CANADIAN HEALTH SCIENCE ASSESSMENT FOR FINE PARTICULATE MATTER ($PM_{2.5}$)

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
APOE	apolipoprotein E
AQMS	Air Quality Management System
BMI	body mass index
CAAQS	Canadian Ambient Air Quality Standards
CAC	coronary artery calcium
CanCHEC	Canadian Census Health and Environment Cohort
CAP	concentrated ambient particle
CCHS	Canadian Community Health Survey
CCME	Canadian Council of Ministers of the Environment
CEB	cerebrovascular
CHF	congestive heart failure
CIMT	carotid intimal medial thickness
CNBSS	Canadian National Breast Screening Study
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CSSA	Canadian Smog Science Assessment
DNA	deoxyribonucleic acid
FMD	flow-mediated dilatation
GSH	glutathione
GSTM1	glutathione-s-transferase mu 1
H6CS	Harvard Six Cities Study
HDL	high-density lipoprotein
HRV	heart rate variability
IARC	International Agency for Research on Cancer
ICAM-1	intercellular adhesion molecule-1
IHD	ischemic heart disease
IL-1ß	interleukin-1ß
IL-6	interleukin-6
LDL	low-density lipoprotein
miRNA	microRNA

mRNA	messenger RNA
NHS	Nurses' Health Study
NMD	nitroglycerin-mediated reactivity
NO_2	nitrogen dioxide
NO_3^-	nitrate
O_3	ozone
PM	particulate matter
PM_{10}	PM of 10 μm or less in median aerodynamic diameter
$PM_{10-2.5}$	coarse PM, PM with a median aerodynamic diameter between 2.5 and 10 μm
$PM_{2.5}$	fine PM, PM of 2.5 μm or less in median aerodynamic diameter
RNA	ribonucleic acid
SO_2	sulphur dioxide
SO_4^{2-}	sulphate
T1	first trimester
T2	second trimester
T3	third trimester
TNF-α	tumour necrosis factor-α
UFP	ultrafine particle, PM with a median aerodynamic diameter less than 0.1 μm
US EPA	United States Environmental Protection Agency
V_2O_5	vanadium pentoxide
VCAM-1	vascular cell adhesion molecule-1
VLDL	very low density lipoprotein
WHIMS	Women's Health Initiative Memory Study
WHO	World Health Organization

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EXECUTIVE SUMMARY

The health effects of air pollution have been extensively studied and are well documented in the peer-reviewed scientific literature. There is consensus among international and national organizations, including Health Canada, World Health Organization (WHO), United States Environmental Protection Agency (US EPA), European Union, and International Agency for Research on Cancer (IARC), that air pollution, even at low levels, adversely impacts health. Health effects include premature mortality, increased hospitalizations, respiratory symptoms, and cardiovascular effects.

According to the 2019 Global Burden of Disease project, air pollution, specifically from ambient (outdoor) fine particulate matter ($PM_{2.5}$), is one of the leading environmental causes of death and disease both globally and in Canada (IHME, 2021). While Canada ranks amongst the countries with the best air quality in the world, Health Canada (2021) estimates that 15,300 (42/100,000) premature deaths per year in Canada are linked to ambient air pollution from $PM_{2.5}$, nitrogen dioxide (NO_2) and ground-level ozone (O_3), with 10,000 of these due to $PM_{2.5}$. In terms of annual morbidity outcomes, the number of asthma symptom days is estimated at 1.72 million, while the number of acute respiratory-symptom days amounts to 24.8 million. The total economic valuation of the health impacts attributable to air pollution in Canada is $120 billion per year (based on 2016 CAD) (Health Canada, 2021). This is true despite air pollution levels in Canada being considered low compared to those of other developed countries (WHO, 2021).

The present report summarizes the health science for $PM_{2.5}$ in the context of ambient air pollution in Canada. The main purpose of this report is to update the conclusions on $PM_{2.5}$ from the *Canadian smog science assessment. Volume 2: health effects* (Health Canada, 2013), which is referred to as CSSA in this report. In addition, the present report provides details on population subgroups with increased sensitivity and a better characterization of the shape of the concentration-response relationships, especially for lower concentrations of $PM_{2.5}$. It provides the basis for the ongoing risk management of $PM_{2.5}$, including establishing the Canadian Ambient Air Quality Standards (CAAQS). This report also identifies emerging health effects and data gaps to guide future research.

CAUSALITY CONCLUSIONS

This report reviews the epidemiological and toxicological studies published between 2007 and 2016, inclusively. Conclusions on the causality relationship between health outcomes (i.e., premature mortality and morbidity) and $PM_{2.5}$ exposure are drawn by following the weight of evidence framework for causality determination of human health effects. Conclusions from the CSSA and from the present report are summarized in Table ES-1.

Causality relationship conclusions

TABLE ES-1: Past and updated conclusions on causality relationship between health outcomes and short- and long-term exposure to ambient $PM_{2.5}$

Health outcome	$PM_{2.5}$ exposure duration	CSSA conclusion on causality relationship	Updated conclusion on causality relationship
All-cause mortality	Short-term	Causal	Causal
	Long-term	Causal	Causal
Cardiovascular effects	Short-term	Mortality: Causal; Morbidity: Causal	Mortality: Causal; Morbidity: Causal
	Long-term	Mortality: Causal; Morbidity: Suggestive	Mortality: Causal; Morbidity: Likely Causal*
Respiratory effects	Short-term	Mortality: Causal; Morbidity: Causal	Mortality: Causal; Morbidity: Causal
	Long-term	Mortality: Inadequate; Morbidity: Suggestive	Mortality: Suggestive*; Morbidity: Likely Causal*
Cancer effects	Long-term	Lung cancer mortality: Likely causal	Lung cancer morbidity and mortality: Likely causal
Neurological effects	Short-term	No conclusion drawn	Inadequate*
	Long-term	No conclusion drawn	Suggestive*
Reproductive and developmental effects	Long-term	Combined outcome: Suggestive (considered all PM fraction sizes)	Reproductive: Inadequate*; Developmental: Suggestive

* represents a change in causality conclusion from the CSSA (Canadian Smog Science Assessment) (Health Canada, 2013). Framework for weight of evidence for causality determination is discussed in section 1.4 of this report.

All-cause mortality

The large epidemiological evidence dataset published since the CSSA continues to support the finding that short- and long-term exposure to $PM_{2.5}$ is strongly associated with all-cause mortality (any premature death not considered to be due to an accident or a homicide). All-cause mortality as well as cause-specific mortality are considered in this report to reduce the risk of bias and uncertainty and to identify target organs and specific diseases. Evidence from cause-specific mortality associations and the progression of disease from morbidity associations provided consistency and biological plausibility supporting the all-cause mortality database. The relationship between $PM_{2.5}$ (short- and long-term exposure) and all-cause mortality is concluded to be **causal**, reconfirming the causal relationship established in the CSSA.

Cardiovascular effects

Short-term exposure

There is strong, robust and consistent evidence from epidemiological studies that short-term exposure to $PM_{2.5}$ is associated with cardiovascular mortality and hospital visits due to adverse cardiovascular health effects. More specific causes of death associated with $PM_{2.5}$ exposure include myocardial infarction (heart attack), congestive heart failure, cerebrovascular (CEB) disease (including stroke) and, to some extent, diabetes. Adverse health effects include life-threatening effects that require urgent care. Clinical cardiovascular conditions, such as congestive heart failure (CHF), myocardial infarction and, to a lesser extent, CEB-related admissions, were associated with exposure to $PM_{2.5}$. Epidemiological panel studies, controlled human exposure studies and toxicological studies provide coherence and biological plausibility support for these population-level associations. Thus, the collective evidence supports a **causal relationship** between short-term exposure to $PM_{2.5}$ and cardiovascular-related morbidity and mortality, reconfirming the causal relationship established in the CSSA.

Long-term exposure

For long-term exposure, the large epidemiological database continues to support the CSSA conclusion that exposure to $PM_{2.5}$ is associated with overall cardiovascular mortality and cause-specific mortality (ischemic heart disease [IHD] including myocardial infarction, with some evidence for CEB and cardiac arrest-related mortality). The morbidity database in the CSSA was small, and evidence at that time suggested that exposure to $PM_{2.5}$ was associated with increased arterial wall thickening, an indicator of atherosclerosis (plaque buildup in blood vessels). With the expansion of the morbidity database since the CSSA, exposure to $PM_{2.5}$ has been found to be associated with cardiovascular-related hospital admissions, development of cardiovascular conditions, and changes in cardiac functions and parameters related to disease progression. Associated health conditions include atherosclerosis, IHD including myocardial infarction, CHF, CEB disease, hypertension, peripheral vascular disease (narrowing or blockage of blood vessel outside of the heart) and possibly diabetes, although some mixed results were reported for particular outcomes. Coherence and biological plausibility support for these associations are provided by toxicological studies, especially with respect to alterations in cardiac tissue, hypertension, plaque formation and atherosclerosis and by a small human dataset that examined associations with subclinical markers. Overall, the substantially increased body of evidence strengthens the confidence in the database. The conclusion on the causality relationship between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity is now **likely causal**, whereas the CSSA had concluded that the evidence was only suggestive of causality. The **causal relationship** between $PM_{2.5}$ exposure and cardiovascular mortality found in the CSSA is reconfirmed.

Respiratory effects

Short-term exposure

The epidemiological database consistently reported associations between short-term exposure to $PM_{2.5}$ and increased respiratory mortality, with increased risk in individuals with chronic obstructive pulmonary disease (COPD). $PM_{2.5}$ exposure is strongly associated with increased respiratory hospital visits, particularly for asthma or COPD exacerbation and pneumonia. Epidemiological studies also reported associations between $PM_{2.5}$ exposure and reduced lung function and increased airway inflammation. Moreover, coherence and biological plausibility are also provided by toxicological studies, as increases in lung injury and enhanced allergic responses accompanying oxidative stress and inflammation were observed in animals exposed to $PM_{2.5}$. Thus, the overall evidence supports a **causal relationship** between short-term exposure to $PM_{2.5}$ and respiratory-related mortality and morbidity, reconfirming the causal relationship established in the CSSA.

Long-term exposure

For long-term exposure to $PM_{2.5}$, a small but growing epidemiological database suggests that there is an association between $PM_{2.5}$ exposure and overall respiratory and COPD-specific mortality. Morbidity outcomes associated with $PM_{2.5}$ exposure included reduced lung function, development of chronic respiratory conditions and related hospital visits and increased respiratory symptoms. There are some limitations in the overall database, specifically, the strength and consistency of the associations in the respiratory mortality dataset, in comparison to that of all-cause or cardiovascular mortality. Furthermore, the toxicological database is limited to shorter-term exposure studies. Nevertheless, there is some evidence of biological plausibility and coherence, mainly for asthma diagnosis and reduced lung function. The weight of evidence supports a **likely causal relationship** between respiratory morbidity and long-term exposure to $PM_{2.5}$, resulting in increased asthma development, asthma exacerbations and reduced lung function, especially in children and asthmatics. This is a change from the CSSA, which found that the evidence was only suggestive of a causal relationship. The evidence of a relationship between respiratory mortality and $PM_{2.5}$ exposure is also **suggestive of, but not sufficient to infer, a causal relationship**, whereas the CSSA had previously found that the evidence was inadequate to draw any conclusion regarding causality.

Cancer effects

Multiple large Canadian and American epidemiological cohort studies have consistently reported an increase in lung cancer incidence and mortality following exposure to $PM_{2.5}$. The toxicological database provides coherence to the epidemiological findings, with numerous studies showing evidence of oxidative stress, inflammation and direct and indirect genotoxicity. Such mechanisms are known to induce mutations and are key to cancer initiation and development; as such they provide biological plausibility to the various epidemiological studies observing increased risk in lung cancer development. However, no complete long-term carcinogenicity studies are available. For other types of cancer (including breast cancer), the lack of high-quality published studies, potential confounding and large confidence intervals (imprecision) of results prevent the drawing of any specific conclusion. Overall, the database continues to support a **likely causal relationship** between exposure to $PM_{2.5}$ and lung cancer morbidity and mortality, whereas the CSSA had sufficient information to conclude on a likely causal relationship for lung cancer mortality only.

Neurological effects

Short-term exposure

A limited number of studies have investigated the relationship between short-term $PM_{2.5}$ exposure and neurological effects. Only one epidemiological study analyzed the impact of short-term exposure to $PM_{2.5}$ on neurological conditions. It reported associations between $PM_{2.5}$ and hospital admission for Parkinson's disease, Alzheimer's disease and dementia. A few toxicological studies provide biological plausibility to this result by showing increases in inflammatory and stress-related biomarkers in the brain of mice, potentially leading to more serious neurological conditions. Because of the small size of the database, it is not possible to assess the consistency, robustness, coherence, or strength of the results. There was no causality conclusion drawn for this outcome in the CSSA, and the evidence is **inadequate to infer a causal relationship** between short-term $PM_{2.5}$ exposure and neurological outcomes.

Long-term exposure

The epidemiological study database on long-term exposure to $PM_{2.5}$ and neurotoxicity is growing, but is still relatively small. A few cohort studies have reported associations between exposure to $PM_{2.5}$ and risk of neurodegenerative diseases, reduced cognitive functions, and smaller white matter volume. In addition, alterations in brain morphology and increases in oxidative stress, inflammation and biomarkers of neurological degeneration provide biological plausibility for the epidemiological results. Some toxicological studies are also reporting alterations in behaviour that are coherent with some of these associations. There was no causality conclusion drawn for this outcome in the CSSA, however, the evidence is now **suggestive of, but not sufficient to infer, a causal relationship** between long-term exposure to $PM_{2.5}$ and neurological outcomes.

Reproductive and developmental effects

The CSSA concluded that the evidence was suggestive of, but not sufficient to infer a causal relationship with reproductive and developmental outcomes for all PM fraction sizes. The CSSA only reviewed a limited number of studies on reproductive and developmental effects of $PM_{2.5}$. Hence, only one conclusion was drawn for these two groups of health effects in the CSSA report.

In this update, the reproductive database is relatively small. Epidemiological evidence has mostly focused on associations with maternal health conditions during pregnancy (i.e., hypertensive disorders and gestational diabetes). Some studies indicate an association between exposure to $PM_{2.5}$ and fertility, but overall the results are inconsistent. The small toxicological database provides some evidence of biological plausibility and coherence based on alterations in placenta tissue and sperm quality observed in experimental animals exposed to $PM_{2.5}$. However, uncertainties remain regarding the strength, robustness, consistency and coherence of the associations and hence the evidence is considered to be **inadequate to infer a causal relationship** between $PM_{2.5}$ exposure and reproductive outcomes.

There is consistency in the epidemiological database relating $PM_{2.5}$ exposure during pregnancy to birth weight-related outcomes. There is also coherence with the toxicological database, with a decrease in fetal weight being observed. Associations were robust, but more studies are needed to examine whether other factors may be at play (e.g., to identify any period(s) of susceptibility or critical window(s) of exposure), especially in relation to the involvement of other ambient air pollutants.

Despite the small size of the epidemiological datasets for birth defects and stillbirth, the toxicological database demonstrates some biological plausibility and coherence, since oxidative stress and inflammation seem to play a role in the mechanisms leading to heart, lung, and neurological malformations in the offspring of experimental animals exposed to $PM_{2.5}$. Overall, the evidence is **suggestive of, but not sufficient to infer, a causal relationship** between $PM_{2.5}$ exposure and developmental effects.

OTHER CONSIDERATIONS

Population subgroups with increased sensitivity

A number of population subgroups have increased sensitivity to $PM_{2.5}$. Carrying certain variants of genes involved in oxidative stress defence, young age, smoking, and having pre-existing health conditions, such as cardiovascular diseases, diabetes, asthma, obesity and COPD, are factors that can enhance the risk of adverse health outcomes (cardiovascular outcomes, hospital visits, premature mortality, and asthma exacerbation) with exposure to $PM_{2.5}$. Together, these factors affect a large proportion of the Canadian population, increasing the health risks of $PM_{2.5}$ exposure.

Shape of the concentration-response relationship

Some epidemiological studies reviewed in this report specifically discussed the shape of the concentration-response relationship between $PM_{2.5}$ exposure and health outcomes. The shape of the concentration-response relationship for both short- and long-term $PM_{2.5}$ exposure and mortality and medical-related visits (i.e., hospital admissions, emergency room visits) appears to be approximately linear, with no clear evidence of a threshold at very low ambient concentrations. A linear concentration-response relationship refers to a straight line where there is a constant rate of increase in response as the concentration increases. In some Canadian epidemiological studies, the analyses covered annual concentrations, which are below established CAAQS for $PM_{2.5}$, in the 3 to 6 $\mu g/m^3$ $PM_{2.5}$ range. This supports the notion that no threshold exists between $PM_{2.5}$ exposure and various health endpoints at levels close to background. A few studies further suggested a steeper slope at the lower $PM_{2.5}$ concentrations than at higher concentrations. Without an apparent population threshold and with health effects observed at ambient concentrations measured in Canada, reductions of already low concentrations of $PM_{2.5}$ can lead to a substantial health benefit to the Canadian population.

Composition and source

Many $PM_{2.5}$ components, including elemental carbon, black carbon, sulphate (SO_4^{2-}), nitrate (NO_3^-), and organic carbon, were associated with adverse health outcomes. Some studies have begun to identify key components that can represent markers of specific sources of $PM_{2.5}$ and their associations with health outcomes. Exposure levels of $PM_{2.5}$ mass were often correlated with its components. The associations between $PM_{2.5}$ components and health outcomes were sometimes similar to that of $PM_{2.5}$ mass. Overall, no comprehensive conclusion on the specific contribution of each individual component to the health effects of $PM_{2.5}$ can be formulated at this time given the wide qualitative and quantitative variations in terms of constituents (i.e. metals, organic compounds). While the evidence continues to report strong and consistent associations with $PM_{2.5}$ mass, evidence related to associations with individual component and specific source of $PM_{2.5}$ continue to emerge.

Effects of other pollutants

Only a small database is available on the modification of the health effects when exposed in combination with other pollutants. There are some indications that O_3 can enhance the adverse effects of $PM_{2.5}$, especially for cardiovascular and respiratory outcomes. However, the small size of the database and the issues with statistical modelling of co-pollutants, such as measurement errors across co-pollutants, collinearity, and spatial analyses, for example, impede drawing conclusions on these complex interactions.

Emerging health effects and research needs

Emerging health effects have been identified in the research conducted since the CSSA. In particular, relationships between $PM_{2.5}$ exposure and metabolic effects (e.g., diabetes), reproductive and developmental outcomes (e.g., maternal hypertensive disorders, lower birth weight), and neurological outcomes (e.g., neurodegenerative diseases and cognitive impairment) were shown in limited but emerging epidemiological and toxicological studies. Studies on the relationship between $PM_{2.5}$ exposure and metabolic effects are discussed under the cardiovascular effects sections in this report, given its interrelation with cardiovascular diseases. No specific causality conclusion was developed for metabolic effects, as the literature database is limited; however, the few studies available provide support to the conclusions on the cardiovascular effects. In the case of reproductive and developmental effects of $PM_{2.5}$, the available literature has been expanding, particularly for developmental epidemiological studies (e.g., birth outcomes), giving rise to separate causality conclusions for reproductive and developmental effects. There was also some evidence of adverse outcomes on the immune system, kidneys, spleen, thymus, and liver, but they did not contribute to the conclusions on the causality relationships as the database was too small. It is biologically plausible that exposure to $PM_{2.5}$ can affect many systems in the body since the induction of oxidative stress, inflammation and alterations of epigenetic and gene expression are toxic effects that can occur in every tissue.

CONCLUSION

The collective weight of evidence continues to support the finding that $PM_{2.5}$ exposure affects human health for a wide range of outcomes. Some of the health effects considered in this report include mortality, hospitalizations, and emergency room visits. Causal relationships between short- and long-term exposure to $PM_{2.5}$ and all-cause mortality were confirmed. Causal relationships between short-term exposure to $PM_{2.5}$ and cardiovascular and respiratory effects (morbidity and mortality) were also confirmed. Likely causal relationships between long-term exposure to $PM_{2.5}$ and cardiovascular and respiratory morbidity effects and lung cancer morbidity and mortality were concluded. There are also emerging studies suggesting that $PM_{2.5}$ exposure can lead to other health outcomes, such as neurological, metabolic and developmental effects, increasing the potential public health impact. This argument is supported by the non-specific mechanism of action of $PM_{2.5}$.

CHAPTER 1: **INTRODUCTION**

Particulate matter (PM) is a complex mixture of small airborne liquid and solid particles that are classified by size. PM can be emitted directly (primary PM) or formed in the atmosphere (secondary PM) by reactions involving different gaseous precursors, including nitrogen oxides, sulphur dioxide (SO_2), volatile organic compounds, and ammonia. Primary PM and the gaseous precursors leading to the formation of secondary PM originate from both natural sources (e.g., windblown soil, sea salt spray, volcanic dust) and anthropogenic sources (e.g., fossil fuel burning, various industrial processes, agricultural activity, road dust) from within and outside Canada. The main particles of concern for human health are those that can penetrate into the respiratory tract; they are classified by size as PM_{10} (≤ 10 µm in mass median aerodynamic diameter), coarse PM (10 to 2.5 µm, $PM_{10\text{-}2.5}$), fine PM (≤ 2.5 µm, $PM_{2.5}$) and ultrafine particle (≤ 0.1 µm, UFP).

1.1. CANADIAN AIR QUALITY POLICY CONTEXT

Air pollution, specifically from ambient $PM_{2.5}$, is one of the leading environmental causes of death and disease both globally and in Canada, according to the 2019 Global Burden of Disease project (IHME, 2021). Despite relatively low levels of air pollution compared to other countries, Health Canada estimates that 15,300 premature deaths per year in Canada are linked to ambient air pollution from $PM_{2.5}$, nitrogen dioxide (NO_2) and ground-level ozone (O_3). Of these, 10,000 premature deaths per year are estimated to be due to $PM_{2.5}$ (Health Canada, 2021).

Ambient air quality management in Canada is a shared responsibility among federal, provincial, territorial and some cases municipal governments, made possible through an array of commitments and initiatives that have evolved over many decades.

Federal, provincial and territorial governments work together in partnership under the framework of the Canadian Council of Ministers of the Environment (CCME). In 2012, Canadian environment ministers[1] agreed to take further action to protect the health of Canadians and the environment with measures to improve air quality in Canada through a comprehensive Air Quality Management System (AQMS) (CCME, 2014). The AQMS includes the establishment of Canadian Ambient Air Quality Standards (CAAQS) for air pollutants of concern and the setting of new base-level industrial emissions requirements for major industrial sectors and equipment groups. It also provides a platform for the management of air quality at local and regional levels and a collaborative process to address mobile source emissions. Implementation of the AQMS is supported by extensive federal science, including research, monitoring and modelling. The CAAQS are established as air quality objectives under the Canadian Environmental Protection Act (Government of Canada, 1999) to drive continuous improvement of air quality across Canada based on the current scientific evidence. Where CAAQS are exceeded, governments may require further emission reductions from industrial and

[1] In October 2012, Ministers of the Environment, with the exception of Quebec, agreed to implement a new Air Quality Management System (AQMS). While Québec supports the general objectives of AQMS, it will not implement it. However, Québec will collaborate with jurisdictions on developing some elements of the system, notably air zones and airsheds.

non-industrial pollution sources to address air quality issues. Intermediate management levels (levels set below the CAAQS) have been established, with the objective of improving air quality, to prevent air quality deterioration and to keep clean areas clean; they may be used by jurisdictions in their own air quality management frameworks. The AQMS also addresses the transboundary movement of air pollutants between provinces and territories and between Canada and the United States.

Canadian ambient air quality standards for $PM_{2.5}$

One of the key elements of the AQMS is the CAAQS for selected air pollutants: $PM_{2.5}$, O_3, NO_2 and SO_2. The CAAQS are developed through a collaborative process involving the federal, provincial and territorial governments and stakeholders (industry associations as well as non-governmental and Indigenous organizations). Under this process, CAAQS were developed for $PM_{2.5}$ for both 2015 and 2020, with future revision of the CAAQS anticipated in response to developments in the understanding of health and environmental effects, as well as analysis in trends in emissions and ambient concentrations. The 24-hour and annual 2020 CAAQS for $PM_{2.5}$ are 27 µg/m^3 and 8.8 µg/m^3, respectively, which are relevant to short-term and chronic exposure scenarios, respectively. The findings from this report will be used to inform the setting of the future CAAQS for $PM_{2.5}$.

1.2. OBJECTIVES AND INCLUSION CRITERIA

Objectives

This report provides an update of the health-related science for the $PM_{2.5}$ fraction in the context of ambient air pollution in Canada since the publication of the *Canadian smog science assessment. Volume 2: health effects* (Health Canada, 2013), which is referred to as CSSA in this report, with the intention to inform the development of the updated CAAQS for $PM_{2.5}$ and risk management strategies. This report also identifies emerging health effects and data gaps to guide future research.

Inclusion criteria

The literature search for this report was conducted using multiple search methods. First, a list of references (up to October 2015) was obtained from the United States Environmental Protection Agency (US EPA) via personal communication, as they were updating their Integrated Science Assessment for PM. Their search was based on the PubMed and Web of Science databases (US EPA, 2019). In addition, the Health Library of Health Canada and the Public Health Agency of Canada conducted searches using the Scopus, Embase and Medline databases to identify additional peer-reviewed studies published between 2007 until the end of 2016. The broad conclusions of the CSSA were also mentioned and used as a reference point to compare with the updated conclusions in this report. The CSSA details scientific articles published before the end of 2006. This update includes scientific peer-reviewed information published from the beginning of 2007 through the end of 2016.

Ambient $PM_{2.5}$ is a complex mixture containing numerous components. This document focuses primarily on health effects from exposure to $PM_{2.5}$ mass, but also highlights information regarding components and sources. Size fractions greater than $PM_{2.5}$ are not considered. In addition, studies that focused specifically on size fractions smaller than $PM_{2.5}$ such as UFP are not considered. This report reviews environmental epidemiological studies, experimental studies conducted in humans and toxicological experimental studies conducted in animals and in vitro. The epidemiological

evidence is further categorized by exposure duration. Short-term exposure to $PM_{2.5}$ refers to hours up to 1 month of exposure and long-term exposure to $PM_{2.5}$ refers to 1 month to years of exposure. Additional inclusion criteria specific to the study categories are described in the Appendix A.

1.3. CONTENT OF THE REPORT

This report summarizes and integrates scientific information pertaining to the health effects induced by exposure to $PM_{2.5}$ as reported in environmental epidemiological studies, experimental studies in humans, and toxicological studies as part of the weight of evidence approach for causality determination. The causality framework is discussed in further detail in section 1.4. This report assesses the causality relationship between the ambient $PM_{2.5}$ concentrations to which Canadians are exposed and health outcomes. It also highlights population subgroups with increased risk of health effects of $PM_{2.5}$ and discusses the shape of the concentration-response relationships between $PM_{2.5}$ and health outcomes. Emerging health effects and research needs are also identified. Together, this information is used to draw inferences about the risk that ambient $PM_{2.5}$ poses to human health.

1.4. FRAMEWORK FOR WEIGHT OF EVIDENCE FOR CAUSALITY DETERMINATION

To evaluate the weight of evidence of the relationship between exposure to $PM_{2.5}$ and adverse health outcomes, it is necessary to examine the various lines of evidence and to assess the evidence as a whole using established criteria for causality determination. The evidence for the various categories of health outcomes is presented in an integrated fashion by reporting the findings from the available epidemiological, controlled human exposure, and toxicological studies together. This collective evidence is then evaluated for various categories of health outcomes in light of considerations such as the Bradford-Hill criteria, which have traditionally been used to assess how likely it is that the observed associations are causal.

These considerations include:

- the *strength of association*, including the magnitude and precision of the risk estimates and their statistical significance;
- the *robustness* of the associations to model specifications and adjustment for potential confounders such as weather, temporal trends, and co-occurring pollutants;
- the *consistency* of reported associations across studies and study designs conducted by different researchers in different locations and times;
- the *coherence* of the relationship between exposure to $PM_{2.5}$ and related endpoints within and across toxicological, controlled human exposure, and various types of epidemiological studies; and
- the *biological plausibility* of the associations in light of what is known regarding $PM_{2.5}$ dosimetry and the types of effects observed and associated potential mechanisms of action, based largely on toxicological and controlled human exposure studies.

Biological gradient was analyzed in chapter 4 (Shape of the concentration-response relationship). Temporal sequence was considered by including and giving higher weight to cohort studies. Using the framework for Weight of Evidence for Causality Determination from the *Preamble to the Integrated Science Assessments* (US EPA, 2015), the above considerations are used to draw conclusion with respect to the weight of evidence for a given health effect or related set of health effects, as detailed in Table 1.1.

TABLE 1.1: Weight of evidence for causality determination–health effects*

Relationship	Description
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., toxicological studies or mode of action information). Evidence includes multiple high-quality studies.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence, but potential issues remain. For example: a) observational studies show an association, but co-pollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories demonstrates effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies.
Suggestive of, but not sufficient to infer a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example: a) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or b) a well-conducted toxicological study, such as those conducted in the National Toxicology Program, shows effects in animal species.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at risk populations, are mutually consistent in not showing an effect at any level of exposure.

* Modified from US EPA, 2015

1.5. ADVANTAGES AND LIMITATIONS OF ENVIRONMENTAL EPIDEMIOLOGICAL STUDIES

Environmental epidemiological studies provide the most extensive and relevant evidence of the adverse human health effects of $PM_{2.5}$ air pollution. They investigate responses in the general population, which takes into account the heterogeneity of the human populations (including susceptible subgroups and disease/illness status). Exposure to $PM_{2.5}$ occurs as a component of the ambient mixture of pollutants in "real world" settings in these studies. These studies represent a major component of the weight of evidence on the relationship between the health of the population and exposure to $PM_{2.5}$ in the ambient air. These studies normally take into consideration participant characteristics, such as age, gender, education level, socioeconomic status and smoking, and ecological and temporal variables to account for confounding. These studies examine both the clinical health outcomes, including mortality, hospital visits and diagnosis of symptomatic diseases, and subclinical outcomes, such as changes in blood pressure, lung function or physiological biomarkers. The analyses often incorporate a very large sample size, with a large number of participants within a city, across different cities or at a national scale. The use of human data avoids the need to extrapolate from animal data, which do not always represent relevant human health outcomes and ambient exposure scenarios (Raffaele et al., 2011). However, environmental epidemiological studies are observational, and the focus is at the population level rather than at individual level.

Co- and multi-pollutant analyses

Ambient air contains pollutants in addition to $PM_{2.5}$. Epidemiological studies conducting single-pollutant analyses focusing only on $PM_{2.5}$ do not always consider the potential influence of other air pollutants. As a result, there can be uncertainty as to whether the associations are due to $PM_{2.5}$ alone or whether $PM_{2.5}$ acts as a surrogate for co-varying air pollutants. Co-pollutant ($PM_{2.5}$ and another air pollutant) and multi-pollutant ($PM_{2.5}$ and two or more other air pollutants) analyses are often conducted within environmental epidemiological studies to address this concern. Multi-pollutant analyses are not as common, because the model can become unstable due to a number of reasons: correlation of several pollutants, differential measurement errors among the pollutants and the fact that certain pollutants (e.g., sulphur oxides, nitrogen oxides) are known precursors of secondary $PM_{2.5}$ (Tolbert et al., 2007). This typically shifts the effect estimates towards the null (effect estimates of smaller magnitude compared with analyses conducted in the absence of error) (Raffaele et al., 2011). Thus, many epidemiological data focused on single-pollutant or co-pollutant analyses.

$PM_{2.5}$ surrogate of exposure

The use of central site monitors to represent population exposure in epidemiological studies had been a common practice in studies included in the CSSA. Although these are actual measurements, monitoring stations can also introduce uncertainty in the results as they can be at a substantial distance from individuals and populations and do not consider the fact that individuals move through a variety of microenvironments and engage in diverse activities. There has since been advancement in new methods that can generate spatial surfaces of exposure (Sorek-Hamer et al., 2016; Hoek, 2017). Some of the limitations of using central monitoring data alone have been compensated by the development of hybrid exposure surfaces, in which central monitoring data are complemented with land-use regression models, and, in some cases, by the incorporation of satellite remote sensing

data and chemical transport models to estimate $PM_{2.5}$ levels at a finer scale. The hybrid exposure surface approach allows greater and ubiquitous coverage of urban and rural areas for large population studies. This approach found that populations living in rural areas are generally exposed to lower concentrations of $PM_{2.5}$ than those in urban centres. In some panel studies with a small number of participants, daily exposure variations can be measured with the use of personal monitoring methods for each participant. For large-scale panel studies, central monitoring or hybrid exposure surface approaches are adopted to allow a larger participant sample size.

Many diseases, such as atherosclerosis, ischemic heart disease (IHD), and cancer, have slow progression and long latent time periods (i.e., it can be decades before diagnosis or onset of symptoms). Due to the lack of past $PM_{2.5}$ exposure data, long-term exposure epidemiological studies often tend to use more recent exposure data to study the associations with these diseases. Alternatively, some researchers have conducted back trajectory analysis of exposure in an attempt to characterize the population's exposure prior to health outcomes. In both cases, the exposure data are appropriate surrogates as empirical $PM_{2.5}$ data were unavailable.

1.6. ADVANTAGES AND LIMITATIONS OF EXPERIMENTAL STUDIES

Controlled human exposure studies

Human experimental studies help support the health outcome findings observed in environmental epidemiological studies. Controlled human exposure studies provide biologically plausible pathophysiological mechanisms underlying the associations observed in epidemiological studies. By controlling the exposure, these studies provide compelling evidence that $PM_{2.5}$ can cause health effects, supporting what is reported in the observational studies. However, human experimental studies are generally limited to examining short-term, mild, reversible, and subtle physiological responses. These studies are typically conducted in small groups of relatively healthy individuals; they do not include those who may be most at risk and are not necessarily representative of the general population. They are therefore unable to capture the range of effects and the profiles of affected populations. The exposed concentration range in these types of studies is above typical Canadian ambient levels, but remain in the ambient range that can be experienced in some other countries. These levels are considered appropriate for experimental settings, as they allow observation of reversible subclinical non-adverse effects in a short period of exposure.

Toxicological studies

In contrast to controlled human studies, experimental animals are exposed to similar or higher $PM_{2.5}$ concentrated ambient particle (CAP) concentrations, sometimes for longer time periods. The control of exposure, co-pollutant(s), diet and genetic homogeneity between exposure groups limit the risk of bias and confounding that can occur in epidemiological studies. However, the health effects observed in animals might not always represent the large variability of health status and conditions found in the human population. Sensitive animal models, developed to mimic specific human sensitivities and conditions, have been used to investigate the role of $PM_{2.5}$ in the progression of certain conditions or system dysfunction. These models are also useful to investigate the mechanism(s) of action involved in the effect of $PM_{2.5}$, providing biological plausibility for the effects observed in humans.

1.7. REPORTING OF RESULTS

The American Statistical Association has published a formal statement to clarify the proper use and interpretation of statistical test results (Wasserstein and Lazar, 2016). Some important aspects include, but are not limited to:

- statistical analysis results should not be viewed as a dichotomy (significant or not significant), but rather as a continuous measure;
- a confidence interval is more informative than a p-value, as it covers a range where the actual effect estimate can lie within the upper and lower confidence interval;
- the lack of statistical significance of individual results and studies does not imply an absence of effect: the totality of the evidence must be considered (e.g., combined analysis of individual studies, which can even result in statistical significant association and persuasive evidence of an effect) (Greenland et al., 2016).

These important aspects are incorporated in this report. As much as possible, this update considers the highest risk estimates (significant or non-significant) reported in each individual study that were adjusted for all the major covariates in quantitative statistical analyses. To enhance the comparability of the risk estimates between studies, these relative risks are presented as a uniform increment of exposure. Forest plots are presented in this report. They were constructed to provide information on estimates of risk for a given health effect outcome per standardized concentration (10 $\mu g/m^3$) of $PM_{2.5}$, assuming a linear association between $PM_{2.5}$ concentration and specific health outcomes. Furthermore, adjusted risk estimates were presented from the main models of the studies in order to control for relevant age, health conditions, behavioural, socio-demographic and geographical covariates. The purpose of the forest plots is to provide a visual representation of the included studies. Meta-analysis of the included studies was not conducted by Health Canada.

The data presented below review the most relevant information, with a discussion on the meaning of these findings in terms of causality. Not all references are cited as the database is large; some key studies are highlighted.

Biomarkers of inflammation (e.g., levels of fibrinogen, interleukin, C-reactive protein) and metabolic effects (e.g., diabetes, insulin sensitivity, circulating lipids) are described under the cardiovascular effects sections, given the interconnected nature of these outcomes with the cardiovascular system. Developmental-related health outcomes that fall under specific organs or systems (i.e., cardiovascular, respiratory, neurological) are described in the respective organ-system-related chapter in detail and are briefly reported in the developmental section.

CHAPTER 2:
SUMMARY AND WEIGHT OF EVIDENCE FOR SELECTED CATEGORIES OF HEALTH EFFECTS ASSOCIATED WITH AMBIENT $PM_{2.5}$

The following sections summarize and evaluate the collective results from environmental epidemiological, controlled human exposure and experimental toxicological studies. Causality relationships are evaluated using the framework for weight of evidence for causality determination discussed in section 1.4.

2.1. ALL-CAUSE MORTALITY

Short-term exposure to $PM_{2.5}$

Conclusion from the CSSA

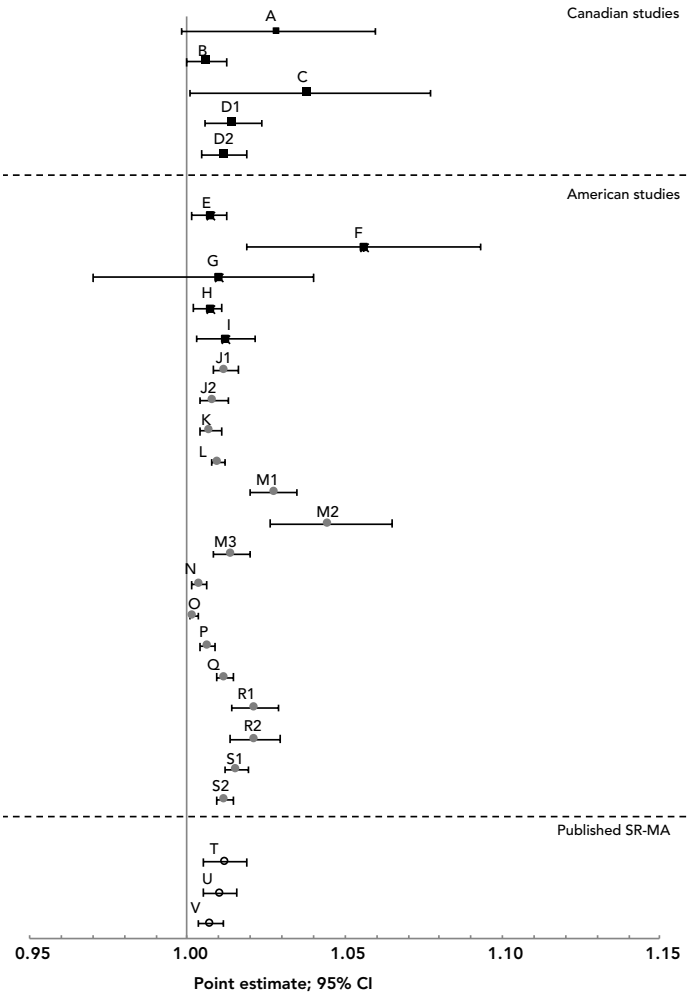
The CSSA concluded that there is a causal relationship between short-term exposure to $PM_{2.5}$ and all-cause mortality, which accounts for deaths due to natural-cause (also known as non-accidental) and external causes such as accidents and homicide. The assessment of causality was based on the evidence from epidemiological mortality databases—all-cause, cardiovascular and respiratory-related mortality databases. In addition, biological plausibility in terms of disease progression was taken from morbidity and toxicological evidence. Epidemiological studies were generally conducted in urban areas with ground monitors providing the exposure data. The association between $PM_{2.5}$ exposure and all-cause mortality was robust since significant associations remained after adjusting for co-pollutants.

Updated information

In this update, we considered all-cause mortality to be equivalent to non-accidental mortality, as the majority of all-cause mortality is due to natural-cause and most of the literature reported non-accidental mortality (although a few older studies did report all-cause mortality). Multi-city epidemiological studies conducted in Canada and the United States continue to report positive and significant associations between $PM_{2.5}$ exposure and all-cause mortality (Figure 2.1). This includes results that analyzed participants residing across different states and cities in the United States (Zanobetti and Schwartz, 2009; Krall et al., 2013; Lippmann et al., 2013; Dai et al., 2014; Lee et al., 2016). Systematic review with meta-analysis studies also reported that short-term $PM_{2.5}$ exposure is associated with a significant increase in the risk of premature all-cause mortality (Levy et al., 2012; Atkinson et al., 2014; Mills et al., 2016). Advancements in exposure methodology led to the creation of improved $PM_{2.5}$ exposure estimate surfaces covering larger geographic areas, thus allowing inclusion of populations spanning a large region (i.e., provinces, states or entire country), instead of only those residing near ground monitors (generally in urban settings). The evidence published since the CSSA

shows that the positive association between $PM_{2.5}$ and all-cause mortality is not limited to urban centres, but is also found in suburban, exurban, rural and semirural locations. In addition, a study investigating the potential impact of co-pollutants reported a positive and significant association even after adjusting for coarse PM (Zanobetti and Schwartz, 2009). This finding complements previous findings observed in the CSSA. Epidemiological evidence continues to support the conclusion that short-term exposure to $PM_{2.5}$ is associated with an increased risk of all-cause mortality.

FIGURE 2.1: Point estimates and 95% confidence intervals for all-cause mortality per standardized increment (10 μg/m³ for 24 h) in short-term ambient $PM_{2.5}$ concentration in single-pollutant models in epidemiological studies



A. Vancouver, BC; Villeneuve et al. (2003); aged ≥65; lag 2 d; 24-h mean (dichotomous samplers) = 11.3 μg/m³

B. 12 Canadian cities; Burnett et al. (2004); all ages; lag 1 d; 24-h mean = 12.8 μg/m³

C. Montreal, QC; Goldberg et al. (2006); aged ≥65 with diabetes (all types); lag 0-2 d; 24-h mean = 17.4 μg/m³

D. 8 Canadian cities; Burnett and Goldberg (2003); all ages; lag 1 d; D1 = GAM with stricter convergence criteria, D2 = GLM with natural splines; 24-h mean = 13.3 μg/m³

E. Los Angeles counties, CA; Moolgavkar (2003); all ages; lag 0 d; 24-h mean not reported

F. Fulton and DeKalb counties, GA; Klemm et al. (2004); aged ≥65; lag 0-1 d; 24-h mean = 19.62 μg/m³

G. Spokane, WA; Slaughter et al. (2005); all ages; lag 1 d; 24-h mean not reported

H. 9 California counties; Ostro et al. (2006); aged ≥65; lag 0-1 d; 24-h mean = 19.4 μg/m³

I. 27 US communities; Franklin et al. (2007); all ages; lag 1 d; 24-h mean = 15.7 μg/m³

J. 6 US cities; Klemm and Mason (2003); all ages; lag 0-1 d; J1 = GAM with stricter convergence criteria, J2 = GLM with natural splines; 24-h mean not reported

K. 25 US cities; Franklin et al. (2008); all ages; lag 0-1 d; 24-h mean not reported

L. 112 US cities; Zanobetti and Schwartz (2009); all ages; lag 0-1 d; 24-h mean = 13.22 μg/m³

M. Massachusetts; Kloog et al. (2013); all ages; lag 0-1 d; M1 = no restriction based on monitor location, M2 = within 20 km of an ambient monitor, M3 = more than 20 km from an ambient monitor; 24-h mean = 9.8 μg/m³

N. 72 US urban communities; Krall et al. (2013); all ages; lag 1 d; 24-h mean = 13.6 μg/m³

O. 148 US cities; Lippmann et al. (2013); all ages; lag 0 d; 24-h mean = 7.89 μg/m³

P. 121 US cities; Zanobetti et al. (2014a); aged ≥65; lag 0-1 d; 24-h mean = 12.06 μg/m³

Q. 75 US cities; Dai et al. (2014); all ages; lag 0-1 d

R. New England states; Shi et al. (2016); aged ≥65; lag 0-1 d; R1 = no restriction, R2 = analyses restricted to $PM_{2.5}$ levels below US NAAQS (<30 μg/m³); 24-h mean = 8.21 μg/m³

S. 3 US states; Lee et al. (2016); all ages; lag 0-1 d; S1 = modelled-$PM_{2.5}$ data, S2 = monitored-based $PM_{2.5}$ data; 24-h mean = 11.1 μg/m³

T. 11 studies (1 Canada, 8 United States, 2 Europe); Levy et al. (2012)

U. 8 single and multi-city studies from WHO regions; Atkinson et al. (2014)

V. 3 studies (1 Canada, 1 United States, 1 Mexico); Mills et al. (2016)

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

○ Published systematic review with meta-analysis studies

The systematic review with meta-analysis by Levy et al. (2012) includes results from the following primary studies: Villeneuve et al. (2003) and Klemm et al. (2004). The systematic review with meta-analysis by Mills et al. (2016) includes results from the following primary study: Burnett et al. (2004). CI = confidence interval; CSSA = Canadian Smog Science Assessment; GAM = generalized additive model; GLM = generalized linear model; km = kilometre; NAAQS = National Ambient Air Quality Standards; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; SR-MA = systematic review with meta-analysis; US = United States; WHO = World Health Organization; WHO regions = African Region, Eastern Mediterranean Region, European Region, Regions of the Americas, South-East Asian Region, Western Pacific Region

Conclusion for short-term $PM_{2.5}$ exposure and all-cause mortality

In summary, population-based epidemiological studies continued to report positive and significant associations between short-term exposure to $PM_{2.5}$ and all-cause mortality. Multi-city analyses as well as systematic review with meta-analysis studies indicated that there is consistency in the results across studies conducted at different times and locations. The advantage of all-cause mortality analysis is that it avoids cause of death misclassifications and covers potential deaths associated with $PM_{2.5}$ exposure in organ and systems that were not well studied. The strength and consistency of the associations were further refined through the use of improved exposure surfaces covering larger geographic areas, which allowed more precise $PM_{2.5}$ exposure estimates spanning urban and rural populations. Adjustments for co-pollutants did not alter the significant association between $PM_{2.5}$ exposure and all-cause mortality, lending further support to the robustness of the evidence. Moreover, coherence of the relationship is supported by studies reporting morbidity due to disease progression and mortality related to cardiovascular and respiratory effects and short-term $PM_{2.5}$ exposure. The results of these studies are discussed in subsequent sections in this chapter. The biological plausibility and coherence of these findings are well supported by mechanistic data in toxicological studies (e.g., by causing oxidative stress and inflammation leading to cardiovascular and respiratory effects, or exacerbation of pre-existing health conditions that can ultimately result in mortality), subclinical findings in epidemiological studies and controlled human exposure studies. Thus, this update further confirms that there is a **causal relationship** between short-term exposure to $PM_{2.5}$ and all-cause mortality.

Long-term exposure to $PM_{2.5}$

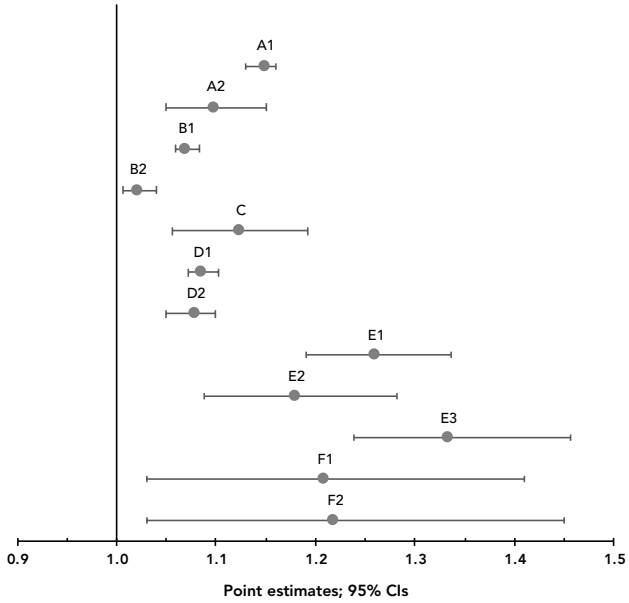
Conclusion from the CSSA

The CSSA concluded that there was a causal relationship between all-cause mortality and long-term exposure to $PM_{2.5}$. The epidemiological database was robust with consistent positive and significant associations between all-cause mortality and $PM_{2.5}$ exposure. This causal relationship is well established and is widely accepted by other international agencies (WHO, 2006, 2013; US EPA, 2009).

Updated information

In this update, all Canadian cohort studies reported positive and significant associations between $PM_{2.5}$ exposure and all-cause mortality (Figure 2.2). Similarly, two large cohort studies (American Cancer Society [ACS] and the Harvard Six Cities Study [H6CS]) and other smaller American cohort studies continued to support the positive and significant associations between long-term exposure to $PM_{2.5}$ and all-cause mortality (Figure 2.3; Figure 2.4; Figure 2.5). In most studies that performed co-pollutant or multi-pollutant analyses, which considered O_3, NO_2 or other size fractions of PM, the positive association between $PM_{2.5}$ exposure and all-cause mortality remained strong (Jerrett et al., 2009, 2013; Puett et al., 2009; Crouse et al., 2015; Thurston et al., 2016a). Furthermore, two systematic review with meta-analysis studies that were based on cohort studies from North America and Europe reported significant positive associations between all-cause mortality and long-term $PM_{2.5}$ exposure (Table 2.1). One Canadian study suggested that survivors of acute myocardial infarction might be more susceptible to the effect of $PM_{2.5}$ with respect to premature mortality (Chen H et al., 2016). Although $PM_{2.5}$ levels have declined in Canada and the United States in the last decade, Canadian and American epidemiological studies have continued to report positive and significant associations between $PM_{2.5}$ exposure and all-cause mortality.

FIGURE 2.2: Point estimates and 95% confidence intervals for all-cause mortality per standardized increment (10 µg/m^3) in long-term ambient $PM_{2.5}$ concentration in single-pollutant models (unless otherwise noted) in Canadian cohort studies



A. CanCHEC; nationwide; Crouse et al. (2012); 10 years of follow-up; A1 = standard Cox proportional hazards model, A2 = nested, spatial random-effects Cox model; annual mean = 8.7 µg/m^3

B. CanCHEC; nationwide; Crouse et al. (2015); 16 years of follow-up; standard Cox proportional hazards model; B1 = $PM_{2.5}$ alone, B2 = $PM_{2.5}$ adjusted for O_3 and NO_2; annual mean = 8.9 µg/m^3

C. CanCHEC; Ontario; Weichenthal et al. (2016a); 18 years of follow-up; standard Cox proportional hazards model; annual mean = 9.8 µg/m^3

D. CanCHEC; nationwide; Cakmak et al. (2016); 16 years of follow-up; standard Cox proportional hazards model; D1 = $PM_{2.5}$ alone, D2 = $PM_{2.5}$ adjusted for O_3; annual mean range from 2 to 8.8 µg/m^3 for the different climate zones*; information obtained via personal communication with authors on July 11, 2019

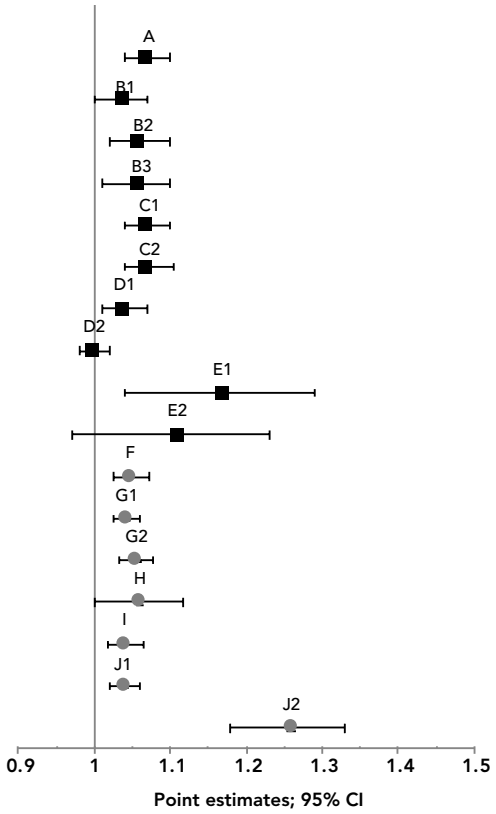
E. CCHS; Pinault et al. (2016); up to 12 years of follow-up; standard Cox proportional hazards model; E1 = full cohort, E2 = females only, E3 = males only; annual mean = 6.32 µg/m^3

F. Ontario; Chen H et al. (2016); acute MI patients; up to 12 years of follow-up; F1 = standard Cox proportional hazards model, F2 = nested, spatial random-effects Cox model; annual mean = 10.7 µg/m^3

● Studies published since the CSSA (Health Canada, 2013)

* climate zones of Canada: Polar, East Coast, Great Lakes St. Lawrence, West Prairies, West Coast, East Prairies, West Central; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CI = confidence interval; MI = myocardial infarction; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = PM of 2.5 µm or less in median aerodynamic diameter

FIGURE 2.3: Point estimates and 95% confidence intervals for all-cause mortality per standardized increment (10 μg/m^3) in long-term ambient $PM_{2.5}$ concentration in single-pollutant models (unless otherwise noted) in the American Cancer Society cohort



A. Pope et al. (1995); original study; 1982–1989; annual mean ranged from 9.0 μg/m^3 to 33.5 μg/m^3

B. Pope et al. (2002); extended analyses: B1 = 1979–1983, B2 = 1999–2000, B3 = 1979–2000; annual means of 21.1 μg/m^3 (1979–1983), 14.0 μg/m^3 (1999–2000) and 17.7 μg/m^3 for the entire period

C. Krewski et al. (2000, 2003, 2005); re-analysis; 1982–1989; C1 = re-analysis of the original study results, C2 = re-analysis with alternative model; annual mean ranged from 9.0 μg/m^3 to 33.5 μg/m^3

D. 25 Californian counties; Enstrom (2005); elderly subjects only; D1 = 1973–1982, D2 = 1983–2002; annual overall mean = 23.4 μg/m^3

E. Los Angeles, CA; Jerrett et al. (2005); 1982–2000; E1 = controlling for 44 individual covariates, E2 = controlling for 44 individual and 8 contextual covariates; annual mean not reported

F. Jerrett et al. (2009); re-analysis including 86 MSAs; annual mean ranged from 11.9 μg/m^3 to 15.4 μg/m^3

G. Krewski et al. (2009); extended analysis; exposure using LUR model including 44 individual level and 7 ecological covariates; G1 = 1979–1983, G2 = 1999–2000; annual mean = 21.20 μg/m^3 for 1979–1983 and 14.02 μg/m^3 for 1999–2000

H. California; Jerrett et al. (2013); exposure using LUR; 42 individual level and 7 ecological covariates; annual mean = 14.09 μg/m^3

I. Lippmann et al. (2013); 42 individual level and 6 ecological covariates; annual mean = 14.2 μg/m^3

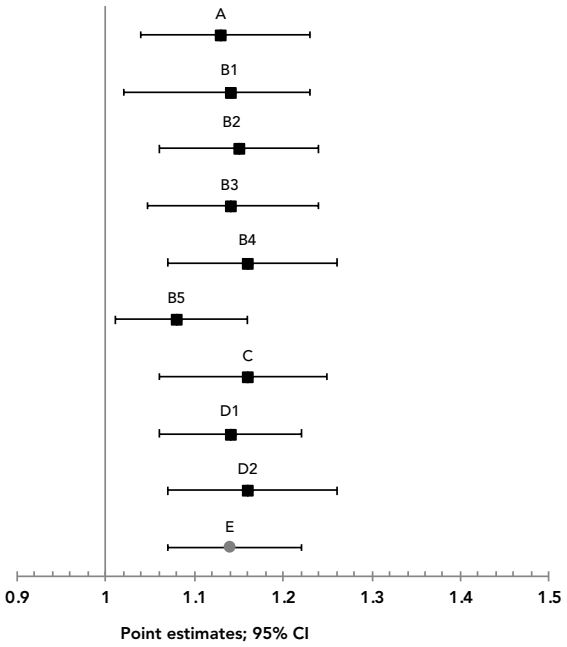
J. Turner et al. (2016); exposure data using a national-level hybrid LUR and BME interpolation model; Cox proportional hazards regression models adjusted for individual and ecological-level covariates; multi-pollutant models adjusted for O_3 and NO_2; J1 = regional $PM_{2.5}$ 1999–2004, J2 = 1982–2004 near-source $PM_{2.5}$; annual mean = 12.6 μg/m^3

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

ACS = American Cancer Society; BME = Bayesian maximum entropy; CI = confidence interval; CSSA = Canadian Smog Science Assessment; LUR = land-use regression; MSAs = metropolitan statistical areas; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter

FIGURE 2.4: Point estimates and 95% confidence intervals for all-cause mortality per standardized increment (10 μg/m^3) in long-term ambient $PM_{2.5}$ concentration in single-pollutant models in the H6CS cohort



A. Dockery et al. (1993); original study; 1974–1991; standard Cox proportional hazards model; annual mean ranged from 11.0 to 29.6 μg/m^3 across the six US cities (overall mean not provided)

B. Krewski et al. (2000 and 2003 re-analysis); 1974–1991; B1 = standard Cox proportional hazards model, re-analysis of the original study results; B2 = standard Cox proportional hazards model, re-analysis with alternative model (original dataset); B3 = standard Cox proportional hazards model, re-analysis with alternative model (extended dataset); B4 = Poisson regression models, re-analysis with alternative analytic approaches, with incorporation of time dependency in smoking and BMI (original data set); B5 = Poisson regression models with incorporation of time dependency in city-specific annual averages of fine particles (original dataset); annual mean ranged from 9.0 to 33.5 μg/m^3 across the six US cities (overall mean not provided)

Villeneuve et al. (2002); 1974–1991; Poisson regression models with temporal changes in $PM_{2.5}$ and individual covariates; annual mean ranged from 10.9 μg/m^3 to 28.6 μg/m^3 across the six US cities (overall mean not provided)

Laden et al. (2006); extended study; 1974–1998; standard Cox proportional hazards model; D1 = with the annual mean of $PM_{2.5}$ level in the year of death, D2 = with $PM_{2.5}$ modelled as average over the entire follow-up; annual mean ranged from 10.2 μg/m^3 to 22.0 μg/m^3 across the six US cities (overall mean not provided)

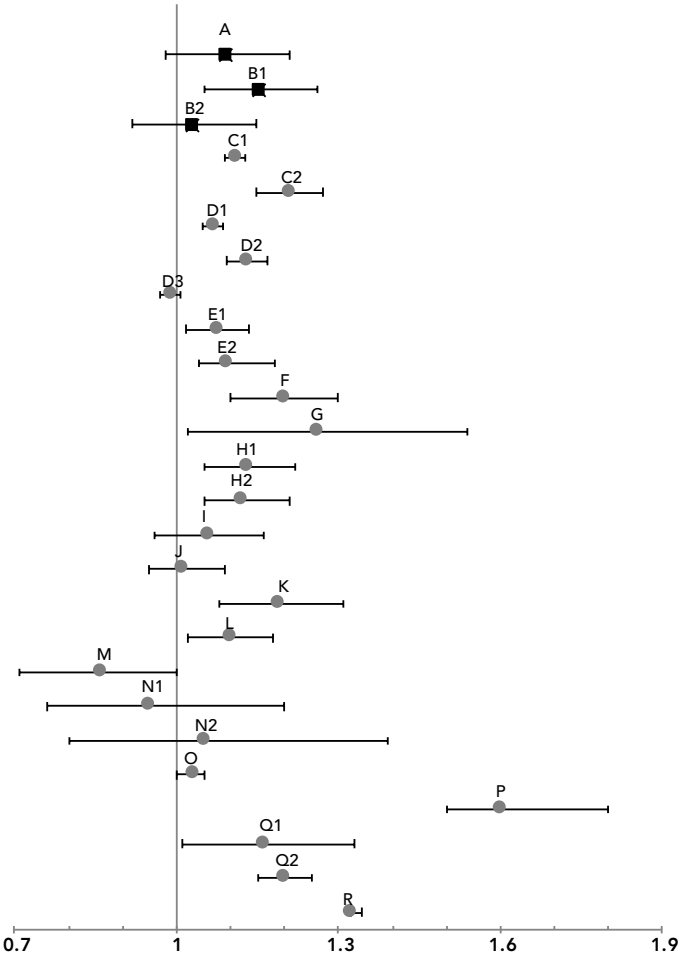
C. Lepeule et al. (2012); extended study; 1974–2009; standard Cox proportional hazards model; annual mean ranged from 11.4 μg/m^3 to 23.6 μg/m^3 across the six US cities (overall mean = 15.9 μg/m^3)

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

BMI = body mass index; CI = confidence interval; CSSA = Canadian Smog Science Assessment; H6CS = Harvard Six Cities Study; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter

FIGURE 2.5: Point estimates and 95% confidence intervals for all-cause mortality per standardized increment (10 μg/m^3) in long-term ambient $PM_{2.5}$ concentration in single-pollutant models in other American cohort studies



A. McDonnell et al. (2000); subset of the AHSMOG cohort; males only; California; 1973–1977; annual mean = 31.9 μg/m^3

B. Lipfert et al. (2006); Veterans cohort (males only); B1 = 1989–1996 (annual mean = 14.3 μg/m^3), B2 = 1997–2001 (annual mean = 14.6 μg/m^3)

C. Eftim et al. (2008); beneficiaries from Medicare Cohort (≥65 years of age) from locations corresponding to subjects included in the ACS or H6CS; 50 MSAs; 2000–2002; C1 = Medicare-ACS (annual mean = 13.6 μg/m^3), C2 = Medicare-SCS (annual mean = 14.1 μg/m^3)

D. Zeger et al. (2008); beneficiaries from Medicare Cohort (≥65 years of age) living 6 miles from a US EPA monitoring station; 668 counties; 2000–2005; D1 = Eastern regions, D2 = Central regions, D3 = Western regions; overall median = 13.2 μg/m^3 (overall mean not reported)

E. Shi et al. (2016); beneficiaries from Medicare Cohort (≥65 years of age); New England states; 2003–2008; E1 = full cohort, E2 = subjects restricted to chronic $PM_{2.5}$ exposure <10 μg/m^3; annual mean = 8.12 μg/m^3

F. Kioumourtzoglou et al. (2016a); beneficiaries from Medicare Cohort (≥65 years of age); 207 cities; 2000–2010; annual mean = 12.6 μg/m^3

G. Puett et al. (2009); subset of the NHS (middle-aged and elderly women); only subjects living from 13 contiguous MSAs in the Northeast and Midwest regions; 1992–2002; annual mean = 13.9 μg/m^3

H. Hart et al. (2015); NHS (middle-aged and elderly women); 50 states; 2000–2006; H1 = exposure assignment based on residential address with spatiotemporal prediction models (annual mean = 12.0 μg/m^3), H2 = exposure assignment based on residential address with levels from the nearest US EPA monitor (annual mean = 12.7 μg/m^3)

I. Ostro et al. (2010, 2011); CTS (females only); 2002–2007; subjects living 30 km from a monitor (annual mean= 17.5 μg/m^3)

J. Lipsett et al. (2011); CTS (females only); 1999–2005; exposure assignment; annual mean = 15.64 μg/m^3

K. Ostro et al. (2015); CTS (females only); 2001–2007; exposure assignment based on residential address with a chemical transport model; annual mean = 17.9 μg/m^3

L. Hart et al. (2011); trucking industry (males only); 1985–2000; annual mean = 14.1 μg/m^3

M. Puett et al. (2011a); HPFS cohort (all males); subjects living in 13 contiguous MSAs in the Northeast and Midwest regions; annual mean = 17.8 μg/m^3

N. Weichenthal et al. (2014b); AHS cohort; Iowa and North Carolina (rural areas); 1993/ 1997–2009; N1 = full cohort, N2 = men only; annual mean = 9.52 μg/m^3

O. Thurston et al. (2016a); NIH-AARP; six US states; 2000–2009; annual mean ranged from 2.9 μg/m^3 to 28.0 μg/m^3

P. Kloog et al. (2013); population-based cohort study; Eastern Massachusetts; 2000–2008; annual mean = 9.9 μg/m^3

Q. Wang et al. (2016); population-based cohort study; New Jersey; 2004–2009; Q1 = difference-in-differences approach, AOD 1 km-1 km; Q2 = pooled meta-analysis, AOD 1 km–1 km; annual mean = 11.3 μg/m^3

R. Eckel et al. (2016); population-based cohort study; California; 1988–2009; exposure assignment based on residential address using air monitoring data; mean = 13.7 μg/m^3

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

ACS = American Cancer Society; AHS = Agricultural Health Study; AHSMOG = Adventist Health Air Pollution Study; AOD = aerosol optical depth; CI = confidence interval; CSSA = Canadian Smog Science Assessment; CTS = California Teachers Study; HPFS = Health Professionals Follow-Up Study; H6CS = Harvard Six Cities Study; MSAs = metropolitan statistical areas; NIH-AARP = National Institutes of Health-American Association of Retired Persons; NHS = Nurses' Health Study; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; US EPA = United States Environmental Protection Agency

TABLE 2.1: Systematic review with meta-analysis studies of the association between $PM_{2.5}$ and all-cause mortality

Reference	Study design, location (no. of studies)	Association with $PM_{2.5}$, pooled estimate, 95% CI per 10 µg/m^3 increase in $PM_{2.5}$
Chen et al. (2008)	Six cohort studies*: United States (five), Europe (one)	Pooled RR = 1.06; 95% CI 1.03, 1.10
Hoek et al. (2013)	Eleven cohort studies: Canada (one), United States (eight), Europe (two)	Pooled RR = 1.06; 95% CI 1.04, 1.08

* Two out of six studies where all-cause mortality may have included accidental deaths according to Chen et al. (2008)

CI = confidence interval; $PM_{2.5}$ = PM of 2.5 µm or less in median aerodynamic diameter; RR = relative risk

Conclusion for long-term $PM_{2.5}$ exposure and all-cause mortality

In summary, population-based epidemiological studies including a number of well-established large cohort studies consistently reported positive and significant associations between long-term exposure to $PM_{2.5}$ and all-cause mortality. The associations were found to be robust, as adjustments to co-pollutants generally did not show evidence of confounding. Given the various effects presented in the following sections of this chapter such as cardiovascular and metabolic, respiratory and cancer effects, there is biological plausibility evidence from epidemiological and toxicological studies to support that long-term exposure to $PM_{2.5}$ can result in premature death from various specific causes. Overall, the evidence continues to support a **causal relationship** for all-cause mortality from long-term exposure to $PM_{2.5}$.

2.2. CARDIOVASCULAR AND METABOLIC EFFECTS

Short-term exposure to $PM_{2.5}$

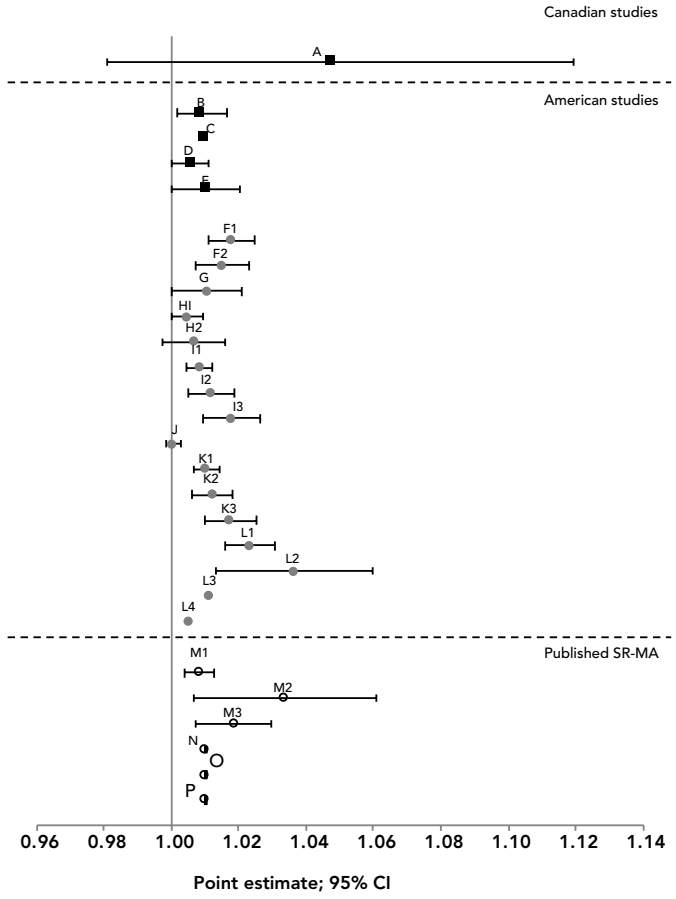
Conclusion from the CSSA

The CSSA concluded that there existed a causal relationship between short-term exposure to $PM_{2.5}$ and cardiovascular morbidity and mortality. This was based on consistent and significant associations between exposure to $PM_{2.5}$ and increases in hospital visits (both emergency room visits and admissions) and premature mortality, for cardiovascular outcomes. The associations were robust in co-pollutant models. Furthermore, panel studies demonstrated increases of vascular coagulation, inflammation and altered cardiac function in human participants, which provided evidence of the potential mechanistic basis of the clinical outcomes observed (i.e., hospital visits, mortality). Controlled human exposure studies, examining the potential cardiovascular effects associated with exposure to $PM_{2.5}$ CAPs, were relatively rare at that time. Cardiac effects such as increased blood fibrinogen and decreased heart rate variability (HRV) were reported, but the results were not entirely consistent. Animals exposed to $PM_{2.5}$ were shown to exhibit vasoconstriction, alterations in blood coagulation, and induction of neural reflexes at concentrations as low as 5 µg/m^3, providing additional coherence to the human database and supporting the overall causality conclusion at that time. The relationship between short-term $PM_{2.5}$ exposure and metabolic effects had not been examined in detail.

Updated information—cardiovascular mortality

Since the publication of the CSSA, epidemiological studies have continued to report positive and significant associations between $PM_{2.5}$ exposure and cardiovascular mortality (Figure 2.6). The precision of the associations has increased as the confidence intervals of the associations have become smaller. Studies have also focused on cause-specific cardiovascular mortality. Increased risks for mortality from myocardial infarction, congestive heart failure (CHF), and cerebrovascular (CEB)-related outcomes (including stroke) were consistently shown to be associated with exposure to $PM_{2.5}$ (Franklin et al., 2008; Zanobetti and Schwartz, 2009; Dai et al., 2014; Lee et al., 2016). These observations were reported in studies conducted in multi-city settings, which likely increase the representativeness of the general population, by taking into account the heterogeneity of the population, and may reduce the selection bias sometimes associated with single-city studies. The observed associations between $PM_{2.5}$ exposure and cardiovascular mortality covered a wide range of concentrations (24-h mean range: 7.89 to 19.44 μg/m^3) and indicated increased susceptibility among some subgroups of the population (e.g., subjects ≥ 65 years of age or with existing cardiovascular or neurological conditions). Systematic review with meta-analysis studies that included locations other than Canada and the United States also supported the increases in the risk of stroke and MI-related mortality associated with short-term exposure to $PM_{2.5}$ (Atkinson et al., 2014; Wang et al., 2014; Shah et al., 2015; Cai et al., 2016). The data reviewed in this update continue to offer strong and consistent evidence of associations between short-term exposure to $PM_{2.5}$ and cardiovascular-related mortality.

FIGURE 2.6: Point estimates and 95% confidence intervals for cardiovascular mortality per standardized increment (10 μg/m³ for 24 h) in short-term ambient $PM_{2.5}$ concentration in single-pollutant models in epidemiological studies



A. Vancouver, BC; Villeneuve et al. (2003); aged ≥65; lag 0 d; 24-h mean (TEOM) = 7.89 μg/m³

B. Los Angeles County, CA; Moolgavkar (2003); all ages; lag 2 d; 24-h mean not reported

C. 7 US counties; Holloman et al. (2004); all ages; lag 2 d; no 95% CI interval provided; 24-h mean = 9.69 μg/m³ *

D. 9 California counties; Ostro et al. (2006); all ages; lag 0–1 d; 24-h mean = 19.44 μg/m³

E. 27 US communities; Franklin et al. (2007); all ages; lag 1 d; stroke; 24-h mean = 15.7 μg/m³

F. 6 US cities; Klemm and Mason (2003); all ages; lag 0–1 d; F1 = GAM with stricter convergence criteria, F2 = GLM with natural splines; 24-h mean not reported

G. 6 California counties; Ostro et al. (2007); all ages; lag 3 d; 24-h mean = 17.89 μg/m³

H. 25 US cities; Franklin et al. (2008); all ages; lag 0–1 d; H1 = all cardiovascular, H2 = stroke; 24-h mean not reported

I. 112 US cities; Zanobetti and Schwartz (2009); all ages; lag 0–1 d; I1 = all cardiovascular, I2 = MI, I3 = stroke; 24-h mean = 13.22 μg/m³

J. 148 US cities; Lippmann et al. (2013); all ages; lag 0 d; 24-h mean = 7.89 μg/m³

K. 75 US cities; Dai et al. (2014); all ages; lag 0–1 d; K1 = all cardiovascular, K2 = MI, K3 = stroke; 24-h mean = 13.3 μg/m³

L. 3 US states; Lee et al. (2016); all ages; lag 0–1 d; L1 = all cardiovascular, L2 = CHF, L3* = MI ($p < 0.05$), L4* = stroke ($p < 0.05$); 24-h mean = 11.1 μg/m³

M. 3–4 single- and multi-city studies from WHO regions); Atkinson et al. (2014); M1 = cardiovascular mortality (4 studies), M2 = IHD (4 studies), M3 = stroke (3 studies)

N. 6 studies (1 US, 4 Europe, 1 Asia); Wang et al. (2014); CEB mortality

O. 12 studies (3 US, 7 Europe, 1 South America, 1 Asia); Shah et al. (2015); stroke mortality

P. 4 studies (2 US, 1 Europe, 1 Asia); Cai et al. (2016); MI mortality

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

○ Published systematic review with meta-analysis studies

* Upper and lower confidence intervals not presented

The systematic review with meta-analysis by Shah et al. (2015) includes results from the following primary studies: Franklin et al. (2007) and Franklin et al. (2008). The systematic review and meta-analysis by Cai et al. (2016) includes results from the following primary study: Dai et al. (2014) and Zanobetti and Schwartz (2009).

CEB = cerebrovascular; CHF = congestive heart failure; CI = confidence interval; CSSA = Canadian Smog Science Assessment; GAM = generalized additive model; GLM = generalized linear model; MI = myocardial infarction; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; TEOM = tapered element oscillating microbalance; SR–MA = systematic review with meta-analysis; US = United States; WHO = World Health Organization; WHO regions = African Region, Eastern Mediterranean Region, European Region, Regions of the Americas, South-East Asian Region, Western Pacific Region

Updated information—cardiovascular and metabolic morbidity

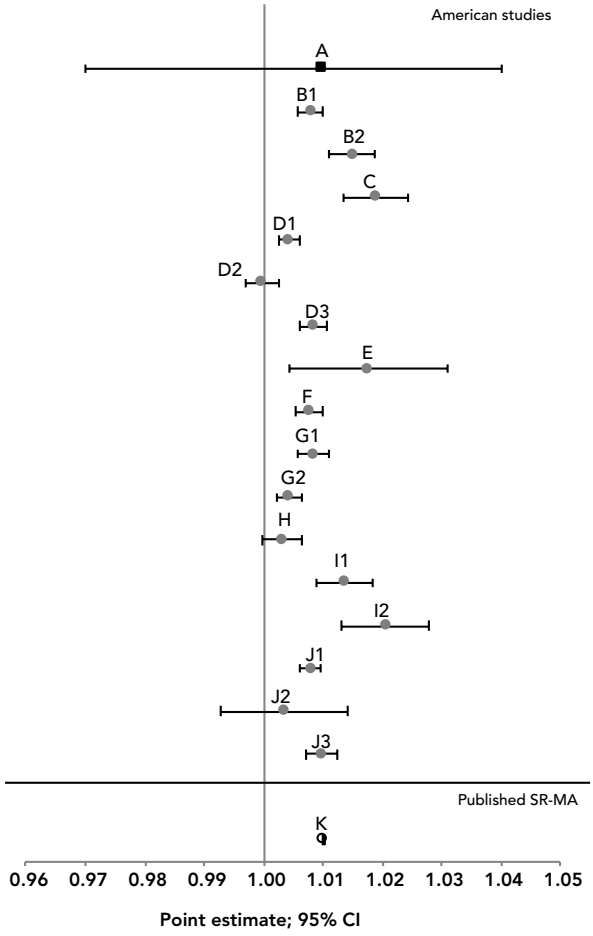
Cardiovascular-related hospital admissions

A significant relationship between $PM_{2.5}$ and cardiovascular hospital admissions was demonstrated in most of the multi-city epidemiological studies (Figure 2.7). No Canadian multi-city studies were identified in this update. The relationship is supported by a systematic review with meta-analysis (Atkinson et al., 2014). This meta-analysis reported significant increases in cardiovascular hospital admissions related to $PM_{2.5}$ exposure.

Since the publication of the CSSA, literature is available on cause-specific cardiovascular hospital admissions. Although the database is relatively small for each individual outcome, the overall appearance of positive and largely significant associations is evident, with some outcomes presenting risk levels well above that for overall cardiovascular hospital admission categorization. The increased risk levels are most striking for CHF and myocardial infarction, with evidence from multi-city studies (Zanobetti et al., 2009; Lippmann et al., 2013) and systematic review with meta-analysis studies (Atkinson et al., 2014; Cai et al., 2016). Also, positive and mostly significant associations were observed for IHD-related hospital admissions in multi-city studies (Lippmann et al., 2013; Kloog et al., 2014) and in a systematic review with meta-analysis study (Atkinson et al., 2014). Epidemiological evidence of associations between short-term exposure to $PM_{2.5}$ and hospital admissions related to CEB outcomes is not always consistent in primary studies (Lippmann et al., 2013; Kloog et al., 2014; Hsu et al. 2017), even thought positive associations were reported in two systematic review with meta-analysis studies when primary studies were pooled (Wang et al., 2014; Shah et al., 2015). It remains unclear why results were consistent for CHF, myocardial infarction and IHD-related outcomes while being less consistent for CEB-related outcomes. One hypothesis is that exposure misclassification could be more common for CEB symptom onset than for other outcomes, as the association with $PM_{2.5}$ can be observed within hours of exposures (Brook et al., 2010). Exposure misclassification might have attenuated the association, resulting in more inconsistent results for CEB-related outcomes.

A limited number of studies examining hospital admissions related to cardiac arrhythmia and peripheral vascular diseases (deep vein thrombosis, peripheral artery disease) reported positive and significant associations with exposure to $PM_{2.5}$ (Haley et al., 2009; Kloog et al., 2015).

FIGURE 2.7: Point estimates and 95% confidence intervals for all cardiovascular hospital admissions per standardized increment (10 μg/m^3 for 24 h) in short-term ambient $PM_{2.5}$ concentration in single-pollutant models in epidemiological studies



A. Spokane, US; Slaughter et al. (2005); all ages; lag 3 d; 24-h mean not reported

B. 202 US counties; Bell et al. (2008); aged ≥65; B1 = all year; B2 = winter; lag 2 d; 24-h mean not reported

C. 26 US communities; Zanobetti et al. (2009); aged ≥65; lag 0–1 d; 24-h mean = 15.3 μg/m^3

D. 148 US cities; Lippmann et al. (2013); aged ≥65; D1 = all year; D2 = warm season; D3 = cold season; lag 0 d; 24-h mean not reported

E. 4 US counties; Bell et al. (2014); aged ≥65; lag 0 d; 24-h mean = 14.0 μg/m^3

F. Mid-Atlantic US (Washington D.C., and the states of Delaware, Maryland, New Jersey, Pennsylvania, Virginia, New York and West Virginia); Kloog et al. (2014); all ages; lag 0-1 d; 24-h mean = 11.92 μg/m^3

G. 213 US counties; Bell et al. (2015); aged ≥65; G1 = women; G2 = men; lag 0 d; 24-h mean = 12.3 μg/m^3

H. 100 US urban counties; Powell et al. (2015) (extended analysis of Peng et al. (2008)); aged ≥65; lag 0 d; 24-h median = 12.6 μg/m^3

I. New York State (New York city, Long Island and Hudson), US; Hsu et al. (2017); all ages; I1 = all year; I2 = winter; lag 0 d; 24-h mean not reported

J. 708 US counties; Bravo et al. (2017); CMAQ; J1=overall, J2 = least urban (≤40% of pop. in urban areas), J3 = most urban (>90% of pop. in urban areas); lag 0 d; 24-h mean = 12.28 μg/m^3

K. 4 single- and multi-city studies from WHO regions; Atkinson et al. (2014)

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

○ Published systematic review with meta-analysis studies

CI = confidence interval; CSSA = Canadian Science Smog Assessment; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; SR-MA = systematic review with meta-analysis; US = United States; WHO = World Health Organization; WHO regions = African Region, Eastern Mediterranean Region, European Region, Regions of the Americas, South-East Asian Region, Western Pacific Region

Cardiovascular-related emergency room visits

Researchers have also evaluated the associations between exposure to $PM_{2.5}$ and cardiovascular-related emergency room visits (i.e., arrhythmia, IHD, CHF, myocardial infarction/ angina, hypertension). Positive associations were observed in all (Stieb et al., 2009; Rappold et al., 2012; Ostro et al., 2016; Weichenthal et al., 2016b) but one (Weber et al., 2016) of the available studies for myocardial infarction/ angina. For other specific causes (IHD, arrhythmia, hypertension and heart failure), the dataset is small and the evidence is not always consistent, with both positive and negative findings and wide confidence intervals. Studies of cardiovascular-related emergency room visits associated with exposure to $PM_{2.5}$ during wildfire events were too few and inconsistent (Alman et al., 2016; Reid et al., 2016) to draw any firm conclusion. However, research interest in this source of exposure is likely, given a warmer climate will intensify some weather extremes in the future, including the increase in risk of wildfire (Bush and Lemmen, 2019).

Overall, the studies exhibit relatively large confidence intervals compared to hospital admissions studies. When considering the hospital admissions and emergency room visits databases together, there is compelling evidence of a positive association between short-term $PM_{2.5}$ exposure and cardiovascular-related hospital visits.

Subclinical effects

Panel studies, repeated-measure studies and cross-sectional studies have examined a variety of subclinical health effects (generally lacks detectable signs and symptoms), with most studies focused on potentially susceptible population subgroups. In the case of cross-sectional studies, they utilized short-term $PM_{2.5}$ exposure levels (a few day lag to 0 day) to calculate association with health endpoints. Exposure to $PM_{2.5}$ was associated with increased risk of arrhythmia, decreased HRV and increased blood pressure in the elderly and in those with cardiovascular diseases or type II diabetes (Ren et al., 2010; Hoffmann et al., 2012; Cakmak et al., 2014a; Zanobetti et al., 2014a; Bind et al., 2016; Wang et al., 2016). Changes in heart rate associated with $PM_{2.5}$ exposure were observed in both the elderly and adults overall (Cakmak et al., 2014b). Other than certain population subgroups, changes in HRV were also associated with $PM_{2.5}$ levels in healthy adults during exercise (Weichenthal et al., 2011, 2014a; Shutt et al., 2017). It is important to note that persistent subclinical changes (blood pressure, HRV, heart rate) may present themselves in individuals continuously exposed to $PM_{2.5}$ and that these changes are known risk factors for adverse cardiovascular effects.

Additional studies have examined the association between exposure to $PM_{2.5}$ and changes in cardiovascular-related markers. Associations were generally reported in susceptible population subgroups, but not in healthy populations. In subjects with cardiac conditions and, to a lesser extent, in individuals with diabetes and in the elderly, $PM_{2.5}$ exposure was associated with increased blood coagulation biomarkers (i.e., fibrinogen, soluble platelet selectin) (Delfino et al., 2009; Schneider et al., 2010; Rich et al., 2012). Blood coagulation action is vital to maintain haemostasis upon injury or infection; however, excessive blood coagulation may lead to an increased risk of thrombosis (blood clots in blood vessels) (Xu XR et al. 2016). In healthy adults and elderly people, exposure to $PM_{2.5}$ was significantly associated with increased levels of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (Bind et al., 2016; Dai et al., 2016a; Pope et al., 2016). VCAM-1 and ICAM-1 are well-established markers of endothelial dysfunction and are involved in the development of atherosclerosis (Hope and Meredith 2003a, b). These findings are further supported by evidence suggesting that non-invasive measurements of changes in endothelial function (bronchial

artery diameter, endothelium-dependent flow-mediated dilatation [FMD], non-endothelium-dependent nitroglycerin-mediated reactivity [NMD], and reactive hyperemia index) are associated with $PM_{2.5}$ exposure in the elderly (Lanzinger et al., 2014; Zhang X et al., 2016), but not in healthy individuals (Liu et al., 2014a; Weichenthal et al., 2014a). Inflammation is suspected to have a significant role in the development of adverse cardiovascular effects. Associations were observed between $PM_{2.5}$ exposure and increased systemic inflammatory biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) (Schneider et al., 2010; Thompson et al., 2010), but the overall database was not entirely consistent. This is possibly due to medication influence or genetic variance. A small dataset of oxidative stress-related biomarkers, including urinary creatinine-indexed 8-epi-prostaglandin, urinary 8-hydroxy-2′-deoxyguanosine and blood myeloperoxidase, were positively associated with exposure to $PM_{2.5}$ in cross-sectional studies (Ren et al., 2011; Li W et al., 2016). Biomarkers of antioxidant capacity, such as copper-zinc superoxide dismutase and glutathione peroxidase-1, had an inverse relationship with exposure to $PM_{2.5}$ in panel studies consisted of elderly participants with IHD (Delfino et al., 2008, 2009). Lower antioxidant capacity indicates an increase likelihood of oxidative stress. Long-term oxidative stress has been suggested to play a significant role in the development of cardiovascular disease, as it can increase inflammatory responses leading to cell and tissue damage.

Other than environmental epidemiological studies, controlled human exposure studies have investigated subclinical changes in the cardiovascular system in healthy participants, asthmatics and those with other health conditions, such as chronic obstructive pulmonary disease (COPD) and cardiovascular diseases of mild severity. These studies typically recruited a relatively small number of participants as compared to observational studies, ranging from 4 to 60. Controlled exposure to $PM_{2.5}$ CAP-induced changes in HRV in the elderly (Hemmingsen et al., 2015), but not in healthy volunteers (Fakhri et al., 2009; Huang et al., 2012). Exposure to $PM_{2.5}$ CAP-induced changes in vascular function biomarkers (reduced FMD, NMD or bronchial artery diameter) in healthy adults, overweight middle-aged adults and the elderly (Brook et al., 2009; Hemmingsen et al., 2015a; Tong et al., 2015). For other subclinical health endpoints (heart rate, blood pressure, biomarkers related to coagulation, systematic oxidative stress, and systemic inflammation), results are considered limited and inconsistent in both healthy adults and those with certain mild health conditions.

Nevertheless, the subclinical cardiovascular changes observed in epidemiological studies including evidence in controlled human exposure studies provide valuable coherence and strong mechanistic support for the relationship between $PM_{2.5}$ exposure and short-term cardiovascular effects.

Metabolic effects

Researchers have investigated the relationship between short-term $PM_{2.5}$ exposure and metabolic effects. Studies on the relationship with metabolic effects were included in this section, given its interrelation with cardiovascular diseases. Positive and significant associations between $PM_{2.5}$ exposure and diabetes-related hospital admissions have been observed in two multi-city studies (Zanobetti et al., 2009, 2014a).

The associations between $PM_{2.5}$ exposure and metabolic-related subclinical effects have been examined. Health endpoints studied include lipid factors involved in the progression of atherosclerosis (high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides) and biomarkers of diabetes (glucose levels and insulin sensitivity). LDL is pro-atherogenic (promote the formation of fatty plaques in the arteries) and HDL is anti-atherogenic. In elderly people and Mexican

Americans, some panel and cross-sectional studies have suggested that $PM_{2.5}$ is associated with increased blood LDL and fasting glucose and reduced insulin sensitivity (Brook et al., 2013a; Bind et al., 2016; Chen Z et al., 2016; Peng et al., 2016). In some cases, it has been shown that the use of medications in participants with existing cardiovascular conditions may have masked or reduced the magnitude of the association between the health endpoint and $PM_{2.5}$.

Controlled human exposure studies have also examined lipid changes after exposure to $PM_{2.5}$ CAPs and reported an increase in LDL and very low-density lipoprotein and a decrease in HDL (Tong et al., 2012; Hazucha et al., 2013). High levels of lipoproteins such as LDL and VLDL and a decrease in HDL levels can lead to the formation of fatty plaques in the arteries.

Overall, there is a small but increasing number of epidemiological studies investigating the relationship between $PM_{2.5}$ exposure and metabolic effects.

Updated information—effects in toxicological studies

The relationship between exposure to $PM_{2.5}$ and various cardiovascular toxicity endpoints is well established in experimental animals documented in the CSSA. Toxicological studies published since the CSSA have therefore focused on exploring the mechanisms by which $PM_{2.5}$ induces adverse cardiovascular effects. This is reflected in the design of most studies, which expose experimental animals to a single dose of $PM_{2.5}$ and compare them to a filtered-air control group. The majority of studies investigating the cardiovascular effects of $PM_{2.5}$ reported increases in oxidative stress and inflammation in blood as well as in cardiovascular tissues following acute or subchronic exposures. Increases in circulating cytokines and inducible nitric oxide synthase, as well as in infiltration of macrophages in the myocardium and decreases in anti-oxidative stores within the myocardium and epicardial adipose tissue, were observed. Limited evidence has shown that acute ex vivo exposure of mice aortic tissue to the serum of mice that had been exposed to road dust $PM_{2.5}$ induced an impairment in the relaxation (vasoconstriction) and an increase in the inflammation and vasodilation of the tissue. Additional significant effects observed in experimental animals include endothelial dysfunction (e.g., increased serum VCAM-1) and a reduction in endothelial progenitor cells. Similarly, mice and rats had impaired vasorelaxation and increased vasoconstriction after short-term exposure to $PM_{2.5}$. A few studies showed that the expression of genes (an area of expanding interest in relation to $PM_{2.5}$) related to inflammation was increased in respiratory tissue. In addition, researchers have started to investigate the roles of the renin-angiotensin-aldosterone endocrine system and the kallikrein-kinin system as potential pathways of $PM_{2.5}$-induced adverse cardiovascular effects. Both systems are involved in regulating inflammation, blood pressure and coagulation, and these studies offer new insight on potential mechanisms of $PM_{2.5}$-induced cardiovascular toxicity. Subchronic exposure of mice and rats to $PM_{2.5}$ CAPs was also found to have direct effects on cardiovascular functions, such as changes in heart rate and overall autonomic tone, length of electrocardiogram intervals and ventricular repolarization and blood pressure. One study, albeit by intraperitoneal injection of PM, suggested that $PM_{2.5}$ can induce direct damage to cardiac tissue as measured by lower cardiomyocyte counts and higher percentages of fibroblasts in heart tissue. Exposure of experimental animals was also shown to increase vascular inflammation and dysfunction in conjunction with increases in blood glucose, glucose intolerance and insulin resistance. Overall, toxicological studies strongly support the cardiovascular effects observed in epidemiological studies and suggest that oxidative stress and inflammation are likely to play important roles in $PM_{2.5}$-mediated adverse cardiovascular effects.

Conclusion for short-term $PM_{2.5}$ exposure and cardiovascular and metabolic effects

There is strong and consistent evidence from epidemiological studies that short-term exposure to $PM_{2.5}$ is associated with risk of adverse cardiovascular effects leading to morbidity and mortality. The database covered within this assessment and the previous CSSA evaluation is large and is considered adequate to assess causality with regard to cardiovascular effects. The consistency of the association is high since positive and mostly significant relationships between exposure to $PM_{2.5}$ and cardiovascular effects were repeatedly observed in all epidemiological study types examined, including multi-city population-based studies and panel studies, with support from controlled human exposure studies. The robustness of the associations was well-established in the previous CSSA, where positive and significant associations between $PM_{2.5}$ exposure and health outcomes were usually maintained in co-pollutant (two pollutants) analyses with NO_2, carbon monoxide (CO) or O_3. Since the causal relationship has already been established, few studies conducted co-pollutant or multi-pollutant (more than two pollutants) analyses in this update. In the case of multi-pollutant analysis, the high correlation between pollutants tends to make the model unstable and generate risk estimates with high uncertainties (Oakes et al., 2014). The evidence follows disease progression in terms of severity of effects, along with subclinical signs of cardiovascular effects, cause-specific emergency room visits and hospital admissions and cardiovascular-related mortality. Data were shown to support numerous types of cardiovascular morbidity and mortality effects including myocardial infarction, IHD, CHF, and CEB outcomes including stroke, with some evidence implicating $PM_{2.5}$ exposure in effects on arrhythmia, peripheral vascular diseases and diabetes. Hence, the evidence suggests that exposure to $PM_{2.5}$ may compromise cardiovascular function in a non-specific way (i.e., affecting multiple systems).

The epidemiological literature is supported by numerous studies in experimental animals demonstrating effects on arrhythmia and a variety of biomarkers suggestive of impaired cardiovascular function. Toxicological studies have shown that oxidative stress and systemic inflammation are key mechanisms for $PM_{2.5}$ effects. Toxicological studies, along with human studies (epidemiological panel and controlled human exposure studies) that have identified subclinical effects of exposure (such as decreased overall HRV, changes in the average beats of heart rate, increased blood pressure, alterations in lipid profiles, glucose intolerance, increased insulin resistance, markers of inflammation, oxidative stress and endothelial dysfunction), provide several lines of evidence for coherence and biological plausibility of the $PM_{2.5}$-induced adverse health effects. Together, epidemiological and toxicological data coherently demonstrate that exposure to $PM_{2.5}$ is associated with adverse cardiovascular effects within the general population and that certain susceptible individuals are more at risk (chapter 3).

More researchers have examined potential metabolic effects of short-term $PM_{2.5}$ exposure. The epidemiological database consists of a small number of studies (cohort and panel studies) reporting positive associations between $PM_{2.5}$ exposure and diabetes-related hospital admissions and changes in diabetes-related biomarkers (glucose levels, insulin sensitivity, blood lipids, and systemic inflammation). Similar changes in diabetes-related biomarkers were also observed in $PM_{2.5}$-exposed experimental animals and controlled human exposure studies. The metabolic database is considered small and inadequate to establish its own causality determination at this time. However, given the interconnected nature of the cardiovascular and metabolic systems, the metabolic database adds support to the causality determination between short-term $PM_{2.5}$ exposure and cardiovascular effects.

The overall evidence therefore continues to support **causal relationships** between short-term exposure to $PM_{2.5}$ and cardiovascular-related morbidity and premature mortality.

Long-term exposure to $PM_{2.5}$

Conclusion from the CSSA

In the CSSA, strong positive and significant associations were observed in the epidemiological database between $PM_{2.5}$ exposure and cardiopulmonary death (combined cardiovascular and respiratory causes), cardiovascular mortality and cardiovascular-specific causes, such as IHD, CHF and cardiac arrest. In most cases, the associations between $PM_{2.5}$ exposure and cause-specific mortality exhibited greater magnitude of associations than that for all-cause, cardiopulmonary or cardiovascular causes of death. An increased cardiovascular risk was also observed in terms of morbidity outcomes, as $PM_{2.5}$ exposure was associated with increased arterial wall thickening (a marker of atherosclerosis). Mechanistic support was provided by controlled human exposure studies, human panel and cross-sectional studies assigned with short-term exposure estimates. However, it was also recognized that certain short-term effects are adaptive and might not progress further to more serious effects. Chronic exposure studies in laboratory animals sensitive to CAPs provided clear mechanistic support for a role of $PM_{2.5}$ in atherosclerosis progression and plaque formation and instability, as well as impacts on the cardiovascular system. Many cardiovascular outcomes were evaluated in laboratory animals following chronic exposure via inhalation or instillation of $PM_{2.5}$, including arrhythmia, atherosclerosis, impaired vasoreactivity, changes in endothelin levels, and thrombogenic alterations. These studies were conducted using various types of PM, specifically CAPs, urban $PM_{2.5}$ and residual oil fly ash. Chronic exposures to $PM_{2.5}$ were found to alter vasoreactivity in animals. Vasoconstriction and thrombogenic responses were suggested as important mechanisms for the cardiovascular effects. Cardiovascular tissue damage and inflammation had also been reported, but a clear mechanism of toxicity for these effects was not established. Overall biological plausibility and coherence were provided by the mechanistic findings from toxicological studies for both cardiovascular morbidity and mortality associated with long-term exposure. At that time, it was concluded that there was a causal relationship between cardiovascular mortality and long-term exposure to $PM_{2.5}$ based on strong and significant associations in epidemiological studies and mechanistic evidence from toxicological studies. For cardiovascular morbidity, the evidence was suggestive of a causal relationship for long-term exposure to $PM_{2.5}$ as the epidemiological database for morbidity outcomes was relatively small. The relationship between long-term $PM_{2.5}$ exposure and metabolic effects had not been examined in detail.

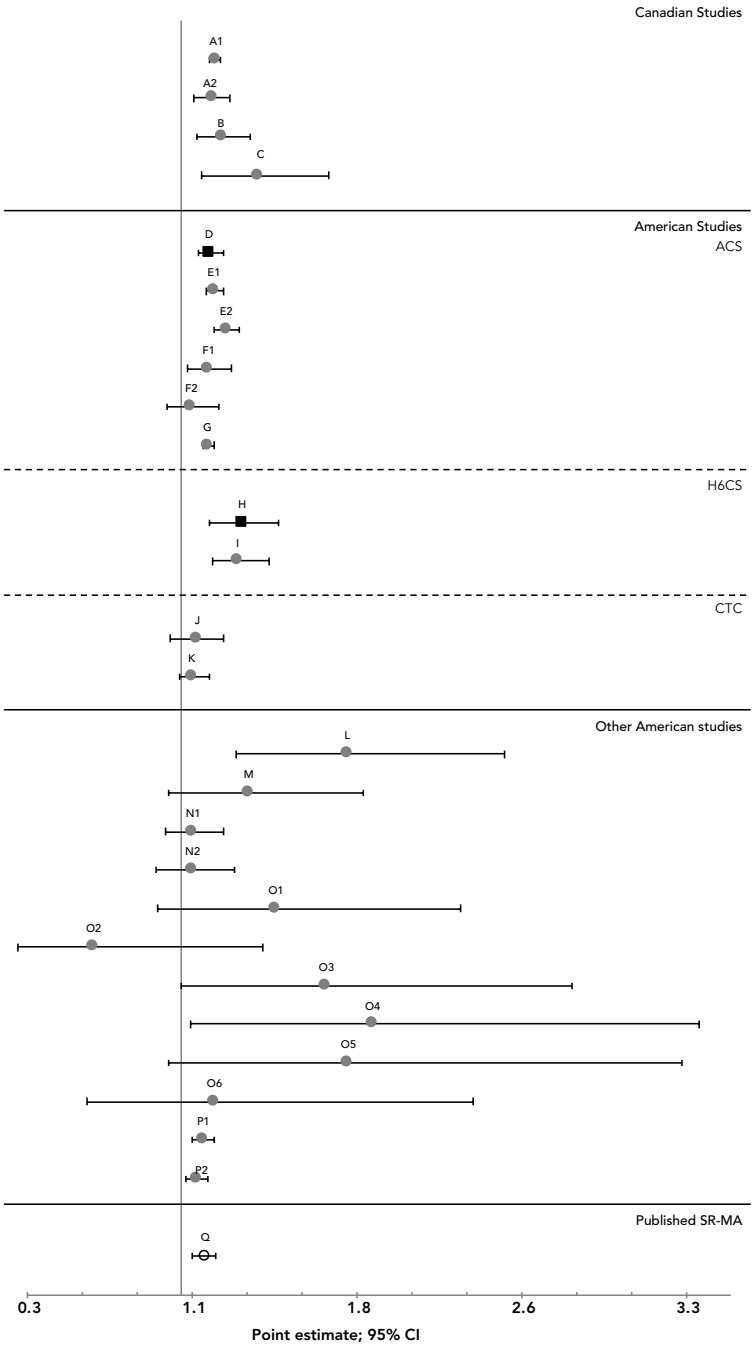
Updated information—cardiovascular and metabolic mortality

Cardiovascular mortality

The cardiovascular mortality database in relation to long-term exposure to $PM_{2.5}$ has expanded greatly. Canadian and American cohort studies evaluating cardiopulmonary or all cardiovascular-related mortality continued to report positive and significant associations with $PM_{2.5}$ exposure (Figure 2.8). The results were consistent across national Canadian cohort studies, namely the Canadian Census Health and Environment Cohort (CanCHEC), the Canadian Community Health Survey (CCHS), and the Ontario Population Health and Environment Cohort (Crouse et al., 2012; Chen H et al., 2016; Pinault et al., 2016), and in major American cohort studies (ACS, H6CS; Lepeule et al., 2012; Pope et al., 2015). The results were also consistent using various exposure estimation methods, including central site monitoring, chemical transport model analysis, and exposure surface modelling using land-use regression with or without remote sensing. Co-pollutant or multi-pollutant analyses performed by a number of studies indicated that positive and significant associations between $PM_{2.5}$ and cardiovascular mortality were robust to adjustment for O_3 and/or NO_2 (Jerrett et al., 2009, 2013; Thurston et al., 2016a), further supporting the role of $PM_{2.5}$ as the major causative agent. Ozone and

NO_2 also show independent associations in some studies. Furthermore, a systematic review with meta-analysis study of ten primary cohort studies from different locations and times covering Canadian, American and European studies indicated that long-term exposure to $PM_{2.5}$ was associated with a significantly increased risk of cardiovascular/ cardiopulmonary mortality across this broad range of studies (Hoek et al., 2013).

FIGURE 2.8: Point estimates and 95% confidence intervals for all cardiovascular-related mortality per standardized increment (10 µg/m³) in long-term ambient $PM_{2.5}$ concentration in single-pollutant model (unless otherwise noted) cohort studies



A. CanCHEC; across Canada; Crouse et al. (2012); A1 = standard Cox proportional hazards model, A2 = nested, spatial random-effects Cox model; 1991–2001; mean = 8.7 µg/m³ (1987–2006)

B. CCHS; across Canada; Pinault et al. (2016); 2000–2011; mean follow-up 7.6 years; mean = 6.3 µg/m³ (1998–2010)

C. Ontario, Canada; Chen H et al. (2016); 1999–2001; mean = 10.7 µg/m³ (2001–2010)

D. ACS; across the United States; Krewski et al. (2005); re-analysis with alternative method 1982–1998; mean = 18.2 µg/m³ (1979–1983 for alternative method)

E. ACS; across the United States; Jerrett et al. (2009); exposure based on nearby central monitoring; E1 = single-pollutant model, E2 = co-pollutant model adjusted for O_3; 1982–2000; mean = 11.9–15.4 µg/m³ (1999–2000)

F. ACS; California, US; Jerrett et al. (2013); F1 = single-pollutant model, F2 = multi-pollutant model adjusted for O_3, NO_2; 1982–2000; mean = 14.09 µg/m³ (1998–2002)

G. ACS; across the United States; Pope et al. (2015); 1982–2004; mean = 12.6 µg/m³ (1991–2004)

H. H6CS; United States; Laden et al. (2006); extended study; 1974–1998; mean = 10.2–22.0 µg/m³

I. H6CS; United States; Lepeule et al. (2012); exposure data based on central monitoring; 1974–2009; mean = 15.9 µg/m³ (1974–2009) (1979–1988)

J. CTS; California, US; Lipsett et al. (2011); women mostly menopausal at baseline; 1995–2000; mean = 15.64 µg/m³ (1999–2005)

K. CTS; California, US; Ostro et al. (2015); women; exposure assignment based on residential address with a chemical transport model; 2001–2007; mean = 17.9 µg/m³ (2000–2007)

L. WHI-OS; metropolitan areas across USA; Miller et al. (2007); post-menopausal women; exposure data based on nearby central monitoring; 1994–2002 annual mean = 13.5 µg/m³ (2000)

M. WHI-OS; metropolitan areas across the United States; Vedal et al. (2013); post-menopausal women; 1994–2005; annual mean = 12.9 µg/m³ (2000)

N. Across the United States; Hart et al. (2011); trucking industry workers; men; exposure data based on nearby central monitoring data; N1 = all, N2 = excludes long-haul drivers; 1985–2000; mean = 14.1 µg/m³ (2000)

O. AHS; mostly Iowa and North Carolina, US; Weichenthal et al. (2014b); farmers, spouses and commercial pesticide applicators; O1 = men, O2 = women, O3 = men, more precise exposure; O4 = men, more precise exposure, non-movers; O5 = men, BMI >26.5 kg/m²; O6 = men, BMI 12–26.5 kg/m²; 1993–2009; mean = 5.7–19.2 µg/m³ (2001–2006)

P. NIH-AARP Diet and Health Study; six states, two metropolitan areas in the United States; Thurston et al. (2016a); P1 = single-pollutant model, P2 = co-pollutant model adjusted for O_3; 2000–2009; mean not reported; range = 2.9–28.0 µg/m³ (2000–2009)

Q. 10 studies (2 Canada, 6 United States, 2 Europe); Hoek et al. (2013)

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA (Health Canada, 2013)

○ Published systematic review with meta-analysis

The systematic review with meta-analysis by Hoek et al. (2013) includes results from the following primary studies: Crouse et al. (2012), Lepeule et al. (2012), Lipsett et al. (2011), Miller et al. (2007), and Hart et al. (2011). The risk estimates reported by Krewski et al. (2005), Laden et al. (2006) and Jerrett et al. (2009, 2013) were RRs; all others were HRs. Lipsett et al. (2011), Crouse et al. (2012) and Pope et al. (2015) used the term "circulatory disease" to refer to all cardiovascular-related mortality. For studies where cardiovascular mortality was not available, Hoek et al. (2013) used cardiopulmonary mortality data.

ACS = American Cancer Society; AHS = Agricultural Health Study; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey cohort; CI = confidence interval; CSSA = Canadian Smog Science Assessment; CTS = California Teachers Study; H6CS = Harvard Six Cities Study; NIH-AARP Diet and Health Study = National Institutes of Health-American Association of Retired Persons Diet and Health Study; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = PM of 2.5 µm or less in median aerodynamic diameter; SR-MA = systematic review with meta-analysis; US = United States; WHI-OS = Women's Health Initiative-Observational Study

In terms of specific causes of cardiovascular mortality, numerous cohort studies reported positive and significant associations between $PM_{2.5}$ exposure and IHD mortality, including Canadian results from CanCHEC (Crouse et al., 2012, 2015; Cakmak et al., 2016) and CCHS (Pinault et al., 2016). The significant associations were generally robust to adjustments for other co-pollutants (O_3, NO_2, black carbon and/or $PM_{10-2.5}$) (Puett et al., 2009; Jerrett et al., 2013; Crouse et al., 2015; Cakmak et al., 2016). Some studies suggested that women may have a greater IHD risk following exposure to $PM_{2.5}$ than men (Puett et al., 2009, 2011a). This was based on separate men and women cohort studies that were purposely constructed to be comparable by using the same geographic region, identical spatiotemporal exposure estimation models, similar outcomes and biennially updated covariates. However, the participants in the women study were generally less physically active, consisted of more current smokers and lived in areas of lower socioeconomic status than the participants in the men study.

The relationship between CEB mortality and $PM_{2.5}$ exposure has also received increased attention. Results from Canadian cohort studies were inconsistent, reporting both positive and negative associations between CEB mortality and exposure to $PM_{2.5}$ (Crouse et al., 2012, 2015; Cakmak et al., 2016; Pinault et al., 2016). American studies reported mostly positive associations, which in many cases were significant (Miller et al., 2007; Pope et al., 2015; Turner et al., 2016). However, adjustment for other co-pollutants (O_3 and/or NO_2) tended to attenuate the associations (Jerrett et al., 2013). The association between CEB mortality and $PM_{2.5}$ exposure was not as strong or consistent as that for cardiovascular disease. The reasons for this discrepancy are not well understood (hypotheses discussed in section 7.2). Other than these cause-specific outcomes that were investigated by different researchers, the ACS dataset conducted subgroup analyses of hypertensive mortality (Pope et al., 2015) and mortality due to arrhythmias, CHF and cardiac arrest (Pope et al., 2015; Turner et al., 2016) and reported positive associations with $PM_{2.5}$ exposure.

Metabolic mortality

Diabetes-related mortality (combined analyses of type 1 and type 2 diabetes) in association with long-term exposure to $PM_{2.5}$ is an emerging area of research. Large Canadian and American cohort studies (CanCHEC, ACS, H6CS) reported positive and mostly significant associations between $PM_{2.5}$ exposure and diabetes mortality (Brook et al., 2013b; Crouse et al., 2015; Pope et al., 2015; Turner et al., 2016). In addition, co-pollutant and multi-pollutant analyses that included O_3 and NO_2 exposure conducted on the CanCHEC dataset reported positive and significant associations between $PM_{2.5}$ exposure and metabolic mortality (Crouse et al., 2015). In Canadian studies that examined the broader category of cardio-metabolic (covering cardiovascular and metabolic causes) mortality, positive and significant associations were also observed in single-pollutant analyses (Crouse et al., 2016; Pinault et al., 2016); no co-pollutant or multi-pollutant analyses were conducted.

Overall, these cohort studies provide consistent evidence to support a positive association between long-term $PM_{2.5}$ exposure and cardiovascular mortality, including cardiopulmonary, all cardiovascular-related and IHD mortality, with some evidence for CEB and cardiac arrest-related mortality. Preliminary evidence suggests an association between $PM_{2.5}$ exposure and diabetes-related mortality.

Updated information—cardiovascular and metabolic morbidity

Cardiovascular morbidity

The morbidity database has also expanded considerably since the CSSA was published. An increased number of epidemiological studies have evaluated subclinical measurements of atherosclerosis and their associations with long-term $PM_{2.5}$ exposure. Measurements of carotid intimal medial thickness (CIMT) (an indicator of arterial wall thickening) and coronary artery calcium (CAC) (an indicator of build-up of calcium in plaque) are common endpoints and provide early indications of the development of cardiovascular disease. In cross-sectional studies, long-term $PM_{2.5}$ exposure was associated with increased CIMT measurements in adults and the elderly, but not in children or young adults (Adar et al., 2013; Breton et al., 2012, 2016a, b; Sun et al., 2013; Kim et al., 2014). Less consistent results were observed in the few cohort studies that followed study participants for 2.5 to 9.2 years (Künzli et al., 2010; Adar et al., 2013; Gan et al., 2014; Kaufman et al., 2016). In terms of CAC, cross-sectional analyses did not find any consistent association between long-term $PM_{2.5}$ exposure and CAC in three studies conducted in adults and the elderly (Sun et al., 2013; Kim et al., 2014; Dorans et al., 2016). However, a cohort study reported a positive non-significant association based on CAC progression over 7 years (Dorans et al., 2016). Given that atherosclerosis progression is a slow process that can develop gradually over several decades, cohort studies with long follow-up periods would be needed to provide evidence for a causal role of $PM_{2.5}$ exposure in the CIMT and CAC progression.

A number of other cardiovascular morbidity outcomes in relation to long-term exposure to $PM_{2.5}$ have been investigated, including hospital admissions, diagnosis of diseases and subclinical changes. In population-based cohort studies, $PM_{2.5}$ was associated with significantly increased risk of hospital admissions for peripheral vascular disease in the elderly (Kloog et al., 2015, 2016), but less consistent results with wide confidence interval for diagnosis were observed in two cohort studies of women (Shih et al., 2011; Pun et al., 2015). With respect to hypertension, large population-based cohort studies conducted in Canada and the United States mostly reported positive associations with exposure to $PM_{2.5}$, especially in diabetic or obese individuals (Chen H et al., 2014; Zhang Z et al., 2016; Coogan et al., 2016). An increased risk of IHD, CHF and stroke-related events (incidence or hospital admissions) was found in women (Lipsett et al., 2011; To et al., 2015b) and an increased risk of myocardial infarction was found in men (Puett et al., 2011a). Additionally, subjects that had undergone cardiac catheterization reported an increased risk for IHD, myocardial infarction and stroke related-events associated with long-term $PM_{2.5}$ exposure (Hartiala et al., 2016; McGuinn et al., 2016). Overall, there is a small but growing database to support an association between long-term $PM_{2.5}$ exposure and an increased risk of various cardiovascular conditions, including peripheral vascular diseases, hypertension, IHD, CHF, and stroke.

Subclinical effects

Other epidemiological studies (panel and cross-sectional studies), which usually focus on short-term exposure scenarios, have also investigated subclinical outcomes and their associations with long-term exposure to $PM_{2.5}$. Positive associations between $PM_{2.5}$ exposure and arrhythmia/ HRV parameters were reported in panel and cross-sectional studies (Mordukhovich et al., 2015, 2016; O'Neal et al., 2017a, b). A few studies have also examined biomarkers of vasomotor functions and systemic inflammation (e.g., FMD, bronchial artery diameter, CRP, Il-6) as well as changes in gene expression and the epigenome (i.e., messenger ribonucleic acid [mRNA], microRNAs [miRNAs], deoxyribonucleic acid [DNA] methylation modifications). The associations between biomarkers and $PM_{2.5}$ exposure were often based on a single study. Two cross-sectional studies have reported that $PM_{2.5}$ exposure was associated

with decreased FMD, a vasomotor function biomarker (Krishnan et al., 2012; Wilker et al., 2014). The database remains limited and inconsistent, and more studies are needed to confirm whether long-term exposure to $PM_{2.5}$ is associated with subclinical changes in the cardiovascular system.

Metabolic morbidity

In relation to metabolic morbidity, exposure to long-term $PM_{2.5}$ is associated with a significantly increased risk of developing diabetes (most incident cases being from type 2) in Canadian cohort studies (Chen H et al., 2013; To et al., 2015b), but less consistent results with much wider confidence intervals were observed in American studies (Puett et al., 2011b; Park et al., 2015; Coogan et al., 2016). $PM_{2.5}$ exposure was also associated with elevated metabolic-associated biomarkers (high levels of circulating LDL, fasting glucose level, fasting insulin level, and insulin resistance) in cross-sectional studies for certain subgroups: Mexican American with history of gestational diabetes (Chen Z et al., 2016), overweight and obese African-American and Latino children (Toledo-Corral et al., 2016). Future studies need to be conducted in the general population to confirm these observations. Overall, there is a growing body of evidence to suggest that long-term $PM_{2.5}$ exposure is associated with an increased risk of metabolic effects, such as diabetes incidence.

Updated information—effects in toxicological studies

In toxicological studies, long-term exposure (longer than 2 months) to $PM_{2.5}$ resulted in cardiovascular effects similar to those observed in the acute and subchronic studies. A few studies showed that inhalation of $PM_{2.5}$ CAPs resulted in oxidative stress (increased heart malondialdehyde levels and decreased heart superoxide dismutase and glutathione peroxidase activity), inflammation of myocardium (interleukin-1β [IL-1β], IL-6 and TNF-α cytokines), cardiac dysfunctions such as increased systolic, diastolic, and mean arterial blood pressure, fibrosis, focal myocarditis, aortal thickening, and foci of myocardial degeneration in mice. One study conducted on male mice also reported that perinatal (during gestation and weaning) exposure to $PM_{2.5}$ CAPs resulted in substantial cardiac remodelling (e.g., left-ventricular end-systolic diameter, ventricular size and wall thickness), alterations in hemodynamic parameters and fibrosis of the left ventricle at 3 months of age. Additionally, in studies using a mouse model of atherosclerosis, increases in oxidative stress, enhanced atherosclerosis progression, aortic plaques, and vascular inflammation were reported following chronic exposure to $PM_{2.5}$ compared with animals exposed to filtered air. In general, toxicological studies focused on investigating the mechanisms of toxicity associated with $PM_{2.5}$ exposure, and most evaluated only a single exposure level or dose. Overall, these studies provide further support that exposure to $PM_{2.5}$ can induce a range of adverse effects at the tissue and system levels, and that non-specific mechanisms of toxicity, such as inflammation and oxidative stress, are likely key in the development and progression of cardiovascular outcomes. They also provide important clues as to the mechanism by which $PM_{2.5}$ could cause the severe adverse effects observed in epidemiological studies.

Toxicological studies have also shown that chronic exposure to $PM_{2.5}$ induces systemic inflammation and insulin resistance in animal models of obesity and diabetes, as well as wild-type animals. Of note, the majority of studies reported increases in oxidative stress (e.g., increased superoxide anion in vascular and adipose tissues) and inflammation (e.g., increased cytokine production and macrophage infiltration) in various tissues, including the adipose, lung, vascular and liver tissues. In addition to the induction of inflammation, other pathways associated with the observed effects included adipogenesis, alterations in energy expenditure, and mitochondrial dysfunction. Some studies reported activation of biochemical pathways favouring lipogenesis and adipocyte formation.

Moreover, associations with adverse effects on the liver, such as steatosis and fibrosis, were reported in a few studies. A single study suggested that vascular insulin resistance was secondary to oxidative stress in the lungs of mice exposed to $PM_{2.5}$. Inflammation, insulin resistance, and cardiac and mitochondrial dysfunctions were enhanced in animal models of metabolic syndrome and models susceptible to type-2-like diabetes. Overall, these results provide evidence of the ability of $PM_{2.5}$ to cause a wide range of adverse cardiovascular effects. While ranging over many outcomes, they provide support for the adverse cardiovascular effects observed in toxicological studies. Moreover, markers of metabolic effects such as insulin resistance and alterations in energy expenditure were observed, with inflammation and oxidative stress playing central mechanistic roles.

Conclusion for long-term $PM_{2.5}$ exposure and cardiovascular effects

In summary, the body of literature on the association between long-term exposure to $PM_{2.5}$ and cardiovascular mortality has expanded considerably since the publication of the CSSA. For cardiopulmonary or all cardiovascular-related mortality, positive and significant associations were consistently observed in Canadian and American cohort studies as well as in a systematic review with meta-analysis covering wider geographical locations. For cause-specific mortality, exposure to $PM_{2.5}$ was associated with a significantly increased risk of IHD mortality. There is also some limited evidence that $PM_{2.5}$ exposure was associated with an increased risk of CEB mortality and, in a much smaller database, with an increased risk of cardiac arrest-related mortality. Positive and significant associations were also observed between cardio-metabolic mortality or diabetes-related mortality and $PM_{2.5}$ exposure. The associations were robust to co-pollutant or multi-pollutant analysis that included O_3, NO_2, black carbon and/or $PM_{10\text{-}2.5}$ co-exposure for all cardiovascular mortality, IHD, CEB, and diabetes-related mortality.

Similarly, the cardiovascular morbidity database related to long-term exposure to $PM_{2.5}$ has also been expanded extensively since the publication of the CSSA. Population-based epidemiological studies have identified increased risk of hospital admissions or development of a number of cardiovascular conditions including IHD, CHF, CEB disease, myocardial infarction, hypertension, and peripheral vascular disease associated with long-term $PM_{2.5}$ exposure. The associations between $PM_{2.5}$ exposure and subclinical measurements of atherosclerosis were not very consistent, likely because the duration of cohort follow-ups was too short to allow the time necessary for the observation of disease progression. Some epidemiological cohort studies have reported an association between long-term $PM_{2.5}$ exposure and an increased risk of diabetes development. The few panel and cross-sectional studies available indicated that long-term $PM_{2.5}$ exposure was associated with an increased risk of arrhythmia, changes in HRV parameters and increased levels of various metabolic-associated and possibly vasomotor biomarkers. Moreover, toxicological studies provided coherence for the cardiovascular conditions observed in epidemiological studies, as changes in cardiac tissue structure and functions and progression of hypertension, plaque formation, and atherosclerosis were reported. Also, physiological changes, such as vascular inflammation, insulin resistance, and changes in adipose tissue, often leading to more serious conditions, were consistently reported in toxicological studies. Oxidative stress and inflammation were shown to play a central role in the induction of cardiovascular outcomes in laboratory animals, which provides biological plausibility for the associations observed in humans. It is important to note that a growing number of these cardiovascular outcomes are considered metabolic disturbances, and therefore have the potential for more widespread perturbations of the cardiovascular system, and of other systems.

A few large cohort studies have reported positive and significant associations between $PM_{2.5}$ exposure and diabetes mortality, and less consistent positive associations between $PM_{2.5}$ exposure and diabetes incidence. Evidence from single studies suggested that exposure to $PM_{2.5}$ was associated with elevated metabolic-associated biomarkers in certain subgroups of the population in cross-sectional studies.

Given the high prevalence of diagnosed cardiovascular disease (over 8.3%; from Public Health Agency of Canada, 2017) in Canada—and this does not account for underdiagnosed populations—the health impact of $PM_{2.5}$ is expected to be substantial. Also, since diabetics are prone to develop various cardiovascular diseases, such as myocardial infarction, exposure to $PM_{2.5}$ is expected to increase the risk of these outcomes. The preliminary evidence showing associations of $PM_{2.5}$ exposure with health effects on the metabolic system is limited and is insufficient to determine causality at this time. However, the positive associations and toxicological effects reported in the metabolic database add support to the causality determination between long-term $PM_{2.5}$ exposure and cardiovascular effects due to the interconnected nature of the two systems.

Overall, the evidence continues to support a **causal relationship** between cardiovascular mortality and long-term exposure to $PM_{2.5}$. The expanded evidence in the morbidity database results in an upgrade to a **likely causal relationship** between cardiovascular morbidity and long-term exposure to $PM_{2.5}$.

2.3. RESPIRATORY EFFECTS

Short-term exposure to $PM_{2.5}$

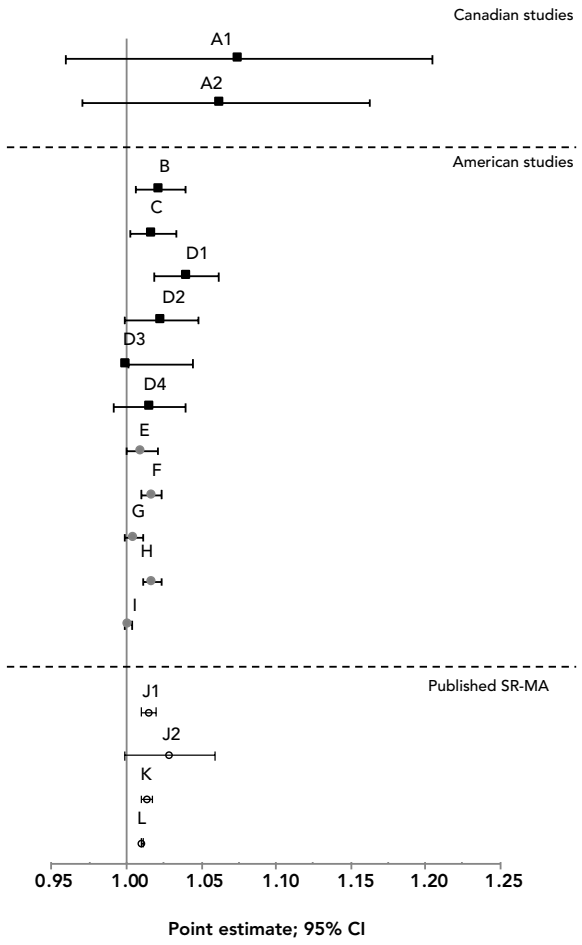
Conclusion from the CSSA

The CSSA concluded that a causal relationship exists between short-term exposure to $PM_{2.5}$ and both respiratory morbidity and respiratory mortality. $PM_{2.5}$ exposure was strongly associated with increased risk of respiratory-related hospital visits as well as with respiratory mortality. In particular, there was strong evidence of increased risk of asthma- and COPD exacerbation-related hospital visits associated with $PM_{2.5}$ exposure. Reduced lung function, increased respiratory symptoms and pulmonary inflammation were observed in panel studies, particularly in asthmatic children and adults with COPD. In a number of controlled human exposure studies, participants (most often healthy adults and in some cases asthmatics or elderly individuals with or without COPD) exposed to $PM_{2.5}$ CAPs exhibited mild pulmonary, systemic or nasal inflammation, though the database was not entirely consistent. A large body of evidence in toxicological studies demonstrated the potential for toxicity effects of $PM_{2.5}$ on the lungs. Studies that examined mechanisms by which pulmonary toxicity occurs identified oxidative stress, neutrophilic infiltration and higher macrophage count and activation in bronchoalveolar lavage fluid (BALF) as important mediators of pulmonary injury (as measured by protein content and lactate dehydrogenase (LDH) activity in BALF), fibrosis, and epithelial hyperplasia. Mechanisms of lung toxicity also included induction of cytochrome P450s enzymes, activation of vanilloid receptors, caspase activation and apoptosis, and mitochondrial dysfunctions. Short-term exposure to $PM_{2.5}$ was also shown to act as an adjuvant with antigens (i.e., allergens), exacerbating airway inflammation and immune responses in experimentally-induced allergic animal models.

Updated information—respiratory mortality

Since the CSSA publication, multi-city epidemiological studies conducted within the United States have continued to report positive and significant associations between $PM_{2.5}$ exposure and respiratory mortality (Figure 2.9). No Canadian multi-city study was identified in this update. A single-city Canadian study that was described in detail in the CSSA indicated much wider confidence interval (Villeneuve et al., 2003) compared to the more recent multi-city studies. Systematic review with meta-analysis studies further supported the observation, where $PM_{2.5}$ exposure was associated with increased overall respiratory mortality as well as specific COPD-related mortality (Atkinson et al., 2014; Chang et al., 2015; Li MH et al., 2016).

FIGURE 2.9: Point estimates and 95% confidence intervals for respiratory mortality per standardized increment (10 μg/m^3 for 24 h) in short-term $PM_{2.5}$ concentration in single-pollutant models in epidemiological studies



A. Vancouver, BC; Villeneuve et al. (2003); aged ≥65; lag 0 d; A1 = TEOM data, A2 = dichotomous data, 24-h mean (TEOM) = 7.89 μg/m^3

B. 9 California counties; Ostro et al. (2006); all ages; lag 0-1 d; 24-h mean = 19.44 μg/m^3

C. 27 US communities; Franklin et al. (2007); all ages; lag 1 d; 24-h mean = 15.7 μg/m^3

D. 6 US cities; Klemm and Mason (2003); all ages; lag 0-1 d; D1 = pneumonia – GAM with stricter convergence criteria, D2 = pneumonia – GLM with natural splines, D3 = COPD – GAM with stricter convergence criteria, D4 = COPD – GLM with natural splines; 24-h mean not reported

E. 25 US cities; Franklin et al. (2008); all ages; lag 0-1 d; 24-h mean not reported

F. 112 US cities; Zanobetti and Schwartz (2009); all ages; lag 0-1 d; 24-h mean = 13.22 μg/m^3

G. 148 US cities; Lippmann et al. (2013); all ages; lag 1 d; 24-h mean = 7.89 μg/m^3

H. 75 US cities; Dai et al. (2014); all ages; lag 0–1 d; 24-h mean = 13.3 μg/m^3

I. 3 US states; Lee et al. (2016); all ages; lag 0–1 d; 24-h mean = 11.1 μg/m^3

J. 3-5 single- and multi-city studies from WHO regions; Atkinson et al. (2014); J1 = respiratory mortality (5 studies), J2 = COPD mortality (3 studies)

K. 9 studies (6 United States, 3 Europe, 3 China); Chang et al. (2015); respiratory mortality

L. 7 studies (2 United States, 1 South America, 4 Europe); Li MH et al. (2016); COPD mortality

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

○ Published systematic review with meta-analysis studies

The systematic review with meta-analysis by Chang et al. (2015) includes results from the following primary studies: Franklin et al. (2007), Ostro et al. (2006), and Zanobetti and Schwartz (2009). CI = confidence interval; COPD = chronic obstructive pulmonary disease; CSSA = Canadian Smog Science Assessment; GAM = generalized additive model; GLM = generalized linear model; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; TEOM = tapered element oscillating microbalance; SR = systematic review with meta-analysis; US = United States; WHO = World Health Organization; WHO regions = African Region, Eastern Mediterranean Region, European Region, Regions of the Americas, South-East Asian Region, Western Pacific Region

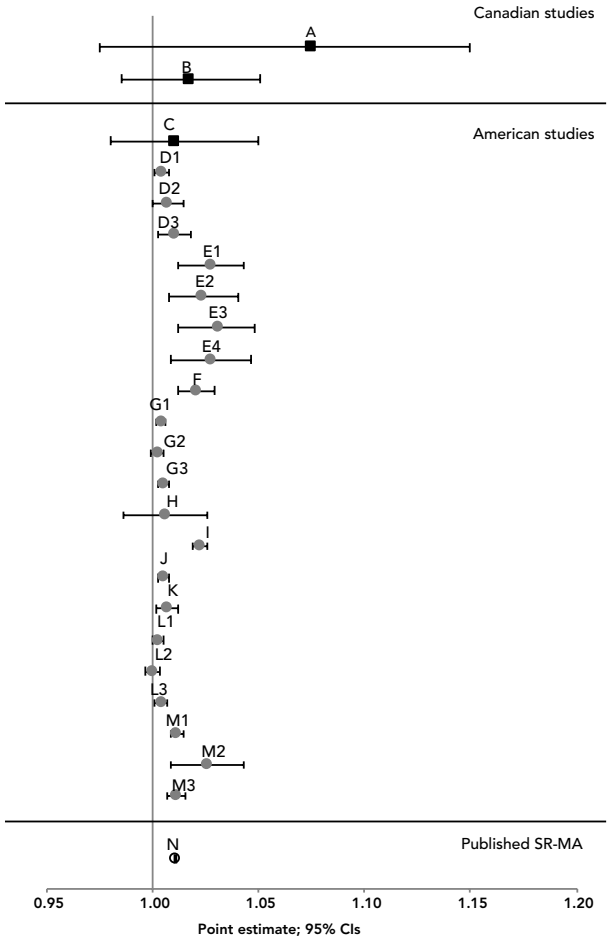
Updated information—respiratory morbidity

Respiratory hospital admissions

In the literature published since the CSSA, there is a large database of multi-city population-based epidemiological studies conducted in the United States, which reported positive and mostly significant associations between exposure to $PM_{2.5}$ and respiratory-related hospital admissions (Figure 2.10). No Canadian multi-city study was identified. The positive association observed in American studies was further supported by a systematic review with meta-analysis. In this pooled analysis, a positive and significant association was observed between $PM_{2.5}$ exposure and all hospital

admissions related to respiratory effects (Atkinson et al., 2014). Some studies have focused on the specific respiratory causes (i.e., COPD and asthma exacerbations, respiratory tract infection including pneumonia) of hospital admissions. Cause-specific analyses reported a significant increase in hospital admissions related to COPD exacerbation and lower respiratory tract infection in elderly individuals (Lippmann et al., 2013; Kloog et al., 2014; Bell et al., 2015). A positive association with hospital admission for asthma exacerbation was observed in children (Ostro et al., 2009), the elderly (Bell et al., 2015) and individuals of all ages (Weber et al., 2016). These associations were further supported by a number of systematic review with meta-analysis studies, in which positive and significant associations were observed for exacerbation of COPD- and asthma-related hospital admissions (Zheng et al., 2015; Li MH et al., 2016; Lim et al., 2016).

FIGURE 2.10: Point estimates and 95% confidence intervals for all respiratory hospital admissions per standardized increment (10 μg/m³ for 24 h) in short-term ambient $PM_{2.5}$ concentration in single-pollutant model in epidemiological studies



A. Vancouver, BC; Chen et al. (2005); aged ≥65; lag 0-1 d; 24-h mean = 13.3 μg/m³

B. Vancouver, BC; Fung et al. (2006); aged ≥65; lag 0 d; 24-h mean = 13.3 μg/m³

C. Spokane, WA; Slaughter et al. (2005); all ages; lag 3 d; 24-h mean not reported

D. 202 US counties; Bell et al. (2008); aged ≥65; D1 = all-year, lag 2 d, D2 = winter, lag 2 d, D3 = winter, lag 0 d; 24-h mean not reported

E. 6 Californian counties; Ostro et al. (2009); children; E1 = aged 0–18, all year, E2 = aged 0–18, cool season, E3 = aged <5, all year, E4 = aged <5, cool season; lag 3 d; 24-h mean (all year) = 19.4 μg/m³; 24-h mean (cold season) = 24.8 μg/m³

F. 26 US communities; Zanobetti et al. (2009); aged ≥65; lag 0-1 d; 24-h mean = 15.3 μg/m³

G. 148 US cities; Lippmann et al. (2013); aged ≥65; lag 0 d; G1 = all year, G2 = warm season, G3 = cold season; 24-h mean not reported

H. 4 US counties; Bell et al. (2014); aged ≥65; lag 2 d; 24-h mean = 14.0 μg/m³

I. Mid-Atlantic region (Washington DC and the states of Delaware, Maryland, New Jersey, Pennsylvania, Virginia, New York and West Virginia); Kloog et al. (2014); all ages; lag 0-1 d; 24-h mean = 11.92 μg/m³

J. New York State; Jones et al. (2015); all ages; lag 0 d; 24-h mean = 8.03 μg/m³

K. 100 US urban counties; Powell et al. (2015) (extended analysis of Peng et al. (2008)); aged ≥65; lag 0 d; 24-h median = 12.6 μg/m³

L. 213 US counties; Bell et al. (2015); aged ≥65; L1 = both sexes, L2 = men, L3 = women; lag 0 d; 24-h mean not reported

M. 708 US counties; Bravo et al. (2017); M1=overall, M2 = least urban (≤40% of pop. in urban areas), M3 = most urban (>90% of pop. in urban areas); age not reported; lag 0 d; 24-h mean = 12.28 μg/m³

N. 4 single- and multi-city studies from WHO regions; Atkinson et al. (2014)

■ Studies from the CSSA (Health Canada, 2013)

● Studies published since the CSSA

○ Published systematic review with meta-analysis studies

CI = confidence interval; CSSA = Canadian Smog Science Assessment; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; SR-MA = systematic review with meta-analysis; US = United States; WHO = World Health Organization; WHO regions = African Region, Eastern Mediterranean Region, European Region, Regions of the Americas, South-East Asian Region, Western Pacific Region

Respiratory emergency room visits

Since the publication of the CSSA, researchers have greatly expanded the study of the relationship between short-term $PM_{2.5}$ exposure and respiratory-related emergency room visits. Multi-city studies conducted in Canada and the United States reported positive and mostly significant relationships between $PM_{2.5}$ exposure and all respiratory-related emergency room visits and specific respiratory diseases (e.g., pneumonia, COPD, respiratory infections) (Malig et al., 2013; Ostro et al., 2016; Weichenthal et al., 2016c). Emergency room visits related to asthma exacerbation have been studied more extensively than other outcomes. There is a large dataset in which nearly all Canadian and American multi-city studies, across all age groups, have reported positive and significant associations between $PM_{2.5}$ exposure and emergency room visits related to asthma exacerbation (To et al., 2015a;

Alhanti et al., 2016; Ostro et al., 2016; Weichenthal et al., 2016c; Xiao et al., 2016). The observation was further supported by systematic review with meta-analysis studies that reported significant associations between asthma-related emergency room visits and exposure to $PM_{2.5}$, in both adults and children (Zheng et al., 2015; Fan et al., 2016; Lim et al., 2016). In many cases, the magnitude of the association for asthma-related emergency room visits was greater than that for all respiratory-related emergency room visits or other specific respiratory causes (Stieb et al., 2009; Weichenthal et al., 2016c). During wildfire events, there was also elevated asthma-related emergency room visits associated with exposure to high levels of $PM_{2.5}$ (Alman et al., 2016; Reid et al., 2016). Together, evidence from hospital visits (emergency room visits and hospital admissions) continued to support the finding that short-term exposure to $PM_{2.5}$ was associated with respiratory adverse effects, especially exacerbation of COPD and asthma-related events.

Subclinical effects

In panel and cross-sectional studies that examined subclinical outcomes, short-term $PM_{2.5}$ exposure was associated with decreased lung function (Liu et al., 2009; Dales et al., 2013) and increased airway inflammation (mostly based on measurement of the fractional exhaled nitric oxide) (Delfino et al., 2013; Weichenthal et al., 2011). Most studies were conducted in asthmatic children, with a few studies looking at either adults with asthma or other chronic respiratory diseases, such as COPD, or healthy adults. For other subclinical outcomes, there was less consistent positive association between exposure to $PM_{2.5}$ and respiratory symptoms (i.e., wheeze, cough, shortness of breath, and chest tightness) and the use of bronchodilator medications, likely due to a wide range of severity of asthma (O'Connor et al., 2008; Patel et al., 2010; Evans et al., 2014). Overall, these epidemiological studies indicated that short-term exposure to $PM_{2.5}$ is associated with some subclinical respiratory effects.

Controlled human exposure studies are usually conducted in healthy individuals or those with mild severity level of health conditions (i.e., asthma, COPD) and are limited to short-term exposures (i.e., 2 hours). After a 2-hour exposure to $PM_{2.5}$ CAPs, most studies reported no change in lung function parameters, changes in pulmonary and nasal inflammatory markers or diffusing capacity in healthy individuals and mild asthmatics (Urch et al., 2010; Huang et al., 2012; Behbod et al., 2013). A single study showed that smokers/ ex-smokers exhibited some transient effects, such as reduced lung function parameters and diffusing capacity (Hazucha et al., 2013). Thus, controlled exposure to $PM_{2.5}$ CAPs appears to have no effect on relatively healthy individuals at the exposure level and duration currently examined.

Updated information—effects in toxicological studies

Acute or subchronic exposure of experimental mice and rats to $PM_{2.5}$ consistently resulted in lung injury and inflammation. In addition, an increase in the number of neutrophils and increased plasma levels of the vasoconstrictor endothelin-1 have been observed in the absence of oxidative stress, inflammation, or cytotoxicity (Bouthillier et al., 1998; Haberzettl et al., 2016a). This suggests that injury and inflammation are likely not the only mechanisms leading to adverse respiratory outcomes. Animals were generally exposed either by intratracheal instillation or to concentrations that can be representative of human exposure levels by inhalation in chambers. $PM_{2.5}$ exposure was shown to induce acute pulmonary oxidative stress in mice (characterized by increases in expression of the antioxidant genes superoxide dismutase and glutathione s-transferase and in extracellular superoxide dismutase protein levels). A few studies also showed exposed rodents had alveolar inflammatory foci, infiltration of inflammatory and immune cells, alveolitis and bronchiolitis by histopathological

examination. In addition to inflammation and oxidative stress, data from toxicological studies suggest that mitochondrial abnormalities and the involvement of the kallikrein-kinin system could also be involved in the development of adverse respiratory effects. Also, a few studies investigating the role of $PM_{2.5}$ in allergic airway disease using rat ovalbumin-induced allergy models reported exacerbation of inflammatory responses on exposure to $PM_{2.5}$. Overall, the evidence consistently shows that exposure to $PM_{2.5}$ causes respiratory effects in association with oxidative stress, inflammation, and other pathways in exposed animals. The data provide mechanistic understanding of how $PM_{2.5}$ could cause adverse respiratory effects consistent with those observed in human studies.

Conclusion for short-term $PM_{2.5}$ exposure and respiratory effects

In summary, the epidemiological database consistently reported that short-term exposure to $PM_{2.5}$ is associated with a significant increased risk of overall respiratory-related premature mortality, particularly in individuals with COPD or pneumonia. In terms of morbidity outcomes, multi-city epidemiological studies consistently reported that $PM_{2.5}$ exposure is positively and significantly associated with an increased risk of respiratory-related hospital admissions and emergency room visits, particularly for asthma, COPD and pneumonia. The increased risk of asthma-related emergency room visits was observed in both children and adults in nearly all studies including systematic review with meta-analysis. The magnitude of the risk was further increased when $PM_{2.5}$ levels were elevated during wildfire events, thus providing additional evidence of the association. Controlled human studies generally did not report any respiratory effects in healthy adults and mild asthmatics exposed to CAPs for 2 hours. Certain individuals such as smokers and those prone to allergic conditions seemed to have more pronounced respiratory effects, but the number of available studies was small. The robustness of the associations was well established in the CSSA, with positive and significant $PM_{2.5}$ effects usually maintained, although slightly attenuated, in co-pollutant analyses (NO_2, CO, O_3). Multi-pollutant or co-pollutant models were rarely conducted in studies reviewed in this update as the causal relationship had already been established. Toxicological studies have shown coherence for the associations observed in epidemiological studies, with increases in lung inflammation and damage and enhanced allergic responses in animals exposed to $PM_{2.5}$. Moreover, the oxidative stress and inflammatory responses, as well as the histopathological changes within the lung tissue, observed in experimental animals provide insight on the mechanisms by which $PM_{2.5}$ may be acting and hence provide biological plausibility for the effects observed in epidemiological studies. Thus, the overall evidence continued to support **causal relationships** between short-term exposure to $PM_{2.5}$ and respiratory-related morbidity and mortality.

Long-term exposure to $PM_{2.5}$

Conclusion from the CSSA

At the time of the CSSA, only a limited number of studies had examined the relationship between long-term $PM_{2.5}$ exposure and respiratory mortality. Therefore, it was concluded that the evidence was inadequate to determine a causal relationship between exposure to $PM_{2.5}$ and respiratory mortality. Between $PM_{2.5}$ exposure and respiratory morbidity, it was determined that the evidence was suggestive of a causal relationship. Epidemiological studies had generally focused on children. $PM_{2.5}$ exposure was found to be associated with a reduction in lung function and an increase in respiratory symptoms, especially with childhood bronchitis symptoms. Very few chronic toxicological studies examining the respiratory effects of $PM_{2.5}$ in animals had been published, with only some evidence of hyperplasia and fibrosis reported at high concentrations. A few chronic studies on

experimental allergy or lung function and airway reactivity had been reported, which showing signs of increased allergy symptoms; however, these studies were limited in number, particle size was not clearly defined and control groups were not always included.

Updated information—respiratory mortality

Studies reviewed in this update have focused on all respiratory-related mortality (typically excluding lung cancer) or cause-specific respiratory-related mortality. Most of the Canadian and American studies reported positive non-significant associations between long-term exposure to $PM_{2.5}$ and all respiratory mortality, including results from CanCHEC, CCHS and ACS cohort studies (Pinault et al., 2016; Turner et al., 2016; Weichenthal et al., 2016a). Studies have also investigated mortality from COPD; most of the American studies reported positive and non-significant associations (Hart et al., 2011; Lepeule et al., 2012; Turner et al., 2016), while the two Canadian studies showed inconsistent results (Crouse et al., 2015; Pinault et al., 2016). Although both studies estimated $PM_{2.5}$ levels with satellites, an important difference is the finer scale of $PM_{2.5}$ exposure estimates (1 km x 1 km grid) by Pinault et al. (2016) reported a positive and significant association. In comparison, no association was observed with the 10 km x 10 km grid used by Crouse et al. (2015). Co-pollutant or multi-pollutant analyses with adjustment for $PM_{10\text{-}2.5}$, black carbon, O_3 and/or NO_2 generally did not modify the $PM_{2.5}$ associations, except for the attenuation observed by O_3, in studies on all respiratory and COPD mortality (McDonnell et al., 2000; Jerrett et al., 2009, 2013; Crouse et al., 2015; Thurston et al., 2016a). Hence, there is some evidence to suggest that long-term exposure to $PM_{2.5}$ is associated with an increase in overall respiratory-related mortality as well as specific COPD-related conditions.

Updated information—respiratory morbidity

For morbidity, studies have continued to report associations between exposure to $PM_{2.5}$ and reduced lung function, as measured by forced expiratory volume in 1 second and forced vital capacity. These associations have now been observed in adults as well as in children. Cohort and cross-sectional studies have reported some significant associations between long-term exposure to $PM_{2.5}$ and reduction in lung function, but the confidence intervals were wide (Rice et al., 2015, 2016; Adar et al., 2015). In terms of respiratory symptoms, long-term exposure to $PM_{2.5}$ is associated with significant increases in respiratory allergy/ hay fever in children in both single-pollutant and co-pollutant (adjusted for SO_2, NO_2, PM_{10}, summer O_3) analyses (Parker et al., 2009). The decline in $PM_{2.5}$ levels in California communities was associated with a reduction in childhood bronchitis symptoms (Berhane et al., 2016). A small dataset suggested that in adults, especially those with asthma and/or rhinitis, $PM_{2.5}$ exposure was associated with increased respiratory symptoms, although results were not entirely consistent (Balmes et al., 2014; Young et al., 2014; Rice et al., 2015). Taken together, the evidence suggests that long-term exposure to $PM_{2.5}$ is associated with respiratory effects in adults as well as in children.

Researchers have investigated the association between long-term exposure to $PM_{2.5}$ and the development of hospital-related events linked to asthma and other chronic respiratory diseases. In women, children and adolescents (men have not yet been studied in Canada or the United States), exposure to $PM_{2.5}$ was associated with a non-significant increase in asthma diagnosis in cohort and case-control studies (McConnell et al., 2010; Nishimura et al., 2013; Young et al., 2014; To et al., 2015b; Tétreault et al., 2016). Moreover, a Canadian study that followed adult women for 17 years reported a positive and significant association between exposure to $PM_{2.5}$ and COPD diagnosis, which remained after adjustment for O_3 (To et al., 2015b). Asthmatic adults were found to have a greater risk of developing asthma-COPD overlap syndrome with exposure to $PM_{2.5}$ (To et al., 2016).

Exposure to $PM_{2.5}$ during prenatal or childhood time periods was associated with increased risk of asthma development in children (Clark et al., 2010; Tétreault et al., 2016b), and a greater risk was reported for certain high-risk infants (due to family history) (Carlsten et al., 2011). Moreover, a systematic review with meta-analysis study found that early childhood exposure to $PM_{2.5}$ was associated with a non-significant increased risk of asthma incidence (Bowatte et al., 2015). Some studies investigated the associations between exposure to $PM_{2.5}$ and asthma exacerbation, including respiratory-related hospital visits (i.e., admissions and emergency room visits) or self-reported asthma exacerbation in children (Akinbami et al., 2010; Tétreault et al., 2016). In addition, exposure to $PM_{2.5}$ was associated with increased COPD exacerbation-related hospital admissions in adults and the elderly (Gan et al., 2013) and increased community-acquired pneumonia hospital admissions in the elderly (Neupane et al., 2010). Multi-pollutant adjustment for black carbon and NO_2 did not affect the non-significant positive association between $PM_{2.5}$ exposure and COPD hospital admissions (Gan et al., 2013). Overall, these studies indicated that long-term exposure to $PM_{2.5}$ is associated with an increased risk of developing chronic respiratory conditions and of respiratory-related hospital visits.

Updated information—effects in toxicological studies

In toxicological studies, very limited evidence is available on the effects of chronic exposure to $PM_{2.5}$ on the respiratory system. This update identified only one study that exposed mice to $PM_{2.5}$ for relatively long periods (6 weeks by oropharyngeal aspiration). Increases in BALF total cell count and inflammatory cytokines (TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1) and macrophage infiltration and in apoptotic cell death in the lung tissue were observed.

Conclusion for long-term $PM_{2.5}$ exposure and respiratory effects

In summary, there is some consistency in the epidemiological data showing positive associations between long-term exposure to $PM_{2.5}$ and overall respiratory mortality as well as cause-specific COPD mortality. Co-pollutant and multi-pollutant analyses generally did not modify the observed associations, indicating robustness of the measured associations. Exposure to $PM_{2.5}$ is associated with reduced lung function in both adults and in children. In many cases, the point estimates had wide confidence intervals and associations were non-significant. Children were found to have increased respiratory allergy symptoms, bronchitis symptoms and, to some extent, wheezing symptoms associated with exposure to $PM_{2.5}$. An increased risk of asthma development, as well as asthma exacerbation-related hospital visits (including hospital admissions, emergency room visits), were observed with long-term exposure to $PM_{2.5}$ in both adults and children. There is some evidence suggesting that exposure to $PM_{2.5}$ might also increase the risk of COPD development and of COPD- or pneumonia-related hospitalization in adults and the elderly. The respiratory associations observed with exposure to $PM_{2.5}$ persisted in the available multi-pollutant analyses (black carbon, NO_2) and co-pollutant analysis (O_3), but some uncertainty of the robustness of the database for respiratory morbidity remain. Children, the elderly, asthmatics and individuals with a family history of asthma have increased susceptibility to the respiratory effects of $PM_{2.5}$. The toxicological database remains limited for chronic exposure; however, the few available results were consistent with the epidemiological data, as cell infiltration in the lung and inflammation can be considered precursors to respiratory and COPD mortality in some individuals. Collectively, the evidence of an increased risk for respiratory mortality associated with long-term exposure to $PM_{2.5}$ is **suggestive of, but not sufficient to infer, a causal relationship**, based on a small but growing epidemiological database suggesting an increased risk of overall respiratory and COPD-specific mortality. The dataset exhibits some limitations with

respect to the strength and robustness of the association, but consistency, biological plausibility and coherence exist to support a **likely causal relationship** between respiratory morbidity and long-term exposure to $PM_{2.5.}$ Exposure to $PM_{2.5}$ results in increased risk of asthma diagnosis and related exacerbations as well as reduced lung functions, especially in children and asthmatics.

2.4. CANCER EFFECTS

Conclusion from the CSSA

The CSSA concluded that there is a likely causal relationship between long-term exposure to $PM_{2.5}$ and lung cancer mortality, and the International Agency for Research on Cancer (IARC, 2013) classified PM from outdoor air pollution as carcinogenic to humans (IARC Group 1). The few epidemiological studies available on the relationship of $PM_{2.5}$ with cancer reported positive associations between $PM_{2.5}$ exposure and lung cancer mortality. With the exception of the extended analysis of the ACS study, that was robust to adjustment to confounders, most of the associations in the epidemiological studies were positive and not significant. No toxicological studies examined the carcinogenicity of environmentally relevant particles in the CSSA. Some studies using very high levels of other particle types (i.e., inhalation of vanadium pentoxide (V_2O_5) for 2 years, and weekly intratracheal instillation of granular dust for 20 weeks) indicated an increase in the incidence of tumours in animals. In addition, $PM_{2.5}$ was reported to cause DNA damage in the form of mutations, chromosomal aberrations, micronuclei and DNA strand breaks in many in vitro and in a limited number of in vivo inhalation studies. The mutagenicity potential of $PM_{2.5}$ was shown to vary across seasons and sources, with winter $PM_{2.5}$ and urban sources such as traffic, industrial emission and residential heating having a higher mutagenic potential. These results provided support to the carcinogenicity and genotoxicity of $PM_{2.5}$.

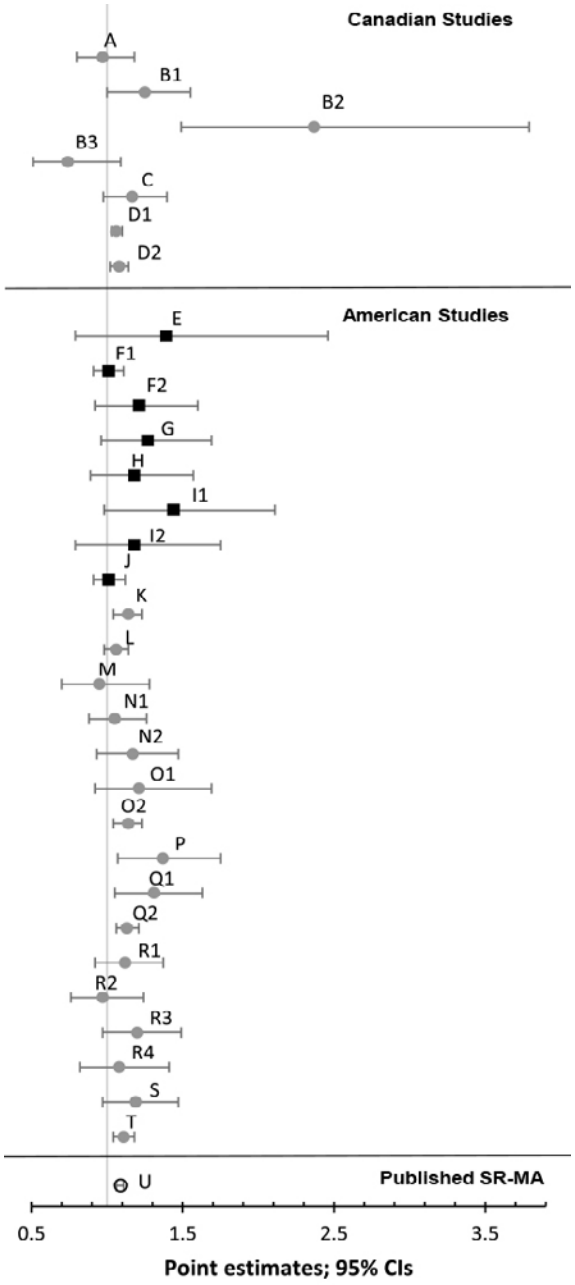
Updated information—cancer mortality and morbidity

As shown in Figure 2.11, the majority of studies reported positive associations between $PM_{2.5}$ exposure and lung cancer mortality based on large Canadian (CanCHEC and Canadian National Breast Screening Study (CNBSS); Crouse et al., 2015; Villeneuve et al., 2015; Pinault et al., 2016; Weichenthal et al., 2016a) and American cohort studies (ACS and H6CS; Krewski et al., 2009; Turner et al., 2011, 2016; Jerrett et al., 2013; Thurston et al., 2013), as well as smaller American cohort studies (Adventist Health Air Pollution Study, Women's Health Initiative, California Teachers Study, California Cancer Registry, and the United States trucking industry; McDonnell et al., 2000; Lipsett et al., 2011; Hart et al., 2011). However, most of these associations were non-significant. In these studies, the $PM_{2.5}$ concentrations ranged from 2 to 40 $\mu g/m^3$ (lower in more recent years and higher in the 1980s). In addition, lung cancer incidence was reported to be associated with $PM_{2.5}$ exposure in two Canadian cohort studies (Hystad et al., 2013; Tomczak et al., 2016) and two American cohort studies (Puett et al., 2014; Gharibvand et al., 2017), but most of these associations were non-significant. The combined risk of lung cancer incidence and mortality was found to be significant in three meta-analysis studies, which included the Canadian and American studies cited above (Hamra et al., 2014; Chen et al., 2015; Yang et al., 2016). The increase in power resulting from the meta-analyses can explain the significance of the pooled estimates. The inclusion of European and Asian studies from the early 1980s, the exclusion of certain studies, and the high weight given to one American study showing positive and significant association can also contribute to the significance of the pooled estimates.

All sub-types of lung cancer (i.e., adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma) examined in three Canadian and American cohort studies and two European studies were found to be positively associated with exposure to $PM_{2.5}$ to some degree, although most associations were non-significant (Hystad et al., 2013; Puett et al., 2014; Hart et al., 2015; Tomczak et al., 2016). Only the CNBSS, which examined $PM_{2.5}$ exposure and lung adenocarcinoma incidence in women, reported a significantly positive association between a lung cancer subtype and exposure to $PM_{2.5}$ (Tomczak et al., 2016).

A limited number of Canadian and American studies have examined the relationship between exposure to $PM_{2.5}$ and other cancers. There were four studies on breast cancer (Hu et al., 2013; Reding et al., 2015; To et al., 2015b; Hart et al., 2016), and one study for the following outcomes: early childhood cancer (Heck et al., 2013), brain (McKean-Cowdin et al., 2009), uterine cancers (Mahalingaiah, 2014), and leukemia (Winters et al., 2015). The CNBSS cohort analysis showed positive but non-significant association with breast cancer incidence (To et al., 2015b), and the analysis of cancer data from the California Surveillance Epidemiology and End Results program showed a positive and statistically significant association between early death among female breast cancer patients and mean monthly county $PM_{2.5}$ levels (Hu et al., 2013). However, residual confounding may be possible, as diet, alcohol consumption, and socioeconomic status were not uniformly addressed in these studies. In addition, the United States Sister Study and Nurses' Health Study (NHS) II cohort studies showed no association of $PM_{2.5}$ with breast cancer incidence (or with cell receptor subtypes) (Reding et al., 2015; Hart et al., 2016). Overall, there may be a weak relationship with other cancers. However, much uncertainty remains because of the small size of the database and the inconsistent results.

FIGURE 2.11: Point estimates and 95% confidence intervals for lung cancer mortality per standardized increment (10 μg/m^3 for 24 h) in $PM_{2.5}$ concentration in epidemiological studies



- ■ Studies from the CSSA (Health Canada, 2013)
- ● Studies published since the CSSA
- ○ Published systematic review with meta-analysis studies

A. CNBSS; Villeneuve et al. (2015); 1980 and 2005; annual mean not reported

B. CanCHEC; Weichenthal et al. (2016); 1991–2009; B1 = $PM_{2.5}$ alone, B2 = $PM_{2.5}$*OP^{AA}, B3 = $PM_{2.5}$*OP^{GSH}, annual mean = 9.81 μg/m^3 (1998–2009)

C. CanCHEC; Pinault et al. (2016); 2000 and 2008–2011; annual mean = 6.3 μg/m^3 (1998–2010)

D. CanCHEC; Crouse et al. (2015); non-immigrant Canadians; D1 = $PM_{2.5}$ alone, D2 = multi-pollutant analysis adjusted for NO_2 and O_3; 1991–2006; annual mean not reported (1984–2006)

E. AHSMOG; California, USA; McDonnell et al. (2000); men who lived near an airport; 1977–1992; annual mean = 29.5 μg/m^3 (1973–1977)

F. H6CS-ACS (re-analysis); Krewski et al. (2000); F1 = H6CS, F2 = ACS; 1974–1991; annual mean not reported

G. H6CS (follow-up); Laden et al. (2006); 1974–1998; annual mean ranged from 40 to 10 μg/m^3 (1979–1988) and (1990–1998)

H. H6CS; USA; Dockery et al. (1993); 1974–1991; annual mean = 18.6 μg/m^3 (1979–1988)

I. ACS; Los Angeles, CA; Jerrett et al. (2005); I1 = $PM_{2.5}$ alone, I2 = adjusted for O_3 and NO_2; 1982–2000; annual mean not reported

J. ACS; Pope et al. (1995); 1982–1989; annual mean = 18.2 μg/m^3 (1979–1983)

K. ACS; Pope et al. (2002); 1982–2000; annual mean = 17.7 μg/m^3 (1979–1983) and (1999–2000)

L. Thurston et al. (2013); 1982–2004; annual mean not reported

M. CTS; Lipsett et al. (2011); 1999–2005; female; annual mean not reported (1999–2005)

N. US trucking industry; Hart et al. (2011); N1 = including long-haul drivers, N2 = excluding long-haul drivers; 1985–2000; annual mean = 14.1 μg/m^3 (2000)

O. H6CS-ACS (extended); Pope et al. (2011); O1 = H6CS, O2 = ACS; 1989–1995; annual mean not reported

P. H6CS (follow-up); Lepeule et al. (2012); 1979–2009; annual mean = 15.9 μg/m^3 (1979–1983) and (1999–2000)

Q. ACS; Turner et al. (2016); Q1 = near-source (LUR), Q2 = regional (LURBME-LUR); 1982–2004; mean range = 1.4–27.9 μg/m^3 (1999–2008)

R. ACS (re-analysis); Jerrett et al. (2013); R1 = $PM_{2.5}$ alone, R2 = adjusted for NO_2, R3 = adjusted for O_3, R4 = adjusted for NO_2 and O_3; 1982–2000; annual mean not reported

S. ACS; Turner et al. (2011); 1982–2008; never-smokers; annual mean = 17.7 μg/m^3

T. ACS (extended and re-analysis); Krewski et al. (2009); 1982–2000; annual mean not reported

U. 12 cohort studies from Europe, North America, Japan; Cui et al. (2014)

The SR/MA by Cui et al. (2014) used relative risk (RR) as point estimates and included results from the following primary studies: Pope et al. (1995), Pope et al. (2002), Jerrett et al. (2005), Jerrett et al. (2013), Krewski et al. (2009), Turner et al. (2011), Dockery et al. (1993), Laden et al. (2006), Lepeule et al. (2012), McDonnell et al. (2000), and Hart et al. (2011).

ACS = American Cancer Society; AHSMOG = Adventist Health Air Pollution Study; CanCHEC = Canadian Census Health and Environment Cohort; CI = confidence interval; CSSA = Canadian Smog Science Assessment; CTS = California Teachers Study; HR = hazard ratio; H6CS = Harvard Six Cities Study; LUR = land-use regression; LURBME = land-use regression Bayesian maximum entropy; NO_2 = nitrogen dioxide; O_3 = ozone; OPGSH = glutathione-related oxidative potential; OPAA = ascorbate-related oxidative potential; $PM_{2.5}$ = PM of 2.5 μm or less in median aerodynamic diameter; SR-MA = systematic review with meta-analysis

Updated information—effects in toxicological studies

Animal and in vitro studies have shown that $PM_{2.5}$ can induce DNA methylation, increase the expression of oncogenes, and lower the expression of tumour-suppressor genes. Only one study evaluated tumour incidence in female mice, and it observed a slight increase in lung tumour formation in the $PM_{2.5}$ group (17 .7 µg/m^3 for 2 months) compared with the group exposed to filtered air ($PM_{2.5}$ mean of 4.5 µg/m^3 in chambers). However, both groups were pre-treated with urethane (a lung carcinogen), suggesting that $PM_{2.5}$ may play a role in increasing vulnerability to carcinogenic substances. The other studies investigated mechanisms involved in tumour formation by measuring changes in gene, miRNA and protein translation in cultured cells or in mice following exposure to $PM_{2.5}$ (all mice studies used inhalation chambers). For example, one potential mechanism of action involves the decrease in specific miRNA such as miRNA-182 and miRNA-185, leading to the overexpression of their target oncogenes (*SLC30A1*, *SERPINB2* and *AKR1C1*). Moreover, the generation of reactive oxygen species by $PM_{2.5}$ was shown to lead to an increase in DNA methyltransferase 3 levels, which in turn methylates the p16 gene, and leads to an increase in the p16 protein, a multi-tumour suppressor protein in a lung alveolar cell line from mice. Similarly, human bronchial epithelial cells exposed to $PM_{2.5}$ showed an increase in the production of reactive oxygen species, in phosphorylation and activation of protein kinase B, in protein levels of DNA methyltransferase 3b, and in methylation of the p53 promoter and expression of the p53 tumour suppressor protein. Alveolitis and bronchial dysplasia were also observed in lung tissue in a study in mice. Changes in gene expression were found in the lungs of the exposed mice.

Conclusion for long-term $PM_{2.5}$ exposure and cancer effects

In summary, the majority of epidemiological studies have reported positive associations between exposure to $PM_{2.5}$ and increased risk of lung cancer. The epidemiological database for other types of cancer was considered to be too limited to derive causality conclusion. Toxicological studies provided support to the previous experiments showing oxidative stress, inflammation and genotoxicity induced by $PM_{2.5}$ exposure reported in the CSSA. However, the animal database remains small. No complete, high-quality inhalation studies focusing on tumour development in animals were identified. Oxidative stress and inflammation, which are known to play a role in cancer development and changes in mRNA, miRNA, and proteins involved in tumorigenesis, provide biological plausibility to the associations between $PM_{2.5}$ and lung cancer observed in epidemiological studies. Overall, the database is limited in terms of robustness to adjustments and there are too few toxicological studies evaluating cancer incidence to provide coherence. However, the consistency in the positive association with lung cancer and the biological plausibility of the cancer mechanisms in toxicological studies, including the central role inflammation plays in cancer and the activation of various pathways involved in tumour formation and progression, support a **likely causal relationship** between lung cancer morbidity and mortality and exposure to $PM_{2.5}$.

2.5. REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Conclusion from the CSSA

The CSSA identified associations between various PM fraction sizes (mostly PM_{10} and in some cases $PM_{2.5}$) and reproductive and developmental endpoints, such as postnatal mortality, preterm birth, intrauterine growth restriction, and low birth weight. However, several caveats were identified in the database, including inconsistency of the results, uncertainties surrounding critical periods of exposure, low number of studies, and unclear role of other co-pollutants and other factors. Associations were often stronger with other pollutants, such as CO and NO_2, and with roadway-based exposure metrics than with $PM_{2.5}$. For $PM_{2.5}$-specific results, only a few epidemiological studies were identified, reporting associations with increased risk of preterm birth and low birth weight-related outcomes. In terms of toxicological studies, the only reproductive study reported alterations in biomarkers of spermatogenesis in male mice exposed to V_2O_5, which is a laboratory produced particle not representative of ambient air. Of the limited number of studies, most evaluated the effects of residual oil fly ash or metals. Overall, it was concluded that the evidence was suggestive of, but not sufficient to infer, a causal relationship with reproductive and developmental outcomes for all PM fraction sizes. Only one conclusion was drawn for these two groups of health effects in the CSSA.

Reproductive effects

Updated information—epidemiological evidence

The literature reviewed in this update examined the potential effect of $PM_{2.5}$ exposure on fertility. A cohort study reported that $PM_{2.5}$ exposure was associated with increased risk of infertility in women, though the causes of infertility (male or female factors or unknown causes) were not identified (Mahalingaiah et al., 2016). In males, inconsistent results were observed in two cross-sectional studies evaluating associations between semen quality and $PM_{2.5}$ levels (Hammoud et al., 2010; Hansen et al., 2010). Exposure to $PM_{2.5}$ was associated with decreased conception success in the case of assisted human reproduction (Legro et al., 2010). Overall, the evidence is considered limited due to the small number of studies available.

Researchers have investigated the relationship between $PM_{2.5}$ exposure and maternal health during pregnancy. In a small dataset, there is some evidence that exposure to $PM_{2.5}$ is associated with increased risk of all pregnancy-related hypertensive disorders (preeclampsia, eclampsia and/or gestational hypertension conditions) when considering $PM_{2.5}$ exposure during the entire pregnancy and in some cases in the specific trimesters of first trimester (T1) and second trimester (T2) (Vinikoor-Imler et al., 2012; Pedersen et al., 2014; Xu et al., 2014). Preeclampsia is a pregnancy disorder where the major symptoms are hypertension and elevated protein in urine and eclampsia is a more severe form marked by seizures and coma. However, the associations with exposure to $PM_{2.5}$ were less consistent when only evaluating preeclampsia/ eclampsia (Lee et al., 2013; Mendola et al., 2016a; Wu et al., 2016) or gestational hypertension (Lee et al., 2012, 2013). Additionally, studies investigating the association between $PM_{2.5}$ exposure during pregnancy and risk of gestational diabetes have reported inconsistent findings (Hu et al., 2015; Robledo et al., 2015; Wu et al., 2016). A major limitation is that not all studies have properly adjusted for all confounders (i.e., known risk factors related to these health conditions). In addition, none of these studies had conducted multi-pollutant or co-pollutant analysis to consider the potential influence of other co-pollutants. A small number of studies investigated the association between exposure to $PM_{2.5}$ and biomarkers

in maternal blood, including metabolic biomarkers (leptin and adiponectin) in umbilical cord blood, intrauterine inflammation and maternal CRP levels and other inflammatory biomarkers (Lee et al., 2011; Ashley-Martin et al., 2016; Lavigne et al., 2016a), in which no conclusion can be drawn at this time. Together, the epidemiological database suggested some maternal health effects related to $PM_{2.5}$ exposure, but the results are not entirely consistent.

Updated information—effects in toxicological studies

A few toxicological studies have reported some evidence of reproductive effects following $PM_{2.5}$ exposure. One study reported alterations in sperm quality in male mice following intratracheal instillation of high doses of $PM_{2.5}$, along with higher oxidative stress in testicular tissue, apoptosis of Sertoli cells, lower expression of genes involved in the blood-testis barrier, and lower fertility compared to controls. Rat dams exposed to high $PM_{2.5}$ levels were also found to have lower maternal weight gains, higher number of absorbed blastocysts, increased oxidation and inflammation, and placental alterations (i.e., neutrophilic infiltration, placental thrombus and fibrin deposition). Overall, the toxicological database remains limited in size and only investigated some reproductive effects.

Conclusion for reproductive effects

In summary, the epidemiological study dataset remains small but suggests that $PM_{2.5}$ exposure is associated with maternal effects (hypertensive disorders, gestational diabetes) during pregnancy. There is insufficient evidence to support that $PM_{2.5}$ exposure is associated with an increased risk of infertility in both males and females. The toxicological database provided evidence of alterations in the placenta tissue and sperm quality of mice. Both effects were likely due to increases in oxidative stress in reproductive tissues, as well as inflammation in the placenta. However, the small size of the toxicological database and a poor characterization of the reproductive effects overall limited the possibility to interpret and conclude on these effects. Given that uncertainties regarding the strength, robustness, consistency, and coherence of the associations exist, the evidence is **inadequate to infer a causal relationship** between exposure to $PM_{2.5}$ and reproductive outcomes.

Developmental effects

Updated information—epidemiological evidence

Birth weight outcomes

This update has identified a large database examining the relationship between maternal $PM_{2.5}$ exposure and birth outcomes (i.e., birth weight parameters, preterm birth incidence). Babies born with low birth weight may have more health problems affecting their survival immediately after birth and may have long-term health consequences. Birth weight outcomes were evaluated using three approaches: risk of low birth weight, change in birth weight in grams, and risk of small for gestational age. Generally, exposure to $PM_{2.5}$ during the entire pregnancy period was associated with increased risk of low birth weight and small for gestational age and a decrease in birth weight in Canadian and American cohort studies (Gray et al., 2014; Ha et al., 2014; Hyder et al., 2014; Laurent et al., 2016a; Stieb et al., 2016a, b). Similar associations between birth weight outcomes and $PM_{2.5}$ exposure were reported in systematic review with meta-analysis studies that considered Canadian, American and European studies (Stieb et al., 2012; Zhu et al., 2015a; Sun et al., 2016; Zhang K et al., 2016). In particular, significant associations were observed for decreased birth weight and small for gestational age with exposure to $PM_{2.5}$. When exposure to $PM_{2.5}$ was limited to specific trimesters of pregnancy,

the associations were less consistent for low birth weight and small for gestational age (Rich et al., 2009; Ha et al., 2014; Hao et al., 2016; Lavigne et al., 2016b). However, consistent associations were observed between decreased birth weight and maternal $PM_{2.5}$ exposure across the three trimesters (Bell et al., 2010; Morello-Frosch et al., 2010; Stieb et al., 2016a). Maternal comorbidities, age during pregnancy, sex of infant and ethnic group, were not found to modify the association between $PM_{2.5}$ exposure and birth weight outcomes (Savitz et al., 2014; Lavigne et al., 2016b; Stieb et al., 2016b). Only a few studies had conducted co-pollutant analyses, and it was suggested that NO_2 may attenuate the association between $PM_{2.5}$ exposure and birth weight outcomes; however, the $PM_{2.5}$ associations were generally not confounded by other pollutants ($PM_{10-2.5}$, O_3, CO) (Rich et al., 2009; Salihu et al., 2012; Ha et al., 2014; Savitz et al., 2014; Stieb et al., 2016b). Overall, there is some evidence that $PM_{2.5}$ exposure during pregnancy is associated with reduced birth weight in newborns, but uncertainties do exist, especially regarding the effect of other co-pollutants and the timing of exposure, as less consistent results were observed using average $PM_{2.5}$ levels for each trimester.

Preterm birth

Preterm birth is defined as birth at less than 37 weeks of pregnancy. Because they are born prematurely, preterm babies may be less developed and may have more immediate or long-term health problems. Exposure to $PM_{2.5}$ during the entire pregnancy period has been associated with increased risk of preterm birth in many American cohort and case-control studies, including Wu et al. (2009, 2011), Kloog et al. (2012), Ha et al. (2014) and Laurent et al. (2016b). The results of a smaller number of Canadian cohort studies are less consistent, where positive and significant association was observed for singleton births in Ontario (Lavigne et al., 2016b), but no association was observed for singleton births across Canada (Stieb et al., 2016a, b). This inconsistency might be due to availability of individual-level data of potential confounding by maternal cigarette smoking in Lavigne et al. (2016b), but not available in the other two studies. In addition, positive (significant or non-significant) associations were observed in all systematic review with meta-analysis studies (Sapkota et al., 2012; Stieb et al., 2012; Lamichhane et al., 2015; Sun et al., 2016; Zhu et al., 2015a). These reviews pooled four to six primary studies (mostly cohort and case-control primary studies) covering Canadian, American, European and Australian studies. When $PM_{2.5}$ exposure is stratified by trimester, the evidence was not as consistent across trimesters, as the database is still relatively small. For exposure to $PM_{2.5}$ at T1, studies generally reported positive associations with risk of preterm birth in American cohort and case-control studies conducted in specific states (Lee et al., 2013; Ha et al., 2014; Pereira et al., 2014), but no association was observed in the only Canadian nationwide study (Stieb et al., 2016a). For $PM_{2.5}$ exposure during T2 and T3, a mix of null and positive associations were reported, with some positive associations being significant (Kloog et al., 2012; Ha et al., 2014; Hao et al., 2016; Pereira et al., 2016). In the systematic review with meta-analysis studies evaluating associations during the specific trimesters, the pooled results were inconsistent, with null associations or positive, non-significant associations being reported (Stieb et al., 2012; Zhu et al., 2015a; Sun et al., 2016). Certain maternal health conditions (pre-existing diabetes mellitus, heart disease and hypertension, or pregnancy-associated preeclampsia) increased the risk of preterm birth associated with $PM_{2.5}$ exposure (Lavigne et al., 2016b). However, maternal asthma did not modify the association between $PM_{2.5}$ and risk of preterm birth (Mendola et al., 2016b). Co-pollutant analyses, often based on a single study, did not find that exposure to other air pollutants (O_3, NO_2, CO) confounded the association between $PM_{2.5}$ exposure and risk of preterm birth, except for $PM_{10-2.5}$, which may attenuate this association (Huynh et al., 2006; Salihu et al., 2012; Ha et al., 2014; Laurent et al., 2016b; Stieb et al., 2016b). The evidence suggests that exposure to $PM_{2.5}$ during pregnancy is associated

with increased risk of preterm birth. Additional co-pollutant or multi-pollutant analyses are needed to confirm that the observation is due to $PM_{2.5}$ exposure. There is also uncertainty regarding the timing of exposure, as less consistent results were observed when analyzed by trimester compared to average $PM_{2.5}$ level over the entire pregnancy. Hence, the critical exposure window(s) remains to be identified.

Birth defects

Some researchers have examined the association between $PM_{2.5}$ exposure during the first 8 to 12 weeks of pregnancy and the risk of birth defects. This time period is crucial for the development of body structure and organ system. The major categories of malformations considered were congenital heart defects, orofacial clefts and spina bifida. The results were generally inconsistent, with positive but non-significant associations and null/negative, non-significant associations being reported (Padula et al. 2013a, b; Vinikoor-Imler et al. 2013, 2015; Stingone et al. 2014; Tanner et al. 2015; Zhu et al. 2015b; Girguis et al. 2016). Given that birth defects are uncommon and that organogenesis occurs during narrow time periods, only large sample-size studies with precise exposure measurements could theoretically observe positive and significant associations, if they were to exist. Thus, it remains unclear whether $PM_{2.5}$ exposure can lead to developmental malformations.

Stillbirth and infant mortality

Apart from birth defects, three studies reported positive associations between $PM_{2.5}$ exposure during pregnancy (entire gestation period, T1, T2, T3, days before delivery) and increased risk of stillbirth (Faiz et al., 2012; Defranco et al., 2015; Green et al., 2015). In addition, $PM_{2.5}$ exposure in the first 2 months of life was associated with increased risk of post-neonatal infant mortality (Woodruff et al., 2008).

Overall, most epidemiological studies focused on birth outcomes, with some evidence that maternal $PM_{2.5}$ exposure is associated with reduced birth weight and preterm birth. The associations between $PM_{2.5}$ exposure and other developmental effects, such as birth defects, stillbirth and infant mortality, are more challenging to determine since these outcomes are either less common or the database is small. As described in an earlier section of this chapter, prenatal and/or postnatal exposure to $PM_{2.5}$ in children increases the risk of respiratory effects, including reduced lung growth, increase in respiratory symptoms and asthma development (section 2.3). Moreover, some studies have found that autistic children had higher risk of increased prenatal exposure to $PM_{2.5}$ compared with control children (section 2.6).

Updated information—effects in toxicological studies

Toxicological studies have reported increases in cardiac fibrosis and cardiac malformations in mice and rats exposed in utero and during the suckling period to $PM_{2.5}$ (36 to 51 $\mu g/m^3$). Additionally, decreases in weight and reductions in lung and erythrocyte anti-oxidative enzyme activities were observed in two studies in mice exposed to $PM_{2.5}$ in utero and during the suckling period (17 to 27 $\mu g/m^3$). Exposure to ambient air containing $PM_{2.5}$ (4-month parental exposure, including both male and female F0, followed by 3-month exposure of the first generation offspring) was also demonstrated to decrease the alveolarization process (i.e., surface-to-volume ratios measured morphometrically which reflect decreased development of alveolar sacs) in the offspring of the exposed pregnant female mice (17 $\mu g/m^3$). Rat dams exposed to $PM_{2.5}$ (gestational day 1 to 18) gave birth to offspring with altered lung histopathology (measured at post-natal day 28). This was characterized by increases in multiple biomarkers of pulmonary dysfunction (increased expression

of mesenchymal and transforming growth factor-β proteins and decreased expression of the epithelial marker E-cadherin protein and mRNA in lung tissue). These are indicative of an increase in scar tissue formation, potentially leading to decreases in respiratory function, as decreases in lung function parameters were reported. Finally, alterations in the expression of miRNA associated with mental development, astrocyte migration, learning ability and motor coordination were reported in the cortex and hippocampus of fetuses of pregnant rats exposed to $PM_{2.5}$, suggesting that exposure to $PM_{2.5}$ during pregnancy may alter neurological development of the fetus.

Conclusion for developmental effects

In summary, the database investigating the associations between maternal $PM_{2.5}$ exposure during pregnancy and birth outcomes has expanded greatly since the publication of the CSSA. In epidemiological studies, $PM_{2.5}$ exposure during the entire length of the pregnancy was often associated with increased risk of adverse birth outcomes in infants (reduced birth weight, increased risk of low birth weight, small for gestational age, preterm birth). Some of these associations were significant, including those reported in systematic review with meta-analysis studies. However, the association observed during specific trimesters or by week of gestation was less consistent. Additional studies are needed to clarify the impact of the exposure period on the observed associations and to identify any period(s) of susceptibility or critical window(s) of exposure. There is some evidence of robustness in the database, as some of the associations with $PM_{2.5}$ were not impacted in co-pollutant analyses with CO and O_3, but some attenuation was observed when including NO_2 or $PM_{10-2.5}$. The associations between birth defects and maternal exposure to $PM_{2.5}$ during pregnancy were inconsistent. The exposure metric in these studies was the average $PM_{2.5}$ level over the first 1 to 12 weeks of gestation, which covers the critical organogenesis period. In the case of stillbirth, all three studies reported positive associations with $PM_{2.5}$ exposure covering the entire pregnancy and specific trimesters of T1, T2, and T3. Additionally, $PM_{2.5}$ exposure during the first 2 months of life was associated with increased risk of post-neonatal infant mortality in one study. Toxicological studies demonstrate coherence in the association between $PM_{2.5}$ exposure and the reduced fetal weight observed in epidemiological studies and support for biological plausibility of an association with increases in oxidative stress and inflammation. In addition, a few toxicological studies have shown adverse effects of $PM_{2.5}$ exposure during pregnancy on the brain, heart, and lungs of the offspring of the exposed pregnant female. However, the toxicological database remains small, there are uncertainties pertaining to exposure level, and the database remains incomplete as some outcomes have not been thoroughly assessed. Hence, the overall evidence is **suggestive of, but not sufficient to infer, a causal relationship** between $PM_{2.5}$ exposure and developmental effects. Uncertainties regarding the strength, robustness and consistency of the database remain.

2.6. NEUROLOGICAL EFFECTS

Conclusion from the CSSA

No causality conclusion was drawn on the relationship between short- or long-term exposure to $PM_{2.5}$ and neurological effects in the CSSA. Also, no epidemiological studies were identified on the risk of neurological outcomes following exposure to $PM_{2.5}$ in the CSSA. Only a few toxicological studies were presented. Amongst these, a reduction in dopaminergic neuron density and in astrocytes in the substantia nigra nucleus were observed in mice (apolipoprotein E deficient or $ApoE^{-/-}$) exposed chronically to $PM_{2.5}$ CAPs. Since the publication of the CSSA, more studies have begun to investigate the potential associations between $PM_{2.5}$ exposure and neurological effects.

Short-term exposure to $PM_{2.5}$

Updated information—epidemiological evidence

Only one short-term study examining neurological effects was published. A multi-city, time-stratified case-crossover study found an increase in the risk of hospital admission for Parkinson's disease, dementia, and Alzheimer's disease with $PM_{2.5}$ exposure in elderly subjects enrolled in Medicare in the northeastern United States (Zanobetti et al., 2014b). Specifically, a significant increase (3.23%; 95% CI 1.08, 5.43; per 10 $\mu g/m^3$) in hospital admissions due to Parkinson's disease was observed per 10 $\mu g/m^3$ increment in $PM_{2.5}$ at lag 0-1 d. Positive and non-significant associations, probably due to the small number of cases in some cities, were observed with Alzheimer's disease and dementia. When the analysis was stratified by age, a positive and significant association (3.48%; 95% CI 0.83, 6.19; per 10 $\mu g/m^3$) was, however, observed with Alzheimer's disease in subjects aged 65–75 compared with subjects over 75 years old.

Updated information—effects in toxicological studies

Mechanisms of $PM_{2.5}$ toxicity were studied; however, many findings were not repeated in different studies, even if many studies were reporting results of toxicity. In a study in mice, inflammatory-related gene expression in the brain was enhanced following exposure to an average of 55.1 $\mu g/m^3$ for 5 days. In a study in rats, three- to four-day repeated exposure to $PM_{2.5}$ CAPs increased the levels of the stress-related neurotransmitters norepinephrine, corticotrophin-releasing hormone, and 5-hydroxyindole acetic acid (main metabolite of serotonin) levels in the hypothalamic paraventricular nucleus of JCR/LA and BN rats, respectively. Another acute exposure study reported alterations in the expression of genes controlling inflammation (e.g., cyclooxygenase 1 and 2) in the hippocampus and in the olfactory bulb of mice exposed to ambient air containing high levels of $PM_{2.5}$. An in vitro study showed that human neuroblastoma cell line acutely exposed to $PM_{2.5}$ had oxidative stress and diminished antioxidant defences. Reductions in protein expression of genes involved in synaptic signal transmission were also observed. Although the database is small, available studies have shown different mechanisms of action of $PM_{2.5}$ toxicity, such as alterations in brain neurotransmitters levels, impacts on the hypothalamic-pituitary-adrenal stress axis, changes in circulating levels of corticosterone, and lowered brain-derived neurotrophic factor transcript levels.

Long-term exposure to $PM_{2.5}$

Updated information—epidemiological evidence

Three American studies have observed positive associations between long-term exposure to $PM_{2.5}$ and the diagnosis of Parkinson's disease, although the relationships were not statistically significant (cohort study by Palacios et al., 2014; cohort study by Kioumourtzoglou et al., 2016b; case-control study by Liu et al., 2016). Associations with other neurological outcomes, such as anxiety, smaller white matter volumes in the brain, alterations in sensory processes (e.g., smell), and cognitive impairment, have also been reported (Power et al., 2015; Ajmani et al., 2016). Two American cohort studies have examined the association between $PM_{2.5}$ exposure and cognitive function, but only the NHS cognitive cohort (composed of elderly American women) reported a positive association (significant) (Weuve et al., 2012; Loop et al., 2013). Two American studies (one cohort including women from the NHS and one cross-sectional in children) investigated behavioural outcomes in association with $PM_{2.5}$ exposure. The cohort study (Power et al., 2015) reported a significant increase in the risk of anxiety in women exposed to increasing levels of $PM_{2.5}$, whereas the cross-sectional study (Harris et al., 2016) reported no association between $PM_{2.5}$ exposure and a higher risk of behavioural problems in children (higher childhood exposure to black carbon component of $PM_{2.5}$ was positively associated with higher behavioural problems).

Two American cohort studies investigated the association between morphological changes in the brain with $PM_{2.5}$ exposure. Both cohorts (Chen et al., 2015; Casanova et al., 2016) used data from older women (71–89 years old) enrolled in the Women's Health Initiative Memory Study (WHIMS). Associations between $PM_{2.5}$ exposure and smaller white matter volumes were found in both studies, and associations between $PM_{2.5}$ exposure and cortical grey matter was found in one study. Also, the three cross-sectional studies investigating cognition reported significant associations with at least one form of cognitive decline (i.e., lower visual motor skills, cognitive function and episodic memory declines, and verbal learning declines) (Ailshire and Crimmins 2014; Gatto et al., 2014; Harris et al., 2015).

The association between autism and prenatal exposure to $PM_{2.5}$ was assessed in four American case-control studies (Becerra et al., 2013; Volk et al., 2013; Raz et al., 2015; Talbott et al., 2015). All four studies found that autistic children had higher risk of prenatal exposure to $PM_{2.5}$ compared with control children, but the conclusions are that confounders (e.g., other pollutants, nutritional factors, and lifestyle) were not appropriately addressed.

Overall, there is a growing database showing that $PM_{2.5}$ is associated with adverse effects ranging from cognitive, behavioural, and morphological changes in the brain to autism and dementia outcomes. However, the epidemiological database remains small.

Updated information—effects in toxicological studies

Two mouse studies reported neurobehavioural changes in response to repeated exposures to $PM_{2.5}$ (for up to 10 months), with increases in depressive-like behaviours, impairment in spatial learning and memory, and morphological changes in the hippocampus. One of these two studies also reported decreases in apical dendritic length, apical and basilar spine densities, and cell body area of the CA1 region of the hippocampus after 4 weeks of $PM_{2.5}$ CAPs exposure. Additional studies have reported potential explanatory $PM_{2.5}$ mechanisms of toxicity associated with these effects. The majority of toxicological studies have reported increases in oxidative stress and inflammation (increases in the expression of proteins and genes, such as cytokines like TNF-α and IL-6) in the central nervous system of rats and mice in response to $PM_{2.5}$ exposure. One mice study also reported an abnormal activation of the hypothalamic-pituitary-adrenal stress axis in parallel to the inflammation response in the hypothalamus after a 6-month exposure to $PM_{2.5}$. Also, inflammatory-related cyclooxygenase-1 and cyclooxygenase-2 enzymes (protein levels) and cytokine levels were reported to be elevated in mice exposed to $PM_{2.5}$ for 9 months. This study also observed an increase in Alzheimer's disease-like amyloid-beta 1-40 biomarker peptide.

Conclusion for Short- and Long-Term Exposure to $PM_{2.5}$ and Neurological Effects

In summary, there is a limited but growing number of studies investigating the relationship between $PM_{2.5}$ exposure and neurological effects. One epidemiological study has reported a positive association between short-term exposure to $PM_{2.5}$ and the risk of hospital admission for neurodegenerative diseases (i.e., Parkinson's disease, Alzheimer's disease and dementia). Additionally, a few toxicological studies showed increases in inflammatory and stress-related biomarkers in the brain of mice that could potentially lead to more serious neurological conditions. Because the database is small, it is not possible to assess the consistency, robustness, coherence, or strength of the results. Overall, the short-term exposure evidence to $PM_{2.5}$ is **inadequate to infer a causal relationship** for neurological effects.

With respect to long-term exposure to $PM_{2.5}$, a number of American epidemiological studies have reported positive associations with neurodegenerative diseases (i.e., Parkinson's disease, Alzheimer's disease and dementia), autism, cognitive functions (e.g., cognitive impairment, visual-motor skills, verbal learning), and morphological changes in the brain (i.e., smaller white and grey matter and total cerebral brain volume). The toxicological database provided some coherence to the epidemiological findings by reporting changes in behaviour (small increases in anxiety- and depressive-like behaviours and impaired learning and memory) following exposure to $PM_{2.5}$. The toxicological studies also provided biological plausibility by presenting mechanisms of toxicity. Changes in brain morphology (decreases in hippocampus apical dendritic length, apical and basilar spine densities and cell body area), increases in oxidative stress, inflammatory and amyloid-beta biomarkers, as well as activation of astrocytes were reported in the hippocampus and cortex of mice exposed to $PM_{2.5}$. These effects can potentially lead to more serious neurological conditions. However, the database on the outcomes observed in epidemiological and toxicological studies remains small. The positive associations observed in epidemiological studies had large confidence intervals, and the models used in these studies did not always adjust for co-pollutants. Overall, the evidence for long-term exposure to $PM_{2.5}$ is **suggestive of, but not sufficient to infer, a causal relationship** for neurological effects.

2.7. OTHER HEALTH EFFECTS

In addition to the health effects described above, epidemiological studies have begun to investigate the association between exposure to $PM_{2.5}$ and other health outcomes, such as autoimmune diseases, dermatitis, and alterations in renal functions. Additionally, toxicological studies have mainly focused on the major health outcomes presented in the earlier sections of this document, other health effects have also been reported. For example, inflammation and immune cell infiltration have been observed in other animal organs, such as the liver (steatosis, fibrosis), spleen, and thymus, after short- and long-term exposures to $PM_{2.5}$. Markers of kidney damage and reduced kidney function were also reported in a study in rats exposed for 3 days to 8 weeks. Another study in female mice showed an increase in a biomarker of skin aging after exposure to high levels of $PM_{2.5}$ for 3 days. The examination of other health effects is a rapidly growing field. Although these results were observed in only a few studies, they are biologically plausible given the roles of the kidneys, liver, and skin as defence or detoxifying systems and the oxidative and inflammatory mechanisms of toxicity presented in other systems.

CHAPTER 3:
POPULATION SUBGROUPS AT HIGHER RISK OF HEALTH EFFECTS

This chapter focuses on the susceptibility factors, i.e., factors that increase the risk of adverse outcomes. Available evidence indicates that a variety of factors can affect an individual's responses to ambient $PM_{2.5}$ exposure, increasing the risk of adverse health outcomes in certain population subgroups. A national analysis estimated the percentage of the total Canadian population (representative sample of over 120,000 participants in 110 administrative health regions) that has at least one risk factor, which is how susceptibility is defined by Stieb et al. (2019). The results indicated that the percentage of the population with at least one risk factor (i.e., less than 10, or 75 years old and older, individuals with heart diseases, asthma, COPD, or diabetes, or pregnant women) was 32.0% (95% CI: 24.4 to 41.2%). The percentage increased to 69.2% (95% CI: 61.2 to 87.0%) when a broader range of potential susceptibility factors (i.e., less than 20, or 65 years old and older, outdoor workers, less than high school education, low vitamin C intake) was considered.

In the sections below, risk factors are classified as either high or low confidence in terms of conferring susceptibility to a group of individuals based on the findings reported in the epidemiological and toxicological databases used to derive the causality conclusions (chapter 2). High confidence is given to factors that have a large database and have been shown to increase the risk of adverse health outcomes in comparison with individuals who do not have this risk factor within a single study. Stratification of risk factors in subgroup analyses highlights the differences in susceptibility between groups. Studies including only one population subgroup can also be informative about susceptibility if the factor is specific to that group (e.g., preeclampsia in pregnant women). High confidence is also given to factors that do not have a direct comparison with another population subgroup, but have strong supporting toxicological evidence for biological plausibility. Low confidence was given to factors that have been shown to be associated with adverse health outcomes based on a limited database. The change in risk of having these factors is not always compared within a single study.

The weight of evidence suggests with high confidence that genetic variants, young age, pre-existing health conditions, and smoking are factors increasing the risk of adverse effects from exposure to $PM_{2.5}$. The weight of evidence suggests with low confidence that sex, older age, dietary factors, ethnicity, socioeconomic status, and other health conditions are factors increasing the risk of adverse effects from exposure to $PM_{2.5}$.

3.1. RISK FACTORS CONFERRING SUSCEPTIBILITY: HIGH CONFIDENCE

Genetic factors

The CSSA suggested that having certain genetic variants could enhance the risk of health outcomes compared with individuals that did not have these genetic variants. Limited evidence was presented suggesting that certain polymorphisms of genes involved in oxidative stress (e.g., glutathione-s-transferase mu 1 (GSTM1) and hemochromatosis genes) might lead to greater sensitivity to the effects of $PM_{2.5}$ (i.e., HRV measurements in cross-sectional study). This was supported by toxicological evidence also showing that genetics (e.g., $ApoE^{-/-}$ mice as an animal model of atherosclerosis) could have a role in inter-individual variability and susceptibility to $PM_{2.5}$.

Since the publication of the CSSA, epidemiological studies have supported previous results by reporting that individuals with impaired responses to oxidative stress, such as polymorphisms of the GSTM1 or glutathione s-transferase genes, had greater magnitude of associations between exposure to $PM_{2.5}$ and arrhythmia (individual with the null compared with individuals with the positive allele of GSTM1, and in those with the theta-1 variants of the glutathione s-transferase) in panel and cross-sectional studies (Schneider et al., 2010; Zanobetti et al., 2014a). Individuals possessing the null genotype for GSTM1 also reported greater associations with levels of circulating inflammatory cytokine IL-6 compared with those with the positive genotype (Schneider et al., 2010). Also, wild-type carriers of variants of APOE and lipoprotein lipase, as well as vascular endothelial growth factor, were reported to have greater HRV fluctuations compared with those carrying the homo- or heterozygous types (Ren et al., 2010).

In terms of toxicological studies, pulmonary oxidative stress induced by acute exposure to $PM_{2.5}$ was blocked in transgenic (i.e., genetically-modified) mice expressing higher levels of superoxide dismutase compared with the wild-type. Also, transgenic mice deficient in a protein that regulates a pathway involved in the protection against oxidative stress had enhanced systemic and hypothalamic oxidative stress and inflammation following $PM_{2.5}$ exposure (Xu et al., 2016).

In summary, the greater magnitude of the associations observed in individuals with certain genetic profiles, supported by evidence from transgenic animal models, indicates that certain groups of individuals carrying specific gene variants are susceptible to the adverse effects of $PM_{2.5}$. The evidence in this update suggests with a high degree of confidence that people carrying variants of genes involved in oxidative stress have greater risk of adverse outcomes, such as cardiovascular diseases.

Young age

Some studies included in the CSSA reported that children may be more susceptible to the health effects of $PM_{2.5}$ exposure. Throughout childhood, the lungs continue to mature and increase in volume, and the physiology and airway size of developing children are thought to contribute indirectly to their susceptibility. The number of particles per lung surface was also reported to be higher in children compared with adults for the same exposure.

Since the publication of the CSSA, a comprehensive review of epidemiological studies (also evaluated controlled human studies and toxicological studies as supportive evidence) indicated that children are generally more susceptible to the respiratory effects of $PM_{2.5}$ (Sacks et al., 2011). The authors

indicated that was due to their greater amount of time spent outdoors, activity level, and volume per unit body weight, all of which increasing the dose per lung area. Moreover, they indicated that epidemiological studies support increased respiratory effects in children compared with adults. Those results are supported by toxicological studies showing altered lung development in young mice exposed to urban air. Moreover, epidemiological studies show a significant increase in the risk of asthma-related emergency room visits in children exposed to $PM_{2.5}$. However, the reviewed studies included only children (no direct comparison with other age groups).

A toxicological study also showed altered lung development and function (altered alveolarization and respiratory volumes) in young mice exposed prenatally and postnatally to urban $PM_{2.5}$ (4-month parental exposure followed by 3-month exposure of offspring) (Mauad et al., 2008).

The evidence in this update suggests with a high degree of confidence that children, due to their inherent sensitivities, physiological characteristics, or activity patterns, are at increased risk of asthma development and exacerbation and function (as reported in animals) from exposure to $PM_{2.5}$ compared with other age groups.

Smoking

Smoking has been shown to be associated with health effects that overlap with those of $PM_{2.5}$, including adverse cardiovascular and respiratory effects and lung cancer incidence. In the CSSA, smoking was mostly referred to as a confounder; it was not determined whether smoking could also be an effect modifier, with smokers having an enhanced risk of health effects. However, the association between $PM_{2.5}$ exposure and mortality was positive and significant only when restricted to current smokers in one study (Pope et al., 2004).

Since then, a Canadian cohort showed that former or current smokers were at higher risk of non-accidental mortality compared with those who never smoked (Pinault et al., 2016). Cross-sectional American studies have also found that positive associations of short-term $PM_{2.5}$ exposure level with ectopy (Liao et al., 2009) as well as with von Willebrand factor (a coagulation marker) and homocysteine levels (O'Neill et al., 2007) were stronger in smokers or ex-smokers than in non-smokers.

In the case of controlled human exposure studies, smokers or ex-smokers were found to have greater decreases in HDL levels, lung function indices and lung diffusion parameters after exposure to $PM_{2.5}$ CAPs compared to non-smokers (Hazucha et al., 2013).

Also, evidence of increased risk of lung cancer incidence with $PM_{2.5}$ exposure has emerged in some studies looking at people with a history of smoking. A higher risk of lung cancer incidence among current and former smokers following $PM_{2.5}$ exposure has been reported (Hystad et al., 2013; Valavanidis et al., 2013; Tomczak et al., 2016). Although the overall evidence is showing a trend towards an increase in risk of lung cancer in smokers with $PM_{2.5}$ exposure, some lung cancer studies (Puett et al., 2014; Gharibvand et al., 2017) have not reported an interaction with smoking.

The evidence in this update suggests with a high degree of confidence that, compared to non-smokers, current or former smokers have a higher risk of adverse outcomes, such as lung cancer and premature mortality, lower HDL levels, decreased lung function and lung diffusing capacity, and higher levels of coagulation biomarker and homocysteine levels.

Pre-existing health conditions

Cardiovascular pre-existing conditions

In the CSSA, individuals with pre-existing respiratory diseases (asthma, COPD), cardiovascular diseases and diabetes were reported to have higher risk of hospital admissions and premature mortality following exposure to PM (all fractions) compared with healthy individuals. Moreover, some studies reported a decrease in HRV (indicator of cardiovascular morbidity and mortality) in association with exposure to $PM_{2.5}$ in individuals with hypertension and ischemic conditions (Park et al., 2005; Schwartz et al., 2005; Lipsett et al., 2006; Luttmann-Gibson et al., 2006; Wheeler et al., 2006).

Since then, studies in people with pre-existing cardiovascular conditions continue to report higher risk estimates for cardiovascular-related hospital admissions and all-cause mortality from short-term and long-term $PM_{2.5}$ exposure, respectively, compared with the general population (Schneider et al., 2010; Krishnan et al., 2012; Ostro et al., 2014). In a multi-city study, the magnitude of the association between $PM_{2.5}$ exposure and smaller white matter volume was stronger in women with a history of cardiovascular disease, compared to those with no history of cardiovascular conditions (Chen et al., 2015).

In toxicological studies, greater increases in circulatory biomarkers of inflammation, plaque progression and cholesterol have been observed in $ApoE^{-/-}$ mice exposed to $PM_{2.5}$ compared with those exposed to filtered air (Quan et al., 2010; Chen and Lippman, 2013; Chen LC et al., 2013; Wan et al., 2014). Another animal study reported an increase in inflammation biomarkers in the hypothalamus of spontaneously hypertensive rats following $PM_{2.5}$ exposure compared with those exposed to filtered air (Ying et al., 2015). Also, $PM_{2.5}$ exposure further decreased mobility and the increase in astrocyte activation in the midbrain (a pathological feature of ischemic stroke) of rats with induced ischemic stroke compared with those with ischemic stroke but no exposure to $PM_{2.5}$ (Zhang C et al., 2016). Another study found a further increase in IL-6 and fibrinogen levels in the blood and higher percentage of glomerulosclerosis and tubular damage index in chemically-induced diabetic rats exposed to $PM_{2.5}$ compared with those exposed to filtered air (Yan et al., 2014).

Metabolic-related pre-existing conditions

In the CSSA, people with diabetes (specific types not distinguished) were reported to be more susceptible to the effects of PM (all size fractions). Diabetics were concluded to have increased mortality compared to those without diabetes with exposure to PM.

In this update, diabetics were also reported to have a greater risk of developing hypertension compared with non-diabetics in association with long-term $PM_{2.5}$ levels in a Canadian study (Chen et al., 2014). Also, a prolongation of heart-rate corrected QT interval duration (a marker for ventricular arrhythmias) was observed with black carbon exposure in diabetics compared with non-diabetics in an American study (Baja et al., 2010). In addition, a small panel study reported a stronger association between $PM_{2.5}$ and IL-6 in type 2 diabetes subjects with higher body mass index (BMI), elevated levels of glycated hemoglobin A1c (a biomarker of high blood glucose levels) and lower levels of adiponectin (a protein that plays an important role in the regulation of circulating glucose and lipids), which are indicators of metabolic effects (Schneider et al., 2010).

As for toxicological studies, metabolic disorder and type 2 diabetes were exacerbated in animal model systems of metabolic disorder and type 2 diabetes by $PM_{2.5}$ exposure for short- and long-term durations (Sun et al., 2009; Kampfrath et al., 2011; Tomino, 2012; Liu et al., 2014b, c; Goettems-Fiorin et al., 2016).

Asthma and COPD pre-existing conditions

In the CSSA, short-term exposure to $PM_{2.5}$ was reported to exacerbate asthma-related (especially in asthmatic children) and COPD-related emergency room visits/hospitalization. Short-term $PM_{2.5}$ exposure was also associated with increased mortality in patients with COPD. In general, children were at risk of more severe asthma exacerbation in response to exposure to $PM_{2.5}$ than adults (Slaughter et al., 2003).

In this update, the evidence has generally continued to indicate that individuals with pre-existing respiratory diseases (i.e., asthma, COPD) are at increased risk of respiratory hospital admissions from short-term exposure to $PM_{2.5}$ (Mirabelli et al., 2015; Reid et al., 2016). In the study by Mirabelli et al. (2015), participants with asthma had worse respiratory health measures 3 hours after being exposed to $PM_{2.5}$ during commute compared with participants without asthma (this was even worse for those with more severe asthma). Different responses were also observed between participant groups. For example, systolic blood pressure increased in healthy subjects, but decreased in asthmatics following controlled exposure to $PM_{2.5}$ CAPs (Gong et al., 2003). However, one study reported no differences in respiratory function between asthmatics and non-asthmatics exposed to $PM_{2.5}$ (Urch et al., 2010).

Evidence from toxicological studies further supported the epidemiological observations. Exposure to $PM_{2.5}$ was found to enhance the allergic airway responsiveness and antigen-induced immune responses in ovalbumin-challenged rats, an animal model of allergic response (Harkema et al., 2009; Heidenfelder et al., 2009; Wagner et al., 2012).

Overall, the evidence in this update suggests with a high degree of confidence that persons with cardiovascular disease, diabetes, asthma, and COPD are at greater risk of hospital visits and premature mortality due to their impaired physiological functions.

3.2. RISK FACTORS CONFERRING SUSCEPTIBILITY: LOW CONFIDENCE

Older age

In the CSSA, older adults (over 65 years old) were reported to be more susceptible to the health effects of $PM_{2.5}$ exposure.

In this update, older adults (over 65 years old) represent the age group where the majority of the pre-existing health conditions are most common. However, the reviewed studies mainly included elderly participants and did not stratify risk by age group. Many large population-based cohort studies were conducted in older adults where short-term $PM_{2.5}$ exposure was associated with an increased risk of premature all-cause mortality and cardiovascular-related or respiratory-related hospital admissions (e.g., asthma-related emergency room visits). In a Canadian study that also conducted cardiac monitoring, slight differences in changes in cardiac rhythm were observed between participants above and below the age of 50 that were exposed to $PM_{2.5}$ (based on daily

3-hour concentrations monitored at central stations) (Cakmak et al., 2014a). Another study showed that Californians under 20 years old had a lower risk of emergency room visits for asthma and pneumonia and of hospitalization for asthma compared with adults of 20–64 years old when exposed to wildfire $PM_{2.5}$ (Reid et al., 2016). During wildfire, individuals aged 20–64 years old had a higher risk of hospital visit for COPD compared with those over 65 years old. Controlled human exposure studies conducted in the elderly also observed HRV changes after transient exposure to concentrated $PM_{2.5}$; the observation was generally more pronounced in those with pre-existing health conditions.

Only a few toxicological studies investigated the interaction between $PM_{2.5}$ exposure and animal age. $PM_{2.5}$ exposure seemed to pose a greater risk of health effects to young and older animals, but most studies did not compare responses across age groups. One study showed that senescent mice were more susceptible to inflammatory responses and cardiac contractility reduction than adult mice in response to acute exposure to $PM_{2.5}$ (Tankersley et al., 2008).

Although many lines of evidence show increased risk of health effects in the elderly exposed to $PM_{2.5}$, very few studies actually compared the risk with younger age groups, and those that did showed inconsistent results. The evidence in this update suggests, albeit with a low degree of confidence, that elderly people are at increased risk of premature mortality and hospital visits for cardiovascular and respiratory outcomes from exposure to $PM_{2.5}$ compared with other age groups.

Sex

In the CSSA, sex was mostly referred to as a confounder. No statement on whether a particular sex could increase the risk of $PM_{2.5}$ effects was presented.

In this update, a few subgroup analyses showed that women tended to be more susceptible to the health effects of $PM_{2.5}$ than men. For example, one study reported a higher risk of respiratory and hypertension-related hospital admissions in women following exposure to short-term wildfire $PM_{2.5}$ levels than in men exposed to the same levels (Reid et al., 2016). A Canadian study found that women tended to have greater changes in cardiac rhythm parameters with short-term $PM_{2.5}$ exposure (based on daily $PM_{2.5}$ 3-hour concentrations) than men (Cakmak et al., 2014a). Regarding long-term $PM_{2.5}$ exposure, women had higher risk of developing IHD, CHF and stroke, whereas men had higher risk of developing MI. In the case of mortality, there was a higher risk of IHD mortality in women than in men.

At this time, it is unclear whether these observations were due to any biological differences between sexes or if they were the result of behavioural differences in seeking medical assistance. The emerging evidence suggests, albeit with a low degree of confidence, that there are sex-specific differences in the response to $PM_{2.5}$ exposure.

Dietary factors

In the CSSA, diet was mostly referred to as a confounder, and no effect information on modification was presented.

Since then, there has been a growing interest in assessing the impact of the diet on the effects of exposure to $PM_{2.5}$. While a cohort reported a lower risk of non-accidental mortality in Canadians having 5 or more servings of fruits and vegetables per day compared to those having less than 5 servings (Pinault et al., 2016), other studies did not find differences in mortality according to diet and fruits and vegetables consumption (Turner et al., 2011; Pope et al., 2015). Also, a controlled

human exposure study showed that middle-aged healthy adults that received a fish oil supplement or olive oil had lower circulating vasoconstrictor protein levels following exposure to $PM_{2.5}$ compared to those without supplementation, showing protection against endothelial dysfunction (Tong et al., 2015).

In toxicological studies, $PM_{2.5}$-exposed animals fed certain diets (e.g., high-fat or high-fructose diets) were found to have more health effects than those not fed these diets. For example, rats exposed to $PM_{2.5}$ and fed a high-fructose diet had greater increases in inflammation in epicardial, lung, liver, and perirenal adipose tissues compared with those fed a normal diet (Sun et al., 2013; Wagner et al., 2014; Zheng et al., 2015; Li et al., 2017). Alterations in glucose and lipid metabolism (hepatic lipogenesis, fasting hyperglycemia, insulin resistance) caused by high $PM_{2.5}$ levels were also increased in animals fed high-fat diets (Haberzettl et al., 2016a). Exposure to $PM_{2.5}$ enhanced the changes in blood pressure (e.g., vasoconstriction) in young mice fed a high-fat diet compared with mice fed a normal diet (Xu et al., 2010; Li et al., 2017). In addition, there was a greater increase in markers of non-alcoholic fatty liver disease (hepatic inflammation grade and fibrosis stage, increase in macrophages, cytokines and collagen-1) in $PM_{2.5}$-exposed mice that were fed a high-fat diet compared with mice fed a high-fat diet and exposed to filtered air (Tan et al., 2009; Zheng et al., 2015).

Given that fruits and vegetables and certain diets (e.g., high-fat or high-fructose diets) can influence antioxidants and anti-inflammatory responses, it can be expected that a diet rich in fruits and vegetables (and possibly fish oil) could lower the risk of adverse effects of $PM_{2.5}$ (and possibly the opposite for high-fat or high-fructose diets, for example). The preliminary evidence suggests, albeit with a low degree of confidence, that a diet rich in fruits and vegetables can potentially have a protective effect for the risk of mortality, inflammation, and high blood pressure associated with $PM_{2.5}$ exposure.

Ethnicity

In the CSSA, ethnicity was mostly referred to as a confounder, and no information on effect modification was presented.

Since then, non-Hispanic and Black Americans were reported to have higher risk of asthma exacerbation with exposure to $PM_{2.5}$. Also, the risk of left-ventricular mass index (marker of long-term cardiac overload) associated with $PM_{2.5}$ exposure was found to be greater in Black compared to White Americans in another study (Hicken et al., 2016). Other studies have reported that the risk of myocardial infarction after exposure to $PM_{2.5}$ was higher in non-Hispanic Whites. A comprehensive review (Sacks et al., 2011) presented a study (Ostro et al., 2006) published before the CSSA showing an increased risk of cardiovascular mortality in American Hispanics compared with American White ethnic groups.

Overall, the preliminary evidence suggests, albeit with a low degree of confidence, that differences in risk of health outcomes exist between ethnic groups with exposure to $PM_{2.5}$.

Socioeconomic status

In the CSSA, socioeconomic status was mostly referred to as a confounder, and no information on effect modification was presented.

As part of this assessment, education income and status of employment influenced non-accidental mortality. For example, a Canadian cohort study showed that individuals with a high school diploma or higher, with a higher income or who are employed were at a lower risk of non-accidental mortality than those who do not have a high school diploma, who have a lower income or who are unemployed (Pinault et al., 2016). The income was based on income adequacy, a measure of the proportion of the income spent on food, shelter and clothing. A study in California showed that the higher-income tertile was associated with a lower risk of emergency room visits for asthma, COPD, pneumonia, and all-cause respiratory compared with the lower-income tertile with exposure to wildfire $PM_{2.5}$ (Reid et al., 2016). The relationship was significant for COPD and respiratory emergency room visits.

In terms of toxicological studies, a model of chronic social stress showed that $PM_{2.5}$-exposed rats exhibited enhanced changes in respiratory functions (i.e., respiratory frequency, decreases in peak inspiratory and expiratory flows, and decreases in tidal and minute volumes) indicative of a rapid, shallow breathing pattern compared with non-stressed rats (Clougherty et al. (2010)).

The emerging evidence suggests, albeit with a low degree of confidence, that individuals with lower socioeconomic status have a higher risk of mortality and respiratory-related hospital visits associated with exposure to $PM_{2.5}$ than individuals with higher socioeconomic status.

Pregnant women with pre-existing health conditions

This particular group was not assessed for increased health risk from exposure to $PM_{2.5}$ in the CSSA.

In this update, one study reported that pregnant women with asthma had a slightly increased risk of preeclampsia in association with $PM_{2.5}$ measured in the whole pregnancy. However, the estimates were non-significant (Mendola et al., 2016a). Another study by the same author (Mendola et al., 2016b) reported that the risk estimate of preterm birth was higher in asthmatic mothers than in non-asthmatic mothers with $PM_{2.5}$ exposure for various gestational weeks (significant for gestational weeks 26 and 29). The author also indicated that there was a significant interaction with asthma for $PM_{2.5}$ exposure during the last six weeks of pregnancy and risk of preterm birth. Likewise, Lavigne et al. (2016b) reported that maternal conditions (i.e., existing diabetes mellitus, preeclampsia, heart disease and hypertension) also increased the risk of having a premature birth associated with exposure to $PM_{2.5}$ during pregnancy.

The emerging evidence suggests, albeit with a low degree of confidence, that pregnant women with pre-existing health conditions may have higher risk of preeclampsia and preterm birth.

Neurological conditions and mental health

Having a neurological condition was not assessed for increased health risk from exposure to $PM_{2.5}$ in the CSSA.

In this update, the risk of brain microbleeds associated with increasing long-term exposure to $PM_{2.5}$ was higher in individuals with a diagnosis of probable Alzheimer's disease than in participants with other diagnoses (unspecified: all participants were from a clinic for mild cognitive complaints or early dementia) in a cross-sectional study of the Framingham Offspring Study cohort (Wilker et al., 2015).

A slightly higher risk for all-cause mortality was also observed with increasing short-term $PM_{2.5}$ exposure in individuals with a previous hospital admission for Parkinson's disease, dementia, or Alzheimer's disease compared with those who had never been hospitalized in an American cohort of Medicare enrolees (Zanobetti et al., 2014b).

Compared with Canadian children (6–17 years old) who self-reported as 'happy', children who self-reported as 'other' had a greater decrease in forced expiratory volume with short-term $PM_{2.5}$ exposure in a cross-sectional epidemiological study. Also, there was a greater decrease in forced vital capacity and increase in heart rate in children reporting at least some emotional symptoms than those reporting none with short-term $PM_{2.5}$ exposure (Dales and Cakmak, 2016). In toxicological studies, the neurobehavioural alterations induced by $PM_{2.5}$ exposure for 7 days were found to be more pronounced in rats having suffered from ischemic stroke (Zhang C et al., 2016).

The emerging evidence suggests, albeit with a low degree of confidence, that $PM_{2.5}$ exposure can increase the risk of brain microbleeds and all-cause mortality in individuals with a dementia diagnosis, and increase the heart rate and the risk of higher blood pressure and more reduction in lung function in those with less than "ideal" mental health.

Body weight status

In the CSSA, body weight status was mostly referred to as a confounder, and no information on effect modification was presented.

Since then, some studies have shown that higher body mass index, obesity or overweight status may increase susceptibility to the health effects associated with $PM_{2.5}$ exposure. Individuals with these conditions tend to have increased inflammation, endothelial dysfunction, nervous system alteration and a greater risk of developing cardiovascular-related conditions such as hypertension and atherosclerosis. In one study, obese women participating in the prospective United States nationwide NHS had a higher risk of developing hypertension with increases in $PM_{2.5}$ exposure (per 10 $\mu g/m^3$) than non-obese women (Zhang Z et al., 2016). Obese (BMI over 35) and underweight (BMI below 18.5) subjects were also found to be at increased risk of non-accidental mortality compared with those with a normal body weight (BMI of 18.5 to 25) in a Canadian cohort study (Pinault et al., 2016). In a multi-city study, obese (BMI>30) American women enrolled in the WHIMS had a more pronounced reduction in the smaller frontal white matter volume (possibly affecting various cognitive functions) in association with long-term $PM_{2.5}$ exposure compared with women with a BMI below 25 (normal to low) (the association with long-term $PM_{2.5}$ exposure was of lower magnitude in the overweight group compared with those with a BMI>30) (Chen et al., 2015). The study also reported that the magnitude of the association between $PM_{2.5}$ exposure and smaller white matter volume was stronger in women with a history of cardiovascular disease than in those with no history of cardiovascular conditions.

In toxicological studies, repeated $PM_{2.5}$ exposures were shown to increase stress (increase in norepinephrine levels in the paraventricular nucleus) in obese, but not in lean rats (Balasubramanian et al., 2013).

The emerging evidence suggests, albeit with a low degree of confidence, that underweight and obese individuals have increased risk of adverse health outcomes.

3.3. SUMMARY

Overall, the body of literature on $PM_{2.5}$ has continued to report differences in the susceptibility to health effects across population subgroups. Children, smokers, people with cardiovascular diseases, diabetes, asthma, and COPD, and individuals carrying oxidative stress-related genetic variants were found to have an increased risk of adverse health outcomes with exposure to $PM_{2.5}$. Adverse effects include increases in cardiovascular outcomes, hospital visits, premature mortality, and asthma exacerbation. Other factors have also been shown to modify the relationship with $PM_{2.5}$ exposure, but the evidence remains limited to date as the number of studies is small and the studies do not always stratify their analysis by risk factor.

CHAPTER 4:
SHAPE OF THE CONCENTRATION-RESPONSE RELATIONSHIP

The shape of the relationship relating $PM_{2.5}$ concentrations to various health outcomes has implications for the setting of ambient air quality standards, as well as for estimating the health impacts and developing the risk management strategies to address these impacts. This aspect of the association between $PM_{2.5}$ exposure and health effects, including the potential for the existence of threshold levels below which health effects are not observed, has been investigated in a number of studies.

The CSSA revealed no evidence of a clear threshold for short-term $PM_{2.5}$ exposure related to all-cause and cardiovascular mortality. Generally, mortality increased in a quasi-linear manner with $PM_{2.5}$ levels, even at the relatively low ambient PM levels experienced in the United States and Europe. A linear concentration-response relationship refers to a straight line where there is a constant rate of increase in response as the concentration increases (Figure 4.1). A near linear concentration-response relationship down to very low concentrations was also observed between short-term $PM_{2.5}$ exposure and cardiovascular hospital admissions. One study examined the shape of the concentration-response relationship for long-term $PM_{2.5}$ exposure and all-cause mortality. It reported a quasi-linear shape with the association being stronger in the lower range of concentrations (9.0 to 16 $\mu g/m^3$) than in the upper range of levels (up to 33.5 $\mu g/m^3$) (Abrahamowicz et al., 2003).

4.1. SHORT-TERM EXPOSURE

In this update, few epidemiological studies have specifically discussed the shape of the concentration-response between $PM_{2.5}$ exposure and health outcomes. The number of studies discussing this particular aspect is small, likely due to the inclusion criteria described in detail in section 1.2. In particular, only multi-city time-series and case-crossover epidemiological studies that examined mortality, hospital admissions and emergency room visits outcomes were included.

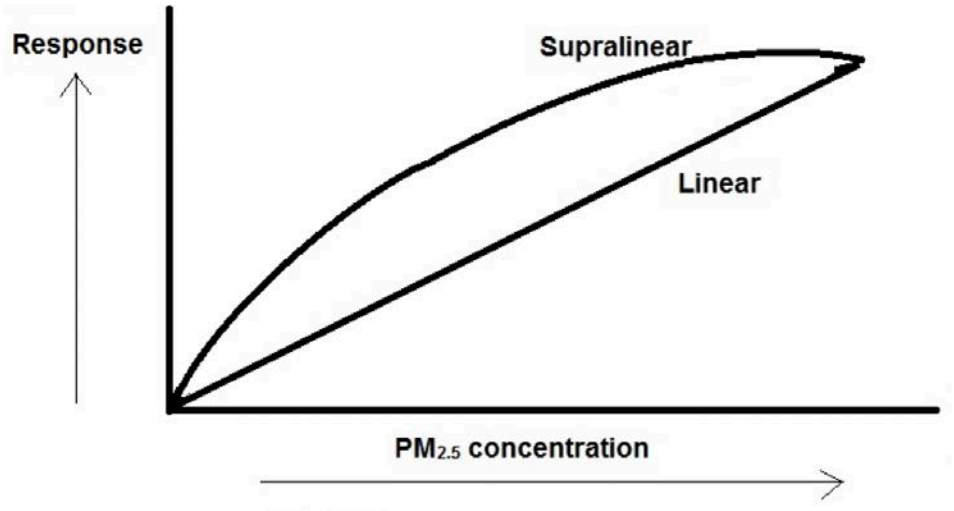
A population-based study has investigated the concentration-response relationship between short-term $PM_{2.5}$ exposure and all-cause mortality using the Medicare population (aged over 65) in six New England states (Shi et al., 2016). The exposure information was based on a hybrid method combining satellite-retrieved aerosol optical depth measurements with ground monitoring and incorporated land-use regression spatial variations and meteorological variables. A linear shape from 3 to 30 $\mu g/m^3$ was observed for the association between short-term $PM_{2.5}$ exposure and all-cause mortality, across the exposure distribution restricted to below 30 $\mu g/m^3$. There was high uncertainty in the shape below 3 $\mu g/m^3$ due to the small number of individuals exposed to such low levels of $PM_{2.5}$.

Other than mortality, shape of the concentration-response relationship between short-term $PM_{2.5}$ exposure and risk of respiratory-related emergency room visits (asthma and/or wheeze, COPD) were examined (Reid et al., 2016; Weichenthal et al., 2016c). Weichenthal et al. (2016c) reported evidence of near linear relationships for increase in risk of emergency room visits for asthma and COPD

associated with $PM_{2.5}$ exposure (range: 0 to 10 µg/m^3) in Ontario, Canada. A subgroup analysis for asthma emergency room visits among children (< 9 year of age) was conducted, as asthma patients tended to be younger than patients with COPD- or respiratory-related emergency room visits as a whole. Compared to asthma emergency room visits for all ages, the shape of the relationship among children had a narrower confidence interval with a supralinear shape. The supralinear shape refers to a concentration-response relationship that is steeper in the lower concentrations than in the upper range of concentrations (Figure 4.1). In another study, Reid et al. (2016) evaluated the shape of the concentration-response relationship based on $PM_{2.5}$ exposure levels during a large wildfire period in California. Exposure levels were classified into four categories: ≤12 µg/m^3, 12.1 to 35.4 µg/m^3, 35.5 to 55.4 µg/m^3, and ≥ 55.5 µg/m^3. A linear concentration-response relationship for asthma emergency room visits was found. The study is limited, however, due to the use of discrete exposure categories rather than continuous exposure levels.

Although this update included only a limited number of studies, due to the restrictive nature of the inclusion criteria, studies reviewed in this update continued to observe a near linear relationship between short-term exposure to $PM_{2.5}$ and health outcomes. This near linear relationship is also present at relatively low ambient $PM_{2.5}$ levels in Canada.

FIGURE 4.1: Linear and supralinear $PM_{2.5}$ concentration-health effect (morbidity or mortality) shapes



4.2. LONG-TERM EXPOSURE

More studies have focused on the shape of the concentration-response relationship between health outcomes and long-term $PM_{2.5}$ exposure, compared to short-term exposure. In Canadian studies, the shape of the concentration-response relationship between long-term $PM_{2.5}$ exposure and all-cause mortality was near linear at low $PM_{2.5}$ levels (1 to 18 μg/m^3) without clear evidence of a threshold (Crouse et al., 2012, 2015; Chen H et al., 2016; Pinault et al., 2016). In most cases, it was found that linear models fit better than other models such as natural cubic spline function. In general, the confidence intervals were wider at very low concentrations (≤ 3 μg/m^3) due to the small number of individuals exposed to these levels. As the concentration increases above 3 μg/m^3, Crouse et al. (2015) noted that the shape of the relationship may be supralinear (Figure 4.1), with a steeper slope between 3.9 to 8.6 μg/m^3 and a less steep slope up to 14.4 μg/m^3. American studies also examined the shape of the concentration-response relationship between $PM_{2.5}$ exposure and all-cause mortality (Lepeule et al., 2012; Shi et al., 2016; Thurston et al., 2016a). Analysis of the H6CS demonstrated a linear shape in the 8 to 40 μg/m^3 range of $PM_{2.5}$ levels (Lepeule et al., 2012). In a population-based study of the elderly in six New England states, researchers conducted a full analysis ($PM_{2.5}$ levels ranged from 0 to 20 μg/m^3) and a restricted exposure analysis ($PM_{2.5}$ levels below the cut-off of 10 μg/m^3) (Shi et al., 2016). When comparing the risk estimates of the full analysis and the restricted exposure subgroup, the risk estimate was lower in the full analysis group compared to the subgroup, which suggested a larger effect in the low concentration range. The shape of the concentration-response relationship was only analyzed in the restricted exposure subgroup, where the curve shape appeared to be linear between 6 to 10 μg/m^3, with high uncertainty of the shape below 6 μg/m^3. The data is limited at very low concentrations (i.e., < 6 μg/m^3), since relatively few individuals live in areas with such low ambient levels. Thurston et al. (2016a) observed a monotonically increasing and significant relationship between all-cause mortality and $PM_{2.5}$ exposure in the annual concentration range from 2.9 to 28 μg/m^3. However, the shape of the relationship was not conclusively defined, since most of the sampled population was exposed in the 10.7 to 15.9 μg/m^3 range. The lowest and highest quantiles covered 2.9 to 10.7 μg/m^3 and 15.9 to 28.0 μg/m^3, respectively.

Some studies examined the shape of the concentration-response relationship for mortality from specific causes. Using the CanCHEC data, Crouse et al. (2012) investigated the concentration-response relationships for cardiovascular, CEB and IHD-related mortality in the range of $PM_{2.5}$ (1.9 to 19.2 μg/m^3) typically observed in Canada. As with all-cause mortality, a linear model fitted well for cardiovascular mortality. In the case of IHD-related mortality, a log-linear shape with higher risk estimates at lower concentrations was observed. The shape for CEB mortality was not as clearly defined, as the relationship was not found to be linear and the association was non-significant compared to strong significant associations for all-cause or cardiovascular mortality. Brook et al. (2013b) analyzed the concentration-response relationship for diabetes mortality in relation to $PM_{2.5}$ exposure. A near linear relationship, with a monotonic increased in mortality risk associated with exposure to $PM_{2.5}$, was observed across the range of $PM_{2.5}$ in Canada (up to 20 μg/m^3).

In the American H6CS analysis, near linear shapes were observed for cardiovascular mortality and lung cancer mortality, where annual average $PM_{2.5}$ ranged from 8 to 40 μg/m^3 (Lepeule et al., 2012). Similarly, a linear shape between $PM_{2.5}$ exposure and cardiovascular mortality risk was observed by Thurston et al. (2016a) in the annual concentration range of 2.9 to 28 μg/m^3.

When considering a wider range of $PM_{2.5}$ levels from ambient air pollution and higher levels from active and second-hand cigarette smoke, the concentration-response relationship between cardiovascular mortality (all cardiovascular, IHD, cardiopulmonary combined) and $PM_{2.5}$ exposure was found to be supralinear (Pope et al., 2009, 2011). This is based on the ACS prospective cohort data collected from 1.2 million adults. The $PM_{2.5}$ levels in the range of ambient air (5 to 35 $\mu g/m^3$) was found to have a steeper slope (larger effects), whereas the slope at higher $PM_{2.5}$ levels due to cigarette smoke tended to plateau (less effects), suggesting a log-linear fit in the lower range of exposure levels. Similar observations were observed for both men and women. In comparison, the same research group found a near linear shape of the concentration-response relationship for lung cancer mortality throughout the full range of $PM_{2.5}$ levels from ambient air pollution, and from higher levels from active and second-hand cigarette smoke, suggesting that the shape of the relationship might be endpoint-specific.

Studies have also begun to evaluate the shape of the concentration-response relationship for $PM_{2.5}$ exposure and morbidity outcomes. Two studies examined the shape of the relationship for CAC, a marker of atherosclerosis. In the American Multi-Ethnic Study of Atherosclerosis cohort, the shape of the concentration-response relationship between $PM_{2.5}$ (ranged from 9.2 to 22.6 $\mu g/m^3$) and CAC progression was near linear at the lower $PM_{2.5}$ levels, with an attenuation at higher levels (Kaufman et al., 2016). In contrast, a non-linear relationship (a positive association at lower levels followed by a negative association at higher levels with wide confidence intervals overall) was found between $PM_{2.5}$ exposure and log-transformed CAC measurements from the American Framingham Heart Study (Dorans et al., 2016). One study evaluated the shape of the concentration-response relationship between $PM_{2.5}$ exposure and incidence of hypertension in Ontario, Canada (Chen et al., 2014). $PM_{2.5}$ levels ranged from 2.9 to 19.2 $\mu g/m^3$, and a near linear relationship was observed. A nationwide Canadian cohort study identified a supralinear relationship between $PM_{2.5}$ exposure and lung cancer incidence, with a steeper slope between 1.3 to 12 $\mu g/m^3$, and a less steep sleep up to 17.6 $\mu g/m^3$ (Tomczak et al. 2016).

To summarize, there is an extensive database on the shape of the concentration-response relationship between long-term $PM_{2.5}$ exposure and mortality. In many cases, a near linear relationship was observed in the range of ambient $PM_{2.5}$ levels experienced in Canada. In the few studies that covered a wider range of exposure levels, preliminary evidence suggests an attenuation of effects or flattening in the shape of the relationship at higher $PM_{2.5}$ levels. The database examining the shape of the relationship for long-term $PM_{2.5}$ exposure and morbidity outcomes is small at this moment.

4.3. IMPLICATIONS OF THE SHAPE OF THE CONCENTRATION-RESPONSE RELATIONSHIP

Compared to the CSSA, there is a better understanding of the shape of the concentration-response relationship in the lower ambient concentration range of $PM_{2.5}$. This is due to a combination of advancement of exposure estimation methods and the declining trend of ambient $PM_{2.5}$ levels in Canada and the United States. Many studies have found a near linear relationship between short- and long-term exposure to $PM_{2.5}$ and mortality (all-cause and specific causes) in population-based epidemiological studies. A near linear relationship was also observed between short-term $PM_{2.5}$ exposure and morbidity (respiratory effects). In some cases, especially in Canadian studies, the analyses covered ambient concentrations below established CAAQS for $PM_{2.5}$, in the 3 to 6 $\mu g/m^3$ $PM_{2.5}$ range, supporting the notion that no identifiable threshold exists between $PM_{2.5}$ exposure and various health endpoints at concentrations close to background. The characterization of the lower portion of the concentration-response relationship remains a challenge at a population level, given the low data density in the lower concentration range of ambient $PM_{2.5}$ (i.e., small number of individuals exposed at these levels) and measurement error associated with using surrogates of exposure that may not reflect realistic personal exposure. Nevertheless, the lack of an identifiable threshold at the population level is consistent with the wide range of increased susceptibility to the effects of $PM_{2.5}$ among individuals and between susceptible groups, as discussed in Chapter 3. Due to large heterogeneity in susceptibility within the general population, a common threshold may not be observed at a population level in epidemiological studies.

Most studies that specifically analyse the shape of the concentration-response relationship focused on important or major outcomes such as mortality or hospital admissions, which are well characterized; however, since $PM_{2.5}$ is a non-threshold pollutant, other morbidity effects are expected at all concentrations when considering population as a whole. Few studies have started examining the shape of the relationship for other health outcomes (i.e., hypertension, atherosclerosis marker). In addition, some evidence suggested a supralinear shape in which a steeper slope at $PM_{2.5}$ in the relatively low concentration range compared to a less steep slope at higher $PM_{2.5}$ concentrations for certain health outcomes. Given that no apparent population threshold has been identified and there is evidence of health effects being observed at current ambient levels in Canada, this further implies that reductions of already low ambient levels of $PM_{2.5}$ can have a significant health benefit to the Canadian population.

CHAPTER 5:
TOXICITY OF $PM_{2.5}$ AS A FUNCTION OF COMPOSITION AND SOURCE

$PM_{2.5}$ is a complex mixture consisting of various organic and inorganic components. Some components have been studied, including black carbon, sulphate (SO_4^{2-}), nitrate (NO_3^-), organic carbon, elemental carbon, non-metal elements (e.g., chlorine, sulphur), metals (e.g., aluminum, beryllium, calcium, copper, iron, potassium, sodium, nickel, manganese, silicon, titanium, vanadium, and zinc) and bioaerosols (e.g., endotoxin, β-1,3-d-glucan). Some major sources of $PM_{2.5}$ in Canada include fossil fuel combustion (e.g., vehicular emissions), industrial activity, biomass burning (e.g., wood smoke), and soil dust. The composition of $PM_{2.5}$ can vary extensively depending on the source, formation pathway, climate and season. Multiple epidemiological studies, including population-based, panel and cross-sectional studies, have investigated the associations of specific $PM_{2.5}$ components and emission sources with various health outcomes (e.g., cardiovascular, respiratory, cancer, neurological, developmental and mortality). Some researchers have also examined the relationship between $PM_{2.5}$ oxidative potential (the ability of $PM_{2.5}$ filter extracts to deplete antioxidant levels) and health outcomes (Delfino et al., 2013; Maikawa et al., 2016; Weichenthal et al., 2016 a, b; Zhang X et al., 2016), since oxidative stress has been shown to be an important mechanism of $PM_{2.5}$ toxicity. $PM_{2.5}$ oxidative potential can be assessed by measuring the depletion of antioxidants (i.e., glutathione [GSH], ascorbate) in the body, reflecting oxidative stress. Other than environmental epidemiological studies, few controlled human exposure studies have analyzed the composition of $PM_{2.5}$ CAPs. Concentrations of the components of $PM_{2.5}$ CAPs were measured and correlated with subclinical outcomes that were observed in participants exposed to $PM_{2.5}$ CAPs. These associations have also been studied in experimental animal and in vitro studies.

The scientific literature of $PM_{2.5}$ composition and sources has expanded. Many $PM_{2.5}$ components were found to be associated with health effects in epidemiological and toxicological studies. Short-term and long-term exposure to elemental carbon, black carbon, SO_4^{2-}, NO_3^-, and organic carbon are the most studied components and tended to have similar associations with all-cause mortality and health outcomes (i.e., mortality, hospital visits) in the cardiovascular and respiratory systems as those for $PM_{2.5}$ mass (Ostro et al., 2007, 2008, 2010, 2011, 2015, 2016; Zanobetti et al., 2009; Peng et al., 2009; Gan et al., 2011, 2013; Levy et al., 2012; Krall et al., 2013; Lippmann et al., 2013; Vedal et al., 2013; Bell et al., 2014; Chung et al., 2015; Jones et al., 2015; Crouse et al., 2016; Thurston et al., 2013, 2016b; Xiao et al., 2016). This is likely because these are the components that dominate $PM_{2.5}$ mass. There are various challenges in identifying which components can be responsible for some of the health effects. A single emission source emits a mixture of many $PM_{2.5}$ components and different emission sources emit a number of common $PM_{2.5}$ components in different proportion. Hence, it is difficult to find the independent effects of each components (Mostofsky et al., 2012). The association reported with a component could be from the component itself, from another component varying with the component (a confounder), or from the positive or multiplicative interaction between the component and other components of $PM_{2.5}$. Given that components having the same emission source

are likely to be correlated with each other and with $PM_{2.5}$ mass, it is challenging to find specific components responsible for the association with health effects (Krall et al., 2015). In some cases, levels of $PM_{2.5}$ mass were highly correlated with the components. The $PM_{2.5}$ GSH oxidative potential was associated with a number of health outcomes, while the ascorbate oxidative potential was not. Studies have begun to identify key components that can represent markers of specific sources of $PM_{2.5}$.

In summary, current evidence continues to report strong and consistent associations with $PM_{2.5}$ mass, with some studies showing that composition, in addition to mass, is a driver of the toxic potency of $PM_{2.5}$. Given the wide qualitative and quantitative variations in the composition of $PM_{2.5}$ in ambient air across various regions, air sheds, emission sources and formation pathways, it is not yet possible to formulate overall comprehensive conclusions on the specific contribution of each individual component, or even combinations of individual species, to the health effects of $PM_{2.5}$. Nevertheless, while the evidence continues to report strong and consistent associations of health outcomes with $PM_{2.5}$ mass, evidence related to associations with individual components and sources of $PM_{2.5}$ continues to emerge, and this remains an important research priority.

CHAPTER 6:
CONFOUNDING AND EFFECT MODIFICATION BY OTHER POLLUTANTS

In addition to $PM_{2.5}$, the ambient air contains a complex mixture of air pollutants, which may modify or confound the association between $PM_{2.5}$ and the observed health effects. Confounding refers to the distortion of an association by a third variable associated with both $PM_{2.5}$ and the health outcome (e.g., smoking is associated with ambient $PM_{2.5}$ exposure and can cause adverse health outcomes, leading to inaccurate effect estimates if not accounted for). Effect modification refers to changes in the magnitude of the effect estimate across levels of a third variable (e.g., the magnitude of the association between $PM_{2.5}$ and a health outcome changes in the population subgroups in which it is measured).

6.1. CONFOUNDING

The CSSA reported that co-pollutants are often correlated with PM (all size fractions) and can be associated with similar adverse health outcomes. Adjusting for these co-pollutants can decrease the accuracy of the associations because of collinearity with $PM_{2.5}$. Despite this limitation, the CSSA indicated that the associations with $PM_{2.5}$ are generally robust to adjustment to other pollutants. Since the publication of the CSSA, it has been common practice in epidemiological studies to conduct single-pollutant analysis, evaluating associations between individual pollutants with specific health outcomes, despite ambient exposure to multiple pollutants. Researchers also conduct co-pollutant or multi-pollutant regressions to assess potential confounding from exposure to other pollutants, these analyses generally include no more than 3 pollutants to reduce collinearity, as air pollutants are often correlated, and to ensure more stable statistical models. The issue of adjustment for co-pollutants due to limits in statistical modelling can limit the ability to conclude on causality (Bateson et al. 2007). Adjustment for one or more other pollutants (e.g., $PM_{10\text{-}2.5}$, SO_2, NO_2, O_3, BC, CO) generally does not affect the statistical significance of the associations between the health outcomes and $PM_{2.5}$, as described in chapter 3. In some cases, the associations with $PM_{2.5}$ were attenuated when accounting for NO_2 exposure.

6.2. EFFECT MODIFICATION

The CSSA reported an enhancement of lung injury, airway responsiveness, and altered lung endothelin system gene expression of $PM_{2.5}$ by O_3 in a few toxicological studies. It concluded that the evidence for interactive effects was limited and inconclusive. Contrary to confounding, which can be considered a type of bias that needs to be controlled and eliminated, effect modification is an important aspect of air pollution, as additive and multiplicative interactions between pollutants are likely to affect the health effects of $PM_{2.5}$.

To date, the co-exposure epidemiological database remains small and inconclusive. A few studies showed that the co-exposure with O_3 enhanced the magnitude of the association between certain health endpoints such as HRV parameters, vascular function, and pulmonary outcomes and $PM_{2.5}$, in comparison with $PM_{2.5}$ alone (Brook et al., 2002; Urch et al., 2004; Sivagangabalan et al., 2011; Huang et al., 2012).

Toxicological studies have shown interactions between $PM_{2.5}$ and O_3, often leading to an enhancement of the effect of $PM_{2.5}$. For example, enhanced cardiovascular function alterations such as lower blood pressure and higher heart rate were observed when animals were co-exposed to $PM_{2.5}$ and O_3 (Kurhanewicz et al., 2014; Wagner et al., 2014a; Farraj et al., 2015). There are also some indications that the source and chemical composition of $PM_{2.5}$ and the season of sampling can influence the magnitude of the effects on the cardiovascular system (Farraj et al., 2015; Gordon et al., 2013). Considering the complexity of the interactions, which depend on the specific chemical composition of $PM_{2.5}$ and health outcome, as well as the levels of various co-pollutants, the database remains too limited to make general conclusions.

CHAPTER 7:
EMERGING HEALTH EFFECTS AND RESEARCH NEEDS

7.1. EMERGING HEALTH EFFECTS

In this update, emerging research on $PM_{2.5}$ exposure outcomes that has contributed to the weight of evidence used in determining the causality conclusions to be drawn has been reported. Various positive associations with metabolic effects, including diabetes, were reported in epidemiological and experimental studies, as discussed in section 2.2. In addition, a limited number of studies suggested positive associations between $PM_{2.5}$ exposure and maternal hypertensive disorders, gestational diabetes during pregnancy, as well as decreased birth weight, small for gestational age, and preterm birth with $PM_{2.5}$ exposure levels measured during the entire pregnancy period (section 2.5). Some epidemiological and experimental studies have also reported that short- and long-term exposure to $PM_{2.5}$ was associated with increases in inflammatory and stress-related biomarkers in the brain of animals and with adverse neurological outcomes, such as increases in the risk of neurodegenerative diseases and cognitive impairment (section 2.6). In addition, associations with the immune system (i.e., autoimmune diseases, dermatitis), reduction in renal glomerular filtration rate, and acceleration of biological aging progression at the molecular level were reported in a few studies (section 2.7).

In the toxicological database, an effect on the cardiac immune system (i.e., susceptibility to viral myocarditis) was also reported. Effects in the spleen, thymus, and liver are also possible, as inflammation (e.g., infiltration of macrophages, neutrophils and T lymphocytes) was observed in these organs in association with oxidative stress.

Given that the mechanistic and toxicological evidence shows that exposure to $PM_{2.5}$ can induce oxidative stress and inflammation and can alter epigenetic and gene expression at the molecular and tissue level, $PM_{2.5}$ is likely to affect many systems and organs in the body, such as the neurological, metabolic, and immune systems. In addition, the progression of various diseases and health conditions may be impacted by $PM_{2.5}$ exposure.

7.2. RESEARCH NEEDS

The section below lists some key areas in which more research is needed in order to confirm or strengthen the causality conclusions presented in Chapter 2. Research in these areas would provide a better understanding of the public health implications of exposure to $PM_{2.5}$.

Relationship with cerebrovascular outcomes

The relationship between exposure to $PM_{2.5}$ and specific cardiovascular outcomes has been consistent for CHF and MI, as shown in various multi-city epidemiological studies (Bell et al., 2008, 2015; Kloog et al., 2014; Powell et al., 2015). However, the relationship with CEB-related outcomes, such as stroke, has been inconsistent. It remains unclear why the associations with CEB-related outcomes are equivocal. Hypotheses for the inconsistent findings include:

- a low total number of patients with CEB-related outcomes and a low number of studies examining CEB-related outcomes;
- a high rate of exposure misclassification for CEB disease patients;
- CEB-related symptoms not initially detected when they start, leading to less hospitalized patients compared with other cardiovascular outcomes;
- Onset of CEB symptoms immediately after short spikes in $PM_{2.5}$ exposure; these spikes are not necessarily well characterized in cohort studies that average the $PM_{2.5}$ exposure over longer periods;
- $PM_{2.5}$ exposure is not associated with CEB-related outcomes, possibly because brain blood vessels are partially protected by the blood brain barrier and are likely exposed to a different environment than the rest of the body.

Relationship with respiratory mortality

It remains unclear why the associations reported in the $PM_{2.5}$ epidemiological database between long-term $PM_{2.5}$ exposure and the two main mortality outcomes–cardiovascular- and respiratory-related mortality–are different. With various large cohort studies consistently showing robust positive associations, cardiovascular-related mortality was concluded to have a causal relationship with exposure to $PM_{2.5}$. However, the evidence on respiratory-related mortality was inconsistent, and it was concluded to be suggestive of, but not sufficient to infer, a causal relationship. The following hypotheses may explain why the associations with respiratory mortality are inconsistent:

- the respiratory mortality database is relatively small and the associations were not always robust to adjustments for other pollutants;
- the cause of death for respiratory-related mortality may not always be diagnosed and registered accurately (leading to an underrepresentation of respiratory-related mortality cases, lowering the risk estimates);
- respiratory-related mortality could occur more readily after sudden increases in $PM_{2.5}$ exposure compared with cardiovascular-related mortality (biasing respiratory-related mortality risk estimates towards the null).

Despite similarities in the biological plausibility of the two major cause-specific mortality outcomes, it is possible that the risk of cardiovascular mortality is, in reality, higher than the risk of respiratory mortality following $PM_{2.5}$ exposure. One mechanistic explanation for this is that the cardiovascular system is under additional stress as a result of lung signalling factors, secreted in response to $PM_{2.5}$. For example, increases in the pulmonary expression of molecular messengers involved in the kallikrein-kinin endocrine system (regulates inflammation and blood pressure processes) were observed in animal exposed to $PM_{2.5}$ (Aztatzi-Aguilar et al., 2015). This can lead to higher circulating levels of these molecules in the blood where they can act as secondary mediators and cause

additional stress on the cardiovascular system. In addition, increases in brain signalling, with activation of the sympathetic nervous system, were reported in toxicological studies. This could also put additional stress on the cardiovascular system.

Shape of concentration-response relationships

Another area of uncertainty in the $PM_{2.5}$ concentration-response relationship is whether the shape of the relationship differs across health outcomes. The CSSA concluded that there was no evidence of a threshold for short-term exposure to $PM_{2.5}$ and cardiovascular and total mortality and cardiovascular hospital admissions. Since then, research has provided support for a linear or near linear concentration-response relationship between short-term $PM_{2.5}$ exposure and all-cause mortality and emergency room visits for respiratory-related causes (Reid et al., 2016; Shi et al., 2016; Weichenthal et al., 2016a). However, these studies have relatively large confidence intervals at the low range of the exposure concentrations close to background concentrations of $PM_{2.5}$. Also, linear or supralinear relationships between long-term $PM_{2.5}$ exposure and all-cause mortality were reported in American and Canadian studies (Crouse et al., 2012, 2015; Chen H et al., 2016; Pinault et al., 2016). However, confidence intervals were large for the lower concentration range. This could be due to the small sample sizes in the lower concentration of exposure range, resulting in lower precision. It also remains unclear whether the shapes of the relationships for long-term exposure to $PM_{2.5}$ and all-cause and cardiovascular mortality differ.

Population subgroups at higher risk of health effects

Some factors are suspected to increase the risk of adverse health outcomes despite a relatively small database. For example, only a few studies compared the risk of adverse health outcomes across sexes, socioeconomic status, and ethnicity. More studies of this type are needed for a better characterization of which groups have a higher risk of health effects in response to $PM_{2.5}$ exposure. There is also growing evidence that the age group, sex, pregnancy, mental health and neurological conditions, certain diets, and socioeconomic status are factors changing the risk of adverse health outcomes following exposure to $PM_{2.5}$.

Contribution of components and sources to the health effects of $PM_{2.5}$

Short- and long-term exposure to various organic and inorganic components of $PM_{2.5}$ have been associated with adverse health outcomes. Although the associations between health outcomes (e.g., cardiovascular, respiratory, and all-cause mortality) with particular components (e.g., black carbon, organic carbon, elemental carbon and NO_3^-) were found to be comparable with the association of $PM_{2.5}$ mass in Canadian and American studies, it remains unclear which particular component, if any, could be responsible for the observed associations between health outcomes and exposure to $PM_{2.5}$. For example, respiratory mortality and all-cause mortality were associated with some components, however no particular components were found to be responsible for the positive associations. Overall, the results vary in terms of the actual components being analyzed and their association with health outcomes, which was also shown to vary with sources of $PM_{2.5}$. Hence, the actual contribution of each component to the associations remains to be determined, especially since the correlation between $PM_{2.5}$ mass and the components can be high. The oxidative potential of $PM_{2.5}$ was also found to modify the relationship between $PM_{2.5}$ and health effects, with greater risk of cardiovascular and respiratory outcomes with higher oxidative potential. The proportion of the oxidative potential of $PM_{2.5}$ to the total effect and how the oxidative potential is dependent on $PM_{2.5}$ composition or source need further investigation.

The risk and intensity of wildfires, which can influence ambient $PM_{2.5}$ concentrations, is expected to increase with a warmer climate in the future in Canada (Bush and Lemmen, 2019). The contribution of this source of $PM_{2.5}$ to the relationship with health outcomes has not been studied extensively, with only a few epidemiological studies reporting associations with wood burning or wildfires. Despite some studies reporting associations with $PM_{2.5}$ from wildfires (short-term exposure associated with respiratory outcomes, but not with cardiovascular outcomes, from Alman et al., 2016; Reid et al., 2016), the database remains too small to draw conclusions on the specific contribution of this source to the effect observed with ambient $PM_{2.5}$.

CHAPTER 8: **CONCLUSIONS**

8.1. STRENGTH OF EVIDENCE AND CAUSALITY RELATIONSHIP CONCLUSIONS

The collective weight of evidence continues to support the overall conclusion that exposure to ambient $PM_{2.5}$ is detrimental to human health for a wide range of outcomes. The evidence is extensive and indicative of the wide and various impacts caused directly by $PM_{2.5}$ exposure. The presented results are largely robust to adjustment for other co-pollutants, coherent across different study types, consistent across different locations, and at concentrations of exposure that are relevant to what Canadians are exposed to in ambient air. In addition, the basis of most of the health effects observed is linked to non-specific mechanisms of toxicity involving oxidative stress and inflammation.

The causality relationship between health outcomes and exposure to $PM_{2.5}$ are summarized in Table 8.1. This table shows the causality conclusions for the relationships between $PM_{2.5}$ exposure and health outcomes that were drawn in the CSSA and in this update. The evidence continues to support the causal relationship between short- and long-term exposure to $PM_{2.5}$ and all-cause mortality, as these conclusions were re-established in this update. The causality relationship conclusions for long-term $PM_{2.5}$ exposure and cardiovascular and respiratory morbidity effects have changed from suggestive of a causal relationship to a likely causal relationship. The likely causal relationship between $PM_{2.5}$ exposure and lung cancer was re-affirmed, and now includes morbidity in addition to only mortality in the CSSA. The database examining the relationship between $PM_{2.5}$ exposure and reproductive and developmental effects has expanded, resulting in separate causality relationship conclusions for these two categories of outcomes. The causality conclusion was suggestive of a causal relationship for the combined reproductive and developmental effects in the CSSA. In this update, the causality conclusions are now inadequate to conclude on causality for reproductive outcomes, and suggestive of a causal relationship for developmental effects. No causality conclusion for neurological effect was drawn in the CSSA. The conclusions are now inadequate to conclude on causality for short-term exposure to $PM_{2.5}$ and neurological outcomes, and suggestive of a causal relationship for long-term exposure to $PM_{2.5}$ and neurological effects.

The extensive weight of evidence demonstrates that under current levels of exposure in ambient air, Canadians are at risk of adverse health effects from $PM_{2.5}$ exposure, which include premature mortality and cardiovascular and respiratory outcomes that require hospital visits. Overall, the database on the adverse health effects of $PM_{2.5}$ is large, composed of diverse high quality human and toxicological studies that show robust, consistent, biologically plausible and coherent results in many organs and systems. This gives high confidence to the conclusion that $PM_{2.5}$ exposure causes a variety of adverse health effects.

TABLE 8.1: Past and updated conclusions on causality relationship between health outcomes and short- and long-term exposure to ambient $PM_{2.5}$

Health outcome	$PM_{2.5}$ exposure duration	Causality relationship conclusion of the CSSA	Causality relationship updated conclusion
All-cause mortality	Short-term	Causal	Causal
	Long-term	Causal	Causal
Cardiovascular effects	Short-term	Mortality: Causal; Morbidity: Causal	Mortality: Causal; Morbidity: Causal
	Long-term	Mortality: Causal; Morbidity: Suggestive	Mortality: Causal; Morbidity: Likely Causal*
Respiratory effects	Short-term	Mortality: Causal; Morbidity: Causal	Mortality: Causal; Morbidity: Causal
	Long-term	Mortality: Inadequate; Morbidity: Suggestive	Mortality: Suggestive*; Morbidity: Likely Causal*
Cancer effects	Long-term	Lung cancer mortality: Likely causal	Lung cancer morbidity and mortality: Likely causal
Neurological effects	Short-term	No conclusion drawn	Inadequate*
	Long-term	No conclusion drawn	Suggestive*
Reproductive and developmental effects	Long-term	Combined outcome: Suggestive	Reproductive: Inadequate*; Developmental: Suggestive

* represents a change in causality conclusion from the CSSA (Canadian Smog Science Assessment) (Health Canada, 2013)

Other considerations

$PM_{2.5}$ acts through non-specific mechanisms of toxicity, including the generation of oxidative stress and inflammation in many tissues, thus increasing the risk of adverse health outcomes for the general population.

Certain population subgroups, such as those with pre-existing health conditions (e.g., cardiovascular diseases, and obesity) and children, are at increased risk of $PM_{2.5}$-related health effects.

Despite the relatively low $PM_{2.5}$ concentrations found in Canada, evidence has reconfirmed the apparent non-threshold and linear concentration-response relationship shape characterizing the relationships between $PM_{2.5}$ and mortality. In some Canadian epidemiological studies, the analyses covered annual ambient levels below established CAAQS for $PM_{2.5}$, in the 3 to 6 $\mu g/m^3$ $PM_{2.5}$ range levels, supporting the notion that no identifiable threshold exists between $PM_{2.5}$ exposure and various health endpoints at levels close to background.

Epidemiological and toxicological studies published since the CSSA have provided more details on the associations of $PM_{2.5}$ components with adverse effects, with some components (i.e., elemental carbon, black carbon, SO_4^{2-}, NO_3^-, and organic carbon) having similar associations with health outcomes as $PM_{2.5}$ mass. However, no comprehensive conclusion on the specific contribution of each individual component to the health effects of $PM_{2.5}$ can be formulated at this time and the current evidence continues to support regulations to focus on $PM_{2.5}$ mass.

Uncertainties remain with respect to the association between $PM_{2.5}$ exposure and adverse reproductive, developmental, metabolic and neurological health outcomes. Emerging results are raising concern given the severity of these health outcomes.

CHAPTER 9: **REFERENCES**

Abrahamowicz M, Schopflocher T, Leffondre K, du Berger R, and Krewski D. 2003. Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study. J Toxicol Environ Health A. 66:1625–54.

Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Diez Roux AV, Budoff M, Jacobs DR Jr, Barr RG, Watson K, et al. 2013. Fine particulate air pollution and the progression of carotid intima-medial thickness: A prospective cohort study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution. PLoS Med. 10(4):e1001430.

Adar SD, Kaufman JD, Diez-Roux AV, Hoffman EA, D'Souza J, Stukovsky KH, Rich SS, Rotter JI, Guo X, Raffel LJ, et al. 2015. Air pollution and percent emphysema identified by computed tomography in the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect. 123(2):144–51.

Ailshire JA, Crimmins EM. 2014. Fine particulate matter air pollution and cognitive function among older US adults. Am J Epidemiol. 180(4):359–66.

Akinbami LJ, Lynch CD, Parker JD, Woodruff TJ. 2010. The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001–2004. Environ Res. 110(3):294–301.

Alhanti BA, Chang HH, Winquist A, Mulholland JA, Darrow LA, Sarnat SE. 2016. Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. J Expo Sci Environ Epidemiol. 26(2):180.

Alman BL, Pfister G, Hao H, Stowell J, Hu X, Liu Y, Strickland MJ. 2016. The association of wildfire smoke with respiratory and cardiovascular emergency department visits in Colorado in 2012: A case crossover study. Environ Health. 15(1):64.

Ashley-Martin J, Lavigne E, Arbuckle TE, Johnson M, Hystad P, Crouse DL, Marshall JS, Dodds L. 2016. Air pollution during pregnancy and cord blood immune system biomarkers. J Occup Environ Med. 58(10):979–86.

Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. 2014. Epidemiological time series studies of $PM_{2.5}$ and daily mortality and hospital admissions: A systematic review and meta-analysis. Thorax. 69(7):660–5.

Baja ES, Schwartz JD, Wellenius GA, Coull BA, Zanobetti A, Vokonas PS, Suh HH. 2010. Traffic-related air pollution and QT interval: Modification by diabetes, obesity, and oxidative stress gene polymorphisms in the Normative Aging Study. Environ Health Perspect. 118(6):840–6.

Balasubramanian P, Sirivelu MP, Weiss KA, Wagner JG, Harkema JR, Morishita M, Mohankumar P, MohanKumar SM. 2013. Differential effects of inhalation exposure to $PM_{2.5}$ on hypothalamic monoamines and corticotrophin releasing hormone in lean and obese rats. Neurotoxicology. 36:106–11.

Balmes JR, Cisternas M, Quinlan PJ, Trupin L, Lurmann FW, Katz PP, Blanc PD. 2014. Annual average ambient particulate matter exposure estimates, measured home particulate matter, and hair nicotine are associated with respiratory outcomes in adults with asthma. Environ Res. 129:1–10.

Bateson TF, Coull BA, Hubbell B, et al. 2007. Panel discussion review: session three--issues involved in interpretation of epidemiologic analyses--statistical modeling. J Expo Sci Environ Epidemiol. 17 Suppl 2:S90–96.

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. 2013. Ambient air pollution and autism in Los Angeles county, California. Environ Health Perspect. 121(3):380–6.

Behbod B, Urch B, Speck M, Scott JA, Liu L, Poon R, Coull B, Schwartz J, Koutrakis P, Silverman F, et al. 2013. Endotoxin in concentrated coarse and fine ambient particles induces acute systemic inflammation in controlled human exposures. Occup Environ Med. 70(11):761–7.

Bell ML, Ebisu K, Peng RD, Walker J, Samet JM, Zeger SL, Dominici F. 2008. Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999–2005. Am J Epidemiol. 168(11):1301–10.

Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P, Leaderer BP. 2010. Prenatal exposure to fine particulate matter and birth weight: Variations by particulate constituents and sources. Epidemiology. 21(6):884–91.

Bell ML, Ebisu K, Leaderer BP, Gent JF, Lee HJ, Koutrakis P, Wang Y, Dominici F, Peng RD. 2014 Associations of $PM_{2.5}$ constituents and sources with hospital admissions: Analysis of four counties in Connecticut and Massachusetts (USA) for persons ≥ 65 years of age. Environ Health Perspect. 122(2):138–44.

Bell ML, Son JY, Peng RD, Wang Y, Dominici F. 2015. Ambient $PM_{2.5}$ and risk of hospital admissions: Do risks differ for men and women? Epidemiology. 26(4):575–9.

Berhane K, Chang C, McConnell R, Gauderman WJ, Avol E, Rapapport E, Urman R, Lurmann F, Gilliland F. 2016. Association of changes in air quality with bronchitic symptoms in children in California, 1993–2012. JAMA. 315(14):1491–501.

Bind MA, Peters A, Koutrakis P, Coull B, Vokonas P, Schwartz J. 2016. Quantile regression analysis of the distributional effects of air pollution on blood pressure, heart rate variability, blood lipids, and biomarkers of inflammation in elderly American men: The Normative Aging Study. Environ Health Perspect. 124(8):1189–98.

Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, Matheson M, Dharmage SC. 2015. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: A systematic review and a meta-analysis of birth cohort studies. Allergy. 70(3):245–56.

Bravo MA, Ebisu K, Dominici F, Wang Y, Peng RD, Bell ML. 2017. Airborne fine particles and risk of hospital admissions for understudied populations: Effects by urbanicity and short-term cumulative exposures in 708 U.S. counties. Environ Health Perspect. 125(4):594–601.

Breton CV, Wang X, Mack WJ, Berhane K, Lopez M, Islam TS, Feng M, Lurmann F, McConnell R, Hodis HN, et al. 2012. Childhood air pollutant exposure and carotid artery intima-media thickness in young adults. Circulation. 126(13):1614–20.

Breton CV, Mack WJ, Yao J, Berhane K, Amadeus M, Lurmann F, Gilliland F, McConnell R, Hodis HN, Kunzli N, et al. 2016a. Prenatal air pollution exposure and early cardiovascular phenotypes in young adults. PLoS One. 11(3):e0150825.

Breton CV, Yao J, Millstein J, Gao L, Siegmund KD, Mack W, Whitfield-Maxwell L, Lurmann F, Hodis H, Avol E, et al. 2016b. Prenatal air pollution exposures, DNA methyl transferase genotypes, and associations with newborn LINE1 and alu methylation and childhood blood pressure and carotid intima-media thickness in the Children's Health Study. Environ Health Perspect. 124(12):1905–12.

Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F. 2002. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. Circulation. 105(13):1534–6.

Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, Morishita M, Marsik FJ, Kamal AS, Kaciroti N, et al. 2009. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. Hypertension. 54(3):659–67.

Brook RD, Rajagopalan S, Pope III CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA. 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 121(21):2331–78.

Brook RD, Xu X, Bard RL, Dvonch JT, Morishita M, Kaciroti N, Sun Q, Harkema J, Rajagopalan S. 2013a. Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. Sci Total Environ. 448:66–71.

Brook RD, Cakmak S, Turner MC, Brook JR, Crouse DL, Peters PA, Van Donkelaar A, Villeneuve PJ, Brion O, Jerrett M. 2013b. Long-term fine particulate matter exposure and mortality from diabetes in Canada. Diabetes Care. 36(10):3313–20.

Burnett RT, Goldberg MS. 2003. Size-fractionated particulate mass and daily mortality in eight Canadian cities. Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report. Health Effects Institute.

Burnett RT, Stieb D, Brook JR, Cakmak S, Dales R, Raizenne M, Vincent R, Dann T. 2004. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Health. 59(5):228–36.

Bush E and Lemmen DS, editors. 2019. Canada's Changing Climate Report; Government of Canada, Ottawa, ON, catalogue no. En4-368/2019E-PDF. 444 pp. www.nrcan.gc.ca/sites/www.nrcan.gc.ca/files/energy/Climate-change/pdf/CCCR_FULLREPORT-EN-FINAL.pdf.

Cai X, Li Z, Scott EM, Li X, Tang M. 2016. Short-term effects of atmospheric particulate matter on myocardial infarction: A cumulative meta-analysis. Environ Sci Pollut Res. 23(7):6139–48.

Cakmak S, Kauri L, Shutt R, Liu L, Green MS, Mulholland M, Stieb D, Dales R. 2014a. The association between ambient air quality and cardiac rate and rhythm in ambulatory subjects. Environ Int. 73:365–71.

Cakmak S, Dales R, Kauri LM, Mahmud M, Van Ryswyk K, Vanos J, Liu L, Kumarathasan P, Thomson E, Vincent R. 2014b. Metal composition of fine particulate air pollution and acute changes in cardiorespiratory physiology. Environ Pollut. 189:208–14.

Cakmak S, Hebbern C, Vanos J, Crouse DL, Burnett R. 2016. Ozone exposure and cardiovascular-related mortality in the Canadian Census Health and Environment Cohort (CANCHEC) by spatial synoptic classification zone. Environ Pollut. 214:589–99.

Canadian Council of Ministers of the Environment (CCME). 2014. Air quality management system. https://ccme.ca/en/resources/aqms [accessed Feb 9, 2022].

Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. 2011. Traffic-related air pollution and incident asthma in a high-risk birth cohort. Occup Environ Med. 68(4):291–5.

Casanova R, Wang X, Reyes J, Akita Y, Serre ML, Vizuete W, Chui HC, Driscoll I, Resnick SM, Espeland MA. 2016. A voxel-based morphometry study reveals local brain structural alterations associated with ambient fine particles in older women. Front Hum Neurosci. 10:495.

Chang X, Zhou L, Tang M, Wang B. 2015. Association of fine particles with respiratory disease mortality: A meta-analysis. Arch Environ Occup Health. 70(2):98–101.

Chen H. 2008. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. Rev Environ Health. 23(4):243–98.

Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, van Donkelaar A, Jerrett M, Martin RV, Brook JR, et al. 2013. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. Environ Health Perspect. 121(7):804–10.

Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, van Donkelaar A, Jerrett M, Martin RV, Kopp A, et al. 2014. Spatial association between ambient fine particulate matter and incident hypertension. Circulation. 129(5):562–9.

Chen H, Burnett RT, Copes R, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, van Donkelaar A, Jerrett M, Martin RV, et al. 2016. Ambient fine particulate matter and mortality among survivors of myocardial infarction: Population-based cohort study. Environ Health Perspect. 124(9):1421–8.

Chen J, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, McArdle JJ, Manson JE, Chui HC, Espeland MA. 2015. Ambient air pollution and neurotoxicity on brain structure: Evidence from Women's Health Initiative Memory Study. Ann Neurol. 78(3):466–76.

Chen LC, Lippmann M. 2013. NPACT Study 1. Subchronic inhalation exposure of mice to concentrated ambient $PM_{2.5}$ from 5 airsheds. National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of Particulate Matter Components. 15–54.

Chen Y, Yang Q, Krewski D, Burnett RT, Shi Y, McGrail KM. 2005. The effect of coarse ambient particulate matter on first, second, and overall hospital admissions for respiratory disease among the elderly. Inhal Toxicol. 17(12):649–55.

Chen Z, Salam MT, Toledo-Corral C, Watanabe RM, Xiang AH, Buchanan TA, Habre R, Bastain TM, Lurmann F, Wilson JP, et al. 2016. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. Diabetes Care. 39(4):547–54.

Chung Y, Dominici F, Wang Y, Coull BA, Bell ML. 2015. Associations between long-term exposure to chemical constituents of fine particulate matter ($PM_{2.5}$) and mortality in medicare enrollees in the eastern United States. Environ Health Perspect. 123(5):467–74.

Clark NA, Demers PA, Karr CJ, Mieke K, Cornel L, Lillian T, Michael B. 2010. Effect of early life exposure to air pollution on development of childhood asthma. Environ Health Perspect. 118(2):284–90.

Clougherty JE, Rossi CA, Lawrence J, Long MS, Diaz EA, Lim RH, McEwen B, Koutrakis P, Godleski JJ. 2010. Chronic social stress and susceptibility to concentrated ambient fine particles in rats. Environ Health Perspect. 118(6):769–75.

Coogan PF, White LF, Yu J, Burnett RT, Seto E, Brook RD, Palmer JR, Rosenberg L, Jerrett M. 2016. $PM_{2.5}$ and diabetes and hypertension incidence in the Black Women's Health Study. Epidemiology. 27(2):202–10.

Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, Villeneuve PJ, Jerrett M, Goldberg MS, Pope III CA, et al. 2015. Ambient $PM_{2.5}$, O_3, and NO_2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect. 123(11):1180–6.

Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, Khan S, Atari DO, Jerrett M, Pope III CA, et al. 2012. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: A Canadian national-level cohort study. Environ Health Perspect. 120(5):708–14.

Crouse DL, Philip S, Van Donkelaar A, Martin RV, Jessiman B, Peters PA, Weichenthal S, Brook JR, Hubbell B, Burnett RT. 2016. A new method to jointly estimate the mortality risk of long-term exposure to fine particulate matter and its components. Sci Rep. 6:18916.

Dai L, Zanobetti A, Koutrakis P, Schwartz JD. 2014. Associations of fine particulate matter species with mortality in the United States: A multicity time-series analysis. Environ Health Perspect. 122(8):837–42.

Dai L, Bind MA, Koutrakis P, Coull BA, Sparrow D, Vokonas PS, Schwartz JD. 2016. Fine particles, genetic pathways, and markers of inflammation and endothelial dysfunction: Analysis on particulate species and sources. J Expo Sci Environ Epidemiol. 26(4):415–21.

Dales R, Kauri LM, Cakmak S, Mahmud M, Weichenthal SA, Van Ryswyk K, Kumarathasan P, Thomson E, Vincent R, Broad G, et al. 2013. Acute changes in lung function associated with proximity to a steel plant: A randomized study. Environ Int. 55:15–9.

Dales RE, Cakmak S. 2016. Does mental health status influence susceptibility to the physiologic effects of air pollution? A population based study of Canadian children. PLoS One. 11(12):e0168931.

DeFranco E, Hall E, Hossain M, Chen A, Haynes EN, Jones D, Ren S, Lu L, Muglia L. 2015. Air pollution and stillbirth risk: Exposure to airborne particulate matter during pregnancy is associated with fetal death. PLoS One. 10(3):e0120594.

Delfino RJ, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen DL, Kleinman MT, Vaziri ND, Longhurst J, Zaldivar F, et al. 2008. Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. Environ Health Perspect. 116(7):898–906.

Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M, Kleinman MT, Vaziri ND, Longhurst J, Sioutas C. 2009. Air pollution exposures and circulating biomarkers of effect in a susceptible population: Clues to potential causal component mixtures and mechanisms. Environ Health Perspect. 117(8):1232–8.

Delfino RJ, Staimer N, Tjoa T, Gillen DL, Schauer JJ, Shafer MM. 2013. Airway inflammation and oxidative potential of air pollutant particles in a pediatric asthma panel. J Expo Sci Environ Epidemiol. 23(5):466–73.

Dockery DW, Pope III CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med. 329(24):1753–9.

Dorans KS, Wilker EH, Li W, Rice MB, Ljungman PL, Schwartz J, Coull BA, Kloog I, Koutrakis P, D'Agostino Sr RB. 2016. Residential proximity to major roads, exposure to fine particulate matter, and coronary artery calcium: The Framingham Heart Study. Arterioscler Thromb Vasc Biol. 36(8):1679–85.

Eckel SP, Cockburn M, Shu YH, Deng H, Lurmann FW, Liu L, Gilliland FD. 2016. Air pollution affects lung cancer survival. Thorax. 71(10):891–8.

Eftim SE, Samet JM, Janes H, McDermott A, Dominici F. 2008. Fine particulate matter and mortality: A comparison of the six cities and American Cancer Society cohorts with a Medicare cohort. Epidemiology. 19(2):209–16.

Enstrom JE. 2005. Fine particulate air pollution and total mortality among elderly Californians, 1973–2002. Inhal Toxicol. 17(14):803–16.

Evans KA, Halterman JS, Hopke PK, Fagnano M, Rich DQ. 2014. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. Environ Res. 129:11–9.

Faiz AS, Rhoads GG, Demissie K, Kruse L, Lin Y, Rich DQ. 2012. Ambient air pollution and the risk of stillbirth. Am J Epidemiol. 176(4):308–16.

Fakhri AA, Ilic LM, Wellenius GA, Urch B, Silverman F, Gold DR, Mittleman MA. 2009. Autonomic effects of controlled fine particulate exposure in young healthy adults: Effect modification by ozone. Environ Health Perspect. 117(8):1287–92.

Fan J, Li S, Fan C, Bai Z, Yang K. 2016. The impact of $PM_{2.5}$ on asthma emergency department visits: A systematic review and meta-analysis. Environ Sci Pollut Res. 23(1):843–50.

Farraj AK, Walsh L, Haykal-Coates N, Malik F, McGee J, Winsett D, Duvall R, Kovalcik K, Cascio WE, Higuchi M. 2015. Cardiac effects of seasonal ambient particulate matter and ozone co-exposure in rats. Part Fibre Toxicol. 12(1):1.

Franklin M, Koutrakis P, Schwartz P. 2008. The role of particle composition on the association between $PM_{2.5}$ and mortality. Epidemiology. 19(5):680–9.

Franklin M, Zeka A, Schwartz J. 2007. Association between $PM_{2.5}$ and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol. 17(3):279.

Fung KY, Khan S, Krewski D, Chen Y. 2006. Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. Inhal Toxicol. 18(13):1005–11.

Gan WQ, Allen RW, Brauer M, Davies HW, Mancini GB, Lear SA. 2014. Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: A prospective cohort study. BMJ Open. 4(4):e004743.

Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. 2013. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med. 187(7):721–7.

Gan WQ, Koehoorn M, Davies HW, Demers PA, Tamburic L, Brauer M. 2011. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. Environ Health Perspect. 119(4):501.

Gatto NM, Henderson VW, Hodis HN, John JAS, Lurmann F, Chen J, Mack WJ. 2014. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology. 40:1–7.

Gharibvand L, Shavlik D, Ghamsary M, Beeson WL, Soret S, Knutsen R, Knutsen SF. 2017. The association between ambient fine particulate air pollution and lung cancer incidence: Results from the AHSMOG-2 study. Environ Health Perspect. 125(3):378–84.

Girguis MS, Strickland MJ, Hu X, Liu Y, Bartell SM, Vieira VM. 2016. Maternal exposure to traffic-related air pollution and birth defects in Massachusetts. Environ Res. 146:1–9.

Goettems-Fiorin PB, Grochanke BS, Baldissera FG, dos Santos AB, de Bittencourt, Paulo Ivo Homem, Ludwig MS, Rhoden CR, Heck TG. 2016. Fine particulate matter potentiates type 2 diabetes development in high-fat diet-treated mice: Stress response and extracellular to intracellular HSP70 ratio analysis. J Physiol Biochem. 72(4):643–56.

Goldberg MS, Burnett RT, Yale J, Valois M, Brook JR. 2006. Associations between ambient air pollution and daily mortality among persons with diabetes and cardiovascular disease. Environ Res. 100(2):255–67.

Gong J, Henry, Linn WS, Sioutas C, Terrell SL, Clark KW, Anderson KR, Terrell LL. 2003. Controlled exposures of healthy and asthmatic volunteers to concentrated ambient fine particles in Los Angeles. Inhal Toxicol. 15(4):305–25.

Gordon T, Lippmann M, Nádas A, Hickey C. 2013. NPACT study 2. Vitro and in vivo toxicity of exposure to coarse, fine, and ultrafine PM from five airsheds. In National Particle Component Toxicity (NPACT) Initiative: integrated epidemiologic and toxicologic studies of the health effects of particulate matter components. p. 55–94.

Government of Canada. 1999. Canadian Environmental Protection Act, 1999. www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/related-documents.html [modified Feb 9, 2022, accessed Feb 9, 2022].

Gray SC, Edwards SE, Schultz BD, Miranda ML. 2014. Assessing the impact of race, social factors and air pollution on birth outcomes: A population-based study. Environ Health. 13(1):4.

Green R, Sarovar V, Malig B, Basu R. 2015. Association of stillbirth with ambient air pollution in a California cohort study. Am J Epidemiol. 181(11):874–82.

Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. 2016. Statistical tests, P values, confidence intervals, and power: A guide to misinterpretations. Eur J Epidemiol. 31(4):337–50.

Ha S, Hu H, Roussos-Ross D, Haidong K, Roth J, Xu X. 2014. The effects of air pollution on adverse birth outcomes. Environ Res. 134:198–204.

Haberzettl P, O'Toole TE, Bhatnagar A, Conklin DJ. 2016a. Exposure to fine particulate air pollution causes vascular insulin resistance by inducing pulmonary oxidative stress. Environ Health Perspect. 124(12):1830–9.

Haley VB, Talbot TO, Felton HD. 2009. Surveillance of the short-term impact of fine particle air pollution on cardiovascular disease hospitalizations in New York State. Environ Health. 8(1):42.

Hammoud A, Carrell DT, Gibson M, Sanderson M, Parker-Jones K, Peterson CM. 2010. Decreased sperm motility is associated with air pollution in Salt Lake City. Fertil Steril. 93(6):1875–9.

Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, Vineis P, Forastiere F, Saldiva P, Yorifuji T, et al. 2014. Outdoor particulate matter exposure and lung cancer: A systematic review and meta-analysis. Environ Health Perspect. 122(9):906–11.

Hansen C, Luben TJ, Sacks JD, Olshan A, Jeffay S, Strader L, Perreault SD. 2010. The effect of ambient air pollution on sperm quality. Environ Health Perspect. 118(2):203–9.

Hao Y, Strosnider H, Balluz L, Qualters JR. 2016. Geographic variation in the association between ambient fine particulate matter ($PM_{2.5}$) and term low birth weight in the United States. Environ Health Perspect. 124(2):250–5.

Harkema JR, Wagner JG, Kaminski NE, Morishita M, Keeler GJ, McDonald JD, Barrett EG, HEI Health Review Committee. 2009. Effects of concentrated ambient particles and diesel engine exhaust on allergic airway disease in brown Norway rats. Res Rep Health Eff Inst. (145)(145):5–55.

Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, Schwartz JD, Gryparis A, Kloog I, Koutrakis P. 2016. Prenatal and childhood traffic-related air pollution exposure and childhood executive function and behavior. Neurotoxicol Teratol. 57:60–70.

Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F. 2011. Long-term ambient multipollutant exposures and mortality. Am J Respir Crit Care Med. 183(1):73–8.

Hart JE, Bertrand KA, DuPre N, James P, Vieira VM, Tamimi RM, Laden F. 2016. Long-term particulate matter exposures during adulthood and risk of breast cancer incidence in the Nurses' Health Study II prospective cohort. Cancer Epidemiol Biomarkers Prev. 25(8):1274–6.

Hart JE, Liao X, Hong B, Puett RC, Yanosky JD, Suh H, Kioumourtzoglou M, Spiegelman D, Laden F. 2015. The association of long-term exposure to $PM_{2.5}$ on all-cause mortality in the Nurses' Health Study and the impact of measurement-error correction. Environ Health. 14(1):38.

Hartiala J, Breton CV, Tang WH, Lurmann F, Hazen SL, Gilliland FD, Allayee H. 2016. Ambient air pollution is associated with the severity of coronary atherosclerosis and incident myocardial infarction in patients undergoing elective cardiac evaluation. J Am Heart Assoc. 5(8):e.003947.

Hazucha MJ, Bromberg PA, Lay JC, Bennett W, Zeman K, Alexis NE, Kehrl H, Rappold AG, Cascio WE, Devlin RB. 2013. Pulmonary responses in current smokers and ex-smokers following a two hour exposure at rest to clean air and fine ambient air particles. Part Fibre Toxicol. 10(1):58.

Health Canada. 2013. Canadian smog science assessment. Volume 2: health effects. Ottawa, Ontario: Health Canada. http://publications.gc.ca/collections/collection_2014/sc-hc/En88-5-2-2013-eng.pdf.

Health Canada. 2021. Health impacts of air pollution in Canada—Estimates of premature deaths and nonfatal outcomes—2021 report. Government of Canada, catalogue no. H144-51/2021E-PDF. 56 pp. www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/2021-health-effects-indoor-air-pollution/hia-report-eng.pdf.

Heck JE, Wu J, Lombardi C, Qiu J, Meyers TJ, Wilhelm M, Cockburn M, Ritz B. 2013. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect. 121(11-12):1385–91.

Heidenfelder BL, Reif DM, Harkema JR, Cohen Hubal EA, Hudgens EE, Bramble LA, Wagner JG, Morishita M, Keeler GJ, Edwards SW. 2009. Comparative microarray analysis and pulmonary changes in brown Norway rats exposed to ovalbumin and concentrated air particulates. Toxicol Sci. 108(1):207–21.

Hemmingsen JG, Rissler J, Lykkesfeldt J, Sallsten G, Kristiansen J, Møller P, Loft S. 2015. Controlled exposure to particulate matter from urban street air is associated with decreased vasodilation and heart rate variability in overweight and older adults. Part Fibre Toxicol. 12(1):6.

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD. 2013. Long-term air pollution exposure and cardio-respiratory mortality: A review. Environ Health. 12(1):43.

Hoek G. 2017. Methods for assessing long-term exposures to outdoor air pollutants. Curr Environ Health Rep. 4(4):450–62.

Hoffmann B, Luttmann-Gibson H, Cohen A, Zanobetti A, de Souza C, Foley C, Suh HH, Coull BA, Schwartz J, Mittleman M, et al. 2012. Opposing effects of particle pollution, ozone, and ambient temperature on arterial blood pressure. Environ Health Perspect. 120(2):241–6.

Holloman CH, Bortnick SM, Morara M, Strauss WJ, Calder CA. 2004. A Bayesian hierarchical approach for relating $PM_{2.5}$ exposure to cardiovascular mortality in North Carolina. Environ Health Perspect. 112(13):1282–8.

Hope SA, Meredith IT. Cellular adhesion molecules and cardiovascular disease. Part I. Their expression and role in atherogenesis. 2003. Intern Med J. 33(8):380–6.

Hope SA, Meredith IT. Cellular adhesion molecules and cardiovascular disease. Part II. Their association with conventional and emerging risk factors, acute coronary events and cardiovascular risk prediction. 2003. Intern Med J. 33(9-10):450–62.

Hsu W, Hwang S, Kinney PL, Lin S. 2017 (available online 2016). Seasonal and temperature modifications of the association between fine particulate air pollution and cardiovascular hospitalization in New York State. Sci Total Environ. 578:626–32.

Hu H, Dailey AB, Kan H, Xu X. 2013. The effect of atmospheric particulate matter on survival of breast cancer among US females. Breast Cancer Res Treat. 139(1):217–26.

Hu H, Ha S, Henderson BH, Warner TD, Roth J, Kan H, Xu X. 2015. Association of atmospheric particulate matter and ozone with gestational diabetes mellitus. Environ Health Perspect. 123(9):853–9.

Huang YT, Rappold AG, Graff DW, Ghio AJ, Devlin RB. 2012. Synergistic effects of exposure to concentrated ambient fine pollution particles and nitrogen dioxide in humans. Inhal Toxicol. 24(12):790–7.

Huynh M, Woodruff TJ, Parker JD, Schoendorf KC. 2006. Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol. 20(6):454–61.

Hyder A, Lee HJ, Ebisu K, Koutrakis P, Belanger K, Bell ML. 2014. $PM_{2.5}$ exposure and birth outcomes: Use of satellite- and monitor-based data. Epidemiology. 25(1):58–67.

Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M. 2013. Long-term residential exposure to air pollution and lung cancer risk. Epidemiology. 24(5):762–72.

International Agency for Research on Cancer (IARC). 2016. Outdoor air pollution. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 109. https://publications.iarc.fr/538.

Institute for Health Metrics and Evaluation (IMME). 2021. GBD Compare. Seattle, WA: IHME, University of Washington, 2015. https://vizhub.healthdata.org/gbd-compare [accessed Feb 3, 2021].

Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y. 2013. Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med. 188(5):593–9.

Jerrett M, Burnett RT, Ma R, Pope III CA, Krewski D, Newbold KB, Thurston G, Shi Y, Finkelstein N, Calle EE. 2005. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology. 16(6):727–36.

Jerrett M, Burnett RT, Pope III CA, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. 2009. Long-term ozone exposure and mortality. N Engl J Med. 360(11):1085–95.

Jones RR, Hogrefe C, Fitzgerald EF, Hwang S, Özkaynak H, Garcia VC, Lin S. 2015. Respiratory hospitalizations in association with fine PM and its components in New York State. J Air Waste Manage Assoc. 65(5):559–69.

Kampfrath T, Maiseyeu A, Ying Z, Shah Z, Deiuliis JA, Xu X, Kherada N, Brook RD, Reddy KM, Padture NP. 2011. Chronic fine particulate matter exposure induces systemic vascular dysfunction via NADPH oxidase and TLR4 pathways. Circ Res. 108(6):716–26.

Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, Daviglus ML, Roux AVD, Gassett AJ, Jacobs DR Jr. 2016. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): A longitudinal cohort study. The Lancet. 388(10045):696–704.

Kim S, Sheppard L, Kaufman JD, Bergen S, Szpiro AA, Larson TV, Adar SD, Diez Roux AV, Polak JF, Vedal S. 2014. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: A cross-sectional analysis based on 2 advanced exposure prediction models in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 180(7):718–28.

Kioumourtzoglou MA, Schwartz J, James P, Dominici F, Zanobetti A. 2016a. $PM_{2.5}$ and mortality in 207 US cities: Modification by temperature and city characteristics. Epidemiology. 27(2):221–7.

Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, Zanobetti A. 2016b. Long-term $PM_{2.5}$ exposure and neurological hospital admissions in the northeastern United States. Environ Health Perspect. 124(1):23–9.

Klemm R and Mason. 2003. Replication of reanalyses of Harvard Six-City Mortality study. Revised Analyses of Time-Series Studies of Air Pollution and Health. Health Effects Institute. Special Report.

Klemm R, Lipfert F, Wyzga R, Gust C. 2004. Daily mortality and air pollution in Atlanta: Two years of data from ARIES. Inhal Toxicol. 16 Suppl 1:131–41.

Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. 2012. Using new satellite based exposure methods to study the association between pregnancy $PM_{2.5}$ exposure, premature birth and birth weight in Massachusetts. Environ Health. 11(1):40.

Kloog I, Nordio F, Zanobetti A, Coull BA, Koutrakis P, Schwartz JD. 2014. Short term effects of particle exposure on hospital admissions in the mid-Atlantic states: A population estimate. PloS One. 9(2):e88578.

Kloog I, Ridgway B, Koutrakis P, Coull BA, Schwartz JD. 2013. Long- and short-term exposure to $PM_{2.5}$ and mortality: Using novel exposure models. Epidemiology. 24(4):555–61.

Kloog I, Zanobetti A, Nordio F, Coull BA, Baccarelli AA, Schwartz J. 2015. Effects of airborne fine particles ($PM_{2.5}$) on deep vein thrombosis admissions in the northeastern United States. J Thromb Haemost. 13(5):768–74.

Kloog I. 2016. Fine particulate matter ($PM_{2.5}$) association with peripheral artery disease admissions in northeastern United States. Int J Environ Health Res. 26(5-6):572–7.

Krall JR, Anderson GB, Dominici F, Bell ML, Peng RD. 2013. Short-term exposure to particulate matter constituents and mortality in a national study of U.S. urban communities. Environ Health Perspect. 121(10):1148–53.

Krall JR, Chang HH, Sarnat SE, Peng RD, Waller LA. 2015. Current Methods and Challenges for Epidemiological Studies of the Associations Between Chemical Constituents of Particulate Matter and Health. Curr Environ Health Rep. 2(4):388–398.

Krewski D, Burnett R, Goldberg M, Hoover BK, Siemiatycki J, Jerrett M, Abrahamowicz M, White W. 2003. Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of particulate air pollution and mortality. J Toxicol Environ Health A. 66(16-19):1507–52.

Krewski D, Burnett R, Jerrett M, Pope III CA, Rainham D, Calle E, Thurston G, Thun M. 2005. Mortality and long-term exposure to ambient air pollution: Ongoing analyses based on the American Cancer Society Cohort. J Toxicol Environ Health A. 68(13-14):1093–109.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, Abrahamowicz M, White W. 2000. Reanalysis oft the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality. Boston, MA: Health Effects Institute. Special Report. www.healtheffects.org/publication/reanalysis-harvard-six-cities-study-and-american-cancer-society-study-particulate-air.

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope III CA, Thurston G, Calle EE. 2009. Extended follow-up and spatial analysis of the American Cancer Society Study linking particulate air pollution and mortality. Boston, MA: Health Effects Institute. Research Report 140. www.healtheffects.org/publication/extended-follow-and-spatial-analysis-american-cancer-society-study-linking-particulate.

Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, O'Neill MS, Herrington DM, Polak JF, Kaufman JD. 2012. Vascular responses to long-and short-term exposure to fine particulate matter: MESA air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). J Am Coll Cardiol. 60(21):2158–66.

Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, Medina M, Peters J, Hodis HN, Mack WJ. 2010. Ambient air pollution and the progression of atherosclerosis in adults. PloS One. 5(2):e9096.

Kurhanewicz N, McIntosh-Kastrinsky R, Tong H, Walsh L, Farraj AK, Hazari MS. 2014. Ozone co-exposure modifies cardiac responses to fine and ultrafine ambient particulate matter in mice: Concordance of electrocardiogram and mechanical responses. Part Fibre Toxicol. 11(1):54.

Laden F, Schwartz J, Speizer FE, Dockery DW. 2006. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities Study. Am J Respir Crit Care Med. 173(6):667–72.

Lamichhane DK, Leem JH, Lee JY, Kim HC. 2015. A meta-analysis of exposure to particulate matter and adverse birth outcomes. Environ Health Toxicol. 30:e2015011.

Lanzinger S, Breitner S, Neas L, Cascio W, Diaz-Sanchez D, Hinderliter A, Peters A, Devlin RB, Schneider A. 2014. The impact of decreases in air temperature and increases in ozone on markers of endothelial function in individuals having type-2 diabetes. Environ Res. 134:331–8.

Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, Escobedo L, Wu J. 2016a. Low birth weight and air pollution in California: Which sources and components drive the risk? Environ Int. 92:471–7.

Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, Escobedo L, Wu J. 2016b. A statewide nested case-control study of preterm birth and air pollution by source and composition: California, 2001–2008. Environ Health Perspect. 124(9):1479–86.

Lavigne E, Ashley-Martin J, Dodds L, Arbuckle TE, Hystad P, Johnson M, Crouse DL, Ettinger AS, Shapiro GD, Fisher M. 2016a. Air pollution exposure during pregnancy and fetal markers of metabolic function: The MIREC study. Am J Epidemiol. 183(9):842–51.

Lavigne E, Yasseen III AS, Stieb DM, Hystad P, Van Donkelaar A, Martin RV, Brook JR, Crouse DL, Burnett RT, Chen H. 2016b. Ambient air pollution and adverse birth outcomes: Differences by maternal comorbidities. Environ Res. 148:457–66.

Lee M, Koutrakis P, Coull B, Kloog I, Schwartz J. 2016. Acute effect of fine particulate matter on mortality in three southeastern states from 2007–2011. J Expo Sci Environ Epidemiol. 26(2):173.

Lee P, Roberts JM, Catov JM, Talbott EO, Ritz B. 2013. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny county, PA. Matern Child Health J. 17(3):545–55.

Lee P, Talbott EO, Roberts JM, Catov JM, Bilonick RA, Stone RA, Sharma RK, Ritz B. 2012. Ambient air pollution exposure and blood pressure changes during pregnancy. Environ Res. 117:46–53.

Lee PC, Talbott EO, Roberts JM, Catov JM, Sharma RK, Ritz B. 2011. Particulate air pollution exposure and C-reactive protein during early pregnancy. Epidemiology. 22(4):524–31.

Legro RS, Sauer MV, Mottla GL, Richter KS, Li X, Dodson WC, Liao D. 2010. Effect of air quality on assisted human reproduction. Hum Reprod. 25(5):1317–24.

Lepeule J, Laden F, Dockery D, Schwartz J. 2012. Chronic exposure to fine particles and mortality: An extended follow-up of the Harvard Six Cities Study from 1974 to 2009. Environ Health Perspect. 120(7):965–70.

Levy JI, Diez D, Dou Y, Barr CD, Dominici F. 2012. A meta-analysis and multisite time-series analysis of the differential toxicity of major fine particulate matter constituents. Am J Epidemiol. 175(11):1091–9.

Li MH, Fan LC, Mao B, Yang JW, Choi AMK, Cao WJ, Xu JF. 2016. Short-term exposure to ambient fine particulate matter increases hospitalizations and mortality in COPD: A systematic review and meta-analysis. Chest. 149(2):447–58.

Li W, Wilker EH, Dorans KS, Rice MB, Schwartz J, Coull BA, Koutrakis P, Gold DR, Keaney JF Jr, Lin H, et al. 2016. Short-term exposure to air pollution and biomarkers of oxidative stress: The Framingham Heart Study. J Am Heart Assoc. 5(5):e002742.

Li X, Hao L, Liu Y, Chen C, Pai VJ, Kang JX. 2017. Protection against fine particle-induced pulmonary and systemic inflammation by omega-3 polyunsaturated fatty acids. Biochimica et Biophysica Acta (BBA)—General Subjects. 1861(3):577–84.

Liao D, Whitsel EA, Duan Y, Lin HM, Quibrera PM, Smith R, Peuquet DJ, Prineas RJ, Zhang ZM, Anderson G. 2009. Ambient particulate air pollution and ectopy—the environmental epidemiology of arrhythmogenesis in Women's Health Initiative study, 1999–2004. J Toxicol Environ Health A. 72(1):30–8.

Lim H, Kwon HJ, Lim JA, Choi JH, Ha M, Hwang SS, Choi WJ. 2016. Short-term effect of fine particulate matter on children's hospital admissions and emergency department visits for asthma: A systematic review and meta-analysis. J Prev Med Public Health. 49(4):205–19.

Lipfert F, Baty J, Miller J, Wyzga R. 2006. $PM_{2.5}$ constituents and related air quality variables as predictors of survival in a cohort of US military veterans. Inhal Toxicol. 18(9):645–57.

Lippmann M, Chen LC, Gordon T, Ito K, Thurston GD. 2013. National particle component toxicity (NPACT) initiative: Integrated epidemiologic and toxicologic studies of the health effects of particulate matter components. Res Rep Health Eff Inst. (177):5–13.

Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L. 2011. Long-term exposure to air pollution and cardiorespiratory disease in the California Teachers Study cohort. Am J Respir Crit Care Med. 184(7):828–35.

Lipsett MJ, Tsai FC, Roger L, Woo M, Ostro BD. 2006. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. Environ Health Perspect. 114(8):1215–20.

Liu C, Fonken LK, Wang A, Maiseyeu A, Bai Y, Wang T, Maurya S, Ko Y, Periasamy M, Dvonch T. 2014c. Central IKKβ inhibition prevents air pollution mediated peripheral inflammation and exaggeration of type II diabetes. Part Fibre Toxicol. 11(1):53.

Liu C, Xu X, Bai Y, Wang TY, Rao X, Wang A, Sun L, Ying Z, Gushchina L, Maiseyeu A, et al. 2014b. Air pollution-mediated susceptibility to inflammation and insulin resistance: Influence of CCR2 pathways in mice. Environ Health Perspect. 122(1):17–26.

Liu L, Kauri LM, Mahmud M, Weichenthal S, Cakmak S, Shutt R, You H, Thomson E, Vincent R, Kumarathasan P, et al. 2014a. Exposure to air pollution near a steel plant and effects on cardiovascular physiology: A randomized crossover study. Int J Hyg Environ Health. 217(2-3):279–86.

Liu L, Poon R, Chen L, Frescura AM, Montuschi P, Ciabattoni G, Wheeler A, Dales R. 2009. Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. Environ Health Perspect. 117(4):668–74.

Liu R, Young MT, Chen JC, Kaufman JD, Chen H. 2016. Ambient air pollution exposures and risk of Parkinson disease. Environ Health Perspect. 124(11):1759–65.

Luttmann-Gibson H, Suh HH, Coull BA, Dockery DW, Sarnat SE, Schwartz J, Stone PH, Gold DR. 2006. Short-term effects of air pollution on heart rate variability in senior adults in Steubenville, Ohio. J Occup Environ Med. 48(8):780–8.

Mahalingaiah S, Hart J, Laden F, Farland L, Hewlett M, Chavarro J, Aschengrau A, Missmer S. 2016. Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. Hum Reprod. 31(3):638–47.

Mahalingaiah S, Hart JE, Laden F, Terry KL, Boynton-Jarrett R, Aschengrau A, Missmer SA. 2014. Air pollution and risk of uterine leiomyomata. Epidemiology. 25(5):682–8.

Maikawa CL, Weichenthal S, Wheeler AJ, Dobbin NA, Smargiassi A, Evans G, Liu L, Goldberg MS, Pollitt KJ. 2016. Particulate oxidative burden as a predictor of exhaled nitric oxide in children with asthma. Environ Health Perspect. 124(10):1616–22.

Malig BJ, Green S, Basu R, Broadwin R. 2013. Coarse particles and respiratory emergency department visits in California. Am J Epidemiol. 178(1):58–69.

Mauad T, Rivero, Dolores Helena Rodriguez Ferreira, de Oliveira RC, de Faria Coimbra Lichtenfels, Ana Julia, Guimarães ET, de Andre PA, Kasahara DI, de Siqueira Bueno, Heloisa Maria, Saldiva PHN. 2008. Chronic exposure to ambient levels of urban particles affects mouse lung development. Am J Respir Crit Care Med. 178(7):721–8.

McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, Gauderman J, Avol E, Kunzli N, Yao L, et al. 2010. Childhood incident asthma and traffic-related air pollution at home and school. Environ Health Perspect. 118(7):1021–6.

McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE. 2000. Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. J Expo Sci Environ Epidemiol. 10(5):427.

McGuinn LA, Ward-Caviness CK, Neas LM, Schneider A, Diaz-Sanchez D, Cascio WE, Kraus WE, Hauser E, Dowdy E, Haynes C. 2016. Association between satellite-based estimates of long-term $PM_{2.5}$ exposure and coronary artery disease. Environ Res. 145:9–17.

McKean-Cowdin R, Calle EE, Peters JM, Henley J, Hannan L, Thurston GD, Thun MJ, Preston-Martin S. 2009. Ambient air pollution and brain cancer mortality. Cancer Causes & Control. 20(9):1645–51.

Mendola P, Wallace M, Hwang BS, Liu D, Robledo C, Männistö T, Sundaram R, Sherman S, Ying Q, Grantz KL. 2016b. Preterm birth and air pollution: Critical windows of exposure for women with asthma. J Allergy Clin Immunol. 138(2):432–440.e5.

Mendola P, Wallace M, Liu D, Robledo C, Männistö T, Grantz KL. 2016a. Air pollution exposure and preeclampsia among US women with and without asthma. Environ Res. 148:248–55.

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med. 356(5):447–58.

Mills IC, Atkinson RW, Anderson HR, Maynard RL, Strachan DP. 2016. Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: A systematic review and meta-analysis. BMJ Open. 6(7):e010751.

Mirabelli MC, Golan R, Greenwald R, Raysoni AU, Holguin F, Kewada P, Winquist A, Flanders WD, Sarnat JA. 2015. Modification of traffic-related respiratory response by asthma control in a population of car commuters. Epidemiology. 26(4):546–55.

Moolgavkar SH. 2003. Air pollution and daily mortality in two US counties: Season-specific analyses and exposure-response relationships. Inhal Toxicol. 15(9):877–907.

Mordukhovich I, Coull B, Kloog I, Koutrakis P, Vokonas P, Schwartz J. 2015. Exposure to sub-chronic and long-term particulate air pollution and heart rate variability in an elderly cohort: The Normative Aging Study. Environ Health. 14(1):87.

Mordukhovich I, Kloog I, Coull B, Koutrakis P, Vokonas P, Schwartz J. 2016. Association between particulate air pollution and QT interval duration in an elderly cohort. Epidemiology. 27(2):284–90.

Morello-Frosch R, Jesdale BM, Sadd JL, Pastor M. 2010. Ambient air pollution exposure and full-term birth weight in California. Environ Health. 9(1):44.

Mostofsky E, Schwartz J, Coull BA, et al. 2012. Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol. 176(4):317–326.

Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. 2010. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. Am J Respir Crit Care Med. 181(1):47–53.

Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, Thyne S, Farber HJ, Serebrisky D, Kumar R. 2013. Early-life air pollution and asthma risk in minority children. the GALA II and SAGE II studies. Am J Respir Crit Care Med. 188(3):309–18.

O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, Evans III R, Gruchalla R, Morgan W, Stout J. 2008. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol. 121(5):1133–1139.e1.

O'Neal WT, Soliman EZ, Efird JT, Howard VJ, Howard G, McClure LA. 2017a. Fine particulate air pollution and premature ventricular contractions: The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Environ Res. 154:115–9.

O'Neal WT, Soliman EZ, Efird JT, Judd SE, Howard VJ, Howard G, McClure LA. 2017b. Fine particulate air pollution and premature atrial contractions: The REasons for Geographic and Racial Differences in Stroke Study. J Expo Sci Environ Epidemiol. 27(3):271–5.

O'Neill MS, Veves A, Sarnat JA, Zanobetti A, Gold DR, Economides PA, Horton ES, Schwartz J. 2007. Air pollution and inflammation in type 2 diabetes: A mechanism for susceptibility. Occup Environ Med. 64(6):373–9.

Oakes M, Baxter L, Long TC. 2014. Evaluating the application of multipollutant exposure metrics in air pollution health studies. Environ Int. 69:90–9.

Ostro B, Broadwin R, Green S, Feng WY, Lipsett M. 2006. Fine particulate air pollution and mortality in nine California counties: Results from CALFINE. Environ Health Perspect. 114(1):29–33.

Ostro B, Feng WY, Broadwin R, Green S, Lipsett M. 2007. The effects of components of fine particulate air pollution on mortality in California: results from CALFINE. Environ Health Perspect. 115(1):13–9.

Ostro B, Hu J, Goldberg D, Reynolds P, Hertz A, Bernstein L, Kleeman MJ. 2015. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: Results from the California Teachers Study cohort. Environ Health Perspect. 123(6):549–56.

Ostro B, Lipsett M, Reynolds P, Goldberg D, Hertz A, Garcia C, Henderson KD, Bernstein L. 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: Results from the California Teachers Study. Environ Health Perspect. 118(3):363–9.

Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, Derby C, Feinstein S, Greendale GA, Jackson EA. 2014. Chronic $PM_{2.5}$ exposure and inflammation: Determining sensitive subgroups in mid-life women. Environ Res. 132:168–75.

Ostro B, Malig B, Hasheminassab S, Berger K, Chang E, Sioutas C. 2016. Associations of source-specific fine particulate matter with emergency department visits in California. Am J Epidemiol. 184(6):450–9.

Ostro B, Reynolds P, Goldberg D, Hertz A, Burnett RT, Shin H, Hughes E, Garcia C, Henderson KD, Bernstein L. 2011. Assessing long-term exposure in the California Teachers Study. Environ Health Perspect. 119(6):A242–3.

Ostro B, Roth L, Malig B, Marty M. 2009. The effects of fine particle components on respiratory hospital admissions in children. Environ Health Perspect. 117(3):475–80.

Ostro BD, Feng WY, Broadwin R, Malig BJ, Green RS, Lipsett MJ. 2008. The impact of components of fine particulate matter on cardiovascular mortality in susceptible subpopulations. Occup Environ Med. 65(11):750–6.

Padula AM, Tager IB, Carmichael SL, Hammond SK, Yang W, Lurmann F, Shaw GM. 2013a. Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin valley of California. Paediatr Perinat Epidemiol. 27(4):329–39.

Padula AM, Tager IB, Carmichael SL, Hammond SK, Lurmann F, Shaw GM. 2013b. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin valley of California. Am J Epidemiol. 177(10):1074–85.

Palacios N, Fitzgerald KC, Hart JE, Weisskopf MG, Schwarzschild MA, Ascherio A, Laden F. 2014. Particulate matter and risk of parkinson disease in a large prospective study of women. Environ Health. 13(1):80.

Park SK, Adar SD, O'Neill MS, Auchincloss AH, Szpiro A, Bertoni AG, Navas-Acien A, Kaufman JD, Diez-Roux AV. 2015. Long-term exposure to air pollution and type 2 diabetes mellitus in a multiethnic cohort. Am J Epidemiol. 181(5):327–36.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. 2005. Effects of air pollution on heart rate variability: The VA Normative Aging Study. Environ Health Perspect. 113(3):304–9.

Parker JD, Akinbami LJ, Woodruff TJ. 2009. Air pollution and childhood respiratory allergies in the United States. Environ Health Perspect. 117(1):140–7.

Patel MM, Chillrud SN, Correa JC, Hazi Y, Feinberg M, Kc D, Prakash S, Ross JM, Levy D, Kinney PL. 2010. Traffic-related particulate matter and acute respiratory symptoms among New York City area adolescents. Environ Health Perspect. 118(9):1338–43.

Pedersen M, Stayner L, Slama R, Sørensen M, Figueras F, Nieuwenhuijsen MJ, Raaschou-Nielsen O, Dadvand P. 2014. Ambient air pollution and pregnancy-induced hypertensive disorders: A systematic review and meta-analysis. Hypertension. 64(3):494–500.

Peng C, Bind MC, Colicino E, Kloog I, Byun HM, Cantone L, Trevisi L, Zhong J, Brennan K, Dereix AE, et al. 2016. Particulate air pollution and fasting blood glucose in nondiabetic individuals: Associations and epigenetic mediation in the Normative Aging Study, 2000–2011. Environ Health Perspect. 124(11):1715–21.

Peng RD, Chang HH, Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. 2008. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. JAMA. 299(18):2172–9.

Peng RD, Bell ML, Geyh AS, McDermott A, Zeger SL, Samet JM, Dominici F. 2009. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. Environ Health Perspect. 117(6):957–63.

Pereira G, Belanger K, Ebisu K, Bell ML. 2014. Fine particulate matter and risk of preterm birth in Connecticut in 2000–2006: A longitudinal study. Am J Epidemiol. 179(1):67–74.

Pereira G, Evans KA, Rich DQ, Bracken MB, Bell ML. 2016. Fine particulates, preterm birth, and membrane rupture in Rochester, NY. Epidemiology. 27(1):66–73.

Pinault L, Tjepkema M, Crouse DL, Weichenthal S, van Donkelaar A, Martin RV, Brauer M, Chen H, Burnett RT. 2016. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian Community Health Survey cohort. Environ Health. 15(1):18.

Pope III CA, Bhatnagar A, McCracken JP, Abplanalp W, Conklin DJ, O'Toole T. 2016. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ Res. 119(11):1204–14.

Pope III CA, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. 2009. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: Shape of the exposure-response relationship. Circulation. 120(11):941–8.

Pope III CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 287(9):1132–41.

Pope III CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. Circulation. 109(1):71–7.

Pope III CA, Burnett RT, Turner MC, Cohen A, Krewski D, Jerrett M, Gapstur SM, Thun MJ. 2011. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: Shape of the exposure-response relationships. Environ Health Perspect. 119(11):1616–21.

Pope III CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med. 151(3 Pt 1):669–74.

Pope III CA, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, Krewski D, Brook RD. 2015. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. Circ Res. 116(1):108–15.

Powell H, Krall JR, Wang Y, Bell ML, Peng RD. 2015. Ambient coarse particulate matter and hospital admissions in the Medicare cohort air pollution study, 1999–2010. Environ Health Perspect. 123(11):1152–8.

Public Health Agency of Canada. 2017. Heart disease in Canada: Highlights from the Canadian chronic disease surveillance system. Government of Canada, catalogue no. HP35-85/2017E-PDF. 5 pp. www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/heart-disease-fact-sheet/heart-disease-factsheet-eng.pdf.

Puett RC, Hart JE, Suh H, Mittleman M, Laden F. 2011a. Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. Environ Health Perspect. 119(8):1130–5.

Puett RC, Hart JE, Schwartz J, Hu FB, Liese AD, Laden F. 2011b. Are particulate matter exposures associated with risk of type 2 diabetes? Environ Health Perspect. 119(3):384–9.

Puett RC, Hart JE, Yanosky JD, Paciorek C, Schwartz J, Suh H, Speizer FE, Laden F. 2009. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. Environ Health Perspect. 117(11):1697–701.

Puett RC, Hart JE, Yanosky JD, Spiegelman D, Wang M, Fisher JA, Hong B, Laden F. 2014. Particulate matter air pollution exposure, distance to road, and incident lung cancer in the nurses' health study cohort. Environ Health Perspect. 122(9):926–32.

Pun VC, Hart JE, Kabrhel C, Camargo CA Jr, Baccarelli AA, Laden F. 2015. Prospective study of ambient particulate matter exposure and risk of pulmonary embolism in the Nurses' Health Study cohort. Environ Health Perspect. 123(12):1265–70.

Quan C, Sun Q, Lippmann M, Chen L. 2010. Comparative effects of inhaled diesel exhaust and ambient fine particles on inflammation, atherosclerosis, and vascular dysfunction. Inhal Toxicol. 22(9):738–53.

Raffaele KC, Vulimiri SV, Bateson TF. 2011. Benefits and barriers to using epidemiology data in environmental risk assessment. Open Epidemiol J. 411(99):99–105.

Rappold AG, Cascio WE, Kilaru VJ, Stone SL, Neas LM, Devlin RB, Diaz-Sanchez D. 2012. Cardio-respiratory outcomes associated with exposure to wildfire smoke are modified by measures of community health. Environ Health. 11(1):71.

Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, Weisskopf MG. 2015. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: A nested case-control analysis within the nurses' health study II cohort. Environ Health Perspect. 123(3):264–70.

Reding KW, Young MT, Szpiro AA, Han CJ, DeRoo LA, Weinberg C, Kaufman JD, Sandler DP. 2015. Breast cancer risk in relation to ambient air pollution exposure at residences in the sister study cohort. Cancer Epidemiol Biomarkers Prev. 24(12):1907–9.

Reid CE, Jerrett M, Tager IB, Petersen ML, Mann JK, Balmes JR. 2016. Differential respiratory health effects from the 2008 Northern California wildfires: A spatiotemporal approach. Environ Res. 150:227–35.

Ren C, Baccarelli A, Wilker E, Suh H, Sparrow D, Vokonas P, Wright R, Schwartz J. 2010. Lipid and endothelium-related genes, ambient particulate matter, and heart rate variability--the VA Normative Aging Study. J Epidemiol Community Health. 64(1):49–56.

Ren C, Fang S, Wright RO, Suh H, Schwartz J. 2011. Urinary 8-hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage induced by ambient pollution in the Normative Aging Study. Occup Environ Med. 68(8):562–9.

Rice MB, Ljungman PL, Wilker EH, Dorans KS, Gold DR, Schwartz J, Koutrakis P, Washko GR, O'Connor GT, Mittleman MA. 2015. Long-term exposure to traffic emissions and fine particulate matter and lung function decline in the Framingham Heart Study. Am J Respir Crit Care Med. 191(6):656–64.

Rice MB, Rifas-Shiman SL, Litonjua AA, Oken E, Gillman MW, Kloog I, Luttmann-Gibson H, Zanobetti A, Coull BA, Schwartz J. 2016. Lifetime exposure to ambient pollution and lung function in children. Am J Respir Crit Care Med. 193(8):881–8.

Rich DQ, Demissie K, Lu SE, Kamat L, Wartenberg D, Rhoads GG. 2009. Ambient air pollutant concentrations during pregnancy and the risk of fetal growth restriction. J Epidemiol Community Health. 63(6):488–96.

Rich DQ, Zareba W, Beckett W, Hopke PK, Oakes D, Frampton MW, Bisognano J, Chalupa D, Bausch J, O'Shea K, et al. 2012. Are ambient ultrafine, accumulation mode, and fine particles associated with adverse cardiac responses in patients undergoing cardiac rehabilitation? Environ Health Perspect. 120(8):1162–9.

Robledo CA, Mendola P, Yeung E, Männistö T, Sundaram R, Liu D, Ying Q, Sherman S, Grantz KL. 2015. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environ Res. 137:316–22.

Sacks JD, Stanek LW, Luben TJ, Johns DO, Buckley BJ, Brown JS, et al. 2011. Particulate matter-induced health effects: Who is susceptible? Environ Health Perspect. 119(4):446–454.

Salihu HM, Ghaji N, Mbah AK, Alio AP, August EM, Boubakari I. 2012. Particulate pollutants and racial/ethnic disparity in feto-infant morbidity outcomes. Matern Child Health J. 16(8):1679–87.

Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. 2012. Exposure to particulate matter and adverse birth outcomes: A comprehensive review and meta-analysis. Air Qual Atmos Health. 5(4):369–81.

Savitz DA, Bobb JF, Carr JL, Clougherty JE, Dominici F, Elston B, Ito K, Ross Z, Yee M, Matte TD. 2014. Ambient fine particulate matter, nitrogen dioxide, and term birth weight in New York, New York. Am J Epidemiol. 179(4):457–66.

Schneider A, Neas LM, Graff DW, Herbst MC, Cascio WE, Schmitt MT, Buse JB, Peters A, Devlin RB. 2010. Association of cardiac and vascular changes with ambient $PM_{2.5}$ in diabetic individuals. Part Fibre Toxicol. 7:14.

Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier R, Stone P, MacCallum G, et al. 2005. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax. 60(6):455–61.

Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. 2015. Short term exposure to air pollution and stroke: Systematic review and meta-analysis. BMJ. 350:h1295.

Shi L, Zanobetti A, Kloog I, Coull BA, Koutrakis P, Melly SJ, Schwartz JD. 2016. Low-concentration $PM_{2.5}$ and mortality: Estimating acute and chronic effects in a population-based study. Environ Health Perspect. 124(1):46–52.

Shih RA, Griffin BA, Salkowski N, Jewell A, Eibner C, Bird CE, Liao D, Cushman M, Margolis HG, Eaton CB, et al. 2011. Ambient particulate matter air pollution and venous thromboembolism in the Women's Health Initiative hormone therapy trials. Environ Health Perspect. 119(3):326–31.

Shutt RH, Kauri LM, Weichenthal S, Kumarathasan P, Vincent R, Thomson EM, Liu L, Mahmud M, Cakmak S, Dales R. 2017. Exposure to air pollution near a steel plant is associated with reduced heart rate variability: A randomised crossover study. Environ Health. 16(1):4.

Sivagangabalan G, Spears D, Masse S, Urch B, Brook RD, Silverman F, Gold DR, Lukic KZ, Speck M, Kusha M. 2011. The effect of air pollution on spatial dispersion of myocardial repolarization in healthy human volunteers. J Am Coll Cardiol. 57(2):198–206.

Slaughter JC, Kim E, Sheppard L, Sullivan JH, Larson TV, Claiborn C. 2005. Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. J Expo Sci Environ Epidemiol. 15(2):153.

Slaughter JC, Lumley T, Sheppard L, Koenig JQ, Shapiro GG. 2003. Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann Allergy Asthma Immunol. 91(4):346–53.

Sorek-Hamer M, Just AC, Kloog I. 2016. The use of satellite remote sensing in epidemiological studies. Curr Opin Pediatr. 28(2):228.

Stieb DM, Chen L, Eshoul M, Judek S. 2012. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. Environ Res. 117:100–11.

Stieb DM, Chen L, Beckerman BS, Jerrett M, Crouse DL, Omariba DW, Peters PA, van Donkelaar A, Martin RV, Burnett RT, et al. 2016a. Associations of pregnancy outcomes and $PM_{2.5}$ in a national Canadian study. Environ Health Perspect. 124(2):243–9.

Stieb DM, Chen L, Hystad P, Beckerman BS, Jerrett M, Tjepkema M, Crouse DL, Omariba DW, Peters PA, van Donkelaar A. 2016b. A national study of the association between traffic-related air pollution and adverse pregnancy outcomes in Canada, 1999–2008. Environ Res. 148:513–26.

Stieb DM, Szyszkowicz M, Rowe BH, Leech JA. 2009. Air pollution and emergency department visits for cardiac and respiratory conditions: A multi-city time-series analysis. Environ Health. 8(1):25.

Stieb DM, Yao J, Henderson SB, Pinault L, Smith-Doiron MH, Robichaud A, van Donkelaar A, Martin RV, Ménard R, Brook JR. 2019. Variability in ambient ozone and fine particle concentrations and population susceptibility among Canadian health regions. Can J Public Health. 110:149–158.

Stingone JA, Luben TJ, Daniels JL, Fuentes M, Richardson DB, Aylsworth AS, Herring AH, Anderka M, Botto L, Correa A, et al. 2014. Maternal exposure to criteria air pollutants and congenital heart defects in offspring: Results from the national birth defects prevention study. Environ Health Perspect. 122(8):863–72.

Sun M, Kaufman JD, Kim S, Larson TV, Gould TR, Polak JF, Budoff MJ, Roux AVD, Vedal S. 2013. Particulate matter components and subclinical atherosclerosis: Common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study. Environ Health. 12(1):39.

Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, Cai Y, Ostrowski MC, Lu B, Parthasarathy S, et al. 2009. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation. 119(4):538–46.

Sun X, Luo X, Zhao C, Zhang B, Tao J, Yang Z, Ma W, Liu T. 2016. The associations between birth weight and exposure to fine particulate matter ($PM_{2.5}$) and its chemical constituents during pregnancy: A meta-analysis. Environ Pollut. 211:38–47.

Talbott EO, Arena VC, Rager JR, Clougherty JE, Michanowicz DR, Sharma RK, Stacy SL. 2015. Fine particulate matter and the risk of autism spectrum disorder. Environ Res. 140:414–20.

Tan H, Fiel MI, Sun Q, Guo J, Gordon RE, Chen L, Friedman SL, Odin JA, Allina J. 2009. Kupffer cell activation by ambient air particulate matter exposure may exacerbate non-alcoholic fatty liver disease. J Immunotoxicol. 6(4):266–75.

Tankersley CG, Champion HC, Takimoto E, Gabrielson K, Bedja D, Misra V, El-Haddad H, Rabold R, Mitzner W. 2008. Exposure to inhaled particulate matter impairs cardiac function in senescent mice. Am J Physiol Regul Integr Comp Physiol. 295(1):R252–63.

Tanner JP, Salemi JL, Stuart AL, Yu H, Jordan MM, DuClos C, Cavicchia P, Correia JA, Watkins SM, Kirby RS. 2015. Associations between exposure to ambient benzene and PM2. 5 during pregnancy and the risk of selected birth defects in offspring. Environ Res. 142:345–53.

Tétreault L, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, Smargiassi A. 2016. Severe and moderate asthma exacerbations in asthmatic children and exposure to ambient air pollutants. Int J Environ Res Public Health. 13(8):771.

Thompson AM, Zanobetti A, Silverman F, Schwartz J, Coull B, Urch B, Speck M, Brook JR, Manno M, Gold DR. 2010. Baseline repeated measures from controlled human exposure studies: Associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. Environ Health Perspect. 118(1):120–4.

Thurston G, Ito K, Lall R, Burnett R, Turner M, Krewski D, Shi Y, Jerrett M, Gapstur S, Diver W. 2013. NPACT study 4: Mortality and long-term exposure to $PM_{2.5}$ and its components in the American Cancer Society's cancer prevention study II cohort. Boston, MA: Health Effects Institute. Report 177. www.healtheffects.org/system/files/RR177-Lippmann.pdf.

Thurston GD, Ahn J, Cromar KR, Shao Y, Reynolds HR, Jerrett M, Lim CC, Shanley R, Park Y, Hayes RB. 2016a. Ambient particulate matter air pollution exposure and mortality in the NIH-AARP diet and health cohort. Environ Health Perspect. 124(4):484–90.

Thurston GD, Burnett RT, Turner MC, Shi Y, Krewski D, Lall R, Ito K, Jerrett M, Gapstur SM, Diver WR. 2016b. Ischemic heart disease mortality and long-term exposure to source-related components of US fine particle air pollution. Environ Health Perspect. 124(6):785.

To T, Feldman L, Simatovic J, Gershon AS, Dell S, Su J, Foty R, Licskai C. 2015a. Health risk of air pollution on people living with major chronic diseases: A Canadian population-based study. BMJ Open. 5(9):e009075.

To T, Zhu J, Larsen K, Simatovic J, Feldman L, Ryckman K, Gershon A, Lougheed MD, Licskai C, Chen H. 2016. Progression from asthma to chronic obstructive pulmonary disease. is air pollution a risk factor? Am J Respir Crit Care Med. 194(4):429–38.

To T, Zhu J, Villeneuve PJ, Simatovic J, Feldman L, Gao C, Williams D, Chen H, Weichenthal S, Wall C. 2015b. Chronic disease prevalence in women and air pollution—a 30-year longitudinal cohort study. Environ Int. 80:26–32.

Tolbert PE, Klein M, Peel JL, Sarnat SE, Sarnat JA. 2007. Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol. 17(2):S29–35.

Toledo-Corral CM, Alderete TL, Habre R, Berhane K, Lurmann FW, Weigensberg MJ, Goran MI, Gilliland FD. 2016. Effects of air pollution exposure on glucose metabolism in Los Angeles minority children. Pediatr Obes.13: 54–62 epub ahead of print.

Tomczak A, Miller AB, Weichenthal SA, To T, Wall C, van Donkelaar A, Martin RV, Crouse DL, Villeneuve PJ. 2016. Long-term exposure to fine particulate matter air pollution and the risk of lung cancer among participants of the Canadian National Breast Screening Study. Int J Cancer. 139(9):1958–66.

Tomino Y. 2012. Lessons from the KK-ay mouse, a spontaneous animal model for the treatment of human type 2 diabetic nephropathy. Nephrourol Mon. 4(3):524–9.

Tong H, Rappold AG, Caughey M, Hinderliter AL, Bassett M, Montilla T, Case MW, Berntsen J, Bromberg PA, Cascio WE, et al. 2015. Dietary supplementation with olive oil or fish oil and vascular effects of concentrated ambient particulate matter exposure in human volunteers. Environ Health Perspect. 123(11):1173–9.

Tong H, Rappold AG, Diaz-Sanchez D, Steck SE, Berntsen J, Cascio WE, Devlin RB, Samet JM. 2012. Omega-3 fatty acid supplementation appears to attenuate particulate air pollution-induced cardiac effects and lipid changes in healthy middle-aged adults. Environ Health Perspect. 120(7):952–7.

Turner MC, Jerrett M, Pope III CA, Krewski D, Gapstur SM, Diver WR, Beckerman BS, Marshall JD, Su J, Crouse DL. 2016. Long-term ozone exposure and mortality in a large prospective study. Am J Respir Crit Care Med. 193(10):1134–42.

Turner MC, Krewski D, Pope III CA, Chen Y, Gapstur SM, Thun MJ. 2011. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med. 184(12):1374–81.

U.S. Environmental Protection Agency (US EPA). 2009. Integrated science assessment (ISA) for particulate matter. Washington, DC: U.S. Environmental Protection Agency. Report No. EPA/600/R-08/139F. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=523390.

U.S. Environmental Protection Agency (US EPA). 2015. Preamble to the integrated science assessments (ISA). Washington, DC: U.S. Environmental Protection Agency. Report No. EPA/600/R-15/067. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=526136.

U.S. Environmental Protection Agency (US EPA). 2019. Integrated science assessment (ISA) for particulate matter (final report, Dec 2019). Washington, DC: U.S. Environmental Protection Agency. Report No. EPA/600/R-19/188. https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=539935.

Urch B, Brook JR, Wasserstein D, Brook RD, Rajagopalan S, Corey P, and Silverman F. 2004. Relative contributions of $PM_{2.5}$ chemical constituents to acute arterial vasoconstriction in humans. Inhal Toxicol 16(6-7):345–52.

Urch B, Speck M, Corey P, Wasserstein D, Manno M, Lukic KZ, Brook JR, Liu L, Coull B, and Schwartz J. 2010. Concentrated ambient fine particles and not ozone induce a systemic interleukin-6 response in humans. Inhal Toxicol. 22(3):210–18.

Valavanidis A, Vlachogianni T, Fiotakis K, Loridas S. 2013. Pulmonary oxidative stress, inflammation and cancer: Respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. Int J Environ Res Public Health. 10(9):3886–3907.

Vedal S, Campen MJ, McDonald JD, Larson TV, Sampson PD, Sheppard L, Simpson CD, Szpiro AA. 2013. National Particle Component Toxicity (NPACT) initiative report on cardiovascular effects. Boston, MA: Health Effects Institute. Report No. 178. 8 p. www.healtheffects.org/publication/national-particle-component-toxicity-npact-initiative-report-cardiovascular-effects.

Villeneuve PJ, Burnett RT, Shi Y, Krewski D, Goldberg MS, Hertzman C, Chen Y, Brook J. 2003. A time-series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. J Expo Sci Environ Epidemiol. 13(6):427.

Villeneuve PJ, Goldberg MS, Krewski D, Burnett RT, Chen Y. 2002. Fine particulate air pollution and all-cause mortality within the Harvard Six-Cities Study: Variations in risk by period of exposure. Ann Epidemiol. 12(8):568–76.

Villeneuve PJ, Weichenthal SA, Crouse D, Miller AB, To T, Martin RV, van Donkelaar A, Wall C, Burnett RT. 2015. Long-term exposure to fine particulate matter air pollution and mortality among Canadian women. Epidemiology. 26(4):536–45.

Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. 2012. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. Paediatr Perinat Epidemiol. 26(2):91–100.

Vinikoor-Imler LC, Davis JA, Meyer RE, Luben TJ. 2013. Early prenatal exposure to air pollution and its associations with birth defects in a state-wide birth cohort from North Carolina. Birth Defects Res A: Clin Mol Teratol. 97(10):696–701.

Vinikoor-Imler LC, Stewart TG, Luben TJ, Davis JA, Langlois PH. 2015. An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas. Environ Pollut. 202:1–6.

Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry. 70(1):71–7.

Wagner JG, Allen K, Yang HY, Nan B, Morishita M, Mukherjee B, Dvonch JT, Spino C, Fink GD, Rajagopalan S, et al. 2014a. Cardiovascular depression in rats exposed to inhaled particulate matter and ozone: Effects of diet-induced metabolic syndrome. Environ Health Perspect. 122(1):27–33.

Wagner JG, Kamal AS, Morishita M, Dvonch JT, Harkema JR, Rohr AC. 2014. $PM_{2.5}$-induced cardiovascular dysregulation in rats is associated with elemental carbon and temperature-resolved carbon subfractions. Part Fibre Toxicol. 11(1):25.

Wagner JG, Morishita M, Keeler GJ, Harkema JR. 2012. Divergent effects of urban particulate air pollution on allergic airway responses in experimental asthma: A comparison of field exposure studies. Environ Health. 11(1):45.

Wan Q, Cui X, Shao J, Zhou F, Jia Y, Sun X, Zhao X, Chen Y, Diao J, Zhang L. 2014. Beijing ambient particle exposure accelerates atherosclerosis in ApoE knockout mice by upregulating visfatin expression. Cell Stress and Chaperones. 19(5):715–24.

Wang M, Utell MJ, Schneider A, Zareba W, Frampton MW, Oakes D, Hopke PK, Wiltshire J, Kane C, Peters A, et al. 2016. Does total antioxidant capacity modify adverse cardiac responses associated with ambient ultrafine, accumulation mode, and fine particles in patients undergoing cardiac rehabilitation? Environ Res. 149:15–22.

Wang Y, Eliot MN, Wellenius GA. 2014. Short-term changes in ambient particulate matter and risk of stroke: A systematic review and meta-analysis. J Am Heart Assoc. 3(4):e.000983.

Wasserstein RL, Lazar NA. 2016. The ASA Statement on p-Values: Context, Process, and Purpose. The American Statistician, 70:2, 129–133.

Weber SA, Insaf TZ, Hall ES, Talbot TO, Huff AK. 2016. Assessing the impact of fine particulate matter ($PM_{2.5}$) on respiratory-cardiovascular chronic diseases in the New York City metropolitan area using hierarchical Bayesian model estimates. Environ Res. 151:399–409.

Weichenthal S, Kulka R, Dubeau A, Martin C, Wang D, Dales R. 2011. Traffic-related air pollution and acute changes in heart rate variability and respiratory function in urban cyclists. Environ Health Perspect. 119(10):1373–8.

Weichenthal S, Hatzopoulou M, Goldberg MS. 2014a. Exposure to traffic-related air pollution during physical activity and acute changes in blood pressure, autonomic and micro-vascular function in women: A cross-over study. Part Fibre Toxicol. 11(1):70.

Weichenthal S, Villeneuve PJ, Burnett RT, van Donkelaar A, Martin RV, Jones RR, DellaValle CT, Sandler DP, Ward MH, Hoppin JA. 2014b. Long-term exposure to fine particulate matter: Association with nonaccidental and cardiovascular mortality in the agricultural health study cohort. Environ Health Perspect. 122(6):609–15.

Weichenthal S, Crouse DL, Pinault L, Godri-Pollitt K, Lavigne E, Evans G, van Donkelaar A, Martin RV, Burnett RT. 2016a. Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Res. 146:92–9.

Weichenthal S, Lavigne E, Evans G, Pollitt K, Burnett RT. 2016b. Ambient $PM_{2.5}$ and risk of emergency room visits for myocardial infarction: Impact of regional $PM_{2.5}$ oxidative potential: A case-crossover study. Environ Health. 15(1):46.

Weichenthal SA, Lavigne E, Evans GJ, Godri Pollitt KJ, Burnett RT. 2016c. Fine particulate matter and emergency room visits for respiratory illness. effect modification by oxidative potential. Am J Respir Crit Care Med. 194(5):577–86.

Wheeler A, Zanobetti A, Gold DR, Schwartz J, Stone P, Suh HH. 2006. The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. Environ Health Perspect. 114(4):560–6.

Wilker EH, Ljungman PL, Rice MB, Kloog I, Schwartz J, Gold DR, Koutrakis P, Vita JA, Mitchell GF, Vasan RS. 2014. Relation of long-term exposure to air pollution to brachial artery flow-mediated dilation and reactive hyperemia. Am J Cardiol. 113(12):2057–63.

Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, Li W, Schwartz J, Koutrakis P, DeCarli C. 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke. 46(5):1161–6.

Winters N, Goldberg MS, Hystad P, Villeneuve PJ, Johnson KC. 2015. Exposure to ambient air pollution in Canada and the risk of adult leukemia. Sci Total Environ. 526:153–76.

WHO. 2016. Global Urban Ambient Air Pollution Database, World Health Organization: www.who.int/phe/health_topics/outdoorair/databases/cities/en.

Woodruff TJ, Darrow LA, Parker JD. 2008. Air pollution and postneonatal infant mortality in the United States, 1999–2002. Environ Health Perspect. 116(1):110–5.

World Health Organization (WHO). 2006. Air quality guidelines: Global update 2005: Particulate matter, ozone, nitrogen dioxide, and sulfur dioxide. World Health Organization. www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/air-quality-guidelines.-global-update-2005.-particulate-matter,-ozone,-nitrogen-dioxide-and-sulfur-dioxide.

World Health Organization (WHO). 2013. Review of evidence on health aspects of air pollution–REVIHAAP project: Final technical report. WHO European Centre for Environment and Health. World Health Organization. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report.

World Health Organization (WHO). 2021. The global health observatory–Concentrations of fine particulate matter ($PM_{2.5}$). [Internet]. World Health Organization; c2021 [cited 2021 July]. Available from: www.who.int/data/gho/data/indicators/indicator-details/GHO/concentrations-of-fine-particulate-matter-(pm2-5).

Wu J, Laurent O, Li L, Hu J, Kleeman M. 2016. Adverse reproductive health outcomes and exposure to gaseous and particulate-matter air pollution in pregnant women. Boston, MA: Health Effects Institute. Report No. 188. 58 p. www.healtheffects.org/publication/adverse-reproductive-health-outcomes-and-exposure-gaseous-and-particulate-matter-air.

Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. 2009. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ Health Perspect. 117(11):1773–9.

Xiao Q, Liu Y, Mulholland JA, Russell AG, Darrow LA, Tolbert PE, Strickland MJ. 2016. Pediatric emergency department visits and ambient air pollution in the U.S. state of Georgia: A case-crossover study. Environ Health. 15(1):115.

Xu M, Zhu Y, Chang H, Liang Y. 2016. Nanoceria restrains $PM_{2.5}$-induced metabolic disorder and hypothalamus inflammation by inhibition of astrocytes activation related NF-κB pathway in Nrf2 deficient mice. Free Radical Biology and Medicine. 99:259–72.

Xu X, Hu H, Ha S, Roth J. 2014. Ambient air pollution and hypertensive disorder of pregnancy. J Epidemiol Community Health. 68(1):13–20.

Xu X, Yavar Z, Verdin M, Ying Z, Mihai G, Kampfrath T, Wang A, Zhong M, Lippmann M, Chen LC, et al. 2010. Effect of early particulate air pollution exposure on obesity in mice: Role of p47phox. Arterioscler Thromb Vasc Biol. 30(12):2518–27.

Xu XR, Carrim N, Neves MA, McKeown T, Stratton TW, Coelho RM, Lei X, Chen P, Xu J, Dai X, Li BX, Ni H. 2016 Platelets and platelet adhesion molecules: novel mechanisms of thrombosis and anti-thrombotic therapies. Thromb J. 14(Suppl 1):29.

Yan Y, Chou CC, Wang J, Tung C, Li Y, Lo K, Cheng T. 2014. Subchronic effects of inhaled ambient particulate matter on glucose homeostasis and target organ damage in a type 1 diabetic rat model. Toxicol Appl Pharmacol. 281(2):211–20.

Yang W, Zhao H, Wang X, Deng Q, Fan W, Wang L. 2016. An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. European Journal of Cancer Prevention. 25(3):163–72.

Ying Z, Xie X, Bai Y, Chen M, Wang X, Zhang X, Morishita M, Sun Q, Rajagopalan S. 2015. Exposure to concentrated ambient particulate matter induces reversible increase of heart weight in spontaneously hypertensive rats. Part Fibre Toxicol. 12(1):15.

Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. 2014. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of US women. Am J Respir Crit Care Med. 190(8):914–21.

Zanobetti A, Coull BA, Gryparis A, Kloog I, Sparrow D, Vokonas PS, Wright RO, Gold DR, Schwartz J. 2014a. Associations between arrhythmia episodes and temporally and spatially resolved black carbon and particulate matter in elderly patients. Occup Environ Med. 71(3):201–7.

Zanobetti A, Dominici F, Wang Y, Schwartz JD. 2014b. A national case-crossover analysis of the short-term effect of $PM_{2.5}$ on hospitalizations and mortality in subjects with diabetes and neurological disorders. Environ Health. 13(1):38.

Zanobetti A, Franklin M, Koutrakis P, Schwartz J. 2009. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environ Health. 8(1):58.

Zanobetti A, Schwartz J. 2009. The effect of fine and coarse particulate air pollution on mortality: A national analysis. Environ Health Perspect. 117(6):898–903.

Zeger SL, Dominici F, McDermott A, Samet JM. 2008. Mortality in the Medicare population and chronic exposure to fine particulate air pollution in urban centers (2000–2005). Environ Health Perspect. 116(12):1614–9.

Zhang C, Meng Q, Zhang X, Wu S, Wang S, Chen R, Li X. 2016. Role of astrocyte activation in fine particulate matter-enhancement of existing ischemic stroke in Sprague-Dawley male rats. J Toxicol Environ Health A. 79(9-10):393–401.

Zhang K, Lu Y, Zhao H, Guo J, Gehendra M, Qiu H, Wu S, He D. 2016. Association between atmospheric particulate matter and adverse pregnancy outcomes in the population. Int J Clin Exp Med. 9(11):20594–20604.

Zhang X, Staimer N, Tjoa T, Gillen DL, Schauer JJ, Shafer MM, Hasheminassab S, Pakbin P, Longhurst J, Sioutas C, et al. 2016. Associations between microvascular function and short-term exposure to traffic-related air pollution and particulate matter oxidative potential. Environ Health. 15(1):81.

Zhang Z, Laden F, Forman JP, Hart JE. 2016. Long-term exposure to particulate matter and self-reported hypertension: A prospective analysis in the nurses' health study. Environ Health Perspect. 124(9):1414–20.

Zheng X, Ding H, Jiang L, Chen S, Zheng J, Qiu M, Zhou Y, Chen Q, Guan W. 2015. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: A systematic review and meta-analysis. PloS One. 10(9):e0138146.

Zheng Z, Zhang X, Wang J, Dandekar A, Kim H, Qiu Y, Xu X, Cui Y, Wang A, Chen LC. 2015. Exposure to fine airborne particulate matters induces hepatic fibrosis in murine models. J Hepatol. 63(6):1397–1404.

Zhu X, Liu Y, Chen Y, Yao C, Che Z, Cao J. 2015a. Maternal exposure to fine particulate matter ($PM_{2.5}$) and pregnancy outcomes: A meta-analysis. Environ Sci Pollut Res. 22(5):3383–96.

Zhu Y, Zhang C, Liu D, Grantz KL, Wallace M, Mendola P. 2015b. Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. Environ Res. 140:714–20.

APPENDIX A

Additional inclusion criteria specific to the study categories included in this assessment are described below:

Primary environmental epidemiological studies

Primary environmental epidemiological studies were restricted to populations within Canada and the United States. Epidemiological studies from the two countries are considered to be the most relevant for this report, with respect to exposure levels, composition of $PM_{2.5}$ and population characteristics. There are considerable similarities between these two countries in terms of their standard of living and, in some regions, climate. The two countries have many similar sources of air emissions (e.g., the automobile industry is integrated on a North American basis), and in urban settings, vehicle emissions are a major source of $PM_{2.5}$ and co-emitted pollutants. Moreover, large parts of Canada share a common airshed with the United States and are impacted by transboundary air pollution.

Epidemiological studies allow the examination of the possible health effects of air pollution at a human population level, based on the associations between ambient levels of $PM_{2.5}$ and particular health endpoints. The quantitative relationships are often of relatively small magnitude, and rigorous statistical analyses adjusting for various confounding factors such as seasonal variations, co-pollutants, socioeconomic characteristics and individual and ecological covariates are necessary in order to avoid drawing conclusion based on spurious relationships.

Six major environmental epidemiological study designs can be identified that focus on either the short-term or the long-term effects of airborne pollution:

Time-series studies, which investigate the short-term effects of $PM_{2.5}$—i.e., temporal associations between the daily variation in $PM_{2.5}$ levels and daily counts of mortality, hospital admissions and emergency room visits.

Case-control studies, which compare the odds of elevated exposure to $PM_{2.5}$ in people with a certain health outcome (cases) to the odds of elevated exposure in those without the health outcome (controls). One limitation is its inability to support a temporal relationship between exposure and an outcome.

Case-crossover studies, a variant of case-control studies, which compare individual health outcomes and the $PM_{2.5}$ level at the time of the event to conditions that prevailed before the health problem occurrence. The participants serve as their own controls. This design is often used to evaluate transient changes in health outcomes.

Panel studies, which investigate the association between variation in $PM_{2.5}$ levels and repeated measurements of health outcomes in a defined group of subjects.

Cohort studies, which explore the development of chronic effects over time by following a large groups of individuals either prospectively or retrospectively —i.e., the association between long-term or cumulative exposure of $PM_{2.5}$ and incidence mortality or morbidity endpoints, such as the development of chronic diseases.

Cross-sectional studies, which focus on the association between current exposure and health endpoints at a particular point in time. One of its major limitations is the inability to support a temporal relationship between exposure and an outcome.

For short-term exposure to $PM_{2.5}$, studies examining the associations with mortality, hospital admissions and emergency room visits analyzed with time-series and case-crossover epidemiological studies that include participants from multiple cities (multi-city) were included. In terms of other morbidity outcomes, panel studies, crossover studies and cross-sectional studies conducted in single-city were also reviewed. For long-term exposure to $PM_{2.5}$, cohort and case-control studies of mortality were included. Since morbidity outcomes covered a variety of health endpoints, various epidemiological designs, including cross-sectional, case-control, panel and cohort studies were reviewed.

Systematic review and meta-analysis studies

Systematic reviews use systematic and reproducible methods to identify, select and critically appraise all relevant research pertaining to a clearly formulated research question, and to collect and analyse data from the studies that are included in the review. Information is assessed in a transparent and reproducible way. Meta-analyses (which can be included in systematic reviews) are the pooling of the findings from the selected studies to provide a statistical quantitative estimate of the assessed relationship. Developments in meta-analytical methods (e.g., assessments of the risk of bias, reporting guidance, and control of confounding) have improved the quality of systematic review with meta-analysis studies. These are powerful analyses as they provide a thorough method of gathering the evidence on a specific question, reducing issues of sample size. Results from systematic review with meta-analysis studies can sometimes include studies performed in different countries. In this report, systematic review with meta-analysis studies are reviewed in order to capture the strengths of this type of analysis, as well as to support results observed in the Canadian and American studies. Given that systematic review with meta-analysis studies can include estimates from multi-city and single-city studies in the amalgamation of results, no restrictions were imposed on the number of cities in the study or the geographical locations.

Controlled epidemiological studies

Primary controlled human exposure studies that involve human volunteers in controlled laboratory settings are also known as clinical studies. These studies are conducted in highly controlled environments to regulate exposure levels and durations. Since controlled human exposure studies are conducted in controlled experimental environments, the location of the study was not limited to particular countries.

Toxicological studies

Toxicological studies are conducted in animals or cell lines that are exposed to predetermined levels of $PM_{2.5}$ in a controlled setting. Toxicological studies described in this report are those that shed light on new aspects and results that remained unclear when the CSSA was published, such as the toxicity mechanisms, susceptibility, or specificity of $PM_{2.5}$ components. Since experimental toxicological studies are conducted in controlled experimental environments, the location of the study was not limited to particular countries.