

Supplement to the 2019 Integrated Science Assessment for Particulate Matter

(External Review Draft)

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EXECUTIVE SUMMARY

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

8 Within this Supplement, the U.S. EPA evaluated recent studies (i.e., published since the literature
9 cutoff date of the 2019 PM ISA) that are of potentially greatest relevance to the reconsideration of the PM
10 NAAQS in the context of the findings of the 2019 PM ISA. The studies that formed the basis of the
11 evaluation presented within this Supplement consist of: (a) U.S. and Canadian epidemiologic studies for
12 health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and
13 long-term PM_{2.5} exposure and cardiovascular effects and mortality); (b) U.S. and Canadian epidemiologic
14 studies that employed causal modeling methods or conducted accountability analyses; (c) studies that
15 examined specific issues of importance including experimental studies conducted at near-ambient PM_{2.5}
16 concentrations, U.S. and Canadian epidemiologic or exposure studies that examined disparities in PM_{2.5}
17 exposure or health risks by race and ethnicity or socioeconomic status, and U.S. and Canadian
18 epidemiologic studies that examined the association between PM_{2.5} exposure and Coronavirus Disease
19 2019 (COVID-19) infection or death; and (d) U.S. and Canadian studies that examined public preferences
20 for visibility impairment and/or developed methodologies or conducted quantitative analyses of light
21 extinction. This Supplement to the 2019 PM ISA is not intended to represent the full multidisciplinary
22 evaluation of evidence that results in the formation of weight-of-evidence conclusions, but instead is an
23 assessment that puts the results of recent studies in the context of the scientific conclusions (i.e., causality
24 determinations) presented within the 2019 PM ISA.

25 This Supplement to the 2019 PM ISA finds that recent studies further support, and in some
26 instances extend, the evidence that formed the basis of the causality determinations presented within the
27 2019 PM ISA that characterizes relationships between PM exposure and health (i.e., cardiovascular
28 effects and mortality) and welfare effects (i.e., visibility impairment). In brief, this Supplement finds the
29 following:

- 30 • Recent U.S. and Canadian epidemiologic studies examining short- and long-term PM_{2.5} exposure
31 and cardiovascular effects and mortality provide evidence that is consistent with the conclusions
32 of the 2019 PM ISA. Relative to the studies evaluated in the 2019 PM ISA, many of the studies
33 report positive associations at lower PM_{2.5} concentrations (i.e., annual PM_{2.5} concentrations
34 ranging from 5.9 to 16.5 µg/m³; mean 24-hour avg PM_{2.5} concentrations ranging from 7.1 to
35 15.4 µg/m³).

- 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 there remains strong evidence 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 cause-specific mortality outcomes.
- A number of recent long-term PM_{2.5} exposure and mortality studies conducted in cohorts consisting of diverse populations and encompassing large geographic locations report consistent, positive associations, with most reporting mean annual PM_{2.5} concentrations ranging from 5.9–11.65 µg/m³.
 - 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 causal modeling methods 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 as well as studies providing initial assessments of short- and long-term PM_{2.5} exposure and COVID-19 infection and death. While some studies examining COVID-19 report positive associations, these studies are subject to methodological limitations and require additional exploration.
- The 2019 PM ISA provided evidence that specific lifestyles 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, specifically among non-White 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

1 The U.S. Environmental Protection Agency (U.S. EPA) completed the Integrated Science
2 Assessment for Particulate Matter (2019 PM ISA) in December 2019 ([U.S. EPA, 2019](#)). The 2019 PM
3 ISA builds upon the evidence evaluated and scientific conclusions presented in prior assessments
4 including the 2009 PM ISA ([U.S. EPA, 2009](#)) and earlier assessments, e.g., 2004 PM Air Quality Criteria
5 Document [AQCD; ([U.S. EPA, 2004](#))] and 1996 PM AQCD ([U.S. EPA, 1996](#)). Within the 2019 PM ISA,
6 evidence spanning scientific disciplines (e.g., atmospheric chemistry, exposure science, animal
7 toxicological, human clinical, epidemiology) was evaluated to assess the causal nature of relationships
8 between PM and health and nonecological welfare effects using a weight-of-evidence approach
9 extensively detailed in the *Preamble to the Integrated Science Assessments* ([U.S. EPA, 2015](#)) and the
10 appendix of the 2019 PM ISA.¹

11 The key science judgments (i.e., causality determinations) detailed within the 2019 PM ISA
12 directly informed the development of conclusions outlined within the *Policy Assessment for the Review of*
13 *the PM NAAQS* (2020 PM PA) ([U.S. EPA, 2020b](#)). These key science judgments formed the basis of the
14 discussion on potential alternative primary and secondary National Ambient Air Quality Standards
15 (NAAQS) for PM within the 2020 PM PA.

16 On June 10, 2021, the U.S. EPA announced it is reconsidering the December 2020 decision to
17 retain the PM NAAQS, and as part of this process, the Agency is developing a supplement to the 2019
18 PM ([EPA Press Office, 2021](#)). As a result, the evidence presented within the 2019 PM ISA, along with
19 the targeted identification and evaluation of new scientific information in this Supplement, provides the
20 scientific basis to support a robust and thorough reconsideration of the 2020 PM NAAQS.

1.2 Rationale and Scope

21 In completing the review of the PM NAAQS in December 2020, U.S. EPA provisionally
22 considered numerous studies published after the literature cutoff date (approximately January 2018) for
23 the 2019 PM ISA. In reviewing these studies, as explained in *Responses to Significant Comments on the*
24 *2020 Proposed Decision on the National Ambient Air Quality Standards for Particulate Matter* the
25 U.S. EPA “concluded that none of the studies materially change any of the broad scientific conclusions of

¹Hereafter 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](#)).

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, the U.S. 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. To facilitate the identification and evaluation of recent studies that warrant review, the U.S. EPA 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 the U.S. EPA in support of the reconsideration of the primary and secondary PM NAAQS.

1.2.1 Rational for Inclusion of Health and Welfare Effects

The causality determinations presented within the 2019 PM ISA and discussed in Section 2 below, 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 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, [the U.S. 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 where 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 where the 2019 PM ISA concluded a *causal relationship*.

In addition, this Supplement also considers recent health effects evidence that addresses key scientific topics where 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 causal modeling methods or conducted accountability analyses, studies that assess the relationship between PM_{2.5} exposure and Coronavirus Disease 2019 (COVID-19) infection and death; and in

accordance with recent U.S. EPA guidance 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.

Consistent with the rationale for the health effects, the selection of welfare effects to evaluate within this Supplement were 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.

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 evaluation. The studies considered for inclusion within the Supplement consist of peer-reviewed studies published from approximately January 2018 through March 2021 that satisfy the following criteria:

Health Effects

- Health effect categories where the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term PM_{2.5} exposure and cardiovascular effects and mortality). Additionally, for these health effect categories the recent studies evaluated are limited to:
 - U.S. and Canadian epidemiologic studies
 - Epidemiologic studies that employed causal modeling methods or conducted accountability analyses (i.e., examined the impact of a policy on reducing PM_{2.5} concentrations)²

Key Scientific Topics

- Experimental studies (i.e., controlled human exposure and animal toxicological) conducted at near-ambient PM_{2.5} concentrations
- At-risk populations

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

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 narrow 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). Therefore, this Supplement critically evaluates and provides key study specific information for 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 in the 2019 PM ISA.

1.3 Organization of the Supplement

The Supplement to the 2019 PM ISA is not intended to be a standalone 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 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. 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,

1 [Section 3](#) evaluates recent studies that assess key science topics that have evolved since the completion of
2 the 2019 PM ISA. [Section 4](#) consists of an evaluation of recent studies that inform visibility effects and is
3 organized similar to the health effects chapter. Therefore, [Section 4](#) first presents the summary and
4 causality determination from the 2019 PM ISA, then evaluates recent studies, and concludes by assessing
5 new evidence in the context of the conclusions for visibility impairment presented in the 2019 PM ISA.
6 Lastly, [Section 5](#) provides a summary and presents overarching conclusions based on the evaluation of
7 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, etc.) and lifestages (e.g., children, older adults, etc.) 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 non-White populations, 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

1 The 2019 PM ISA evaluated relationships between short-term and long-term exposures to PM
2 (i.e., PM_{2.5}, PM_{10-2.5}, and UFPs) and an array of health effects described in epidemiologic, controlled
3 human exposure, and animal toxicological studies. In the assessment of the overall evidence, the strengths
4 and limitations of individual studies were evaluated based on scientific considerations detailed in the
5 appendix to the 2019 PM ISA. Short-term exposures are defined as those with durations of hours up to
6 1 month, with most studies examining effects related to exposures in the range of 24 hours to 1 week.
7 Long-term exposures are defined as those with durations of more than 1 month to years. As detailed in the

1 Preface of the 2019 PM ISA, the evaluation of the health effects evidence focuses on exposures
2 conducted at concentrations of PM that are relevant to the range of human exposures across ambient
3 microenvironments (up to 2 mg/m³, which is one to two orders of magnitude above ambient
4 concentrations), and studies that (1) include a composite measure of PM³ or (2) apply some approach to
5 assess the direct effect of a specific PM size-fraction when the exposure of interest is a source-based
6 mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke).

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

³Composite 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., O₃, NO₂, SO₂, 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

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

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

2.1.1.2 Cardiovascular Effects

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

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

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

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

7 Consistent with the 2009 PM ISA, the strongest evidence comes from epidemiologic studies that
8 reported consistent positive associations between short-term PM_{2.5} exposure and cardiovascular-related
9 ED visits and hospital admissions particularly for IHD (2019 PM ISA, Section 6.1.2.1) and HF (2019 PM
10 ISA, Section 6.1.3.1), as well as cardiovascular-related mortality (2019 PM ISA, Section 6.1.9) across
11 studies that used different approaches to control for the potential confounding effects of weather
12 (e.g., temperature). While associations remained relatively unchanged across the copollutants evaluated,
13 the evidence was especially consistent for air pollutants that are not typically associated with traffic
14 (i.e., ozone, SO₂, PM_{10-2.5}). In some instances, associations in copollutant models were attenuated, but this
15 was only observed for the traffic-related pollutants (i.e., NO₂, CO), which generally had higher
16 correlations with PM_{2.5} than other copollutants. This evidence from copollutant analyses from studies
17 evaluated in the 2019 PM ISA generally indicates that the associations observed between short-term
18 PM_{2.5} exposure and cardiovascular effects are not artifacts due to confounding by another air pollutant
19 (2019 PM ISA, Section 6.1.14.1). These epidemiologic studies reduce a key uncertainty identified in the
20 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the
21 PM_{2.5}-cardiovascular effects relationship.

22 The independence of PM_{2.5} effects is further addressed by findings of controlled human exposure
23 and animal toxicological studies evaluated in the 2019 PM ISA. The most consistent evidence from
24 controlled human exposure studies was for a PM_{2.5} effect on endothelial function (2019 PM ISA,
25 Section 6.1.13). Multiple recent controlled human exposure studies reported that PM_{2.5} impaired some
26 measure of vessel dilation following reactive hyperemia or pharmacological challenge relative to filtered
27 air. Given the relationship between endothelial function and BP, these results were coherent with multiple
28 controlled human exposure studies that reported changes in BP following short-term PM_{2.5} CAPs
29 exposure (2019 PM ISA, Section 6.1.6.3). However, these results were inconsistent with some controlled
30 human exposure studies from previous reviews that did not find changes in endothelial function or BP.
31 The results of controlled human exposure studies evaluated in the 2019 PM ISA are also coherent with
32 evidence from animal toxicological studies demonstrating endothelial dysfunction and changes in BP or
33 the renin angiotensin system following short-term PM_{2.5} exposure (2019 PM ISA, Section 6.1.13.3 and
34 Section 6.1.6.4). Moreover, changes in endothelial function and BP reported in recent experimental
35 studies were consistent with epidemiologic studies reporting associations between short-term PM_{2.5}
36 exposure and IHD, as well as with limited epidemiologic panel study evidence of associations with BP. In
37 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, 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 µg/m³ (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

1 in the 2019 PM ISA examining cardiovascular morbidity endpoints consisted of several large U.S. cohort
2 studies each focusing on populations with distinct demographic characteristics (e.g., postmenopausal
3 women, male doctors, etc.) and extensive consideration of potential confounders. These studies have
4 reported heterogeneous results, with several studies that adjusted for important confounders, including
5 socioeconomic status (SES), reporting positive associations for cardiovascular morbidity endpoints. The
6 strong associations reported between long-term PM_{2.5} exposure and coronary events (e.g., coronary heart
7 disease [CHD] and stroke) among postmenopausal women in the Women's Health Initiative (WHI)
8 cohort, highlighted in 2009 PM ISA, were strengthened in an extended analysis that considered individual
9 and neighborhood-level SES (2019 PM ISA, Section 6.2.3; Section 6.2.10). Recent analyses of other
10 cohorts of women (i.e., Nurses' Health Study, California Teachers Study) that were comparable to WHI
11 in that they considered menopausal status or hormone replacement therapy did not show consistent
12 positive associations with CHD, myocardial infarction, or stroke. Longitudinal studies demonstrated that
13 changes in the progression of atherosclerosis in relation to long-term exposure to PM_{2.5} were variable
14 across cohorts and found to depend, in part, on the vascular bed in which atherosclerosis was evaluated
15 (2019 PM ISA, Section 6.2.4.1). However, within a study focusing on the progression of atherosclerosis
16 in a healthy population, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA-Air), an
17 association was observed between long-term PM_{2.5} exposure and coronary artery calcification (CAC),
18 which is a strong predictor of CHD (2019 PM ISA, Section 6.2.4). A small number of studies reported
19 positive associations between long-term PM_{2.5} exposure and HF, BP changes, and hypertension.
20 Longitudinal epidemiologic analyses also supported the observation of positive associations with markers
21 of systemic inflammation, coagulation, and endothelial dysfunction. These HF studies were coherent with
22 animal toxicological studies demonstrating decreased contractility and cardiac output and increased
23 coronary artery wall thickness following long-term PM_{2.5} exposure (2019 PM ISA, Section 6.2.4.2).
24 Moreover, animal toxicological studies finding a relationship between long-term exposure to PM_{2.5} and
25 changes in BP in rats and mice were coherent with epidemiologic studies reporting positive associations
26 between long-term exposure to PM_{2.5} and hypertension. Similarly, evidence of atherosclerotic plaque
27 progression in a genetically susceptible mouse model was consistent with epidemiologic studies reporting
28 associations between atherosclerosis and long-term PM_{2.5} exposure.

29 The body of evidence evaluated in the 2019 PM ISA also reduced uncertainties identified in the
30 2009 PM ISA related to potential copollutant confounding and the shape of the concentration-response
31 (C-R) relationship for CVD effects following long-term PM_{2.5} exposure. Generally, most of the PM_{2.5}
32 effect estimates relating long-term PM_{2.5} exposure to cardiovascular mortality remained relatively
33 unchanged or increased in copollutant models adjusted for O₃, NO₂, SO₂, and PM_{10-2.5} (2019 PM ISA,
34 Section 6.2.15). In addition, most of the results from analyses examining the C-R function for
35 cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality,
36 especially at mean annual PM_{2.5} concentrations $\leq 12 \mu\text{g}/\text{m}^3$ (2019 PM ISA, Section 6.2.10). Some studies
37 reported that the slope of the C-R curve tended to be steeper at lower concentrations, especially for IHD
38 mortality, suggesting a supralinear C-R relationship. A limited number of cardiovascular morbidity
39 studies examined the shape of the C-R relationship and generally reported a steeper C-R curve at lower

concentrations (starting at ~10 µg/m³) 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 effect 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.

1 There was strong evidence for biologically plausible pathways that may underlie nervous system
2 effects resulting from long-term exposure to PM_{2.5}. Studies demonstrated modulation of the autonomic
3 nervous system leading to downstream consequences including cardiovascular effects (2019 PM ISA,
4 Section 6.2.1). In addition, the pathway involving neuroinflammation in specific regions of the brain
5 (i.e., the hippocampus, cerebral cortex, and hypothalamus) and morphologic changes in the brain
6 indicative of neurodegeneration, is well substantiated and coherent across animal toxicological and
7 epidemiologic studies (2019 PM ISA, Section 8.2.3 and Section 8.2.4). Specifically, morphologic changes
8 induced in the hippocampus of animals were accompanied by impaired learning and memory and there
9 was consistent evidence from multiple epidemiologic studies that long-term PM_{2.5} exposure is associated
10 with reduced cognitive function (2019 PM ISA, Section 8.2.5). Further, the presence of early markers of
11 Alzheimer's disease pathology was demonstrated in animals following long-term exposure to PM_{2.5}
12 CAPs, which was consistent with a small number of epidemiologic studies that reported positive
13 associations with neurodegenerative changes in the brain (i.e., decreased brain volume) and Alzheimer's
14 disease or all-cause dementia (2019 PM ISA, Section 8.2.6). Although the loss of dopaminergic neurons
15 in the substantia nigra, which is a hallmark of Parkinson's disease, was demonstrated in animals
16 (2019 PM ISA, Section 8.2.4), epidemiologic studies did not report associations with Parkinson's disease
17 (2019 PM ISA, Section 8.2.6). Overall, the lack of consideration of copollutant confounding introduces
18 some uncertainty in the interpretation of the epidemiologic studies but this uncertainty was addressed, in
19 part, by the direct evidence of effects provided by animal toxicological studies.

20 In addition to the findings described above, which are mostly relevant to adults, several recent
21 studies of neurodevelopmental effects in children have also been conducted. Positive associations
22 between long-term exposure to PM_{2.5} during the prenatal period and autism spectrum disorder (ASD)
23 were consistently observed across multiple epidemiologic studies (2019 PM ISA, Section 8.2.7.2).
24 However, several studies of performance on tests of cognitive function provided little support for an
25 association. Overall, these epidemiologic studies of developmental effects were limited due to their lack
26 of control for potential confounding by copollutants, the small number of studies, and uncertainty
27 regarding critical exposure windows. A study in animals that found inflammatory and morphologic
28 changes in the corpus collosum and hippocampus, as well as ventriculomegaly in young animals
29 following prenatal exposure to PM_{2.5} CAPs provided initial evidence indicating a potential biologically
30 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

31 Experimental and epidemiologic evidence indicating genotoxicity, epigenetic effects (e.g., DNA
32 methylation), and increased carcinogenic potential due to PM_{2.5} exposure, along with strong

1 epidemiologic evidence for increases in lung cancer incidence and mortality, supported a *likely to be*
2 *causal relationship* between long-term PM_{2.5} exposure and cancer ([Table 2-2](#)). This causality
3 determination represented a change from the *suggestive of a causal relationship*⁴ determination reported
4 in the 2009 PM ISA. The evidence base underlying this conclusion encompasses the decades of research
5 on whole PM exposures and research evaluated in the 2019 PM ISA focusing specifically on PM_{2.5}.

6 PM_{2.5} exhibits various characteristics of carcinogens, as shown in studies demonstrating
7 genotoxic effects (e.g., DNA damage), epigenetic alterations, oxidative stress, and electrophilicity. The
8 examination of the role of PM_{2.5} in cancer development has often focused on whether whole PM, not
9 specific size fractions, has mutagenic properties and whether exposure to whole PM results in
10 genotoxicity or carcinogenicity. Additionally, it has been well characterized that some components of
11 PM_{2.5}, specifically hexavalent chromium, nickel, arsenic, and PAHs are known human carcinogens.
12 Extensive analyses of PM_{2.5} and PM_{2.5} extracts in the Ames *Salmonella*/mammalian-microsome
13 mutagenicity assay demonstrated that PM_{2.5} contains mutagenic agents (2019 PM ISA, Section 10.2.2.1).
14 Additional in vitro and in vivo toxicological studies indicated the potential for PM_{2.5} exposure to result in
15 DNA damage, which was supported by limited human evidence (2019 PM ISA, Section 10.2.2.2). Some
16 studies have also demonstrated that PM_{2.5} exposure can result in cytogenetic effects, specifically
17 micronuclei formation and chromosomal aberrations (2019 PM ISA, Section 10.2.2.3), as well as
18 differential expression of genes potentially relevant to genotoxicity or other aspects of cancer
19 pathogenesis (2019 PM ISA, Section 10.2.2.4). Although inconsistently examined across studies, changes
20 in cellular and molecular markers of genotoxicity and epigenetic alterations, which may lead to genomic
21 instability, are demonstrated in response to PM_{2.5} exposure. Further, the carcinogenic potential of PM_{2.5}
22 was demonstrated in an animal toxicological study in which chronic inhalation enhanced tumor formation
23 that was initiated by exposure to urethane (2019 PM ISA, Section 10.2.4). Additionally, epidemiologic
24 studies evaluated in the 2019 PM ISA encompassing multiple cohorts that are diverse in terms of both
25 geographic coverage and population characteristics have provided evidence of primarily consistent
26 positive associations between long-term PM_{2.5} exposure and lung cancer incidence and mortality,
27 particularly in never smokers (2019 PM ISA, Section 10.2.5.1). Experimental and epidemiologic evidence
28 of genotoxicity, epigenetic effects, and carcinogenic potential provides biological plausibility for
29 epidemiologic results of lung cancer incidence and mortality. Although evaluated in a limited number of
30 studies, the assessment of potential copollutant confounding, particularly with O₃, indicated that PM_{2.5}
31 associations with lung cancer incidence and mortality are relatively unchanged in copollutant models
32 (2019 PM ISA, Section 10.2.5.1.3). There was limited evidence that long-term PM_{2.5} exposure is
33 associated with cancers in other organ systems; however, there was initial evidence that PM_{2.5} exposure
34 may reduce survival in individuals with cancer.

⁴Since 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*.

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 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 0.19–2.80% at lags of 0 to 1 day in studies in which mean 24-hour avg concentrations were primarily <20 µg/m³ (2019 PM ISA, Figure 11-1; Table 11-1).⁵ 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 PM₁₀ 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

⁵Throughout 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-µg/m³ increase in 24-hour avg PM_{2.5} concentrations and long-term exposures are for a 5-µg/m³ increase in annual concentrations, unless otherwise noted.

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); 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 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, etc.) provided further evidence of positive associations between long-term PM_{2.5} exposure and total mortality, particularly in areas with annual mean concentrations <20 µg/m³, and in some cases below 12 µg/m³ (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 O₃, with fewer studies examining NO₂, 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

1 provided by the coherence of effects across scientific disciplines for cardiovascular morbidity,
2 particularly for CHD, stroke and atherosclerosis, and for respiratory morbidity, particularly for the
3 development of COPD. Recent studies extensively examined the C-R relationship between long-term
4 PM_{2.5} exposure and total mortality, specifically in several U.S. and Canadian cohorts, and collectively
5 continued to support a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.2.4; Table 11-7).

6 A series of studies evaluated in the 2019 PM ISA, examined the relationship between long-term
7 exposure to PM_{2.5} and mortality by examining the temporal trends in PM_{2.5} concentrations to test the
8 hypothesis that decreases in PM_{2.5} concentrations are associated with increases in life expectancy (2019
9 PM ISA, Section 11.2.2.5). These studies reported that decreases in long-term PM_{2.5} concentrations were
10 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 <i>No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>		
Section 5.1.12 Table 5-18	<p>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., O₃, NO₂, SO₂, 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.</p>	<p>Mean ambient concentrations from epidemiologic studies for: <i>Hospital admissions and ED visits for asthma, COPD, respiratory infections, and combinations of respiratory-related diseases:</i> U.S. and Canada: 4.7–24.6 µg/m³ Europe: 8.8–27.7 µg/m³ Asia: 11.8–69.9 µg/m³ <i>Respiratory mortality:</i> 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: <i>Allergic airway disease:</i> 442–596 µg/m³ <i>COPD:</i> 171–1,200 µg/m³ <i>Altered host defense:</i> 100–350 µg/m³</p>

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		
<i>No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>		
Section 5.2.13 Table 5-27	<p>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 O₃, NO₂, 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.</p>	<p>Mean ambient concentrations from epidemiologic studies for:</p> <p><i>Decrement in lung function growth:</i> 6–28 µg/m³</p> <p><i>Asthma development in children:</i> 5.2–16.5 µg/m³</p> <p><i>Bronchitic symptoms in children with asthma:</i> 9.9–13.8 µg/m³</p> <p><i>Accelerated lung function decline in adults:</i> 9.5–17.8 µg/m³</p> <p><i>Respiratory mortality:</i> 6.3–23.6 µg/m³</p> <p>Concentrations from animal toxicological studies for:</p> <p><i>Impaired lung development:</i> 16.8 µg/m³</p> <p><i>Development of allergic airway disease:</i> 100 µg/m³</p>

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		
<i>No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>		
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: <i>IHD</i> : 5.8–18.6 µg/m ³ <i>HF</i> : 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		
<i>No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>		
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: <i>Cardiovascular mortality:</i> 4.1–17.9 µg/m ³ <i>Coronary events:</i> 13.4 µg/m ³ <i>CAC:</i> 14.2 µg/m ³ <i>CHD and stroke (in those with preexisting disease):</i> 13.4–23.9 µg/m ³ Concentrations from animal toxicological studies for: <i>BP:</i> 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		
<i>Not Evaluated in the 2009 PM ISA; New Evidence Showing Brain Inflammation and Oxidative Stress, Neurodegeneration, Cognitive Effects, and Neurodevelopmental Effects.</i>		
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: <i>Brain volume:</i> 11.1–12.2 µg/m ³ <i>Cognition:</i> 8.5 (5-yr avg)–14.9 µg/m ³ <i>Autism:</i> 14.0–19.6 µg/m ³ Concentrations from animal toxicological studies for: <i>Brain inflammation/oxidative stress:</i> 65.7–441.7 µg/m ³ <i>Neurodegenerative changes:</i> 94.4 µg/m ³ <i>Neurodevelopment:</i> 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		
<i>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.</i>		
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: <i>Lung cancer incidence and mortality:</i> 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: <i>Carcinogenic potential:</i> 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 <i>No Change in Causality Determination From the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>		
Section 11.1.12 Table 11-4	<p>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/m³. 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.</p>	<p>Mean 24-h avg concentrations from epidemiologic studies for:</p> <p><i>Total mortality:</i></p> <p>U.S. and Canada: 4.37–17.97 µg/m³</p> <p>Europe: 13–27.7 µg/m³</p> <p>Asia: 11.8–69.9 µg/m³</p>

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		
<i>No Change in Causality Determination From the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>		
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: <i>Total mortality:</i> ACS/HSC cohorts: 11.4–23.6 µg/m ³ Medicare cohort: 8.12–12.0 µg/m ³ Canadian cohorts: 8.7–9.1 µg/m ³ Employment cohorts: 12.7–17.0 µg/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; µg/m³ = micrograms per cubic meter; MI = myocardial infarction; NO₂ = nitrogen dioxide; O₃ = 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; SO₂ = sulfur dioxide.

^aA 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

1 In the process of evaluating the current state of the science with respect to the effect of short- and
2 long-term PM exposure on health, studies were identified and evaluated within the 2019 PM ISA that
3 conducted analyses focused on addressing some of the main policy-relevant questions of this review, as
4 detailed in the PM IRP ([U.S. EPA, 2016](#)), such as:

- 5 • Is there new evidence aimed at disentangling the effect of PM from the complex air pollution
6 mixture to inform a direct effect of PM on health, specifically the assessment of potential
7 copollutant confounding?
- 8 • Is there new evidence to inform the current indicators (i.e., PM_{2.5} for fine particles and PM₁₀ for
9 thoracic coarse particles), averaging times (i.e., 24-hour avg, annual average), and levels of the
10 PM NAAQS?
- 11 • Is there new evidence on the shape of the C-R relationship and whether a threshold hold exists
12 between PM exposure and various health outcomes (e.g., mortality, hospital admissions, etc.),
13 especially for concentrations near or below the levels of the current PM NAAQS?
- 14 • Is there new evidence that individual PM component(s) or source(s) (e.g., industrial facilities,
15 roads, atmospheric formation), are more strongly associated with health effects than PM mass,
16 particularly for health effects for which there is sufficient evidence of a strong relationship
17 (e.g., cardiovascular effects, mortality) with PM exposure?
- 18 • Is there new evidence indicating that specific populations or lifestyles are at increased risk of a
19 PM-related health effect compared with a referent population?

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

2.2.1 Potential Copollutant Confounding

24 Studies evaluated in the 2019 PM ISA further examined the potential confounding effects of
25 copollutants, both gaseous and particulate, on the relationship between short- and long-term PM_{2.5}
26 exposure and health effects. These studies built upon the evidence detailed in the 2009 PM ISA and
27 continued to provide evidence indicating that associations with PM_{2.5} are relatively unchanged in
28 copollutant models. Evidence from epidemiologic studies, in combination with experimental studies
29 detailed in multiple chapters of the 2019 PM ISA (i.e., “Respiratory Effects”—Chapter 5 and
30 “Cardiovascular Effects”—Chapter 6 within the 2019 PM ISA) that examined exposure to PM
31 (e.g., CAPs, resuspended PM, and whole mixtures in the presence and absence of a particle trap),
32 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., O₃, NO₂, SO₂, 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., <0.7) observed for NO₂, SO₂, CO, and PM_{10-2.5}, and correlations spanning from low to high for O₃. Across the studies that assessed copollutant confounding, O₃ was most commonly examined, followed by NO₂ and PM_{2.5} results were relatively unchanged in copollutant models. Although fewer studies focused on SO₂ 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 NO₂ and CO, with low to moderate correlations for O₃, SO₂, 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 NO₂ 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., NO₂, 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 or coherently indicated a stronger or weaker effect of combined exposure to PM_{2.5} and another pollutant compared to 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., NO₂, NO_x, and CO) and O₃, 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 O₃, with a limited number of studies examining NO₂, SO₂, PM_{10-2.5}, and benzene. Studies that examined

O₃ reported correlations that were generally moderate (ranging from $r = 0.49$ – 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 NO₂, PM_{10–2.5}, SO₂, 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 0–5 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

1 immediate effects of PM_{2.5} on cardiovascular morbidity outcomes, specifically those related to ischemic
2 events, were consistent with the lag structure of associations observed in studies of cardiovascular
3 mortality that reported immediate effects (i.e., lag 0–1 day). There was some evidence indicating
4 PM_{2.5}-cardiovascular mortality associations with exposures over longer durations, but this was not
5 supported by studies examining single-day lags that encompassed the same number of days.

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

2.2.3 Concentration-Response Relationship

13 In assessing the relationship-between short- and long-term PM exposure and health effects, an
14 important consideration is whether the relationship is linear across the full range of ambient
15 concentrations and whether there is a threshold concentration below which there is no evidence of an
16 effect. As detailed in the 2004 AQCD and 2009 PM ISA, conducting C-R and threshold analyses is
17 challenging because of the “(1) limited range of available concentration levels (i.e., sparse data at the low
18 and high end); (2) heterogeneity of (at-risk) populations (between cities); and (3) influence of
19 measurement error” ([U.S. EPA, 2004](#)). Studies evaluated in the 2019 PM ISA that focused on the shape
20 of the C-R curve expanded upon the health effects evaluated in previous reviews and continued to provide
21 evidence of a linear, no-threshold relationship between both short- and long-term PM_{2.5} exposure and
22 several respiratory and cardiovascular effects, and mortality. Some evidence indicated a steeper slope
23 (i.e., supralinear curve) at lower concentrations for some outcomes (i.e., long-term PM_{2.5} exposure and
24 mortality). Cutpoint analyses that focused on whether risk changed at different concentration ranges
25 provided some evidence of nonlinearity, specifically in the relationship between short-term PM_{2.5}
26 exposure and respiratory-related ED visits and hospital admissions. Although studies evaluated in the
27 2019 PM ISA have used many different statistical methods to examine the shape of the C-R relationship
28 and generally provided evidence for a linear, no-threshold relationship, many of these studies have not
29 systematically evaluated alternatives to a linear relationship.

2.2.3.1 Short-Term Exposure

30 Epidemiologic studies evaluated in the 2019 PM ISA that examined the C-R relationship between
31 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 µg/m³. 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 PM₁₀. 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 µg/m³. 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 µg/m³ in some studies.

1 Additionally, there was initial evidence indicating that the slope of the C-R curve may be steeper
2 (supralinear) at lower concentrations for cardiovascular mortality.

3 Few epidemiologic studies have examined the C-R relationship for long-term PM_{2.5} exposure and
4 respiratory effects (2019 PM ISA, Section 5.2.3.1.2). The ones that do have focused on asthma incidence
5 and childhood wheeze. Studies of asthma incidence that examined the shape of the C-R curve and
6 whether risk changes at different quartiles of PM_{2.5} concentrations did not find any evidence of deviations
7 in linearity and monotonically increasing risk, respectively. In an initial study of childhood wheeze,
8 specifically repeated wheeze events, there was evidence of a linear C-R relationship with confidence in
9 the linear relationship at long-term PM_{2.5} concentrations as low as 10 to 12 µg/m³.

10 A limited number of studies reported initial assessments of the C-R relationship for long-term
11 PM_{2.5} concentrations and cardiovascular effects, specifically IHD incidence, CAC, and hypertension
12 (2019 PM ISA, Section 6.2.1.6). For IHD incidence, there was evidence of a linear C-R relationship at
13 concentrations below 15 µg/m³, which was consistent with the shape of the curve when compared with
14 the full range of PM_{2.5} concentrations. Analyses of the relationship between long-term PM_{2.5} exposure and
15 CAC indicated both linear and nonlinear relationships, while there is preliminary evidence of a linear
16 relationship between long-term PM_{2.5} exposure and incidence of hypertension. A few studies that
17 examined the relationship between long-term PM_{2.5} exposure and lung cancer incidence and mortality
18 also examined the shape of the C-R curve by assessing its linearity and conducting cutpoint and threshold
19 analyses (2019 PM ISA, Section 10.2.5.1.4). These collective assessments provided initial evidence
20 supporting a no-threshold, linear relationship across the range of PM_{2.5} concentrations observed in the
21 U.S., with confidence in a linear relationship as low as 5–10 µg/m³ in some studies.

2.2.4 PM Components and Sources

22 Building on the initial evaluation conducted in the 2004 PM AQCD, the 2009 PM ISA formally
23 evaluated the relationship between exposures to PM components and sources and health effects. This
24 evaluation found that many components and sources representative of combustion-related activities
25 (e.g., motor vehicle emissions, coal combustion, oil burning, vegetative burning) were associated with a
26 range of health effects. The 2009 PM ISA, therefore, concluded that “many [components] of PM can be
27 linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those
28 components or sources that are more closely related to specific health outcomes.”

29 Building upon the evaluation of PM sources and components in the 2009 PM ISA, and as detailed
30 in the Preface of the 2019 PM ISA, the 2019 PM ISA systematically evaluated whether specific PM
31 components or sources were more strongly associated with health effects than PM mass by focusing on
32 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
33 case of ultrafine particles [UFP] mass, particle number, etc.) and PM components; (2) applied some
34 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,

1 but there was no evidence that any one component was more strongly associated with respiratory effects
2 than PM_{2.5} mass.

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

2.2.4.2 Cardiovascular Effects

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

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

25 Epidemiologic and animal toxicological studies conducted source-based analyses using
26 mathematical methods to apportion PM_{2.5} components into source factors (2019 PM ISA, Section 6.1.15.6
27 and Section 6.1.15.8). Epidemiologic studies focused on cardiovascular-related ED visits and hospital
28 admissions and reported positive associations with sources representative of combustion-related activities
29 (e.g., industrial combustion, traffic), with more limited evidence for wildfires. Animal toxicological
30 studies, which focused on markers of heart function (e.g., HR, HRV), reported associations with a variety
31 of source categories, but the associations were dependent on the location of the study (i.e., where the
32 PM_{2.5} CAPs were collected). Additional studies focusing on long-term exposures to PM_{2.5} sources were
33 fewer, with epidemiologic studies only examining traffic sources and animal toxicological studies
34 reporting associations between a number of sources and various cardiovascular effects.

2.2.4.3 Mortality

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

9 Compared with the 2009 PM ISA, in which most epidemiologic studies of mortality conducted
10 formal source apportionment analyses, studies evaluated in the 2019 PM ISA have focused more
11 exclusively on PM_{2.5} components. Of the limited number of studies that examined associations between
12 short- and long-term source exposures and mortality, positive associations were observed for those
13 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

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

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

25 The evaluation of populations and lifestages potentially at increased risk builds off the approach
26 used in the 2009 PM ISA and involved application of a framework detailed in the 2013 O₃ ISA to
27 characterize the evidence informing whether a population or lifestage is at increased risk ([U.S. EPA,](#)
28 [2013](#)). The focus of this evaluation was on determining the extent to which specific factors may increase
29 the risk of a PM-related health effect in a population or lifestage relative to a reference population, where
30 applicable. Importantly, this evaluation builds on the conclusions drawn elsewhere in the 2019 PM ISA,
31 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).

Based on the causality determinations briefly summarized within this section, and more fully detailed in the health effects chapters of the 2019 PM ISA, 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 vs. 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 non-White populations 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 non-White populations are at greater risk for both PM_{2.5}-related health effects and PM_{2.5} exposure than are Whites.

1 There was “*suggestive evidence*” that populations with preexisting cardiovascular (2019 PM ISA,
2 Section 12.3.1) or respiratory (2019 PM ISA, Section 12.3.5) disease, those that are overweight or obese
3 (2019 PM ISA, Section 12.3.3), those with particular genetic variants (2019 PM ISA, Section 12.4), those
4 that are of low SES (2019 PM ISA, Section 12.5.3), and those who are current or former smokers (2019
5 PM ISA, Section 12.6.1) are at increased risk for PM_{2.5}-related health effects. Epidemiologic studies that
6 conducted analyses stratified by preexisting cardiovascular disease tended to focus on hypertension, one
7 of the most easily measurable cardiovascular conditions, and did not consistently indicate increased risk
8 for several outcomes examined (e.g., mortality, stroke, BP). However, the strong evidence supporting a
9 *causal relationship* between short- and long-term PM_{2.5} exposure and cardiovascular effects, which
10 included cardiovascular-related mortality and ischemic heart disease (2019 PM ISA, Section 6.1.16 and
11 Section 6.2.18) indicated that individuals with underlying cardiovascular conditions related to these
12 serious outcomes may be at increased risk of a PM_{2.5}-related health effect. Similarly, there were few
13 studies that evaluated whether there is evidence of increased risk of a PM_{2.5}-related health effect between
14 people with preexisting asthma (2019 PM ISA, Section 12.3.5) and COPD (2019 PM ISA, Section 12.3.5)
15 compared with people that do not have a preexisting respiratory disease. However, epidemiologic studies,
16 particularly those studies examining short-term PM_{2.5} exposure and asthma or COPD ED visits and
17 hospital admissions reported generally consistent positive associations (2019 PM ISA, Section 5.1.2.1 and
18 Section 5.1.4.1), which represent exacerbations that are only possible in people with asthma or COPD.
19 Therefore, there was limited evidence to support that people with preexisting respiratory diseases,
20 specifically asthma or COPD, are at increased risk for a PM_{2.5}-related health effect, but there was
21 generally consistent evidence demonstrating these populations experience health effects due to a PM_{2.5}
22 exposure.

23 Studies that examined whether being obese or overweight increased the risk of a PM_{2.5}-related
24 health effect, reported evidence of increased risk for mortality associated with long-term exposures to
25 PM_{2.5}, but inconsistent evidence was found for subclinical cardiovascular outcomes, when comparing
26 obese or overweight individuals with normal weight individuals. However, the evaluation of studies
27 focusing on differences in risk by weight were complicated by the different definitions of obesity used
28 across studies.

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

35 Epidemiologic studies have examined several measures of SES (e.g., income level, educational
36 attainment, etc.) in assessing whether populations are at increased risk of a PM_{2.5}-related health effect. In
37 studies examining both differential exposure as well as increased risk of health effects, there was some

1 evidence that low SES populations are more likely to have higher PM_{2.5} exposures and that low SES
2 populations, as measured by metrics for income, are at increased risk of PM_{2.5}-related mortality when
3 compared with populations defined as higher SES. Finally, there was some epidemiologic evidence from
4 studies examining long-term PM_{2.5} exposure and lung cancer incidence and mortality, as well as total
5 mortality, that people who currently smoke or were former smokers may be at increased risk of a
6 PM_{2.5}-related health effect compared with never smokers.

7 For the remaining factors evaluated, “*inadequate evidence*” exists to determine whether having
8 diabetes (2019 PM ISA, Section 12.3.2), being in an older lifestage (i.e., older adults; 2019 PM ISA,
9 Section 12.5.1.2), residential location (including proximity to source and urban residence; 2019 PM ISA,
10 Section 12.5.5), sex (2019 PM ISA, Section 12.5.2), or diet (2019 PM ISA, Section 12.6.2) increase the
11 risk of PM_{2.5}-related health effects. Across these factors there was either limited assessment of differential
12 risk or exposure (i.e., residential location, diet), or inconsistency in results across studies to support
13 evidence of increased risk of a PM_{2.5}-related health effect (i.e., diabetes and sex). Instead, the
14 inconsistency in the evidence makes the determination of disproportionately increased risk more difficult.
15 For example, for older adults (2019 PM ISA, Section 12.5.1.2) there was a relatively small number of
16 studies that examined whether there is evidence of differential risk between age groups. In the evaluation
17 of these studies there was limited evidence indicating that older adults are at increased risk of
18 PM_{2.5}-related health effects compared with other age ranges; however, epidemiologic studies focusing
19 only on older adults demonstrated associations with respiratory-related ED visits and hospital admissions
20 with additional, but more limited, evidence of subclinical cardiovascular effects from epidemiologic panel
21 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 2002–2012 (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 responsible for more light extinction than any other single species, 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 American and Europe because this greenhouse-gas warming was unmasked (2019 PM ISA, Section 13.3.6). In developing countries in Asia, by contrast, there has been an increase in PM concentrations 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 <i>No Change in Causality Determination From the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>	
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 <i>No Change in Causality Determination From the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>	
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 <i>No Change in Causality Determination From the 2009 PM ISA; New Evidence Further Supports the Previous Determination.</i>	
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.

^aThe 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

1 The following section focuses on the evaluation of recent health effects studies that fall within the
2 scope of this Supplement as detailed in [Section 1.2.2](#). Within this section the evaluation of recent studies
3 is performed in the context of the studies evaluated and scientific conclusions presented in the 2019 PM
4 ISA. As a result, within each of the following sections, the summary and causality determination from the
5 2019 PM ISA is presented prior to the evaluation of recent studies published since the literature cutoff
6 date of the 2019 PM ISA that examine the relationship between short-term and long-term PM_{2.5} exposure
7 and cardiovascular effects ([Section 3.1](#)) and mortality ([Section 3.2](#)).⁶ This approach allows for a full
8 accounting of the evidence that formed the basis of the key scientific conclusions in the 2019 PM ISA and
9 the identification of specific sections of the 2019 PM ISA that provide additional details on the total
10 evidence base being considered in the process of reconsidering the PM NAAQS.

11 In addition to the evaluation of recent U.S. and Canadian epidemiologic studies that examine the
12 relationship between short-term and long-term PM_{2.5} exposure cardiovascular effects and mortality this
13 section also evaluates studies that address key scientific topics where the literature has evolved since the
14 2020 PM NAAQS review was completed, specifically since the literature cutoff date for the 2019 PM
15 ISA ([Section 3.3](#)). These topics that further inform the health effects attributed to PM_{2.5} exposure include
16 experimental studies conducted at near-ambient concentrations ([Section 3.3.1](#)), studies that examine the
17 role of PM_{2.5} exposure on COVID-19 infection and death ([Section 3.3.2](#)), and studies that examine
18 whether there are disparities in exposure to PM_{2.5} or the risk of PM_{2.5}-related health effects by
19 race/ethnicity or socioeconomic status (SES).

20 The studies evaluated within the following sections represent only those studies most informative
21 in considering potential revisions to the PM NAAQS as defined by the scope of this Supplement
22 ([Section 1.2.2](#)), i.e., U.S. and Canadian epidemiologic studies and other studies that address key scientific
23 topics. Therefore, the scientific information presented within this section does not represent the full
24 multidisciplinary evaluation presented within the 2019 PM ISA, which would lead to the formation of a
25 causality determination. As a result, the summary sections for each health effects category convey how
26 the evidence from recent studies fits within the scientific conclusions of the 2019 PM ISA, and indicates
27 whether recent evidence supports (is consistent with), supports and extends (is consistent with and
28 reduces uncertainties), or does not support (is not consistent with) the causality determinations in the
29 2019 PM ISA.

⁶Throughout 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-µg/m³ increase in 24-hour avg PM_{2.5} concentrations and long-term exposures are for a 5-µg/m³ increase in annual concentrations, unless otherwise noted.

3.1 Cardiovascular Effects

3.1.1 Short-Term PM_{2.5} Exposure

1 The following sections represent a summary of the evidence and the corresponding causality
2 determination for short-term PM_{2.5} exposure and cardiovascular effects presented within the 2019 PM
3 ISA ([Section 3.1.1.1](#)) along with an evaluation of recent epidemiologic studies that fall within the scope
4 of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature
5 cutoff date of the 2019 PM ISA ([Section 3.1.1.2](#)). In addition, with the expansion of epidemiologic
6 studies using causal modeling methods, recent studies that employed such methods are also evaluated
7 ([Section 3.1.1.3](#)), which can further inform the relationship between short-term PM_{2.5} exposure and
8 cardiovascular morbidity. Lastly, a summary of the results of recent studies evaluated within the section is
9 presented in the context of the scientific conclusions detailed in the 2019 PM ISA ([Section 3.1.1.4](#)). The
10 evaluation of recent studies presented in this Supplement adds to the collective body of evidence
11 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

12 A large body of evidence evaluated in the 2019 PM ISA confirmed and extended the evidence
13 from the 2009 PM ISA ([U.S. EPA, 2009](#)) indicating a *causal relationship* between short-term PM_{2.5}
14 exposure and cardiovascular effects. The strongest evidence in the 2009 PM ISA was from epidemiologic
15 studies of emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD)
16 and heart failure, with supporting evidence from epidemiologic studies of cardiovascular mortality.
17 Changes in various measures of cardiovascular function in controlled human exposure studies provided
18 some biological plausibility for these associations. In addition, animal toxicological studies reporting
19 some evidence of reduced myocardial blood flow during ischemia, altered vascular reactivity, and ST
20 segment depression provided additional biological plausibility. In the 2019 PM ISA, evidence supporting
21 the causality determination included generally positive associations from epidemiologic studies of
22 hospital admissions and ED visits for cardiovascular-related effects, and in particular, for IHD and heart
23 failure. Results from these observational studies were supported by experimental evidence from
24 controlled human exposure and animal toxicological studies of endothelial dysfunction, as well as
25 endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in heart rate
26 variability (HRV), increases in blood pressure (BP), and increases in indicators of systemic inflammation,
27 oxidative stress, and coagulation. Additional results from observational panel studies, although not
28 entirely consistent, provided at least some evidence of increased risk of arrhythmia, decreases in HRV,
29 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 3-4](#), 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 (µg/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

Table 3-1 (Continued): 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 (µg/m ³)
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	
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	

AOD = aerosol optical depth; CMAQ = Community Multiscale Air Quality; ED = emergency department; IHD = ischemic heart disease; µg/m³ = 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.

^aBased 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](#)).

^bDescribes 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.

^cDescribes the PM_{2.5} concentrations with which the evidence is substantiated.

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

24 Results from additional controlled human exposure studies published since the 2009 PM ISA also
25 support a *causal relationship* between short-term PM_{2.5} exposure and cardiovascular effects. The most
26 consistent evidence from these studies is for endothelial dysfunction as measured by changes in BAD or
27 FMD. More specifically, and in contrast to the 2009 PM ISA where a couple of studies did not find
28 changes in endothelial function, multiple studies evaluated in the 2019 PM ISA that examined the
29 potential for endothelial dysfunction reported an effect of PM_{2.5} on measures of blood flow (2019 PM
30 ISA, Section 6.1.13.2) relative to FA exposure. Nevertheless, all studies were not in agreement with
31 respect to the timing of the effect or the mechanism by which reduced blood flow occurred
32 (i.e., endothelial-independent vs. endothelial-dependent mechanisms). In addition to endothelial
33 dysfunction, controlled human exposure studies evaluated in the 2019 PM ISA that used CAPs, but not
34 filtered DE, generally reported evidence for small increases in blood pressure, although there were
35 inconsistencies across studies with respect to changes in SBP and DBP. It is notable however, that CAPs
36 studies evaluated in the 2019 PM ISA that reported increases in one measure of BP (e.g., SBP), but not
37 the other (e.g., DBP) was found to be statistically significant, that other measure of BP usually changed as
38 well, but the change was not found to be statistically significant (2019 PM ISA, Section 6.1.6.3). That

1 said, the results of studies evaluated in the 2019 PM ISA are not in agreement with a couple of older
2 controlled human exposure studies that reported no appreciable changes in blood pressure following
3 short-term PM_{2.5} exposure. In addition, although not entirely consistent, there is further evidence from
4 controlled human exposure studies evaluated in the 2019 PM ISA for conduction
5 abnormalities/arrhythmia (2019 PM ISA, Section 6.1.4.3), changes in HRV (2019 PM ISA,
6 Section 6.1.10.2), changes in hemostasis that could promote clot formation (2019 PM ISA,
7 Section 6.1.12.2), and increases in inflammatory cells and markers (2019 PM ISA, Section 6.1.11.2).
8 Thus, although uncertainties remain, controlled human exposure studies are in coherence with
9 epidemiologic studies by demonstrating that short-term exposure to PM_{2.5} may result in the types of
10 cardiovascular endpoints that could lead to ED visits and hospital admissions.

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

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

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

human exposure and animal toxicological studies. There is a limited number of studies evaluating some of 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, there continues to be sufficient evidence 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

In addition to evaluating epidemiologic studies that examined the relationship between short-term PM_{2.5} exposure and cardiovascular effects, the 2019 PM ISA 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 emergency department (ED) visits and hospital admissions for IHD and heart failure, and ultimately mortality (2019 PM ISA, Figure 6-1).

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 previous assessments, that 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

1 confounding ([Section 3.1.1.2.7](#)) and the lag structure of associations ([Section 3.1.1.2.8](#)). The following
2 sections evaluate recent epidemiologic studies conducted in the U.S. and Canada that inform each of the
3 aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM
4 ISA.

3.1.1.2.1 Ischemic Heart Disease and Myocardial Infarction

5 IHD is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart.
6 Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death
7 occurs that is secondary to prolonged ischemia. The effect of short-term PM_{2.5} exposure on acute MI,
8 complications from recent MI, and other acute or chronic IHD are generally evaluated using ICD codes
9 recorded when a patient is admitted or discharged from the hospital or ED (ICD9: 410–414 or ICD10:
10 I20–I25). In experimental or epidemiologic panel studies, indicators of MI include ST segment
11 depression as measured by an electrocardiograph (ECG). The ST segment of an electrocardiogram
12 recorded by surface electrodes corresponds to the electrical activity of the heart registered between
13 ventricular depolarization and repolarization and is normally isoelectric.

14 The epidemiologic studies reviewed in the 2019 PM ISA ([U.S. EPA, 2019](#)) strengthened the
15 evidence characterized in the previous ISA ([U.S. EPA, 2009](#)). Most of the evidence for IHD and MI in the
16 2009 PM ISA was from multicity epidemiologic studies of ED visits and hospital admissions [i.e., the
17 U.S. Medicare Air Pollution Study (MCAPS) ([Dominici et al., 2006](#)), a four-city study in Australia
18 ([Barnett et al., 2006](#)), and a study among older adults in several French cities ([Host et al., 2008](#))]. The
19 positive associations reported in these studies were an important line of evidence in the 2009 PM ISA
20 concluding a *causal relationship* between short-term PM_{2.5} exposure and cardiovascular effects.
21 Uncertainties noted in the 2009 PM ISA with respect to exposure measurement error for those not living
22 near a PM_{2.5} monitor were reduced in the 2019 PM ISA with the consideration of studies that applied
23 hybrid exposure assessment techniques that combine land use regression data with satellite aerosol optical
24 depth (AOD) measurements and PM_{2.5} concentrations measured at fixed-site monitors to estimate PM_{2.5}
25 concentrations. Further, compared to the 2009 PM ISA the evidence in the 2019 PM ISA was expanded to
26 include studies examining the association of short-term PM_{2.5} exposure ST segment depression in addition
27 to ED visits and hospital admissions for MI.

28 A recent study extends the evidence presented in the 2019 PM ISA through its examination of the
29 association between short-term PM_{2.5} exposure with hospital admissions for MI among the low income
30 and/or disabled Americans comprising the Medicaid population ([deSouza et al., 2021](#)). [deSouza et al.](#)
31 ([2021](#)) reported a positive association between PM_{2.5} concentration (0–1 day average) and acute MI (OR:
32 1.1 [95% CI: 1.03, 1.7]). Recent studies have also addressed methodological challenges. Specifically,
33 [Krall et al. \(2018\)](#) conducted an analysis to elucidate the interpretation of potentially uncertain single-city
34 estimates. These authors used Poisson time-series regression to estimate the associations of 24-hour
35 average PM_{2.5} concentration (lag Day 0) with ED visits for IHD and other cardiovascular outcomes for

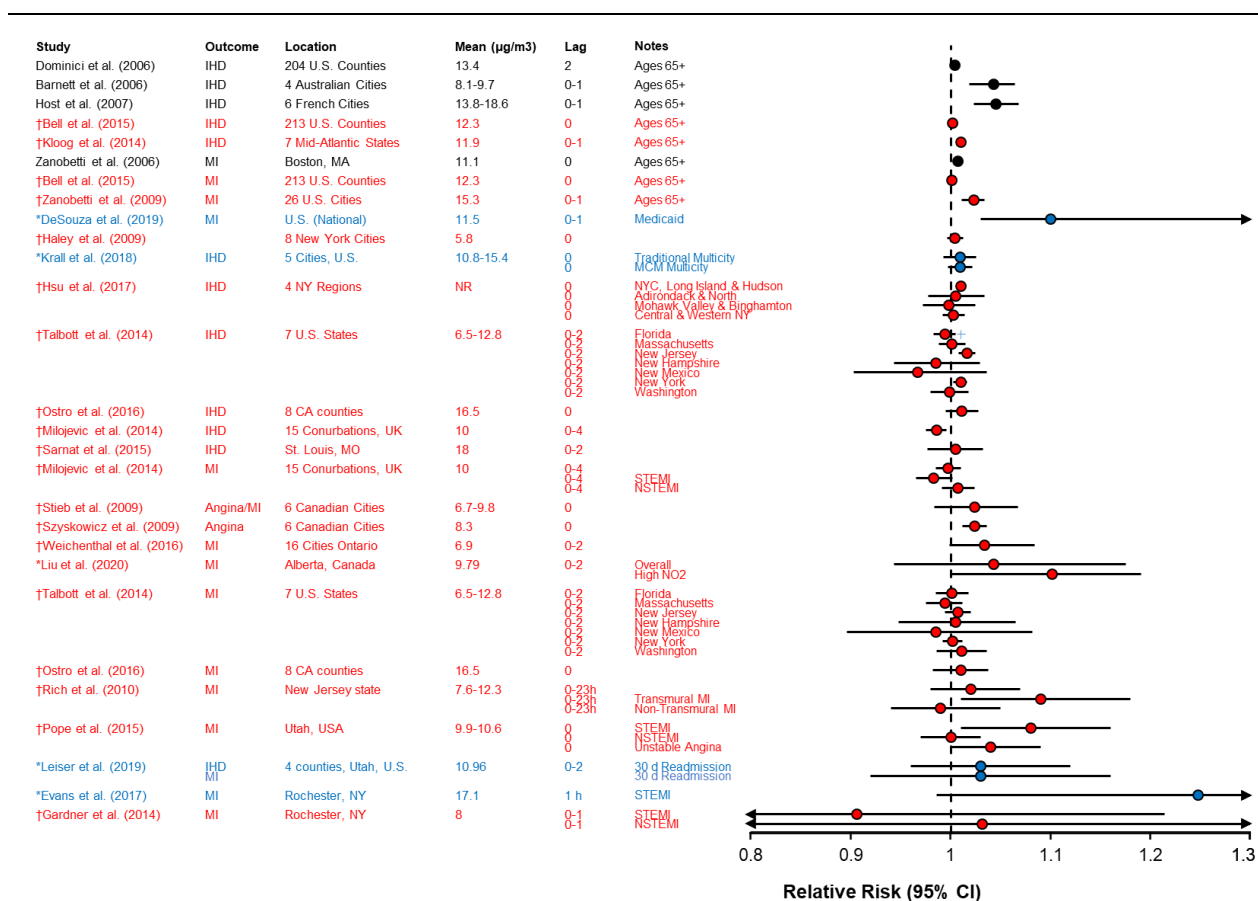
each of the five cities included in their study. To estimate the association across all cities and the posterior city-specific associations, they fit both traditional Bayesian hierarchical models in which associations were estimated for each outcome separately, and multi-cause multicity (MCM) Bayesian 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 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 NO₂ 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). The OR for the association between 0–2-day average PM_{2.5} concentration with hospital admissions for MI among the entire population was 1.03 (95% CI: 0.96, 1.12). The association was null in the lowest tertile of long-term NO₂ concentration (OR: 0.94 [95% CI: 0.86, 1.18]), but increased with increasing NO₂ 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.](#)

1 [\(2017\)](#) performed a case-crossover analysis to examine the relationship between short-term PM_{2.5}
2 concentration and STEMI in acute coronary syndrome or unstable angina patients (n = 362) in Monroe
3 County, NY (2007–2012). The association between previous 1-hour PM_{2.5} concentration and STEMI
4 reported by these authors (OR: 1.25 [95% CI: 0.99, 1.59]) was virtually identical to the association (OR:
5 1.26 [95% CI: 1.01, 1.57]) reported in a previous analysis of this population conducted by [Gardner et al.](#)
6 [\(2014\)](#) that reported fewer patients (n = 338) and a shorter follow-up time (2007–2010).

7 Results of studies of IHD and MI included in the 2009 PM ISA, the 2019 PM ISA and recent
8 studies published since the literature cutoff date of the 2019 PM ISA are summarized in [Figure 3-1](#).
9 Overall, recent studies support and extend the findings of the 2019 PM ISA with additional studies
10 reporting positive associations between short-term PM_{2.5} exposure and both IHD and MI hospital
11 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 segment elevation MI. Risk estimates are standardized to a 10 µg/m³ 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 ICD10 codes I60–I69 (ICD9: 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). Older age, female sex, smoking, obesity, and prior stroke are known risk factors for stroke and should be considered in epidemiologic

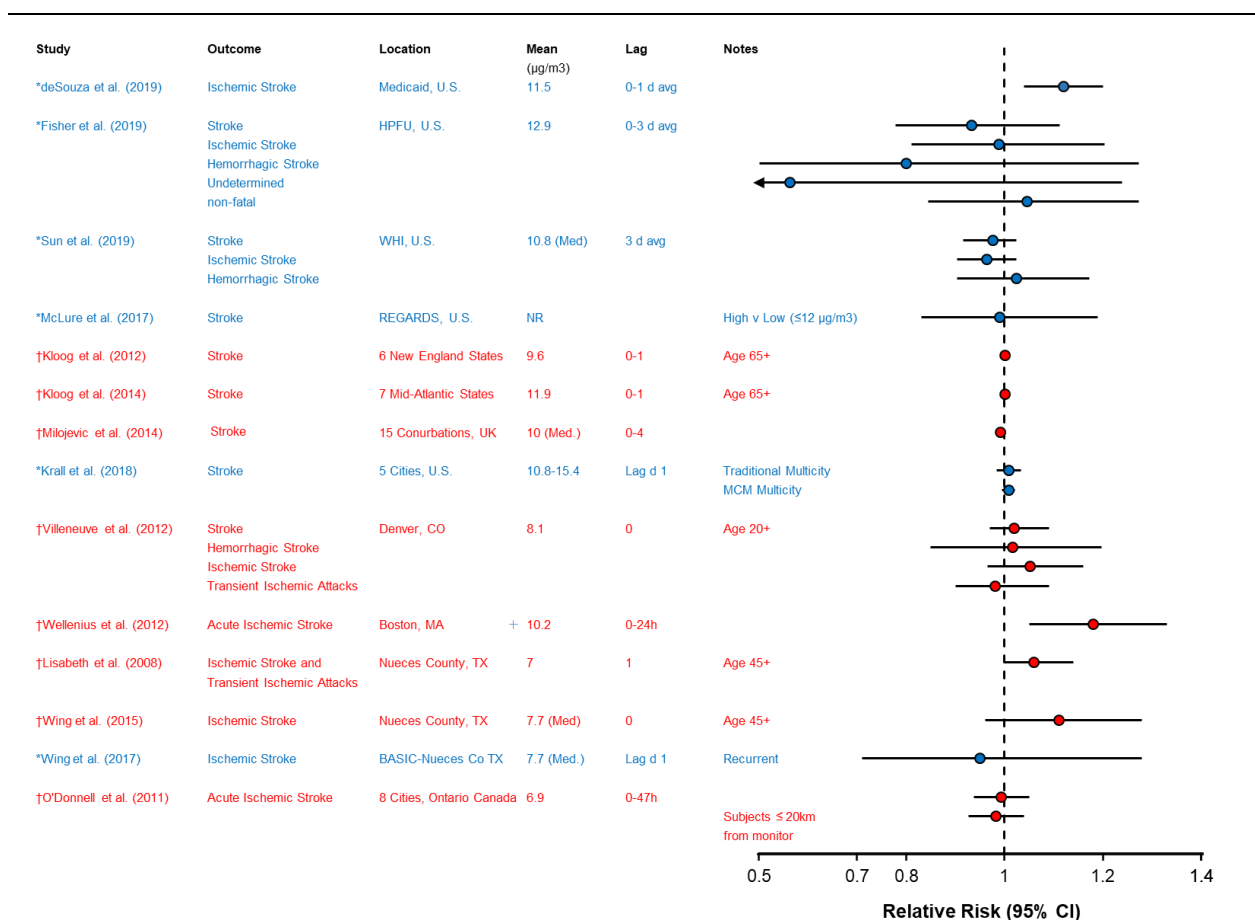
analysis. Comorbidities that increase stroke risk but may also be associated with PM_{2.5} exposure include hypertension, diabetes, CHD, and atrial fibrillation. The 2009 PM ISA and the 2019 PM ISA described inconsistent results across epidemiologic studies that considered the relationship between short-term 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 non-fatal 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 ($\leq 12 \mu\text{g}/\text{m}^3$ vs. 12 to $150.4 \mu\text{g}/\text{m}^3$) and the odds of stroke in the higher category was compared to 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

1 stroke subtype or exposure lag. Overall, analyses from three established and diverse cohorts did not
2 present evidence of an association between short-term PM_{2.5} exposure and stroke.

3 Unlike the analyses described above, [deSouza et al. \(2021\)](#) examined the relationship between
4 PM_{2.5} concentration (0–1 day average) and hospital admissions for IS among the low income and/or
5 disabled Americans comprising the Medicaid population. The OR for the association between PM_{2.5} (lag
6 0–1 day average) and IS was 1.12 (95% CI: 1.04, 1.20). In a study designed to gain an understanding of
7 the heterogeneity in results across single-city studies, [Krall et al. \(2018\)](#) examined the associations of
8 24-hour PM_{2.5} concentration (lag Day 0) with ED visits for stroke. These authors estimated the
9 associations across five cities using a traditional Bayesian hierarchical approach and a MCM Bayesian
10 hierarchical model in which all outcomes were modelled simultaneously. The association of 24-hour
11 PM_{2.5} concentration (lag 0) with ED visits for stroke was 1.008 (95% CI: 0.984, 1.034) in the traditional
12 multicity model and more precise (i.e., narrower confidence intervals) 1.008 (95% PI: 0.995, 1.021) in the
13 MCM model. However, in a single city study of recurrent IS in Nueces county Texas, [Wing et al. \(2017\)](#)
14 did not report evidence of an association between PM_{2.5} concentration during the previous day (lag 1), and
15 the odds of recurrent stroke (OR: 0.95 (95% CI: 0.71–1.28)).

16 Results of studies of short-term exposure to PM_{2.5} and ED visits or hospital admissions for stroke
17 included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff
18 date of the 2019 PM ISA are summarized in [Figure 3-2](#). Consistent with the evidence evaluated in the
19 2019 PM ISA, some recent studies report evidence of a positive association with stroke while others
20 report null or inverse associations.



Source: Update of Figure 6-5, 2019 P MISA.

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/m³ 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

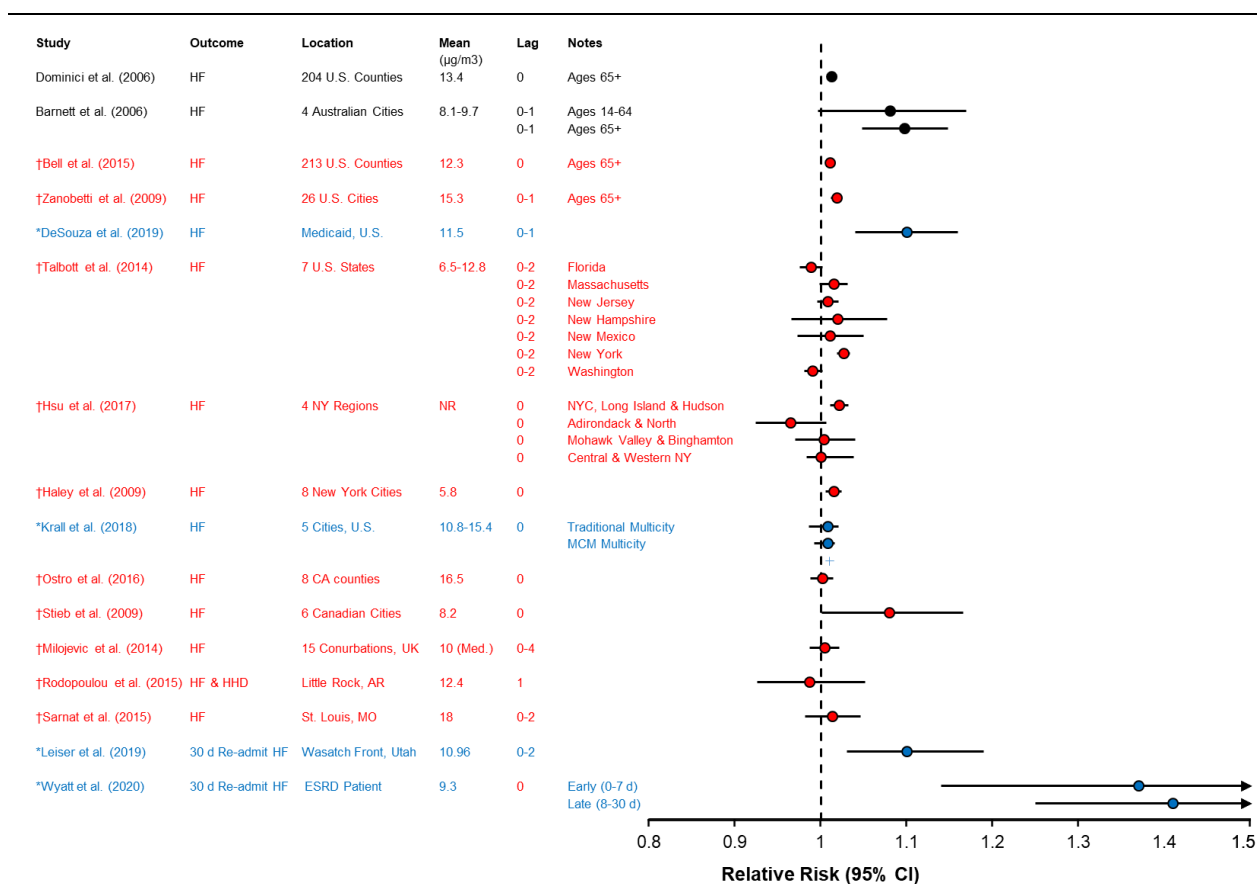
Heart failure (HF) refers to a set of conditions in which pumping action of the heart is weakened. In congestive heart failure (CHF), the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other 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 ICD9 428 and ICD10 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

1 [al., 2006](#)) and Australia ([Barnett et al., 2006](#))]. Studies evaluated in the 2019 PM ISA strengthened this
2 line of evidence with additional multicity epidemiologic studies conducted in the U.S., Canada, and
3 Europe generally reporting positive associations between short-term PM_{2.5} exposure and hospital
4 admissions and ED visits for HF. Results from single-city studies tended to be less consistent. Several
5 recent studies add to the body of evidence providing additional support for a positive association between
6 short-term PM_{2.5} exposure and ED visits and hospital admissions for exacerbations of HF.

7 Recent studies conducted examined the association of short-term PM_{2.5} exposure with
8 readmission to the hospital for HF within 30 days of an index hospitalization. [Leiser et al. \(2019\)](#) used
9 Medicare data to examine the association of short-term PM_{2.5} exposure and cardiac hospital re-admissions
10 among older adults within 30 days of the index hospitalization. These authors reported an association of
11 3-day average PM_{2.5} concentration (lag 0–2 day) with readmission for HF (HR: 1.10 [95% CI: 1.03,
12 1.19]). Confidence intervals of the age and sex stratified results were generally overlapping. In another
13 study of 30-day hospital readmission, [Wyatt et al. \(2020c\)](#) characterized the association of short-term
14 PM_{2.5} exposure with CHF among end stage renal disease patients (i.e., those undergoing hemodialysis).
15 Both readmission within 1 to 7 days and readmission between 8 to 30 days was evaluated. The RR for the
16 association of 24-hour PM_{2.5} concentration (lag 0) with HF readmission within 1–7 days was 1.37 (95%
17 CI: 1.14, 1.60). The association with late readmission (8–30 days) was 1.41 (95% CI: 1.25, 1.58). In
18 another unique population, [deSouza et al. \(2021\)](#) estimated the association of PM_{2.5} concentration
19 (0–1 day average) with CHF hospital admissions among the low income and/or disabled Americans
20 comprising the Medicaid population. The OR for the association between PM_{2.5} (lag 0–1 day average)
21 and CHF was 1.10 (95% CI: 1.04, 1.16).

22 In addition to the studies described above that focus on 30-day hospital readmission, [Krall et al.](#)
23 [\(2018\)](#) examined the association of 24-hour PM_{2.5} concentration (lag Day 0) with ED visits for CHF in an
24 analysis in five cities that was designed to compare methods used for multicity studies. These authors
25 estimated the multicity associations using a traditional Bayesian hierarchical approach and a MCM
26 Bayesian hierarchical model in which all outcomes were modelled simultaneously. The association of
27 24-hour PM_{2.5} concentration (lag 0) with CHF was 1.003 (95% CI: 0.986, 1.021) in the traditional
28 multicity model and 1.003 (95% PI: 0.992, 1.016) in the MCM model. In another study, [Wei et al. \(2019\)](#)
29 used Medicare data (i.e., inpatient hospital claims) to estimate the association of short-term PM_{2.5}
30 exposure with CHF hospital admissions in the continental U.S. between 2000 and 2012. Rather than
31 report a relative risk estimate, the authors reported the absolute increase in risk of admission to hospital
32 per 10 million person-days associated with each 1 µg/m³ increase in lag 0–1 PM_{2.5} (i.e., 0.68 [95% CI:
33 0.52 to 0.84]).

34 Results of studies of HF included in the 2009 PM ISA, the 2019 PM ISA and recent studies
35 published since the literature cutoff date of the 2019 PM ISA are summarized in [Figure 3-3](#). Overall,
36 these studies support and extend the limited evidence in the 2019 PM ISA, reporting positive associations
37 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/m³ increase in PM_{2.5} concentrations.

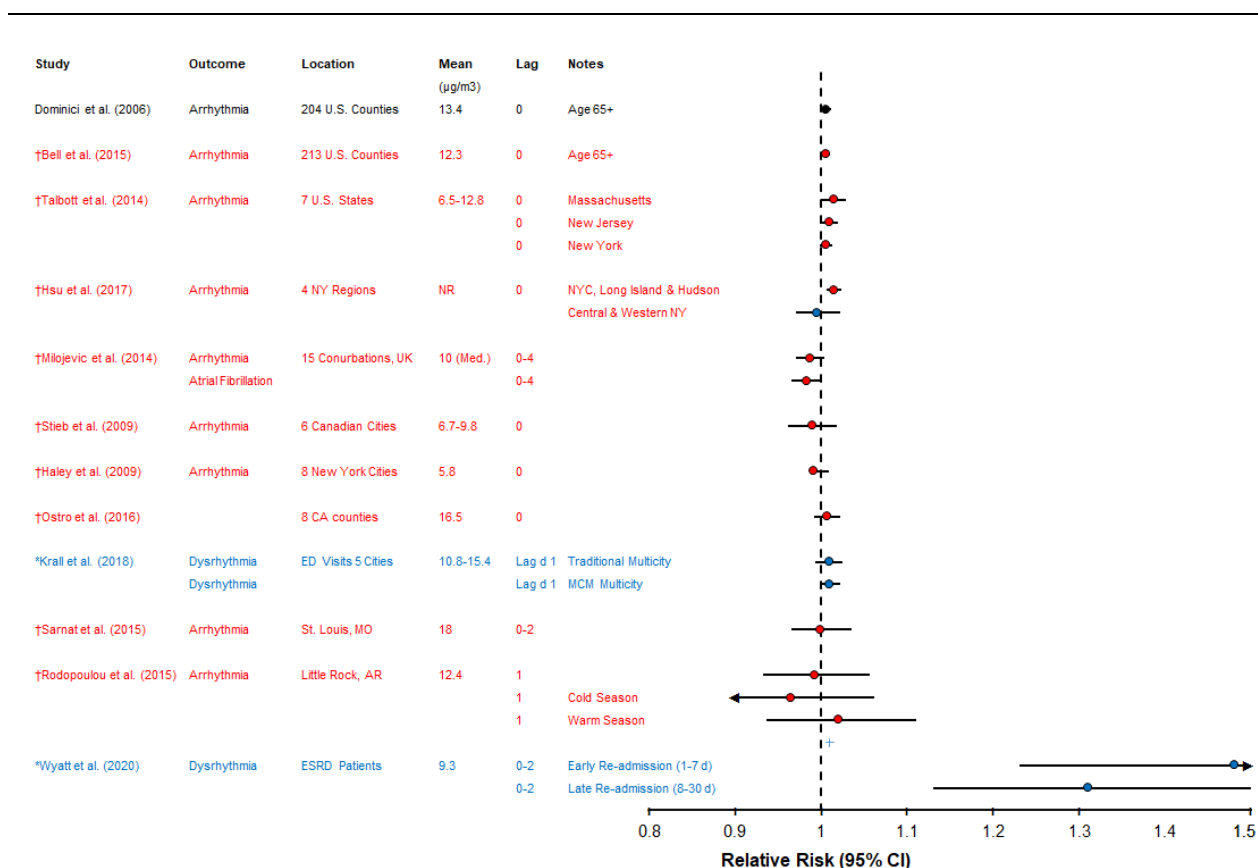
Figure 3-3 Results of studies of short-term PM_{2.5} exposure and hospital admissions and emergency department visits for heart failure.

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 (ICD9 427 or ICD10 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 there was some evidence from epidemiologic panel studies of 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 arrhythmias.

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 and examined differences across sex and age in models that adjusted for the competing risk of mortality. 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 modelled 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 relative risk estimate, the authors reported the absolute increase in risk of admission to hospital per 10 million person-days associated with each 1 µg/m³ increase in lag 0–1 PM_{2.5} concentration (i.e., 0.26 [95% CI: 0.13 to 0.38]).

Results of studies of arrhythmia 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 support and extend the limited evidence in the 2019 PM ISA.



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 $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentrations.

Figure 3-4 Results of studies of short-term $\text{PM}_{2.5}$ 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 cardiovascular diseases (e.g., MI, stroke, and HF), epidemiologic studies examined cardiovascular diseases (CVD) in aggregate (i.e., specific combination of cardiovascular diseases). The 2009 PM ISA and the 2019 PM ISA reviewed multicounty 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 perform stratified analyses. Several recent studies examine the association between short-term exposure to $\text{PM}_{2.5}$ and CVD hospital admissions and ED visits, and report results that are generally consistent with studies evaluated in the 2019 PM ISA.

1 In a study of low income and/or disabled Americans enrolled in Medicaid [deSouza et al. \(2021\)](#)
2 estimated the association of PM_{2.5} concentration (0–1 day average) with cardiovascular hospital
3 admissions. The association of PM_{2.5} concentration (0–1 day average) with all CVD hospital admissions
4 was 1.09 (95% CI: 1.06, 1.11). The association with all CVD hospital admissions was larger in magnitude
5 at PM_{2.5} concentrations <25 µg/m³ (OR: 1.13 [95% CI: 1.09, 1.16]). The association was similar among
6 older and younger adults (OR: 1.09 [95% CI: 1.06, 1.13]) among those <65 years old 1.08 (95% CI: 1.06,
7 1.09) versus among those ≥65 years old. In another study, [Wyatt et al. \(2020c\)](#) examined hospital
8 admissions among end stage renal disease patients (i.e., those undergoing hemodialysis). Same-day PM_{2.5}
9 concentration (lag 0) was associated with an increase in the risk of CVD hospital admissions in this
10 population (RR: 1.09 [95% CI: 1.02, 1.17]).

11 Some recent studies of ED visits report null associations between short-term PM_{2.5} concentration
12 and aggregated CVD outcomes in adjusted models. [Krall et al. \(2018\)](#) examined the associations of
13 24-hour PM_{2.5} concentration (lag Day 0) with CVD ED visits, estimating the association across five cities
14 using a traditional Bayesian hierarchical approach. A null association between 24-hour PM_{2.5}
15 concentration (lag 0) with CVD ED visits was observed (1.0 [95% CI: 0.992, 1.009]) while positive
16 associations were reported for specific cardiovascular outcomes evaluated. [Ye et al. \(2018\)](#) performed a
17 study to estimate the association between short-term exposure to PM_{2.5} components that are not routinely
18 measured, including water soluble metals, and CVD ED visits for a five-county area of Atlanta during the
19 period 1998 to 2013. In a single-pollutant model, these authors reported a positive association of 24-hour
20 PM_{2.5} concentration (lag 0) with CVD ED visits; however, the association was null after adjustment for
21 water soluble iron (WS Fe), which may be an indicator for certain aspects of traffic pollution.

3.1.1.2.6 Cardiovascular Mortality

22 The limited assessment of cause-specific mortality in recent studies provides similar results to
23 previously evaluated studies demonstrating a consistent relationship between short-term PM_{2.5} exposure
24 and cardiovascular mortality. Consistent with studies evaluated in the 2019 PM ISA, recent studies
25 indicate that associations between short-term PM_{2.5} exposure and cardiovascular mortality are relatively
26 unchanged in copollutant models and may be larger in magnitude in the presence of some co-occurring
27 pollutants (i.e., oxidant gases). In addition, factors that have been shown to vary between cities and
28 regions of the U.S., such as housing characteristics, have been shown to explain some of the city-to-city
29 and regional variability observed in PM_{2.5}-mortality associations in multi-city epidemiologic studies. The
30 continued assessment of the concentration-response (C-R) relationship between short-term PM_{2.5}
31 exposure and mortality further supports a linear relationship, with less confidence in the shape at
32 concentrations below 5 µg/m³.

3.1.1.2.7 Potential Copollutant Confounding

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. The evidence reviewed in the 2019 PM ISA represented an expanded set of studies that performed analyses using two-pollutant models. These studies addressed a data gap, generally supporting an association of PM_{2.5} with cardiovascular related health effects that was independent of copollutant exposures (i.e., O₃, NO₂, SO₂, 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. This limited evidence neither consistently nor coherently indicated a stronger or weaker effect of combined exposure to PM_{2.5} and another pollutant compared to exposure to a single pollutant alone ([Luben et al., 2018](#)). A small number of recent studies expand upon the overall assessment of potential confounding of the relationship between short-term PM_{2.5} exposure and cardiovascular effects by copollutants.

In the study of Medicaid recipients conducted by [deSouza et al. \(2021\)](#) the positive single-pollutant association (OR: 1.09 [95% CI: 1.06, 1.11]) between all CVD and short-term PM_{2.5} persisted in a two-pollutant model adjusted for ozone (OR: 1.10 [95% CI: 1.07, 1.12]). By contrast, [Ye et al. \(2018\)](#) reported that the single-pollutant association between short-term exposure to PM_{2.5} was null after adjustment for water soluble iron (WS Fe), which is a PM_{2.5} component that may be an indicator for certain aspects of traffic pollution. [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.

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, delayed, or prolonged 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 to immediate single-day lag periods (i.e., 0, 1).

Several recent studies conducted analyses to determine if 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 Studies Examining the PM_{2.5}-Cardiovascular Effects Relationship through Accountability Analyses and Causal Modeling Methods

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 causal modeling methods. Since the literature cutoff date for the 2019 PM ISA several studies that conducted accountability analyses or implemented causal modeling methods 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 evaluated whether associations between short-term PM_{2.5} exposures and cardiovascular hospital admissions differed before, during, 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 associated with short-term PM_{2.5} exposure, from the previous day (lag 0) and averaged over the previous 7 days (lag 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” period and weaker associations observed in the “after” period.

Similar results were reported for cerebrovascular disease, ischemic stroke, chronic rheumatic heart disease, hypertension, ischemic heart disease, and myocardial infarction. Conversely, there were increases in the excess rate of hospital admissions for cardiac arrhythmia and congestive heart failure in the “after” period compared to the “before” and “during” periods. Overall, across the endpoints examined, there were notable differences (i.e., reductions in hospital admissions) after policies were implemented compared to before.

[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 to 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 the interquartile range (7.59 µg/m³) 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.

The use of causal modeling methods can further inform the causal nature of the relationship between short-term PM_{2.5} exposure and cardiovascular effects, specifically in studies examining cardiovascular hospital admission rates, through the use of statistical methods to reduce uncertainties with respect to confounding. Inverse probability weighting (IPW) is a causal modeling method 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), congestive heart failure (CHF) and ischemic stroke (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, conditional logistic regression models were then used to regress cardiovascular hospital admissions against each exposure lag, using the weights generated from the propensity score models to that lag, to estimate the marginal effect of that particular lag of that exposure independent of covariates.

Based on 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 µg/m³ increase in 24-hour average PM_{2.5} concentrations. While [Qiu et al. \(2020\)](#) reported associations in a causal modeling framework 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 there was no unmeasured confounding, with the caveat that the authors had the resources to obtain all the potential unmeasured confounders. This assumption was tested through a series sensitivity analyses of temperature by including more lags of temperature and spline adjustments. The second assumption was positivity, meaning that 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.

The recent accountability and causal modeling studies 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 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.

Uncertainty related to exposure assessment was generally reduced with consideration of studies included in the 2019 PM ISA that applied hybrid exposure assessment techniques that combined land use regression with satellite AOD measurements and PM_{2.5} concentrations measured at fixed site monitors. The majority of 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; however, another recent study introduces the possibility for water soluble metals to confound the association between short-term PM_{2.5} exposure and cardiovascular effects. 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. Lastly, recent studies that employed causal modeling methods 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.

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](#)). In addition, with the expansion of epidemiologic studies using causal modeling methods, 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. Lastly, 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

1 evaluation of recent studies presented in this Supplement adds to the collective body of evidence
2 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

3 The evidence reviewed in the 2009 PM ISA provided the rationale to conclude that there is a
4 “causal relationship between long-term PM_{2.5} exposure and cardiovascular effects” ([U.S. EPA, 2009](#)).
5 Studies of mortality from cardiovascular causes provided the strongest evidence in support of this
6 conclusion. While several studies included in the 2009 PM ISA reported associations between long-term
7 PM₁₀ exposure and morbidity outcomes such as post-MI CHF and deep vein thrombosis (DVT), studies
8 of PM_{2.5} were limited. One large prospective study of postmenopausal women reported an increased risk
9 of cardiovascular events, including CHD and stroke, in association with long-term exposure to PM_{2.5}
10 ([Miller et al., 2007](#)). Cross-sectional analyses provided supporting evidence and experimental studies
11 demonstrating enhanced atherosclerotic plaque development and inflammation following long-term
12 exposures to PM_{2.5}. CAPs provided biological plausibility for the epidemiologic findings. In addition,
13 evidence from the limited number of toxicological studies reporting CAPs-induced effects on
14 hypertension and vascular reactivity were drawn upon to support the causality determination. With
15 respect to the 2019 PM ISA, the evidence for the relationship between long-term exposure to PM_{2.5} and
16 cardiovascular effects is described below and summarized in [Table 3-2](#), using the framework for causality
17 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 (µg/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 concentration response (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 µg/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

Table 3-2 (Continued): Summary of evidence for a causal relationship between long-term PM_{2.5} exposure and cardiovascular effects.

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 (µg/m ³)
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
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	

CAC = coronary artery calcification; CCHS = Canadian Community Health Survey; CHD = coronary heart disease; HPFU = Health Professionals Follow-Up; MESA = Multi-Ethnic Study of Atherosclerosis; µg/m³ = micrograms per cubic meter; NHS = Nurses' Health Study; NO₂ = nitrogen dioxide; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; PM₁₀ = 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; SO₂ = sulfur dioxide.

^aBased 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](#)).

^bDescribes 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.

^cDescribes the PM_{2.5} concentrations with which the evidence is substantiated.

1 The studies of long-term exposure to PM_{2.5} and cardiovascular mortality evaluated in the 2019
2 PM ISA continue to provide strong evidence of a *causal relationship* between long-term exposure to
3 PM_{2.5} and cardiovascular effects. Results from U.S. and Canadian cohort studies demonstrated consistent,
4 positive associations between long-term PM_{2.5} exposure and cardiovascular mortality (2019 PM ISA,
5 Figure 6-19). Overall, the studies reporting positive associations examined the relationship at varying
6 spatial scales and employed different exposure assessment and statistical methods (2019 PM ISA,
7 Section 6.2.10). The studies were conducted in locations where mean annual average concentrations
8 ranged from 4.08–17.9 µg/m³. Generally, most of the PM_{2.5} effect estimates relating long-term PM_{2.5}
9 exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models
10 adjusted for ozone, NO₂, PM_{10–2.5}, or SO₂. In addition, most of the results from analyses examining the
11 C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular
12 mortality, especially at lower ambient concentrations of PM_{2.5}.

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

30 Longitudinal change in measures of atherosclerosis in relation to long-term exposure to PM_{2.5} add
31 to the collective evidence base ([Hartiala et al., 2016](#); [Kaufman et al., 2016](#); [Gan et al., 2014](#); [Künzli et al.,](#)
32 [2010](#)). Findings were somewhat variable across cohorts and depended, in part, on the vascular bed in
33 which atherosclerosis was evaluated. [Kaufman et al. \(2016\)](#) reported an association of PM_{2.5} with CAC
34 among middle to older aged adults in the MESA study, while [Dorans et al. \(2016\)](#) reported no association
35 in the Framingham Heart Study. Associations of long-term exposure to PM_{2.5} with cIMT were not
36 consistently observed across cohorts or between analyses of the same cohort with variable methods.
37 Relationships between PM_{2.5} and cIMT at younger ages were not observed. However, a recent

toxicological study adds to 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. (2019 PM ISA, Section 6.2.4.2). 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

In addition to evaluating epidemiologic studies 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 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 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).

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 previous assessments, that 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 evaluate 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.

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. The majority of 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 to 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 NO₂ and O₃ (Ox). A stronger association was observed in the highest tertile of (>38.97 ppm) Ox concentrations (HR: 1.12 [95% CI: 1.09, 1.15]).

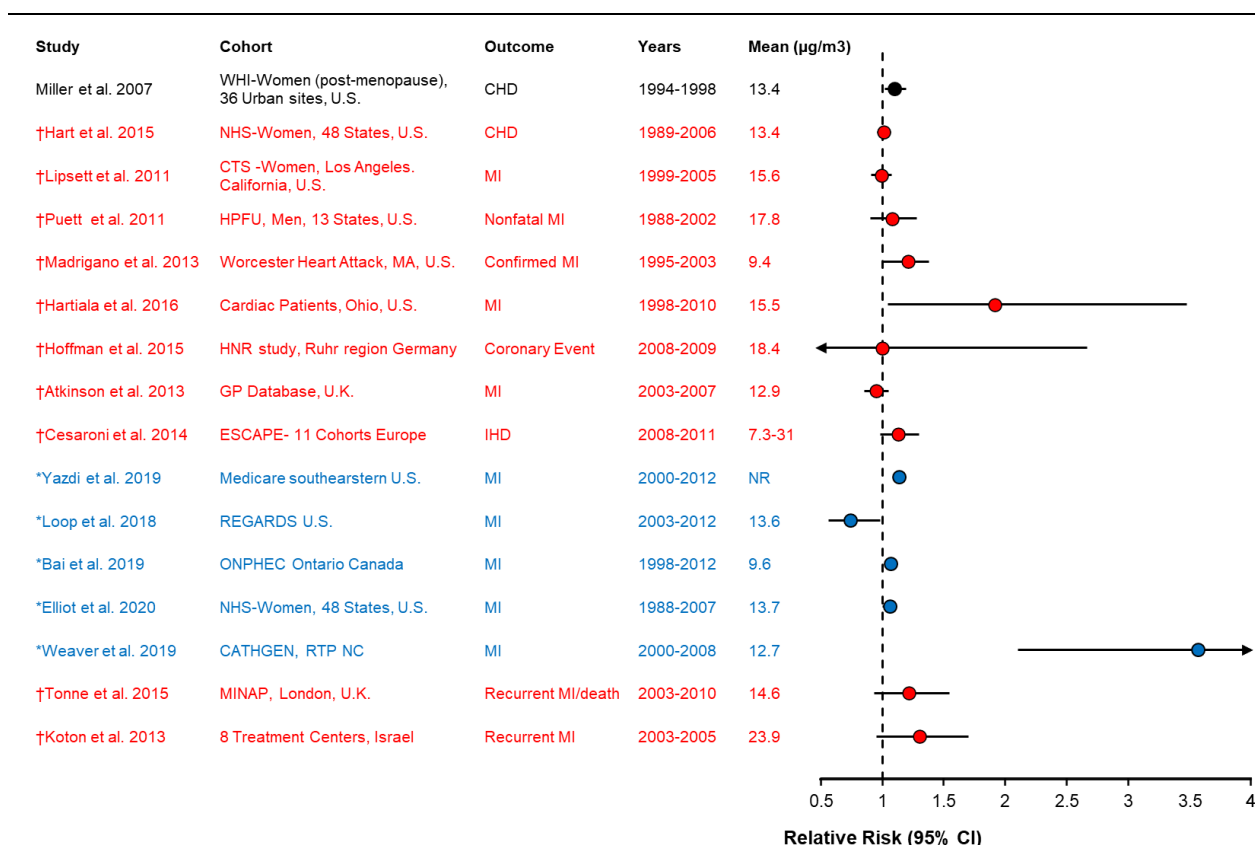
[Chen et al. \(2020\)](#) also analyzed data from the ONPHEC study but examined the association of annual average PM_{2.5} in the previous year with the incidence of acute MI. The authors conducted single pollutant analyses using both a traditional Cox proportional hazards model where PM_{2.5} is fit as a linear term and a Cox proportional hazards model where PM_{2.5} was fit as a non-linear 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., sulphate, 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 to 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 Nurses' Health Study (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}

1 concentration with MI, CAD, and hypertension. Among the objectives of this study was to understand the
2 effect of sociodemographic characteristics on associations by assigning study participants to clusters
3 based on the census block group of their residence that indicated specific sets of sociodemographic
4 characteristics. Positive associations of annual average PM_{2.5} concentration with both CAD and MI were
5 observed. The association with MI was observed across all sociodemographic clusters (OR for all
6 clusters: 3.57 [95% CI: 2.10, 5.77]). The association with CAD was also observed across all clusters (OR:
7 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
8 was urban and characterized by low poverty, low unemployment, and composed of relatively highly
9 educated residents with managerial jobs.

10 In another study, [Loop et al. \(2018\)](#) conducted an analysis of the REasons for Geographic and
11 Racial Differences in Stroke (REGARDS) cohort, a nationwide study which oversampled participants
12 from states in the southern U.S. where there is known to be an increased risk of stroke. Participants who
13 were free from CHD at baseline were followed for an average of 6 years. [Loop et al. \(2018\)](#) reported an
14 inverse association between annual average PM_{2.5} concentration at baseline and non-fatal MI (HR: 0.74
15 [95% CI: 0.56, 0.98]). [Loop et al. \(2018\)](#) also examined associations for total CHD, i.e., CHD deaths and
16 non-fatal MI cases combined, and reported no evidence of an association (HR: 0.89 [95% CI: 0.71, 1.11]).

17 The evidence informing the relationship between long-term exposure to PM_{2.5} and IHD, including
18 the recent studies of ML, is summarized in [Figure 3-5](#). Recent studies do not all report positive
19 associations; however, the strongest evidence of a relationship continues to be for those with preexisting
20 disease 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 µg/m³. Hazard Ratios are standardized to a 5 µg/m³ 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.

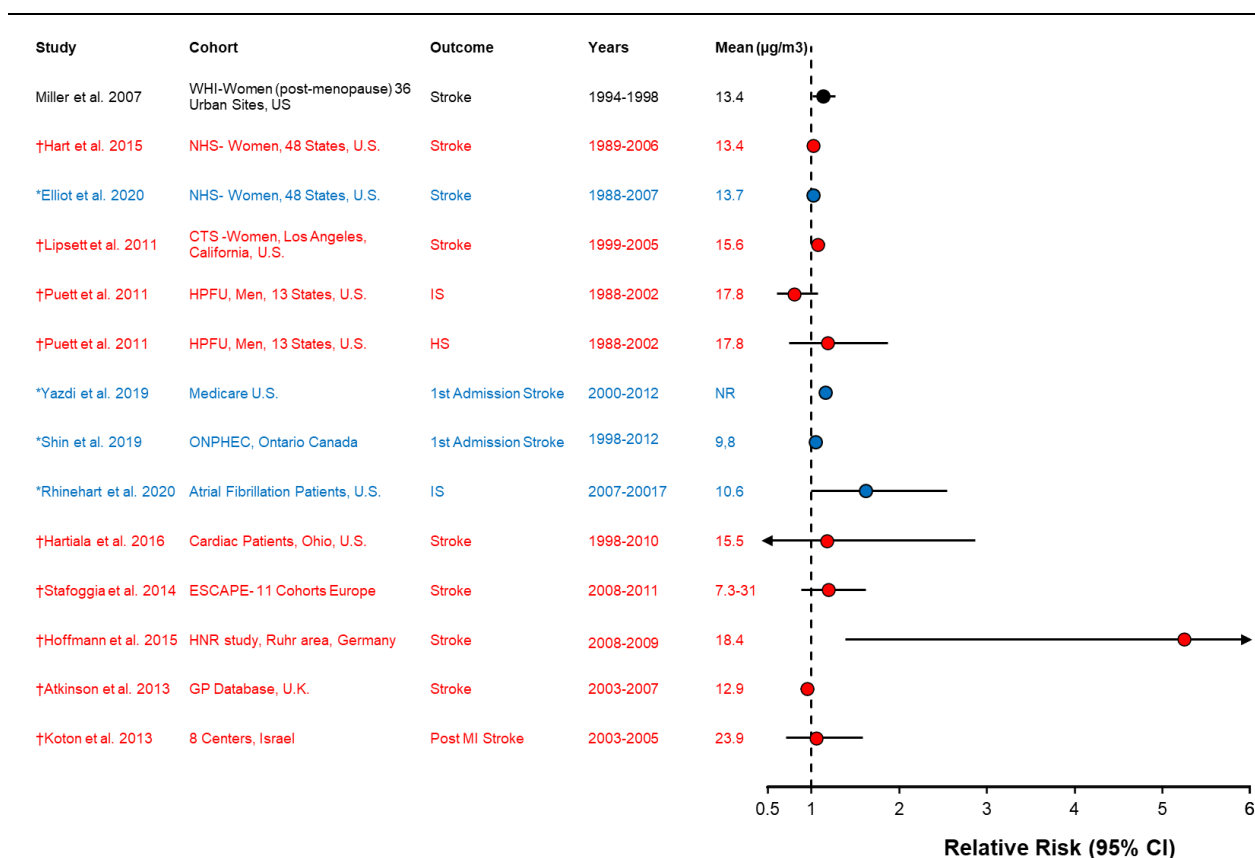
Figure 3-5 Associations between long-term PM_{2.5} exposure and ischemic heart disease or myocardial infarction.

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 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).

1 Several studies examined the association between long-term PM_{2.5} concentration and stroke. In a
2 study of women enrolled in the NHS cohort, [Elliott et al. \(2020\)](#) reported an imprecise (i.e., wide
3 confidence intervals relative to the size of the HR) association between 24 month average PM_{2.5}
4 concentration and stroke that overlapped the null value (HR: 1.02 [95% CI: 0.96, 1.09]). An earlier
5 analysis examining the association with annual average PM_{2.5} concentration in the NHS, reported an
6 increased risk among women with diabetes (HR: 1.29 [95% CI: 1.14, 1.45]) but not in the population,
7 overall (HR: 1.01 [95% CI: 0.96, 1.05]) ([Hart et al., 2015b](#)). [Rhinehart et al. \(2020\)](#) estimated the
8 association of annual average PM_{2.5} concentration within 300 meters of the residence with stroke in a
9 prospective analysis of residents of Allegheny county Pennsylvania who were diagnosed with atrial
10 fibrillation but had no history of stroke. This study reported a positive association (HR: 1.62 [95% CI:
11 1.00, 2.55]). As opposed to examining annual or 24-month average PM_{2.5} exposures, [Shin et al. \(2019\)](#)
12 estimated the association between 5-year PM_{2.5} concentration and incident cases of stroke in a prospective
13 analysis of the Canadian ONPHEC study and reported a positive association (HR: 1.05 [95% CI: 1.03,
14 1.07]).

15 Studies that examined the relationship of long-term PM_{2.5} exposure with CBVD and stroke are
16 summarized in [Figure 3-6](#). Recent studies support the evidence in the 2019 PM ISA and extend the
17 evidence relating to the observation of associations among patients that are followed after a cardiac event
18 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 µg/m³. Hazard Ratios are standardized to a 5-µg/m³ 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,

1 exposure assessment methods, and measures of atherosclerosis. Notably, an extended MESA analysis
2 reported a longitudinal increase in CAC (4.1 Agatston unit increase per year [95% CI: 1.4, 6.8]) in
3 association with annual average PM_{2.5} exposure, but no association with cIMT ([Kaufman et al., 2016](#)).
4 Exposure measurement error, variation in baseline measures of atherosclerosis as well as statistical power
5 were noted as possible explanations for the lack of association observed in these studies. Consideration of
6 copollutant confounding was generally limited across the evidence base reviewed in the 2019 PM ISA.

7 Several recent studies expand the evidence available to consider the association of long-term
8 PM_{2.5} exposure with atherosclerosis. Following the analysis by [Kaufman et al. \(2016\)](#), [Keller et al. \(2018\)](#)
9 estimated the association of PM_{2.5} concentration (i.e., multi-year average during the study period,
10 2000–2012) with CAC progression among participants in MESA air residing in Baltimore, MD. The
11 authors also assessed whether this association was modified by membership in clusters with different
12 traffic related air pollution (TRAP) component profiles. The authors reported a 23.0 Agatston unit per
13 year increase (95% CI: 14.2, 31.7) among participants overall. [Keller et al. \(2018\)](#) also reported a larger
14 magnitude association with CAC progression (42.6 Agatston unit per year increase [95% CI: 25.7, 59.4])
15 in the cold season among those belonging to a cluster that was characterized as downtown with above
16 average ratios of ultrafine and accumulation mode particles relative to NO_x.

17 Among women enrolled in the Study of Women's Health Across the Nation (SWAN), a cohort of
18 U.S. women transitioning through menopause, [Duan et al. \(2019a\)](#) estimated the association of 5-year
19 average PM_{2.5} concentration with cIMT. The study reported a 27.95 μm (95% CI: -2.90, 58.75) thicker
20 mean cIMT in association with 5-year mean PM_{2.5} concentration in adjusted models. PM_{2.5} was also
21 associated with an increase in increased mean inter-adventitial diameter (IAD), which is a marker of
22 vascular remodeling and aging as well as a predictor of cardiovascular events, of 105.90 (95% CI:
23 -63.00, 274.80). No association was reported with plaque presence (OR: 0.90 [95% CI: 0.50, 1.61]) or
24 plaque severity index (plaque index 0–2, OR: 1.05 [95% CI: 0.53, 8.95] and plaque index >2, OR: 0.62
25 [95% CI: 0.25, 1.47]) in the SWAN study. In an analysis of a subset of SWAN participants (Pittsburgh
26 and Chicago only), [Duan et al. \(2019b\)](#) estimated the association of the same measures of atherosclerosis
27 as [Duan et al. \(2019a\)](#) with annual average PM_{2.5} concentration reporting a 11.25 μm per year increase
28 (95% CI: -3.05, 25.60) in mean cIMT. The authors also reported associations with plaque presence (OR:
29 2.10 [95% CI: 0.66, 6.63]) and plaque index progression (OR: 2.70 [95% CI: 0.77, 9.24]).

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

3.1.2.2.4 Heart Failure and Impaired Heart Function

33 Heart failure (HF) refers to a set of conditions including congestive heart failure (CHF) in which
34 the heart's pumping action is weakened. With CHF the blood flow from the heart slows, failing to meet

1 the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs
2 or other tissues (typically in the legs and ankles). Risk factors for HF include IHD, high blood pressure,
3 atrial fibrillation, and diabetes. The small number of epidemiologic studies reviewed in the 2019 PM ISA
4 provided evidence supporting a possible relationship between heart failure and long-term exposure to
5 PM_{2.5}. In addition, an association with increased right ventricular (RV) mass was observed among MESA
6 participants. Right sided HF is typically a consequence of left-sided HF but can also result from damage
7 to the pulmonary vasculature, which can result in RV mass, reduced flow to the left ventricle and reduced
8 left ventricular (LV) mass. Recent studies provide consistent evidence of an association between
9 long-term PM_{2.5} and HF.

10 A recent study examining the association between long-term PM_{2.5} exposure and HF was
11 conducted among participants in the Canadian ONPHEC study. In this prospective analysis, [Bai et al.](#)
12 [\(2019\)](#) examined the relationship between 3-year moving average PM_{2.5} concentration with new cases of
13 CHF. A positive association was reported, overall (HR: 1.07 [95% CI: 1.06, 1.07]), and a larger
14 magnitude association was reported in the highest tertile of Ox concentrations in a stratified analysis
15 examining potential effect modification (HR: 1.12 [95% CI: 1.10, 1.13]).

3.1.2.2.5 Cardiac Electrophysiology and Arrhythmia

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

25 In an analysis of the WHI, which was reviewed in the 2009 PM ISA, [Liao et al. \(2009\)](#) found no
26 association of long-term PM_{2.5} concentrations with supraventricular or ventricular ectopy, which are the
27 most frequent forms of arrhythmia in the general population. A limited number of studies reviewed in the
28 2019 PM ISA found associations of long-term PM_{2.5} exposure with premature atrial contractions and
29 ventricular conduction abnormalities, but not arrhythmias recorded on implantable cardioverter
30 defibrillators. In a recent prospective analysis of the Canadian OPHEC study, [Shin et al. \(2019\)](#) estimated
31 the association between 5-year average PM_{2.5} concentration and incident cases of atrial fibrillation (AF)
32 and reported a positive association (HR: 1.03 [95% CI: 1.01, 1.04]).

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 the 2009 PM ISA with longitudinal analyses generally showing small magnitude increases in SBP, PP, and 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. (1.17 [95% CI 1.10, 1.22]). The association with PM_{2.5} concentration increased among non-White 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 Jackson Heart Study (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).

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 found consistently 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

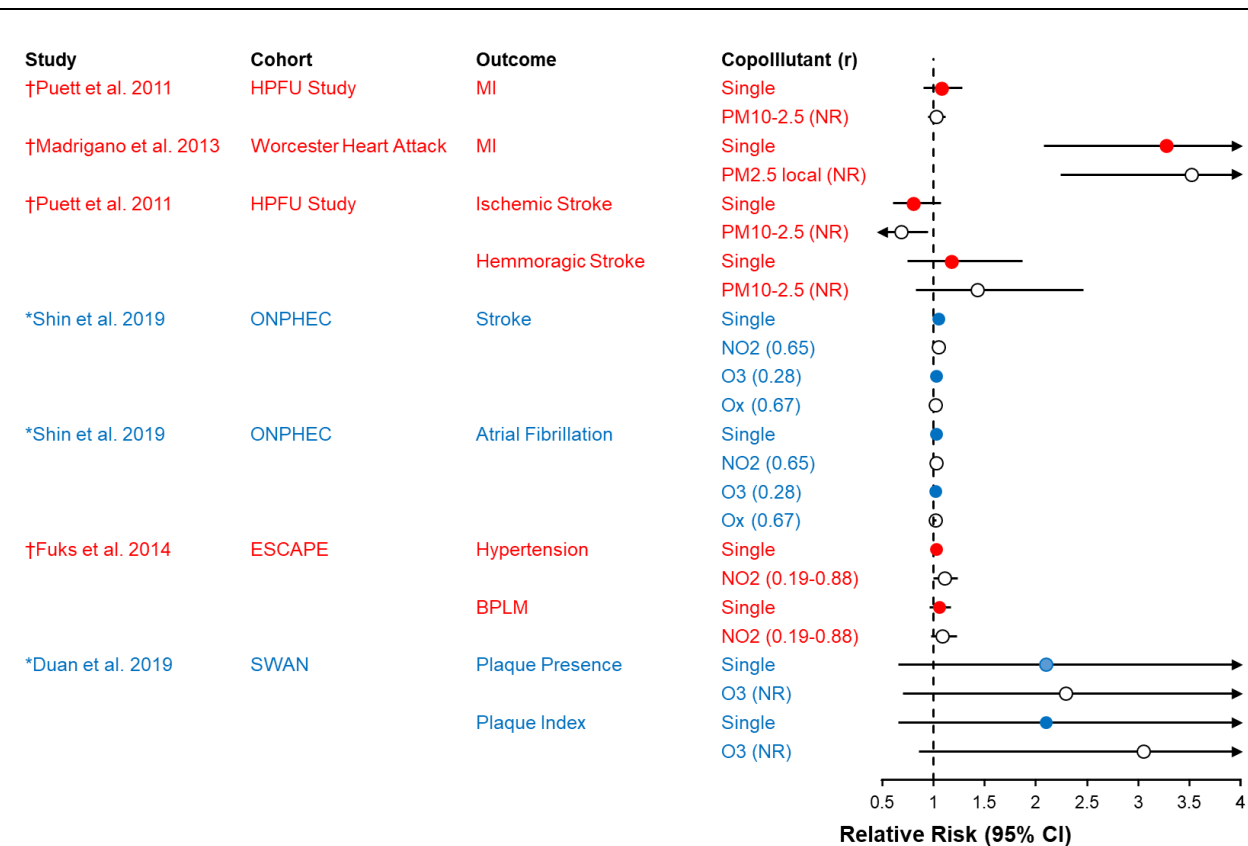
1 ozone, NO₂, PM_{10-2.5}, or SO₂. Recent cohort studies, which are reviewed in detail in [Section 3.2.2.2.2](#)
2 provide additional evidence for associations with cardiovascular mortality outcomes across the
3 distribution of PM_{2.5} concentrations ([Hayes et al., 2020](#)), the potential implications of a comorbidity on
4 the PM_{2.5}-cardiovascular mortality relationship ([Pinault et al., 2018](#)), and associations with individual
5 cardiovascular mortality outcomes including IHD ([Crouse et al., 2020](#); [Wang et al., 2020](#); [Cakmak et al.,](#)
6 [2018](#); [Pinault et al., 2017](#)) and stroke ([Crouse et al., 2020](#); [Hayes et al., 2020](#); [Wang et al., 2020](#); [Pope et](#)
7 [al., 2019](#); [Pinault et al., 2017](#)). Overall, these recent studies support the conclusions in the 2019 PM ISA
8 of consistent positive associations of long-term PM_{2.5} exposure with cardiovascular mortality, and
9 specifically with IHD- and stroke-related mortality. Although [Pope et al. \(2014\)](#) reported positive
10 associations of long-term PM_{2.5} exposure with congestive heart failure (CHF) mortality in a study of the
11 ACS cohort evaluated in the 2019 PM ISA, a recent analysis of the Medicare cohort [Wang et al. \(2020\)](#)
12 reported a null association. Recent studies also indicate that the combination of cardiovascular disease
13 and diabetes together has a greater mortality risk than cardiovascular mortality alone and that
14 cardiovascular diseases such as heart failure or previous MI may increase the risk of PM_{2.5}-related
15 all-cause mortality ([Ward-Caviness et al., 2020](#); [Malik et al., 2019](#)).

3.1.2.2.8 Copollutant Confounding

16 The independence of the association between long-term exposure to PM_{2.5} and cardiovascular
17 health effects can be examined through the use of copollutant models. A change in the PM_{2.5} risk
18 estimates, after adjustment for copollutants, may indicate the potential for confounding. A limited number
19 of studies were available in the 2019 PM ISA to assess copollutant confounding of the association
20 between long-term exposure to PM_{2.5} and cardiovascular morbidity. Considering these few available
21 studies, risk estimates remained largely unchanged after adjustment for PM_{10-2.5}, NO₂, and PM_{2.5} from
22 traffic sources. The limited number of recent analyses report some attenuation of risk estimates in models
23 adjusted for O₃ and NO₂.

24 Several recent analyses of the ONPHEC study add to the evidence pertaining to copollutant
25 confounding ([Figure 3-7](#)). [Shin et al. \(2019\)](#) reported that the association of long-term PM_{2.5} exposure
26 with stroke persisted after adjustment for NO₂ but was attenuated in the models with O₃ and oxidant gases
27 (Ox) represented by the redox weighted average of NO₂ and O₃ (HR: 1.05 [95% CI: 1.03, 1.06] and HR:
28 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
29 authors found that the association was slightly attenuated, but remained positive, in two-pollutant models
30 that adjusted for NO₂, O₃ and redox weighted average of NO₂ and O₃ (Ox) (HR: 1.03 [95% CI: 1.02, 1.04]
31 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
32 of atherosclerosis in the SWAN cohort, [Duan et al. \(2019a\)](#) reported that the estimate for the association
33 of long-term PM_{2.5} exposure with cIMT was slightly attenuated in a two-pollutant model that adjusted for
34 O₃ (24.45 μm [95% CI: -18.35, 67.25]). In a separate analysis of a subset of this cohort, however, [Duan](#)
35 [et al. \(2019b\)](#) reported that associations with plaque presence and plaque index progression persisted in

models adjusted for ozone (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/m³ 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 if there are concentration ranges where there are 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 µg/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.	1st 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 µg/m ³	Statistical Analysis Summary
			C-R relationship continued down to low exposure levels and persisted when the dataset was restricted <12 µg/m ³ . The relationship was generally linear at concentrations below 14 µg/m ³ .
Loop et al. (2018) Figure 3-11 U.S. Nationwide REGARDS	Non-fatal MI incidence	Median (IQR): 13.6 (2.7)	Predicted log hazard modelled as a linear function (non-linear 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 µg/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.	1st 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 µg/m ³ . The relationship was generally linear at concentrations below 14 µg/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 µg/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.

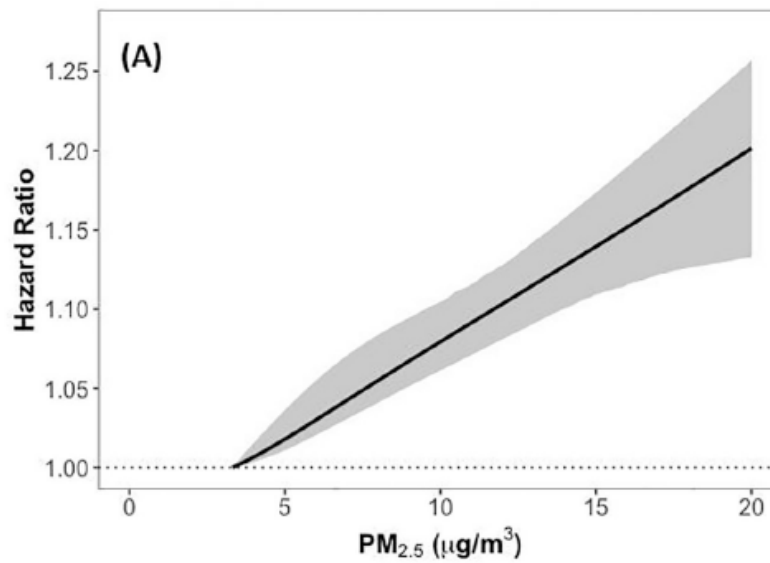
AIC = Akaike information criterion; C-R = Concentration-Response; CAC = coronary artery calcification; CHF = congestive heart failure; ESCAPE = European Study of Cohorts for Air Pollution Effects; HR = hazard ration, IHD = ischemic heart disease, IQR = interquartile range; MI = myocardial infarction; 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.

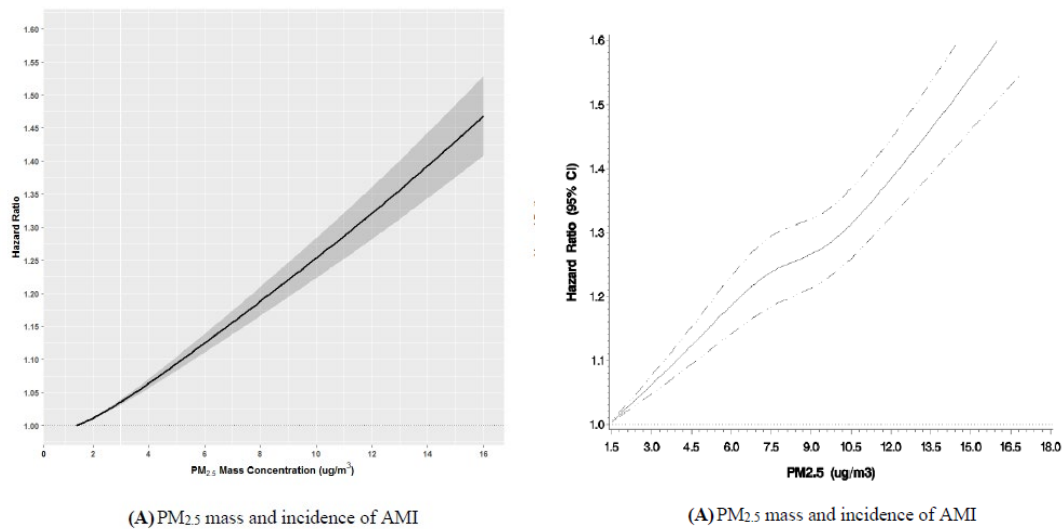
*Recent studies published since the literature cutoff date (~January 2018) for the 2019 Integrated Science Assessment for Particulate Matter.

1 Several studies evaluated the shape of the C-R function for the relationship between long-term
2 PM_{2.5} exposure and MI, including two analyses of the ONPHEC study ([Figure 3-8](#) and [Figure 3-9](#)), an
3 analysis of the U.S. Medicare population ([Figure 3-10](#)), and an analysis of the REGARDS cohort ([Figure](#)
4 [3-11](#)). Approximately linear relationships were observed in the ONPHEC analyses ([Chen et al., 2020](#); [Bai](#)
5 [et al., 2019](#)) using Shape Constrained Health Impact Function (SCHIF) method ([Nasari et al., 2016](#)),
6 which is described as a new class of variable coefficient risk functions that can capturing potentially
7 non-linear associations, and in the Medicare analysis using penalized splines, which is described in
8 [Section 3.1.2.1](#) ([Danesh Yazdi et al., 2019](#)). Both methods allow for deviations from linearity. By
9 contrast, [Loop et al. \(2018\)](#) found an inverse relationship between annual average PM_{2.5} exposure and
10 nonfatal MI.



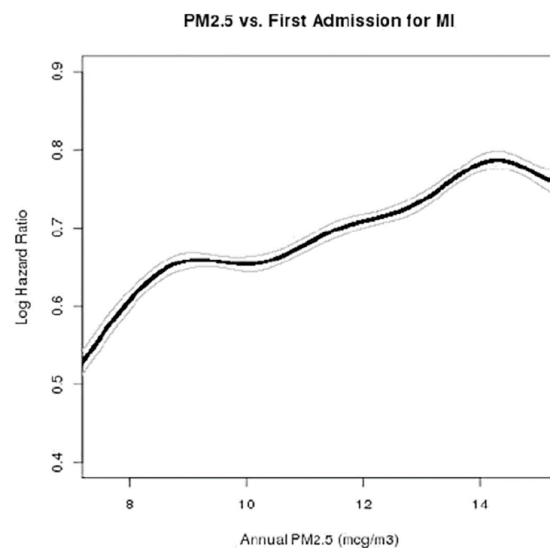
Source: [Bai et al. \(2019\)](#), copyright permission pending
 Note: The grey shaded area represents the 95% confidence interval.

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



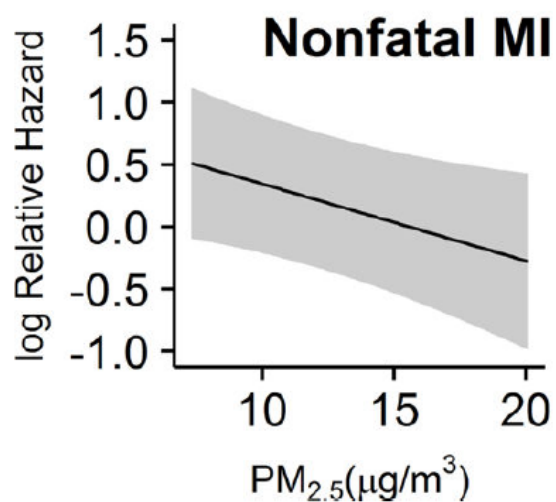
Source: [Chen et al. \(2020\)](#), copyright permission pending.
 Note: The grey shaded area represents the 95% confidence interval.

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. \(2019\)](#), copyright permission pending.
Note: The grey 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. \(2018\)](#), copyright permission pending.
Note: Grey bands are 95% prediction intervals.

Figure 3-11 Predicted log hazard for incident non-fatal 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/m³ ([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/m³) 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 around 14 µg/m³ ([Bai et al., 2019](#)).

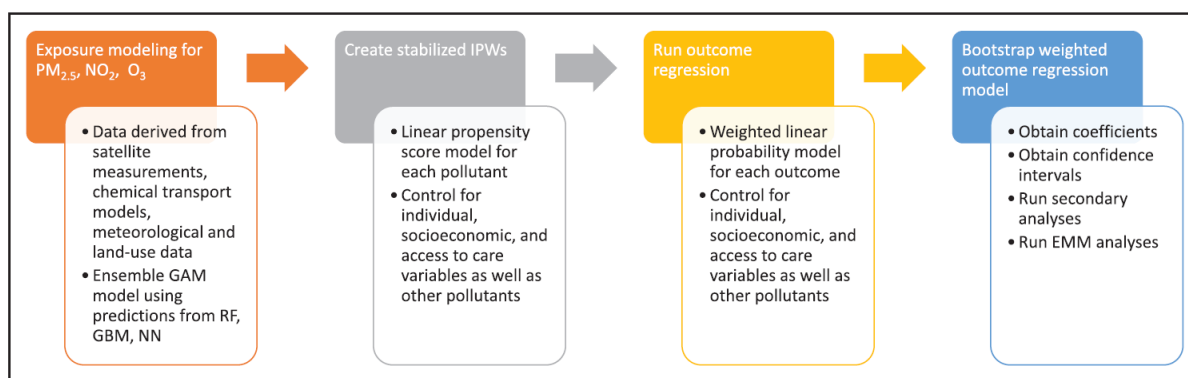
3.1.2.3 Recent Studies Examining the PM_{2.5}-Cardiovascular Effects Relationship through Accountability Analyses and Causal Modeling Methods

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 causal modeling methods. Since the literature cutoff date of the 2019 PM ISA, a few recent studies conducted accountability analyses or employed causal modeling methods 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 2005–2012 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/m³ 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 NO₂), 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 NO₂) 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 µg/m³ 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: From [Danesh Yazdi et al. \(2021\)](#), copyright permission pending.

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.

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 utilize 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 Mortality

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 µg/m³ 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, NO₂, PM_{10-2.5}, or SO₂, 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 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}, NO₂, and PM_{2.5} from traffic sources. The few recent analyses report some attenuation of risk estimates in models adjusted for O₃ and NO₂. 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 NO₂. 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. Though 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,

1 there is some evidence for a sublinear or supralinear C-R relationship for specific outcome (i.e., CHF and
2 AF). Lastly, a few recent epidemiologic studies that employed causal modeling methods to reduce
3 uncertainties related to potential confounding bias provide additional support for a relationship between
4 long-term PM_{2.5} exposure and cardiovascular effects.

3.2 Mortality

3.2.1 Short-Term PM_{2.5} Exposure

5 The following sections represent a summary of the evidence and the corresponding causality
6 determination for short-term PM_{2.5} exposure and mortality presented within the 2019 PM ISA
7 ([Section 3.2.1.1](#)) along with an evaluation of recent epidemiologic studies that fall within the scope of the
8 Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff
9 date of the 2019 PM ISA ([Section 3.2.1.2](#)). In addition, with the expansion of epidemiologic studies using
10 causal modeling methods, recent studies that employed such methods are also evaluated ([Section 3.2.1.3](#)),
11 which can further inform the relationship between short-term PM_{2.5} exposure and mortality. Lastly, a
12 summary of the results of recent studies evaluated within the section is presented in the context of the
13 scientific conclusions detailed in the 2019 PM ISA ([Section 3.2.1.4](#)). The evaluation of recent studies on
14 short-term PM_{2.5} exposure and mortality presented in this Supplement adds to the collective body of
15 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

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

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.

^aBased 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 \(2015\)](#).

^bDescribes 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.

^cDescribes the PM_{2.5} concentrations with which the evidence is substantiated.

^dMedian concentration from [Samoli et al. \(2013\)](#).

^eStatistics 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., 2013](#)) 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 approaches that used all available PM_{2.5} data (i.e., monitor, satellite, and LUR), allowing for the inclusion of less urban and rural locations in the 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., 2013](#)) 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 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

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

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

20 A number of studies evaluated conducted systematic evaluations of the lag structure of
21 associations for the PM_{2.5}-mortality relationship by examining either multiday lags or a series of
22 single-day lags, and these studies continued to support an immediate effect (i.e., lag 0 to 1 days) of
23 short-term PM_{2.5} exposures on mortality (2019 PM ISA, Section 11.1.8.1). Studies also conducted
24 analyses comparing the traditional 24-hour avg exposure metric with a subdaily metric (i.e., 1-hour max).
25 These initial studies provided evidence of a similar pattern of associations for both the 24-hour avg and
26 1-hour max metric, with a larger association for the 24-hour avg metric. Additionally, some studies
27 examined alternative exposure metrics representing size fractions smaller than PM_{2.5} and reflecting
28 number concentration (NC) and surface-area concentration (SC). The generally positive associations
29 reported with mortality for these smaller PM size fractions supported the larger body of PM_{2.5}-mortality
30 evidence, but it is difficult to compare NC and SC metrics with the traditional mass-based metric.

31 Building off the initial analysis of the C-R relationship between short-term PM exposure and
32 mortality that focused on PM₁₀, multicity studies conducted in the U.S. and Europe examined the shape of
33 the C-R relationship and whether a threshold exists specifically for PM_{2.5} (2019 PM ISA,
34 Section 11.1.10). These studies used different statistical approaches and consistently demonstrated a
35 linear relationship with no evidence of a threshold. Additionally, recent analyses conducted at lower
36 PM_{2.5} concentrations (i.e., 24-hour avg PM_{2.5} concentrations <30 µg/m³) provided initial evidence
37 indicating that PM_{2.5}-mortality associations persist and may be stronger (i.e., a steeper slope) at lower

1 concentrations. However, to date, extensive analyses have not been conducted to systematically explore
2 alternatives to linearity when examining the shape of the PM_{2.5}-mortality C-R relationship.

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

3.2.1.2 Recent U.S. and Canadian Epidemiologic Studies

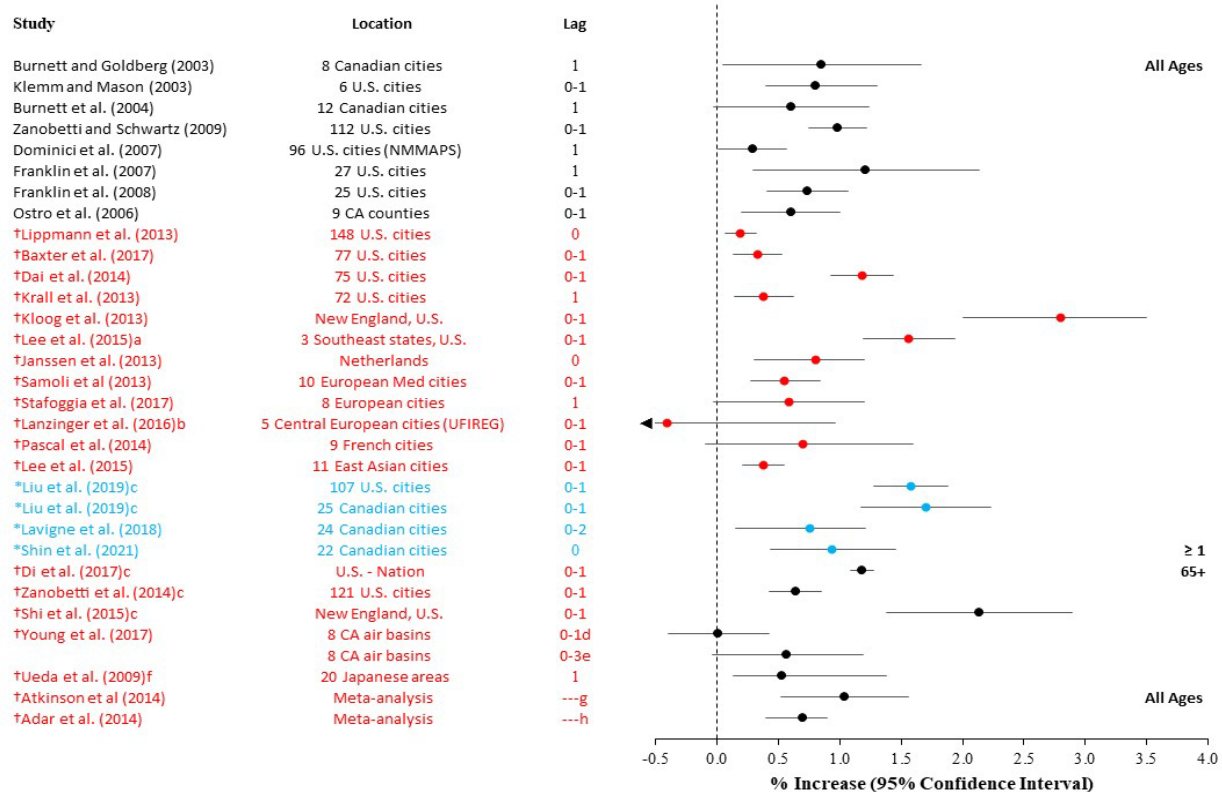
11 In addition to evaluating epidemiologic studies that examined the relationship between short-term
12 PM_{2.5} exposure and mortality, the 2019 PM ISA characterized whether evidence supported biologically
13 plausible mechanisms by which short-term PM_{2.5} exposure could lead to mortality. This evaluation
14 consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies
15 of morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically,
16 cardiovascular and respiratory morbidity (2019 PM ISA, Section 6.1.1 and Section 5.1.1, respectively).
17 Plausible mechanisms were identified by which inhalation exposure to PM_{2.5} could progress from initial
18 events to endpoints relevant to the cardiovascular system and to population outcomes such as emergency
19 department (ED) visits and hospital admissions due to cardiovascular disease, particularly ischemic heart
20 disease and congestive heart failure (2019 PM ISA, Section 6.1.1). Similarly, available evidence was
21 characterized by which inhalation exposure to PM_{2.5} could progress from initial events to endpoints
22 relevant to the respiratory system (2019 PM ISA, Section 5.1.1). However, the evidence for how the
23 initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and
24 hospital admissions, in particular for chronic obstructive pulmonary disease (COPD) and asthma was
25 limited. Collectively, the progression demonstrated in the available evidence for cardiovascular morbidity
26 (and to a lesser extent, respiratory morbidity) supported potential biological pathways by which
27 short-term PM_{2.5} exposures could result in mortality (2019 PM ISA, Section 11.1).

28 The few recent multicity studies conducted in the U.S. and Canada build upon the strong
29 epidemiologic evidence base evaluated in the 2019 PM ISA, as well as previous assessments, that
30 provided the scientific rationale supporting a *causal relationship* between short-term PM_{2.5} exposure and
31 mortality ([Section 3.1.1.1](#)). In addition to examining the relationship between short-term PM_{2.5} exposure
32 and all-cause or nonaccidental mortality ([Section 3.1.1.2.1](#)) and cause-specific mortality
33 ([Section 3.1.1.2.2](#)), additional analyses within these recent studies also further examined issues relevant to
34 expanding the overall understanding of the effect of short-term PM_{2.5} exposure on mortality. Specifically,

1 recent studies have assessed potential copollutant confounding ([Section 3.1.1.2.3](#)), examined effect
2 modification of the PM_{2.5}-mortality relationship ([Section 3.1.1.2.4](#)), the lag structure of associations
3 ([Section 3.1.1.2.5](#)), and assessed the shape of the concentration-response (C-R) relationship
4 ([Section 3.1.1.2.6](#)). The following sections evaluate recent multicity studies that inform each of the
5 aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM
6 ISA.

3.2.1.2.1 All Cause and Total (Nonaccidental) Mortality

7 Since the literature cutoff date for the 2019 PM ISA, a limited number of multicity studies have
8 been conducted within the U.S. and Canada ([Shin et al., 2021a](#); [Liu et al., 2019](#); [Lavigne et al., 2018](#)).
9 Although few in number, these recent studies add to the extensive number of multicity studies evaluated
10 in the 2019 PM ISA that were conducted worldwide, specifically in locations where mean 24-hour
11 concentrations were generally <20 µg/m³ (2019 PM ISA, Section P.3.1). Taken together, these studies
12 provide consistent evidence of positive associations between short-term PM_{2.5} exposure and mortality
13 across diverse geographic locations; in populations with a wide range of demographic characteristics; and
14 using a variety of statistical models, approaches to confounder adjustment, and exposure assessment
15 approaches ([Figure 3-13](#)).



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

avg = average; $\mu\text{g}/\text{m}^3$ = microgram per cubic meter; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; PM = particulate matter; $\text{PM}_{2.5}$ = 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 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentrations.

^aResults are from modeled $\text{PM}_{2.5}$ analysis, analysis focusing on measured $\text{PM}_{2.5}$ reported 1.21% (95% CI: 0.94, 1.47).

^bOnly four of the five cities measured $\text{PM}_{2.5}$.

^cShi et al. (2015), Zanobetti et al. (2014), and Liu et al. (2019) only had data for all-cause mortality including accidental mortalities.

^dMain 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.

^eSensitivity 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.

^fUeda 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.

^gAtkinson et al. (2014) primarily focused on single-day lag results.

^hAdar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Figure 3-13 Summary of associations between short-term $\text{PM}_{2.5}$ 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 worldwide 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). Liu et al. (2019)

established a Multi-City Multi-Country (MCC) Collaborative Research Network that allowed the investigators to collect data globally, resulting in air pollution and mortality data from 652 urban areas in 24 countries from 1986–2015. 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 models to pool city-specific estimates into a country-specific estimate. All analyses relied on PM_{2.5} data where the highest and lowest 5% of data was trimmed to remove outliers. In analyses of 25 Canadian cities from 1986–2011 and 107 U.S. cities from 1987–2006, 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 3.1.1.2.4](#)). 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](#)).

Other nonaccidental mortality

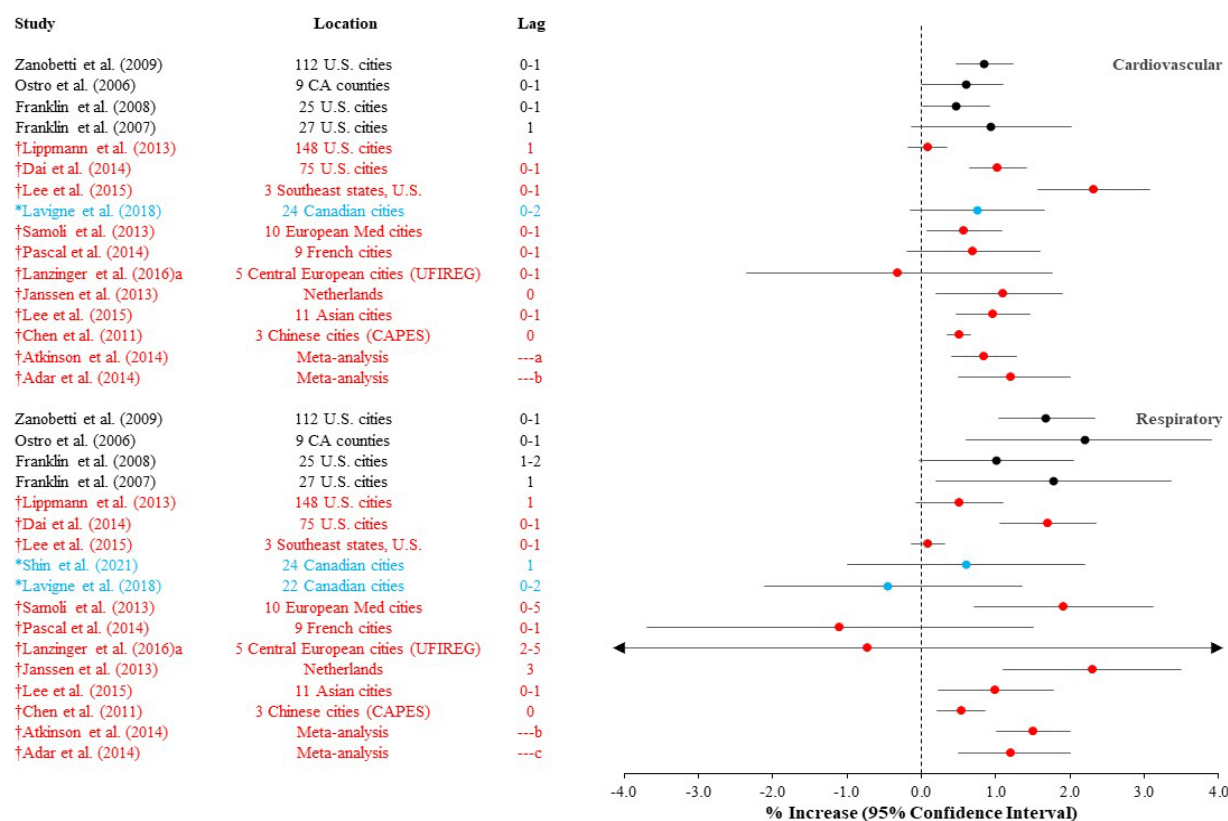
The 2009 PM ISA reviewed a handful of small studies examining the association between PM_{2.5} exposure and out-of-hospital cardiac arrest (OHCA). No evidence of an association was reported. Section 6.1.4.1 of the 2019 PM ISA evaluated studies published since the 2009 PM ISA, which provided evidence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

1 previously evaluated studies focused on a cardiovascular outcome, i.e., OHCA, and as a result where
2 discussed within the evidence for short-term PM_{2.5} exposure and cardiovascular effects, the results of
3 these previous studies are summarized here as they can inform a recent study by [Rappazzo et al. \(2019\)](#)
4 that examined out-of-hospital sudden unexpected deaths.

5 [Rappazzo et al. \(2019\)](#) conducted a time-stratified case-crossover analysis to examine the
6 relationship between short-term PM_{2.5} exposure and out-of-hospital nonaccidental sudden unexpected
7 deaths in a small population of individuals (n = 399) over a 2-year period that resided in Wake County,
8 NC. In analyses examining both single-day lags ranging from 0 to 3 days and a 0–1 day lag, the authors
9 reported a positive association at lag 1 (OR = 1.39 [95% CI: 0.96, 1.99]) that was smaller in magnitude
10 when using a 0–1 day lag (OR = 1.18 [95% CI: 0.79, 1.78]). However, due to the small sample size
11 within this study confidence intervals are large. In addition to single-pollutant models, the authors
12 examined copollutant models across the single-day lags and reported that PM_{2.5} associations are relatively
13 unchanged in models with NO₂, SO₂, ozone, and CO. This initial study focusing out-of-hospital sudden
14 unexpected deaths from all nonaccidental causes, provides evidence consistent with the relatively limited
15 number of previous studies examining OHCA.

3.2.1.2.2 Cause-specific Mortality

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



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

avg = average; $\mu\text{g}/\text{m}^3$ = microgram per cubic meter; PM = particulate matter; $\text{PM}_{2.5}$ = 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 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentrations. All ages examined for all studies except Lanzinger et al. (2016) and Shin et al. (2021b) which focused on ages ≥ 1 year old.

^aOnly four of the five cities measured $\text{PM}_{2.5}$.

^bAtkinson et al. (2014) primarily focused on single-day lag results.

^cAdar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

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

3.2.1.2.3 Potential Copollutant Confounding of the $\text{PM}_{2.5}$ -Mortality Relationship

- 1 At the time of the 2009 ISA, only a few studies had assessed the potential for confounding of the
- 2 $\text{PM}_{2.5}$ -mortality association by co-occurring pollutants. In contrast, the 2019 ISA included a number of
- 3 multicity studies that used copollutant models to evaluate this issue, including studies that examined both
- 4 gaseous pollutants and other particle size fractions. These studies reported that associations were

1 relatively unchanged in copollutant models, albeit with wider confidence intervals than single pollutant
2 models (2019 PM ISA, Figure 11-3).

3 Of the recent multicity studies conducted in the U.S. and Canada, only [Lavigne et al. \(2018\)](#)
4 conducted an assessment of copollutant confounding, with a focus on oxidant gases. Within this study,
5 oxidant gases were defined as the daily combined oxidant capacity of ozone and NO₂ based on the
6 redox-weighted averages of both pollutants. In a copollutant model with oxidant gases, the association
7 between short-term PM_{2.5} exposure and mortality is unchanged compared to the single pollutant model
8 with both reporting a 0.76% increase in mortality at lag 0–2 days.

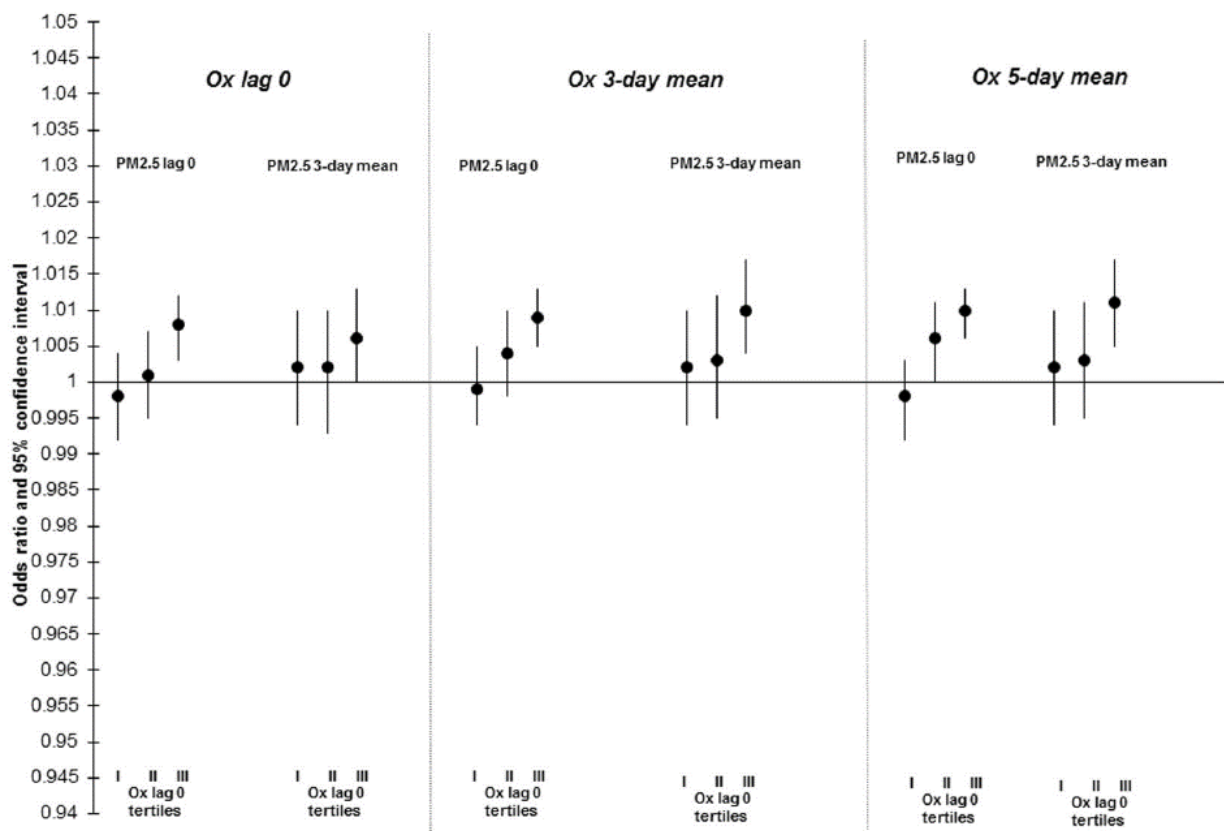
3.2.1.2.4 Effect Modification of the PM_{2.5}-Mortality Relationship

9 Multicity epidemiologic studies evaluated in the 2009 PM ISA and 2019 PM ISA provided
10 evidence of city-to-city and regional heterogeneity in PM_{2.5}-mortality associations. Within the 2019 PM
11 ISA, studies were evaluated that examined factors that could modify the PM_{2.5}-mortality association and
12 potentially explain some of the observed heterogeneity in associations, including season (2019 PM ISA,
13 Section 11.1.6.1), temperature (2019 PM ISA, Section 11.1.6.2), and city and regional characteristics
14 (Section 11.1.6.3) such as composition/mixtures (2019 PM ISA, Section 11.1.6.3.1) and exposure factors
15 (2019 PM ISA, Section 11.1.6.3.2). Recent multicity studies provide additional insight into some of these
16 factors that could modify the PM_{2.5}-mortality association.

17 The 2009 PM ISA reported some evidence that PM_{2.5}-mortality associations are larger in
18 magnitude during the warm season, specifically the spring, with the majority of this evidence coming
19 from U.S. multicity studies ([Zanobetti and Schwartz, 2009](#); [Franklin et al., 2008](#)). As discussed in
20 Section 11.1.6.1 of the 2019 PM ISA, across recent multicity studies, there was general agreement that
21 PM_{2.5}-mortality associations were larger in magnitude during warmer months. However, it remained
22 unclear whether copollutants confound the seasonal patterns in the associations observed. Across most
23 studies, the pattern of seasonal associations persisted using different methods to examine whether there
24 was evidence of seasonal differences in associations, with some studies relying on stratified analyses ([Dai](#)
25 [et al., 2014](#); [Samoli et al., 2013](#)) and others incorporating interaction terms between PM_{2.5} and season
26 ([Pascal et al., 2014](#); [Lippmann et al., 2013](#)). The recent studies conducted by [Shin et al. \(2021a\)](#) and [Shin](#)
27 [et al. \(2021b\)](#) further inform seasonal analyses, but do not address the uncertainties identified in the 2019
28 PM ISA. Both studies assessed associations by season through stratified analyses where the warm season
29 is defined as April–September and the cold season as October–March. In [Shin et al. \(2021a\)](#), when
30 focusing on lag 0, which had the largest magnitude of an association in all-year analyses, there is a clear
31 pattern of the warm season driving the overall association; however, the reverse pattern is reported when
32 focusing on lag 1, complicating the overall interpretation of results from this study. However, in [Shin et](#)
33 [al. \(2021b\)](#), which focused on respiratory mortality a slight larger association, with wide confidence
34 intervals, is reported for the warm season (1.0% [95% CI: –1.6, 3.5]) compared to the cold season (0.6%
35 [95% CI: –2.2, 4.1]) at lag 1, the main lag examined for PM_{2.5} and mortality within the study. Across

1 these recent studies there continues to be some evidence indicating larger associations during the warm
2 season, but there are inconsistencies across the individual lags examined.

3 Within the 2019 PM ISA, an assessment of composition and mixtures (2019 PM ISA,
4 Section 11.1.6.3.1) focused on whether differences in the pollutant mixture across cities could explain
5 heterogeneity in the PM_{2.5}-mortality association across cities and regions of the U.S. In the process of
6 examining the association between short-term PM_{2.5} exposure and mortality across 24 Canadian cities,
7 [Lavigne et al. \(2018\)](#) did not focus on whether effect modification by other pollutants could explain
8 heterogeneity, but broadly whether oxidant gases modify the PM_{2.5}-mortality association. In the process
9 of evaluating effect modification, the authors conducted stratified analyses across tertiles of oxidant gases
10 based on the distribution of oxidant gases across all cities. For nonaccidental mortality, in analyses
11 examining both lag 0 and lag 0–2 days for PM_{2.5}, there was a consistent pattern of the PM_{2.5}-mortality
12 association being larger in magnitude for the 3rd tertile of oxidant gases. However, there is some
13 variability in the PM_{2.5}-mortality association depending on the lag structure used to represent oxidant
14 gases, with some evidence indicating that as the exposure for oxidant gases increased in length, there are
15 larger PM_{2.5}-mortality associations for both the 2nd and 3rd tertiles ([Figure 3-15](#)). The pattern of
16 associations for nonaccidental mortality is similar for cardiovascular mortality, but there is no evidence of
17 effect modification for respiratory mortality.

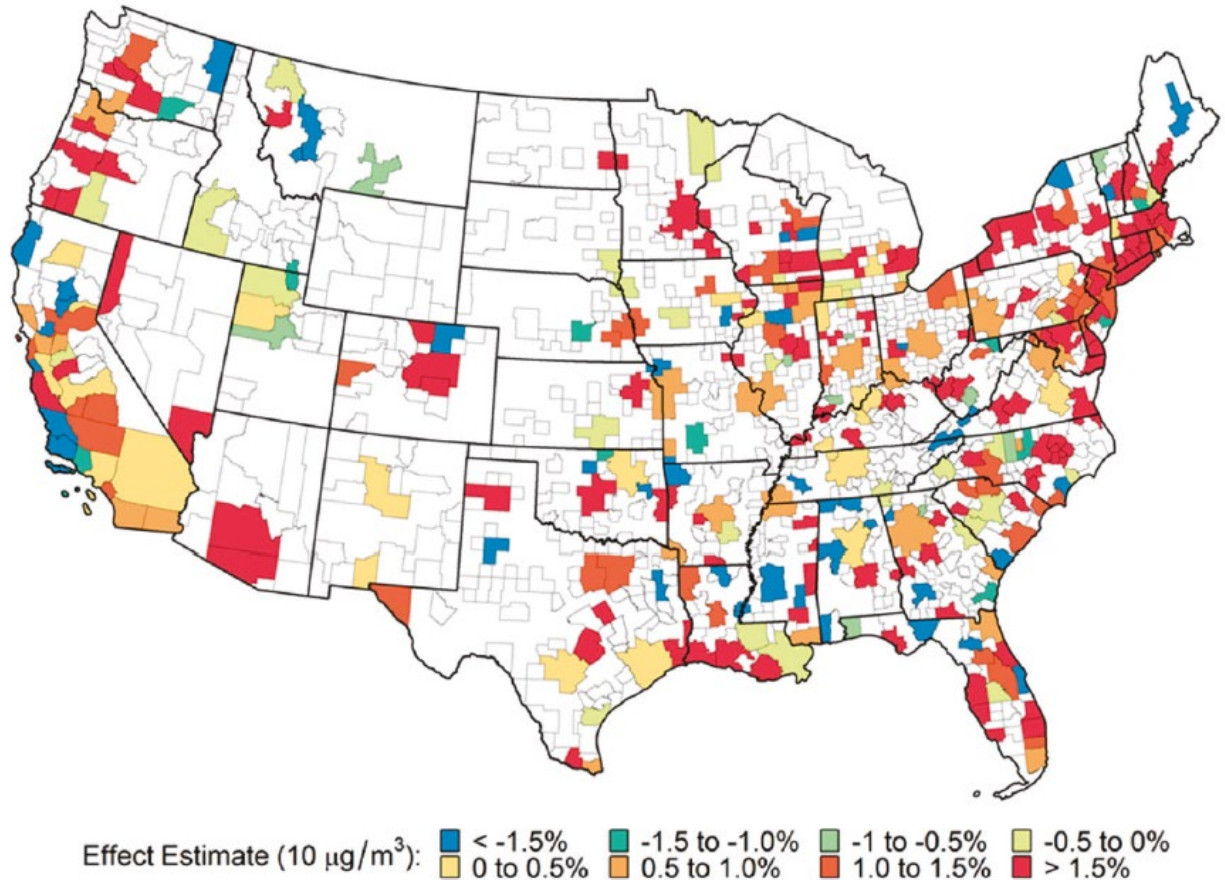


Source: Copyright permission pending from [Lavigne et al. \(2018\)](#).

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. 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)⁷ 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: Copyright permission pending from [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 individual factor explained much of the heterogeneity as reflected by $R^2 < 1\%$. For the multivariate model, a backwards selection approach was used to develop the final model that included variables for

⁷95% CIs were not presented in this study.

gas heating use, heating degree days, cooling degree days, and variables for home size and age. Compared to the univariate models, the multivariate models explained a larger amount of the heterogeneity in mortality associations across the CBSAs examined, ranging from 11–13%. 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](#).

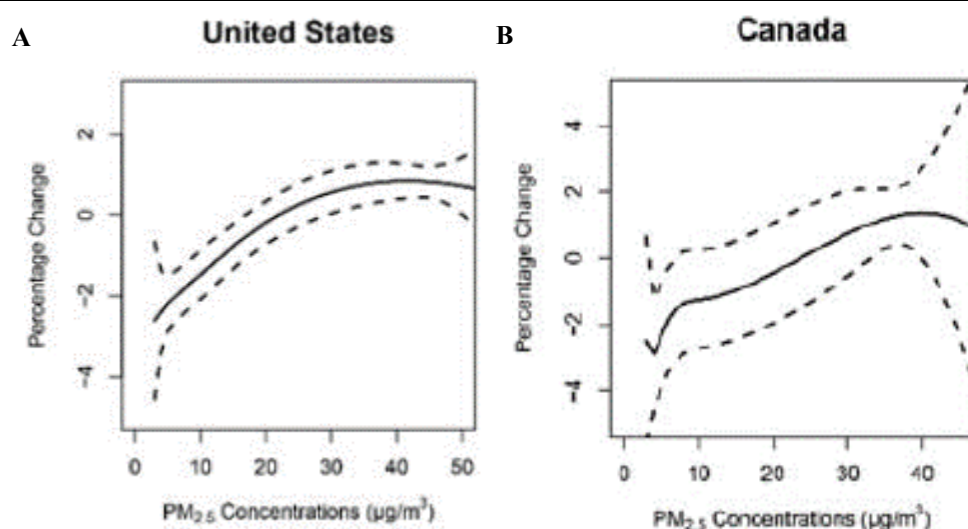
Of the recent studies evaluated, [Lavigne et al. \(2018\)](#) and [Shin et al. \(2021a\)](#) in multi-city studies conducted in Canada examined the lag structure of associations primarily through examining single-day lags ranging from 0 to 2 days, with [Lavigne et al. \(2018\)](#) also examining a multi-day 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 PM₁₀. 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 $5 \mu\text{g}/\text{m}^3$. Additionally, those studies that conducted analyses focused on examining associations at lower $\text{PM}_{2.5}$ concentrations provided initial evidence indicating that associations persist and may be larger (i.e., have a steeper slope) at lower $\text{PM}_{2.5}$ concentrations.

[Liu et al. \(2019\)](#) in the worldwide analysis examining the association between short-term $\text{PM}_{2.5}$ exposure and mortality in 652 cities, also examined country-specific C-R relationships. For each country, a linear term for $\text{PM}_{2.5}$ was added to the main model with a B-spline function with knots at the 25th and 75th percentiles of the mean $\text{PM}_{2.5}$ 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 $8 \mu\text{g}/\text{m}^3$ and greater than $30 \mu\text{g}/\text{m}^3$.

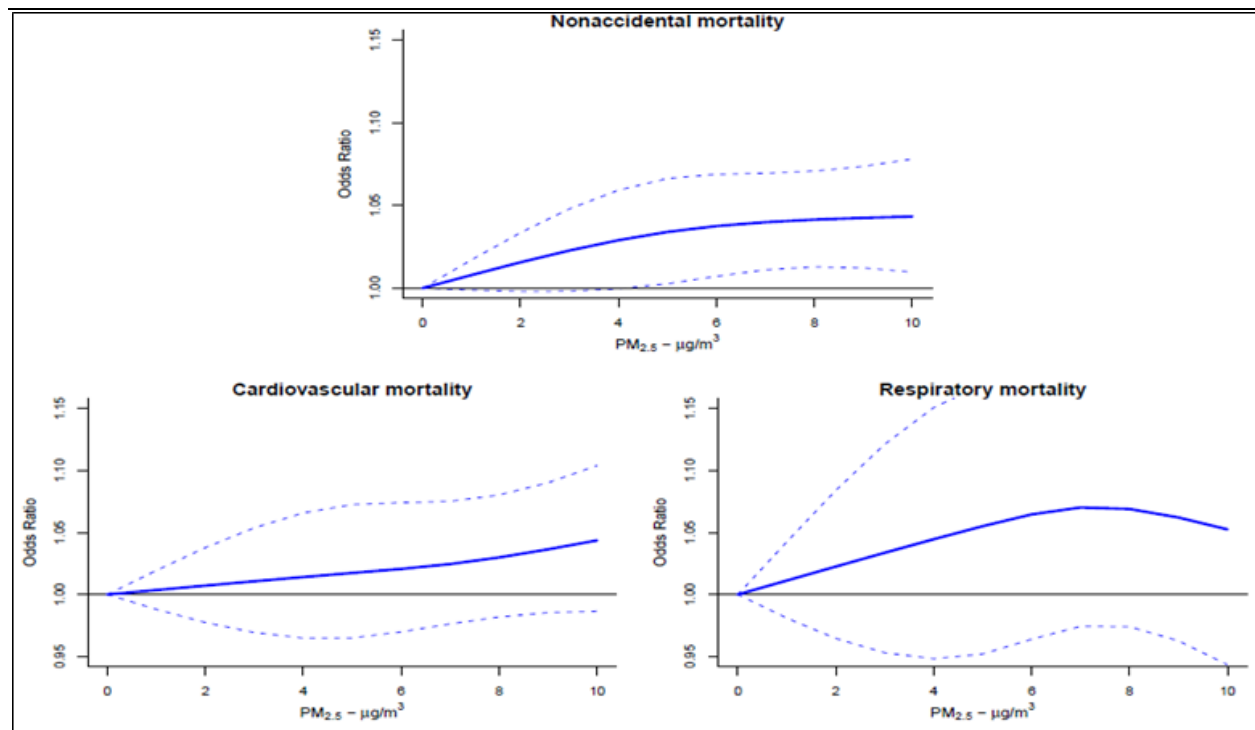


Source: Adapted from [Liu et al. \(2019\)](#), copyright permission pending.

Figure 3-17 Concentration-response curves for the U.S. (A) and Canada (B) using a B-spline function with knots at the 25th and 75th percentiles of $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ exposures. Across mortality outcomes, C-R curves support a linear relationship at $\text{PM}_{2.5}$ 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 $5 \mu\text{g}/\text{m}^3$ and some evidence of nonlinearity in the respiratory mortality C-R relationship occurring around $7 \mu\text{g}/\text{m}^3$ (Figure 3-18). However, compared to nonaccidental and cardiovascular mortality, confidence intervals were much wider for respiratory mortality resulting in less confidence in the overall shape of the C-R curve.



Source: Copyright permission pending from [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 $\text{PM}_{2.5}$ across 24 Canadian cities.

Overall, recent studies, although limited in number continue to provide evidence of a linear, no-threshold relationship between short-term $\text{PM}_{2.5}$ 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 $5\text{--}8 \mu\text{g}/\text{m}^3$. However, consistent with studies evaluated in previous assessments, neither study conducted systematic evaluations of alternatives to linearity.

3.2.1.3 Recent Studies Examining the PM_{2.5}-Mortality Relationship through Accountability Analyses and Causal Modeling Methods

Within the 2019 PM ISA, in assessing the relationship between short-term PM_{2.5} exposure and mortality several studies were evaluated that employed causal modeling methods (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 causal modeling methods, which further inform the relationship between short-term PM_{2.5} exposure and mortality ([Table A-6](#)).

Causal modeling methods 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. In other words, the probability of being exposed is the same as the probability of being unexposed and the exposure can be considered “random” ([Wei et al., 2020](#)). 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 NO₂ ([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 µg/m³ 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 µg/m³ increase in short-term PM_{2.5} exposure increased from 3.33 (PM_{2.5} concentrations <35 µg/m³; 95% CI: 2.41, 4.11) to 14.56 (PM_{2.5} concentrations <5 µg/m³; 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 O₃, and NO₂ 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 non-linear 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 $m \ll n$ ([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 µg/m³ 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 µg/m³, 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 causal modeling study, using data from the National Center for Health Statistics in 135 U.S. cities, [Schwartz et al. \(2018a\)](#) utilized three causal 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. 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 $\mu\text{g}/\text{m}^3$ increase in 24-hour avg $\text{PM}_{2.5}$ concentrations. When restricted to days with 24-hour average $\text{PM}_{2.5}$ concentrations below 25 $\mu\text{g}/\text{m}^3$, the instrument for $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ concentrations below 25 $\mu\text{g}/\text{m}^3$, 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 $\text{PM}_{2.5}$ exposure and mortality.

Recent epidemiologic studies that employed causal modeling methods to examine the association between short-term $\text{PM}_{2.5}$ exposure and mortality reported consistent positive associations within large cohorts across multiple cities in the U.S. Furthermore, the use of causal modeling methods 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ exposure and

mortality at lower mean 24-hour average concentrations, generally below 12 $\mu\text{g}/\text{m}^3$, 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ -mortality associations in multi-city epidemiologic studies. The continued assessment of the C-R relationship between short-term $\text{PM}_{2.5}$ exposure and mortality further supports a linear, no-threshold relationship, with less confidence in the shape at concentrations below 5 $\mu\text{g}/\text{m}^3$. Additionally, recent studies that employed causal modeling methods provide additional support for a relationship between short-term $\text{PM}_{2.5}$ exposure and mortality.

3.2.2 Long-Term $\text{PM}_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for long-term $\text{PM}_{2.5}$ 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](#)). In addition, with the expansion of in epidemiologic studies using causal modeling methods, recent studies that employed such methods are also evaluated ([Section 3.2.2.3](#)), which can further inform the relationship between long-term $\text{PM}_{2.5}$ exposure and mortality. Lastly, 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 $\text{PM}_{2.5}$ exposure and 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 $\text{PM}_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mainly in North America and Europe. Many analyses further evaluated the association between long-term $\text{PM}_{2.5}$ 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 $\leq 12 \mu\text{g}/\text{m}^3$ (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. 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](#).

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 $\leq 12 \mu\text{g}/\text{m}^3$ ([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 $\leq 12 \mu\text{g}/\text{m}^3$). 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.

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 (µg/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	<p>Positive associations observed between long-term PM_{2.5} exposure and total mortality remain relatively unchanged after adjustment for O₃, NO₂, and PM_{10–2.5}.</p> <p>When reported, correlations with copollutants were highly variable (low to high).</p>	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 (µg/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

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; µg/m³ = microgram per cubic meter; NO₂ = nitrogen dioxide; O₃ = 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.

^aBased on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

^bDescribes 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.

^cDescribes the PM_{2.5} concentrations with which the evidence is substantiated.

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 NO₂ (2019 PM ISA, Figure 11-21) in copollutant models and observed similar hazard ratios for PM_{2.5} regardless of whether ozone or NO₂ 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., SO₂, 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., aerosol optical depth [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 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 µg/m³. 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 to 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 O₃ and NO₂. **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

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. 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. Collectively, the progression demonstrated in the available evidence for cardiovascular and respiratory morbidity and metabolic disease supported potential biological pathways by which long-term PM_{2.5} exposures could result in mortality (2019 PM ISA, Section 11.2).

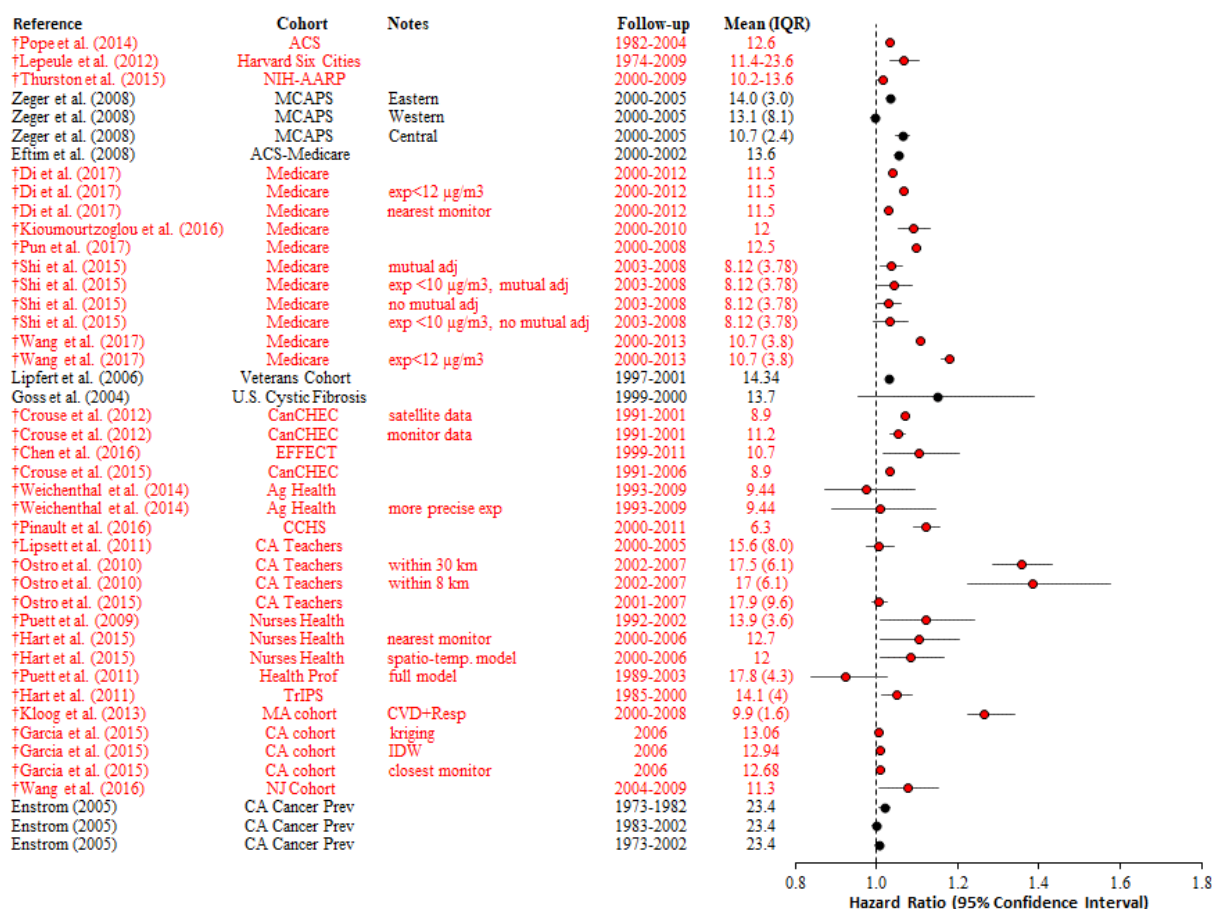
Recent cohort studies conducted in the U.S. and Canada build upon the strong evidence base evaluated in the 2019 PM ISA, as well as previous assessments, that provided the scientific rationale supporting a *causal relationship* between long-term PM_{2.5} exposure and mortality ([Section 3.2.2.1](#)). 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

1 confounding ([Section 3.2.2.2.5](#)), explored new and innovative methods for assessing confounding
2 ([Section 3.2.2.2.6](#)), and assessed the shape of the concentration-response (C-R) relationship
3 ([Section 3.2.2.2.7](#)). The following sections evaluate recent cohort studies that inform each of the
4 aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM
5 ISA.

3.2.2.2.1 All Cause and Total (Nonaccidental) Mortality

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

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

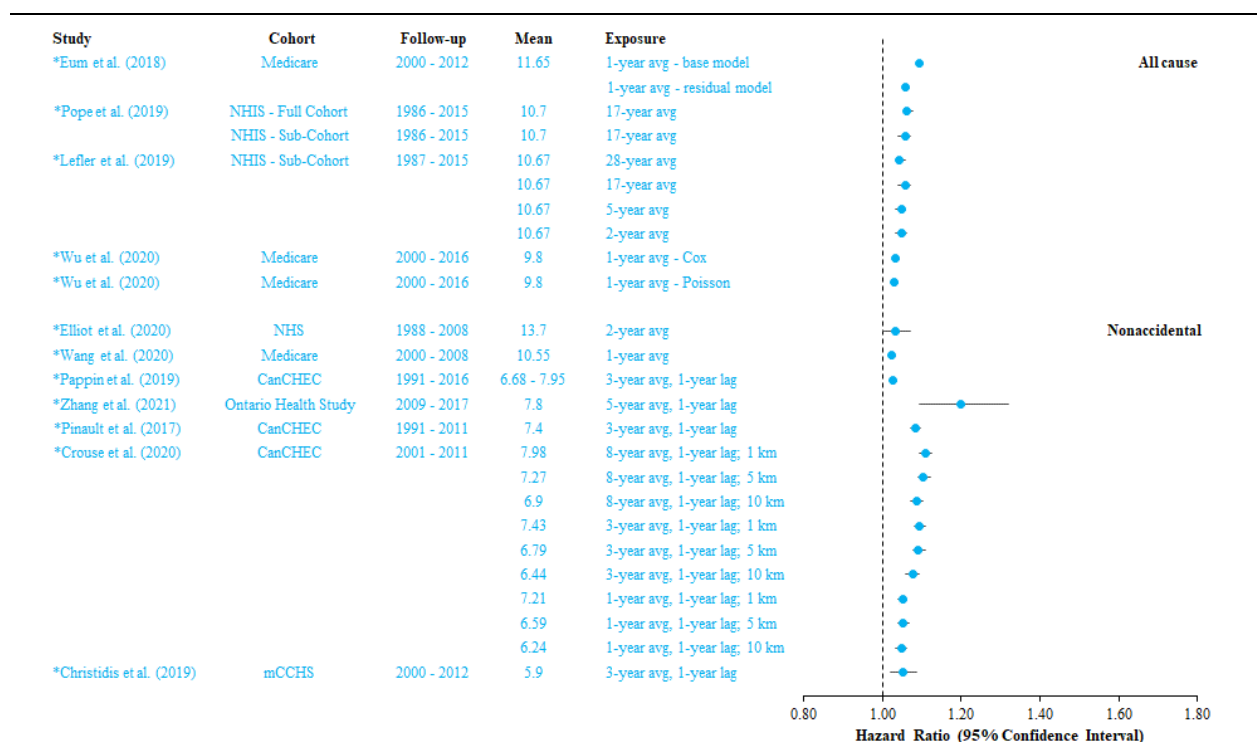


Source: Figure 11-18, 2019 PM ISA.

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/m³ = 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/m³ increase in pollutant concentration. 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 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; $\mu\text{g}/\text{m}^3$ = microgram per cubic meter; NHIS = National Health Interview Survey; PM = particulate matter; $\text{PM}_{2.5}$ = 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 $\mu\text{g}/\text{m}^3$ increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $\text{PM}_{2.5}$. Blue text and circles represent U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA.

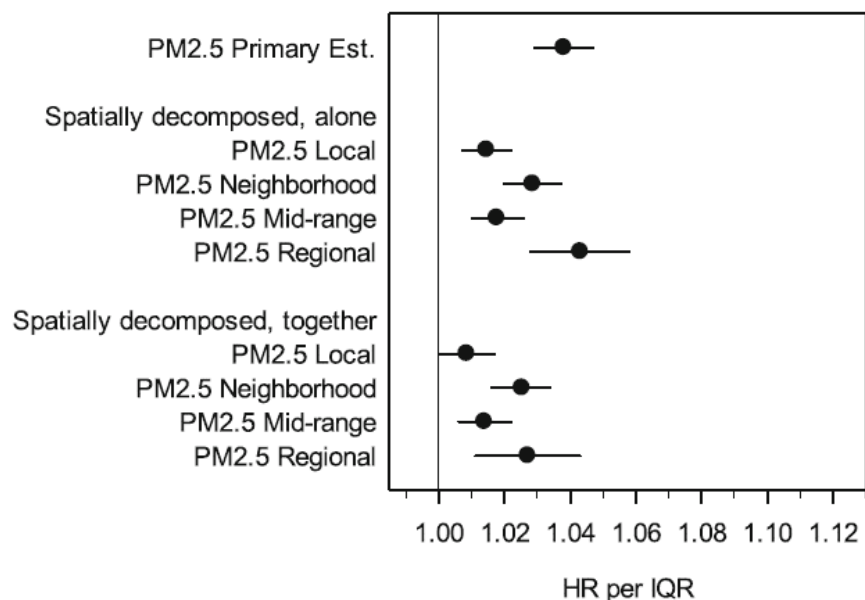
Figure 3-20 Associations between long-term $\text{PM}_{2.5}$ exposure and all cause and total (nonaccidental) mortality in cohort studies in the U.S. and Canada published since the 2019 Integrated Science Assessment for Particulate Matter.

In the continuous evolution of studies aimed at assessing the relationship between long-term $\text{PM}_{2.5}$ 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 1986–2014 with mortality data through 2015 resulting in approximately 1.5 million participants. The authors also formed a subcohort comprised of 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 $\text{PM}_{2.5}$ data (see Table A-7) to estimate population-weighted 17-year average $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ concentrations were imputed from 1988–1998, allowing for the

1 use of a 28-year average PM_{2.5} exposure window. In both the full cohort and subcohort, associations were
2 attenuated, but remained positive when using the 28-year average exposure window, in comparison to the
3 main analyses using the 17-year average exposure window (quantitative results not presented).

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

18 In the spatial decomposition approach, the authors developed exposure indicators indicative of
19 PM_{2.5} emanating from different sources and defined them as local (<1 km); neighborhood (1–10 km);
20 mid-range (10–100 km); and regional (>100 km). In developing each exposure indicator, [Lefler et al.](#)
21 [\(2019\)](#) subtracted the minimum PM_{2.5} concentration identified within the defined circular buffers around
22 each census tract for each year from 2000–2015. While there was some variability across each of the
23 exposure metrics based on an IQR increase in PM_{2.5} concentrations, overall the regional metric was closer
24 in magnitude to the primary PM_{2.5} exposure indicator ([Figure 3-21](#)).



Source: Copyright permission pending, [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 2000–2008. 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 socioeconomic status (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 Nurses' Health Study [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 the Health Effects Institute (HEI) initiating 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 HEI 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 µg/m³.

As detailed in the 2019 PM ISA (Section 11.2.2.1), the initial publication from the HEI Medicare study applied a hybrid exposure model at a refined spatial resolution (i.e., 1 km² 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 HEI Medicare study primarily focus on causal modeling methods and are evaluated in [Section 3.1.2.3](#). However, a recent study by [Wu et al. \(2020a\)](#) builds upon 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 causal modeling methods ([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 HEI 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 km² 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 km² 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 is 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](#)). Lastly, building upon [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 where 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 km² 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 km² spatial scale versus the 10 km² 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.

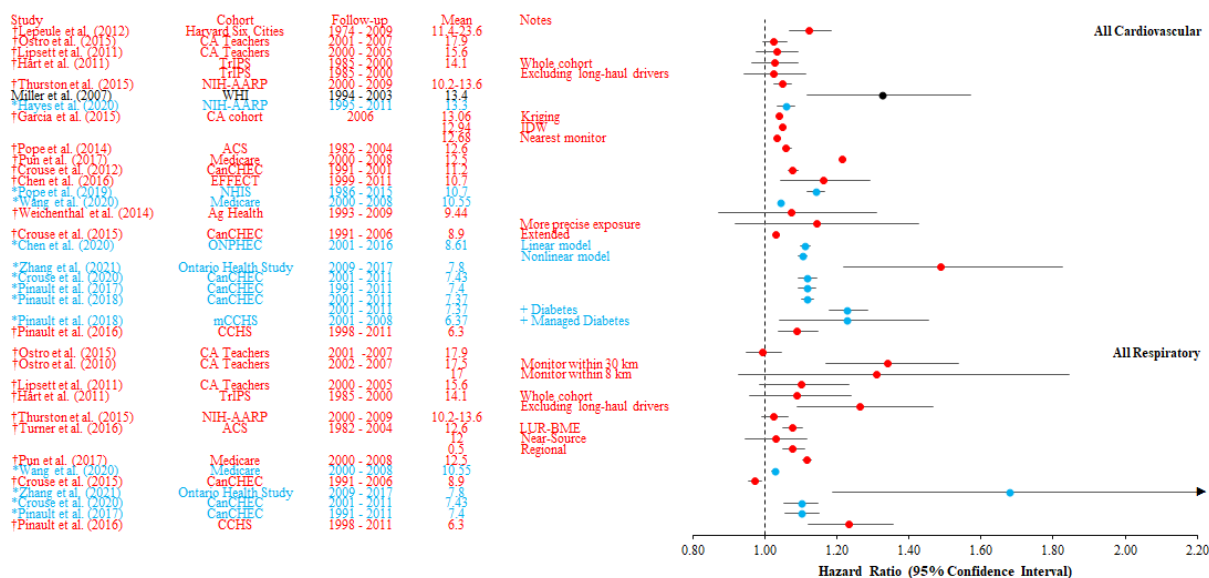
In addition to the MAPLE studies focusing on the larger CanCHEC cohort, other studies either focused solely on the CCHS-mortality (mCCHS) cohort ([Christidis et al., 2019](#)) or relied on data from it due to its extensive individual-level data [[Pinault et al. \(2018\)](#) in [Section 3.1.2.2.2](#) 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 to 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 to 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 2009–2017. 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 upon 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; $\mu\text{g}/\text{m}^3$ = 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; $\text{PM}_{2.5}$ = 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 $\mu\text{g}/\text{m}^3$ 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 $\text{PM}_{2.5}$. 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 $\text{PM}_{2.5}$ concentrations at 1 km resolution.

Figure 3-22 Associations between long-term $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ effect estimates relating long-term $\text{PM}_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in magnitude in copollutant models adjusted for ozone, NO_2 , $\text{PM}_{10-2.5}$, or SO_2 . The results of recent cohort studies provide additional evidence for associations with cardiovascular mortality outcomes across the distribution of $\text{PM}_{2.5}$ concentrations, the potential implications of comorbidity on the $\text{PM}_{2.5}$ -cardiovascular mortality relationship, and associations with individual cardiovascular mortality outcomes.

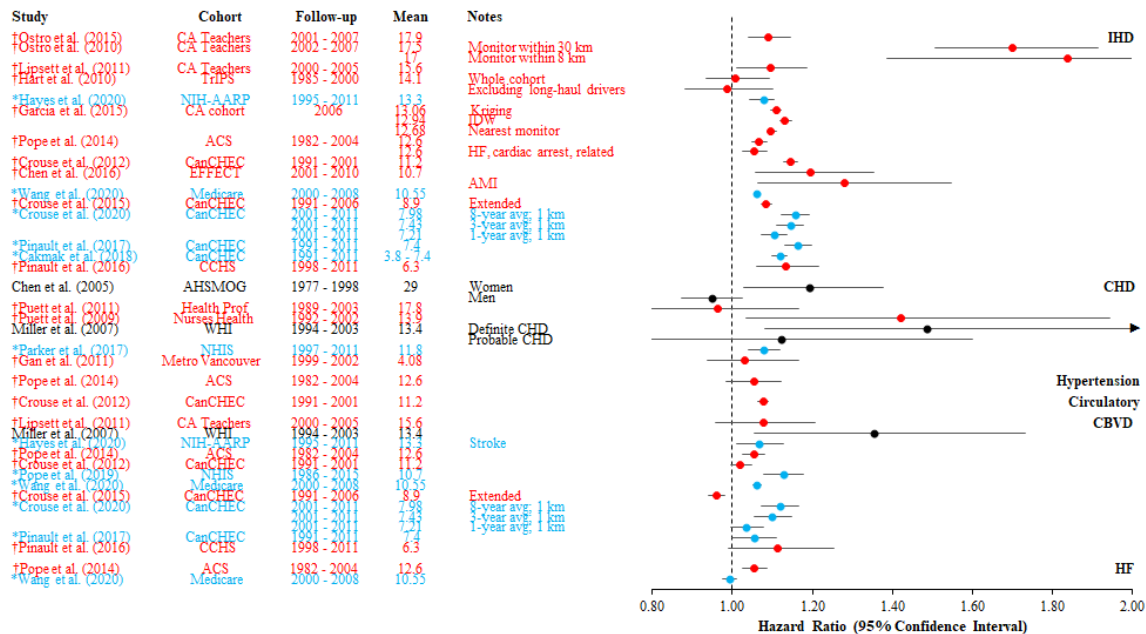
1 In a study of the NIH-AARP cohort, which consists of participants ranging from 50–71 years of
2 age, [Hayes et al. \(2020\)](#) examined not only the overall relationship between long-term PM_{2.5} exposure and
3 cardiovascular-related mortality, but whether associations changed over different ranges of PM_{2.5}
4 concentrations. In the main analysis, the authors applied a spatiotemporal model that predicted PM_{2.5}
5 concentrations at the census tract and reported a HR of 1.06 (95% CI: 1.03, 1.08) for all cardiovascular
6 mortality. This result was consistent with a sensitivity analysis that assigned exposure based on distance
7 to monitor from participant residence when focusing on monitors 0–25 km away (HR = 1.07 [95% CI:
8 1.03, 1.10]), with more variability and less precision for greater distances (i.e., 25–50 km and
9 50–100 km) due to the smaller sample size and the increased exposure error that can occur as distance to
10 monitor increases.

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

32 While there is evidence of consistent positive associations between long-term PM_{2.5} exposure and
33 cardiovascular mortality ([Figure 3-22](#)), it is plausible that comorbidities may increase the overall risk of
34 cardiovascular mortality. As a result, [Pinault et al. \(2018\)](#) examined both the CanCHEC and mCCHS
35 cohorts to assess whether the combination of cardiovascular disease and diabetes together yielded larger
36 PM_{2.5}-mortality risk estimates than cardiovascular disease alone. Within CanCHEC, the authors identified
37 all participants where in addition to having cardiovascular disease as the primary cause of death, there
38 was also mention of diabetes 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 to 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 ischemic heart disease (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-µg/m³ increase in pollutant concentration. 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 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.

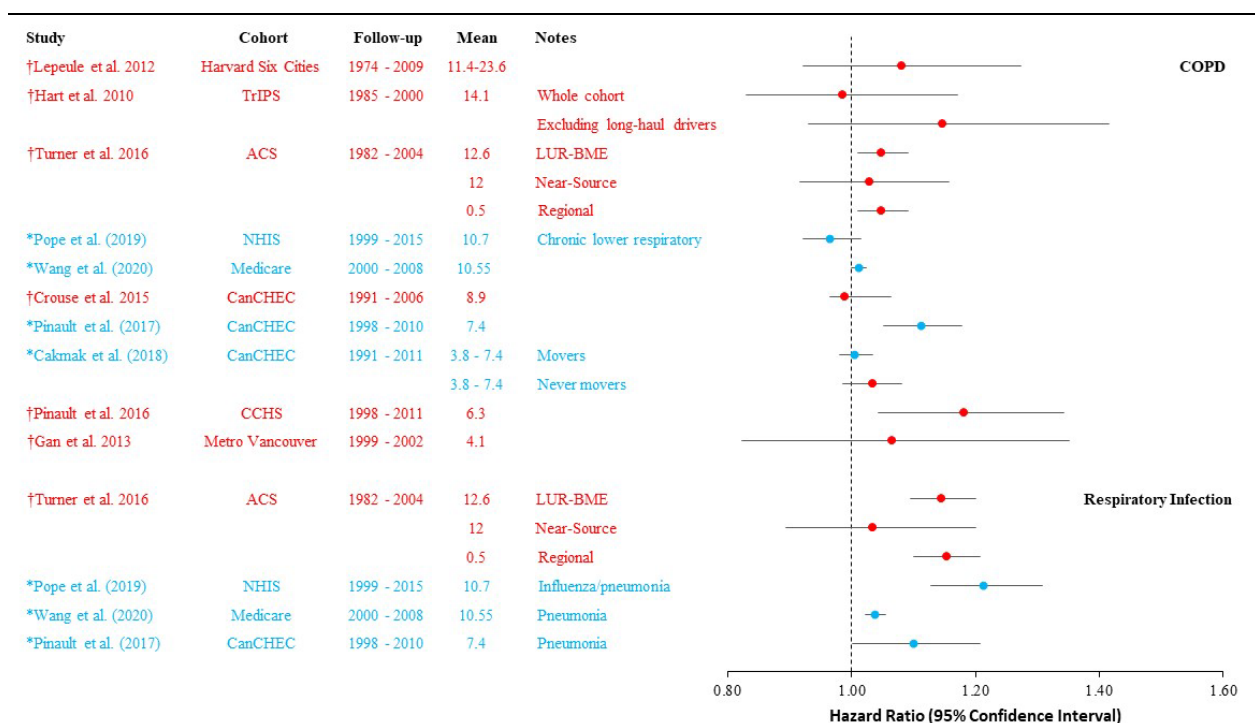
Few studies to date have examined associations between long-term PM_{2.5} exposure and cerebrovascular disease or stroke mortality, but studies by [Wang et al. \(2020\)](#), [Pinault et al. \(2017\)](#), [Crouse et al. \(2020\)](#), and [Hayes et al. \(2020\)](#) along with a study within the NHIS cohort 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 congestive heart failure (CHF) mortality, in a recent study of the Medicare cohort [Wang et al. \(2020\)](#) reported a null association. Lastly, 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 to [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 O₃, 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; $\mu\text{g}/\text{m}^3$ = micrograms per cubic meter; NHIS = National Health Interview Survey; $\text{PM}_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to $2.5 \mu\text{m}$; 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 $5\text{-}\mu\text{g}/\text{m}^3$ increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $\text{PM}_{2.5}$. 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 heart failure (HF) ([Ward-Caviness et al., 2020](#)) and previous myocardial infarction (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 km² ([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.

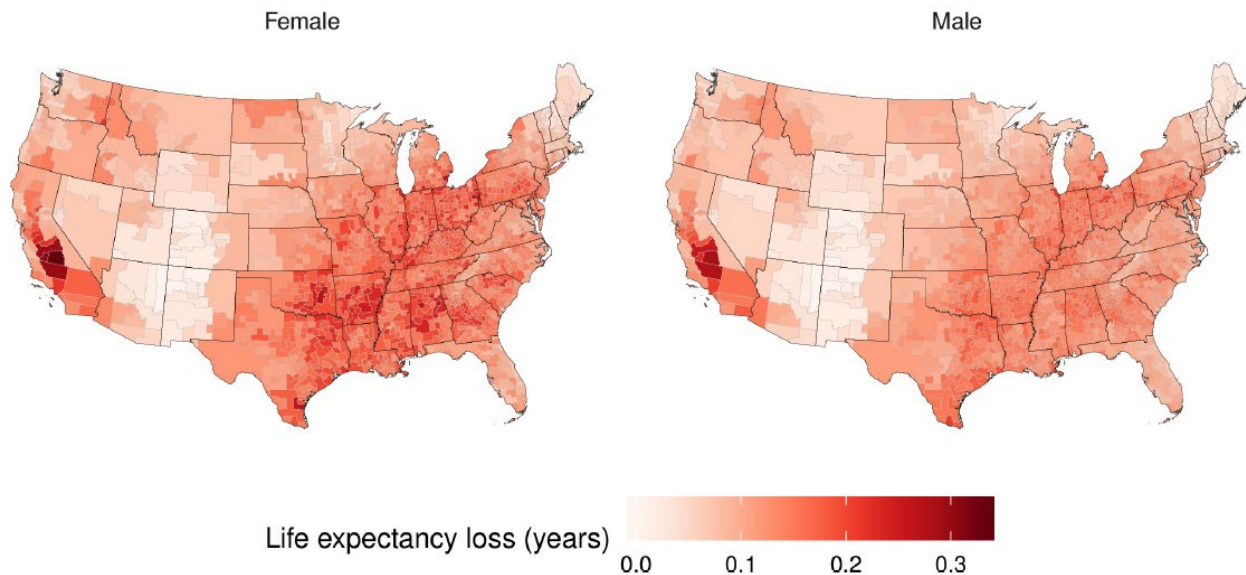
Whereas [Ward-Caviness et al. \(2020\)](#) examined the risk of mortality attributed to long-term PM_{2.5} exposure in the years following HF diagnosis over the entire study duration, [Malik et al. \(2019\)](#) focused on examining the 5-year survival for all-cause mortality following an MI event. A 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 Infarction: 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 µg/m³) 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 µg/m³ to participants living in areas with PM_{2.5} concentrations <12 µg/m³ 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: Copyright permission pending from [Bennett et al. \(2019\)](#).

Figure 3-25 Life expectancy losses by county for females and males as estimated by [Bennett et al. \(2019\)](#).

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

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 O₃ (Figure 11-20), NO₂, PM_{10-2.5}, SO₂, 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 remained relatively unchanged in copollutant models adjusted for NO₂, PM_{10-2.5}, SO₂, 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 SO₂, NO₂, O₃, 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 NO₂ in a copollutant model, [Wang et al. \(2020\)](#) regressed 12-month PM_{2.5} on NO₂ and used the residuals as the

1 exposure metric to estimate the PM_{2.5} association that is unrelated to traffic. The authors reported
2 associations similar in magnitude in both a single (HR = 1.03 [95% CI: 1.02, 1.03]) and copollutant
3 model with ozone (HR = 1.03 [95% CI: 1.02, 1.03]). Positive associations were also reported for the
4 non-traffic PM_{2.5} analyses, and although the association was smaller in magnitude to the total PM_{2.5}
5 analysis, this result provides evidence that the PM_{2.5}-mortality association persists independent of traffic
6 related-pollutants (HR = 1.01 [95% CI: 1.00, 1.01]).

7 A few studies within the MAPLE study also conducted analyses to assess potential copollutant
8 confounding by gaseous pollutants. Within CanCHEC, [Crouse et al. \(2020\)](#) assessed potential copollutant
9 confounding by ozone, NO₂, and oxidant gases in sensitivity analyses using both 3-year and 8-year
10 average PM_{2.5} concentrations at 1 km² resolution. Associations between PM_{2.5} and mortality were found
11 to be slightly attenuated but remained positive in copollutant models with each of the gaseous pollutants
12 when using either 3-year or 8-year average PM_{2.5} exposures.

13 While there was no evidence of copollutant confounding in the analysis of CanCHEC by [Crouse](#)
14 [et al. \(2020\)](#), there was some evidence in the pooled analysis of CanCHEC by [Pappin et al. \(2019\)](#). In the
15 single-pollutant analysis, the authors reported a HR of 1.03 (95% CI: 1.02, 1.03) in the fully adjusted
16 model, which is consistent with the copollutant model including NO₂ (HR = 1.02 [95% CI: 1.01, 1.03]).
17 However, there was no evidence of a PM_{2.5}-mortality association in copollutant models with ozone
18 (HR = 0.99 [95% CI: 0.98, 1.00]) and oxidants (HR = 0.98 [95% CI: 0.97, 0.98]). The ozone and oxidants
19 results of [Pappin et al. \(2019\)](#) are consistent with those of [Christidis et al. \(2019\)](#) within the mCCHS
20 cohort. However, [Christidis et al. \(2019\)](#) reported evidence of potential confounding by NO₂. In a
21 single-pollutant analysis, the authors reported a HR of 1.05 (95% CI: 1.02, 1.09). In copollutant models,
22 PM_{2.5}-mortality associations are null in models with ozone (HR = 1.00 [95% CI: 1.00, 1.01]) and oxidants
23 (HR = 1.00 [95% CI: 0.99, 1.01]), and attenuated in a model with NO₂ (HR = 1.01 [95% CI: 1.00, 1.02]).

24 [Zhang et al. \(2021\)](#) also conducted copollutant analyses when examining associations between
25 long-term PM_{2.5} exposure and mortality in the Ontario Health Study. The authors reported that the
26 PM_{2.5}-mortality association in a single-pollutant model (HR = 1.20 [95% CI: 1.09, 1.32]) is relatively
27 unchanged in a model with NO₂ (HR = 1.18 [95% CI: 1.08, 1.30]), which is consistent with [Lefler et al.](#)
28 [\(2019\)](#) in the NHIS cohort and [Pappin et al. \(2019\)](#) within CanCHEC. However, it is inconsistent with the
29 results from the mCCHS cohort where [Christidis et al. \(2019\)](#) reported evidence of attenuation of the
30 PM_{2.5}-mortality association.

31 While there is some evidence from recent studies that PM_{2.5}-mortality associations remain
32 relatively unchanged in copollutant models, there are some differences in results across studies,
33 particularly for copollutant analyses including ozone. This difference in results is most evident between
34 MAPLE studies and other studies that previously examined copollutant confounding by ozone as
35 summarized in Figure 11-20 of the 2019 PM ISA. This difference between studies could be attributed to
36 the MAPLE studies using different spatial resolutions in estimating air pollutant concentrations, 1 km² for
37 PM_{2.5} and 21 km² for ozone, potentially resulting in some degree of exposure error.

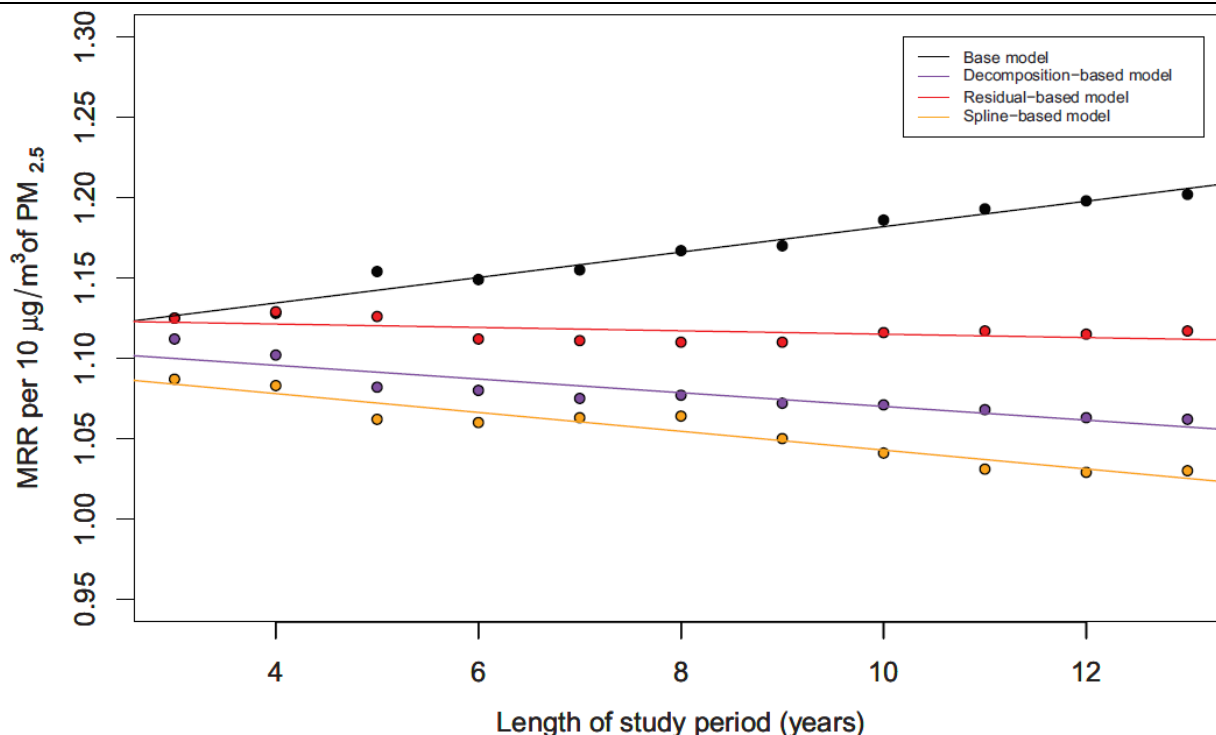
As discussed in Section 11.2.2.4 of the 2019 PM ISA, some recent studies used statistical techniques to reduce uncertainties related to potential confounding that can further inform the relationship between long-term PM_{2.5} exposure and mortality. An initial study conducted by [Janes et al. \(2007\)](#) 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 2000–2006. 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, analogous to what was done 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 uninterpretable 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 2000–2012. 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

1 there was evidence of unmeasured confounding. Consistent with the previous studies larger associations
2 were reported for the “temporal” compared to the “spatiotemporal” component, with results being
3 positive for both components. As a result of the magnitude of associations between these two components
4 being different, [Eum et al. \(2018\)](#) attempted to assess whether temporal confounding of the
5 PM_{2.5}-mortality relationship could explain the observed difference in results. The authors developed a
6 base model which used data for the entire 13 year period and shorter periods ranging from 3 to 12 years
7 (e.g., 2001–2012, 2009–2012, etc.) as well as three additional models: (1) residual-base model: calculated
8 the residuals of a linear regression of PM_{2.5} on time in 4-year intervals (i.e., 2000–2004, 2005–2008, and
9 2009–2012), where the residuals were then used as the exposure in the base model; (2) spline-based
10 model: added a penalized spline with two knots per year to the base model; and (3) decomposition-based
11 model: added the temporal component of decomposed PM_{2.5} to the base model based on the approach
12 described in [Greven et al. \(2011\)](#). In analyses of the base model, the authors observed that as the years of
13 data included in the analysis increased so did the magnitude of the mortality risk ratio (MRR) ([Figure](#)
14 [3-26](#)). Contrary to the base model, as depicted in [Figure 3-26](#), there was a steady decline in the MRR for
15 both the spline-based and decomposition-based models while MRRs remained relatively stable using the
16 residual-based model. These results provide some evidence indicating that long-term temporal trends in
17 PM_{2.5} concentrations may be one source of unmeasured confounding to consider in long-term exposure
18 studies lasting many years, and that a residual-based approach could potentially account for those trends.

19 The results of [Eum et al. \(2018\)](#) are consistent with a confounder analysis of temporal trends
20 conducted by [Wu et al. \(2020a\)](#), originally discussed in [Section 3.1.2.2.1](#). In the main analysis, the
21 authors controlled for temporal trends by adjusting for calendar year and also included meteorological
22 variables to account for season (i.e., summer and winter), maximum daily temperature, and relative
23 humidity. In Cox and Poisson models that did not adjust for calendar year, HRs increased in analyses of
24 both the entire cohort (Cox, main analysis, HR = 1.03 [95% CI: 1.03, 1.04]; Cox, minus calendar year,
25 HR = 1.08 [95% CI: 1.08, 1.09]) and those limited to individuals living in locations where PM_{2.5}
26 concentrations were $\leq 12 \mu\text{g}/\text{m}^3$ for the entire study duration (main analysis, HR = 1.17 [95% CI: 1.16,
27 1.18]; minus calendar year, HR = 1.25 [95% CI: 1.24, 1.27]), indicating that not accounting for temporal
28 trends may overestimate associations. In addition, in analyses that excluded meteorological variables,
29 HRs were relatively unchanged compared to the main analysis (Cox, HR = 1.03 [95% CI: 1.02, 1.03]),
30 indicating they are not a source of residual confounding in long-term exposure studies.



Source: Copyright permission pending, [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

1 using the mCCHS cohort as the ancillary data set that contained information, missing in CanCHEC, on
2 cigarettes/day, alcohol use, fruit and vegetable intake, and leisure exercise.

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

27 In the internal and external validations, which focused on the educational and income variables,
28 in analyses of non-accidental, cardiovascular, IHD, and lung cancer mortality, the authors reported an
29 overall reduction (i.e., bias) in the HRs compared to the “True Model” when indirectly adjusting for the
30 covariates. There was a 3–5.6% bias across mortality outcomes for the “Partial Model,” which did not
31 control for either covariate, which was reduced to 1.7–2.9 and 1.3–2.3% in the internal and external
32 validation analyses, respectively. The results of the validation analyses were further confirmed in the
33 main analysis using the mCCHS cohort as the ancillary data set, where there was an approximately 1.5%
34 increase in the HR when indirectly adjusting for missing covariates in the CanCHEC cohort.
35 Additionally, the results using the ancillary data set within the CanCHEC cohort for nonaccidental,
36 cardiovascular, and IHD mortality were consistent in magnitude to those reported in mCCHS.

1 The methods detailed by [Erickson et al. \(2019\)](#) provide an approach to address the issue of
2 unmeasured confounders, but this method is limited by the availability of an ancillary data set. In
3 addition, the direction and magnitude of the bias is dependent upon the direction and magnitude of the
4 correlation between air pollution and the missing covariates within the population of interest. However,
5 the direction of the bias can vary when using this confounder adjustment approach, with an
6 underestimation of the HR observed when using a time-varying exposure and an overestimation observed
7 when using a static exposure when compared to the “True Model.” Overall, the results of [Erickson et al.
8 \(2019\)](#) indicate that the lack of data for some covariates leads to an underestimation, not an
9 overestimation, of the PM_{2.5}-mortality association.

10 In conclusion, recent studies that further evaluate the potential implications of unmeasured
11 confounders on the association between long-term PM_{2.5} exposure and mortality indicate that bias can
12 occur in either direction. However, across the studies evaluated, the control for unmeasured confounders
13 as detailed in [Eum et al. \(2018\)](#), [Wu et al. \(2020a\)](#), and [Erickson et al. \(2019\)](#) do not result in the
14 elimination of the association, but instead provide additional confirmation that an association between
15 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

16 An important consideration in characterizing the association between long-term PM_{2.5} exposure
17 and mortality is whether the concentration-response (C-R) relationship is linear across the full
18 concentration range that is encountered, or if there are concentration ranges where there are departures
19 from linearity. The 2009 PM ISA characterized the results of an analysis by [Schwartz et al. \(2008\)](#) that
20 demonstrated that the shape of the C-R curve was generally linear. A substantially larger number of
21 studies was evaluated in the 2019 PM ISA, which provided strong evidence for a linear, no-threshold
22 concentration-response relationship for long-term PM_{2.5} exposure and total (nonaccidental) mortality
23 [[U.S. EPA \(2019\)](#); Section 11.2.4]. Evidence presented in the 2019 PM ISA demonstrated less certainty
24 in the shape of the C-R curve at mean annual PM_{2.5} concentrations generally below 8 µg/m³, though some
25 studies characterized the C-R relationship with certainty down to 4 µg/m³.

26 A number of recent studies conducted analyses that further inform the shape of the C-R
27 relationship for the association between long-term PM_{2.5} exposure and mortality and are summarized in
28 [Table 3-6](#). Generally, the results of these analyses continue to support a linear, no-threshold relationship
29 for total (nonaccidental) mortality, though there is some evidence for a sublinear ([Zhang et al., 2021](#);
30 [Pope et al., 2019](#)) or supralinear ([Christidis et al., 2019](#); [Pappin et al., 2019](#); [Pinault et al., 2017](#))
31 relationship at lower ambient PM_{2.5} concentrations. Many of the recent studies that conducted C-R
32 analyses include concentration ranges that extend below the level of the current annual PM_{2.5} NAAQS.

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 µg/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 7.37 (0.37–20.0)	C-R: Shape Constrained Health Impact Function (SCHIF) fits a class of flexible, but monotonically nondecreasing functions to select best fitting model Supralinear at lower concentrations (<5 µg/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, 3 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 shape constrained health impact function (SCHIF) to the MISS predictions Supralinear at lower concentrations (<5 µg/m ³)
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: Shape Constrained Health Impact Function (SCHIF) fits a class of flexible, but monotonically nondecreasing functions to select best fitting model (counterfactual is 0 µg/m ³); cutpoint analyses: 0–5, 5–10, >10 µg/m ³ Supralinear at lower concentrations (<5 µg/m ³); HRs remained positive and statistically significant in the 2 lowest cutpoint categories with highest HRs for the 0–5 µg/m ³ category, consistent with the supralinear C-R function

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 µg/m ³	Statistical Analysis
		Summary
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 µg/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 µg/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 µg/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 µg/m ³); C-R: limited to PM _{2.5} concentration within inner 95% of distribution (8–14 µg/m ³) HRs remained positive and statistically significant when only participants with exposure concentrations below 12 µg/m ³ were included; linear C-R curve, with greatest certainty between 9 and 13 µg/m ³
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 µg/m ³) HRs remained positive and statistically significant when only participants with exposure concentrations below 12 µg/m ³ were included

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.

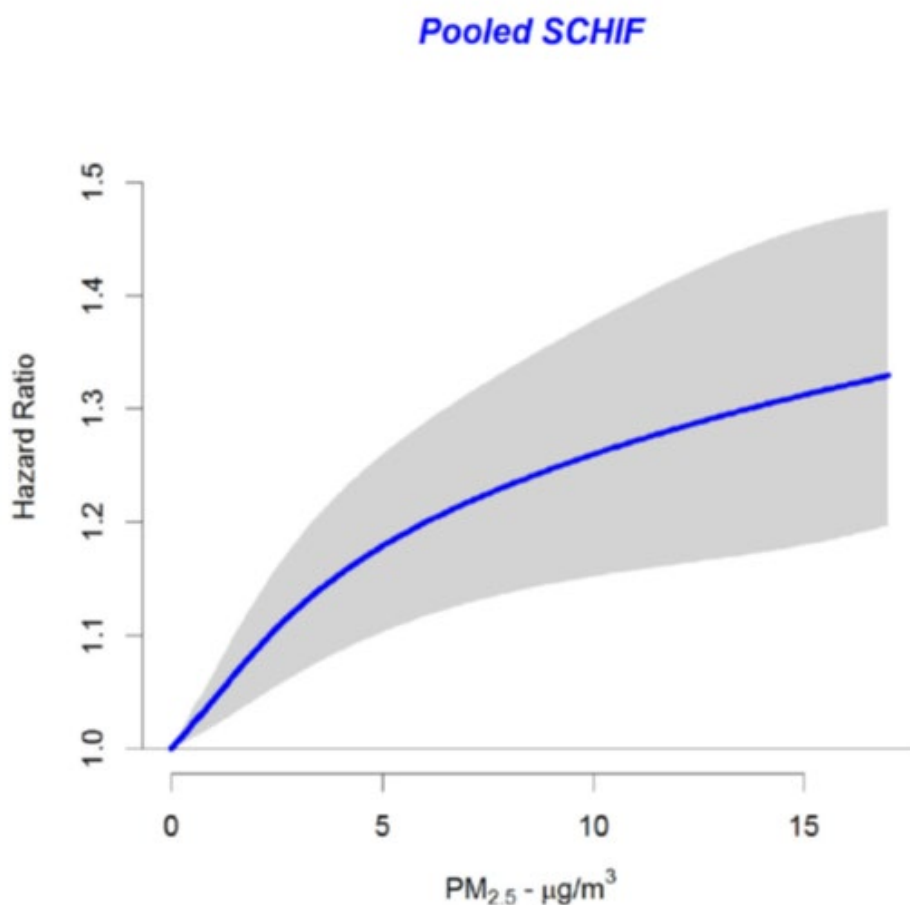
Study Location—Cohort Table/Figure from Reference	Exposure; PM _{2.5} Mean; Range in µg/m ³	Statistical Analysis
		Summary
Zhang et al. (2021) Ontario Health Study (Figure 2; Tables S3, S8)	PM _{2.5} estimates at 1 km ² over 3-yr average (5-yr/1-km model) with single-yr lag assigned to postal code of residence 7.8 (NR)	C-R: Shape Constrained Health Impact Function (SCHIF) fits a class of flexible, but monotonically nondecreasing functions to select best fitting model; threshold model (PM _{2.5} <10 and <8.8 µg/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 µg/m ³ were included. Results were positive but attenuated and no longer statistically significant below 8.8 µg/m ³ ; categorical exposure results demonstrate sublinear relationship, similar to C-R function with strongest association for concentrations >8.5 µg/m ³

CanCHEC = Canadian Census Health and Environment Cohort; HF = heart failure; HR = hazard ratio; km = kilometer; mCCHS = mortality Canadian Community Health Survey; 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 µg/m³, 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 Shape Constrained Health Impact Function (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/m³) (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/m³. Analyses of exposure categories (i.e., quartiles) by [Zhang et al. \(2021\)](#) provides additional support for a sublinear concentration-response

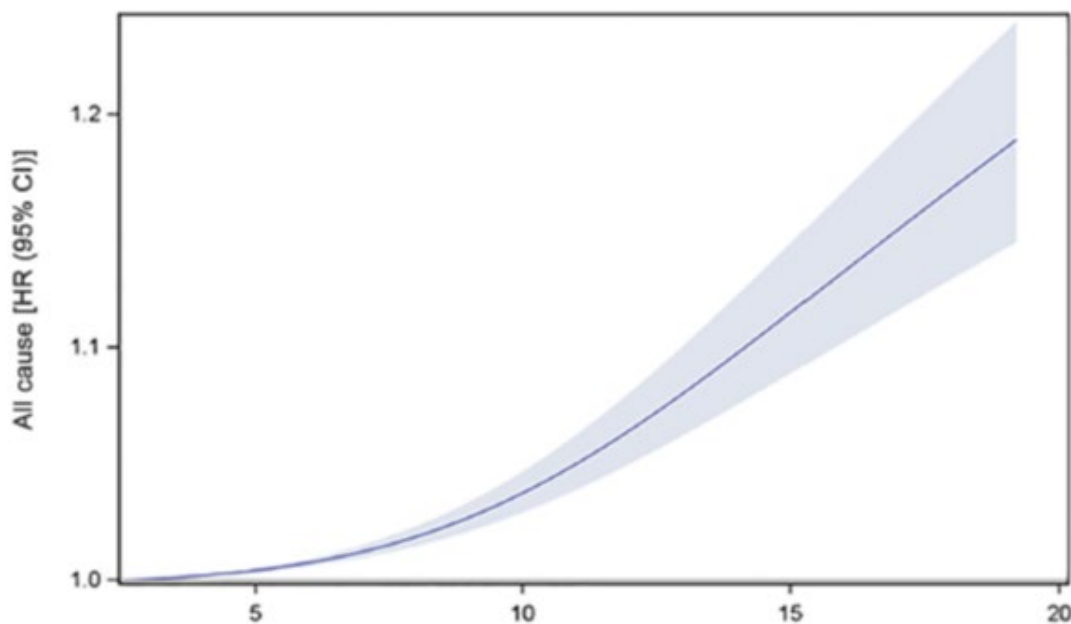
1 relationship. A similar sublinear relationship was reported by [Pope et al. \(2019\)](#) for a U.S. cohort ([Figure](#)
2 [3-28](#)).



Source: Copyright permission pending from [Pappin et al. \(2019\)](#).

Note: Uncertainty bounds are displayed as gray shaded area.

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



Source: Copyright permission pending from [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/m³, with the highest HRs for the 0–5 µg/m³ 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/m³. 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/m³. [Zhang et al. \(2021\)](#) noted that HRs remained positive and statistically significant when only participants with exposure concentrations below 10 µg/m³ were included, though the results were positive, but attenuated, and no longer statistically significant when restricting to exposure concentrations below 8.8 µg/m³.

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 $\mu\text{g}/\text{m}^3$. 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 $\mu\text{g}/\text{m}^3$. In analyses stratified by $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ concentrations examined increased from 8–12, to 12–20, and finally to over 20 $\mu\text{g}/\text{m}^3$. When evaluating deaths due to diabetes, [Lim et al. \(2018\)](#) observed a linear C-R relationship, with the greatest confidence between 10 and 15 $\mu\text{g}/\text{m}^3$. Overall, recent studies that evaluated the C-R relationship for long-term $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\mu\text{g}/\text{m}^3$. The evidence remains consistent in supporting a no-threshold relationship, and in supporting a linear relationship for $\text{PM}_{2.5}$ concentrations $>8 \mu\text{g}/\text{m}^3$. However, some uncertainties remain about the shape of the C-R curve at relatively low $\text{PM}_{2.5}$ concentrations ($<8 \mu\text{g}/\text{m}^3$), with some recent studies providing evidence for either a sublinear, linear, or supralinear relationship at these lower concentrations.

3.2.2.3 Recent Studies Examining the $\text{PM}_{2.5}$ -Mortality Relationship through Accountability Analyses and Causal Modeling Methods

Within the 2019 PM ISA, a few studies were evaluated that conducted analyses that further informed the relationship between long-term $\text{PM}_{2.5}$ exposure and mortality through the use of causal modeling methods (2019 PM ISA, Section 11.2.2.4). These initial studies provided additional support for a causal relationship between long-term $\text{PM}_{2.5}$ 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 causal modeling methods that have the ability to reduce uncertainties related to confounding bias in the examination of the relationship between long-term $\text{PM}_{2.5}$ 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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wei et al. (2020)	Generalized Propensity Score (GPS): estimates the conditional probability of an individual being exposed to the observed concentration level, accounting for all measured potential confounders	35.4 (95% CI: 33.4, 37.6) excess deaths per 10 million person-days for each 1 µg/m ³ increase in annual PM _{2.5} concentrations
Massachusetts	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.	
Medicare		
2000–2012		

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied causal modeling statistical methods in examining long-term PM_{2.5} exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wei et al. (2021b)	Three GPS approaches were used:	Linear Probability Model and Weighted Least Squares:
Massachusetts	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.	1053 (95% CI: 984, 1,122) annual early deaths for a 1 µg/m ³ increase in annual PM _{2.5} concentrations
Medicare		
2000–2012	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.	Moon RF: 1,058 (95% CI: 988, 1,127) annual early deaths for a 1 µg/m ³ increase in annual PM _{2.5} concentrations
	Moon RF: 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.	

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied causal modeling statistical methods in examining long-term PM_{2.5} exposure and mortality.

Study/Location/Population (Cohort)/Years	Statistical Method	Results
Wu et al. (2020a)	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.	For a 10 µg/m ³ decrease in annual PM _{2.5} concentrations GPS matching: HR = 1.068 (95% CI: 1.054, 1.083)
U.S.		
Medicare	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: HR = 1.076 (95% CI: 1.065, 1.088)
2000–2016	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: HR = 1.072 (95% CI: 1.061, 1.082)
	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.	

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied causal modeling statistical methods 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	<p>GPS: Regression calibration-GPS (RC-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.</p> <p>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:</p> <p>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.</p> <p>Inverse Probability of Treatment Weighting (IPTW) GPS: weights each individual by the inverse of their GPS.</p> <p>GPS matching: involves matching individuals who receive one category of exposure to individuals who received another category of exposure based on the estimated GPS.</p> <p>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 incidence rate ratio (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).</p>	<p>Subclassification GPS: IRR = 1.03 (95% CI: 1.01, 1.05)</p> <p>IPTW GPS: IRR = 1.02 (95% CI: 1.01, 1.04)</p> <p>Matching GPS: IRR = 1.03 (95% CI: 1.01, 1.05)</p>

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied causal modeling statistical methods 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) 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 causal modeling statistical methods 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 2000–2005 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 causal modeling statistical methods 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 mortality 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 µg/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 impact of coal plant retirements on PM _{2.5} and mortality among populations older than 65.	<p>IV: a 1-µg/m³ 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</p> <p>DID: power plant retirement decreased both monthly PM_{2.5} concentrations by 2.1 µg/m³, and the monthly age-adjusted mortality by approximately 15 people per 100,000 people (or 3.6%) in treated counties, relative to control counties</p>

Table 3-7 (Continued): Description of methods from epidemiologic studies that applied causal modeling statistical methods 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 was 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 non-linear time trend using a natural spline 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 causal modeling statistical methods 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} . Secondly, 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 mortality 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 mortality rates.	3.88 (95% CI: 3.56, 4.21) fewer deaths per 100,000 persons for each 1-µg/m ³ reduction in annual PM _{2.5} concentrations

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.

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

8 [Wei et al. \(2020\)](#) evaluated the association of long-term PM_{2.5} concentrations and all-cause
9 mortality among Medicare beneficiaries residing in Massachusetts during 2000–2012 using a GPS
10 approach. The authors define long-term exposure as a 1-year moving average of the PM_{2.5} concentration.
11 [Wei et al. \(2020\)](#) reported that each 1 µg/m³ increase in long-term PM_{2.5} concentrations was associated
12 with 35.4 (95% CI: 33.4, 37.6) excess deaths per 10 million person-days. When the analysis was
13 restricted to different low-level concentrations, the number of excess deaths associated with a 1 µg/m³
14 increase in annual PM_{2.5} concentrations increased to 35.5 per 10 million person-days (95% CI: 33.4, 37.7)
15 when restricting to PM_{2.5} concentrations ≤14 µg/m³ and to 60.7 per 10 million person-days (95% CI: 47.9,
16 73.9) when restricting to PM_{2.5} concentrations ≤7 µg/m³.

17 Whereas [Wei et al. \(2020\)](#) focused on a single GPS approach, [Wei et al. \(2021b\)](#) presented three
18 GPS-based approaches in examining long-term PM_{2.5} concentrations and mortality including a linear
19 probability model, weighted least squares, and m-out-of-n random forests (moonRF), for assessing the
20 effect of long-term PM_{2.5} exposures on mortality rates among Medicare beneficiaries residing in
21 Massachusetts between 2000 and 2012. The moonRF method is based on the random forest method,
22 which is a non-parametric machine learning approach of classification for possible non-linear
23 relationships and interactions through building individual decision trees through resampling. To reduce
24 the computational burden of the linear probability model GPS approach, weighted least squares and
25 moonRF GPS approaches were proposed as alternatives. [Wei et al. \(2021b\)](#) showed that the linear
26 probability model and the weighted least squares model produced nearly identical results. The annual
27 number of early deaths associated with 1 µg/m³ increase in annual PM_{2.5} concentrations was 1,053 (95%
28 CI: 984, 1,122) using linear probability model and weighted least squares approaches and was 1,058 (95%
29 CI: 988, 1,127) using moonRF. When restricting the analysis to annual PM_{2.5} concentrations below
30 <12 µg/m³, 1,203 (95% CI: 1,126, 1,280) annual early deaths were associated with a 1 µg/m³ increase in
31 annual PM_{2.5} concentrations when using both the linear probability model and weighted least squares
32 approaches with a slightly higher number of early deaths with the moonRF approach (1,214 [95% CI:
33 1,137, 1,292]).

34 Similar to [Wei et al. \(2021b\)](#), [Wu et al. \(2020a\)](#) also assessed the association between long-term
35 PM_{2.5} concentrations and mortality among Medicare beneficiaries between 2000 and 2016 using multiple
36 GPS approaches including: (1) matching by GPS; (2) weighting by GPS; and (3) adjustment by GPS,
37 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 $\mu\text{g}/\text{m}^3$ decrease in annual $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ concentrations were lower than 12 $\mu\text{g}/\text{m}^3$: 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ concentrations ($8 < \text{PM}_{2.5} \leq 10 \mu\text{g}/\text{m}^3$) to low concentration ($\text{PM}_{2.5} \leq 8 \mu\text{g}/\text{m}^3$). When comparing high levels of $\text{PM}_{2.5}$ concentrations ($\text{PM}_{2.5} > 10 \mu\text{g}/\text{m}^3$) to low concentrations ($\text{PM}_{2.5} \leq 8 \mu\text{g}/\text{m}^3$), 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 causal modeling methods 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 $\text{PM}_{2.5}$ on mortality among Medicare beneficiaries, while controlling for similar confounders ([Table A-8](#)). [Schwartz et al. \(2018b\)](#) estimated the marginal effect of annual $\text{PM}_{2.5}$ concentrations on the distribution of life expectancy among Medicare beneficiaries residing in the Northeastern and Mid-Atlantic region of the U.S. between 2000–2013 by applying an IPW survival model. The estimated mean age at death for a population with an annual average $\text{PM}_{2.5}$ concentration of

1 12 $\mu\text{g}/\text{m}^3$ was 0.89 (95% CI: 0.88, 0.91) years less than estimated for a counterfactual $\text{PM}_{2.5}$
2 concentrations of 7.5 $\mu\text{g}/\text{m}^3$. [Schwartz et al. \(2018b\)](#) estimated that 23.5% of the Medicare population
3 would die before 76 years of age if they were exposed to an annual $\text{PM}_{2.5}$ concentration of 12 $\mu\text{g}/\text{m}^3$
4 compared with 20.1% if the Medicare population was exposed to an annual average $\text{PM}_{2.5}$ concentration
5 of 7.5 $\mu\text{g}/\text{m}^3$. Furthermore, the authors estimated that 40.8% of Medicare recipients would live past
6 85 years of age if exposed to an annual $\text{PM}_{2.5}$ concentration of 12- $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ compared with 44.5% at
7 7.5- $\mu\text{g}/\text{m}^3$.

8 [Awad et al. \(2019\)](#) estimated the effect of a change in annual $\text{PM}_{2.5}$ concentrations due to moving
9 on the risk of mortality among Medicare beneficiaries from 2000 to 2012 in the U.S. from Cox
10 proportional hazards using an IPW approach to control for potential confounding ([Table A-8](#)). The Cox
11 proportional model estimated the effect of change in $\text{PM}_{2.5}$ concentrations on the risk of all-cause
12 mortality, stratified by ZIP code before moving, with the IPW to account for confounding after moving
13 and follow-up time. [Awad et al. \(2019\)](#) estimated a HR of 1.21 (95% CI: 1.20, 1.22) among White
14 individuals and 1.12 (95% CI: 1.08, 1.15) among Black individuals for a 10 $\mu\text{g}/\text{m}^3$ increase in annual
15 $\text{PM}_{2.5}$ concentrations for all-cause mortality. When restricting the analysis to movers with $\text{PM}_{2.5}$
16 concentration $\leq 12 \mu\text{g}/\text{m}^3$, the hazard ratio was 1.25 (95% CI: 1.24, 1.27) for White individuals and 1.08
17 (95% CI: 1.01, 1.14) for Black individuals for all-cause mortality.

18 [Wei et al. \(2021a\)](#) used an IPW approach to emulate a dose-response between $\text{PM}_{2.5}$ and all-cause
19 mortality from Medicare beneficiaries between 2000–2016. This newer IPW approach used a decile
20 binning, which divided $\text{PM}_{2.5}$ concentrations into ten equally sized deciles and predicted the inverse
21 probability of being assigned to the observed group for each observation, adjusting for copollutants
22 (i.e., ozone and NO_2) and other covariates ([Table A-8](#)). The lowest decile group is treated as the reference
23 with effects estimated for the other decile groups compared to the reference. The relative risk of all-cause
24 mortality associated with long-term exposure to $\text{PM}_{2.5}$ ranged from 1.02 (95% CI: 1.02, 1.03) at
25 6.60 $\mu\text{g}/\text{m}^3$ (2nd decile group) to 1.21 (95% CI: 1.20, 1.21) at 15.47 $\mu\text{g}/\text{m}^3$ (10th decile group). Assuming
26 that the IPW models were correctly specified and the counterfactual framework is valid, the
27 dose-response curves demonstrated that in general, higher concentrations of $\text{PM}_{2.5}$ are associated with a
28 greater risk of all-cause mortality ([Wei et al., 2021a](#)). While the previous studies all used the IPW
29 approach in analyses of Medicare beneficiaries, [Higbee et al. \(2020\)](#) examined the association between
30 long-term exposure to $\text{PM}_{2.5}$ and all-cause and cardiopulmonary mortality from the National Health
31 Interview Survey from 1986 to 2015. Within this study the authors applied a series of Cox proportional
32 hazards models, adjusted using IPW. The hazard ratio for all-cause mortality was 1.12 (95% CI: 1.08,
33 1.15) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration and for cardiopulmonary mortality, it was 1.23 (95%
34 CI: 1.17, 1.29) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration.

35 In addition to GPS and IPW, additional epidemiologic studies used a difference-in-difference
36 (DID) approach to control for unmeasured confounders. In this method, the mean exposure is calculated
37 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 µg/m³ 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 µg/m³ 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 2000–2013 ([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 µg/m³ (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 2005–2012 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 µg/m³ reduction in annual PM_{2.5} concentrations during the time period. [Fan and Wang \(2020\)](#) also used Medicare data from 1999–2013 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-µg/m³ 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

1 decreased both monthly PM_{2.5} concentrations by 2.1 µg/m³, and the monthly age-adjusted mortality by
2 approximately 15 people per 100,000 people (or 3.6%) in treated counties, relative to control counties,
3 based on the DID approach.

4 [Yitshak-Sade et al. \(2019b\)](#) and [Schwartz et al. \(2021\)](#) also used DID approaches to evaluate the
5 changes in long-term exposure to PM_{2.5} over time on mortality rates among Medicare beneficiaries.
6 [Yitshak-Sade et al. \(2019b\)](#) applied a DID approach to the Medicare population of the Northeastern and
7 mid-Atlantic states to incorporate individual covariates and assess the effect of annual PM_{2.5}
8 concentrations on all-cause mortality rates from 2000 to 2013 ([Table A-8](#)). For an IQR (3 µg/m³) increase
9 in annual PM_{2.5} concentrations, the authors reported a 4.04% (95% CI: 3.49, 4.59) increase in mortality
10 rates. In a sensitivity analysis, the mortality effect was modified by eligibility to Medicaid insurance and
11 race, with larger associations among people who are eligible to receive Medicaid services (5.99% [95%
12 CI: 4.38, 7.62] and among Black individuals (10.10% [95% CI: 8.56, 11.67]. Whereas [Yitshak-Sade et al.](#)
13 [\(2019b\)](#) applied DID to a portion of Medicare beneficiaries, [Schwartz et al. \(2021\)](#) applied two DID
14 approaches to assess whether changes in PM_{2.5} are associated with changes in mortality rates nationally
15 among Medicare participants between 2000 and 2016 ([Table A-8](#)). The authors reported that the
16 probability of dying in each year increased by 3.85×10^{-4} (95% CI: 1.95×10^{-4} , 5.76×10^{-4}) for each
17 1 µg/m³ increase in PM_{2.5} in that year. When the analysis was restricted to those beneficiaries residing in
18 locations where PM_{2.5} concentrations are below 12 µg/m³ during the follow-up period, the probability of
19 dying in each year increased to 4.26×10^{-4} (95% CI 1.43×10^{-4} , 7.09×10^{-4}) for 1 µg/m³ increase in
20 annual PM_{2.5} concentrations.

21 Lastly, [Peterson et al. \(2020\)](#) conducted an accountability analysis to examine which portion of
22 the observed declining trend in cardiovascular mortality from the National Center for Health Statistics
23 between 1990 and 2010 was associated with changes in ambient PM_{2.5}. To determine the portion of the
24 temporal change in cardiovascular mortality attributable to the temporal change in the ambient
25 concentration of PM_{2.5}, [Peterson et al. \(2020\)](#) fit linear models, and adjusted for time-variant covariates
26 (age-standardized annual COPD mortality rates) and time-invariant covariates (median household
27 income, percent of non-White population, and population). On average, each 1-µg/m³ reduction in annual
28 PM_{2.5} concentrations was associated with 3.88 (95% CI: 3.56, 4.21) fewer deaths per 100,000 persons.
29 When combined with the annual decline in PM_{2.5} concentrations, the PM_{2.5}-trend accounted for 0.52 (95%
30 CI: 0.48, 0.57) fewer deaths per 100,000 persons each year, for a total change of 10.44 (95% CI: 9.56,
31 11.32) fewer deaths per 100,000 persons over the entire study period.

32 Overall, recent epidemiologic studies employed a variety of causal modeling methods such as
33 GPS, IPW, and DID and reported consistent results among large study populations across the U.S. These
34 causal modeling methods in combination with accountability analyses further informs the relationship
35 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.

1 Lastly, a number of recent studies employed causal modeling methods or conducted
2 accountability analyses in the process of examining the relationship between long-term PM_{2.5} exposure
3 and mortality. These studies which used different statistical approaches in a causal modeling framework
4 in combination with accountability analyses that examined the impact of policies or interventions on
5 PM_{2.5} concentrations and mortality, collectively provide additional support for the consistent positive
6 associations between long-term PM_{2.5} exposure and mortality reported in cohort studies spanning diverse
7 geographic locations and populations.

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

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

3.3.1 Recent Experimental Studies at Near-Ambient Concentrations

16 Few controlled human exposure studies have investigated the effects of exposure to near ambient
17 concentrations of PM_{2.5}, i.e., at or below the 24-hour NAAQS PM_{2.5} standard of 35 ug/m³. As discussed in
18 Sections 6.1.10, 6.1.11, and 6.1.13 of the 2019 PM ISA, one such study was conducted in Copenhagen
19 ([Hemmingsen et al., 2015b](#); [Hemmingsen et al., 2015a](#)). In this study, older (55–83 years) overweight
20 study participants (n = 60) were exposed for 5 hours to urban street air or filtered urban street air while at
21 rest. The average PM_{2.5} concentration was 24 ug/m³. The study was a randomized, repeated measures,
22 single blinded cross-over study. One arm of the study reported decreased vasomotor function immediately
23 (within 1 hour) after exposure. The decrease in nitroglycerin-mediated vasodilation was statistically
24 significant, while the decrease in reactive hyperemia-induced vasodilation was not. These two responses
25 represent endothelium-independent and endothelium-dependent mechanisms, respectively. No changes in
26 blood biomarkers of oxidative stress or inflammation were observed. Similarly, blood pressure, blood
27 lipids, and metabolic biomarkers were unaffected by exposure. However, decreases in heart rate
28 variability (HRV) were observed in participants exposed to nonfiltered street air, with a statistically
29 significant reduction in the high frequency domain and a statistically significant increase in the low
30 frequency domain. In the other arm of the study, no oxidative stress or DNA damage was found in
31 peripheral blood monocytes of participants exposed to unfiltered street air.

1 A recent study conducted at near ambient PM_{2.5} concentrations by [Wyatt et al. \(2020a\)](#) adds to
2 this limited evidence base of controlled human exposure studies conducted at near ambient
3 concentrations. This study was a randomized double-blind crossover study in healthy young participants
4 (18–35 years, n = 21) who were subject to intermittent moderate exercise. Study participants were
5 exposed for 4 hours to clean air or to an average concentration of 37.8 ug/m³ PM_{2.5} CAPs in Chapel Hill,
6 NC. Ventilation rate was monitored, and workload adjusted so that participants achieved a ventilation rate
7 of 20 L/min/m² body surface area. Thus, dose was approximately the same among participants. Changes
8 in lung function were observed in PM_{2.5} exposed participants, including a statistically significant decrease
9 in FEV1/FVC of 1.2% at 1-hour postexposure that returned to baseline by 20 hours postexposure.
10 Decreases in PEF (1.8%) and FEV1 (0.8%) were also observed 1-hour postexposure, but they did not
11 achieve statistical significance. Markers of the acute phase response—serum amyloid A and C reactive
12 protein—were increased at both 1 and 20 hours postexposure. Serum amyloid A was increased by 8.7% at
13 1-hour postexposure and by 34.6% at 20 hours postexposure. C reactive protein was increased by 9.1% at
14 1-hour postexposure and by 22.8% at 20 hours postexposure. These changes, except for C reactive protein
15 at 20 hours postexposure, were statistically significant. Other statistically significant changes observed
16 were increases in markers of vascular inflammation, sICAM (10.7%) and sVCAM (6.6%), at 1-hour
17 postexposure, decreases in percent blood neutrophils (5.7%) at 20 hours postexposure and decreases in
18 blood LDH levels of 6.9 and 11.2% at 1 and 20 hours postexposure, respectively. The percentage of white
19 blood cells other than neutrophils were unchanged by exposure, as were cytokines, red blood cells, and
20 measures of blood chemistry. Hematocrit levels were decreased, but this change failed to reach statistical
21 significance. No statistically significant changes were found in measures of HRV in the study population
22 overall, but sex-specific changes were noted for men and women, albeit they were in opposite directions.
23 P-wave duration, a measure of cardiac repolarization, was increased by 10.5% at 1-hour postexposure, a
24 statistically significant change. Another measure of cardiac repolarization, QRS complex, was altered by
25 PM_{2.5} exposure, but this change did not reach statistical significance. Some sex-related changes that
26 reached statistical significance were found in HRV measures, cardiac repolarization parameters, FEV1
27 and PEF, however the small sample size precludes any conclusions.

28 The higher ventilation rate and longer exposure duration of [Wyatt et al. \(2020a\)](#) compared to
29 most controlled human exposure studies of PM, is roughly equivalent to a 2-hour exposure of
30 75–150 µg/m³ PM_{2.5}. Thus, dosimetric considerations may explain the observed changes in lung function
31 and inflammation in this population of young healthy individuals exposed to near-ambient concentrations
32 of PM_{2.5}. While [Wyatt et al. \(2020a\)](#) provides evidence of some effects at lower PM_{2.5} concentrations,
33 overall there is inconsistent evidence for changes in lung function (2019 PM ISA, Section 5.1.7.2 and
34 Section 5.1.2.3.3) and inflammation (2019 PM ISA, Section 6.1.11.2.1) in other controlled human
35 exposure studies evaluated in the 2019 PM ISA. Strengths of [Wyatt et al. \(2020a\)](#) include power
36 calculations made based on the primary endpoints, normalization of results, and good diurnal control
37 (i.e., all exposures occurred within a half hour of the same time—9:30 a.m.). However, a limitation of this
38 study is that no Bonferroni corrections were made to account for the multiple comparisons made in the
39 study; this limitation was acknowledged by the study authors.

3.3.2 PM_{2.5} Exposure and COVID-19 Infection and Death

With the advent of the global Coronavirus Disease 2019 (COVID-19) pandemic, several recent studies examined the role of ambient air pollution, specifically PM_{2.5}, on COVID-19 infections and deaths, including a few with study locations in the U.S. and Canada. The following sections evaluate 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 COVID-19, including infections, hospital admissions, replication rate, 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 which 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 emergency department (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](#)).

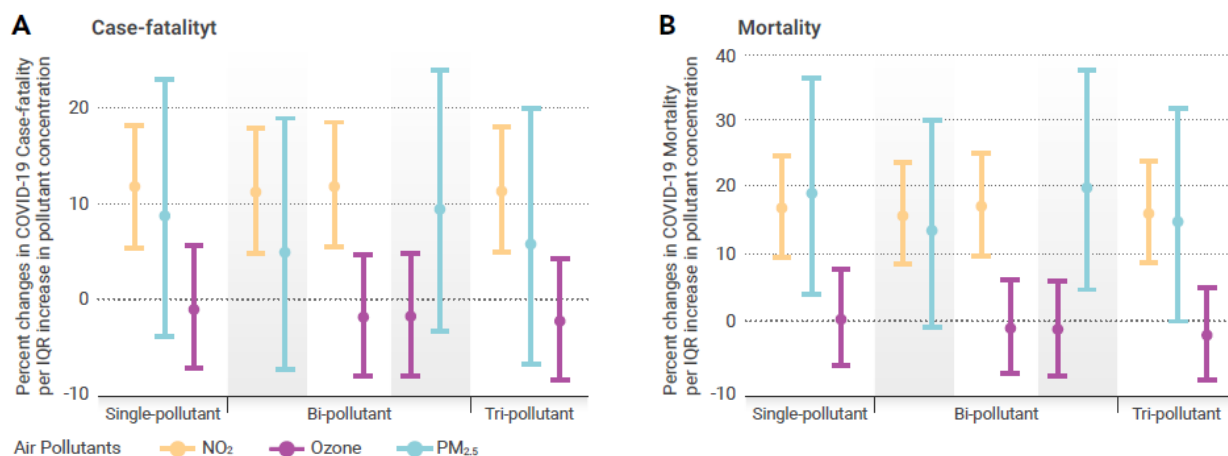
3.3.2.1 Short-Term PM_{2.5} Exposure

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 COVID-19 infections and 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 (<https://www1.nyc.gov/site/doh/covid/covid-19-data-trends.page>). 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 COVID-19 cases and deaths, controlling for the lagged outcome 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 COVID-19 infection (Incidence Rate Ratio [IRR]: 0.02 [95% CI: 0.01, 0.02] or 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 0 cases. The Mortality Rate Ratio (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 ecologic 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 to July 17, 2020. At that point in the pandemic there were still over 30% of U.S. counties reporting 0 cases (<https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/>). This study also relied on negative binomial regression but 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 NO₂ or O₃ in the model, the results remained consistent ([Figure 3-29](#)).



Source: [Liang et al. \(2020\)](#), copyright permission pending.

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 ecologic study by [Stieb et al. \(2020\)](#) evaluated COVID-19 infections within 111 Canadian Health Regions through May 18, 2020. These data were used to estimate the incidence rate ratio (IRR) of COVID-19 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 COVID-19 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 COVID-19 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 COVID-19 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 to those without COPD or asthma (OR: 0.42 [95% CI: 0.12, 1.54]).

In a departure from examining solely COVID-19 infections, deaths, or 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)

1 model, confirmed COVID-19 cases were recorded by state and R_0 was predicted, while controlling for
2 over 40 different state-level variables. This study showed that long-term $PM_{2.5}$ exposure was associated
3 with increases in the R_0 (ΔR_0 : 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

4 The body of evidence that examined associations between long- and short-term $PM_{2.5}$ -exposure
5 and COVID-19 outcomes consists mostly of studies employing an ecological study design. While some of
6 these studies exploring the relationship between $PM_{2.5}$ concentrations and COVID-19 infections and
7 deaths reported positive associations, there are a number of methodological issues that may influence
8 results. Specifically, all of these studies were conducted in the midst of an ongoing pandemic before
9 COVID-19 had reached many parts of the country and at that time the etiology of COVID-19 was still not
10 well understood. However, recent investigations have noted important differences in COVID-19 related
11 health outcomes based on occupation, race, socioeconomic status, and health insurance status, among
12 others.

13 While all the included studies account for population density, with the exception of [Mendy et al.](#)
14 [\(2021\)](#), they mostly do not consider other crucial factors which may strongly influence the spread of
15 COVID-19. In particular, factors such as social distancing, stay-at-home orders, use of N95 masks, as
16 well as other preventative measures are important for slowing the spread of SARS-CoV-2 (the virus
17 responsible for COVID-19 infection). Two critiques of the $PM_{2.5}$ exposure and COVID-19 literature
18 conducted by [Bourdrel et al. \(2021\)](#) and [Villeneuve and Goldberg \(2020\)](#) highlight the importance of
19 control for race/ethnicity and other sociodemographic factors, which may strongly influence exposure or
20 susceptibility to SARS-CoV-2. Additionally, they indicate the potential for exposure misclassification and
21 the likelihood of underreporting of cases and deaths, particularly in the early stages of the pandemic.
22 Taken together, there is limited evidence at this point in the COVID-19 pandemic to determine if short- or
23 long-term exposure to air pollutants, such as $PM_{2.5}$, influence the spread or susceptibility of SARS-CoV-2
24 in the population.

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

25 As discussed in the 2019 PM ISA in Chapter 12, the NAAQS are intended to protect public health
26 with an adequate margin of safety, which includes protection for the population as a whole and for those
27 groups potentially at increased risk for health effects from exposure to a criteria air pollutant [e.g., PM;
28 see Preamble to the ISA ([U.S. EPA, 2015](#))]. While there is strong evidence for PM-related health effects
29 occurring in the exposed general population and in some specific populations or lifestages, it is also
30 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 conducted 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 socioeconomic status (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 healthcare in the U.S., therefore indicating that SES may underlie differential risk for PM_{2.5}-related health effects. 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 a proxy 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 to higher SES populations. The following sections evaluate 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 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, that there is a disparate PM_{2.5} exposure among lower SES communities. When considered together, these additional studies provide further evidence that lower SES communities are exposed to higher concentrations of PM_{2.5} compared to higher SES communities ([Figure 3-30](#)—SES exposure, [Table A-11](#)).

Educational attainment is a common metric in which to assess the SES of a community. A study by [Lee \(2019\)](#) in the state of California, observed that census block-groups with a high percent (≥ 75 th percentile) of low educational attainment had a higher exposure to PM_{2.5} ($9.7 \mu\text{g}/\text{m}^3$) compared to those with a low percent (< 25 th percentile) of low educational attainment ($8.7 \mu\text{g}/\text{m}^3$). [Rosofsky et al. \(2018\)](#) conducted a study in Massachusetts that examined exposure differences by 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 high school education were exposed to PM_{2.5} concentrations of $11.3 \mu\text{g}/\text{m}^3$ in 2003 and $8.2 \mu\text{g}/\text{m}^3$ in 2010; whereas those with a Master's degree or higher were exposed to $11.2 \mu\text{g}/\text{m}^3$ in 2003 and $8.0 \mu\text{g}/\text{m}^3$ 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 – $11.2 \mu\text{g}/\text{m}^3$ in 2003 and 7.9 – $8.0 \mu\text{g}/\text{m}^3$ 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 the study conducted by [Rosofsky et al. \(2018\)](#) noted above. Within this study it was observed that census block groups with a median household income categories with ranges $< \$75,000$ were exposed to slightly higher PM_{2.5} concentrations of PM_{2.5} in 2003 11.2 – $11.4 \mu\text{g}/\text{m}^3$ and 2010 8.0 – $8.2 \mu\text{g}/\text{m}^3$ compared to block groups with median household income $\geq \$75,000$ ($11.1 \mu\text{g}/\text{m}^3$ in 2003 and $7.9 \mu\text{g}/\text{m}^3$ in 2010). Another study evaluating income differential in North Carolina, provided some evidence that those living in census tracts with a median household income $\geq \$52,269$ (75th percentile) ($11.3 \mu\text{g}/\text{m}^3$) are exposed to slightly higher concentrations of PM_{2.5} compared to census tracts above the 75th percentile ($11.2 \mu\text{g}/\text{m}^3$) for median household income ([Son et al., 2020](#)). Instead of examining specific household income cutpoints, [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 ($9.7 \mu\text{g}/\text{m}^3$) were shown to be exposed to higher concentrations of PM_{2.5} compared to block groups not in poverty ($8.7 \mu\text{g}/\text{m}^3$).

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 to 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 vs. 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 composite neighborhood level SES characteristics and 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 µg/m³) compared to a ZIP code with high SES characteristics (9.6 µg/m³) ([Han et al., 2017](#)). Similarly, a study by [Lee and Park \(2020\)](#) in the state of California, compared vulnerable to less vulnerable communities based on the Social and Health Vulnerability (SHV) metric within the Environmental Justice Screening Method. The SVH score is on a scale between 1–5 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 (SVH score 1–2) (6.8 µg/m³) had lower PM_{2.5} exposure, compared to communities with higher vulnerability (SVH score 4–5) (10.8 µg/m³). 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 µg/m³) compared to non-EJ communities (10.3 µg/m³). A study by [Weaver et al. \(2019\)](#) evaluated certain neighborhood clusters located within three counties (Durham, Orange, and Wake) in Central North Carolina. 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. Lastly, Cluster 6 was similar to Cluster 5 but was more urban. When compared to Cluster 3 (urban, high Bachelor's degrees) (12.8 µg/m³), Cluster 2 (urban, high poverty, Black race) (13.2 µg/m³) and Cluster 1 (urban, high Black race) (12.9 µg/m³) 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 to Cluster 3 (11.9–12.8 µg/m³).

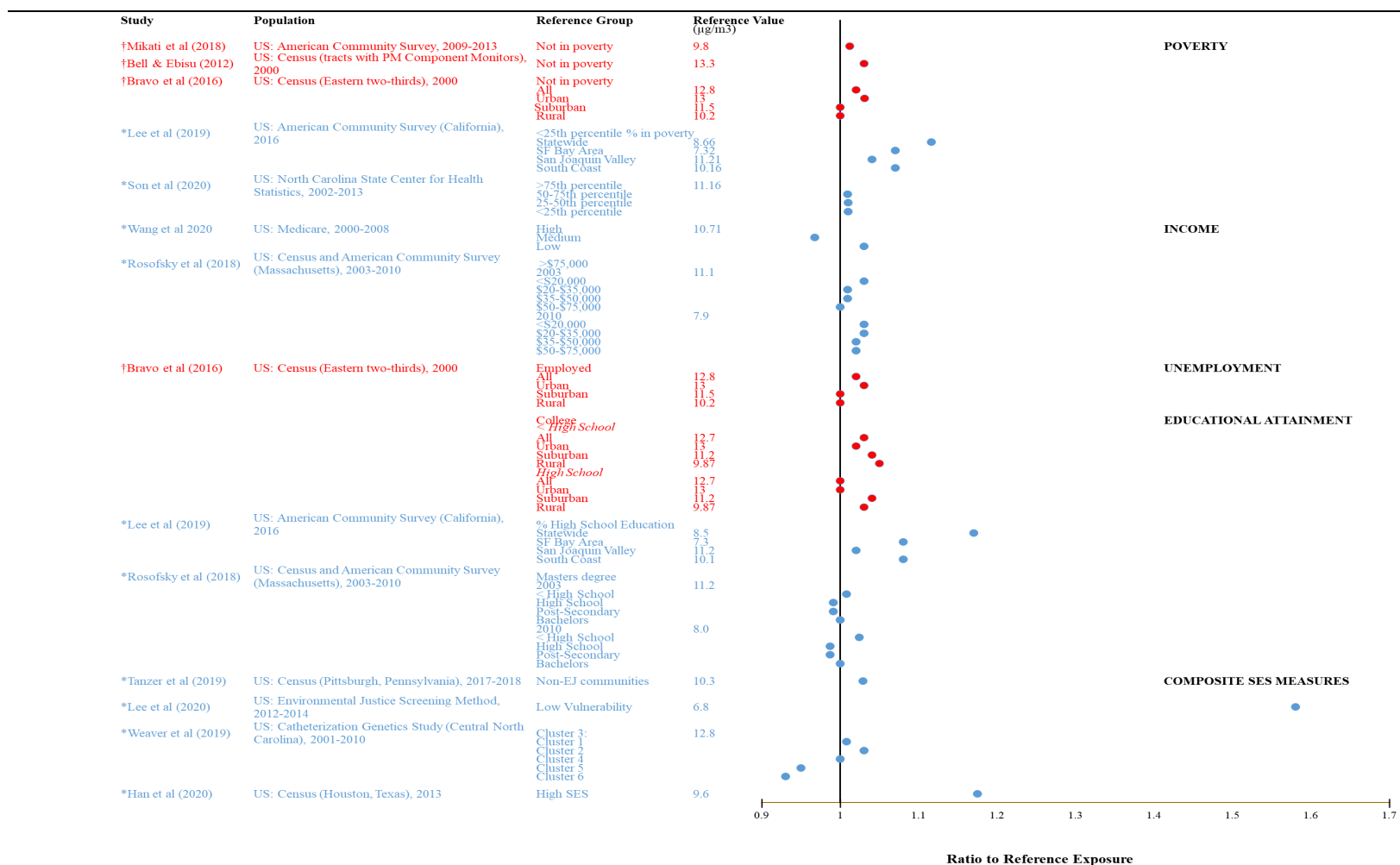


Figure 3-30 Differences in PM_{2.5} exposure by socioeconomic status.

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 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 non-accidental 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.

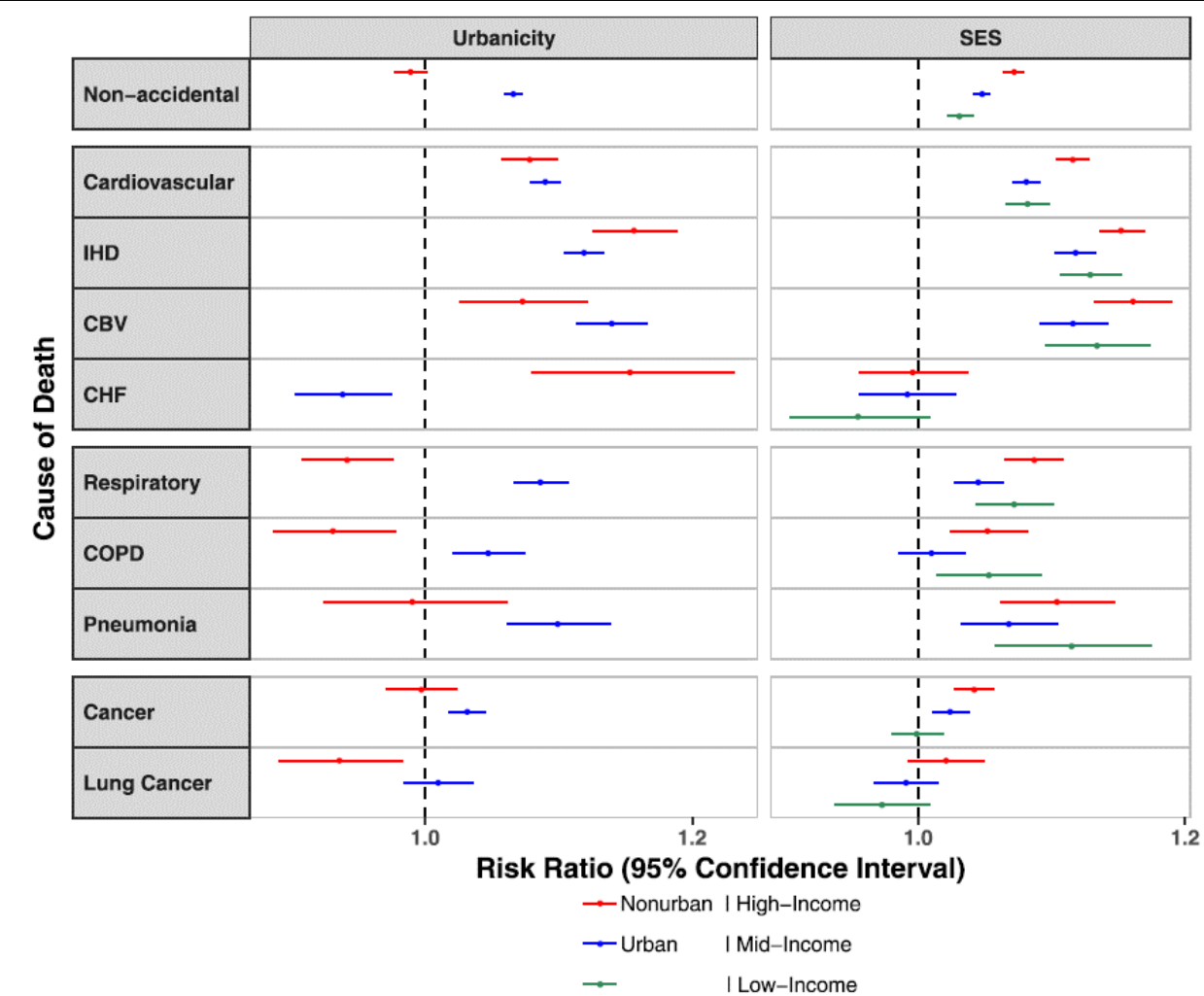
Short-Term PM_{2.5} Exposure

In a time-stratified case-crossover, [Yitshak-Sade et al. \(2019a\)](#) examined the intersection of greenspace, cardiovascular mortality, and PM_{2.5} exposure. 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

Recent studies explore whether SES modifies the relationship between exposure to PM_{2.5} and premature total 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 non-accidental mortality by income (high, medium, low) ([Figure 3-31](#)). However, a

Canadian study evaluating household income and PM_{2.5}-related non-accidental mortality reported the greatest magnitude of association in the lowest income category (<\$25,000CAD Hazard Ratio [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.

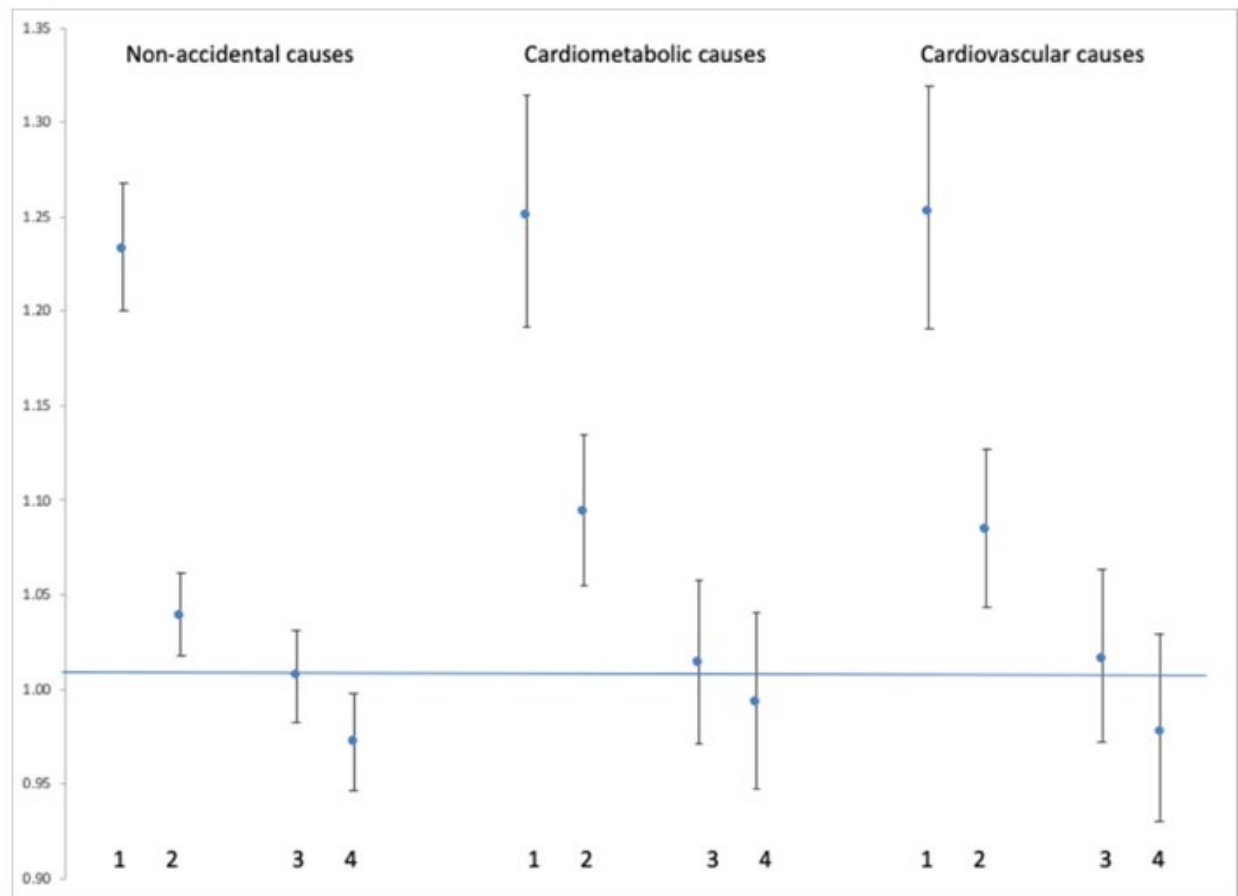


Source: Wang et al. (2020), copyright permission pending.
SES = socioeconomic status.

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

Using a more comprehensive method of assessing 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 non-accidental 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 non-accidental mortality compared to groups with high deprivation and low greenspace. However, there was little differences in the association comparing high to low deprivation in areas with high greenspace ([Figure 3-32](#)).



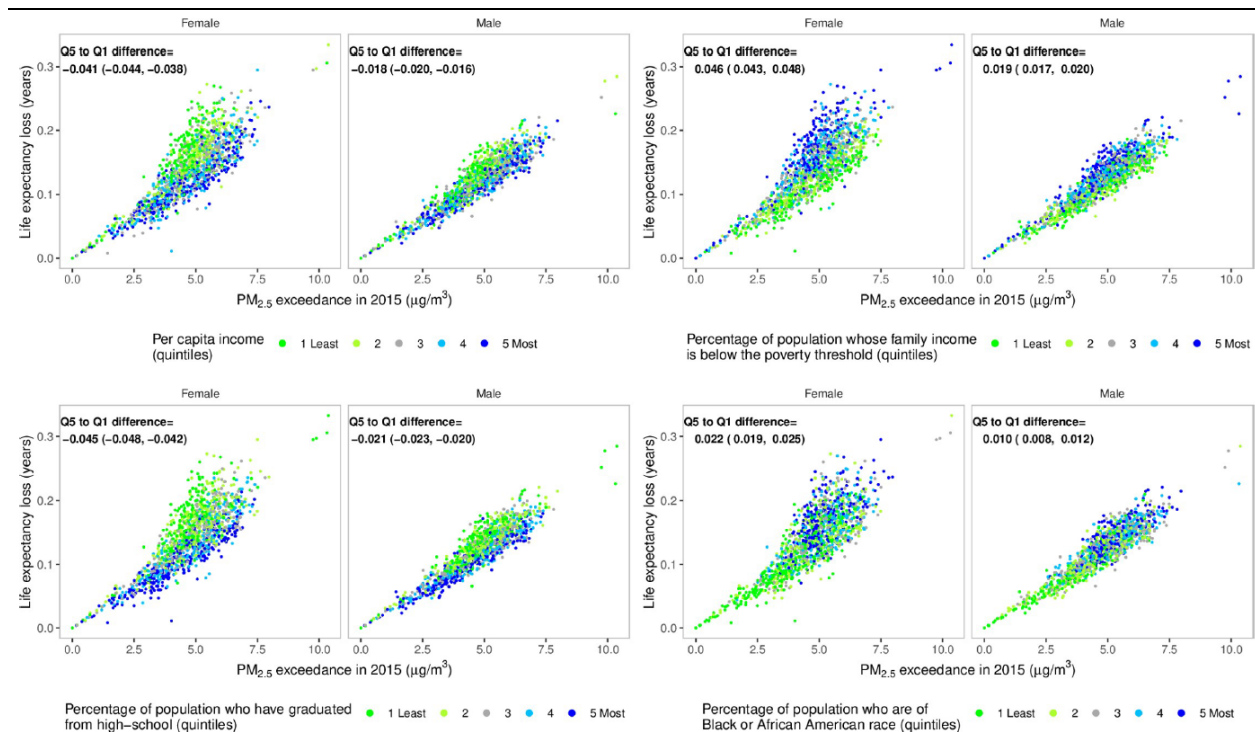
Source: [Crouse et al. \(2019\)](#), copyright permission pending.

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 µg/m³ 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 to 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 impact of PM_{2.5} exposure on life expectancy at birth.



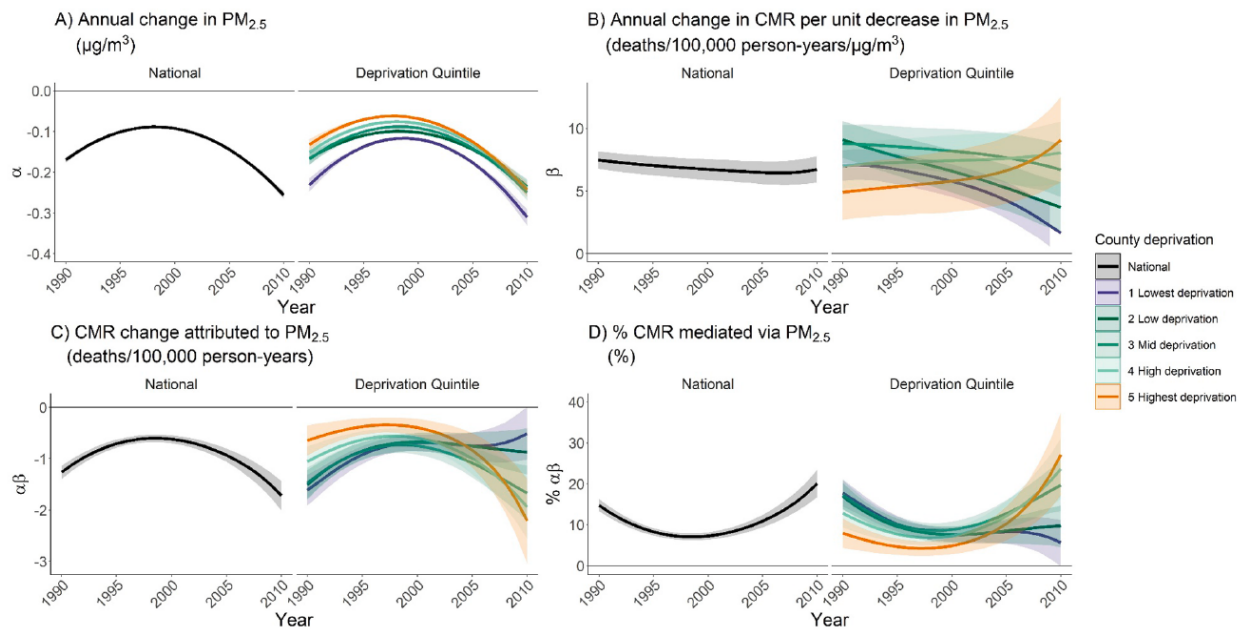
Source: Bennett et al. (2019), copyright permission pending.

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 SES. The Canadian study by Zhang et al. (2021) 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 income category for cardiovascular (<25,000CAD HR: 4.58 [95% CI: 2.48, 8.47]) compared to the highest income category (≥\$100,000CAD HR: 1.46 [95% CI: 0.94, 2.25]). Less 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]) income categories and respiratory mortality. However, 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).

1 A cross-sectional study by [Bevan et al. \(2021\)](#) evaluated the association between PM_{2.5} exposure
2 and age-adjusted cardiovascular mortality, modified by the 2015 Social Deprivation Index (SDI). The
3 SDI is generated from a factor analysis using information collected from the American Community
4 Survey (ACS), including county-level descriptors of race/ethnicity, income, housing, and education. The
5 SDI ranges between 1 (least deprived) and 100 (most deprived). [Bevan et al. \(2021\)](#) demonstrated that
6 when examining the annual average PM_{2.5} and age-adjusted cardiovascular mortality, stratified by SDI,
7 there is increased risk of cardiovascular mortality in counties with higher social deprivation (SDI 1–25:
8 39.1 deaths/100,000 persons [95% CI: 32.1, 46.1]; SDI 26–50: 48.2 deaths/100,000 persons [95% CI:
9 38.5, 57.9]; SDI 51–75: 71.0 deaths/100,000 persons [95% CI: 57.6, 84.4]; SDI 76–100: 52.0
10 deaths/100,000 persons [95% CI: 30.9, 73.1]). In another study focusing on social deprivation, [Wyatt et](#)
11 [al. \(2020b\)](#) estimated the change in PM_{2.5} concentration between 1990 and 2010 and the associated annual
12 change in the age-adjusted cardiovascular mortality rate (CMR) in the U.S. A social deprivation variable
13 was created using 1990 U.S. Census measures including: percent of households below the poverty line,
14 median household income, percent of those ≥ with at least a high school education, civilian
15 unemployment rate, percent female households with no spouse, percent vacant housing units, and percent
16 owner occupied housing units. Overall, in the earliest years, the counties with the highest social
17 deprivation benefited the least by the reduction in PM_{2.5}. However, as time progressed through to 2010,
18 reductions in CMR were the largest in the most deprived counties ([Figure 3-34](#)).



Source: [Wyatt et al. \(2020b\)](#), copyright permission pending.

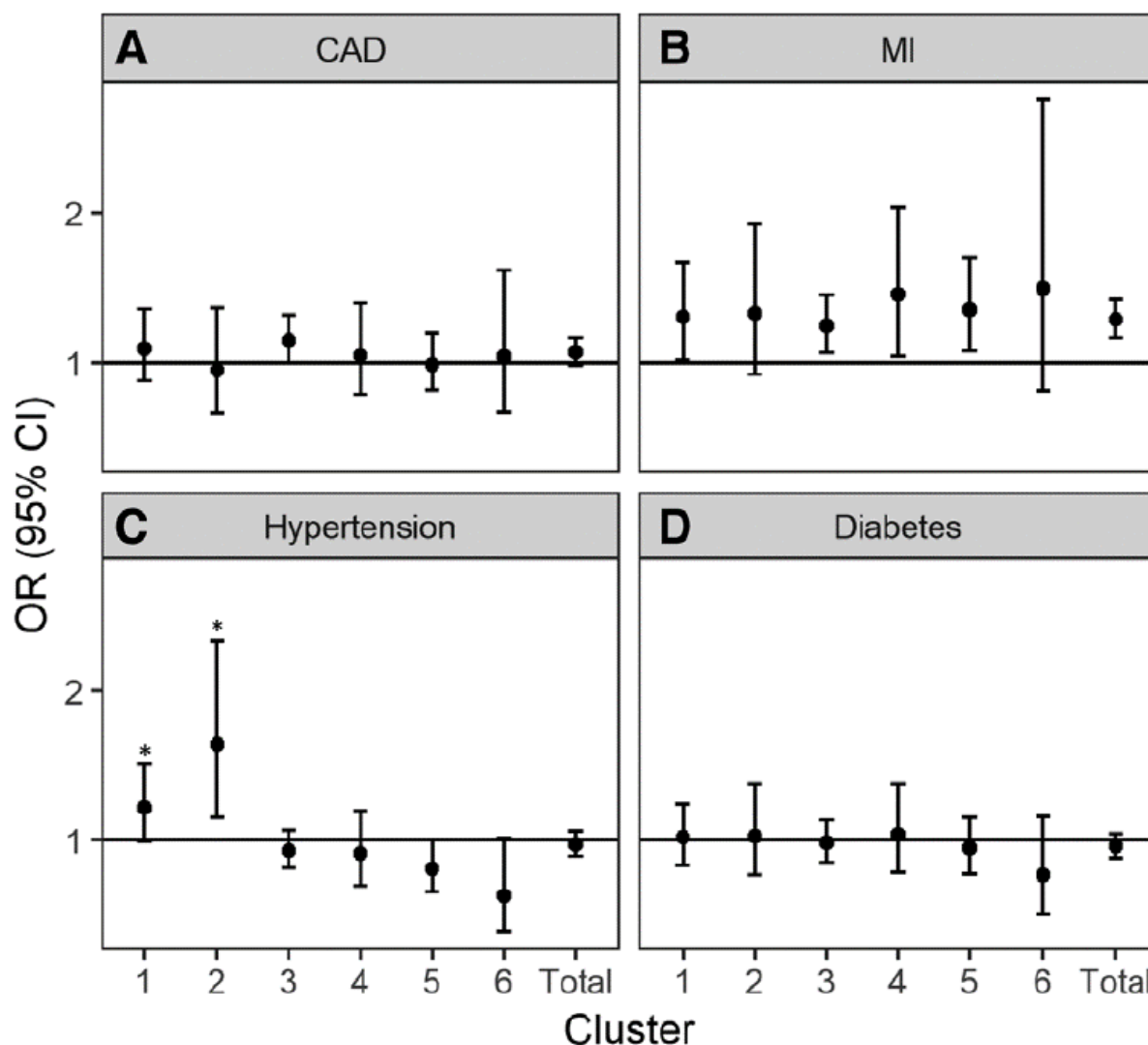
Note: Estimated national and socioeconomic deprivation (SED) quintile specific annual rates (95% confidence intervals). (A) depicts the change in $PM_{2.5}$ (α); (B) depicts the change in cardiovascular mortality rate (CMR) per 1 $\mu g/m^3$ change in $PM_{2.5}$ (β); (C) depicts $PM_{2.5}$ -related change in CMR ($\alpha\beta$); 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 $\alpha\beta$ indicates a net reduction in CMR related to $PM_{2.5}$ change, while 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 ischemic heart disease (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 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 congestive heart failure (CHF) or acute myocardial infarction (AMI) using the Canadian Ontario Population Health and Environment Cohort (ONPHEC). The authors observed the strongest association

1 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
2 the lowest income groups, compared to the uppermost income groups (CHF HR: 1.01 [95% CI: 1.00,
3 1.04], AMI HR: 1.03 [95% CI: 1.00, 1.06]). A study based on the same cohort also showed stronger
4 associations for atrial fibrillation (HR: 1.06 [1.04, 1.08]) and stroke (HR: 1.08 [1.04, 1.13]) among the
5 lowest income groups ([Shin et al., 2019](#)). The central North Carolina study by [Weaver et al. \(2019\)](#)
6 evaluated the relationship between certain health outcomes, such as: coronary artery disease, myocardial
7 infarction (MI), hypertension, and diabetes, among cardiac catheterization patients. When compared to
8 Cluster 3 (urban, high percent with Bachelor's degrees, and low percentages of: nonmanagerial
9 occupations, poverty, and unemployment) (OR: 0.70 [95% CI: 0.86, 1.07], per 5 $\mu\text{g}/\text{m}^3$), there was a
10 greater association between PM_{2.5} and hypertension in Cluster 1 (urban and having a high percent of
11 Black residents and nonmanagerial occupations) (OR = 2.70, [95% CI: 0.95, 7.59], per 5 $\mu\text{g}/\text{m}^3$) and 2
12 (urban and having a high percent of: poverty, Black residents, public assistance, single-parent homes,
13 unemployment, and nonmanagerial occupations) (OR = 11.86, 95% [95% CI: 2.10, 67.21], per 5 $\mu\text{g}/\text{m}^3$).
14 While PM_{2.5} was associated with MI, the associations did not vary by cluster, and there were null
15 associations noted for diabetes. However, the strongest association observed among coronary artery
16 disease (CAD) outcomes was in Cluster 3 (OR = 1.15 [95% CI: 1.00, 1.31], per 5 $\mu\text{g}/\text{m}^3$) ([Figure 3-35](#)).



Source: [Weaver et al. \(2019\)](#), copyright permission pending.

CAD = Coronary Artery Disease, MI = Myocardial Infarction. Results resented for 1 $\mu\text{g}/\text{m}_3$ increase in $\text{PM}_{2.5}$ concentrations.

Figure 3-35 Odds ratios for the association between $\text{PM}_{2.5}$ and cardiometabolic outcomes 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 $\text{PM}_{2.5}$ -related health effects. The 2009 PM ISA observed little evidence for increased $\text{PM}_{2.5}$ -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 $\text{PM}_{2.5}$ exposure across the U.S., particularly for Black/African Americans, compared to non-Hispanic White individuals. Additionally, some studies provided evidence of increased $\text{PM}_{2.5}$ -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 non-White individuals, particularly Black individuals, are at increased risk for PM_{2.5}-related health effects, in part due to disparities in exposure. The following sections evaluate 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](#)).

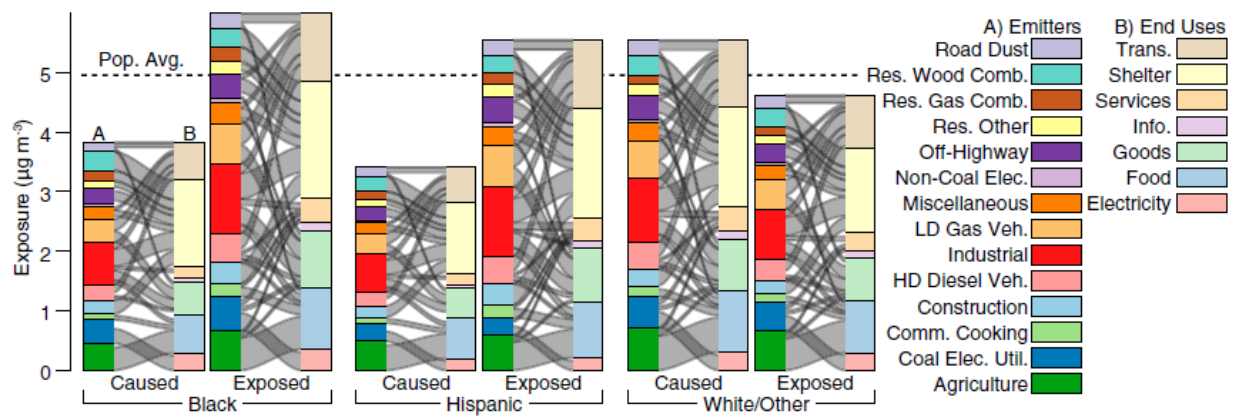
3.3.3.2.1 Exposure Disparity

Several recent studies 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, that there are disparities in PM_{2.5} exposure by race and ethnicity. When considered together, these additional studies provide further evidence that non-White communities are exposed to higher concentrations of PM_{2.5} compared to White communities ([Figure 3-38](#)—Race exposure, [Table A-14](#)—Race exposure).

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 Pittsburgh, PA between 2001–2014, observed that Black participants (16.1 µg/m³) were exposed to slightly higher concentrations of PM_{2.5} compared to White participants (15.7 µg/m³) ([Erqou et al., 2018](#)). Similarly, the Veterans Cohort Study, conducted between 1976 and 2001 also showed that Black participants (15.7 µg/m³) were exposed to a substantially higher concentration of PM_{2.5} compared to White participants (13.9 µg/m³) ([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 to White race (10.9 µg/m³), those of Black race (12.3 µg/m³) experience higher exposures to PM_{2.5}, followed by Asian, Pacific Islander, or American Indian/Alaska Native (11.9 µg/m³) and Hispanic (11.4 µg/m³) 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 µg/m³, Post-move: 12.12 µg/m³) and White (Pre-move: 11.88 µg/m³, Post-move: 11.15 µg/m³) beneficiaries, a disparity in exposure was still present, with Black individuals being exposed to elevated concentrations of PM_{2.5} compared to White individuals ([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 to White individuals (21.3%). Additionally, most White (26.1%) and Hispanic (34.7%) individuals lived in the lowest PM_{2.5} quartile, compared to only 10.5% of non-Hispanic Black individuals.

Other recent studies used data from the U.S. Census or American Community Survey (ACS) 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 µg/m³, 2010: 8.4 µg/m³), non-Hispanic Asian (2003: 11.6 µg/m³, 2010: 8.2 µg/m³), and Hispanic (2003: 11.6 µg/m³, 2010: 8.4 µg/m³), populations experiencing higher PM_{2.5} exposures compared to non-Hispanic White (2003: 11.1 µg/m³, 2010: 7.8 µg/m³) 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 to areas with a higher percentage of White individuals. Additionally, compared to 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 (≥75th percentile) of people of color (9.98 µg/m³) compared to those with a low percent (<25th percentile) of people of color (7.90 µg/m³) were exposed to higher concentrations of PM_{2.5}.

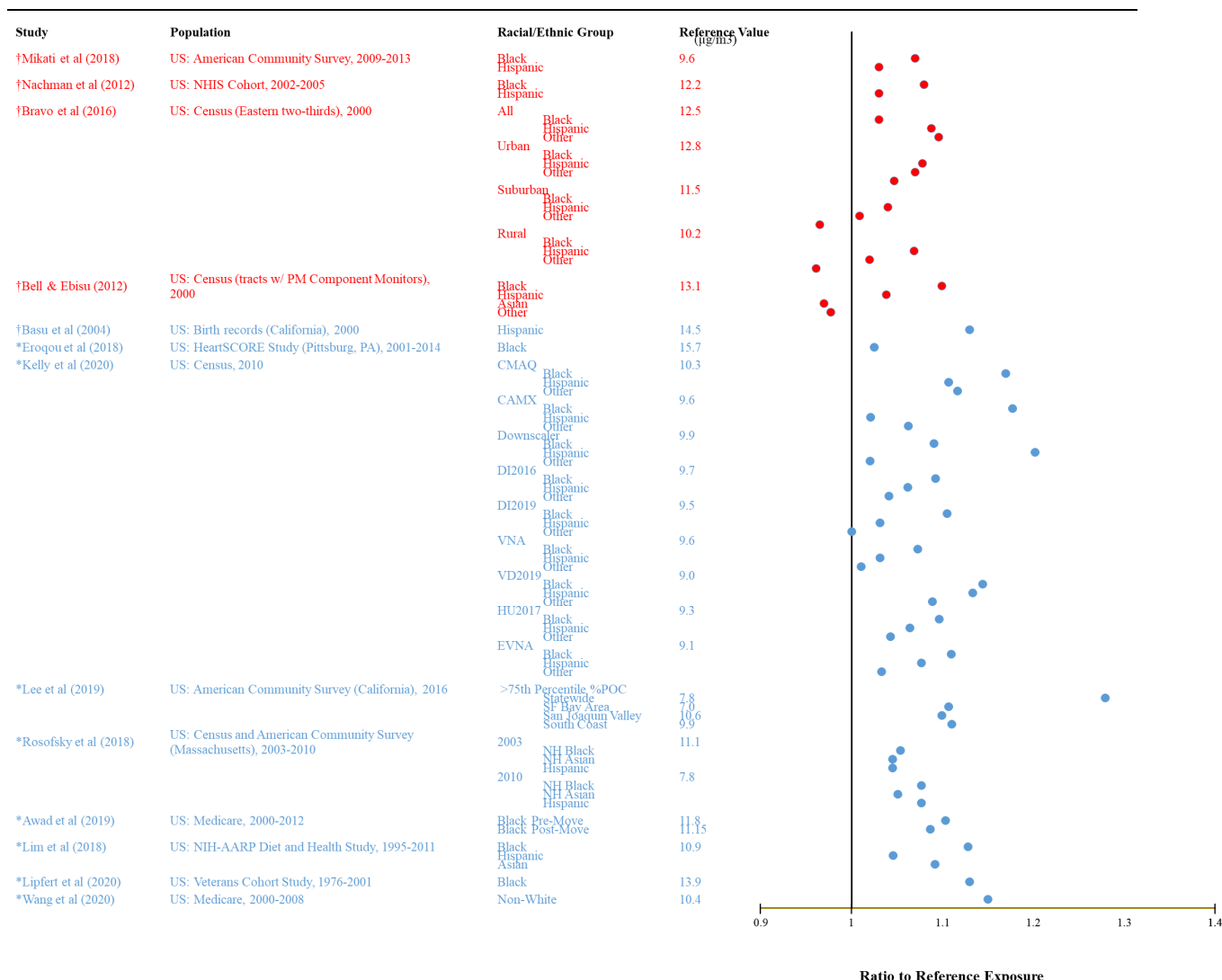
Several recent studies used data from the National Emissions Inventory (NEI) to evaluate racial and ethnic disparities in PM_{2.5} exposure. [Richmond-Bryant et al. \(2020\)](#) evaluated changes in burden due to the closure of 92 coal-fired electricity generating units (EGUcf). Estimated from the American 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 tracts 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 µg/m³), while only consuming 3.8 µg/m³, meaning that their estimated pollution inequity is 56%. Hispanic individuals were estimated to have a pollution inequity of 63% (exposed to 5.5 µg/m³, consuming 3.4 µg/m³), while White individuals have an estimated pollution inequity of -17% (exposed to 4.6 µg/m³, consume 5.5 µg/m³) ([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/m³), Asian (7.7 µg/m³), Hispanic (7.2 µg/m³) individuals are exposed to greater proportions of PM_{2.5} compared to White (5.9 µg/m³) individuals ([Figure 3-37](#)).



Source: [Tessum et al. \(2019\)](#), copyright permission pending.

Note: Within 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 Average PM_{2.5} experienced and caused, by racial-ethnic group.



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 $\mu\text{g}/\text{m}^3$. NH: non-Hispanic. This figure builds upon 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

- 1 Since the literature cutoff date of the 2019 ISA, several additional studies evaluated disparities in
- 2 the risk of PM_{2.5}-related health effects, stratified by race and ethnicity. A small number of studies were
- 3 included in the 2009 PM ISA, that summarized racial and ethnic disparities in PM_{2.5} mortality risk. The
- 4 2019 PM ISA further identified several studies which provided evidence for an increased association

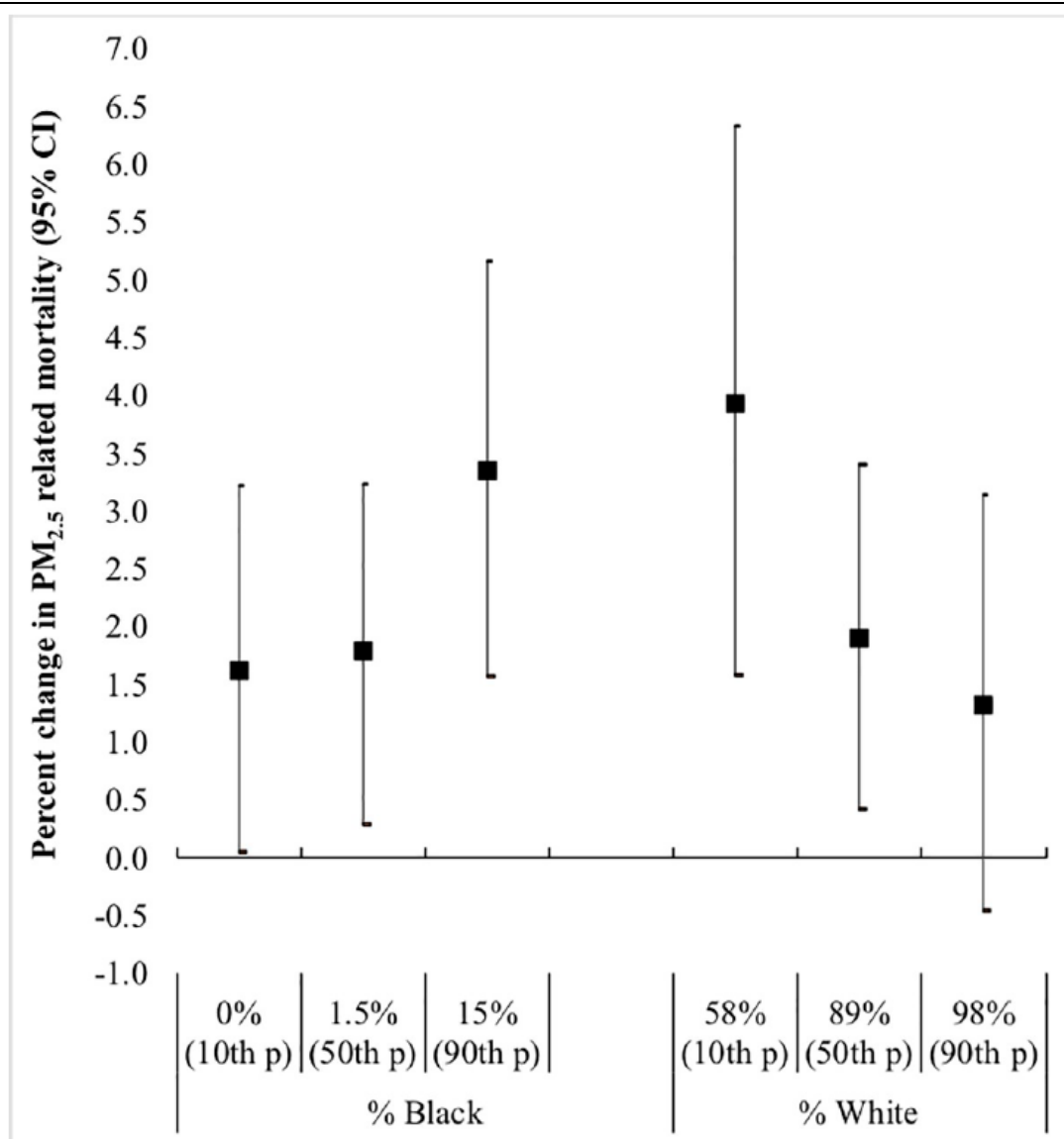
1 between mortality and long-term exposure to PM_{2.5} among non-White groups. However, evidence of any
2 racial or ethnic disparities and PM_{2.5}-related health outcomes was inconsistent. The most recent evidence
3 is consistent with differences in the risk of PM_{2.5}-related health effects by race and ethnicity, as detailed in
4 the 2019 PM ISA. While the studies that evaluated all-cause or total (nonaccidental) mortality were
5 inconsistent, there was stronger evidence to indicate a greater risk of cause-specific mortality and some
6 other health endpoints among people of color. In particular, individuals of Black race consistently were
7 shown to have a greater risk for health outcomes associated with PM_{2.5} exposure. The following sections
8 evaluate recent studies pertaining to short-term ([Table A-15](#)) and long-term ([Table A-16](#)) PM_{2.5} exposure
9 and PM_{2.5}-related health risks among different racial groups.

Short-Term PM_{2.5} Exposure

10 In a time-stratified case-crossover analysis, [Yitshak-Sade et al. \(2019a\)](#) examined the intersection
11 of greenspace, cardiovascular mortality, and PM_{2.5} exposure in Massachusetts. This study demonstrated
12 that among census block groups with a low percentage of White individuals, there was a 3.55% (95% CI:
13 1.49, 5.65) increase in cardiovascular mortality in less green areas, and a 2.47% (95% CI: 0.43, 4.56)
14 increase in cardiovascular mortality in more green areas associated with two-day average (lag 0–1) PM_{2.5}
15 exposure. However, in census block groups with a high percentage of White individuals, less greenspace
16 was associated with a 1.14% (95% CI: –1.00, 3.33) increase, in cardiovascular mortality, while more
17 greenspace was associated with a 2.8% (95% CI: 0.62, 5.02) increase in cardiovascular mortality ([Figure](#)
18 [3-39](#)). These results indicate that regard less of greenspace, census block groups with low percentage of
19 White individuals have a higher risk of PM_{2.5}-related cardiovascular mortality.

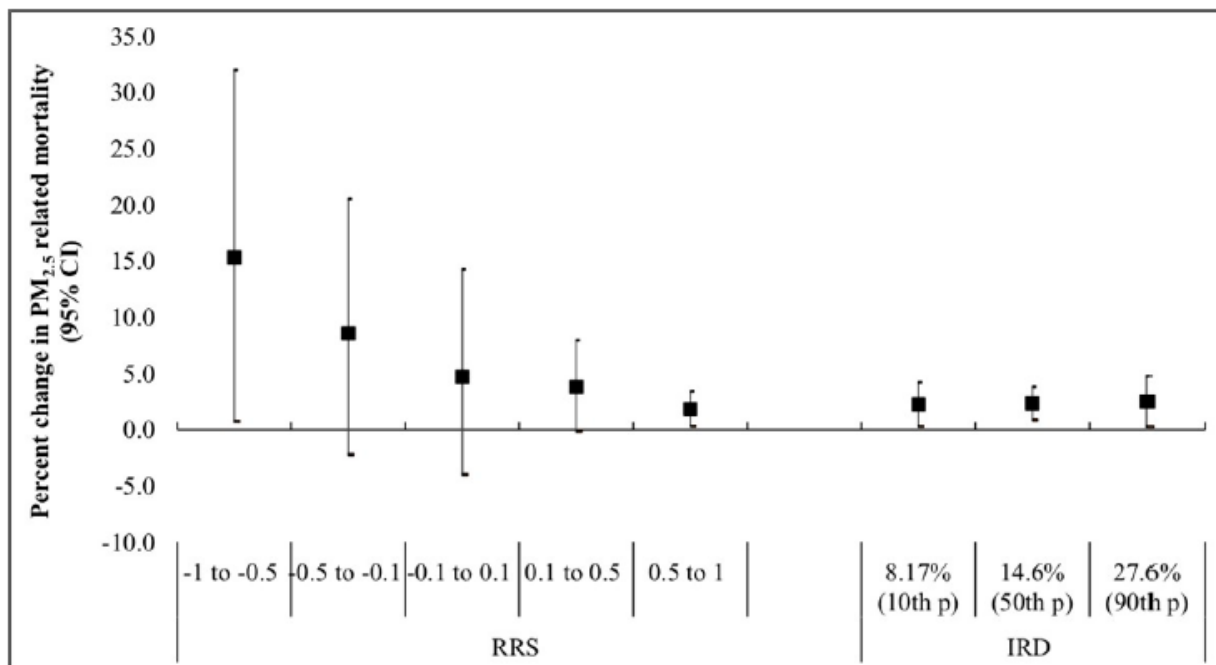
20 Another study examining short-term PM_{2.5} exposure and cardiovascular mortality conducted in
21 Massachusetts used four different metrics in which to evaluate race and ethnicity within the state
22 ([Yitshak-Sade et al., 2020](#)). There was a higher percent change in cardiovascular mortality among Black
23 (4.78% [95% CI: –1.99, 12.02]) individuals compared to White (2.25% [95% CI: 0.80, 3.23]) associated
24 with the two-day moving average (lag 0–1) of PM_{2.5}. When evaluating the racial composition by census
25 block group, there was a 1.62% (95% CI: 0.05, 3.22) increase in cardiovascular mortality in census block
26 groups with 0% Black (10th percentile) compared to a 3.35% (95% CI: 1.57, 5.16) increase in
27 cardiovascular mortality in census block groups with more than a 15% Black population (90th percentile)
28 (see [Figure 3-39](#)). This study also evaluated two novel measures of racial segregation. The first was the
29 Racial Residential Segregation (RRS) metric which quantified the concentration of non-Hispanic Black
30 and non-Hispanic White individuals in each census block group and could range between –1 (more Black
31 individuals) to 1 (more White individuals). In census block groups with more White individuals (RRS 0.5
32 to 1) there was a 1.84% (95% CI: 0.31, 3.40) increase in cardiovascular mortality, whereas in census
33 block groups with more Black individuals (RRS –1 to –0.5) there was a 15.37% (95% CI: 0.76, 31.99)
34 increase in cardiovascular mortality. The second indicator examined was the Index of Racial Dissimilarity
35 (IRD) which measured the dissimilarity between the distribution of non-Hispanic Black and non-Hispanic
36 White individuals within the census block group to the larger census tract. A higher IRD is indicative of

1 greater dissimilarity in the proportion of Black residents between the census block group and the census
 2 tract. There was no evidence of differences in cardiovascular mortality risk attributed to short-term PM_{2.5}
 3 exposure among any of the groups ([Figure 3-40](#)).



Source: [Yitshak-Sade et al. \(2020\)](#), copyright permission pending.
 Note: Results presented for a 10 µg/m³ 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. \(2020\)](#), copyright permission pending.
 Note: Results percented for a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$.
 RRS = Racial Residential Segregation, IRD = Index of Racial Dissimilarity.

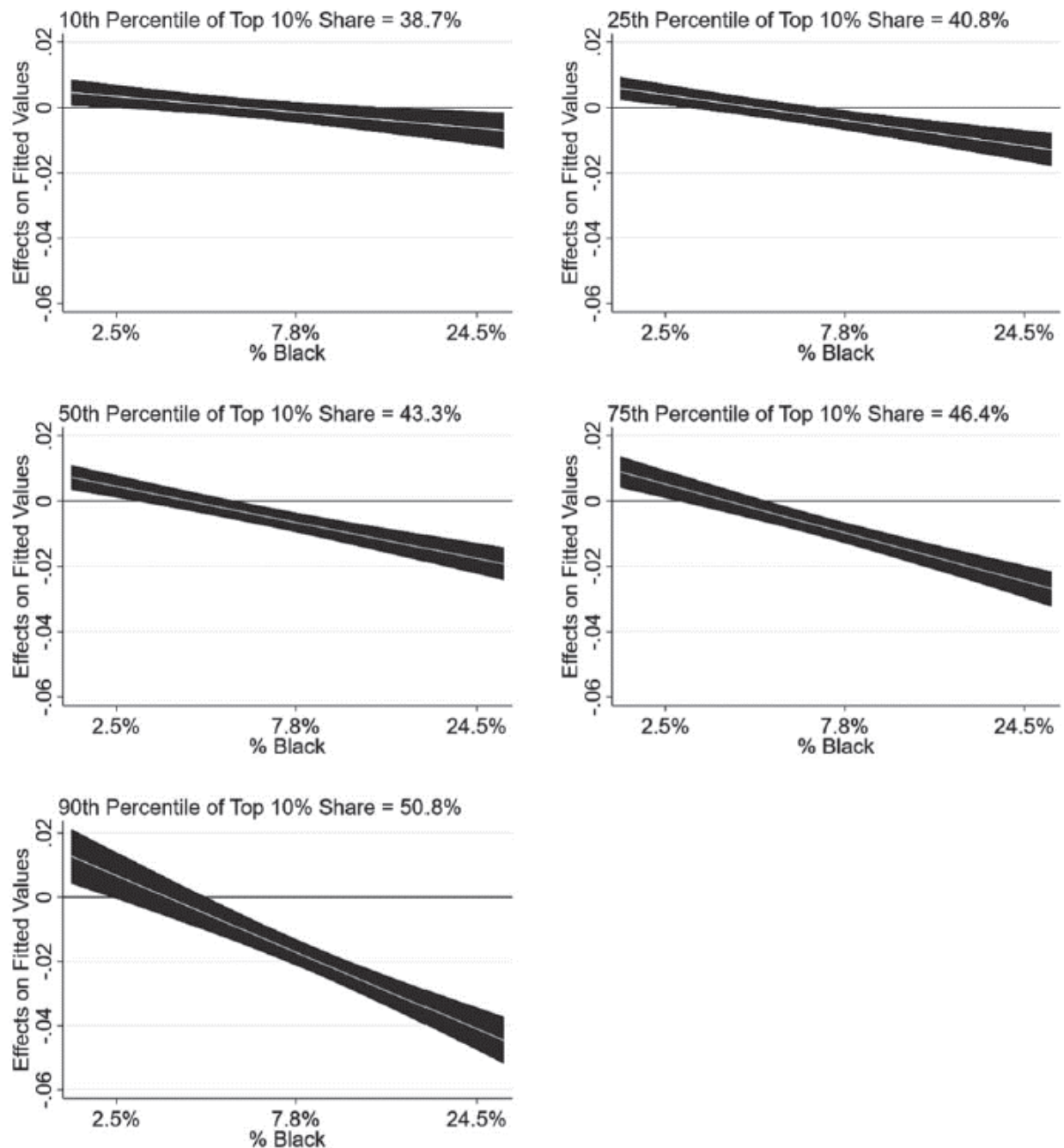
Figure 3-40 Percent change in cardiovascular disease mortality by $\text{PM}_{2.5}$ exposure, stratified by the racial residential segregation and index of racial dissimilarity in Massachusetts (2001–2011).

Long-Term $\text{PM}_{2.5}$ Exposure

A number of recent epidemiologic studies further evaluated whether race and ethnicity modify the association between all-cause (non-accidental) mortality and long-term $\text{PM}_{2.5}$ exposure. A study by [Parker et al. \(2018\)](#) using National Health Interview Survey data evaluated all-cause mortality (excluding unintentional injuries) and $\text{PM}_{2.5}$ 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. \(2018\)](#). Since moving was essentially random, this created a natural experiment that 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 to White movers (HR: 1.10 [95% CI: 1.10, 1.10]). Similarly, a recent study using data from the Veterans Cohort Mortality Study from 1976–2001 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 $\text{PM}_{2.5}$, and the results are interpreted as the change in mortality that would

1 result if all cohort members were exposed to the minimum concentration of PM_{2.5}. The mortality rate
2 using years 1976–2001 and PM_{2.5} measured between 1999–2001 was higher among White veterans
3 (RR:1.05 [95% CI: 1.01, 1.10]) compared to Black veterans (RR: 0.82 [95% CI: 0.75, 0.89]). This effect
4 was less pronounced when only examining the cohort between 1997 and 2001 (White RR: 1.03 [95% CI:
5 0.91, 1.17], Black RR: 0.96 [95% CI: 0.76, 1.21]) ([Lipfert and Wyzga, 2020](#)). Another study of
6 non-accidental mortality among Medicare beneficiaries by [Wang et al. \(2020\)](#) observed positive, but
7 equal, relative risks (RR) among Black (RR: 1.02 [95% CI: 1.02, 1.02]) and White (RR: 1.03 [95% CI:
8 1.02, 1.03]) beneficiaries. Additionally, the North Carolina case-crossover study by [Son et al. \(2020\)](#) also
9 observed very little racial and ethnic differences for total mortality when stratified by race/ethnicity
10 (non-Hispanic White OR: 1.01 [1.01, 1.01]; non-Hispanic Black OR: 1.01 [1.00, 1.02]; Hispanic OR:
11 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]).

12 [Bennett et al. \(2019\)](#) evaluated life-expectancy changes and PM_{2.5} among differing racial groups
13 in the U.S. In this study, counties with PM_{2.5} concentrations that exceeded 2.8 µg/m³ and had a high
14 proportion of Black or African Americans were associated with lower life expectancy. This difference
15 was also greater among females compared to males ([Figure 3-33](#)). The study by [Jorgenson et al. \(2020\)](#)
16 that assessed the intersection between PM_{2.5} exposure, Black race, and income inequality also
17 demonstrated that states with a high percentage of Black populations had worse life expectancy at birth
18 associated with PM_{2.5}. When including a three-way interaction between PM_{2.5}, Black race, and income
19 inequality, the slope for PM_{2.5} and life expectancy becomes more negative as the percent of the population
20 that is Black and the income inequality increase. Overall, this study states that PM_{2.5} appears to have the
21 largest effect on life expectancy in states with a high level of income inequality and a larger percentage of
22 people of Black race ([Figure 3-41](#)).



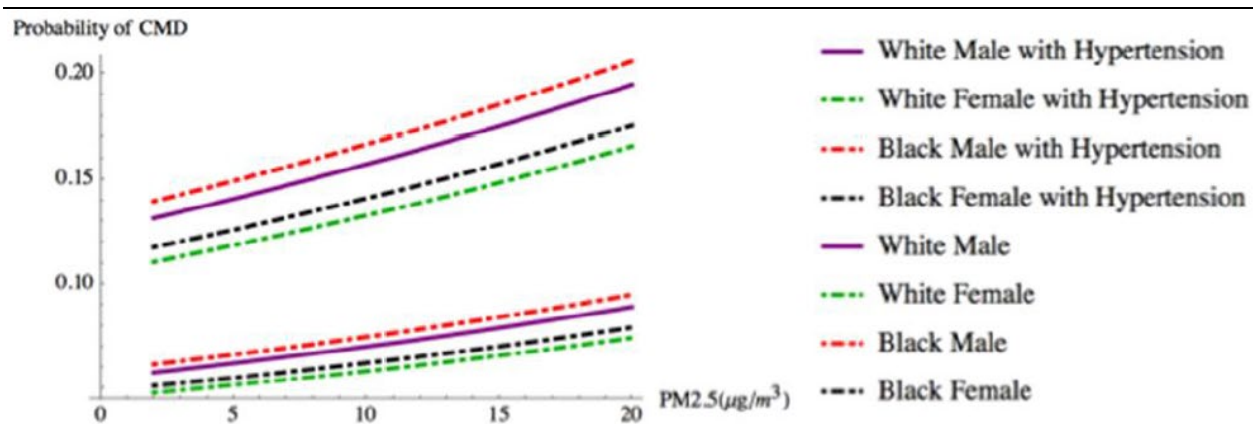
Source: [Jorgenson et al. \(2020\)](#), copyright permission pending.

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

- 1 Recent epidemiologic studies also evaluated specific causes of death attributable to PM_{2.5}
- 2 stratified by race and ethnicity. In an analysis of the NIH-AARP Diet and Health Study (1995–2011),
- 3 [Lim et al. \(2018\)](#) evaluated diabetes mortality. Black participants had an association larger in magnitude
- 4 between annual PM_{2.5} exposure and diabetes mortality (HR: 1.27 [95% CI: 1.02, 1.58]), compared to

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 do not report results consistent with [Lim et al. \(2018\)](#). The study by [Parker et al. \(2018\)](#) that used the National Health Interview Survey (NHIS) between 1997–2001 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]). Lastly, the study by [Wang et al. \(2020\)](#) evaluating over 53 million Medicare beneficiaries showed associations larger in magnitude among White beneficiaries compared to non-White beneficiaries for cardiovascular mortality (White RR: 1.05 [95% CI: 1.05, 1.06], non-White RR 1.03 [95% CI: 1.02, 1.03), heart disease mortality (White RR: 1.07 [95% CI: 1.07, 1.08], non-White RR 1.03 [95% CI: 1.02, 1.04), and vascular disease mortality (White RR: 1.07 [95% CI: 1.06, 1.08], non-White RR 1.05 [95% CI: 1.04, 1.06]).

In a study of post-menopausal women enrolled in the Women’s Health Initiative (WHI), [Honda et al. \(2017\)](#) estimated that the association between long-term exposure to PM_{2.5} and incident hypertension was larger in magnitude among Asian/Pacific Islander (HR: 1.34 [95% CI: 1.00, 1.64]), non-White (HR: 1.27 [95% CI: 1.17, 1.38]), and Black participants (HR: 1.26 [95% CI: 1.06, 1.44]) compared to 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 (CMD) 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. \(2020\)](#), copyright permission pending.

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

1 Within the 2019 PM ISA, evidence was evaluated that indicated some populations and lifestyles
2 are at increased risk of a PM_{2.5}-related health effect (2019 PM ISA, Chapter 12). These disparities
3 between populations and lifestyles were in some cases found to be attributed to differences in health risks
4 as well as exposure. When considering proxies for SES, such as income or educational attainment, having
5 low income, or residing in a low-income area studies were evaluated that reported associations larger in
6 magnitude between mortality and long-term PM_{2.5} exposure, compared to populations with higher income
7 or living in higher income neighborhoods. However, there was inconsistent evidence of differential risk
8 when comparing across populations with low and high educational attainment. Additionally, evidence
9 was presented in the 2019 PM ISA that indicated a consistent disparity in PM_{2.5} exposure among different
10 racial and ethnic groups. This disparity also translated to PM-related health risks, specifically
11 demonstrating that Black individuals were at higher risk for PM_{2.5}-related health outcomes, such as
12 mortality. Taken together, the 2019 PM ISA determined that the evidence was suggestive that people of
13 low SES and adequate to indicate that race and ethnicity, specifically non-White and Black populations,
14 are at increased risk of PM_{2.5}-related health effects, in part due to disparities in exposure. Overall, the
15 recent studies support the conclusions of the 2019 PM ISA.

16 Recent epidemiologic studies published since the 2019 PM ISA supports the evidence that SES
17 may modify the association between PM_{2.5} exposure and PM_{2.5}-related health risk. Studies
18 evaluating PM_{2.5}-related health risks by SES add to the growing evidence presented in the 2019 PM ISA.
19 In addition to the proxy-SES metrics (e.g., income, educational attainment), several recent studies
20 explored composite measures of neighborhood SES, which consistently demonstrated a disparity in both
21 PM_{2.5} exposure and the risk of PM_{2.5}-related health outcomes. Additionally, the recent evidence supported
22 the conclusions that lower SES is associated with cause-specific mortality and certain health endpoints
23 (i.e., MI and CHF), but less so for all-cause or total (non-accidental) mortality ([Section 3.3.3.1](#)).

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

4. EVALUATION OF RECENT WELFARE EFFECTS EVIDENCE

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

14 The studies evaluated within the following sections represent only those studies most informative
15 in considering potential revisions to the PM NAAQS, i.e., that provide new information on public
16 preferences and/or methodologies or quantitative analyses of visibility impairment. As a result, the
17 summary section ([Section 4.3](#)) for visibility effects conveys how the evidence from recent studies fits
18 within the scientific conclusions of the 2019 PM ISA, and indicates whether recent evidence supports (is
19 consistent with), supports and extends (is consistent with and reduces uncertainties), or does not support
20 (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

21 Overall, visibility in most regions of the U.S. has improved since the 2009 PM ISA, as indicated
22 by lower estimates of PM_{2.5} mass extinction. The greatest improvements have occurred in the eastern half
23 of the U.S., in regions with the poorest visibility. This has likely occurred because of a reduction in SO₂
24 emissions, resulting in lower ammonium sulfate concentrations, because ammonium sulfate has
25 historically accounted for a larger fraction of PM_{2.5} mass than other PM_{2.5} components, and also because
26 ammonium sulfate is more effective than other PM_{2.5} components at scattering light. The resulting
27 decrease in PM_{2.5} in the eastern U.S. has resulted in better visibility.

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

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

4.2 Recent Studies that Inform the Relationship between PM and Visibility Effects

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

4.2.1 Visibility Preference and Light Extinction

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

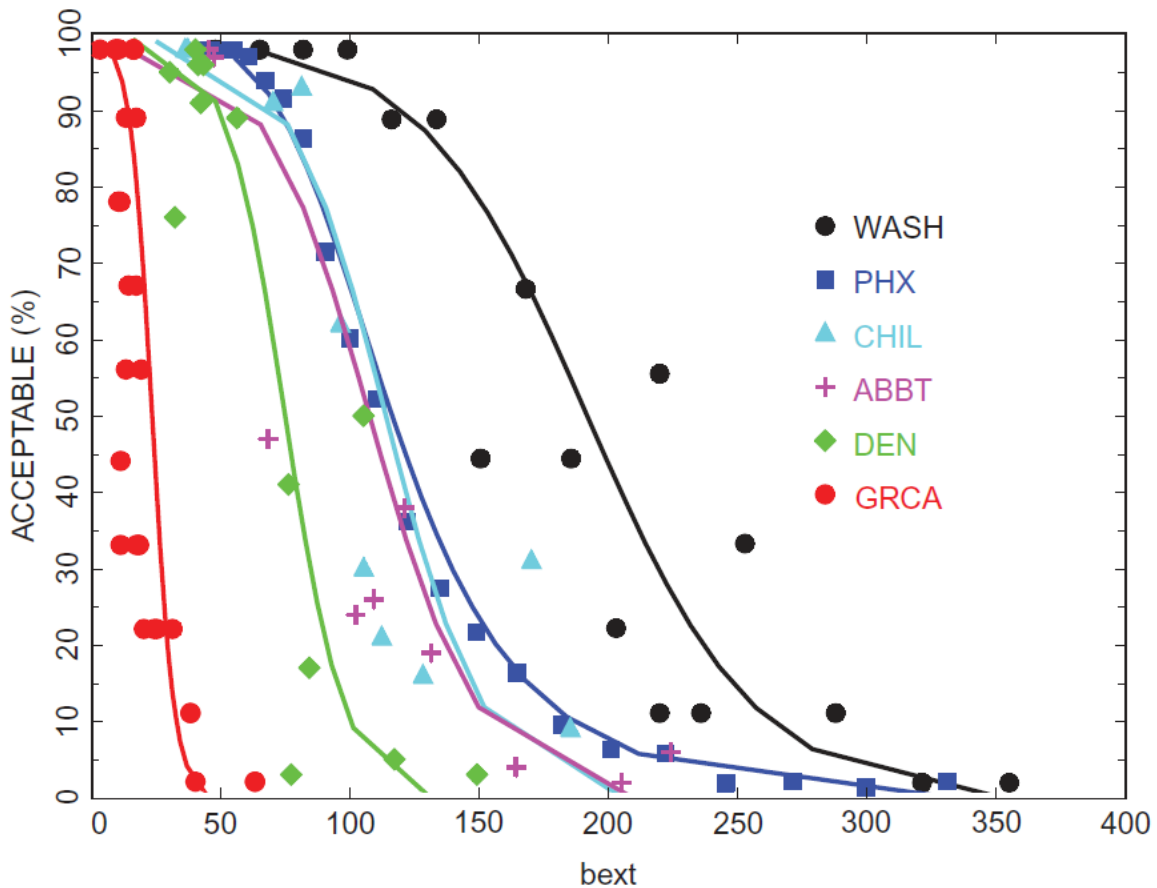
characteristics of atmospheric visibility impairment are (1) a reduction in visual range, the greatest distance through the atmosphere at which a prominent object can be identified, and (2) a reduction in contrast, the sharpness with which an object can be distinguished from another object or background (Malm, 2016). Both of these concepts can be expressed in terms of an *atmospheric extinction coefficient* (b_{ext}), that relates the distance of an observed object to atmospheric 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. Considerable effort has been devoted to the development of an algorithm to estimate light extinction (b_{ext}) with reasonable accuracy from PM species monitoring data using data on dry mass extinction efficiency and hygroscopicity growth functions for major species. Because it was developed based on measurements from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, this algorithm is widely referred to as the IMPROVE equation. Light extinction (b_{ext}) estimated from IMPROVE network data using the IMPROVE equation is widely used to describe visibility impairment as well as to explore the relationship between atmospheric visibility and PM_{2.5} concentrations. The 2009 PM ISA (U.S. EPA, 2019) reviewed evidence that in polluted environments most of the light extinction (b_{ext}) responsible for visibility impairment is due 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}) was generally elevated in urban centers compared to surrounding rural areas, particularly in the western U.S.

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 hardcopy 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 as a function of atmospheric extinction coefficient 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), copyright permission pending.

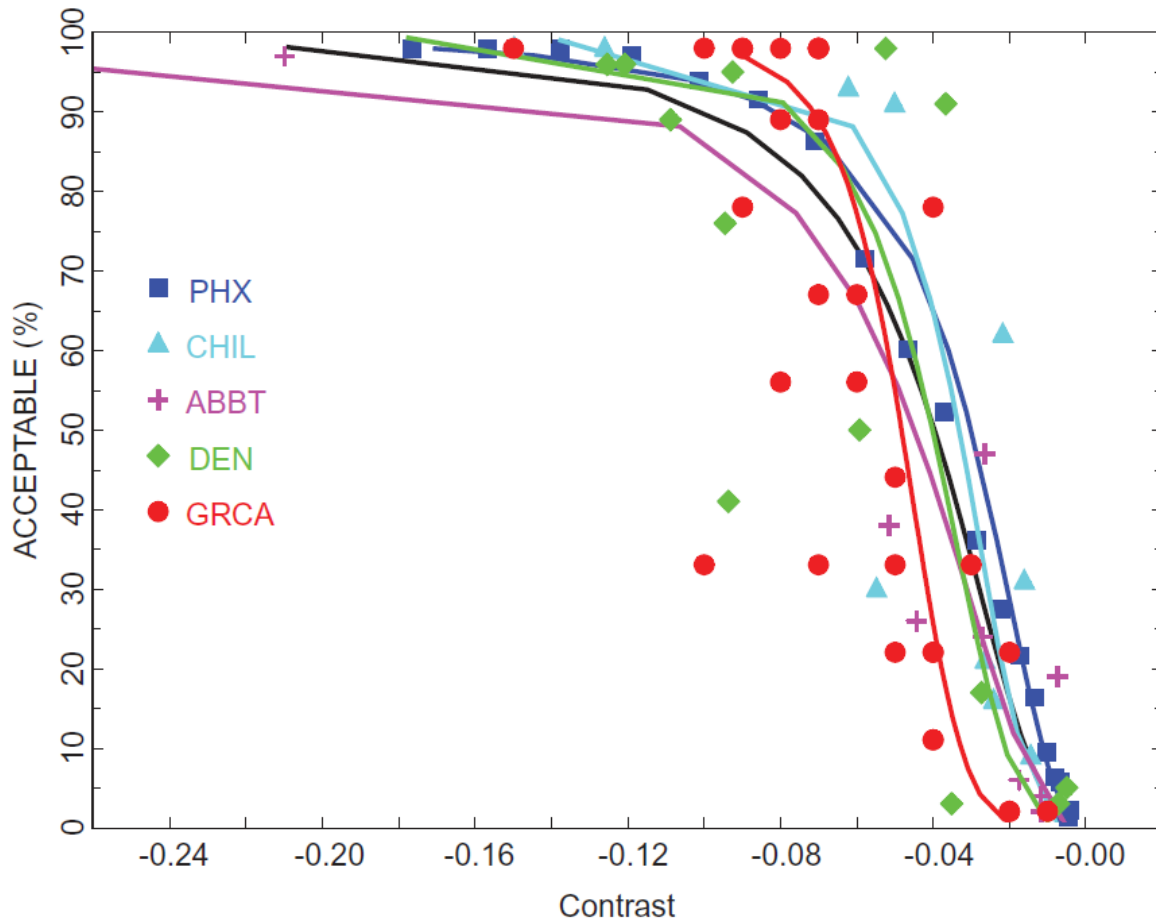
Figure 4-1 Percent acceptability levels plotted against atmospheric extinction coefficient for each of the images used in studies for Washington, DC (WASH), Phoenix, AZ (PHX), Chilliwack, BC (CHIL), Abbotsford, BC (ABBT), Denver, CO (DEN), and the Grand Canyon, AZ (GRCA).

These results clearly demonstrate a large range in atmospheric extinction coefficient (b_{ext}) at a given level of acceptability, indicating that metrics based on extinction are not universal indicators of visibility preference levels. For example, considerably more atmospheric extinction coefficient was needed for the Washington, DC scene to be regarded as unacceptable (192 Mm^{-1}) than for the Grand

1 Canyon, AZ scene (23 Mm^{-1}) ([Malm et al., 2019](#)). For other locations the amount of extinction
2 corresponding to an unacceptable level of visibility impairment was intermediate between Washington,
3 DC and the Grand Canyon, AZ ([Malm et al., 2019](#)). For context, urban monthly average b_{ext} derived from
4 2011–2014 Chemical Speciation Network (CSN) data presented in the 2019 PM ISA was within this
5 range for at least 1 month in all 31 U.S. regions analyzed ([U.S. EPA, 2019](#)).

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

20 [Figure 4-2](#) shows acceptability levels for the same studies in [Figure 4-1](#) plotted against apparent
21 contrast of the distant feature most sensitive to haze. When the features approximately reach the visual
22 range, corresponding to a contrast between about -0.03 to -0.05 , about 50% of observers rated the image
23 as not acceptable. When acceptability is expressed as a function of contrast in [Figure 4-2](#), the response
24 was less dependent on scene, as indicated by a smaller difference between average acceptability in Grand
25 Canyon, AZ and Washington, DC than when acceptability is expressed as a function of extinction in
26 [Figure 4-1](#). This is because most features in the Grand Canyon, AZ scene were more than 10 km distant,
27 while landscape elements in the Washington, DC scene were only a few kilometers apart, and foreground
28 features less than 1 km apart ([Malm et al., 2019](#)).



Source: [Malm et al. \(2019\)](#), copyright permission pending.

Figure 4-2 Percent acceptability levels plotted against apparent contrast of distant landscape features 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).

- 1 [Malm et al. \(2019\)](#) concluded that visibility preference studies suggest that about 50% of
- 2 individuals would find visibility unacceptable if at any time the more distant landscape features nearly
- 3 disappear, and that this occurs when these features are near the visual range and have contrast levels of
- 4 approximately -0.02 to -0.05 . Further, an acceptability level of 90% would require contrast levels to
- 5 remain above a level of about -0.01 .

4.2.2 Recent Advancements in Visibility Monitoring and Assessment

[Hand et al. \(2020\)](#) recently analyzed national and regional trends in light extinction based on reconstructed total light extinction estimated from IMPROVE network speciated PM concentrations in remote areas. On average the atmospheric 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 atmospheric extinction coefficient decreased by 4.3% per year from 2002–2018 and was associated with major reductions of SO₂ and NO_x emissions ([Hand et al., 2020](#)). The reduction in atmospheric 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](#)). [Hand et al. \(2020\)](#) concluded that regulation of SO₂ and NO_x emissions have improved atmospheric visibility, but that the relative contribution of unregulated sources like biomass burning, dust, and international transport to visibility impairment is increasing.

In addition, some recent studies suggest that this rapidly changing PM composition can impact the accuracy of light extinction estimates. As described in detail in the 2019 PM ISA, light extinction is estimated from IMPROVE network data using an algorithm that combines PM species mass, PM size, PM species mass scattering coefficients, and relative humidity ([Malm et al., 1994](#)). This algorithm was modified with the goal of reducing bias that had been observed in applications of the original IMPROVE equation by splitting major PM components between small and large size modes in recognition that atmospheric PM generally follows a bimodal size distribution ([Pitchford et al., 2007](#)). This approach has been referred to as the revised IMPROVE equation ([U.S. EPA, 2019](#)) or the split component algorithm ([Prenni et al., 2019](#)). However, by the time of publication of the 2019 PM ISA, new studies had concluded that the modified IMPROVE equation had not been generally successful in decreasing the bias in atmospheric extinction estimates associated with the original equation ([U.S. EPA, 2019](#)).

Since the literature cutoff date of the 2019 PM ISA, additional bias due to changing PM composition has been described ([Prenni et al., 2019](#)). Estimates of atmospheric extinction based on the modified IMPROVE equation were compared to light scattering directly measured with a nephelometer at 11 IMPROVE network sites from 2001–2016. The relationship between measured and reconstructed light scattering had changed over time, and light scattering was underestimated at many sites in recent years ([Prenni et al., 2019](#)). During the period when light scattering was underestimated, large decreases in sulfate and organic mass concentrations also occurred. A 25% underprediction was also reported when reconstructed extinction was compared to 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 atmospheric extinction estimates from the IMPROVE equation was reasonable at average relative humidity, but substantially lower at both higher and lower humidities.

The importance of including relative humidity in estimating atmospheric 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 µg/m³ and

1 the variability of atmospheric extinction was controlled primarily by differences in PM concentrations.
2 However, substantially higher concentrations, averaging 18.4 $\mu\text{g}/\text{m}^3$ were observed for westerly PM
3 transport from the Ohio River Valley, PM was more hygroscopic, and the variability of atmospheric
4 extinction was controlled by both $\text{PM}_{2.5}$ concentration and relative humidity ([Beyersdorf et al., 2016](#)).

5 The observations of persistent and potentially increasing bias in the main method for estimating
6 atmospheric extinction from national monitoring network data is a continued concern, and research is
7 progressing on how to reduce it. Most recently, an alternative approach to the split component revised
8 IMPROVE algorithm was explored to evaluate the bias associated with component contributions to
9 extinction estimated by scaling to annual average mass by component, year, and site ([Prenni et al., 2019](#)).
10 This approach successfully reduced biases in extinction estimates from the split component revised
11 IMPROVE algorithm.

12 As described in the 2019 PM ISA, recent decreases in SO_2 and NO_x emissions have coincided
13 with increasing PM emissions from wildland fires ([U.S. EPA, 2019](#)). As a result, recent studies have
14 focused on visibility impairment specifically from fire related PM. Recent estimates of mass scattering
15 efficiencies for wildland fire smoke ranged from 2.50 to 4.76 m^2/g , and increased with particle median
16 diameter, as expected from theoretical predictions ([Laing et al., 2016](#)). Mass scattering efficiencies of fire
17 related PM were observed to increase by 56% during the first 2–3 hours after emission, at least in part
18 due to increasing particle size during atmospheric aging ([Kleinman et al., 2020](#)). The large and rapid
19 change in mass scattering efficiencies during atmospheric aging presents a challenge for accurately
20 estimating atmospheric light extinction based on constant mass scattering coefficients, as in the
21 IMPROVE equation.

22 Recent studies have also introduced new instrumentation and measurement methods that could
23 help to reduce uncertainties in extinction. Multi-wavelength light attenuation methods used as a part of
24 thermal/optical carbon analysis in the IMPROVE and Chemical Speciation Networks (2019 PM ISA,
25 Section 2.4 and Section 13.2.4) were initiated in 2016 and are used to estimate brown carbon, which in
26 turn can be used to estimate biomass burning contributions to atmospheric light absorption ([Chow et al.,
27 2021](#)). Application of a paired-wavelength method to estimate light absorption by brown carbon resulted
28 in a factor of two increase in the estimate of the contribution of brown carbon to light absorption in CSN
29 network samples from 2016–2017 ([Chow et al., 2021](#)). These results suggest that a considerably greater
30 contribution of organic PM to light absorption by PM than could be estimated using network
31 thermal/optical methods in place before 2016. This is a highly relevant result given that organic matter
32 has recently overtaken sulfate as the most abundant $\text{PM}_{2.5}$ component in many locations, and that
33 wildland fire emissions are an increasing source of PM ([U.S. EPA, 2019](#)).

Capabilities for estimating atmospheric extinction from photographic images have also progressed. In the 2019 PM ISA photography is identified as one of several methods of measuring atmospheric extinction ([U.S. EPA, 2019](#)), and results from image processing techniques had been shown to be highly correlated with measured atmospheric extinction in hazy atmospheres under hazy conditions. Additional, a recent study demonstrated that atmospheric extinction could also be estimated quantitatively from photographic images under more pristine conditions, like webcams that are routinely operated at 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 has 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 atmospheric extinction or related metrics. Evaluation of uncertainties and development of alternative approaches to estimating atmospheric 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:

- A wide range in response to the level of acceptable visibility observed across different settings is reduced by accounting for the distance between observer and landscape feature as a part of a visibility metric. This was demonstrated by observation of a smaller variation across different settings using apparent contrast than 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 to 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

1 The 2019 Integrated Science Assessment for Particulate Matter (PM ISA) is a comprehensive,
2 systematic evaluation of the state of the science with respect to the health and welfare effects of PM that
3 built upon previous assessments conducted in support of the National Ambient Air Quality Standards
4 (NAAQS) for PM ([U.S. EPA, 2019](#)). While the 2019 PM ISA presented key scientific conclusions that
5 informed many policy-relevant questions, as detailed in [Section 2](#), a subset of these conclusions was most
6 informative in the process of establishing the 2020 PM NAAQS (as discussed in [Section 1.2](#)), which is
7 under reconsideration. Specifically, extensive evidence spanning scientific disciplines supported the
8 conclusion of a *causal relationship* between both short- and long-term PM_{2.5} exposure and cardiovascular
9 effects and mortality. In addition, an assessment of those populations potentially at increased risk of a
10 PM-related health effect identified many populations and lifestages that experience both health risk and/or
11 exposure disparities with some of the strongest evidence being for non-White populations, with more
12 limited evidence for people of low socioeconomic status (SES). Lastly, in the assessment of welfare
13 effects, there is extensive evidence indicating a *causal relationship* between PM and visibility effects,
14 specifically visibility impairment. These topics are the basis of the scientific evaluation conducted in this
15 Supplement.

16 Recent studies published in the U.S. and Canada provide additional support for the conclusions of
17 the 2019 PM ISA. Overall: (a) recent studies support, and in some instances strengthen, the evidence
18 presented in the 2019 PM ISA; (b) many of the recent epidemiologic studies evaluated report positive
19 associations in areas with annual average or mean 24-hour avg PM_{2.5} concentrations similar to, or in many
20 cases lower, than those studies evaluated in the 2019 PM ISA; (c) some recent studies address key
21 scientific topics where the literature has evolved since the 2020 PM NAAQS review was completed,
22 specifically since the literature cutoff date for the 2019 PM ISA, including examining health effects at
23 near-ambient PM_{2.5} concentrations in experimental settings, and examining the association between PM_{2.5}
24 exposure and COVID-19 infection and death, which both provide preliminary evidence to further inform
25 the PM_{2.5}-health effects relationship; (d) recent studies support, and in some instances extend, the
26 evidence base indicating that non-White populations, specifically Black individuals, and low SES
27 individuals, experience disparities in both PM_{2.5}-related health risks and exposures compared to
28 non-Hispanic White populations; and (e) recent studies further inform the role of PM on light extinction
29 and visibility impairment. In conclusion, the results of recent studies evaluated in this Supplement to the
30 2019 PM ISA support, and in some instances extend, the scientific conclusions of the 2019 PM ISA.

31 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 diverse populations 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 7.1–15.4 µg/m³. 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 causal modeling methods 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.

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 µg/m³. 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 more diverse populations, 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 non-linearity at lower concentrations for some outcomes. Lastly, a few recent epidemiologic studies that employed causal modeling methods, reduce some uncertainties related to potential confounding bias and further support a relationship between long-term PM_{2.5} exposure and cardiovascular effects.

Mortality

Short-Term PM_{2.5} Exposure

- Since the literature cut-off 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 based evaluated in the 2019 PM ISA and 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/m³; 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, there continues to be evidence that the heterogeneity in city-to-city PM_{2.5}-mortality risk estimates can partly be attributed 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/m³. The relationship between short-term PM_{2.5} exposure and mortality is further supported by recent epidemiologic studies that employed causal modeling methods and report consistent, positive associations.

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 generally below 12 µg/m³, with the majority ranging from 5.9 to 11.65 µg/m³, 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 generally support a linear, no-threshold relationship with certainty down to 4 µg/m³. However, some uncertainties remain about the shape of the C-R curve at relatively low PM_{2.5} concentrations (<8 µg/m³), with some recent studies providing evidence for either a sublinear, linear, or supralinear relationship at these lower concentrations. Lastly, an extensive number of epidemiologic studies that conducted accountability analyses or employed causal modeling methods have been conducted since the literature cut-off 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.

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/m³). 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 to other studies.

COVID-19 Infection and 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 COVID-19 infection and 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

1 study design, studies were conducted during on ongoing pandemic while the etiology of
2 COVID-19 was still not understood (e.g., there are important differences in COVID-19 related
3 health such as by race and SES), and studies did not account for crucial factors that could
4 influence results (e.g., stay at home orders, social distancing, use of masks, and testing capacity).

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

Socioeconomic Status

- 5 • Recent studies that use a variety of metrics to represent SES including educational attainment and
6 income, along with studies that used composite metrics to represent neighborhood SES provide
7 additional support indicating there may be disparities in PM_{2.5} exposure and health risk by SES.
8 These studies indicate that the strongest evidence of a health risk disparity for low SES is for
9 cause-specific mortality and certain health endpoints (i.e., MI and CHF) when compared to higher
10 SES groups.

Race and Ethnicity

- 11 • Building upon the conclusions of the 2019 PM ISA, recent studies continue to support disparities
12 in PM_{2.5} exposure and health risks by race and ethnicity, with the strongest evidence for
13 non-White, specifically Black, populations. Black populations or individuals that live in
14 predominantly Black neighborhoods experience higher PM_{2.5} exposures, in comparison to
15 non-Hispanic White populations. Additionally, there is evidence of health risk disparities for both
16 Hispanic and non-Hispanic Black populations compared to non-Hispanic White populations for
17 cause-specific mortality and incident hypertension.

Visibility Effects

- 18 • Recent studies indicate that using contrast instead of light extinction as a metric greatly reduced
19 the variability in results in visibility preference studies. In addition, rapidly decreasing sulfate and
20 increasing fire related contributions to PM have led to a changing relationship between PM and
21 visibility impairment, likely impacting estimates of atmospheric extinction. In response, alternate
22 approaches to the application of the traditional IMPROVE algorithm for estimating atmospheric
23 light extinction have been developed that reduce the bias in atmospheric extinction estimates.
24 Parallel efforts have better characterized light extinction by major contributors to PM, particularly
25 for biomass burning.

Appendix A

Table A-1 Study-specific details for epidemiologic studies of short-term exposure to PM_{2.5} and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations (µg/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 R ² = 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) Four counties in Wasatch Front, UT 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 (ICD9 410), HF (ICD9 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations (µg/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 didn't 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, 1 monitor, Eastside 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–April 9.80 May–Oct Upper (Max): 79.2 all year; 79.20 Nov–April; 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations (µg/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 3 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 (16 counties) MO and IL 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 (ICD9 428); Cardiac dysrhythmia (ICD9 427); IHD (ICD9 410–414); Stroke (ICD9 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu\text{g}/\text{m}^3$) ^a	Outcome	Confounders Considered	Copollutant Examination
Ye et al. (2018) Five counties in Atlanta, GA Aug 14, 1998–Dec 15, 2013		24 h avg from 1 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) (0.99, 1.01) Estimate from Fig 1	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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations (µg/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 age 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location, Years	Study Population	Exposure Assessment	Mean and Upper Percentile Concentrations ($\mu\text{g}/\text{m}^3$) ^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 R ² = 0.86 (Di et al., 2019). Lag Day 0–1 used in all analyses.	Mean (SD) 11.5 (7.3)	First HA for CVD (ICD9 390–495); IHD (ICD9 410–414); CHF (ICD9 428); AMI 410.9; IS: (ICD9 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; h = hour; LUR = land use regression; HA = hospital admission; STEMI = ST segment elevated myocardial infarction; RH = relative humidity; IHD = ischemic heart disease; CHF = congestive heart disease; ICD-9 = International Classification of Disease 9th revision; HPFU = Health Professionals Follow-up Study; CMAQ = Community Multi-Scale Air Quality; REGARDS = REasons for Geographic And Racial Differences in Stroke; SPE = standardized prediction error; PE = prediction error; RMSS = root mean square standardized; BASIC = Brain Attack Surveillance in Corpus Christi; USRDS = U.S. Renal Data System; WS Fe = water soluble iron.

Table A-2 Study-specific details for epidemiologic studies using accountability analyses or causal modeling methods to examine short-term exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentration (µg/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; chronic 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 causal modeling methods to examine short-term exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentration (µg/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, µg/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 sensing 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

Table A-3 Study-specific details for epidemiologic studies of long-term exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (µg/m ³)	Confounders Considered	Copollutant Examination
Rhinehart et al. (2020) Allegheeny County, PA Jan 1, 2007 Rhinehart et al. (2020) Dec 1, 2017	Resident of Allegheeny County, PA and diagnosed with AF (ECG, ablation, cardioversion [ICD10 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (µg/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) 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (µg/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), non-fatal 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (µg/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 R ² = 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): PM ₁₀ : 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., 2015 ; 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (µg/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., 2015 ; 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 June 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 R ² = 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 exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	Mean and Upper Percentile Concentration (µg/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 (1st 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 exposure to PM_{2.5} 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. (CV 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 (Di et al., 2016) Cross validated R ² = 0.86		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; CAC = coronary artery calcium; CATHGEN = Catheterization Genetics study; CHF = congestive heart failure; JHS = Jackson Heart Study; MESA = Multi-Ethnic Study of Atherosclerosis and Air Pollution; IAD = inter-adventitial diameter ; NHS = Nurses Health Study; ONPHEC = Ontario Population Health and Environment Cohort; Ox = redox weighted average of NO₂ and O₃; REGARDS = REasons for Geographic and Racial Differences in Stroke; SWAN = Study of Women's Health Across the Nation.

Table A-4 Study-specific details for epidemiologic studies using accountability analyses or causal modeling methods to examine long-term exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentration (µg/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 3 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 1 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 1 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

Table A-4 (Continued): Study-specific details for epidemiologic studies using causal modeling methods to examine long-term exposure to PM_{2.5} and cardiovascular effects.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentration (µg/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: HYSPLIT 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 (<i>r</i>): NA Copollutant models with: NA

Table A-5 Study-specific details for epidemiologic studies of short-term exposure to PM_{2.5} and mortality.

Study/Location Years	Study Population	Mortality Outcome	Exposure Assessment	Confounders in Statistical Model	Mean and Upper Percentile Concentrations (µg/m ³)	Copollutant Examination
Liu et al. (2019) 652 cities worldwide; 107 U.S. cities; 25 Canadian cities (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. 24 cities in Canada 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 Ox: 0.28 Copollutant models with: Ox
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 (r): NA Copollutant models with: NA

Table A-5 (Continued): Study-specific details for epidemiologic studies of short-term exposure to PM_{2.5} and mortality.

Study/Location Years	Study Population	Mortality Outcome	Exposure Assessment	Confounders in Statistical Model	Mean and Upper Percentile Concentrations (µg/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 March 2013–February 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 through the U.S. 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 the U.S. 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; MCC = Multi-City Multi-Country Collaborative Research Network; MD = metropolitan division; NAPS = National Air Pollution Surveillance System.

Table A-6 Study-specific details for epidemiologic studies using causal modeling methods to examine short-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 causal modeling methods to examine short-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 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
Schwartz et al. (2018a) 135 U.S. 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

Table A-7 Study-specific details for epidemiologic studies of long-term exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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, R ² = 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 1988–1998, based on the relationship between monitored PM ₁₀ and PM _{2.5} concentrations, and primary modeled data from 1999–2015. 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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-km ² 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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+ mos 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/m ³)	Copollutant Examination
Pinault et al. (2017) U.S. PM _{2.5} :1998–2010 Follow-up: 5/15/1991– 12/31/2011	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 R ² = 0.82 in locations where PM _{2.5} <20 µg/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 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/m ³)	Copollutant Examination
Erickson et al. (2020) Canada PM _{2.5} : 1998–2106 Follow-up: 5/15/2001–12/31/2016	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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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 R ² 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 1998–2011 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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} sulphate 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 km ² 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 (R ² = 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 Sulphate: 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/m ³)	Copollutant Examination
Pinault et al. (2018) Canada CanCHEC PM _{2.5} :1998–2012 Follow-up: 5/15/2001– 12/31/2011 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 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. 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, R ² = 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 (R ²): 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/m ³)	Copollutant Examination
Ward-Caviness et al. (2020) North Carolina, U.S. PM _{2.5} : 2003–2016 Follow-up: July 2004–December 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 the U.S. 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: r ² = 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 exposure to PM_{2.5} and mortality.

Study	Study Population	Mortality Outcomes	Exposure Assessment	Confounders in Statistical Model	PM _{2.5} Concentrations (µg/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 75h: 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; 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 Multi-scale Air Quality model; GEOS-Chem = Goddard Earth Observing System-Chem; GWR = geographically weighted regression; mCCHS = Canadian Community Health Survey—Mortality cohort; 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; PREMIER = Prospective Registry Evaluating Myocardial Infarction: Events and Recovery; RH = relative humidity; SD = Standard Deviation; SES = socioeconomic status; TRIUMPH = Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction.

Table A-8 Study-specific details for epidemiologic studies using accountability analyses or causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 1 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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 Optical 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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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: HYSPLIT 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 counties (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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 the U.S. EPA Air Quality System (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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 Air Quality System 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 (LDLC) 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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 4 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
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 1999–2015 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 causal modeling methods to examine long-term exposure to PM_{2.5} and mortality.

Study/Location Years	Population (Cohort)	Outcome	Exposure Assessment	PM _{2.5} Concentrations (µg/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 (LDLC) 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

Table A-9 Study-specific details for epidemiologic studies of short-term PM_{2.5} exposure and COVID-19.

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 March 1, 2020–April 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 (<i>r</i>): O ₃ = -0.82 Copollutant models with: NA

Table A-10 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
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, ICU beds, liquid asset poverty rate, total healthcare and social services workers, total essential workers, fraction of total healthcare 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 2 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
Liang et al. (2020) 3,122 U.S. Counties January 22, 2020 to July 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

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
Mendy et al. (2021) University of Cincinnati Hospital System March 13, 2020–July 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 2008–2017 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) 111 Canadian health regions up to May 13, 2020	COVID-19 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
Wu et al. (2020b) 3,089 U.S. Counties Up to June 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

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 June 2013–November 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 April 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 Rea-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 North Carolina	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

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/m ³)	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 Maximum: 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 Case-crossover	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) Maximum: 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

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 (µg/m ³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Bai et al. (2019) Ontario, Canada	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. See Figure	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/m ³)	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	Non-accidental 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. See Figure.	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 Maximum: 19.02	PM _{2.5} more detrimental in states with high percent of income inequality. See Figure.	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 Maximum: 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/m ³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Shin et al. (2019) Ontario, Canada	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 Maximum: 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. (see Figure)	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 (µg/m ³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Weaver et al. (2019) 2001–2010 Duke University Medical Center Wake, Durham, and Orange Counties in North Carolina	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) (see Figure)	Odds ratios were adjusted for age, sex, BMI, race, and smoking status	Correlation (r): NA Copollutant models with: NA
Wyatt et al. (2020b) 3,132 counties in the U.S. 1990–2010	National Center for Health Statistics	Cardiovascular mortality	Annual average PM _{2.5} concentrations were estimated using CMAQNR	In the 1990's, 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} (see Figure)	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/m ³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Zhang et al. (2021) Ontario, Canada 2009–2017	Ontario Health Study n = 88,615	Total non-accidental 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) Non-Accidental <\$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

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 2000–2012 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
Ergou 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 9 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) Maximum: 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 × 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) 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 × 1 km grid	NR	Correlation (r): NA Copollutant models with: NA

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 (µg/m ³)	Select Results	Covariates in Statistical Model	Copollutant Examination
Yitshak-Sade et al. (2019a) Massachusetts 2001–2011 Case-crossover	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 × 1 km grid Mean: 10.2 Maximum: 17.4	Change in CV mortality <u>High % White</u> Green: 2.80% (0.62, 5.02) Less green: 1.14% (–1.00, 3.33) <u>Low % White</u> 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 <u>Individual</u> Black: 4.78% (–1.99, 12.02) White: 2.25% (0.80, 3.23) <u>Block group</u> Low % Black: 1.62% (0.05, 3.22) High % Black: 3.35% (1.57, 5.16) <u>Racial Residential Segregation (RRS)</u> More White (RRS 0.5, 1): 1.84% (0.31, 3.40) More Black (RRS –1, –0.5): 15.37% (0.76, 31.99) <u>Index of Racial Dissimilarity (IRD)</u> No difference—see figure	Temperature and day of the week	Correlation (r): NA Copollutant models with: NA

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 ($\mu\text{g}/\text{m}^3$)	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 2000–2012 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	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

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 (µg/m ³)	Select Results	Covariates	Copollutant Examination
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 Maximum: 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
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	Hyper- tension	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

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 (µg/m ³)	Select Results	Covariates	Copollutant Examination
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) Maximum: 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
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

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 (µg/m ³)	Select Results	Covariates	Copollutant Examination
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
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) Maximum: 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

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