3: 0.57, peak SO_2: 0.20, PM_{10}: 0.45 Black: SO_4^{2}: 0.50, NO_2: 0.58, peak CO: 0.16, peak O_3: 0.19, peak SO_2: 0.43, PM_{10}: 0.49 Copollutant models with: NA
Parker et al. (2018) U.S. 1997−2011	National Health Interview Survey n = 657,238	All-cause mortality (excluding unintentional injuries), heart disease mortality	Annual average $PM_{2.5}$ concentrations estimated from stationary monitors Median: 11.8 90th percentile: 14.7	HR (95% CI) All-cause Black: 1.05 (1.03, 1.09) White: 1.03 (1.02, 1.03) Hispanic: 0.98 (0.94, 1.03) Heart disease Black: 1.04 (0.94, 1.15) White: 1.10 (1.05, 1.15) Hispanic: 1.03 (0.95, 1.12) Other: 0.90 (0.75, 1.07)	Sex, family income as a % of the poverty threshold, marital status, education, county-level income, region of county, urbanization, and survey year	Correlation (*r*): NA Copollutant models with: NA

Table A-16 (Continued): Study-specific details for epidemiologic studies examining long-term $PM_{2.5}$ exposure and health risk disparity by race/ethnicity.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment and Long-Term Mean and Upper Percentile Concentrations ($\mu g/m^3$)	Select Results	Covariates	Copollutant Examination
Son et al. (2020) North Carolina 2002−2013	Death Records n = 775,338	Total Mortality	Daily average $PM_{2.5}$ concentrations estimated from the CMAQ downscaler model on a 12 ×12 grid Mean (SD): 11.4 (5.7) Max: 70.8	OR (95% CI) NH-White: 1.01 (1.01, 1.01) NH-Black: 1.01 (1.00, 1.02) Hispanic: 0.97 (0.93, 1.02) NH-Asian: 1.01 (0.97, 1.02) NH-Other 1.01 (0.97, 1.04)	Case crossover	Correlation (*r*): O_3: 0.48 Copollutant models with: NA
Wang et al. (2020) U.S. 2000−2008	Medicare, ≥ 65 n = 52,954,845	Mortality	Daily average $PM_{2.5}$ concentrations estimated from a validated spatiotemporal generalized additive model on a 6 km grid Mean (SD): 10.32 (3.15)	Associations were null by race.	Age, sex, race, and ZIP code with additional control for ZIP code and state SES	Correlation (*r*): NO_2: 0.59, O_3: 0.24 Copollutant models with: O_3

AARP = American Association of Retired Persons; AMI = acute myocardial infarction; BMI = body mass index; CMAQ = Community Multi-Scale Air Quality; CI = confidence interval; CV = cardiovascular; km = kilometer(s); HR = hazard ratio; IRD = Index of Racial Dissimilarity; NA = not applicable; NIH = National Institutes of Health; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5; PM_{10} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10; $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 and less than or equal to 10; *r* = correlation coefficient; RRS = racial residential segregation; SD = standard deviation; SES = socioeconomic status; WHI = Women's Health Initiative.

A.1 Advances in Estimating Light Extinction

Equation 4-1, which across studies has been referred to as the original IMPROVE equation was originally the basis for estimating light extinction to track progress in reducing haze in visibility protected areas for the 1999 Regional Haze Rule (Malm et al., 1994):

$$b_{ext} \approx 3 \times f(RH) \times [Ammonium\ Sulfate] + 3 \times f(RH) \times [Ammonium\ Nitrate] + 4 \times [Organic\ Mass] + 10 \times [Elemental\ Carbon] + 1 \times [Fine\ Soil] + 0.6 \times [Coarse\ Mass] + Rayleigh\ scattering \quad (Eq.\ A\text{-}1)$$

Light extinction (b_{ext}) is in units of per Mm; [Ammonium Sulfate], [Ammonium Nitrate], [Organic Mass], [Elemental Carbon], [Fine Soil], and [Coarse Mass] are the concentrations in μg/m^3 of ammonium sulfate, ammonium nitrate, organic matter, elemental carbon, fine soil, and coarse mass, respectively; $f(RH)$ is the relative-humidity-dependent water growth function for both ammonium sulfate and ammonium nitrate, and the various coefficients are empirically derived mass scattering and absorption coefficients originally proposed by (Malm et al., 1994). Organic mass is derived from organic carbon measurements by multiplying measured organic carbon by a factor of 1.4 to account for the non-carbon elements that also contribute to organic mass. Details on PM size distribution assumptions, component mass scattering extinction efficiencies, hygroscopicity, and other assumptions used to develop Equation A-1 are discussed in detail by Malm et al. (1994) and reviewed in Section 9.2.2 of the 2009 PM ISA (U.S. EPA, 2009) and Section 13.2.3 of the 2019 PM ISA (U.S. EPA, 2019).

Generally good performance was attributed to Equation A-1, but it underestimated high light extinction values and overestimated low light extinction values. Over the years, changes to the original IMPROVE equation have been adopted or proposed. Equation A-2 was developed to address bias at the low and high light extinction values of Equation A-1 (Pitchford et al., 2007). Equation A-2 has been referred to as the revised IMPROVE equation.

$$b_{ext} \approx 2.2 \times f_S(RH) \times [Small\ Ammonium\ Sulfate] + 4.8 \times f_L(RH) \times [Large\ Ammonium\ Sulfate] + 2.4 \times f_S(RH) \times [Small\ Ammonium\ Nitrate] + 5.1 \times f_L(RH) \times [Large\ Ammonium\ Nitrate] + 2.8 \times [Small\ Organic\ Mass] + 6.1 \times [Large\ Organic\ Mass] + 10 \times [Elemental\ Carbon] + 1 \times [Fine\ Soil] + 1.7 \times f_{SS}(RH) \times [Sea\ Salt] + 0.6 \times [Coarse\ Mass] + Rayleigh\ Scattering\ (Site\ Specific) + 0.33 \times [NO_2\ (ppb)] \quad (Eq.\ A\text{-}2)$$

Term definitions are the same as for Equation A-1. f_S and f_L are the relative-humidity-dependent water growth functions of ammonium sulfate and ammonium nitrate in the small and large modes, respectively,

and f_{SS} is the water growth function for sea salt. Small and large ammonium sulfate, ammonium nitrate, and organic mass are used to refer to the splitting of the concentrations of each of those three species into two size modes.

Equation A-2 is the result of five revisions to Equation A-1: (1) the addition of a sea salt term, (2) a change in the ratio of organic mass to organic carbon mass from 1.4 to 1.8, (3) a change in the Rayleigh scattering term to a site-specific term based on elevation and annual temperature, (4) introduction of split-component extinction efficiency terms to represent two particle size modes for sulfate, nitrate, and organic mass along with a new water growth term for sulfate and nitrate, and (5) addition of a NO_2 light absorption term for monitors where NO_2 concentration data are available. Sulfate, nitrate, and organic mass are each split into a small mode and a large mode, with the fraction of the large mode estimated by dividing the component concentration by 20 μg/m^3 and the remaining component mass attributed to the small mode if the $PM_{2.5}$ concentration is under 20 μg/m^3 and attributing all component mass to the large mode if the concentration is greater than 20 μg/m^3. This approach is consistent with an assumption that lower concentrations are associated with fresher emissions and smaller particle sizes, and higher concentrations with more aged PM and larger particle sizes. Because of this particular feature, Equation A-2 is sometimes referred to as the split-component algorithm. Further explanation of this calculation is available at (http://vista.cira.colostate.edu/Improve/the-improve-algorithm/). Light extinction and hygroscropicity are based on literature values, but component splitting between size modes is based on empirical observations (Prenni et al., 2019). Details on component mass scattering extinction efficiencies and hygroscopicities, and other assumptions used to develop Equation A-2 are discussed by Pitchford et al. (2007) and in Section 9.2.3 of the 2009 PM ISA (U.S. EPA, 2009).

Good performance of Equation A-2 was reported for a wide range of PM composition and sample loadings through 2003 (Prenni et al., 2019). However, Equation 4-2 was based on data from 1995 to 2003, when PM concentrations were higher than they are now, and PM composition and source contributions have also changed since then (Prenni et al., 2019). By the time of publication of the 2019 PM ISA, new results indicated that the Equation A-2 had not been generally successful in decreasing the bias in light extinction estimates associated with Equation A-1. For example, Equation A-2 was evaluated by Lowenthal and Kumar (2016), who recommended a further increase in the ratio of organic mass to organic carbon from 1.8 to 2.1, as well as the introduction of a relative-humidity-dependent water growth function for organic mass. The basis for these recommendations was discussed in detail by Lowenthal and Kumar (2016) and summarized in the 2019 PM ISA (U.S. EPA, 2019). Implementation of their recommendations results in Equation A-3, which is identical in form to Equation A-2, except for the insertion of the water growth terms $f_S(RH)_{OM}$ and $f_L(RH)$ for small and large organic mass, respectively:

$$b_{ext} \approx 2.2 \times f_S(RH) \times [Small\ Ammonium\ Sulfate] + 4.8 \times f_L(RH) \times [Large\ Ammonium\ Sulfate] +$$
$$2.4 \times f_S(RH) \times [Small\ Ammonium\ Nitrate] + 5.1 \times f_L(RH) \times [Large\ Ammonium\ Nitrate]$$
$$+ 2.8 \times f_S(RH)_{OM} \times [Small\ Organic\ Mass] + 6.1 \times f_L(RH)_{OM} \times [Large\ Organic\ Mass] +$$
$$10 \times [Elemental\ Carbon] + 1 \times [Fine\ Soil] + 1.7 \times f_{SS}(RH) \times [Sea\ Salt] +$$
$$0.6 \times [Coarse\ Mass] + Rayleigh\ Scattering\ (Site\ Specific) + 0.33 \times [NO_2\ (ppb)] \quad (Eq.\ A\text{-}3)$$

The 2011 IMPROVE report (Hand et al., 2011) and the 2019 PM ISA (U.S. EPA, 2019) also recognized concerns with Equation A-2, and returned to the use of Equation 4-1, but with the following changes that had been incorporated into Equation A-2: (1) the sea salt term was added, (2) the factor used to compute organic mass concentration from organic carbon measurements increased from 1.4 to 1.8, and (3) the site-specific term based on elevation and mean temperature was substituted for the constant value 10/Mm for Rayleigh scattering (U.S. EPA, 2019; Hand et al., 2011). These modifications resulted in Equation A-4, sometimes referred to as the modified original IMPROVE equation:

$$b_{ext} \approx 3 \times f(RH) \times [Ammonium\ Sulfate] + 3 \times f(RH) \times [Ammonium\ Nitrate] +$$
$$4 \times [Organic\ Mass] + 10 \times [Elemental\ Carbon] + 1 \times [Fine\ Soil] + 1.7 \times f(RH) \times [Sea\ Salt] +$$
$$0.6 \times [Coarse\ Mass] + Rayleigh\ scattering \quad (Eq.\ A\text{-}4)$$

More detailed discussions of Equations A-1 through A-4, as well as additional studies that have evaluated their performance are reviewed are in Sections 9.2.2 and 9.2.3 of the 2009 PM ISA (U.S. EPA, 2009) and Section 13.2.3 of the 2019 PM ISA (U.S. EPA, 2019).

The observations of persistent and potentially increasing bias in the established method for estimating light extinction from national monitoring network data are a concern and, as a result, it continues to be investigated. Since publication of the 2019 PM ISA, a comparison of direct measurements of light extinction using an integrating nephelometer with estimates of reconstructed light extinction based on Equation A-2 at 11 monitoring locations from 2002 to 2018 showed that the relationship between measured and reconstructed light extinction is changing (Prenni et al., 2019). As large decreases in sulfate and organic mass occurred over this 16-year period, the difference between measured and reconstructed light extinction increased at the five eastern monitoring locations, indicating that Equation A-2 increasingly underestimated light extinction over time. Multiple linear regressions of light extinction against PM components resulted in increasing regression coefficients over time for ammonium sulfate and particulate organic matter at these locations.

As PM concentrations have decreased, an increasingly larger portion of PM mass has been allocated to the smallest of the two size modes of Equation A-2 because, as described above, species mass is apportioned between size modes by dividing the decreasing species concentration by the same fixed factor of 20 μg/m^3 each year (Prenni et al., 2019). Prenni et al. (2019) used particle size distribution data

from intensive field studies and from model simulations to demonstrate that changes in particle size distributions have not actually occurred as PM concentrations have decreased, and they concluded that a part of the apparent decreasing trend in light extinction by ammonium sulfate and particulate organic matter is likely an artifact of Equation A-2, leading to calculations of changes in mass scattering efficiencies that have not occurred in the atmosphere. Estimating the fraction of the large size mode by dividing the component concentration by five times the annual median component mass calculated for ammonium sulfate, ammonium nitrate, and organic mass for each monitor and year instead of by the 20 $\mu g/m^3$ factor previously used for all sites and years, reduced the bias, especially in later years (Prenni et al., 2019).

Other sources of bias associated with both Equations A-1 and A-2 that could affect reconstructed light extinction have also been documented and reviewed by Prenni et al. (2019). Among the potential sources of biases that have been investigated are (1) the assumption of a constant ratio for converting measured organic carbon mass to total organic mass, in spite of spatial and seasonal variability and observed changes during atmospheric aging; (2) the assumption that organic mass is not hygroscopic while there is increasing evidence to the contrary; and (3) the assumption that ammonium sulfate is the only form of atmospheric sulfate even though recent research provides evidence that it is not fully neutralized in many U.S. locations (Prenni et al., 2019). While these could also lead to increased bias in light extinction estimates, the results of Prenni et al. (2019) indicate that a better understanding and correction of the potential biases is necessary before additional revision of Equation A-2 could be effective.

A.2 Quality Assurance Summary

The use of quality assurance (QA) and peer review help ensure that EPA conducts high-quality science assessments that can be used to help policymakers, industry, and the public make informed decisions. Quality assurance activities performed by EPA ensure that environmental data are of sufficient quantity and quality to support the Agency's intended use. The ISA for Particulate Matter is classified as a Highly Influential Scientific Assessment (HISA), which is defined by the Office of Management and Budget (OMB) as a scientific assessment that is novel, controversial, or precedent-setting, or has significant interagency interest. OMB requires a HISA to be peer reviewed before dissemination. To meet this requirement, EPA engages the Clean Air Scientific Advisory Committee (CASAC) as an independent federal advisory committee to conduct peer reviews. Both peer-review comments provided by the CASAC panel and public comments submitted to the panel during its deliberations about the external review draft were considered in the development of this ISA. Agency-wide, EPA Quality System provides the framework for planning, implementing, documenting, and assessing work performed by the Agency, and for carrying out required quality assurance and quality control (QA/QC) activities. Additionally, the Quality System covers the implementation of EPA Information Quality Guidelines. This ISA follows all Agency guidelines to ensure a high-quality document. Within EPA, Quality Assurance Project Plans (QAPPs) are developed to ensure that all Agency materials meet a high standard for quality. U.S. EPA has developed a Program-level QAPP (PQAPP) for the ISA Program to describe the technical approach and associated QA/QC procedures associated with the ISA Program (PQAPP ID# L-HEEAD-0030253-QP-1-5). In addition, QAPP (L-HEEAD-0030768-QP-1-0) was applied to the PM ISA Project. All QA objectives and measurement criteria detailed in the PQAPP and QAPP have been employed in developing this ISA. Quality assurance checks were conducted on numerical entries used in the appendices, and at a minimum, the numbers obtained from every tenth reference cited in the appendices were verified against the original source by an independent scientist for accuracy. Furthermore, publicly available databases (e.g., National Emissions Inventory, Air Quality System database) from which data were used in analyses were verified to have their own QA processes in place. U.S. EPA QA staff are responsible for the review and approval of all quality-related documentation. Because this is a HISA, U.S. EPA QA staff performed a Technical System Audit on the 2019 PM ISA in August 2019 and September 2020, and the Supplement to the 2019 PM ISA in March 2022. These audits verified that the appropriate QA/QC procedures and reviews were adequately performed and documented.

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