South Coast AQMD

2022
DRAFT AIR QUALITY MANAGEMENT PLAN

Appendix I

Health Effects

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INTRODUCTION

This document presents a summary of scientific findings on the health effects of ambient air pollutants. The California Health and Safety Code Section 40471(b) requires that the South Coast Air Quality Management District (South Coast AQMD) prepare a report on the health impacts of particulate matter in the South Coast Air Basin (SCAB) in conjunction with the preparation of the Air Quality Management Plan (AQMP) revisions. This document, which was prepared to satisfy that requirement, also includes sections discussing the health effects of the other major pollutants. The intention of this document is to provide a brief summary of the conclusions of scientific reviews conducted by U.S. EPA and other scientific agencies, with some additional information from more recently published studies.

In addition to the air pollutant health effects summaries, this Appendix also includes a Reference section which lists publications that have resulted from health-related research projects sponsored by South Coast AQMD over the past several years. Some of these studies are discussed in this Appendix, as appropriate, although there are many other studies referenced. These studies also help inform the South Coast AQMD's work in characterizing the air pollution and its effects in our local region and the influences of sources of air pollution in the Basin.

While information on ambient air quality statistics, attainment status, spatial distribution of air pollutants, environmental justice, socioeconomic impacts, control strategies, and cost-effectiveness are important issues that may relate to health effects, these issues are not the focus of this Appendix. These issues are instead discussed in detail in other chapters and appendices of the AQMP, or in the AQMP Socioeconomic Report.

HEALTH EFFECTS OF AIR POLLUTION

Ambient air pollution is a major public health concern. Excess deaths and increases in illnesses associated with high air pollution levels have been documented in several episodes as early as 1930 in Meuse Valley, Belgium; 1948 in Donora, Pennsylvania; and 1952 in London. Although levels of pollutants that occurred during these acute episodes are now unlikely in the United States, ambient air pollution continues to be linked to increases in illness and other health effects (morbidity) and increases in death rates (mortality).

Adverse health outcomes linked to air pollution include cardiovascular effects, premature mortality, respiratory effects, cancer, reproductive effects, neurological effects, and other health outcomes. The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological), toxicological studies, as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on the mechanisms - how specific organs, cell types, and biomarkers are involved in the human body's response to air pollution. Yet the underlying biological pathways for these effects are not always clearly understood.

Although individuals inhale pollutants as a mixture under ambient conditions, the regulatory framework and the control measures developed are pollutant-specific for six major outdoor pollutants covered under Sections 108 and 109 of the Clean Air Act. This is appropriate, in that different pollutants can differ in their sources, their times and places of occurrence, the kinds of health effects they may cause, and their overall levels of health risk. Different pollutants, from the same or other sources, often occur together. Evidence

from recent studies is consistent with the 2020 Ozone Integrated Science Assessment (ISA) and 2019 Particulate Matter ISA (U.S. EPA, 2020, U.S. EPA, 2019) in supporting an association between a single pollutant concentrations and respiratory health effects independent of coexposures to correlated pollutants. For example, across pollutants, single-pollutant associations reported between ozone and a range of respiratory-related hospital admissions and emergency department (ED) visits were persistent, although sometimes lessened, in copollutant models (U.S. EPA, 2020). While the combined effects of multiple air pollutants that occur simultaneously may be important, single-pollutant associations still hold true. Furthermore, the air quality standards address each criteria pollutant separately. Therefore, this Appendix is divided into sections by pollutant. A brief overview of the health effects observed and attributed to various air pollutants is presented in this Appendix. Because the region exceeds the federal standards for ozone and PM2.5, this Appendix focuses more on discussing these two pollutants. Furthermore, the health impacts within the region are potentially greater for these two pollutants compared to the health impacts of the other criteria pollutants. In addition, EPA published the Ozone ISA in 2020 and a Policy Assessment for the reconsideration of PM in 2021 which include new relevant information for the health effects assessment of these two pollutants. For the other pollutants, a brief summary of the associated health effects is provided.

This summary is drawn substantially from reviews presented previously (South Coast Air Quality Management District 1996; South Coast Air Quality Management District 2003; South Coast Air Quality Management District 2007; South Coast Air Quality Management District 2013b; South Coast Air Quality Management District 2016), and from the most recent U.S. EPA Integrated Science Assessment (ISA) reviews for Ozone (U.S. EPA, 2020), Carbon Monoxide (U.S. EPA 2010), Particulate Matter (U.S. EPA 2019), Nitrogen Oxides (U.S. EPA 2016), Sulfur Dioxide (U.S. EPA 2017), and Lead (U.S. EPA, 2013a). In addition to the ISAs is the Draft Policy Assessment for the Reconsideration of the National Ambient Air Quality Standards for Particulate Matter (2021). Additional reviews prepared by the California Air Resources Board and the California EPA Office of Environmental Health Hazard Assessment for Particulate Matter (California Air Resources Board and Office of Environmental Health Hazard Assessment 2002), for Ozone (California Air Resources Board and Office of Environmental Health Hazard Assessment 2005) and for Nitrogen Dioxide (California Air Resources Board and Office of Environmental Health Hazard Assessment 2007) were included in the summary. In addition, several large review articles on the health effects of air pollution also helped inform this Appendix (American Thoracic Society 1996a; Brunekreef et al. 2002). More detailed citations and discussions on air pollution health effects can be found in these references. Additionally, a supplemental literature review of mortality and morbidity impacts of the criteria pollutants was included, particularly those published since the most recent ISA's. This summary highlights studies that were conducted in the South Coast Air Basin or in Southern California, or alternatively, in California, if few studies from our local region are available on the specific topic. Studies conducted in Southern California give an important "local perspective" in understanding and evaluating the health effects of air pollution. However, studies conducted in other locations also provide critical information that is pertinent to advancing the scientific understanding of the health effects of air pollution, including effects on our local population. As such, this summary also discusses key studies that were conducted in other locations.

EPA's Evaluation of Health Effects Data

Over the decades of national reviews of outdoor air pollution and their health impacts, the U.S. EPA has developed a list of five criteria by which the strength and credibility of data can be judged. This five-tier weight-of-evidence approach provides an objective basis for assessing the breadth, specificity, and consistency of evidence concerning a particular health outcome. Table I-1 shows the five descriptors used by the U.S. EPA for assessing causality, using a weight-of-evidence approach. Within each section discussing a specific pollutant are tables showing summaries of the U.S. EPA conclusions regarding the causality of air pollution health effects, which are the conclusions of their scientific evaluation of the research studies they have reviewed. For the criteria pollutants, the discussion in this Appendix will focus only on those categories of health effects for which the U.S. EPA has determined there is a causal or likely causal relationship with the pollutant, while other health effects may be discussed briefly.

The U.S. EPA is tasked with assessing new and emerging air quality science, including health studies, as part of the process of setting the federal air quality standards. In other words, the U.S. EPA's role is to assess the causal relationships between the pollutants and the different types of health endpoints. It is South Coast AQMD's role to describe the public health impacts of poor air quality in our region, as well as to develop and implement an emission reduction strategy to attain the federal and state ambient air quality standards. Therefore, it is not the intention of this Appendix to assess whether there is or is not an effect of a specific air pollutant on any particular health endpoint, but rather to summarize the health effects and causal determinations as assessed by U.S. EPA and other scientific agencies, to discuss some recent studies published since the latest U.S. EPA reviews, to give some quantitative estimates of the health impacts of air pollution in the South Coast Air Basin, and to present a "local perspective" by highlighting studies conducted in the South Coast Air Basin, Southern California, or California.

TABLE I-1

U.S. EPA'S WEIGHT OF EVIDENCE DESCRIPTIONS FOR CAUSAL DETERMINATION OF HEALTH EFFECTS

DETERMINATION	WEIGHT OF EVIDENCE
Causal Relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.
Likely To Be a Causal Relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant 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 (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on 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, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species, or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.
Inadequate to Infer the Presence or Absence of 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.

DETERMINATION	WEIGHT OF EVIDENCE
Not Likely to Be a Causal Relationship	Evidence indicates there is 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 and life stages, are mutually consistent in not showing an effect at any level of exposure.

(Adapted from U.S. EPA, 2020)

OZONE

Ozone is a gaseous air pollutant that is a highly reactive compound and a strong oxidizing agent. When ozone comes into contact with the respiratory tract, it can react with tissues and cause damage in the airways. Ozone, or its reaction products, can penetrate the gas exchange region of the deep lung. Both short-term and long-term exposures to ozone have been linked to respiratory effects. Ozone from man-made sources is formed by photochemical reactions when pollutants such as volatile organic compounds, nitrogen oxides, and carbon monoxide react with sunlight. The main sources of such ozone precursors are discussed in detail in the draft 2022 AQMP Chapter 3. Additionally, a discussion of the spatial distribution of ozone is provided in the draft 2022 AQMP Chapter 2.

In 1997, the U.S. EPA established the first National Ambient Air Quality Standards (NAAQS) for ozone averaged over 8 hours, at 0.08 ppm. In 2005, the California Air Resources Board (CARB) established standards of 0.09 ppm averaged over one hour and at 0.070 ppm averaged over eight hours. In 2008, the U.S. EPA lowered the federal standard for ozone to 0.075 ppm averaged over eight hours. In 2015, the U.S. EPA concluded that the current national standard was not adequate to protect public health and lowered the 8-hour ozone standard to 0.070 ppm (annual fourth-highest daily max 8-hour concentration averaged over 3 years) (U.S. EPA 2015b). On December 23, 2020, EPA completed its review of the full body of currently available scientific evidence and exposure/risk information and decided to retain the existing ozone NAAQS. While the federal standards must be attained within a specified time frame, the California standards do not have specific defined deadlines, but must be attained by the earliest practicable date.

The table below provides the overall U.S. EPA staff conclusions on the causality of short-term (i.e., hours, days, weeks) and long-term (i.e., months, years) ozone health effects for the health outcomes evaluated (U.S. EPA, 2020).

TABLE I-2

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATIONS FOR HEALTH EFFECTS OF OZONE

Health Outcome	Conclusion in 2020 ISA
Short-term exposure of ozone	
Respiratory effects	Causal relationship
Cardiovascular effects	Suggestive of, but not sufficient to infer, a causal relationship
Metabolic effects	Likely to be causal relationship
Total mortality	Suggestive of, but not sufficient to infer, a causal relationship
Central nervous system effects	Suggestive of, but not sufficient to infer, a causal relationship
Long-term exposure to ozone	
Respiratory effects	Likely to be causal relationship
Cardiovascular effects	Suggestive of, but not sufficient to infer, a causal relationship
Metabolic effects	Suggestive of, but not sufficient to infer, a causal relationship
Total mortality	Suggestive of, but not sufficient to infer, a causal relationship
Reproductive effects	Effects of fertility and reproduction: suggestive of, but not sufficient to infer, a causal relationship
	Effects on pregnancy and birth outcomes: suggestive of, but not sufficient to infer, a causal relationship
Central nervous system effects	Suggestive of, but not sufficient to infer, a causal relationship
Cancer	Inadequate to infer the presence of absence of a causal relationship

(From U.S. EPA, 2020 Table ES-1)

Short-Term Exposure Effects of Ozone

Consistent with conclusions from the 2013 Ozone ISA (U.S. EPA 2013b), the 2020 Ozone ISA (U.S. EPA 2020) concludes that there is a "causal relationship" between short-term ozone exposure and respiratory effects. The relationship between short-term ozone exposure and central nervous system effects is still "suggestive, but not enough evidence to infer, a causal relationship." Short term ozone exposure that was thought to "likely cause" cardiovascular effect and mortality has been downgraded to "suggestive" of a causal relationship in the most recent Ozone ISA. EPA also determined in that document that it is also "likely" that there is a causal relationship between short term ozone exposure and metabolic effects (U.S. EPA 2020).

Several adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (American Thoracic Society 1996b; U.S. EPA 2006; U.S. EPA, 2013, U.S. EPA, 2020). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, asthma exacerbation, an increased risk of hospitalization, and increased risk of mortality (U.S. EPA, 2020).

The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate, the depth of the breaths, and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching deeper into the lungs. Children are considered to be a particularly vulnerable population to air pollution effects because their lungs are still growing, they

typically spend more time outdoors, are generally more physically active, and have a higher ventilation rate relative to their body weight, compared to adults (U.S. EPA, 2013).

Respiratory effects

Studies have found associations between short exposure to ozone and markers of lung function decrements, respiratory symptoms, airway responsiveness, respiratory tract inflammation, injury and oxidative stress, and emergency department (ED) visits and hospital admissions for asthma and respiratory infections (U.S. EPA, 2020).

Lung Function

In the laboratory, exposure of human subjects to low levels of ozone causes reversible decreases in lung function as assessed by various measures such as respiratory volumes, airway resistance and reactivity, irritative cough and chest discomfort. The results of several studies where human volunteers were exposed to ozone for 6.6 hours at levels between 0.04 and 0.12 ppm were summarized by Brown (Brown et al. 2008) showing a reduction in lung function (FEV_1) and other respiratory effects. A study published after the analysis by Brown et al. exposed healthy young adults for 6.6 hours under intermittent moderate exercise to each of the following: filtered air, and ozone at 0.06, 0.07, 0.08, and 0.087 ppm (Schelegle et al. 2009). The study found decreases in lung function (forced expiratory volume in 1 second, or FEV_1) with each of the different levels of ozone exposure, although the decrease in lung function at 0.06 ppm was not statistically different from exposure to filtered air. Lung function (FEV_1) decreases were approximately 5%, 7%, and 11% at ozone exposure levels of 0.07, 0.08, and 0.087 ppm. A more recent study (Kim et al. 2011) exposed young healthy adults to ozone in the range of 0.06 to 0.10 ppm for 6.6 hours while engaging in intermittent moderate exercise, and found that the study participants exhibited an approximately 2 percent reduction in lung function (FEV_1) and an increase in pulmonary inflammation after exposure to ozone at the 0.06 ppm concentration. Figure I-1 taken from the Ozone ISA 2020 summarizes results from multiple studies showing an increasing response on lung function with increasing exposure levels in subjects.
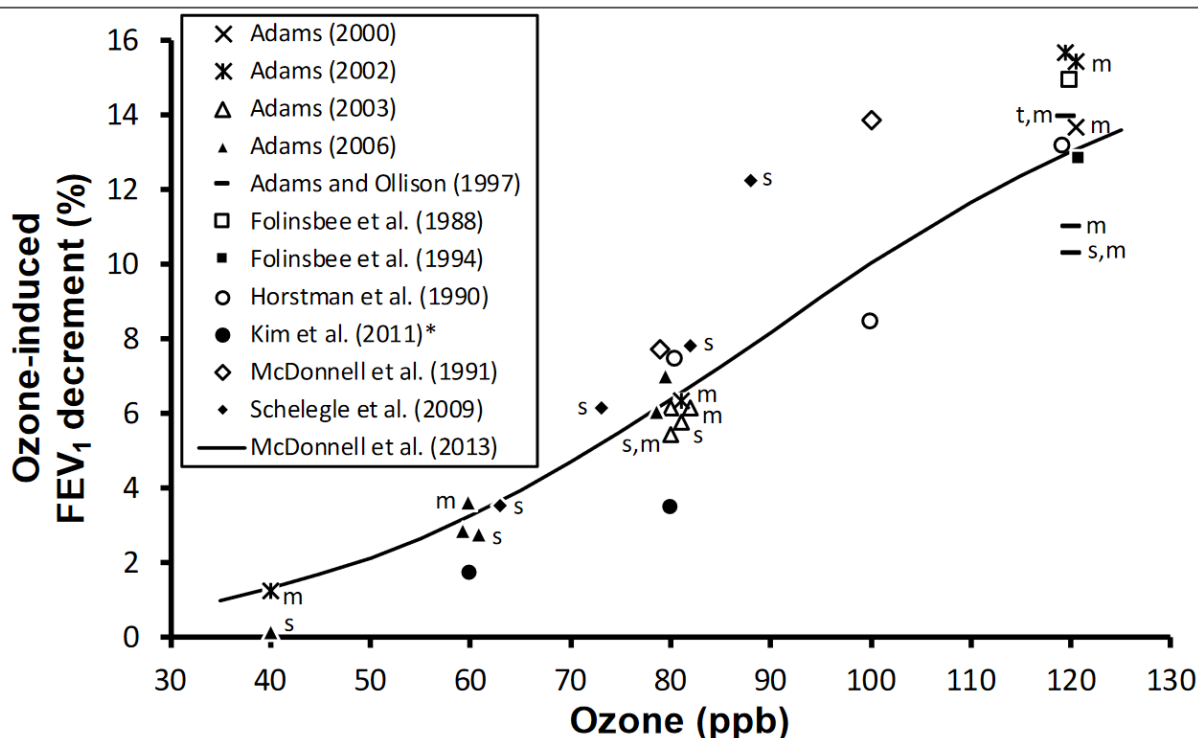
"All illustrated studies used a constant target quasi-continuous exercise ventilation rate of ~20 L/minute per m2 body surface area (BSA). For studies using step-wise (s) or triangular (t) increases and decreases in ozone concentration, the FEV1 response is plotted at the average ozone exposure concentration for the 6.6-hour exposure. Some exposures were conducted using a facemask (m), all other studies were conducted within a chamber. All responses at and above 70 ppb (targeted concentration) were statistically significant relative to filtered air exposure. At a constant exposure concentration of 60 ppb in a chamber, statistically significant FEV1 responses were found by Kim et al. (2011) and in the Adams (2006) study based on the analysis of Brown et al. (2008). With the exception of the Schelegle et al. (2009) data, the data at 60, 80, and 120 ppb have been offset along the x-axis for illustrative purposes. The McDonnell et al. (2013) line illustrates the predicted FEV1 decrements at 6.6 hours as a function of ozone concentration using Model 3 coefficients for a 23.5-year-old with a BMI of 23.1 kg/m2 having a ventilation rate during rest and exercise of 6 and 20 L/minute per m2 BSA. 80 ppb data for 30 health subjects were collected as part of the Kim et al. (2011) study, but only published in Figure 5 of McDonnell et al. (2012)."

FIGURE I-1

CROSS-STUDY COMPARISONS OF MEAN OZONE-INDUCED FORCED EXPIRATORY VOLUME IN 1 SECOND (FEV1) DECREMENTS IN YOUNG HEALTHY ADULTS FOLLOWING 6.6 HOURS OF EXPOSURE TO OZONE.

(ADAPTED FROM FIGURE 3-3 OF 2020 OZONE ISA (U.S. EPA, 2013A). STUDIES APPEARING IN THE FIGURE LEGEND ARE: ADAMS (2006), ADAMS (2003A), ADAMS (2002), ADAMS (2000), ADAMS AND OLLISON (1997), FOLINSBEE ET AL. (1994), FOLINSBEE ET AL. (1988), HORSTMAN ET AL. (1990), KIM ET AL. (2011), MCDONNELL ET AL. (2013), MCDONNELL ET AL. (1991), AND SCHELEGLE ET AL. (2009).)

There are more recent studies looking at lung function with ozone exposure. One study evaluated the effect of ozone on lung function at concentrations below 80 ppb. The results of this study of older adults (55–70 years) exposed for 3 hours to 0, 70, and 120 ppb ozone showed small decrements in lung function, with a group mean ozone-induced FEV1 decrement of only 1.2% (Arjomandi et al., 2018). Several studies have investigated the effects of 100–300 ppb ozone exposure on lung function (Biller et al. 2011, Ghio et al. 2014, Frampton et al. 2015, Hoffmeyer et al. 2013, Madden et al. 2014, Stiegel et al. 2017, Tank et al. 2011. Given that lower ambient concentrations are more common currently, these studies are more

relevant when studying mechanistic information or existence of associations between lung function and other indicators of respiratory health.

Looking at repeated exposure Madden et al. (2014), consistent with older studies, reported that 2 consecutive days of ozone exposure caused a statistically greater decrement in FEV_1 (18.2 ± 4.5%) than the decrement immediately after the first day of ozone exposure (i.e., 9.9 ± 2.5%; $p < 0.05$) and immediately after ozone exposure (i.e., 10.9 ± 2.6%) preceded by an air exposure on the prior day. However previous studies have also shown attenuated responses or a reduction in magnitude of responses when exposures are repeated (Linn et al. 1988). It has been argued that the observed shift in response is evidence of a probable development of tolerance, it appears that while functional changes may exhibit attenuation, biochemical and cellular changes which may be associated with episodic and chronic exposure effects may not exhibit an attenuation. Cellular and biochemical changes associated with respiratory tract inflammation have been consistently found in the airway lining after low- level exposure to ozone. These changes include an increase in specific cell types and in the concentration of biochemical mediators of inflammation and injury such as Interleukin-1, Interleukin-6, Interleukin-8, Tumor Necrosis Factor α (TNF-α), and fibronectin (Van Bree et al. 2002; Johnston et al. 2007; U.S. EPA, 2013). Significant relationships have also been reported between FEV_1 decrements and plasma ferritin [r = −0.67, p = 0.003; i.e., larger FEV_1 decrements in individuals with lower baseline plasma ferritin (Ghio et al., 2014), and with the inflammatory cytokine IFN-γ in the blood (Stiegel et al., 2017). That is to show that, internal damage to the respiratory system may continue with repeated ozone exposures, even if externally observable effects (chest symptoms and reduced lung function) disappear. An additional argument against toleration is that after several days or weeks without ozone exposures, the responsiveness (in terms of lung function as well as symptoms) returns, which is evidence that any tolerance developed is relatively short-lived (U.S. EPA, 2013).

Lung function changes were also studied in sensitive populations. Based on studies reviewed in the 1996 and 2006 Ozone AQCDs (U.S. EPA, 1996a, 2006) and the 2013 Ozone ISA (U.S. EPA, 2013), it was concluded that individuals with asthma were at least as sensitive to acute effects of ozone as healthy individuals. In the 2013 Ozone ISA (U.S. EPA, 2013), the study by Horstman et al. (1995) was recognized as showing clearly larger FEV_1 responses in individuals with asthma relative to those without (19 vs. 10% FEV_1 decrements, respectively, p = 0.04) following 7.6-hour exposures to 160 ppb ozone with light quasi-continuous exercise. In asthmatics, ozone-induced FEV_1 decrements were also well correlated with baseline percent predicted FEV_1 (r = 0.53, p < 0.05); that is, responses to ozone increased with severity of disease, and individuals using bronchodilators experienced greater ozone-induced lung function decrements. Based on FEV_1/FVC, this study also showed that the obstructive response to ozone is greater in individuals with asthma than those without. Kreit et al. (1989) also reported a large statistically significant difference in ozone-induced FEV_1 decrements between individuals with asthma and those without (25 vs. 16%, respectively, p < 0.05) exposed to 400 ppb ozone with heavy intermittent exercise for 2 hours.

Since the 2013 Ozone ISA, four controlled human exposure studies examining ozone effects on lung function in individuals with asthma have been published (Arjomandi et al., 2015; Leroy etal., 2015; Bartoli et al., 2013; Fry et al., 2012). Neither Arjomandi et al. (2015) nor Fry et al. (2012) reported FEV_1 responses to ozone differentiated by the presence of asthma. Bartoli et al. (2013) found that the magnitude of ozone-induced FEV_1 response increased with decreasing baseline FEV_1 (p = 0.02). Bartoli et al. (2013) also found that inhaled corticosteroid treatment was associated with a decrease in ozone-induced FEV_1

decrements (p = 0.04). This study, however, did not include a healthy non-asthmatic control group, limiting our understanding of differences between asthmatic and non-asthmatic individuals. In a smaller study of healthy non-asthmatic individuals (5 F, 7 M; 31.8 ± 6.0 years) and subjects with mild asthma (5 F, 3 M; 33.7 ± 10.1 years), although baseline FEV_1 and FEV_1/FVC were significantly lower in asthmatics than non-asthmatics, there was no significant association between the presence of asthma and lung function response to ozone (Leroy et al., 2015). Overall, most controlled human exposure studies found little to no difference in ozone-induced lung function responses between individuals with and without asthma.

Laboratory studies have also compared the degree of lung function change seen in healthy individuals versus those with chronic obstructive pulmonary disease (COPD). In several laboratory studies of individuals with COPD, the percent decreases in lung function from short-term ozone exposures ≤0.30ppm among patients with COPD generally did not differ from the lung function decrements experienced by healthy patients (Linn et al. 1982; Solic et al. 1982; Linn et al. 1983; Kehrl et al. 1985). That finding, however, may not accurately reflect the true impact of exposure on these respiration-compromised individuals. Since the respiration-compromised group may have lower lung function to begin with, the same total percent change in lung function may represent a substantially greater relative adverse effect overall.

With overweight individuals, the 2013 Ozone ISA (U.S. EPA, 2013) included two retrospective analyses of controlled human exposure studies showing ozone-induced FEV_1 decrements increased with increasing BMI. There is a new controlled human exposure study and a larger retrospective analysis demonstrating an effect of BMI on lung function responses to ozone discussed in the 2020 Ozone ISA (U.S. EPA, 2020). Bennett et al. (2016) exposed obese (19 F; 27.7 ± 5.2 years) and normal-weight (19 F;24 ± 3.7 years) women to 0 and 400 ppb ozone for 2 hours during intermittent exercise (15-minute periods of seated rest and exercise at 25 L/minute per m2 BSA). The ozone-induced FVC decrement was significantly (p < 0.05) greater in the obese women (12.5%) than normal-weight women (8.0%). The FVC decrement also tended (p = 0.08) to be greatest in the obese African-Americans (15.7%) relative to other obese subjects (9.6%). There was also a tendency (p = 0.11) for greater ozone-induced FEV1 decrements in obese women (15.9%) relative to the normal-weight women (11.7%). While respiratory function was diminished, respiratory symptoms in response to ozone exposure did not differ between obese and normal-weight women. The new retrospective analysis by McDonnell et al. (2013) includes data from prior studies of young healthy adults (104 F, 637 M; 18–36 years) exposed one or more times to ozone and/or filtered air. The prior analysis by McDonnell et al. (2010), discussed in the 2013 Ozone ISA in relation to BMI effects, used data from 541 healthy nonsmoking white males (18–35 years). The analysis based on a larger data set continues to show that the BMI effect is of the same order of magnitude but in the opposite direction of the age effect. Thus, the model predicts FEV1 responses increase with increasing BMI and diminish with increasing age. In animal studies changes in frequency of breathing and tidal volume, reflecting a pattern of rapid, shallow breathing, were commonly observed at ozone concentrations of about 0.2 ppm. Decreased lung volumes were observed in rats exposed to 0.5 ppm, while changes in compliance and resistance were observed at ozone concentrations of 1 ppm and above. Repeated acute exposures over several days led to attenuation of the pulmonary function decrement response. A lung imaging study found that continuous or half-day exposure to 0.5 ppm ozone for several days led to ventilatory abnormalities that suggested narrowing of peripheral small airways and increased airway resistance (U.S. EPA, 2013). While ozone concentrations in animal toxicological studies seem to be high, it should be noted that deposition of ozone resulting from a 2-hour exposure to 2 ppm ozone in a resting rat is roughly equivalent to

deposition of ozone resulting from a 2-hour exposure to 0.4 ppm ozone in an exercising human (Hatch et al., 1994). More recently, Hatch et al. (2013) showed that resting rats and resting humans receive similar alveolar ozone doses.

A large number of recent animal studies have further evaluated changes in lung function in response to even lower concentrations, short term ozone exposure. All these studies were conducted in rodent strains with varying degrees of sensitivity to ozone. Lung function was assessed by changes in ventilatory parameters such as tidal volume and enhanced pause. Enhanced pause is a measure of respiratory distress that may or may not be related to an increase in airway resistance. These recent studies demonstrated that exposure to 0.1–2 ppm ozone results in changes in lung function, as measured by altered ventilatory parameters (Ghio et al., 2014; Bao et al., 2013; Lee et al., 2013). Changes in enhanced pause and evidence of sensory and pulmonary irritation were observed following acute exposure to 2 ppm ozone (Hansen et al. (2016). Changes in enhanced pause and tidal volume were observed with acute exposure to 0.5–1 ppm ozone (Gordon et al., 2016b; Dye et al., 2015; Schelegle and Walby, 2012; Dye et al., 2015). Repeated exposure to ozone resulted in numerous effects, with decreased respiratory frequency occurring at concentrations of 0.1 ppm ozone (Wolkoff et al., 2012; Snow et al., 2016; Miller et al., 2016b, Gordon et al., 2017b; Henriquez et al., 2017).

There have been recent animal studies looking at short term ozone exposure in sensitive populations as well. Several recent studies evaluated respiratory effects of acute ozone exposure (0.2–1 ppm, 3–6 hours) in rodent models of cardiovascular disease. Some of the studies provide evidence that cardiovascular disease exacerbates the respiratory effects of ozone exposure, like lung function changes (U.S. EPA, 2020).

Regarding obesity and FEV response to short term ozone exposure a recent study (Gordon et al., 2016b) involved male and female rats fed normal, high-fructose or high-fat diets prior to acute and subacute ozone exposure (0.8 ppm × 5 hours). While there were some differences in effects depending on duration of exposure, diet, and sex of rat, ozone exposure generally resulted in statistically significant increases in enhanced pause and tidal volume, which are ventilatory parameters that reflect a change in lung function.

In addition to controlled laboratory conditions for both human and animal subjects, epidemiological studies of individuals exercising outdoors, as well children attending summer camp (Berry et al., 1991; Spektor and Lippmann, 1991; Avol et al., 1990; Burnett et al., 1990; Higgins et al., 1990; Raizenne et al., 1989; Spektor et al., 1988), have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals. U.S. EPA's 2013 ISA indicated that most studies found reductions in lung function (FEV$_1$) in the range of approximately <1 to 2 percent when standardized to an increase of 0.04 ppm for a 1-hour maximum, an increase of 0.03 ppm for an 8-hour maximum, and an increase of 0.02 ppm for a 24-hour average (U.S. EPA, 2013). A more recent study in Canada also reports a positive association between short-term ambient ozone concentrations and lung function effects in a healthy population (Dales et al. (2013).

A large body of epidemiologic studies reviewed in the 2020 Ozone ISA (U.S. EPA, 2020) provides generally consistent evidence that increases in short-term ozone concentrations are associated with decreased lung function in children with asthma. Associations were observed across a range of ozone concentrations, daily averaging times (e.g., 24-hour avg, 8-hour avg, 8-hour max, and 1-hour max), and diverse geographic locations, including multicity U.S. studies (O'Connor et al., 2008; Mortimer et al., 2002; Mortimer et al., 2000). Somewhat greater decrements in lung function (4.9 to 7.3 percent) were found in children with asthma who had respiratory infections or were using corticosteroid medication. In addition to studies of

children with asthma, the 2013 Ozone ISA evaluated a limited number of studies that examined lung function in adults with asthma (U.S. EPA, 2013). In contrast to results from studies of children, short-term ozone concentrations were not consistently associated with lung function decrements in adults with asthma.

In a 2007 study, short-term ozone concentrations were associated with decreases in lung function in older adults with airway hyperresponsiveness (Alexeeff et al., 2007). The observed association was stronger among those who were obese. A recent analysis of the Offspring and Third Generation Framingham Heart Study cohorts also found that obese participants had significantly stronger associations between 8-hour max summertime ozone concentrations and reduced lung function (Rice et al., 2013).

Respiratory symptoms

In addition to lung function decrements, controlled human exposure studies clearly indicate ozone-induced increases in respiratory symptoms including pain on deep inspiration, shortness of breath, and cough. In brief, the available evidence during the last AQMP (2016) indicated that respiratory symptoms increase with increasing ozone concentration, duration of ozone exposure, and activity level of exposed subjects. For exposures of 1–2 hours to ≥120 ppb, statistically significant respiratory symptoms and effects on FEV_1 were observed when exercise sufficiently increased ventilation rates (McDonnell et al., 1999b). During exposures at rest, 5% of young healthy adults exposed to 400 ppb ozone for 2 hours experienced pain on deep inspiration, but not at 1 hour of exposure. Respiratory symptoms were also not observed following 1 to 2 hours of resting exposure at lower concentrations of 120 to 300 ppb. However, when exposed during light to moderate intermittent exercise (22–35 L/minute) to 120 ppb for 2 hours, 9% of individuals experienced pain on deep inspiration, 5% experienced cough, and 4% experienced shortness of breath. For longer duration, 6.6-hour exposures to 80 ppb with moderate quasi-continuous exercise, FEV_1 decrements and total respiratory symptoms diverge from filtered air responses after 3 hours and become statistically different by 6.6 hours (Adams, 2006). For the 6.6-hour exposures to ozone, 70 ppb is the lowest concentration where statistically significant ozone-induced lung function decrements and subjective symptoms have been reported (Schelegle et al., 2009). Although several studies have investigated the effects of 6.6-hour exposures during moderate exercise to 60 ppb ozone, none have observed a statistically significant increase in respiratory symptoms following ozone relative to filtered air. Horstman et al. (1995) showed that after 7.6 hours of exposure to 160 ppb ozone with light quasi-continuous exercise there was a statistically significant increase in the incidence of wheeze in subjects with asthma relative to healthy controls, which did not experience wheeze. There was also a statistically significant increase in the incidence of wheeze in the subjects with asthma on their ozone exposure day relative to their filtered-air exposure day.

In a recent study by Pepper et al. (2020) ambient ozone exposure was positively associated with asthma rescue inhaler use (p = 0.01). Age-specific associations were identified (interaction p = 0.01), with a larger increase in asthma rescue inhaler use for children (11.3%; 95% CI: 7.0%-18.2%) than adults (8.4%; 95% CI: 6.4%-11.0%) per interquartile range (IQR) increase of ozone (16.8 ppb). These findings support existing evidence that short-term exposure to ozone can cause respiratory symptoms in individuals with asthma, and suggest that ozone exposures below the current U.S. EPA standard may be associated with increased asthma rescue inhaler use.

A recent study in guinea pigs and rabbits found that ozone acts through sensory nerves to enhance coughing that is elicited by citric acid (Clay et al., 2016). Acute exposure to 2 ppm ozone for 0.5–1 hour

resulted in statistically significant increases in cough frequency and decreases in time to cough in response to citric acid. Experiments with pharmacological agents implicated TRPV1 receptors, a type of sensory nerve receptor often found on C-fibers, in mediating the hypertussive response to ozone (U.S. EPA, 2020).

Several epidemiologic panel studies evaluated in the 2013 Ozone ISA (U.S. EPA, 2013a) examined the relationship between short-term ozone exposure and incidence of respiratory symptoms and increased symptom scores in children with asthma. Evidence from a limited number of multicity U.S. studies was inconsistent, but many single-city studies provided evidence of an association. These studies conducted in various cities in the U.S. and in other countries have reported increased respiratory symptoms among children with asthma, including wheeze, cough, difficulty breathing, and chest symptoms/tightness. The Children's Health Study, conducted by researchers at the University of Southern California, followed for several years a cohort of children that live in 12 communities in Southern California with differing levels of air pollution. A publication from this study reported that school absences in fourth graders for respiratory illnesses were positively associated with short-term increases in ambient ozone levels. An increase of 20 ppb (0.02 ppm) ozone was associated with a 63 percent increase in illness-related absence rates and an 83 percent increase in respiratory illnesses (Gilliland et al. 2001). A small panel study of Hispanic children with asthma living in the Huntington Park neighborhood of Los Angeles, California reported that a 10.8 ppb increase in ozone averaged over 8 hours nearly doubled the odds of having asthma symptoms that interfered with daily activities (Delfino et al. 2003). One recent panel study of school-aged children in Detroit tracked respiratory symptoms in children with asthma for periods of 14 consecutive days during 11 seasons (Lewis et al., 2013). The authors reported increases in a range of respiratory symptoms, including cough, wheeze, shortness of breath, and chest tightness, associated with increases in 1- and 8-hour daily max ozone concentrations. Consistent with results from studies evaluated in the 2013 Ozone ISA, Lewis et al. (2013) observed associations that were larger in magnitude in children taking corticosteroids. However, these associations were much less precise (i.e., wider 95% CIs) than the associations for children not taking steroids.

Airway Responsiveness

Ozone has been shown to cause an increase in airway responsiveness in controlled human exposure studies. In general, airway responsiveness is assessed by increasing inhaled concentrations of a broncho constrictive drug and measuring the effect on lung mechanics (FEV_1 or sRaw). A dose-dependent increase in airway responsiveness of young, healthy, nonsmoking males following exposures to 0, 80, 100, and 120 ppb ozone (6.6 hours, quasi-continuous moderate exercise at 39 L/minute) has been demonstrated. Changes in airway responsiveness appear to persist longer than changes in pulmonary function, although this has been studied only on a limited basis. Studies suggest that ozone-induced increases in airway responsiveness usually resolve 18 to 24 hours after exposure but may persist in some individuals for longer periods. Although FEV_1 decrements and respiratory symptoms become attenuated following several consecutive days of ozone exposure, the ozone-induced increase in airway responsiveness (measured by increase in sRaw upon methacholine challenge) over 5 consecutive days is not attenuated. Increases in airway responsiveness following ozone exposure do not appear to be associated with ozone-induced changes in lung function, respiratory symptoms, or changes in epithelial permeability. First described in the 1986 ozone AQCD (U.S. EPA, 1986), a mechanistic study of subjects exposed to 600 ppb ozone while exercising added to the understanding of mechanisms underlying changes in airway responsiveness caused by ozone exposure. Atropine inhibited an ozone-induced increase in airway responsiveness to

histamine, indicating the involvement of the parasympathetic nervous system in this response (U.S. EPA, 2013).

A recent study of 38 healthy adult women (average age, 26 years) exposed to 0 and 400 ppb ozone for 2 hours performing light intermittent exercise (15-minute periods of exercise at 25 L/minute and seated rest) showed a tendency for increases in airway responsiveness due to ozone with 4 and 12 subjects being responsive to methacholine after exposure to filtered air and ozone, respectively (Bennett et al., 2016).

Controlled human exposure studies previously evaluated in the 2013 Ozone ISA indicate that individuals with and without asthma exhibit similar relative increases in ozone-induced airway responsiveness. However, in general individuals with asthma have greater baseline airway responsiveness than individuals without asthma. Increased airway responsiveness can result in the narrowing of airways upon inhalation of a variety of stimuli, providing biological plausibility for ozone-induced asthma exacerbation, as supported by the epidemiologic associations observed between increases in ozone and hospital and emergency room visits for asthma and prevalence of respiratory symptoms in children with asthma (U.S. EPA, 2020).

Concerning airway responsiveness in overweight individuals, a recent study showed no difference between normal-weight and obese women in airway responsiveness after ozone exposure (Bennett et al., 2016).

Most of the animal studies discussed in the 2013 Ozone ISA (U.S. EPA, 2013) found increased airway responsiveness in guinea pigs, rats, or mice exposed to 1 ppm and higher concentrations of ozone, although increased airway responsiveness was, in a few cases, demonstrated after exposure to less than 0.3 ppm ozone. While ozone concentrations in animal toxicological studies seem to be high, it should be noted that deposition of ozone resulting from a 2-hour exposure to 2 ppm ozone in a resting rat is roughly equivalent to deposition of ozone resulting from a 2-hour exposure to 0.4 ppm ozone in an exercising human (Hatch et al., 1994). More recently, Hatch et al. (2013) showed that resting rats and resting humans receive similar alveolar ozone doses.

In more recent experimental animal studies, increases in airway responsiveness resulted from ozone exposures in the range of 0.8 to 2 ppm but not in response to acute and repeated exposures of 0.25 and 0.5 ppm (U.S. EPA, 2020; Zychowski et al., 2016; Groves et al., 2012; Cho et al., 2018; Mathews et al., 2018; Malik et al., 2017; Stoberet al., 2017; Elkhidir et al., 2016; Kasahara et al., 2015; Razvi et al., 2015; Barreno et al., 2013; Cho et al., 2013; Sunil et al., 2013; Zhu et al., 2016). Mechanistic studies provide evidence that local reflex responses and activation of parasympathetic pathways mediate increases in airway responsiveness due to ozone exposure (Verhein et al., 2013; Barker et al., 2015). This may explain the ability of ozone to act as a nonallergic asthma trigger resulting in bronchoconstriction (U.S. EPA, 2020).

In mouse models of obesity, airways were innately more responsive and responded more vigorously to acute ozone exposure (2 ppm for 3 hours) than lean controls. Newly available information confirms and extends these findings. Several recent studies evaluated the respiratory effects of acute ozone exposure (2 ppm, 3 hours) in mouse models of obesity (Mathews et al., 2018; Mathews et al., 2017a; Mathews et al., 2017b; Williams et al., 2015). Baseline and nonspecific (i.e., methacholine challenge) airway responsiveness were greater in obese mice than lean mice in the absence of ozone exposure. Acute ozone exposure increased baseline and nonspecific airway responsiveness in obese mice, but not in lean mice.

Respiratory Tract Inflammation, Injury, and Oxidative Stress

Controlled human exposure studies evaluated in the 1996 and 2006 Ozone AQCDs (U.S. EPA, 2006, 1996a) established evidence of respiratory tract inflammation in response to acute ozone exposures. Acute ozone exposure initiates an acute inflammatory response throughout the respiratory tract that has been observed to persist for at least 18−24 hours post-exposure. A single acute exposure (1−4 hours) of humans to moderate concentrations of ozone (200−600 ppb) while exercising at moderate to heavy intensities results in a number of cellular and biochemical changes in the lung, including an inflammatory response characterized by increased numbers of white blood cells (Polymorphonuclear Leukocytes (PMNs)), increased permeability of the epithelial lining of the respiratory tract, cell damage, and production of proinflammatory cytokines and prostaglandins. These changes also occur in humans exposed to 80 and 200 ppb ozone for 6−8 hours.

The presence of PMNs in the lung has long been accepted as a hallmark of inflammation and is an important indicator that ozone causes pulmonary inflammation. Notably, these inflammatory responses are not correlated with lung function changes but are at least partially correlated with airway resistance. These results indicate that changes in pulmonary inflammation and airway obstruction may share similar underlying mechanisms, while inflammation and lung function as measured by FEV_1 may not. Additionally, the evidence suggested that there is interindividual variability in inflammatory responses to ozone. In the 2013 Ozone ISA (U.S. EPA, 2013), significant (p = 0.002) increases in sputum PMN (16−18 hours post-exposure) relative to filtered air responses had been reported for 60 ppb ozone which is the lowest exposure concentration that has been investigated in young healthy adults. This was expanded upon in the 2013 Ozone ISA (U.S. EPA, 2013) in studies that demonstrated GSTM1 genotype interaction with ozone exposure on pulmonary inflammation. A more recent study (Alexis et al., 2013) provides some further evidence suggesting that young healthy GSTM1-null adults may be more susceptible to ozone-related inflammatory responses, although the evidence is not entirely consistent, with a relatively large study of older adults by Arjomandi et al. (2018) reporting that inflammatory responses to ozone are not dependent on GSTM1 genotype (50 GSTM1 null, 37 GSTM1 positive).

Controlled human exposure studies evaluated in the 2013 Ozone ISA (U.S. EPA, 2013a) established evidence of enhanced allergic inflammation to ozone in individuals with asthma. Specifically, markers of airway and lung inflammation, and innate immunity, were increased in response to short-term ozone exposures. As with the findings for lung function, there is limited evidence that ozone-induced inflammatory responses differ due to the presence of asthma.

Bennett et al. (2016) recently investigated PMN responses in obese (19 F; 27.7 ± 5.2 years) and normal-weight (19 F; 24 ± 3.7 years) women exposed to 0 and 400 ppb for 2 hours during intermittent exercise. Although PMN were significantly increased after ozone exposure relative to air, the PMN response did not differ between groups. Arjomandi et al. (2015) also found that adjustment for age, sex, and BMI did not affect the association between PMN responses and ozone exposure. A recent panel study of adults with type 2 diabetes mellitus reported decreases in pulmonary inflammation corresponding to 6- (3:00 a.m. to 9:00 a.m.) and 24-hour avg ozone concentrations (Peng et al., 2016). The apparent protective association may be explained by negative correlations between ozone and NO_X, black carbon (BC), and particle number (PN), each of which demonstrated strong positive associations with pulmonary inflammation (U.S. EPA, 2020).

Consistent with experimental studies in humans, a large body of evidence from recent animal toxicological studies and studies previously evaluated in the 2013 Ozone ISA (U.S. EPA, 2013a) demonstrate inflammatory responses to acute, subacute, and repeated ozone exposures in various animal models. Additionally, results from recent experimental animal studies are also consistent with previous findings of ozone-related pulmonary injury (0.3–2 ppm ozone) and oxidative stress (0.15–2 ppm ozone) (U.S. EPA, 2020). Mechanistic studies present a plausible pathway by which ozone reacts with respiratory tract components, produces oxidized species that injure barrier function and activates innate immunity, resulting in a cycle of inflammation, injury, and oxidative stress.

Several recent studies evaluated respiratory effects of acute ozone exposure (0.2–1 ppm, 3–6 hours) in rodent models of cardiovascular disease. Injury, inflammation, oxidative stress, lung function changes, and increased airway responsiveness were seen in animals with cardiovascular disease in response to ozone exposure (U.S. EPA, 2020). Two recent studies employed an animal model of progressive pulmonary inflammation as a surrogate for COPD. Results suggest that chronic inflammation enhanced sensitivity to short-term ozone exposure (Groves et al. 2012, 2013).

Several recent studies have evaluated the respiratory effects of ozone exposure in animal models of obesity, high fructose/fat diet, and diabetes. Enhanced inflammatory and injury responses were found in obese compared with lean mice and in animals fed high-fat/high-fructose diets compared with those fed a normal diet (U.S. EPA, 2020) In mouse models of obesity, respiratory tract inflammation and injury responses to acute ozone exposure (2 ppm for 3 hours) were enhanced compared with lean controls (Mathews et al., 2018; Mathews et al., 2017a; Mathews et al., 2017b; Williams et al., 2015). However, the inflammatory response to subacute ozone exposure (0.3 ppm for 72 hours) was dampened (Ying et al., 2016; Zhong et al., 2016).

A limited number of epidemiologic panel studies evaluated in the 2013 Ozone ISA (U.S. EPA, 2013a) observed evidence of pulmonary inflammation in children without asthma associated with short-term ambient ozone exposure. These results are coherent with results from experimental studies in humans and animals. Recent studies have examined pulmonary inflammation in general population studies of children (Patel et al., 2013; Salam et al., 2012), with asthma prevalence ranging from 14 to 47%.

Respiratory Infection and other Associated Health Effects
The inflammatory effects of ozone involve the innate immune system, as indicated by increases in airway neutrophils. The adaptive immune system may also be involved via alterations in antigen presentation and co-stimulation by innate immune cells such as macrophages and dendritic cells, which may lead to T-cell activation. Controlled human exposure studies show that ozone exposure results in airway neutrophilia, reflecting activation of the innate immune system, and altered antigen presentation in macrophages and dendritic cells. Subjects involved in these studies were exposed to 80–400 ppb ozone with moderate intermittent exercise. Enhanced adaptive immunity may bolster defenses against infection, as well as increase allergic responses via T-cell activation. Other controlled human exposure studies showed minimal effects of ozone exposure on macrophage phagocytosis or function. In asthmatics, there is increased uptake of particles by airway macrophages that may also enhance the processing of particulate antigens and lead to greater progression of allergic airway disease and contribute to an increased risk of asthma exacerbation (U.S. EPA, 2020).

In animal toxicological studies there is evidence of impaired host defense resulting from exposure to ozone. Increased susceptibility to challenge with infectious agents was observed at ozone concentrations

of 0.08–0.5 ppm. Decreases in mucociliary clearance occurred following exposure to 1 ppm ozone and altered macrophage phagocytosis or function following exposure to 0.1 ppm ozone. In addition, effects on adaptive immunity, such as altered T cell subsets in the spleen (0.6 ppm), decreased antibody response following influenza virus infection (0.5 ppm), and decreased mitogen activated T-cell proliferation (0.5 ppm), have been reported. Effects on natural killer cells, which are effectors of innate and adaptive immunity, have also been reported with decreased activity at concentrations of 0.6–1 ppm, and increased activity or no effect at lower concentrations. Acute exposures to 2 ppm ozone resulted in SP-A oxidation and impairment of SP-A dependent phagocytosis, which led to increased susceptibility to pneumonia. This ozone exposure (2 ppm, 3 hours) increased the area and severity of lung inflammation in both male and female mice, with a larger response observed in females. In addition, spleen red pulp congestion, indicating compromised spleen immune function, occurred in female mice (U.S. EPA, 2020).

There are larger epidemiological studies that have looked at the association between ozone exposure and respiratory infection ED visits. Stieb et al. (2009) observed no evidence of an association between ozone exposure and respiratory infection ED visits at any lag examined (i.e., 0, 1, or 2 days) in an all-year analysis across seven Canadian cities. However, several recent studies provide generally consistent evidence of an association between short-term exposure to ozone and ED visits for a range of respiratory infection endpoints (U.S. EPA, 2020). The large multicity studies in the U.S., including California (Malig et al. 2016), and Canada reported associations between ozone and ED visits for pneumonia (Malig et al., 2016; Xiao et al., 2016), acute respiratory infections (Malig et al., 2016), upper respiratory tract infections (Barry et al., 2018; Szyszkowicz et al.,2018; Malig et al., 2016; Xiao et al., 2016), and ear infections (Xiao et al., 2016). Increases in ED visits ranged from about 2 to 6% per standardized increase in 24-hour avg (Szyszkowicz et al.,2018), 8-hour max (Barry et al., 2018; Xiao et al., 2016), and 1-hour max (Malig et al., 2016) ozone concentrations. Large single-city studies in Atlanta (Darrow et al., 2014), Edmonton (Kousha and Rowe, 2014), and St. Louis (Sarnat et al., 2015; Winquist et al., 2012) also provided generally consistent evidence that ozone is associated with increases in ED visits for pneumonia (Sarnat et al., 2015; Darrow et al., 2014), upper respiratory tract infection (Darrow et al., 2014), and acute bronchitis (Kousha and Rowe, 2014). In contrast to results to these studies, a time-series study in St. Louis did not observe an association between ozone and ED visits for pneumonia (Winquist et al., 2012). Notably smaller studies in Windsor, Canada (Kousha and Castner, 2016) and Little Rock, AR (Rodopoulou et al., 2015) did not observe associations between ozone and ED visits for acute respiratory infections, pneumonia, or ear infections. The observed effect estimates were imprecise (i.e., wide 95% CIs), likely due to the limited sample sizes. Malig et al. (2016) evaluated copollutant confounding for ED visits for respiratory infection.

Respiratory Related Hospital Admissions and Emergency Department (ED) Visits for Aggregated Respiratory-Related Diseases

Numerous studies have found associations of short-term ozone levels and hospital admissions and emergency department admissions for respiratory conditions (U.S. EPA, 2020). The strongest evidence from the 2013 Ozone ISA came from multicity studies of hospital admissions (Katsouyanni et al., 2009; Cakmak et al., 2006; Malig et al. 2016, O' Lenick et al. 2017; Barry et al. 2018) and large single-city studies examining ED visits (Tolbert et al., 2007; Darrow et al., 2011; Sarnat et al., 2015). The studies generally found stronger associations for asthma and COPD in the warm season or in the summer months, compared to the cold season, and also provided evidence that children are at greatest risk of ozone-related respiratory health effects. Several of these studies reviewed in the ISA had average ozone concentrations well below 60 ppb averaged over 8 hours and still reported associations with respiratory

outcomes. One study of asthma emergency department visits reported ozone effects at concentrations as low as 30 ppb (Strickland et al. 2010). A large time-series study in St. Louis, MO (Winquist et al., 2012) reported that 8-hour daily max ozone concentrations were associated with hospital admissions for respiratory disease in children ages 2 to 18 years. Figure I-2, taken from the U.S. EPA Ozone ISA (2020) presents examples of studies regarding all-year and seasonal analysis of ozone exposure and hospital admissions or emergency department visits. This figure illustrates the associations found between ambient ozone exposure and key respiratory outcomes (asthma, COPD and pneumonia), and shows the stronger effects with summertime ozone exposures.
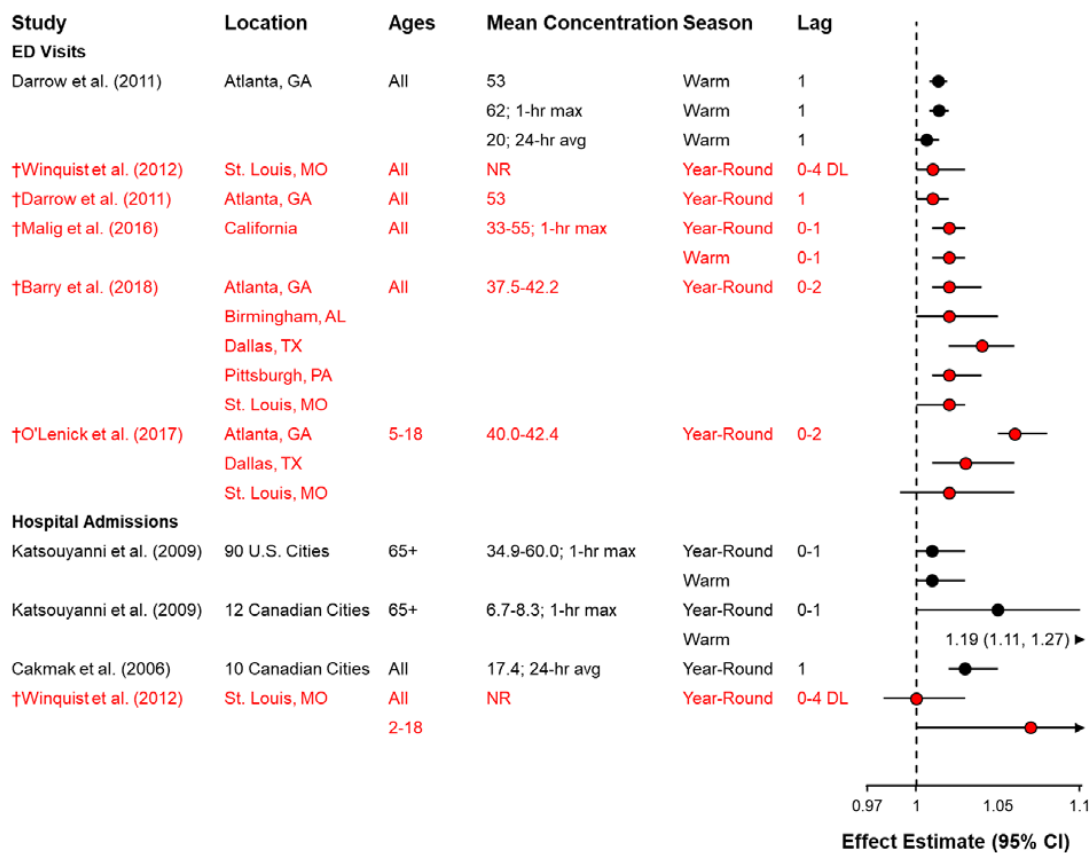
DL = distributed lag.
Note: †Studies published since the 2013 Ozone ISA. Black text = studies included in the 2013 Ozone ISA.
aMean concentrations reported in ppb and are for an 8-hour daily max averaging time unless otherwise noted.
Results standardized to a 15-ppb increase in 24-hour avg, 20-ppb increase in 8-hour daily max, or 25-ppb increase in 1-hour daily max ozone concentrations. Corresponding quantitative results are reported in Table 3-40 and Table 3-41.

FIGURE I-2

SUMMARY OF ASSOCIATIONS FROM STUDIES OF SHORT-TERM OZONE EXPOSURES AND RESPIRATORY-RELATED HOSPITAL ADMISSIONS AND EMERGENCY DEPARTMENT (ED) VISITS FOR A STANDARDIZED INCREASE IN OZONE CONCENTRATIONS.

A recent study in Central California also confirmed that short-term exposure to O_3 is associated with asthma ED visits but also looked at this association by sex (female and male), race (White, Black and

Hispanic), age (2-5, 6-18, 19-40, 41-64 and > = 65) and county (Merced, Madera, Kings, Fresno and Kern) (Gharibi et al., 2019). *The* results showed that an IQR range (18.1 ppb) increase in O_3 exposure three days before an asthma attack was associated with a 6.6% [OR: 1.066 (95% CI: 1.032, 1.082)] increase in the odds of having an asthma ED visit. The overall ORs differed across age groups and races/ethnicities, with strongest for children aged 6-18 years [OR: 1.219 (95% CI: 1.159, 1.280)], adults 19-40 years [OR: 1.102 (95% CI: 1.053, 1.154)] and Blacks [OR: 1.159 (95% CI: 1.088, 1.236)], respectively. O_3 exposure was not positively associated with asthma ED visits for Whites, while it was for other underrepresented groups. Fresno had the highest number of asthma ED visits and positive association among all five counties.

Respiratory Mortality

The U.S. EPA, 2020 ISA concluded that there was a suggestive causal relationship between mortality and short-term ozone exposures. Many studies have found positive associations between short-term increases in ozone levels and excess risk of mortality from all non-accidental causes, cardiovascular causes, and respiratory causes (Bell et al. 2004; Bell et al. 2005; Huang et al. 2005; Ito et al. 2005; Levy et al. 2005; Bell et al. 2008; Zanobetti et al. 2008). Studies conducted across multiple cities in the U.S., Canada, Europe, and Asia reported increased cardiovascular and respiratory mortality risks with increased short-term ozone exposures, and several studies additionally reported increased mortality risk for summer season ozone exposures (Katsouyanni et al. 2009; Samoli et al. 2009; Stafoggia et al. 2010; Wong et al. 2010). Vanos et al. (2014) examined respiratory mortality and reported positive associations in all-year and summer season analyses, which is consistent with the multicity studies previously evaluated. Studies have demonstrated that positive associations with mortality persist even when other variables including season and levels of particulate matter are accounted for, indicating that ozone mortality effects may be independent of other pollutants, although there is some variability across studies with regard to the sensitivity of the ozone associations to adjustment for PM (Bell et al. 2004; Huang et al. 2005; Katsouyanni et al. 2009; Stafoggia et al. 2010).

Inconsistent with the large body of evidence from the above multicity studies Klemm et al. (2011) conducted a study in Atlanta, GA that included 7.5 additional years of data compared with Klemm and Mason (2000) and Klemm et al. (2004) and reported no evidence of an association with respiratory mortality (−0.44% change in mortality [95% CI: −6.06, 5.51] for a 20-ppb increase in 8-hour max ozone concentrations).

Examples of studies showing the relative change in mortality risks for all-year and summer-only analyses are shown in Figure I-3.
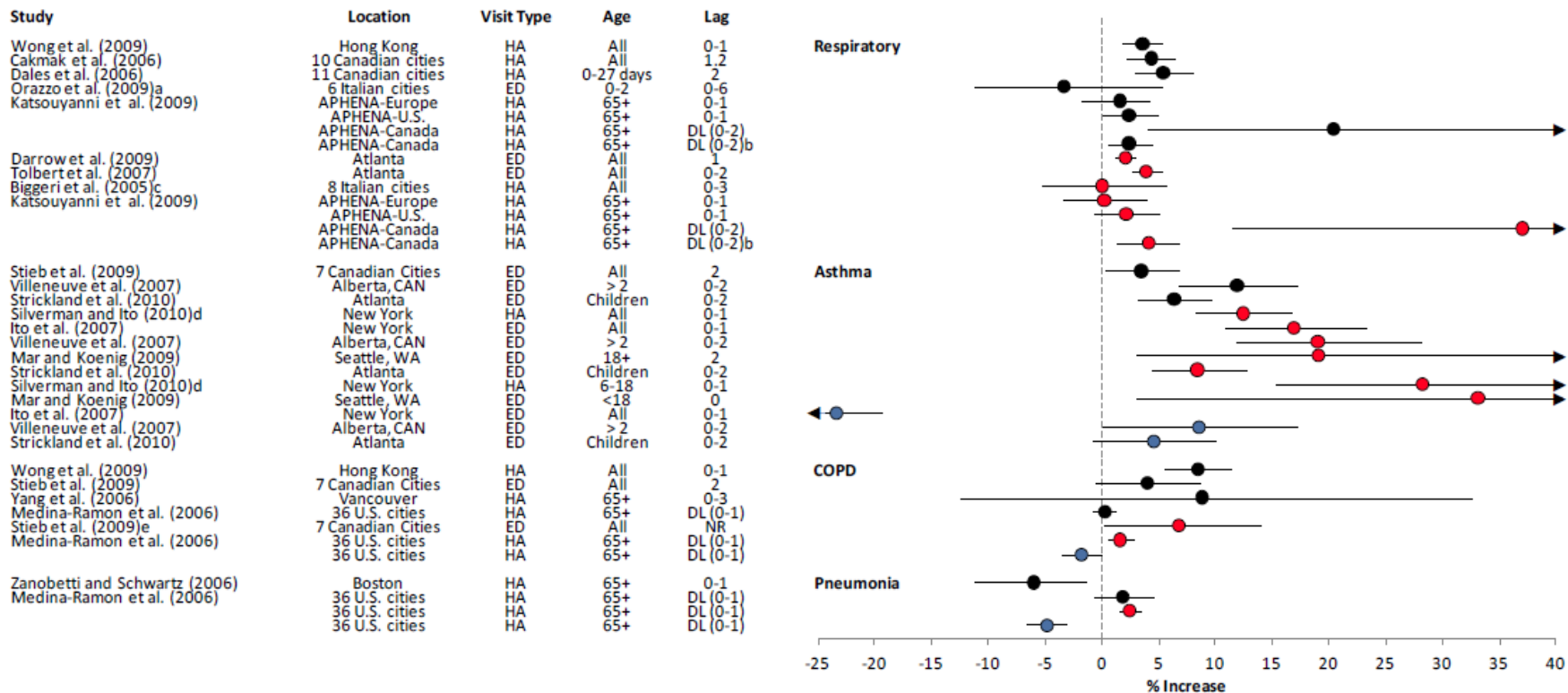
Note: Effect estimates are for a 20 ppb increase in 24-hour; 30 ppb increase in 8-hour max; and 40 ppb increase in 1-hour max O_3 concentrations. HA=hospital admission; ED=emergency department. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis. (Taken from U.S. EPA (2013), Figure 6-19)

FIGURE I-3

CHANGE IN RESPIRATORY-RELATED HOSPITAL ADMISSION AND EMERGENCY DEPARTMENT VISITS IN STUDIES THAT PRESENTED ALL-YEAR AND/OR SEASONAL RESULTS.

Cardiovascular effects

Heart Failure, Impaired Heart Function, and Associated Cardiovascular Effects

Heart failure refers to a set of conditions in which the heart's pumping action is compromised. In congestive heart failure (CHF), the flow of blood from the heart slows and fails to meet the body's oxygen demand. Several studies in the U.S., Canada, and the U.K., observed null results for the association between CHF-related emergency department or hospital visits and ozone exposure averaged over either 8 or 24 hours (Rodopoulou et al., 2015; Milojevic et al., 2014, U.S. EPA, 2020). However, a study in St. Louis, MO reported a 5% increase in ED visits (RR: 1.05; 95% CI: 1.01, 1.09) Winquist et al., 2012) associated with 8-hour max ozone. Similarly, an additional study in St. Louis observed a 4% (RR: 1.04; 95% CI: 0.99, 1.10) increase in ED visits for CHF, which increased to 6% (RR: 1.06; 95% CI: 1.00, 1.12) when CO was included in the model (Sarnat etal., 2015). Copollutant models with either PM2.5 or NO_2 did not change the predicted risk for ozone and hospital admissions (95% CI: 1.02, 1.09) for CHF. Studies evaluating the role of life stage in ozone's effects on heart failure reported no notable differences for older adults (≥65 or 70 years) compared with other adult age groups [19−64 or<70 years; Milojevic et al. 2014; Winquist et al. 2012).

In a recent controlled human study in healthy subjects with or without deletion of GSTM1, Frampton et al. (2015) reported that short-term exposure (3 hours) to ozone (0.1, 0.2 ppm) did not result in statistically significant changes in stroke volume or left ventricular ejection time. Results were independent of the GSTM1 phenotype.

Many recent animal studies provide additional evidence that short-term exposure (3−4 hours, some studies with multiple day exposures) to ozone can result in impaired cardiac function (U.S. EPA, 2020).

Ischemic Heart Disease (IHD) and Associated Cardiovascular Effects

Ischemic Heart Disease (IHD) is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart. Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death occurs secondary to prolonged ischemia due to occlusion of the coronary artery. All the studies involving U.S. or European populations reported null effect estimates for IHD and myocardial infarction (MI), but mixed findings for angina. A multicity study in Europe reported no association for MI, but the same study observed a positive association (OR: 1.19; 95% CI: 1.05, 1.35) for angina pectoris during the warm season [April−September; von Klot et al. (2005)]. In contrast, a study in London, reported null results for angina [OR: 0.98; 95% CI: 0.94, 1.03; Poloniecki et al. (1997)]. Recent studies from Europe, Canada, and the U.S. consistently reported null or small positive effect estimates (i.e., OR ≤ 1.02) in analyses of MI (Nuvolone et al. 2017). A study in Iceland that analyzed associations with air pollutants, including ozone, and dispensing glyceryl trinitrate against angina pectoris did not observe increases in odds ratios in single pollutant models (Finnbjornsdottir et al., 2013).

Endothelial Dysfunction

Endothelial dysfunction is the physiological impairment of the inner lining of blood vessels. Recent panel studies have specifically evaluated short-term ozone exposure and the effects on endothelial function (e.g., FMD, BAD) and biomarkers. Considering a number of endpoints in epidemiologic panel studies, there is some evidence from a small number of these studies of endothelial dysfunction following short-term ozone exposures (Lanzinger et al., 2014, Mirowsky et al., 2017).

Animal toxicological evidence is generally consistent. Studies, including a handful of recent studies, have demonstrated increased vasoconstriction while others showed impaired vasodilation. This evidence is further supported by studies reporting increased blood markers associated with vasoconstriction and/or endothelial injury (U.S. EPA, 2020)

Cardiac Depolarization, Repolarization, Arrhythmia, and Arrest

Two studies in the U.S. and Australia reported no positive associations for out-of-hospital cardiac arrest (Dennekamp et al., 2010; Silverman et al., 2010). A modest elevation in risk of arrhythmia was associated with 8-hour max ozone concentrations during the warm season in Helsinki, Finland [OR: 1.04; 95% CI: 0.8, 1.35; Halonen et al. (2009)], but null results were reported in Atlanta, London, and a multicity study in Canada (Stieb et al., 2009; Peel et al., 2007; Poloniecki et al., 1997). Several recent studies in the U.S., Europe, and Australia have analyzed the association between ozone concentration and cardiac arrest, arrhythmias, or dysrhythmias. Findings from these studies indicate increases in out-of-hospital cardiac arrests associated with 8-hour max or 24-hour avg increases in ozone concentrations; however, null associations are reported for other endpoints.

There is little evidence from a small number of controlled human exposure studies indicating that ozone exposure may result in conduction abnormalities or arrhythmia (U.S. EPA 2020).

In animal studies short-term ozone exposure in rats induced premature atrial contraction, indicators of atrial block, and arrhythmia (U.S. EPA, 2013). Recent studies demonstrate similar effects resulting from short-term exposure (3–4 hours, some studies with multiple day exposures) to ozone (U.S. EPA, 2020).

Blood Pressure Changes and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 130 mm Hg or a diastolic blood pressure above 80 mm Hg. Prolonged high blood pressure is known as hypertension and can lead to a thickening of the ventricular wall resulting in diminished filling during diastole. This can ultimately contribute to the development of arrythmia and heart failure.

A study of emergency department (ED) visits for hypertension in two Canadian cities, Calgary and Edmonton, reported an increased OR of 1.15 among women (95% CI: 1, 1.31), but not men, during the warm season (Brook and Kousha, 2015). No association was observed for women or men during the cold season. A study in Lithuania analyzed emergency medical service records of emergency calls for exacerbations of essential hypertension with elevated arterial blood pressure and found associations with 8-hour max ozone concentrations primarily during the warm season (Vencloviene et al., 2017). While median ozone concentrations in the two study areas were similar (approximately 20 ppb), the maximum concentration in Kaunas, Lithuania (102 ppb) was twice that in the two Canadian cities (50 ppb). No association with ED visits for hypertension and 8-hour max ozone concentration was reported in a time-series study in Arkansas, an area with a higher median ozone concentration (39 ppb) compared with the two other studies that analyzed associations with hypertension (Rodopoulou et al., 2015). A study of elderly non-smokers in the Los Angeles area with a history of heart disease found no associations between ozone exposure and blood pressure nor ST-segment depression, a measure of cardiac ischemia (Delfino et al. 2010; Delfino et al. 2011). This recent evidence is limited in number and generally inconsistent. Evidence from recent epidemiological panel studies remains inconsistent (U.S. EPA, 2020).

There is some evidence for animal studies to suggest that short-term exposure (3–8 hours, some studies with multiple day exposures) to ozone can result in changes in blood pressure in animals (U.S. EPA, 2020).

Heart Rate (HR) and Heart Rate Variability (HRV)

Heart rate (HR) is a key indicator of autonomic function. Heart rate variability (HRV) represents the degree of difference in the inter-beat intervals of successive heartbeats. Given that both arms of the autonomic nervous system contribute, changes in HRV are an indicator of the relative balance of sympathetic and parasympathetic tone to the heart and their interaction (Rowan III et al., 2007). Low HRV is associated with an increased risk of cardiac arrhythmia and an increased risk of mortality in patients with congestive heart failure awaiting a heart or lung transplant (Fauchier et al., 2004; Bigger et al., 1992). Low HRV has also been shown to be predictive of coronary artery disease (Kotecha et al., 2012). Notably, increases in HRV have also been associated with increases in mortality (Carll et al., 2018).

Epidemiological studies evaluating heart rate (HR) and HRV have continued to have inconsistent results. The inconclusive evidence may result from the variations in studies, including, but not limited to, sample size, demographics, exposure, and time lags evaluated for these endpoints (U.S. EPA, 2020).

Past studies have demonstrated some evidence of changes in HRV following short-term ozone exposure (Devlin et al., 2012; El Fakhri et al., 2009). One CHE study reported an increase in HR following ozone exposure in a combined group of hypertensive and healthy controls (Gong et al., 1998). Recent CHE studies have examined the relationship between short-term exposure (1 to 4 hours) to ozone and HRV-related measures, but evidence of an ozone-mediated effect remains limited. There is also no evidence from more recent CHE studies for an ozone effect on HR (U.S. EPA, 2020).

Animal studies show some evidence that short-term exposure to ozone could result in changes in HR and HRV (U.S. EPA, 2013). With respect to HR, recent studies in animals have reported inconsistent results following short-term ozone exposure (3−8 hours, some studies with multiple-day exposures) (U.S. EPA, 2020).

Coagulation and Thrombosis

Coagulation refers to the process by which blood changes from a liquid to a semisolid state to form a clot. Increases in coagulation factors (e.g., fibrinogen, thrombin) or decreases in factors that promote fibrinolysis like tissue plasminogen activator (tPA) can promote clot formation, and thus, increase the potential for MI.

In a case-crossover study of cases identified from discharge data in Spain from 2001−2013, an increased risk of pulmonary embolism was reported for ozone concentrations averaged over the 3 days around the time of diagnosis as compared to the average concentration for a similar period 3 weeks prior (de Miguel-Diez et al., 2016). No associations were observed when control periods closer to the time of diagnosis were analyzed. No associations with first diagnosis for pulmonary embolism and average monthly ozone concentration were reported by a case-control study in Italy (Spiezia et al., 2014) or in a case-crossover study in the U.K. that analyzed 8-hour max ozone concentrations and lags of 0−4 days (Milojevic et al., 2014).

A controlled human exposure study demonstrated changes in markers of coagulation following short-term ozone exposure (Devlin et al., 2012). Several recent CHE studies have examined the potential for short-term ozone exposure (1−2 hours) to result in changes to markers of coagulation or fibrinolysis, but evidence of an effect on these endpoints remains limited (U.S. EPA, 2020).

Very limited animal toxicological evidence shows that short-term exposure (4 hours, some studies with multiple-day exposures) to ozone could result in changes to factors related to coagulation or fibrinolysis (U.S. EPA, 2020).

Systemic Inflammation and Oxidative Stress

Systemic inflammation has been linked to a number of CVD-related outcomes. For example, circulating cytokines such as IL-6 can stimulate the liver to release inflammatory proteins (e.g., CRP) and coagulation factors that can ultimately increase the risk of thrombosis and embolism. Other indicators of systemic inflammation include an increase in inflammatory cells such as neutrophils and monocytes and other cytokines such as TNF. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and further increase the inflammatory response. Recent and older epidemiologic panel studies provide evidence that short-term ozone exposure is associated with increased inflammatory responses (U.S. EPA, 2020).

Controlled human exposure studies have provided limited additional evidence for changes in inflammatory markers following short-term ozone exposure (0.5–4 hours). A biomarker study of students at UC Berkeley who spent their summer vacation in either the Los Angeles or San Francisco Bay Area found that ozone exposures over a period of 2 weeks or 1 month were associated with increases in a biomarker of lipid peroxidation, but no association was found for a biomarker of antioxidant capacity (Chen et al. 2007). Lipid peroxidation is an indicator of oxidative stress, which may be triggered by pulmonary inflammation caused by ozone exposure.

Biller et al. (2011) reported an increase in percentage blood neutrophils ($p < 0.05$) relative to FA exposure at 5, 7, but not 24 hours post-exposure (0.25 ppm) in healthy volunteers. In a time course study, Bosson et al. (2013) reported a decrease in blood neutrophils ($p < 0.05$) in healthy volunteers at 1.5 hours post-exposure (0.2 ppm) when compared to FA exposure. In healthy volunteers, Stiegel et al. (2016) reported an increase in percentage neutrophils following ozone exposure (0.3 ppm) immediately after ($p > 0.05$), but not 24 hours post-exposure when compared to pre-exposure. Arjomandi et al. (2015) reported a decline in eosinophil levels from 0–4 ($p < 0.05$), but not 0–24 hours associated with increasing ozone concentrations from 0.1 to 0.2 ppm in adults with or without asthma. In addition, a study reported statistically significant increases in blood CRP levels across exposures ranging from 0 to 200 ppb, while another reported a significant increase in CRP when comparing post-exposure to pre-exposure levels (Arjomandi et al., 2015; Biller et al., 2011). However, Frampton et al. (2017) found no statistically significant changes in CRP, IL-6, P-selectin, or 8-isoprostane (an oxidative stress marker) levels in older adults following 70 or120 ppb ozone exposure. Ramanathan et al. (2016) also demonstrated that ozone exposure (0.12 ppm) did not alter HDL antioxidant or anti-inflammatory capacity in healthy adults.

In the 2013 Ozone ISA, animal toxicological studies demonstrated that short-term exposure to ozone resulted in an increase in inflammatory markers (U.S. EPA, 2013). In addition, studies in mice and monkeys demonstrated that short-term exposure to ozone resulted in an increase in markers of oxidative stress. Although not entirely consistent within and across studies, more recent animal toxicological studies provide some evidence that short-term exposure (2–24 hours, some studies with multiple-day exposures) to ozone results in an increase in markers of inflammation and oxidative stress (U.S. EPA, 2020).

Stroke and Associated Cardiovascular Effects

A Canadian study reported a weak elevated risk of ischemic and hemorrhagic stroke for 24-hour avg ozone concentrations during the warm season, but not in other seasons; however, confidence intervals were

wide (Villeneuve et al., 2006). In contrast, an inverse association with transient ischemic stroke during the warm season was observed. Recent studies have been inconsistent. Confidence intervals around the risk ratios tended to be wide, indicating the relative imprecision in the reported associations (U.S. EPA, 2020).

Nonspecific Cardiovascular Effects

Several studies of ozone concentrations and cardiovascular hospital admissions and ED visits for all CVD diagnoses combined did not report an association between ozone concentrations and an increased risk of aggregated CVD in populations in the U.S., Canada, Europe, and Australia (U.S. EPA, 2013). Studies conducted in the Los Angeles area or in California also do not provide consistent evidence of short-term ozone effects on cardiovascular morbidity. A Los Angeles-based study of cardiovascular hospital admissions did not find increased risk with ozone exposures (Linn et al. 2000). Recent studies that reported a risk ratio for combined cardiovascular disease outcomes show a similar pattern, although associations were positive during the cold season and negative during the warm season (U.S. EPA, 2020).

Cardiovascular Mortality

Epidemiological studies, including some multi-city studies show relatively consistent associations between short-term ozone exposures and cardiovascular mortality (U.S. EPA, 2013). All studies reported positive associations for cardiovascular mortality in all-year and summer/warm season analyses. Of the recent multicity studies evaluated, only Vanos et al. (2014) examined cardiovascular mortality and reported positive associations in all-year and summer season analyses, which is consistent with the multicity studies previously evaluated.

Metabolic Effects

Metabolic Syndrome

Individuals with metabolic syndrome are at a fivefold increased risk for developing type 2 diabetes and a twofold increased risk for developing cardiovascular disease within 5–10 years (Alberti et al., 2009). Criteria for metabolic syndrome include elevated fasting blood glucose (hyperglycemia), elevated triglycerides, low levels of high-density lipoprotein (HDL), obesity (particularly abdominal obesity), and high blood pressure. The presence of three out of the five criteria meets the clinical diagnosis for metabolic syndrome (U.S. EPA, 2020).

Most available animal toxicological evidence shows short-term ozone exposure results in hyperglycemia and elevated triglycerides, with inconsistencies between studies potentially arising from differences in rodent strain, sex, or diet (U.S. EPA, 2020). In the controlled human exposure study, while circulating free fatty acids increased, there were no significant changes in triglycerides following short-term ozone exposure (Miller et al., 2016a). Some epidemiologic studies examining changes in glucose and lipids provide support for effects associated with short-term ozone exposure, reporting, for example, a positive association between the 5-day mean ozone concentration and fasting glucose and triglyceride levels (Kim and Hong, 2012).

Complications from Diabetes

Dales et al. (2012) evaluated associations of short-term ozone exposure and hospital admissions for diabetic ketoacidosis and diabetic coma in the Santiago region of Chile. Using a 6-day distributed lag, a null association was observed for the relationships of hospital admissions for diabetic ketoacidosis or diabetic coma (1.02; 95% CI: 1.00, 1.04). However, the effect increased in populations aged 75–84 years

(1.08; 95% CI: 1.01, 1.15) and over 85 years (1.08; 95% CI: 1.01, 1.1). While increases were noted in the higher age brackets, the risks were not higher in other age groups (<64 or 65–74 years).

Other Indicators of Metabolic Function

A limited number of animal toxicological studies provide evidence that short-term exposure to ozone may result in inflammation of the visceral or perirenal adipose tissue (U.S. EPA, 2020). Inflammation has been implicated in the development of type 2 diabetes and atherosclerosis leading to coronary heart disease (Ray et al., 2009).

Multiple metabolic indicators from the liver provide evidence that ozone exposure induces hepatic changes affecting glucose homeostasis. Healthy volunteers who exercised with ozone exposure in controlled human exposure studies had increased ketone body formation. In animal toxicological studies, ozone exposure induced changes to the liver including hepatic gluconeogenesis, altered bile acid profile, alterations to β-oxidation, and alterations to proteins in hepatic metabolic pathways (Miller et al, 2015, Miller et al., 2016b).

Following short-term ozone exposure, elevated circulating stress hormones were consistently observed in animal models and in a single controlled human exposure study. Removal of the adrenal glands prevented the release of adrenaline and corticosterone, and further, prevented ozone-induced metabolic effects. Thus, neuroendocrine stress activation may be a primary mechanism through which adverse metabolic outcomes develop from short-term ozone exposure (U.S. EPA, 2020).

Recent animal studies indicate exposure to ozone may alter the composition of the gut microbiota. The study by Fouladi et al. (2020) provides the first evidence of significant associations between exposure to ozone and the compositional and functional profile of the human gut microbiome. These results identify O_3 as an important pollutant that may alter the human gut microbiome (Fouladi et al., 2020).

Total Mortality

Relatively few recent studies have been conducted within the U.S. and Canada that examined the relationship between short-term ozone exposure and total (nonaccidental) mortality. The strongest recent evidence comes from a study by Di et al. (2017a), who evaluated more recent air quality data (i.e., 2000–2012) and analyzed the largest study population, with over 22 million case days included in the case-crossover analysis. Using a well-validated hybrid exposure model, the authors reported a 1.1% increase in all-cause mortality (95% CI: 0.96, 1.24) at lag 0–1 for a 20-ppb increase in 8-hour max ozone concentrations in a single-pollutant model. When limiting ozone data to days where 8-hour max ozone concentrations were less than 60 ppb, there continued to be evidence of a positive association with all-cause mortality in copollutant models with PM2.5 (1.16% [95% CI: 0.92, 1.40]; lag 0–1). A recent study by Madrigano et al. (2015) provides additional evidence for a positive association between short-term ozone exposure and total mortality and characterizes the variation in the association across urban and nonurban areas. The authors examined older air quality data (i.e., 1988–1999) and used kriging to spatially interpolate ozone concentrations using available monitoring data in 12 counties to examine associations between short-term ozone exposure and total mortality across 91 northeastern U.S. counties. The authors examined associations in both urban (≥1,000 persons/mile2) and nonurban (<1,000 persons/mile2) counties. The authors reported positive associations when using both observed and interpolated ozone concentrations (Figure 6-1); they reported evidence of associations that are larger in magnitude for non-

urban counties (1.47% [95% CI: 0.38, 2.54], lag 0 for 20-ppb increase in 8-hour max ozone concentrations) than for urban counties (0.90% [95% CI: 0.16, 1.67], lag 0).

Multiple recent studies that relied on data from NMMAPS spanning the years 1987–2000 also provide evidence of positive associations between short-term ozone exposure and mortality, but the studies vary by the number of cities, lags, exposure metrics, and seasons examined (Liu et al.,2016; Jhun et al., 2014; Moolgavkar et al., 2013). Peng et al. (2013) provides additional evidence of positive associations for short-term ozone exposure and mortality using 1987–1996 air quality data from NMMAPS (50 U.S. cities all-year data; 36 U.S. cities summer only) as well as data from 12 Canadian cities as part of the Air Pollution and Health: A European and North American Approach (APHENA) study. Positive associations were observed in both all-year and summer season analyses, with evidence of associations that are larger in magnitude in the summer in the U.S. when using the NMMAPS data.

Reproductive and Developmental Effects

Male reproduction

Associations between male reproductive health and ozone exposure have been examined through effects on sperm. There is evidence from a limited number of epidemiologic studies that associations between reductions in sperm concentration and both short- and long-term ozone exposures (U.S. EPA 2013). A toxicological study provided evidence of impaired spermatogenesis with ozone exposure that was attenuated by antioxidant supplements (Jedlinska-Krakowska et al., 2006a).

Female Reproduction

Legro et al. (2010) showed some evidence for increased *in vitro* fertilization (IVF) success with short-term ozone exposure during ovulation, but long-term exposure during gestation reduced the likelihood of a live birth. In recent studies, the overall findings are mixed. In a French population undergoing IVF, Carré et al. (2016) observed an increased number of top embryos (i.e., those considered of the best quality) with at least 1 day of high ozone exposure in the 30-day period before ovulation. Another study found no evidence of association with exposures that occurred up to 2 months before conception, but did show an improvement in fecundity with ozone exposure post-conception (Slama et al., 2013). However, a longitudinal study in 500 U.S. couples reported decreased fecundity with short-term ozone exposure near time of ovulation (Nobles et al., 2018).

Evidence from the 2013 Ozone ISA showed that, in most toxicological studies, reproductive success appears to be unaffected by ozone exposure. Nonetheless, one study reported that 25% of the BALB/c mouse dams in the highest ozone exposure group (1.2 ppm, short-term exposure GDs 9–18), compared to 55% in the filtered air group, did not complete a successful pregnancy (Sharkhuu et al., 2011).

Nervous System

Cognitive and Behavioral Effects

In a recent study, Lim et al. (2012) examined older adults in South Korea during a 3-year, follow-up study using the Korean Geriatric Depression Scale-Short Form (SGDS-K). An increase in SGDS-K score, indicating increased depressive symptoms, largely driven by the emotional component of the test, was associated with 3-day moving avg ozone concentration. This finding was supported by a toxicological study of FSL rats (Mokoena et al., 2015). Experimental animal studies reported decreased motor activity and impaired

learning and memory following short-term exposure to ozone (Gordon et al., 2016; Mokoena et al., 2015; Pinto-Almazan et al., 2014). There were no epidemiologic studies of cognition or motor function-related effects. Some of the behavioral effects in animals are supported by data showing effects on neurotransmitter levels that are associated with these outcomes (U.S. EPA, 2020).

Neuroendocrine Effects

Two older studies provide evidence that ozone alters neuroendocrine function, affecting levels of thyroid hormones and corticosterone following short-term exposure (U.S. EPA, 2013). A recent study evaluated potential neuroendocrine effects of ozone in the nervous system following a short-term ozone exposure in rats (Thomson et al., 2013). A 4-hour exposure to ozone concentrations of 0.4 or 0.8 ppm induced a transient effect on a wide array of genes involved in antioxidant response, xenobiotic metabolism, inflammation, and endothelial dysfunction.

Hospital Admissions and Emergency Department Visits

Some positive associations with hospitalizations for migraine, dementia, and multiple sclerosis were observed in single studies. Several studies also reported associations of short-term ozone exposure with mental health hospital admissions or emergency department (ED) visits for conditions such as depression and panic attack, but the results were not entirely consistent (U.S. EPA, 2020). Because hospitalizations or ED visits among those with chronic diseases may be related to comorbid conditions, the extent to which these studies are informative regarding the effect of short-term ozone exposure on nervous system health is uncertain.

Long-Term Exposure Effects of Ozone

The U.S. EPA, 2020 ISA for Ozone concluded that there was a likely causal relationship between long-term ozone exposure and respiratory effects. Evidence supporting this determination comes from epidemiological and toxicological studies, particularly studies of asthma and related symptoms, asthma-related hospital admissions, lung function, lung inflammation and oxidative stress. Long term ozone exposure was suggestive of casual relationship but not sufficient to infer cardiovascular effects, metabolic effects, total mortality, reproductive effects, and central nervous system effects. The 2020 Ozone ISA confirmed these classifications from the 2013 Ozone ISA except that metabolic effects went from "no determination made" to "suggestive of casual relationship."

Respiratory Health Effects

Development of Asthma and Asthma Symptoms

The Adventist Health and Smog Study (AHSMOG) and Children's Health Study cohorts are two large long-term studies conducted in California that examined several aspects of long-term ozone effects in adults and children, respectively. Several of these studies focused on asthma development and exacerbation. The AHSMOG study included adult, non-smoking, non-Hispanic white Seventh Day Adventists living in California. The 10-year follow-up AHSMOG study reported that a 10 ppb increase in annual mean ozone exposures increased the risk of asthma development in males by three-fold (relative risk 3.12, 95 percent confidence interval: 1.16, 5.85), but no effect was seen among females (relative risk 0.94, 95 percent confidence interval: 0.65, 1.34) (Greer et al. 1993). The 15-year follow-up AHSMOG study used an ozone metric focusing on 8-hour average exposures, and reported that a 10 ppb increase was associated with a 30 percent increased risk of developing asthma in males (relative risk 1.31, 95 percent confidence interval: 1.01, 1.71), and these effects persisted even after accounting for other pollutants (McDonnell et al. 1999). The latter study also found no effect in females, although this may reflect a greater potential for misclassification of air pollution exposure in females compared to males, due to different time-activity patterns resulting in greater time spent outdoors among males (U.S. EPA, 2013). In the Children's Health Study, among children living in 12 Southern California communities with high ozone concentrations, the relative risk of developing asthma in children playing three or more sports was found to be over three times higher than in children playing no sports (McConnell et al. 2002). The high ozone communities had a 4-year mean daytime ozone concentration of 59.6 ppb, compared to 40.0 ppb for the low-ozone communities. These findings indicate that new cases of asthma in children may be associated with performance of heavy exercise in communities with high levels of ozone. In an analyses of a large administrative database birth cohort in Quebec, an increase in average summertime ozone concentrations at participants' birth addresses were associated with a 19% increase (95% CI: 16, 23%) in asthma onset in children of all ages (Tétreault et al., 2016a). While it has long been known that air pollution can exacerbate symptoms in individuals with preexisting respiratory disease, these studies indicate that ozone exposure may contribute to asthma onset. Additionally, decreases in baseline ozone concentrations in three CHS cohorts, enrolled in 1993, 1996, and 2006, were associated with decreased asthma incidence. A recent CHS analysis examined asthma incidence in relation to improved air quality in nine southern California communities (Garcia et al., 2019). The findings indicate that improved air quality is associated with lower asthma incidence.

With differing results three recent Southern California studies did not find an association between ozone exposures and childhood asthma incidence but did report increased risks of asthma onset with higher exposures to particulate matter or NO_2 (Islam et al. 2007; McConnell et al. 2010; Nishimura et al. 2013). These studies did not examine whether genetic factors may have played a role in making some people more susceptible than others to the respiratory effects of ozone exposure. Some analyses from the Children's Health Study identified specific genetic variants that, when combined with ambient ozone exposure, either increase or decrease the risk of developing asthma (Islam et al. 2008; Islam et al. 2009; Salam et al. 2009). These genetic variants are involved with antioxidant and/or anti-inflammatory pathways, and are likely involved in key elements of asthma development (U.S. EPA, 2013). A recent pooled retrospective case-control analysis of minority children in the U.S. reported null associations between early-life ozone exposure and asthma incidence (Nishimura et al.,2013). The study was much smaller than above mentioned Quebec study (Tétreault et al., 2016a) and consequently had less precision (i.e., wider 95% CIs).

Other studies examined the impact of long-term ozone exposures and respiratory symptoms, particularly among asthmatics. Studies have linked long-term ozone exposures to increased risk of having poorly controlled asthma, increased asthma symptoms, and respiratory-related school absences (Gilliland et al. 2001; Akinbami et al. 2010; Jacquemin et al. 2012). Notably, Meng et al. (2010) reported an association between ozone concentrations and self-reported asthma symptoms. Similarly, McConnell et al. (2003) observed that bronchitic symptoms in children with asthma were associated with yearly variation in ozone within CHS communities, although the association was reduced when accounting for other pollutants. Like McConnell et al. (2003), Berhane et al. (2016) and Gilliland et al. (2017) observed decreased prevalence of bronchitic symptoms in children with asthma associated with decreased ozone exposure over two decades of follow-up of CHS cohorts. Another cross-sectional study, in the U.K., reported that ozone concentrations (annual accumulated ozone over 40 ppb per daylight hour) were associated with more severe emphysema, as measured by a density mask analysis of a CT Scan (Wood et al., 2009). Contrary to this evidence though an analysis from the CHS found no association between long-term ozone exposures and chronic lower respiratory tract symptoms (McConnell et al. 1999).

Two studies from the CHS demonstrated gene-environment interactions for genes that are involved in inflammation or antioxidant pathways. One study found that asthmatic children with a particular genetic variant that reduces expression of the cytokine TNF-α (as part of an inflammatory response) had reduced risk of bronchitic symptoms for children in low-ozone communities, but not for children in high-ozone communities (Lee et al. 2009). A second study found that a particular genetic variant reduced the risk of respiratory-related school absences among children living in communities with high levels of ozone (defined in this study as being above the median value of 46.9 ppb) (Wenten et al. 2009).

Results of epidemiologic studies of hospital admissions and emergency department visits support the relationship between ozone exposure and respiratory effects. In a 2007 study conducted in Southern California, an increased risk of having poorly controlled asthma was associated with living in areas above the 90th percentile ozone level (28.7 ppb, annual average) among men and elderly individuals (Meng et al. 2007). A study in the South Coast Air Basin found that ozone was associated with increased hospital discharges for asthma among children (Moore et al. 2008). Another study in the South Coast Air Basin looked at infants hospitalized for bronchiolitis. This study found a reduced risk of infant bronchiolitis hospitalization with increased ozone exposure, although there was no association for ozone when accounting for the effect of PM2.5, which was positively associated with this respiratory outcome (Karr et

al. 2007). A study of people with asthma was conducted in the San Joaquin Valley of California, and found that a 10 ppb increase in ozone exposures averaged over one year increased the odds of asthma-related hospital admissions and emergency department visits by approximately 50 percent, and the odds of asthma symptoms among adults by about 40 percent (Meng et al. 2010). Studies conducted in other locations have also reported increases in asthma hospitalizations (U.S. EPA, 2013).

There is also animal toxicological evidence of the development of asthma resulting from ozone exposure during the early postnatal period (U.S. EPA, 2013). Several studies found that cyclic challenge of infant rhesus monkeys to allergen and ozone during the postnatal period compromised airway growth and development and resulted in changes that favor allergic airways responses, increased airway responsiveness, and persistent effects on the immune system. These changes observed in airway responsiveness provide support for the long-term effects of ozone in asthma development or exacerbation (U.S. EPA, 2013).

Recent studies in the infant monkey model of allergic airway disease demonstrated airway smooth muscle hyperreactivity, an enhanced allergic phenotype, and priming of responses to oxidant stress as a result of postnatal ozone exposure. In nonallergic infant monkeys, recent studies demonstrated increased serotonin-positive airway cells and immunomodulation as a result of postnatal ozone exposure. Recent studies in rats demonstrated impaired airway growth and altered airway sensory nerve innervation as a result of postnatal ozone exposure (U.S. EPA, 2020). These animal studies indicate possible chronic effects including functional and structural changes of the lung. However, morphological, developmental, and immunological differences make it difficult to apply these results to humans experiencing ambient exposures.

Lung Function and Development

Epidemiologic studies provided inconsistent evidence of an association between long-term exposure to ozone and lung development in children. In an 8-year follow-up of the CHS cohort, Gauderman et al. (2004) observed a null association between mean annual 8-hour ozone concentrations and deficits in lung function growth (FEV_1). In contrast, in a subsequent CHS analysis, Breton et al. (2011) reported ozone-related deficits in 8-year lung function growth among children without a particular GSS glutathione gene haplotype. Cross-sectional studies of ozone and lung function in children or adults were similarly inconsistent.

A limited number of recent studies in the U.S. continue to provide inconsistent evidence of an association between ozone and lung development or lung function. An extended follow-up of the CHS combined data obtained from three separate cohorts to examine the association between long-term reductions in air pollution and lung development in children between the ages of 11 and 15 (Gilliland et al., 2017; Gauderman et al., 2015). The authors did not observe a notable change in lung function growth or cross-sectional lung function corresponding to decreasing ozone concentrations. Other cross-sectional studies reported modest decreases in lung function metrics associated with ozone, including a pooled retrospective case-control analysis of minority children with asthma in the U.S. (Neophytou et al., 2016), another analysis of a recent CHS cohort that overlaps with one of the cohorts included in the Gauderman et al. (2015) study (Urman et al., 2014), and another study conducted in Greece that looked at long-term exposure to O_3 on respiratory health outcomes in 10-11-year old children (Dimakopoulou et al., 2020). Dimakopoulou et al. (2020) saw that a 10 μg/m3 increase in calibrated long-term O_3 exposure, using measurements from fixed site monitors was associated with lower FVC and FEV_1 by 17 mL (95%

Confidence Interval: 5-28) and 13 mL (3-21) respectively and small decreases in lung growth: 0.008% (0.002-0.014%) for FVC and 0.006% (0.000-0.012%) in FEV_1 over the study period. A recent longitudinal study of lung function in older adults in the U.S. reported decrements in FEV_1 and FVC relative to ozone concentrations (Eckel et al., 2012).

In contrast to the limited and inconsistent evidence from epidemiologic studies, recent experimental studies in animals provide consistent evidence that postnatal ozone exposure may affect the developing lung. Results from studies of neonatal rodents demonstrate ozone-induced injury and changes in inflammatory and oxidative stress responses during lung development. In an infant monkey model with similarities to childhood asthma, postnatal ozone exposure resulted in impaired alveolar morphogenesis, a key step in lung development. Notably, these studies indicated some capacity for repair. Additional studies in adult rats suggest that chronic ozone exposure may alter ventilatory parameters (U.S. EPA, 2020).

Development of Chronic Obstructive Pulmonary Disease (COPD) and Other Associated Respiratory Effects

One recent study used the Ontario Asthma Surveillance Information System to identify adults with asthma and found that ozone was associated with an increase in the odds of COPD incidence in this population (To et al., 2016).

Animal toxicological studies reviewed in the 2013 Ozone ISA found that chronic ozone exposure can damage the distal airways and proximal alveoli, resulting in persistent inflammation and lung tissue remodeling that leads to irreversible changes including fibrotic- and emphysematous-like changes in the lung. Additionally, recent animal toxicological studies provide consistent evidence that subchronic ozone exposure can lead to airway injury and inflammation. In adult animals these changes may underlie the progression and development of chronic lung disease and provide biological plausibility for ozone-induced development of COPD (U.S. EPA, 2020).

Respiratory Infection and Other Associated Respiratory Effects

Two recent studies observed inverse associations between ozone and respiratory infection. Smith et al. (2016) reported an inverse association between 2-year avg ozone concentrations and pulmonary tuberculosis in a nested case-control study of adults in northern California. The authors did observe a strong positive association with NO_2 and a negative correlation between ozone and NO_2, which may explain the inverse association. In a study of otitis media in the first 2 years of life, 2-month avg ozone concentrations were associated with decreased risk of infection (MacIntyre et al., 2011).

Allergic Responses

Cross-sectional studies reported increases in prevalence of hay fever (Parker et al., 2009) and rhinitis (Hwang et al., 2006; Penard-Morand et al., 2005), and increased total serum IgE levels (Rage et al., 2009) associated with ozone concentrations. In copollutant models adjusting for NO_2, the observed association between ozone and rhinitis was persistent (Penard-Morand et al., 2005), while the association with IgE levels was attenuated, but still positive (Rage et al., 2009). In contrast to generally consistent evidence of an association, one study reported null associations between ozone and hay fever (Ramadour et al., 2000).

One recent cross-sectional study provides additional support for an association between long-term exposure to ozone and allergic response. A 2005–2006 National Health and Nutrition Examination Survey (NHANES) analysis, comprising a nationally representative sample of the U.S. population,

examined allergic sensitization measured by detectable allergen-specific IgE levels (Weir et al., 2013). Weir et al. (2013) found that annual average ozone concentrations were associated with increased odds of sensitization to indoor allergens and inhalants.

Another recent large study from China also shows evidence for allergic rhinitis and bronchitic symptoms (e.g., persistent cough and phlegm) associated with O_3. This study included a total of 59,754 children from the seven northeastern cities study (SNEC), who were aged 2 to 17 years and from 94 kindergarten, elementary and middle schools. A higher level of O_3 was significantly associated with increased risk of allergic rhinitis and bronchitic symptoms. After controlling for potential confounders, the OR (95% CI) were 1.13 (1.07-1.18), 1.10 (1.06-1.16), and 1.12 (1.05-1.20) for AR, persistent cough, and persistent phlegm, respectively, associated with each interquartile range (IQR) rise in O_3 concentration. Interaction analyses showed stronger adverse effects of O_3 on allergic rhinitis in children aged 7-17 years than those aged 2-6 years, while the adverse association of O_3 with cough was more prominent in females and children aged 7-12 years than in males and children aged 2-6 and 13-17 years. This study showed that long-term exposure to ambient O_3 was significantly associated with higher risk of allergic rhinitis and bronchitic symptoms in children, and the association varies across age and gender (Zhou et al., 2021).

Animal toxicological evidence also shows allergic responses resulting from exposure to ozone. A 4-week exposure to ozone (0.5 ppm for 5 hours, once a week) increased injury, inflammation, and allergic responses in a rodent model of allergic airway disease. Newly available evidence shows that repeated subchronic exposure to 0.1 ppm ozone promoted eosinophilic airway inflammation in a model of allergic sensitization (U.S. EPA, 2020).

Respiratory Effects in Pregnancy

Newly available evidence shows that pregnant rats responded to ozone exposure with immediate effects on ventilatory parameters and later effects reflecting airway injury. A recent study in pregnant rats (Miller et al., 2017) demonstrated that exposure to 0.4 and 0.8 ppm ozone on Gestational Days 5 and 6 resulted in altered ventilatory parameters (decreased minute volume and increased enhanced pause) immediately post-exposure and increased markers of injury (gamma glutamyl transferase and N-acetyl-glutaminidase) in BALF on Gestational Day 21. The observed alterations in enhanced pause were dose dependent.

Respiratory Effects in Populations with Metabolic Syndrome

A recent study (Gordon et al., 2016b) was conducted in male and female rats fed high-fructose and high-fat diets prior to and during 4 weeks of ozone exposure (0.8 ppm for 5 hours/day, once a week). Ozone exposure increased a marker of injury (albumin) and a marker of inflammation(eosinophils) in BALF of males on the high-fructose and high-fat diets. Females on the high-fat diet had increased albumin and females on the high-fructose diet had increased eosinophils in response to ozone exposure. The high-fructose and high-fat diets enhanced some of the effects of ozone on inflammatory or injury-related markers.

Respiratory Mortality

Unlike short-term ozone exposures, there is limited evidence linking long-term ozone exposures with mortality. A large study based on the American Cancer Society Cancer Prevention Study II (CPS-II) cohort included 96 metropolitan statistical areas in the U.S., and reported that a 10 ppb increase in daily maximum 1-hour ozone concentrations averaged between April and September (warm season) was associated with a relative risk of 1.040 (95 percent confidence interval: 1.010, 1.067) for respiratory deaths, but no association with cardiovascular deaths (Jerrett et al. 2009). A U.S. study of Medicare

enrollees reported increased risk of mortality with higher ozone exposures averaged over the warm season, among patients who had previously been hospitalized for congestive heart failure, myocardial infarction, COPD and diabetes (Zanobetti et al. 2011). Two recent large-scale studies found increased risk of all-cause, cardiovascular, and respiratory mortality with long-term ozone exposures, even after accounting for the effects of PM2.5 and NO_2, as well as other behavioral and demographic factors, including smoking (Turner et al. 2016; Kim et al. 2020). In contrast, Jerrett et al. (2013) reported a null association between long-term ozone exposure and respiratory mortality in an analysis of the ACS cohort limited to participants from California. Several recent analyses of the CanCHEC cohort in Canada provide inconsistent evidence for an association between long-term ozone exposure and respiratory mortality, with one reporting a positive association (Weichenthal et al., 2017) and the other reporting a negative association (Crouse et al., 2015). Cohort studies conducted in France (Bentayeb et al., 2015) and the U.K. (Carey et al., 2013) also report negative associations between long-term ozone exposure and respiratory mortality.

Other studies have found temperature to be an important potential risk factor for mortality and may confound or modify the associations between air pollution exposure and mortality (Basu et al. 2002; Cheng et al. 2008). The Turner 2016 study examined the role of temperature, and found that the associations between ozone and mortality differed based on average daily maximum temperatures (Turner et al. 2016).

Cardiovascular Effects

Atherosclerosis

A recent U.S. cohort study evaluated long-term ozone exposure, averaged in early life (ages 0–5 years), during elementary school (ages 6–12 years) and during the first 20 years of life (Breton et al., 2012). These authors observed positive associations between ozone averaged over all three exposure windows and increases in CIMT measured in southern California college students.

The 2013 Ozone ISA (U.S. EPA, 2013) presented evidence that long-term exposure to ozone in ApoE−/− mice resulted in enhanced aortic atherosclerotic lesions when compared with filtered air exposure. Recent studies have provided inconsistent evidence of an effect of long-term ozone exposure (4–17 weeks) on potential markers of atherosclerosis (U.S. EPA, 2020).

Heart Failure and Impaired Heart Function

A recent national cohort study conducted in England observed an inverse association between long-term ozone exposure and heart failure (Atkinson et al., 2013), and a cohort study conducted in South Korea observed an inverse association Kim et al. 2017.

There was evidence from an animal toxicological study that long-term ozone exposure decreased LVDP, rate of pressure development, and rate of change of pressure in isolated perfused rat hearts (U.S. EPA, 2013). Similarly, two recent studies from the same laboratory reported a decrease in LVDP following long-term exposure (4–8 weeks) to ozone (0.8 ppm) in isolated perfused rat hearts [$p < 0.05$; Perepu et al. (2012); Sethi et al. (2012). Moreover, Perepu et al. (2012) also reported a decrease in the rate of pressure development and a decrease in pressure decay in these hearts ($p < 0.05$). This decrease in pressure decay is consistent with impaired diastolic function (i.e., cardiac filling) and is consistent with additional results from this study indicating an increase in left ventricular end diastolic pressure. Thus, both studies demonstrate that long-term ozone exposure can result in abnormal cardiac function (U.S. EPA, 2020).

Blood Pressure Changes and Hypertension

Chuang et al. (2011) investigated the relationship between long-term ozone exposure and blood pressure and observed increases in both systolic and diastolic blood pressure associated with ozone concentrations among older adults in Taiwan, although these increases were attenuated in models that included copollutants. A number of recent studies, conducted mainly in Asia, observed inconsistent results between long-term ozone exposure and blood pressure or hypertension among healthy adults. However, there is some emerging evidence that long-term ozone exposure may be associated with changes in blood pressure or hypertension among different life stages or those with pre-existing disease. A U.S. cohort study observed positive associations between long-term ozone exposure and incident hypertension among black women (Coogan et al., 2017). Similarly, cross-sectional studies conducted in China observed positive associations between long-term ozone concentrations and prevalent prehypertension (Yang et al.,2017) and hypertension (Dong et al., 2015; Dong et al., 2014; Dong et al., 2013b; Zhao et al.,2013).

Heart Rate and Heart Rate Variability

A recent cohort study observed positive associations between annual average ozone concentrations and increases in heart rate in a Spanish population (Cole-Hunter et al., 2018). Recently, Gordon et al. (2013) reported that long-term exposure (17 weeks) to ozone (0.8 ppm) did not result in changes in HR in adult or senescent rats. However, in an additional study using a different exposure protocol this group did find an increase in HR following long-term episodic exposure (13 weeks) to ozone (1.0 ppm; $p < 0.05$) in adult or senescent rats (Gordon et al., 2014).

Coagulation

There is some evidence that long-term exposure to ozone results in changes in factors involved in coagulation (U.S. EPA, 2020).

Systemic Inflammation and Oxidative Stress

Epidemiological studies provide inconsistent results. Animal studies do provide some evidence that long-term exposure (4–17 weeks) to ozone can result in an increase in markers of inflammation and oxidative stress (U.S. EPA, 2020).

Stroke and Associated Cardiovascular Effects

A recent national cohort study conducted in England observed null associations between long-term ozone exposure and both stroke and cerebrovascular disease (Atkinson et al., 2013). In addition, several recent publications report results from a cross-sectional study conducted in 33 Chinese communities, noting positive associations between long-term ozone exposure and stroke (Dong et al., 2013a). When stratified by obesity status, positive associations were observed between long-term ozone exposure and stroke for adults that were overweight or obese, and null associations for adults with normal weight (Qin et al., 2015).

Other Cardiovascular Endpoints

A recent case-control study conducted in Italy (Spiezia et al., 2014) reported negative associations between monthly average ozone concentrations and unprovoked acute isolated pulmonary embolism.

A recent U.S. nationwide study in a cohort of older men (Tallon et al., 2017) observed positive (though imprecise) associations between self-reported incident erectile dysfunction and long-term warm-season ozone exposure averaged over 1 to 7 years.

Cardiovascular Mortality

The strongest evidence for an association between long-term ozone exposure and cardiovascular mortality comes from nationwide analyses of the ACS cohort, demonstrating positive associations with cardiovascular mortality (Turner et al., 2016; Jerrett et al., 2013; Jerrett et al., 2009), IHD mortality (Jerrett et al., 2013), cerebrovascular disease mortality (Turner et al., 2016), and mortality due to dysrhythmia and heart failure (Turner et al., 2016). Several recent analyses of the CanCHEC cohort in Canada provide consistent evidence for a positive association between long-term ozone exposure and cardiovascular and IHD mortality (Cakmak et al., 2018; Cakmak et al., 2016; Crouse et al., 2015). However, cohort studies conducted in France (Bentayeb et al., 2015), the U.K. (Carey et al., 2013), and South Korea (Kim et al., 2017) report negative associations between long-term ozone exposure and respiratory mortality. Furthermore, several recent studies conducted in the U.S. and Canada provide limited and inconsistent evidence for an association between long-term ozone exposure and mortality due to cerebrovascular disease (U.S. EPA, 2020).

Metabolic Effects

Metabolic Syndrome

Individuals with metabolic syndrome are at a fivefold increased risk for developing type 2 diabetes and a twofold increased risk for developing cardiovascular disease within 5–10 years (Alberti et al., 2009). Criteria for metabolic syndrome include elevated fasting blood glucose (hyperglycemia), elevated triglycerides, low levels of high-density lipoprotein (HDL), obesity (particularly abdominal obesity), and high blood pressure.

Results from one animal study suggest ozone impairs insulin secretion, and in another, that senescent animals are more sensitive to ozone-induced effects on insulin (Bass et al., 2013; Miller et al., 2016b). These same studies suggest long-term ozone exposure may result in decreased serum triglycerides and decreased HDL-C in some groups, with differences potentially mediated by age and the amount of time elapsed since ozone exposure. Kim et al., (2019) showed that higher exposure to regional air pollutants, including ozone, was associated with higher fasting serum lipid measures. These associations were more pronounced in obese participants, suggesting obesity may exacerbate the effects of air pollution exposure on lipid levels in young adults.

A few recent epidemiological studies have shown that long-term exposure to ozone is associated with increased weight gain and obesity, although these studies do not specifically address waist circumference (Dong et al., 2014; Li et al., 2015, White et al., 2016). Huang et al., 2020 did a meta-Analysis in Chinca and O_3 were associated with higher level of body mass index, with the pooled β (95% CIs) of 0.34 (0.30–0.38) and 0.21 (0.17–0.24) per 10 μg/m3 increment, respectively. In addition, increased NO_2, SO_2 and O_3 were associated with higher risk of having overweight/obesity, with the corresponding pooled OR (95% CI) of 1.13 (1.01–1.26), 1.04 (1.01–1.06) and 1.07 (1.02–1.13) per 10 μg/m3 increment.

There is some emerging evidence that long-term ozone exposure may be associated with changes in blood pressure or hypertension among different life stages or in those with pre-existing disease (U.S. EPA, 2020).

Chen et al., 2019 indicates that near roadway air pollution exposure is associated with altered fatty acid metabolism, which could contribute to the metabolic perturbation in obese youth.

Development of Diabetes

Recent studies, that include large cohort studies around the world provide evidence for increased incidence for type 2 diabetes and metabolic syndrome. Jerrett et al. (2017) analyzed data from the Black Women's Health Study Cohort in a prospective study of type 2 diabetes. The 43,003 women were greater than 30 years old, resided in56 metropolitan areas, and had BMI information at baseline. The study observed increased hazard ratios for incident diabetes (1.28; 95% CI: 1.06, 1.55); when adjusted for NO_2, this relationship was slightly weaker and had wider confidence intervals (1.20; 95% CI: 0.96, 1.50). Renzi et al. (2017) evaluated the effects of ozone exposure in over one million subjects over 35 years old without diabetes at baseline. The study observed modest positive hazard ratios for incidence of diabetes for those living in Rome (1.01; 95% CI: 1.00, 1.02). Yang et al. (2018) looked at the odds of developing metabolic syndrome due to exposure to ozone in adults from the 33 Communities Chinese Health Study Cohort in participants that were 18–74 years of age and had lived in the same location for more than 5 years. The study reported high correlations of ozone with PM10 (r = 0.81) and SO_2 (r = 0.84); these high correlations may indicate copollutant confounding and are a source of uncertainty in estimating the direct effect of ozone on metabolic syndrome (U.S. EPA, 2020).

The evidence relating to the effect of long-term exposure to ozone on Type 1 Diabetes (T1D) is limited to a prospective study in Scania, Sweden (Malmqvist et al., 2015). The study evaluated prenatal exposure during first, second, and third trimesters of pregnancies for children born between 1999–2005. There were elevated ORs for T1D in the highest quartile of ozone concentrations in the first (1.52; 95% CI: 0.88, 2.61) and second trimester (1.62; 95% CI: 0.99, 2.65), although confidence intervals were wide. There was no evidence of association with third-trimester exposure levels.

Several studies of gestational diabetes were conducted. Generally, the results of the studies were inconsistent, although several reported positive associations with gestational diabetes or impaired glucose tolerance with ozone exposures during the second trimester (U.S. EPA, 2020).

Metabolic Disease Mortality

A recent analysis from the ACS cohort in the U.S. and the CanCHEC cohort in Canada provide consistent evidence for positive associations between long-term ozone exposure and mortality due to diabetes or cardiometabolic diseases (Turner et al., 2016; Crouse et al., 2015).

Total Mortality

A limited number of recent epidemiologic studies have assessed the relationship between long-term ozone exposure and total mortality in adults. The strongest evidence for an association between long-term ozone exposure and total mortality comes from an analysis among four sub cohorts with pre-existing disease from the Medicare cohort (Zanobetti and Schwartz, 2011), demonstrating positive associations among those with pre-existing heart failure, MI, diabetes, or COPD. A recent analysis of the entire Medicare cohort, including over 61 million older adults, observed positive associations between long-term ozone exposure and total mortality, even when limited to areas in the U.S. where the predicted annual average ozone concentrations were less than 50 ppb (Di et al., 2017b). Several recent analyses of the CanCHEC cohort in Canada provide additional evidence of a modest positive association [consistent in magnitude with the association reported by Di et al.(2017b)] between long-term ozone exposure and total mortality (Cakmak et al., 2018; Weichenthal et al., 2017; Cakmak et al., 2016; Crouse et al., 2015). A recent study conducted in California among a cohort of individuals with cancer observed a positive association

between long-term ozone exposure and total mortality (Eckel et al., 2016). However, evidence from the ACS cohort provide little evidence for an association between long-term ozone exposure and total mortality (Turner et al., 2016; Jerrett et al., 2013; Jerrett et al., 2009) and several studies conducted outside of North America report negative associations between long-term ozone exposure and total mortality, specifically in France (Bentayeb et al., 2015), the U.K. (Carey et al., 2013), and South Korea (Kim et al., 2017).

Reproductive and Developmental Effects

Male reproduction

Recent evidence includes a small panel study in Brazilian men with systematic lupus erythematosus that reported decreases in sperm concentration and count with long-term (0–90 days before collection) ozone exposure (Farhat et al., 2016), and a Chinese cohort that observed no evidence of association (Liu et al., 2017).

Female Reproduction

Legro et al. (2010) showed some evidence for increased *in vitro* fertilization (IVF) success with short-term ozone exposure during ovulation, but long-term exposure during gestation reduced the likelihood of a live birth.

Pregnancy and Birth Outcomes

There is some epidemiologic evidence for the effects of ozone on fetal growth, especially for continuous-term birth weight (Vinikoor-Imler et al. 2014; Laurent et al. 2013; Laurent et al. 2016; Tu et al., 2016, Chen et al. 2017, Smith et al., 2017; Ha et al., 2014; Olsson et al.,2013), a conclusion supported by toxicological evidence in rodents (Sharkhuu et al., 2011; Haro and Paz, 1993, Miller et al., 2017).

There is also consistent evidence for an association between ozone exposures during early to mid pregnancy with preterm birth in epidemiologic studies (U.S. EPA, 2020). In a meta analysis, Rapazzo et al. (2021) showed that an increase in ozone exposure during early pregnancy is associated with preterm birth across studies 18 different studies.

Some studies conducted in California have examined reproductive or developmental effects, including birth defects, low birth weight or birth weight reductions, stillbirth and autism (Ritz et al. 2002; Ritz et al. 2007; Morello-Frosch et al. 2010; Becerra et al. 2013; Mobasher et al. 2013; Trasande et al. 2013; Laurent et al. 2014; Green et al. 2015; Laurent et al. 2016; Symanski et al. 2016, Jo et al., 2019; Steurer et al., 2020, Sarovar et al., 2020, Patterson et at., 2021).

Nervous System

Brain Inflammation and Morphology

Long-term ozone exposure elicited similar effects on the brain versus short-term exposure, with many studies showing increases of inflammatory and oxidative-stress responses, elevated cell death, and changes in neuronal morphology in various regions of the brain. In general, the magnitude and severity of the effects was generally increased with longer exposure durations; however, some studies found these effects could be mitigated by coexposure with antioxidants (U.S. EPA, 2020).

Effects on Cognition, Motor Activity, and Mood

A cross-sectional analysis of NHANES III (1988–1991) data showed declines on tests of cognitive function measured using Neurobehavioral Evaluation System-2 (NES2) (Chen and Schwartz, 2009). A small number of recent studies examine the effect of long-term exposure to ozone with performance on neurobehavioral tests, Alzheimer's disease, and other forms of dementia.

Domain-specific (i.e., executive function) decrements were observed in association with long-term exposure to ozone in a cross-sectional analysis of older adult women in Los Angeles, CA (Gatto et al., 2014). Cleary et al. (2018) examined the rate of cognitive decline using the MMSE among subjects followed through U.S. Alzheimer's Disease Centers, reporting an effect of ozone among those who had normal cognition at baseline. Overall, the limited number of epidemiologic studies support an effect of long-term exposure to ozone on reduced cognitive function, but effect estimates reported in studies of dementia are inconsistent (U.S. EPA, 2020).

Motor Function-Related Effects

A prospective cohort study of depression onset among older women enrolled in the Nurses' Health Study (NHS) reports an association of long-term exposure to ozone with use of antidepressant medication (HR: 1.08; 95% CI: 1.02, 1.14) but not with self-reported doctor-diagnosed depression (HR: 1.00; 95% CI: 0.92, 1.08) (Kioumourtzoglou et al., 2017). The animal data do not support an association between long-term ozone exposure and mood disorders (U.S. EPA, 2020).

Neurodevelopmental Effects

Several recent studies conducted in the U.S. and Taiwan report positive associations, but associations are imprecise (i.e., wide confidence intervals) and are not consistently observed across pregnancy periods. Becerra et al. (2013) conducted a case-control study of autistic disorder, diagnosed between 3 and5 years of age, in Los Angeles, CA. Ozone exposure during the entire pregnancy but not trimester-specific exposures was associated with autistic disorder (OR: 1.05; 95% CI: 1.01, 1.10). Also in California, among children enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, Volk et al. (2013) reported small imprecise (relative the width of the confidence interval) associations of full syndrome autism with ozone concentrations during the 1st year of life, during the entire pregnancy and with trimester-specific ozone concentrations (e.g., OR: 1.05; 95% CI: 0.84, 1.31; entire pregnancy). Additional analyses of the CHARGE cohort reported an interaction between ozone exposure and chromosome copy number variation, indicating a larger risk for the joint effect compared to the effect of ozone or duplication burden alone (Kim et al., 2017), but not between ozone exposure and folic acid (Goodrich et al., 2017). A cohort study in Taiwan reported an association between long-term ozone exposure and Autism Syndrome Disorder [HR: 1.59; 95% CI: 1.42, 1.78; Jung et al. (2013)].

Cancer and Related Health Effects

Genotoxicity

Several epidemiologic studies evaluated in the 2013 Ozone ISA (U.S. EPA 2013) observed positive associations between long-term ozone exposure and DNA damage (i.e., DNA adduct levels, oxidative DNA damage, DNA strand breaks). In addition, there was some evidence of cytogenetic damage (i.e., micronuclei frequency among lymphocytes and buccal cells) after long-term. Such DNA and cytogenic damage may be relevant to mechanisms leading to cancer development and serve as early indicators of an elevated risk of mutagenicity. A few recent studies have looked at the relationship between ozone

exposure and the potential for DNA damage and found inconsistent results (U.S. EPA, 2020). Studies in experimental animals and in vivo have indicated that ozone can produce oxidative stress and induce genetic effects (Di Mauro et al., 2019).

Cancer Incidence, Mortality, and Survival

The number of studies examining the relationship between ozone exposure and the potential for carcinogenesis reman few. The reanalysis of the full American Cancer Society (ACS) Cancer Prevention Study II (CPS II) cohort reported no association between lung cancer mortality and ozone concentration [HR: 1.00; 95% CI: 0.96, 1.04; Krewski et al. (2009)]. Additionally, no association was observed when the analysis was restricted to the summer months. There was also no association between ozone concentration and lung cancer mortality present in a sub analysis of the cohort in the Los Angeles area. Animal toxicological studies did not demonstrate enhanced lung tumor incidence in male or female rodents. However, there was an increase in the incidence of oviductal carcinoma in mice exposed to 0.5 ppm ozone for 16 weeks (U.S. EPA, 2013) The implications of this result are unclear because the report lacked statistical information.

However, several recent cohort and case-control studies have observed positive associations between long-term ozone exposure and lung cancer incidence or mortality. A case-control study conducted in Canada (Hystad et al., 2013) and a cohort study conducted in China (Guo et al., 2016) observed positive associations between long-term ozone exposure and lung cancer incidence. Two U.S.-based cohort studies (Eckel et al., 2016; Xu et al., 2013) reported positive associations between long-term ozone exposure and lung cancer mortality or respiratory cancer mortality among individuals that had already been diagnosed with cancer. Wu et al. (2020) showed that O_3 exposure was associated with meningioma risk in men (HR = 1.77, 95% CI = 1.02 to 3.06).

Nonetheless recent studies conducted in the U.S., Canada, and Europe provided limited and inconsistent evidence for an association between long-term ozone exposure and lung cancer mortality (Cakmak et al., 2018; Turner et al., 2016; Crouse et al., 2015; Carey et al., 2013; Jerrett et al., 2013). A case-crossover study conducted in Shenyang, China observed null associations between short-term ozone exposure and lung cancer mortality (Xue et al., 2018). Additionally, studies of childhood leukemia (Badaloni et al., 2013) and breast tissue density, an indicator of breast cancer (Yaghjyan et al., 2017), observed null associations with long-term ozone exposure.

Sensitive Populations for Ozone-Related Health Effects

Several population groups are potentially at increased risk for ozone exposure effects. The U.S. EPA has identified several populations as having adequate evidence for increased risk from ozone exposures. These include children, older adults, outdoor workers, and individuals with asthma, certain variations in genes related to oxidative metabolism or inflammation, or reduced intake of certain nutrients such as Vitamins C and E (Kreit et al. 1989; Horstman et al. 1995; Sienra-Monge et al. 2004; Romieu et al. 2012; U.S. EPA, 2013; Bell et al. 2014, U.S. EPA, 2020). There is suggestive evidence for other potential factors, such as a person's sex, socioeconomic status, and obesity (U.S. EPA, 2020). Some other factors that could affect sensitivity to ozone have also been studied; however, there was inadequate evidence to conclude whether these were risk factors for ozone sensitivity. The table below summarizes the evidence for factors affecting sensitivity to ozone from the 2020 ISA for ozone.

TABLE I-3

SUMMARY OF EVIDENCE FOR POTENTIAL INCREASED SUSCEPTIBILITY TO OZONE-RELATED HEALTH EFFECTS

Evidence Classification	Potential At Risk Factor
Adequate evidence	Pre-existing Asthma Children Older adults Outdoor worker Genetic factors Diet
Suggestive evidence	Sex Pre-existing obesity Socio economic status (SES)
Inadequate evidence	Race/ethnicity Pre-existing COPD Pre-existing CVD Pre-existing diabetes Smoking
Evidence of no effect	--

From (U.S. EPA, 2020) Table IS-10

As previously mentioned, one group that has been recognized as being particularly sensitive to the effects of ozone is young children with asthma, because their lungs are still developing, their potential for increased exposure due to time spent exercising outdoors, and their high ventilation rates relative to body weight (U.S. EPA, 2013). Some factors that may contribute to the increased sensitivity among people with asthma include having an altered innate immune function and factors that decrease their antioxidant defenses (Alexis et al. 2014). Ozone creates secondary oxidation products that are electrophilic, and certain genetic factors influence a person's ability to metabolize these electrophiles, which can affect respiratory function (U.S. EPA, 2013). Asthma exacerbations are more prevalent and severe in young boys than in girls, but the evidence on whether boys are more susceptible than girls to the effects of air pollution on asthma symptoms is not consistent (Guarnieri et al. 2014).

Summary – Ozone Health Effects

Outdoor ozone exposures have been associated with a range of negative human health effects. The strongest evidence for negative health impacts is on the respiratory system. Recent evidence continues to support this. For short-term ozone exposure, controlled human exposure studies conducted over many decades provide experimental evidence for ozone-induced lung function decrements, airway responsiveness, respiratory symptoms, and respiratory tract inflammation. Epidemiologic studies continue to provide evidence that ozone concentrations in ambient air are associated with a range of respiratory effects, including asthma exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation, respiratory infection, and hospital admissions and emergency department (ED) visits for combined respiratory diseases. A large body of animal toxicological studies demonstrate ozone-induced alterations in lung function, inflammation, increased airway responsiveness, and impaired lung host defense (U.S. EPA, 2020). With respect to long-term ozone exposure, there is strong coherence between animal toxicological studies of changes in lung morphology and epidemiologic studies reporting positive associations between long-term ozone exposure and new-onset asthma, respiratory symptoms in children with asthma, and respiratory mortality.

In addition, recent evidence indicates that short-term exposure to ozone is likely to induce metabolic effects. Recent evidence from animal toxicological, controlled human exposure, and epidemiologic studies indicate there is a "likely to be causal relationship" between short-term ozone exposure and metabolic effects (U.S. EPA, 2020)."

There is also some evidence that ozone exposure can affect the cardiovascular and nervous systems, reproduction and development, and mortality, although there are more uncertainties associated with interpretation of the evidence for these effects. Notably, there are changes in the causality determinations for short-term ozone exposure and cardiovascular effects, as well as for total mortality. In both cases new evidence indicating inconsistent results, a paucity of positive evidence from epidemiologic studies, and uncertainties due to a lack of control for potential confounding by copollutants in epidemiologic studies, has elicited the reclassification from "likely to be causal relationship," to "suggestive of, but not sufficient to infer, a causal relationship" between short-term ozone exposure and cardiovascular effects or total mortality in the most recent ISA (U.S. EPA 2020).

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in physical, chemical, and biological dimensions. Physically, particles can vary by size, surface area and roughness, shape, and mass. Chemically, they vary by chemical composition. Biologically, they can vary by toxicity. In addition, particles vary by source, and can come from anthropogenic (man-made, such as from combustion of fuels, or frictional abrasion) or "natural" (plants – for example, pollens and spores) origins. The composition of particulate matter can vary across sub-regions, and a description of the spatial differences in PM composition can be found in the draft 2022 AQMP Chapter 2 and Appendix II.

The National Ambient Air Quality Standard for particulate matter was established in 1971 and set limits on the ambient level of Total Suspended Particulates (TSP). In 1987, the national particulate matter standards were revised to focus on particles sized 10 µm (micrometers) aerodynamic diameter and smaller. These can be inhaled and deposited throughout the upper and lower respiratory system, depositing in both airways and gas-exchange areas of the lung. These particles are referred to as PM10. U.S. EPA initially promulgated ambient air quality standards for PM10 of 150 µg/m³ averaged over a 24-hour period, and 50 µg/m³ for an annual average. U.S. EPA has since rescinded the annual PM10 standard but kept the 24-hour standard.

As more health research data has become available, concerns have centered on smaller and smaller particles. Additional focus has been placed on particles having an aerodynamic diameter of 2.5 µm or less (PM2.5). A greater fraction of particles in this size range can penetrate and deposit deep in the lungs. The U.S. EPA established standards for PM2.5 in 1997 and in 2006 lowered the air quality standards for PM2.5 to 35 µg/m³ for a 24-hour average and reaffirmed 15 µg/m³ for an annual average standard. There was considerable controversy and debate surrounding the review of particulate matter health effects and the consideration of ambient air quality standards (Kaiser 1997; Vedal 1997) when the U.S. EPA promulgated the initial PM2.5 standards in 1997. In 2002, the California Air Resources Board adopted an air quality standard for PM2.5 at a level of 12 µg/m³, in the form of an annual average.

Since that time, additional studies have been published and some of the key studies were closely scrutinized and the data reanalyzed by additional investigators. The reanalysis confirmed the original findings, and there are now additional data confirming and extending the range of the adverse health effects of PM2.5 exposures. In 2012, the U.S. EPA revised the PM2.5 annual average standard to 12.0 µg/m3 (U.S. EPA 2013c). This federal standard is set at same level as the current California PM2.5 annual standard, although the California standard does not have a specified attainment date. Most recently in December of 2020, after reviewing the most recent available scientific evidence and technical information, and consulting with the Agency's independent scientific advisors, EPA announced its decision to retain, without revision, the existing primary (health-based) and secondary (welfare-based) National Ambient Air Quality Standards (NAAQS) for particulate matter. However, in June of 2021, the U.S. EPA announced it will reconsider the decision made in December of 2020. The draft AQMP Chapter 2 and Appendix II provide additional information about how PM levels in the South Coast Air Basin compare to the federal and state standards.

There have been several reviews of the health effects of ambient particulate matter (American Thoracic Society 1996a; Brunekreef et al. 2002; U.S. EPA 2004; U.S. EPA 2009; Brook et al. 2010; U.S. EPA 2019; U.S. EPA 2021). In addition, the California Air Resources Board (CARB) and the Office of Environmental Health

and Hazard Assessment (OEHHA) have reviewed the adequacy of the California Air Quality Standards for Particulate Matter (California Air Resources Board and Office of Environmental Health Hazard Assessment 2002).

The major types of health effects associated with particulate matter include:

- Increased mortality

- Increased respiratory infections

- Increased number and severity of asthma attacks

- COPD exacerbation

    - Increased combined respiratory-diseases and number of hospital admissions

    - Adverse birth outcomes

- Effects on lung function

- Changes in lung morphology

Higher levels of PM2.5 have also been related to increased mortality due to:

- Cardiovascular or respiratory diseases

- Hospital admissions for acute respiratory conditions

- Increased school absences and lost work days

- A decrease in respiratory function in children

- Increased medication use in children and adults with asthma.

Long-term exposure to PM has been found to be associated with:

- Reduced lung function growth in children

- Changes in lung development

- Development of asthma in children

- Increased risk of cardiovascular diseases in adults

- Increased total mortality (reduction in life-span and increased mortality) from lung cancer.

In addition, new evidence is suggestive of metabolic, nervous system, and reproductive and developmental effects for short-term and long-term exposure to PM2.5.

In the 2019 Integrated Science Assessment for Particulate Matter, the U.S. EPA presented conclusions on the particulate matter causal determination of several health effects based on an updated review of scientific studies (U.S. EPA 2019). In 2021 a supplement to this assessment was drafted (U.S. EPA, 2021). The conclusions are presented separately for particulates in the size range of 2.5 to 10 micrometers (µm) in aerodynamic diameter (PM10-2.5, often referred to as the coarse fraction), ≤2.5 µm (PM2.5, or fine

particles), and ultrafine particles. Of note, there is currently no federal or California standard for PM10-2.5, although a PM10 standard remains in effect. These conclusions are depicted in the following tables.

TABLE I-4

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATIONS FOR HEALTH EFFECTS OF PM10-2.5, PM2.5, UFP

Size Fraction	Causality Determination
Respiratory Effects	
Short-Term Exposure	
PM2.5	Likely to be causal
PM10-2.5	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Long-Term Exposure	
PM2.5	Likely to be causal
PM10-2.5	Inadequate
UFP	Inadequate
Cardiovascular Effects	
Short-Term Exposure	
PM2.5	Causal
PM10-2.5	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Long-Term Exposure	
PM2.5	Causal
PM10-2.5	Suggestive of, but not sufficient to infer
UFP	Inadequate
Metabolic Effects	
Short-Term Exposure	
PM2.5	Suggestive of, but not sufficient to infer
PM10-2.5	Inadequate
UFP	Inadequate
Long-Term Exposure	
PM2.5	Suggestive of, but not sufficient to infer
PM10-2.5	Suggestive of, but not sufficient to infer
UFP	Inadequate
Nervous System Effects	
Short-Term Exposure	
PM2.5	Suggestive of, but not sufficient to infer
PM10-2.5	Inadequate
UFP	Suggestive of, but not sufficient to infer
Long-Term Exposure	
PM2.5	Likely to be causal
PM10-2.5	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Reproductive and Developmental Effects	
PM2.5	Suggestive of, but not sufficient to infer

PM10-2.5	Inadequate
UFP	Inadequate

(Taken from U.S. EPA (2019) Table ES 1)

There are also differences in the composition and sources of particles in the different size ranges that may have implications for health effects. The particles in the coarse fraction (PM10-2.5) are mostly produced by mechanical processes. These include automobile tire wear, industrial processes such as cutting and grinding, and resuspension of particles from the ground or road surfaces by wind and human activities, such as agricultural, mining, and construction operations, which may be particularly important in rural areas.

In contrast, particles smaller than 2.5 µm are mostly derived from combustion sources, such as automobiles, trucks, and other vehicle exhaust, as well as from stationary combustion sources. The particles are either directly emitted or are formed in the atmosphere from gases that are emitted. Components from material in the earth's crust, such as dust, are also present, with the amount varying in different locations.

Attention to another range of very small particles has been increasing over the last several years. These are generally referred to as "ultrafine" particles, with diameters of 0.1 mm or less. Ultrafine particles are mainly composed of particles from fresh emissions of combustion sources but are also formed in the atmosphere by condensation of vapors that are emitted or by chemical or photochemical reactions with other contaminants in the air.

Ultrafine particles have relatively short half-lives (minutes to hours) and the particle size rapidly grows through condensation and coagulation processes into particles within the PM2.5 size range. Ultrafine particles are garnering interest since a limited number of epidemiological and some laboratory studies, though not all, indicate that their toxicity may be higher on a mass basis than larger particles. There is also evidence that these small particles, or toxic components carried on their surface, can translocate from the lung to the blood and to other organs of the body, or through the olfactory bulb into the brain (U.S. EPA 2019). Currently, there are no federal or California standards for ultrafine particles, but its health effects will be discussed as a subsection in the short-term and long-term health effects.

The current federal and California standards for particulate matter are listed in Table I-6.

TABLE I-5

AMBIENT AIR QUALITY STANDARDS FOR PARTICULATE MATTER

STANDARD	FEDERAL	CALIFORNIA
PM10 24-Hour average	150 mg/m^3	50 mg/m^3
PM10 Annual Average	--	20 mg/m^3
PM2.5 24-Hour Average	35 mg/m^3	--
PM2.5 Annual Average	12 mg/m^3	12 mg/m^3

Short-Term Exposure Effects of PM

PM2.5

Respiratory Effects

Like the previous ISA's the 2019 ISA concluded that there is likely to be causal relationship between short-term PM2.5 exposure and respiratory effects (U.S. EPA, 2019). This conclusion was based mainly on epidemiologic evidence demonstrating associations between short-term PM2.5 exposure and various respiratory effects. The more limited evidence from controlled human exposure and animal toxicological studies provided coherence and biological plausibility for a subset of respiratory effects for which PM2.5-related associations were observed in epidemiologic studies. In addition, the epidemiologic evidence consistently showed PM2.5-associated increases in hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease (COPD) and respiratory infection among adults or people of all ages, as well as increases in respiratory mortality (U.S. EPA, 2019).

Previous studies have indicated the following respiratory outcomes, asthma exacerbation, COPD exacerbation, respiratory infection, combinations of respiratory-related disease hospital admissions and ED visits, and respiratory mortality. Newer studies are now indicating allergy exacerbation, and showing respiratory effects in healthy populations, and respiratory effects in populations with cardiovascular disease. These studies are discussed below.

Asthma Exacerbation

Recent epidemiologic studies strengthen the evidence for a relationship between short-term PM2.5 exposure and asthma exacerbation in children. Recent studies add evidence supporting associations between short-term PM2.5 concentration and asthma hospital admissions, ED visits, and physician visits in children. This evidence is supported by studies that examined associations with PM2.5 within a state, across multiple cities, or individual cities. In 12 California counties encompassing the south coast and Central Valley, Yap et al. (2013) focused on examining the influence of socioeconomic status (SES) on hospital admissions for pediatric (children ages 1 to 9 years) respiratory conditions associated with PM2.5 exposure. For childhood asthma hospital admissions, the authors reported positive associations across each individual city with varying width of confidence intervals, resulting in relative risks for south coast and Central Valley combined ranging from 1.03–1.07 at lag 0–2 days. While Yap et al. (2013) reported evidence of positive associations in children, Bell et al. (2015) in a study of 213 U.S. counties focusing on older adults (i.e., .65 years of age), 70 of which had asthma data, did not observe an increase in asthma hospital admissions (RR: 1.00 [95% CI: 0.99, 1.01]; lag 1), but the authors only examined single-day lags.

Additional single-city studies conducted in the U.S., Canada, and internationally further examined associations between short-term PM2.5 exposure and asthma hospital admissions in different age groups (i.e., people of all ages, children, and older adults). In New York City, NY, Silverman and Ito (2010) focused on asthma hospital admissions consisting of severe episodes that required a stay in the intensive care unit (ICU) and those that did not (non-ICU) across several different age ranges. Due to the focus on both PM2.5 and O_3, the study authors limited analyses to the warm season (April–August). The authors examined people of all ages as well as children and adults. An increased risk for total asthma hospital admissions (combined ICU and non-ICU) for children 6–18 years of age was reported for PM2.5 (RR: 1.16 [95% CI:

1.10, 1.22]; lag 0−1). An elevated risk due to PM2.5 exposure was also evident when examining both ICU and non-ICU admissions for children 6−18 years of age. Results similar in magnitude were observed for both children and people of all ages, with associations smaller in magnitude and with wider confidence intervals for ages 50 and older. The results of Silverman and Ito (2010) are consistent with a study conducted by Winquist et al. (2012) in St. Louis, MO that also examined associations across several age ranges. The authors reported the strongest evidence of an association when examining people of all ages and children 2−18 years of age, with no evidence of an association for older adults. Kim et al. (2012), in a study in Denver, CO examined a longer lag structure, a 14-day distributed lag model, and reported evidence of a positive association between short-term PM2.5 exposure and asthma hospital admissions for people of all ages. However, Liu et al. (2016), in a study conducted in the greater Houston, TX area, did not report evidence of an association with PM2.5 and unscheduled hospital admissions. It is important to note that the population examined in Liu et al. (2016) consisted of individuals with private insurance, which differs from the other studies evaluated in this section that did not differentiate among insurance coverage when identifying hospital admissions; therefore, the results may not be comparable.

Studies that examined several age ranges tended to indicate stronger associations, in both magnitude and precision, for children. Additional studies focusing only on children provide supporting evidence for associations between short-term PM2.5 exposure and asthma hospital admissions. Li et al. (2011) in Detroit, MI; Chen et al. (2016) in Adelaide, Australia; and Iskandar et al. (2012) in Copenhagen, Denmark all reported evidence of positive associations at lag 0−4 days.

Like hospital admission studies, recent ED visit studies provide evidence of generally consistent positive associations with short-term PM2.5 exposures, particularly in studies focusing only on children and people of all ages, but not older adults. However, compared to the hospital admission studies, the magnitude of the association tends to be smaller for ED visits. Both Malig et al. (2013) and Ostro et al. (2016) in multilocation studies conducted in California that focused on people of all ages, 35 counties and 8 metropolitan areas, respectively, provided evidence of positive associations at lag 0. These results are consistent with those of Weichenthal et al. (2016) who also reported a positive association with asthma ED visits for people of all ages in a study in Ontario, Canada. This study, however, examined a multiday lag of 0−2 days. Krall et al. (2016) in a study of four U.S. cities (i.e., Atlanta, GA; Birmingham, AL; St. Louis, MO; and Dallas, TX) that primarily focused on PM2.5 sources also reported positive associations with asthma/wheeze ED visits in city-specific analyses for people of all ages at lag 3 (quantitative results not presented). Additional evidence from single-city studies conducted in St. Louis, MO (Sarnat et al., 2015; Winquist et al., 2012) and Seoul, South Korea (Kim et al., 2015) reported associations similar in magnitude to the multilocation studies, but with wider confidence intervals. However, Byers et al. (2015) reported no evidence of an association for asthma hospital admissions for people of all ages in a study conducted in Indianapolis, IN (RR: 0.99 [95% CI: 0.98, 1.01]; lag 0−2).

Several recent studies have focused exclusively on the relationship between short-term PM2.5 exposure and asthma ED visits in children. Both Winquist et al. (2012) and Byers et al. (2015) reported associations larger in magnitude in children compared with people of all ages combined in St. Louis, MO (RR: 1.05 [95% CI: 1.02, 1.09]; lag 0−4) and Indianapolis, IN (RR: 1.01 [95% CI: 0.98, 1.05]; lag 0−2), respectively. The results of Winquist et al. (2012) and Byers et al. (2015) are consistent with single-city (Strickland et al., 2010) and whole-state (Xiao et al., 2016; Gleason and Fagliano, 2015; Strickland et al., 2015) analyses that focused on pediatric asthma ED visits, with ORs and RRs across studies ranging from 1.01−1.05. An additional study encompassing three U.S. cities (i.e., Atlanta, GA, St. Louis, MO; and Dallas, TX), which also

examined associations in older adults, provides additional support for the associations observed in other recent studies focusing on children [RR: 1.03 (95% CI: 1.01, 1.05); lag 0–2; Alhanti et al. (2016)].

Looking at short-term exposure and asthma ED visits in adults, both Byers et al. (2015) in Indianapolis, IN and Winquist et al. (2012) in St. Louis, MO reported evidence of a null association with asthma ED visits in adults 45 and older, and 65 and older, respectively.

Additional evidence of PM2.5-related increases in asthma symptoms, lung function decrements, and pulmonary inflammation is provided by recent panel studies in children with asthma. Findings were not entirely consistent, but overall, several well-conducted studies measuring total personal exposure, residential outdoor concentration, and school outdoor PM2.5 concentration observed associations with asthma-related effects (U.S. EPA, 2019). A limited number of panel studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provide evidence of an association between PM2.5 and respiratory symptoms (Mar et al., 2004; Gent et al., 2003; Slaughter et al., 2003) and medication use (Gent et al., 2009; Rabinovitch et al., 2006; Slaughter et al., 2003) in children with asthma. In studies that examined copollutant confounding, associations between PM2.5 and asthma severity were robust to the inclusion of CO in a copollutant model (Slaughter et al., 2003), while PM2.5 associations with persistent cough, chest tightness, and shortness of breath no longer persisted in models adjusting for O_3 (Gent et al., 2003).

A few recent studies provide some additional evidence of an association between PM2.5 and a composite index of multiple symptoms. In a panel study including 90 school children with asthma in Santiago, Chile, PM2.5 concentrations were associated with increases in coughing and wheezing, as well as a composite index of respiratory symptoms (Prieto-Parra et al., 2017). The observed associations were strongest in magnitude for 7-day avg PM2.5. Similarly, among children at two schools in El Paso, TX, 5-day avg PM2.5 concentrations measured outside of the schools were associated with poorer asthma control scores, which reflect symptoms and activity levels (Zora et al., 2013). The two schools included in the study differed in nearby traffic levels but varied similarly in outdoor PM2.5 concentration over time. In contrast, students attending schools with varying nearby traffic levels were also examined in the Bronx, NY, although asthma symptoms were not associated with outdoor school or total personal PM2.5 concentrations (Spira-Cohen et al., 2011). A low correlation between school and personal PM2.5 concentrations (r = 0.17) and a reportedly high proportion of time spent indoors (89%), suggests that personal PM2.5 exposure was largely influenced by indoor rather than ambient sources. In an additional study related to respiratory symptoms, asthma-related school absence was associated with 19-day avg PM2.5 concentrations in a U.S. multicity study (O'Connor et al., 2008). Notably, it is difficult to control for confounding by meteorological factors over long averaging times.

In addition to respiratory symptoms, recent studies of medication use in children add to the limited evidence base, providing some additional evidence of PM2.5-associated increases in the use of bronchodilators, which can provide quick relief from asthma symptoms. Panel studies of school children with asthma in Denver, CO (Rabinovitch et al., 2011) and Mexico City (Escamilla-Nuñez et al., 2008) observed associations between PM2.5 concentrations and bronchodilator use. Escamilla-Nuñez et al. (2008) reported comparable associations using lag 0 and 5-day avg PM2.5, while Rabinovitch et al. (2011) observed associations that were stronger in magnitude when estimated using 2-day moving avg PM2.5 compared with single-day lags. In contrast, PM2.5 concentrations were associated with decreased bronchodilator use in a panel study in Santiago, Chile (Prieto-Parra et al., 2017).

Overall, panel studies in children with asthma find generally consistent evidence of associations between short-term PM2.5 exposure and lung function decrements. In Seattle, WA, decrements in some measures of lung function (PEF – peak expiratory flow, MEF-maximal expiratory flow, FEV_1- forced expiratory volume in the first second of expiration) were associated with PM2.5 concentrations (Allen et al., 2008; Trenga et al., 2006). PM2.5 concentrations at fixed-site monitors were associated with larger decrements in FEV_1 among children with asthma in Denver, CO after adjusting for an estimate of the ambient-generated portion based on the ratio of personal to ambient sulfur concentrations (Strand et al., 2006). Several recent studies continue to provide evidence of an association between short-term PM2.5 exposure and FEV_1 decrements in children with asthma (U.S. EPA 2019). In Riverside and Whittier, CA, personal PM2.5 and monitor PM2.5 concentrations were associated with decreased FEV_1 (Delfino et al., 2008). However, uncertainty regarding potential copollutant confounding remains. Evidence is more limited and less consistent in panel studies involving adults with asthma. Further, several controlled human exposure studies failed to observe lung function decrements in adults with asthma following short-term PM2.5 exposure. Evidence for a relationship between short-term PM2.5 exposure and asthma exacerbation in adults continues to be inconsistent (U.S. EPA, 2019).

Allergy Exacerbation

Animal toxicological studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provided evidence that PM2.5 can facilitate delivery of allergenic material to the airways, promote allergic sensitization, and exacerbate allergic responses. The epidemiologic evidence, however, was limited, with a single study reporting an association between short-term PM2.5 concentrations and hospital admissions for allergic rhinitis in children in Turkey (Tecer et al., 2008). Recent evidence that PM2.5 exposure enhances allergic inflammation in animal models of allergic airway disease, supports PM2.5-related asthma exacerbation and also indicates that PM2.5 exposure could affect respiratory responses in people with allergies, but not asthma. Several recent epidemiologic studies add to the evidence base, but do not consistently link short-term PM2.5 exposure to allergy exacerbation in children or adults (U.S. EPA, 2019). Recent studies have examined an array of outcomes, including allergy symptoms and lung function changes and pulmonary inflammation in populations with allergies (Kousha and Valacchi, 2015; Song et al., 2011; Kousha and Valacchi, 2015).

Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Recent studies generally support an association between short-term increases in PM2.5 concentration and exacerbation of COPD. Overall, the evidence links short-term PM2.5 exposure to COPD hospital admissions and ED visits. These recent studies report positive associations across both multi-and single-city studies, especially for hospital admissions in populations aged 65 years and older (U.S. EPA, 2019). In a multicity study conducted in the Mid-Atlantic region of the U.S., Kloog et al. (2014) examined associations between short-term PM2.5 exposure and COPD hospital admissions. The authors reported a 1.83% (95% CI: 1.18, 2.48) increase in COPD hospital admissions at model lag 0−1 days. Bell et al. (2015) also examined COPD hospital admissions in adults ages 65 years and older in a multicounty time-series analysis conducted in 213 U.S. counties and reported a 0.34% (95% CI: −0.05, 0.74) increase in COPD hospital admissions at lag 0. Consistent with the U.S. multicity studies, Hwang et al. (2017) also reported a positive association of 2% (95% CI: 0.8, 2.9; lag 0−2) with COPD hospital admissions in a study of four cities in southwestern Taiwan focusing on people of all ages.

Several recent single-city studies in the U.S. reported inconsistent evidence of an association between short-term exposure to PM2.5 and hospital admissions for COPD. Kim et al. (2012) found no evidence of

an association with COPD hospital admissions in Denver, CO. Several single-city international studies examined the association with COPD hospital admissions and support the evidence reported in the U.S. multicity studies (U.S. EPA, 2019). A single-city study conducted in Rome, Italy focusing on adults aged 35 years and older investigated the association between PM2.5 and COPD hospital admissions in a case-crossover analysis (Belleudi et al., 2010). Halonen et al. (2009a) observed a 3% increase (95% CI: −1.9, 8.1) at lag 0 in a model adjusted for O_3 for hospital admissions in Helsinki, Finland, but with a wide confidence interval due to the low count of hospital admissions compared with other studies. Cheng et al. (2015), examining hospital admissions in a case-crossover study in Kaohsiung, Taiwan, found no association between PM2.5 at a 0–2-day lag (RR: 1.00 [95% CI: 0.98, 1.03]).

Several recent multicity studies conducted in the U.S. examined associations between short-term PM2.5 exposure and COPD ED visits. In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term PM2.5 exposures and respiratory ED visits, including COPD. In a time-stratified case-crossover analysis, the authors examined single-day lags and reported positive associations at lags 1 and 2 days, with the most precise estimate at lag 2 (1.47% [95% CI: 0.40, 2.6]). In a copollutant model with PM10₋2.5, the PM2.5 association was relatively unchanged [1.58% (95% CI: 0.56, 2.62); Malig et al. (2013)]. The positive association observed in the multicounty study conducted by Malig et al. (2013) is supported by a study conducted in Little Rock, AR (Rodopoulou et al., 2015) that observed a 3.08% increase (95% CI: −0.98, 7.30) in COPD ED visits at lag 2. Rodopoulou et al. (2015) also examined the PM2.5-COPD ED visits association in a copollutant model with O_3 and reported that the association remained positive, but confidence intervals increased in size (2.86% [95% CI: −1.35, 7.24]). A multicity case-crossover study of 15 cities in Ontario, Canada found an increase on the same order (2.2%) with higher precision (95% CI: 1.4, 2.9) than (Rodopoulou et al., 2015) using a 3-day mean lag structure. In contrast, Sarnat et al. (2015) in a time-series study of PM2.5 and cardiorespiratory ED visits in the St. Louis Missouri-Illinois (MO-IL) metropolitan area also reported no evidence of an association with COPD ED visits (RR: 0.99 [95% CI: 0.95, 1.03]) in a 3-day unconstrained distributed lag model (i.e., lag 0−2).

A limited number of recent studies followed populations consisting of adults with moderate or severe COPD to show some evidence indicating associations between PM2.5 concentrations and increases in respiratory symptoms in adults with COPD. Wu et al. (2016) examined the self-reported occurrence of several respiratory symptoms in relation to short-term PM2.5 concentrations in a panel study of 23 adults in Beijing. The authors reported associations between most multiday (2−7) avg PM2.5 concentrations and sore throat, cough, sputum, wheeze, and dyspnea symptoms. Similarly, in a panel of 29 adults in Mexico City, total personal PM2.5 exposure was associated with cough and phlegm, but not wheeze (Cortez-Lugo et al., 2015). A notable limitation of the study was the high loss to follow-up, with only 4 of the 29 subjects completing all three of the 2-week study phases. In contrast, in a study of adults in Worcester, MA, PM2.5 was associated with a decrease in COPD exacerbations, defined as a worsening of respiratory symptoms (Devries et al., 2016). A few recent studies also evaluated lung function changes in populations with COPD and the results were inconsistent (U.S. EPA, 2019).

Information from a few available recent studies continues to support a relationship between PM2.5 and increases in pulmonary inflammation in adults with COPD (Chen et al., 2015b, Wu et al., 2016). A strength of these studies is their assessment of personal PM2.5 exposures. Overall, copollutant confounding was not adequately examined. Thus, the extent to which the results can be attributed specifically to PM2.5 exposure is unclear. However, experimental studies in individuals with COPD and in an animal model of COPD support an independent effect of short-term PM2.5 exposure on exacerbation of COPD. Changes in

lung function-related parameters (oxygen saturation and tidal volume), as well as lung injury and inflammation, were observed following short-term PM2.5 concentrated ambient particles (CAPs) exposure and provide biological plausibility for the findings of the epidemiologic studies (U.S. EPA, 2019).

Respiratory Infections

The body of evidence for associations between short-term exposure to PM2.5 and respiratory infection consists mainly of studies of hospital admissions and ED visits. In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term PM2.5 exposures and ED visits, including pneumonia and acute respiratory infections. Using a time-stratified case-crossover analysis, the authors reported positive associations at 1-day lags between short-term PM2.5 and acute respiratory infections (1.9% [95% CI: 1.1, 2.7]) and pneumonia (0.86% [95% CI: −0.06, 1.8]) ED visits in single-pollutant models.

Recent single-city studies have also expanded the evidence for associations with ED visits. Winquist et al. (2012) observed a positive association for hospital admissions through ED visits, which can be compared with a more recent study conducted in the same St. Louis, Missouri-Illinois (MO-IL) metropolitan area, that found similar results except there was no evidence of an associations between PM2.5 and pneumonia ED visits (RR: 0.98 [95% CI: 0.96, 1.00]) at lag 0−2 days (Sarnat et al. (2015).

Several studies investigated the associations between PM2.5 and ED visits related to several respiratory infections in Atlanta, GA. Darrow et al. (2014) conducted an 18-year (1993−2010) study examining the association between PM2.5 and pediatric (ages 0−4) ED visits for respiratory infections, including bronchitis and bronchiolitis, pneumonia, and upper respiratory infection (URI). Pneumonia ED visits were positively associated with PM2.5 (for children aged 0−4 years, RR: 1.01 [95% CI: 0.99, 1.03]). PM2.5 at lag 0−2 days was not associated with an increase in ED visits for bronchiolitis and bronchitis, but results for URI and pneumonia were positive, albeit with wide confidence intervals, for children aged 1−4 years. In the same location, Strickland et al. (2015) examined children ages 0−18 years old between 2002−2010. The authors found that the association with ED visits for bronchitis and upper respiratory infection increased slightly at lag 0-day (OR: 1.010 [95% CI: 0.994, 1.027], and OR: 1.015 [95% CI: 1.008, 1.022]). In contrast, the association for pneumonia-related ED visits were essentially null at both a 0-day lag (OR: 0.999 [95% CI: 0.979, 1.019]) and a 1-day lag (OR: 1.001 [95% CI: 0.981, 1.022]).

In contrast to the results of Winquist et al. (2012), other single-city studies such as Darrow et al. (2014), Strickland et al. (2015), and Rodopoulou et al. (2015) found no associations for respiratory infection ED visits. For example, in Little Rock, AR, Rodopoulou et al. (2015) found an association of −1.34% (95% CI: −5.31, 2.79) among all age groups using a 2-day lag. The association slightly increased to −0.82% after the inclusion of O_3 in a copollutant model (95% CI: −4.96, 3.50). These mentioned studies varied in the type of respiratory infection outcome examined, thus the overall interpretation of findings is more complicated.

When examining the association between PM2.5 exposure and respiratory-related outpatient visits, a study conducted in Atlanta, GA, Sinclair et al. (2010) examined the association with upper and lower respiratory infections, of which they found positive associations with both.

Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

In addition to individual respiratory diseases, epidemiologic studies have examined respiratory diseases in aggregate where, in some cases, the aggregate represents all respiratory diseases while, in others, a specific combination of respiratory diseases is represented (e.g., COPD, asthma, and respiratory infections). Past and recent studies generally have shown a positive association across studies of hospital admissions and ED visits for all age ranges, particularly in multicity studies. As in the individual respiratory diseases discussed above, positive associations with respiratory-related diseases are more consistently observed among children and when examining people of all ages. However, recent studies further expand analyses with older adults, with multicity studies conducted in the U.S. providing evidence of consistent, positive associations between short-term PM2.5 exposure and respiratory-related diseases (U.S. EPA, 2019).

Respiratory Effects in Healthy Populations

Evaluation of the current epidemiologic evidence indicates that short-term PM2.5 exposures are inconsistently related to respiratory effects in healthy adults. Where there is supporting evidence, changes tend to be transient, and confounding by copollutants is inadequately examined. For general community daily average exposures, there is some consistent epidemiologic evidence for PM2.5-related respiratory effects in healthy children, but the evidence is limited in number for any one endpoint. In addition to the limited supporting evidence, uncertainties remain as to whether short-term PM2.5 exposure leads to overt and persistent respiratory effects in healthy populations or is related to such effects across a wide range of PM2.5 concentrations (U.S. EPA, 2019). The studies looking at respiratory effects in healthy populations is discussed below.

Respiratory Symptoms

In a study of school children in Santiago, Chile, 7-day avg PM2.5 was associated with increased odds of cough and a composite index of respiratory symptoms (Prieto-Parra et al., 2017). The associations were relatively unchanged in two-pollutant models with PM10, NO_2, SO_2, or O_3. However, copollutant correlations were not reported, limiting the interpretability of the models.

Lung Function

Past studies included a study of adult school crossing guards in New Jersey that observed decreases in lung function associated with 1-hour max PM2.5 concentrations (Fan et al., 2008). In contrast, Holguin et al. (2007) did not observe an association between PM2.5 and lung function or lung inflammation in a study of school children in Ciudad Juarez, Mexico.

Most recent studies on lung function changes in relation to PM2.5 concentrations examined adults during scripted exposures and exposure interventions. Studies examining lung function changes in adults after commuting in cars, buses, or on bicycles, did not observe associations between personal ambient PM2.5 exposure and forced expiratory volume in the first second (FEV_1) (forced expiratory volume in the first second (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). In a study of adults commuting 2 hours through Atlanta, GA traffic, Mirabelli et al. (2015) reported PM2.5-related decreases in FVC immediately after the commute. The association appeared to be transient, with no association observed 3 hours post commute.

A number of studies in the U.S. (Mirowsky et al., 2015), Canada (Dales et al., 2013), and Europe (Matt et al., 2016; Kubesch et al., 2015; Steenhof et al., 2013; Strak et al., 2012) used quasi-experimental designs to assign participants to either rest or exercise in different locations with notable pollutant contrasts. Like the studies of scripted commutes through traffic, many of these quasi-experimental studies observed null associations between lung function and PM2.5 (Kubesch et al., 2015; Mirowsky et al., 2015; Strak et al., 2012). In contrast, Dales et al. (2013) observed decreases in FEV_1 in Sault Ste. Marie, Canada. Associations were observed despite low mean concentrations of 8-hour avg PM2.5. Additionally, in Barcelona, Spain, Matt et al. (2016) reported that healthy adults experienced decreased FEV_1 associated with 2-hour avg PM2.5 immediately after exposure. Notably, PM2.5 was associated with increased FEV_1 7 hours after exposure, again indicating potentially transient effects. Another study in China implemented an exposure intervention by moving healthy, nonsmoking adults from an industrial town to a less polluted city for 9 days (Hong et al., 2010). Participants experienced increased FEV_1 and peak expiratory flow (PEF) associated with decreased 24-hour avg PM2.5.

Only a few studies examined lung function is healthy children. School children in an agricultural area of Brazil experienced decreases in PEF in association with PM2.5 concentrations measured outside of school; concentrations were averaged over the 6, 12, or 24 hours preceding spirometry (Jacobson et al., 2012). In Seoul, South Korea (Hong et al., 2010), composite monitor 24-hour avg PM2.5 was associated with a small, imprecise decrease in PEF in school children at lags 0 and 3, but no other lags up to 4 days.

In controlled human studies Petrovic et al. (2000) observed that a 2-hour exposure to PM2.5 (92 $\mu g/m^3$) resulted in decreases in thoracic gas volume, other measures of lung function (spirometry, diffusing capacity, airway resistance) were unaffected. No clear effect of short-term exposure to PM2.5 on lung function was demonstrated in several studies investigating the exposure of healthy volunteers to PM2.5 CAPs (Gong et al., 2003; Ghio et al., 2000; Gong et al., 2000) or urban traffic particles. In a recent study, Huang et al. (2012) exposed healthy volunteers to PM2.5 CAPs collected from Chapel Hill, NC. The authors reported no changes in multiple markers of lung function or in the marker for diffusion capacity at 1 and 18 hours postexposure.

Past animal studies discussed in the 2004 PM AQCD (U.S. EPA, 2004) and the 2009 PM ISA (U.S. EPA, 2009) measured pulmonary function following single or multiday exposure to PM2.5 CAPs. Decreased breathing frequency (or respiratory rate) was observed in dogs exposed to PM2.5 CAPs in Boston, MA by tracheostomy exposure (Godleski et al., 2000). In addition, a strong increase in airway irritation, as indicated by decreases in end inspiratory pause and increases in end expiratory pause, pause, and enhanced pause (Penh) was observed (Nikolov et al., 2008). Increased tidal volume was found in rats exposed to PM2.5 CAPs in Boston, MA (Clarke et al., 1999) but not in New York City, NY (Gordon et al., 2000). Increases in inspiratory and expiratory times were not seen in Wistar Kyoto rats exposed to PM2.5 CAPs in Research Triangle Park, NC (Kodavanti et al., 2005). Results of these studies, showing changes in breathing frequency and depth of breathing, indicate that short-term PM2.5 exposure stimulated airway irritant responses by activating sensory nerves and local reflexes.

Recently, Diaz et al. (2013) evaluated the effects of exposure to PM2.5 roadway tunnel particles on pulmonary function in Sprague-Dawley rats. A 2-day exposure to tunnel particles with gases removed by a denuder resulted in increased rapid shallow breathing, as indicated by increased frequency and decreased tidal volume, minute volume, inspiratory time, and expiratory time ($p < 0.05$).

The effect of social stress on pulmonary function was examined in older Sprague-Dawley rats exposed to PM2.5 CAPs in Boston, MA (Clougherty et al., 2010). In stressed animals, PM2.5 CAPs exposure was associated with increased breathing frequency ($p = 0.001$), lower tidal volume ($p = 0.001$), lower PEF ($p = 0.003$), and shorter times ($p < 0.001$), suggesting rapid shallow breathing. In unstressed animals, PM2.5 CAPs exposure was associated with increased PIF ($p = 0.03$) and greater MV ($p = 0.05$).

Effects on other pulmonary function parameters have been reported. Amatullah et al. (2012) found that a 4-hour exposure of BALB/c mice to PM2.5 CAPs in Toronto increased quasi-static elastance of the lung ($p < 0.05$). Yoshizaki et al. (2017) examined sex-related differences in tracheal hyperreactivity of BALB/c mice due to a multiday exposure to PM2.5 CAPs in São Paulo, Brazil. Tracheal rings from male mice that were exposed to PM2.5 CAPs were hyporesponsive to methacholine, a bronchoconstrictor, compared with tracheal rings from male mice exposed to ambient air ($p < 0.05$). Tracheal rings from diestrus female mice that were exposed to PM2.5 CAPs responded similarly to methacholine as tracheal rings from female mice exposed to ambient air. However, tracheal rings from estrus and proestrus female mice were hyperresponsive to methacholine compared with air controls ($p < 0.05$).

Subclinical Effects

Most recent studies of subclinical respiratory effects in healthy populations examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation. Many of the same studies that were evaluated in the previous subsection on lung function also measured eNO. Therefore, the majority of recent studies similarly examined adults during scripted exposures. Studies of adults during and after commuting in cars, buses, or on bicycles, generally observed associations between personal ambient PM2.5 exposure and subclinical respiratory effects (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b).

Results from studies using quasi-experimental designs were less consistent than scripted exposure studies, despite having similarly high mean concentrations of PM2.5. In New York, PM2.5 exposure while walking near high-traffic roads and in a forest was associated with eNO 24 hours after exposure (Mirowsky et al., 2015). However, eNO was not associated with PM2.5 in studies in which participants were randomized to exercise or rest at locations with air pollution exposure contrasts in Barcelona, Spain (Kubesch et al., 2015) or Utrecht, the Netherlands (Strak et al., 2012). As part of the same project in the Netherlands, Steenhof et al. (2013) reported an association between PM2.5 exposure and nasal lavage levels of the pro-inflammatory cytokine, IL-6. The observed association was persistent in two-pollutant models including NO_X, O_3, or SO_2 (Steenhof et al., 2013).

A single study examined subclinical effects in school children. Carlsen et al. (2016) observed a 5.4 ppb (95% CI: −3.1, 13.0 ppb) increase in eNO associated with 2-day avg PM2.5 at two schools in Umea, Sweden. PM2.5 was measured at monitors located within 1.5 km of the two schools. Although copollutant models were not examined, PM2.5 was weakly correlated with NOX and only moderately correlated with O_3.

In controlled human studies Ghio et al. (2000) reported an increase in airway and alveolar neutrophils following exposure to PM2.5 CAPs. A follow-up analysis of Ghio et al. (2000) determined the increase in BALF neutrophils was associated with the Fe, Se, and SO_4^{2-} content of the particulate matter (Huang et al., 2003). Recently, the healthy population respiratory response to PM2.5 has been further examined by Behbod et al. (2013) and Huang et al. (2012). Behbod et al. (2013) reported that relative to filtered air, no significant airway (sputum) responses were observed in subjects exposed to Toronto, Ontario PM2.5 CAPs. Huang et al. (2012) corroborated the same results at lower concentrations.

Respiratory Tract Impacts

Short-term PM2.5 exposures are inconsistently related to respiratory effects in healthy adults. Where there is supporting evidence, changes tend to be transient, and confounding by copollutants is inadequately examined. For general community daily average exposures, there is some consistent epidemiologic evidence for PM2.5-related respiratory effects in healthy children, but the evidence is limited in number for any one particular endpoint. In addition to the limited supporting evidence, uncertainties remain as to whether short-term PM2.5 exposure leads to overt and persistent respiratory effects in healthy populations or is related to such effects across a wide range of PM2.5 concentrations (U.S. EPA, 2019).

Respiratory Effects in Populations with Cardiovascular Disease

Numerous animal toxicological studies have been conducted in animal models of cardiovascular disease. Overall, short-term PM2.5 exposure results in pulmonary effects in some studies but not others. Among the respiratory endpoints, the most consistent evidence is for changes in pulmonary function (U.S. EPA, 2019).

Respiratory Mortality

Across studies, the PM2.5 effect on respiratory mortality was observed to be immediate, with associations occurring in the range of lag 0 to 2 day(s). A limitation within the evidence was that multicity studies did not extensively examine potential copollutant confounding, but evidence from single-city studies suggested that the PM2.5-respiratory mortality relationship was not confounded by gaseous copollutants (U.S. EPA, 2029). Some recent studies have also further evaluated the PM2.5-respiratory mortality relationship by examining cause-specific respiratory mortality outcomes [i.e., COPD, pneumonia, and LRTI; Janssen et al. (2013) and Samoli et al. (2014)]. Overall, the results reported in the studies that examine cause-specific respiratory mortality outcomes are generally consistent with the results for all respiratory mortality, but the smaller number of mortality events observed results in unstable estimates with larger uncertainty.

There is limited coherence across epidemiologic and controlled human exposure studies, complicating the interpretation of the associations observed for short-term PM2.5 exposure and respiratory mortality. Overall, these studies continue to support a relationship between PM2.5 and respiratory mortality and provide additional evidence that: (1) gaseous pollutants do not confound the PM2.5-respiratory mortality relationship; (2) PM2.5 effects on respiratory mortality may not be limited to the first few days after exposure; (3) the magnitude of the association tends to be largest during warmer months; and (4) there is inconsistent evidence that temperature extremes modify associations between short-term PM2.5 exposure and respiratory mortality (U.S. EPA, 2019).

Cardiovascular Effects

A large body of recent evidence confirms a causal relationship between short-term PM2.5 exposure and cardiovascular effects (U.S. EPA, 2019). The strongest evidence is from epidemiologic studies of ED visits and hospital admissions for IHD and heart failure, with supporting evidence from epidemiologic studies of cardiovascular mortality. Changes in various measures of cardiovascular function in controlled human experiment (CHE) studies provided some biological plausibility for these associations. In addition, animal toxicological studies reporting some evidence of reduced myocardial blood flow during ischemia, altered vascular reactivity, and ST segment depression provided additional biological plausibility (U.S. EPA, 2019).

Recent epidemiologic studies of hospital admissions and ED visits for cardiovascular-related effects, and in particular, for ischemic heart disease (IHD) and heart failure report positive associations. Results from these observational studies are supported by experimental evidence from CHE and animal toxicological studies of endothelial dysfunction, as well as endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in heart rate variability (HRV), increases in blood pressure (BP), and increases in indicators of systemic inflammation, oxidative stress, and coagulation. Additional results from observational panel studies, although not entirely consistent, provide at least some evidence of increased risk of arrhythmia, decreases in HRV, increases in BP, and ST segment depression. Thus, epidemiologic panel studies also provide some support to the causality determination and to biological plausibility. Finally, epidemiologic studies of cardiovascular disease (CVD)-related mortality provide additional evidence that demonstrates a continuum of effects from biomarkers of inflammation and coagulation, subclinical endpoints (e.g., HRV, BP, endothelial dysfunction), ED visits and hospital admissions, and eventually death.

The current body of evidence also reduces uncertainties from the previous review related to potential copollutant confounding and limited biological plausibility for CVD effects following short-term PM2.5 exposure (U.S. EPA, 2019). The 2019 PM ISA states there is sufficient evidence to conclude that a causal relationship exists between short-term PM2.5 exposure and cardiovascular effects. However, the body of evidence that supported this causality determination did not include any epidemiologic studies that conducted accountability analyses or employed causal modeling methods. The supplemental document to the 2019 PM ISA includes studies that expands on this and further informs the relationship between short-term PM2.5 exposure and cardiovascular effects, specifically cardiovascular hospital admissions. Evidence supporting the causality determination for short-term PM2.5 exposure and cardiovascular effects is discussed below.

Emergency Department (ED) and Hospital Admissions

In general, there are positive associations observed in numerous epidemiologic studies of ED visits and hospital admissions for IHD, heart failure, and combined cardiovascular-related endpoints and short-term PM2.5 exposure. The strongest evidence for this came from multicity studies in the U.S. (Dominici et al., 2006) and Australia (Barnett et al., 2006).

Several recent multicity studies in the U.S., Canada, and Europe examined the relationship between PM2.5 and ED visits and hospital admissions for heart failure and generally observed positive associations. Two large Medicare studies (Bell et al., 2015; Zanobetti et al., 2009) observed similar estimates to those published by Dominici et al. (2006), reporting a 1.1% (95% CI: 0.8, 1.5) and 1.9% (95% CI: 1.2, 2.5) increase in hospital admissions, respectively. Talbott et al. (2014) examined hospital admissions in seven U.S. states and, although they did not pool their results, they observed positive associations between same-day hospital admissions for heart failure and PM2.5 concentrations in Massachusetts, New Jersey, and New York, but not in New Hampshire, Washington, New Mexico, or Florida. Similarly, another large administrative data study in New York reported a positive association with heart failure in the greater NYC region, but null associations throughout the remainder of the state (Hsu et al., 2017). The observed difference in effect estimates within or between states in Talbott et al. (2014) and Hsu et al. (2017) indicated the potential for regionally heterogeneous associations. Smaller multicity studies in New York (Haley et al., 2009), California (Ostro et al., 2016), and Canada (Stieb et al., 2009) reported positive associations between PM2.5 exposure and ED visits and hospital admissions for heart failure, which showed increases ranging from 1.1 to 8.0%. In contrast, a study of hospital admissions for heart failure in

England and Wales reported a null association between short-term PM2.5 exposure and heart failure (Milojevic et al., 2014).

Epidemiologic studies that examined the effect of PM2.5 on CVD ED visits and hospital admissions generally observed evidence of consistent positive associations. Several recent multicity studies in the U.S. and Europe provide additional support for positive associations between short-term PM2.5 exposure and CVD ED visits and hospital admissions. Studies using Medicare hospital admissions in the Northeast and Mid-Atlantic reported a 1.03% (95% CI: 0.69, 1.45) and 0.78% (95% CI: 0.54, 1.01) increase in CVD admissions over the previous two days (lag 0–1), respectively (Kloog et al., 2014; Kloog et al., 2012). A similar study of 708 urban and rural U.S. counties also reported a 0.79% (95% CI: 0.62, 0.97) increased risk of CVD-related hospital admissions associated with PM2.5 exposure over the previous 2 days (Bravo et al., 2017). Additionally, a study of seven U.S. states reported positive associations in Massachusetts, New Jersey, and New York, but did not observe a positive association in the other four states (Talbott et al., 2014), while a study of New York state observed a positive association near New York City, NY at lag 0, but null results across the remaining regions of the state (Hsu et al., 2017).

There have been several recent multicity studies in the U.S. using PM2.5 concentrations measured from single monitors or averaged across monitors to assign PM2.5 exposure. Most of these studies examined Medicare populations in cities across the U.S. Studies using Medicare hospital admissions records for CVD in 213 (Bell et al., 2015), 119 (Peng et al., 2009), and 26 (Zanobetti et al., 2009) geographically diverse U.S. counties. All reported increases in risk ranging from 0.6 to 1.9% (Figure 6-6). A Medicare study in four northeastern counties also showed evidence of a positive association (Bell et al., 2014). In non-Medicare populations, a study of eight California counties reported a positive increase in risk with PM2.5 at lag 2 [0.61% (95% CI: −0.18, 1.49); Ostro et al. (2016)].

Multicity studies in Europe also provide generally consistent evidence of a positive association between short-term PM2.5 exposure and cardiovascular-related ED visits and hospital admissions. The MED-PARTICLES study performed in eight southern European cities reported a 0.51% (95% CI: 0.12, 0.90) higher rate of cardiovascular-related hospital admissions for PM2.5 concentrations averaged over the same and previous days [lag 0–1; Stafoggia et al. (2013)]. A four-city MED-PARTICLES study in Spain and Italy also observed a positive, but less precise (i.e., wider 95% CIs), association between PM2.5 exposure and cardiovascular-related hospital admissions [1.18% (95% CI: 0.32, 2.04); Basagaña et al. (2015)]. On the other hand, Milojevic et al. (2014) considered cardiovascular-related hospital admissions in England and Wales and reported a negative association for PM2.5 concentrations at lag 0–4. Results from a number of single-city studies tended to be inconsistent, likely due to their generally smaller sample size and focus on a single location (Sarnat et al., 2015; Rodopoulou et al., 2014; Kim et al., 2012; Ito et al., 2011; Lall et al., 2011).

Ischemic Heart Disease (IHD), Myocardial Infarction (MI), Heart Failure (HF), and Heart Function

IHD is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart. Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death occurs that is secondary to prolonged ischemia. Heart failure (HF) refers to a set of conditions in which pumping action of the heart is weakened. The recent body of IHD and heart failure epidemiologic evidence agrees with the evidence from previous U.S. EPA ISAs reporting mainly positive associations between short-term PM2.5 concentrations and ED visits and hospital admissions (U.S. EPA, 2019). In addition,

several of the more recent controlled human exposure (CHE), animal toxicological, and epidemiologic panel studies provide plausible evidence that PM2.5 exposure could result in IHD or heart failure through pathways that include endothelial dysfunction, arterial thrombosis, and arrhythmia (U.S. EPA, 2019).

Vieira et al. (2016b) have reported that in both exercising heart-failure patients and control patients, short-term exposure to diesel exhaust (DE) results in statistically significant ($p < 0.05$) decreases in estimated left ventricular stroke volume (i.e., the amount of blood the left ventricle pumps per beat).

Recent studies have generally found positive associations between ectopic measures and short-term PM2.5 exposures. Among a large cohort of older men in the Boston, MA area included in the Normative Ageing Study, positive associations were observed (Zanobetti et al. (2014a). Similarly, in a study of nursing home residents with coronary artery disease in Los Angeles, CA, ventricular tachycardia was associated with exposure to PM2.5 in the prior 24-hour period [29% higher daily rate (95% CI: 1, 63); Bartell et al. (2013)]. Another measure of ectopy, premature ventricular contractions, was positively associated with 30-minute personal exposures to PM2.5 in a large panel of healthy, nonsmoking adults in central Pennsylvania (He et al., 2011). Characteristics of cardiac rate and rhythm, including measures of supraventricular or ventricular ectopic runs, were also associated with PM2.5 exposures in a study conducted in Ottawa, Canada in patients having ECGs for clinical purposes, but confidence intervals around these associations were large (Cakmak et al., 2014). In addition, Cakmak et al. (2014) reported strong, positive associations with heart block.

Atrial fibrillation has also been examined with PM2.5 exposures in a few recent studies. This arrhythmic disorder in the atria can cause symptoms such as fatigue, palpitations, shortness of breath, and anxiety. Atrial fibrillation also greatly increases risk for stroke, dementia, congestive heart failure, and premature mortality (Kwok et al., 2011; Paquette et al., 2000; Benjamin et al., 1998). Rich et al. (2006b) found positive, but imprecise associations between atrial fibrillation and 24-hour PM2.5 exposures in a cohort of patients with implantable cardioverter defibrillators (ICD). A recent study, also conducted in Boston, MA observed associations between PM2.5 over the subsequent 0–24 hours and higher risk of atrial fibrillation in a cohort of patients with ICDs (26% [95% CI: 8, 47]) Link et al. (2013)). This study also found that associations were stronger when analyses were limited to study participants residing within 25 km of the monitoring station compared with those residing within a 50 km radius (Link et al., 2013). Similar results were observed by Liao et al. (2011) in a panel study in Pennsylvania that observed associations with atrial fibrillation for PM2.5 exposures 30 minutes to 2 hours prior. In contrast, other studies examining atrial fibrillation or premature atrial contractions found weak or null associations with 24-hour PM2.5 exposures (Cakmak et al., 2014; He et al., 2011).

A small number of recent studies also support a positive association of short-term PM2.5 exposure with arrythmias (Wyatt et al., 2020c; Leiser et al., 2019; Krall et al., 2018; Wei et al., 2019).

Recent epidemiologic panel studies support the plausibility for IHD and heart failure endpoints by reporting some evidence of ST segment depression. In a study of 38 older adults with IHD in nursing homes in Los Angeles, CA, Delfino et al. (2011) observed that PM2.5 concentrations averaged over 1 hour up to 4 days were associated with ST segment depression 1.0 mm (OR: 1.68 [95% CI: 1.20, 2.35]). Notably, this association was attenuated in models including black carbon (BC) or primary organic carbon (OC) but remained positive. In another study, Zhang et al. (2009) observed associations between PM2.5 concentrations and ST segment abnormality in the Women's Health Initiative at lag 0–2 days (4% [95% CI: −3, to 10]). Kurhanewicz et al. (2014) show decreased cardiac function following short-term PM2.5

exposure. A recent study extends this evidence through its examination of the association between short-term PM2.5 exposure with hospital admissions for MI among the low income and/or disabled Americans comprising the Medicaid population (deSouza et al., 2021). deSouza et al. (2021) reported a positive association between PM2.5 concentration (0–1 day average) and acute MI (OR: 31 1.1 [95% CI: 1.03, 1.7]).

In another recent study, Leiser et al. (2019) designed an analysis to examine the association between short-term PM2.5 exposure and IHD and MI hospital admissions in which the competing risk of mortality was controlled and differences across sex and age categories were examined. These authors used Medicare data for residents, 65 years and older, of the contiguous counties of the Wasatch Front in Utah to examine the association between PM2.5 concentration and cardiac hospital re-admissions within 30 days of an index hospitalization, controlling for competing mortality risk. These authors found an association of 3-day average PM2.5 concentration (lag 0–2 day) with IHD (HR: 1.03 17 [95% CI: 0.96, 1.12]) and MI (HR: 1.03 [95% CI: 0.92, 1.16]). In another analysis of older adults using Medicare data, Wei et al. (2019) estimated the association of short-term PM2.5 exposure with MI hospital admissions and a range of other health conditions, including some diseases that are rarely studied in relationship to PM2.5 exposure. Hospital admission data were ascertained using discharge data recorded for Medicare inpatient hospital claims in the continental U.S. (2000–2012). Rather than report a relative risk estimate, the authors reported the absolute risk per 10 million person-days associated with each 1 unit increase in lag 0–1 PM2.5 concentration (i.e., 0.29 [95% CI: 0.17, 0.40]).

Recent single city studies also add to the evidence base. Liu et al. (2020) examined the modification of the association between short-term PM2.5 exposure and MI hospital admissions by long-term NO_2 exposure. These authors performed a case-crossover study to estimate the association of short-term exposure to PM2.5 among individuals living in Calgary neighborhoods with higher long-term NO_2 exposure (2004–2012). The OR for the association between 0–2-day average PM2.5 concentration with hospital admissions for MI among the entire population was 1.03 (95% CI: 0.96, 33 1.12). The association was null in the lowest tertile of long-term NO_2 concentration (OR: 0.94 [95% CI: 34 0.86, 1.18]), but increased with increasing NO_2 concentration tertile (tertile 2, OR: 1.04 [95% CI: 0.94, 35 1.18]) and (tertile 3, OR: 1.10 [95% CI: 1.00, 1.19]).

Animal toxicological studies also support a causal relationship between short-term PM2.5 exposure and heart failure. A recent study demonstrating decreased cardiac contractility and left ventricular pressure in mice is coherent with the results of epidemiologic studies reporting associations between short-term PM2.5 exposure and heart failure (Kurhanewicz et al., 2014). There is generally consistent evidence in animal toxicological studies for indicators of endothelial dysfunction (O'Toole et al., 2010; Haberzettl et al., 2012; Davel et al., 2012; Aragon et al., 2015).

Studies in animals also provide evidence for changes in several other cardiovascular endpoints following short-term PM2.5 exposure. In an animal study Yan et al. (2008) found decreased contractility after exposure to black carbon in mice. Kurhanewicz et al. (2014) demonstrated that in mice, short-term PM2.5 exposure caused statistically significant decreases ($p < 0.05$) in LVDP and contractility compared with filtered air controls. However, a separate study in rats did not report cardiac gene expression consistent with cardiac damage (Aztatzi-Aguilar et al., 2015) following short-term PM2.5 exposure. Although not entirely consistent, these studies provide at least some evidence of conduction abnormalities and arrhythmia, changes in HRV, changes in BP, and evidence for systemic inflammation and oxidative stress.

Finally, these toxicological studies also suggest that genetic background, diet, and PM composition may influence the effect of short-term PM2.5 exposure on some of these health endpoints (U.S. EPA, 2019).

Combinations of Cardiovascular-Related Outcomes

In addition to analyses of individual cardiovascular diseases (e.g., MI, stroke, and HF), epidemiologic studies examined cardiovascular diseases (CVD) in aggregate (i.e., specific combination of cardiovascular diseases). The past two ISAs (U.S. EPA, 2009; U.S. EPA, 2019) reviewed multicity studies of adults ages 65 years and older that provided strong evidence of an association [(Bell et al., 2008; Host et al., 5 2008; Barnett et al., 2006). Several recent studies examine the association between short-term exposure to PM2.5 and CVD hospital admissions and ED visits, and report results that are generally consistent with past studies.

In a study of low income and/or disabled Americans enrolled in Medicaid, deSouza et al. (2021) estimated the association of PM2.5 concentration (0–1 day average) with cardiovascular hospital admissions. The association of PM2.5 concentration (0–1 day average) with all CVD hospital admissions was 1.09 (95% CI: 1.06, 1.11). In another study, Wyatt et al. (2020c) examined hospital admissions among end stage renal disease patients (i.e., those undergoing hemodialysis). Same-day PM2.5 9 concentration (lag 0) was associated with an increase in the risk of CVD hospital admissions in this population (RR: 1.09 [95% CI: 1.02, 1.17]). Krall et al. (2018) reported a null association between 24-hour PM2.5 concentration (lag Day 0) with CVD ED visits.

Cardiovascular Mortality

Recent studies continue to indicate positive associations between short-term PM2.5 exposure and cardiovascular mortality. Results remain the same in copollutant models and may be larger in magnitude in the presence of some co-occurring pollutants (i.e., oxidant gases). In addition, factors that have been shown to vary between cities and regions of the U.S., such as housing characteristics, have been shown to explain some of the city-to-city and regional variability observed in PM2.5-mortality associations in multi-city epidemiologic studies. The continued assessment of the concentration-response (C-R) relationship between short-term PM2.5 exposure and mortality further supports a linear relationship, with less confidence in the shape at concentrations below 5 μg/m3 32 (U.S. EPA, 2021).

Metabolic Effects

Recent studies provide some evidence supporting the effects of exposure on glucose and insulin homeostasis and other indicators of metabolic function. Recent epidemiologic studies have demonstrated increased FBG, insulin, and HOMA-IR (Lucht et al., 2018a; Peng et al., 2016; Brook et al., 2013b) in association with short-term PM2.5 exposure. Yitshak Sade et al. (2016) found no association with blood glucose or lipids and PM2.5 exposure, although a positive association between PM2.5 exposure (3-month avg) and HbA1c, a measure of blood glucose control, was observed. An animal toxicological study provided some evidence for PM2.5-related impairment of the insulin signaling pathway (Haberzettl et al., 2016). Limited animal toxicological studies provided some evidence for inflammation in the visceral adipose tissue (Xu et al., 2013). Although the controlled human exposure evidence is inconsistent, possibly due to the transient nature of inflammation, there is epidemiologic evidence of an increase in inflammatory markers (i.e., γ-GTP, ALT, and AST) in the liver (Kim et al., 2015). In summary, evidence for a relationship between short-term PM2.5 exposure and metabolic effects is based on a small number of epidemiologic

and toxicological studies reporting effects on glucose and insulin homeostasis and other indicators of metabolic function such as inflammation in the visceral adipose tissue and liver.

Nervous System Effects

Recent studies strengthen the evidence that short-term exposure to PM2.5 can affect the nervous system.

Effects on the autonomic nervous system (ANS) and downstream consequences on the heart were observed in toxicological studies. In addition, changes in hypothalamic neurotransmitters, including norepinephrine, and central corticotropin-releasing hormone (CRH) were found in a study of mice exposed to PM2.5 CAPs (Balasubramanian et al., 2013); these studies add to the evidence of increased norepinephrine in the hypothalamus and olfactory bulb and increased serum corticosterone (Sirivelu et al., 2006). Such evidence that PM2.5 exposure leads to changes in norepinephrine indicates that the hypothalamus plays an important role in mediating effects such as activation of the SNS and the HPA stress axis. Preliminary evidence shows a dampening of these responses after repeated exposures in lean, but not obese animals. Findings that short-term exposure to PM2.5 results in altered expression of proinflammatory and antioxidant genes in hippocampus and olfactory bulb regions, in the absence of pulmonary or systemic inflammation, point to a direct effect of PM2.5 on the brain (Tyler et al., 2016; Bos et al., 2012). The evidence from epidemiologic studies of the effects of PM2.5 that focus on specific diseases of the nervous system, however, remains limited. A small increase in hospital admissions for Parkinson's disease was reported in a large national study of Medicare recipients indicating that short-term exposure to PM2.5 may exacerbate a range of symptoms experienced by Parkinson's disease patients (Zanobetti et al., 2014). Finally, a study of school children reported associations of PM2.5 with some tests of neuropsychological function (Saenen et al., 2016). None of the epidemiologic studies considered confounding by copollutant exposures, and studies of components were limited in number.

Mortality

Recent studies that conducted multicity analyses in the U.S. and Canada include a large international study that performed a worldwide multicity analysis (Liu et al., 2019) and a few studies in Canada that relied on data from over 20 cities (Shin et al., 2021a; Lavigne et al., 2018). Liu et al. (2019) established a Multi-City Multi-Country (MCC) Collaborative Research Network that allowed the investigators to collect data globally, resulting in air pollution and mortality data from 652 urban areas in 24 countries from 1986–2015. Although the goal of the study was to estimate a global estimate of the association between short-term PM2.5 exposure and mortality, the authors presented country specific estimates as well, including for the U.S. and Canada. In analyses of 25 Canadian cities from 1986–2011 and 107 U.S. cities from 1987–2006, the authors reported a 1.70% (95% 11 CI: 1.17, 2.23) and 1.58% (95% CI: 1.28, 1.88) increase in mortality, respectively, at lag 0–1 days. Recent studies conducted in Canada by Lavigne et al. (2018) and Shin et al. (2021a) focused on more recent years of data, 1998–2011 and 2001–2012, respectively, in comparison to Liu et al. (2019). Lavigne et al. (2018) focused on examining whether oxidant gases modified the association between short-term PM2.5 exposure and mortality in 24 Canadian cities. The authors reported a 0.76% (95% CI: 18 0.15, 1.21) increase in mortality at lag 0–2 days. Shin et al. (2021a) reported associations with mortality similar in magnitude at lag 0 (0.94% [0.43, 1.46]) and 1 day (0.90% [95% CI: 24 0.33, 1.41]) with no evidence of an association at lag 2.

PM10-2.5

Respiratory Effects

The EPA ISA concluded that the relationship between short-term exposure to PM10₋2.5 and respiratory effects is suggestive of a causal relationship. Epidemiologic findings were consistent for respiratory infection and combined respiratory-related diseases, but not for chronic obstructive pulmonary disease COPD. Controlled human exposure studies of short-term PM10₋2.5 exposure found no lung function decrements and inconsistent evidence for pulmonary inflammation in healthy individuals or human subjects with asthma. Recent studies strengthen the evidence base for asthma exacerbation and respiratory mortality (U.S. EPA, 2019). Potential copollutant confounding caused uncertainty in the exposure assignment for many studies. The studies that provide evidence for these findings are discussed below.

Respiratory Infection and Respiratory-related Diseases

The recent literature adds to the evidence base and provides some support for an association between short-term PM10₋2.5 exposure and hospital admissions/ED visits for pneumonia and respiratory infections considered in aggregate. In 110 U.S. counties, Powell et al. (2015) reported a positive, but uncertain, association between short-term PM10₋2.5 exposure and respiratory infection hospital admissions among residents older than 65 years in single pollutant models (0.07% [95% PI: −0.46, 0.61]; lag 0). The authors also reported a positive, but imprecise association with COPD hospital admissions in single pollutant models (0.31% [95% Posterior Interval (PI): −0.39, 1.01]). Cheng et al. (2015) assessed the relationship between PM10₋2.5 and pneumonia-related hospital admissions among residents older than 65 years of age in a case-crossover study in Kaohsiung, Taiwan between 2006−2010. This study observed a small positive association, with an increase in hospital admissions of 1.02% (95% CI: 1.01, 1.03) per 10-μg/m^3 increase in PM10₋2.5. This association was consistent after model adjustment for SO_2, NO_2, CO, and O_3 and was slightly stronger on colder days below 25°C (1.03% [95% CI: 1.02, 1.04]).

In a multicity study conducted in 35 California counties, Malig et al. (2013) reported no association between short-term PM10₋2.5 exposures at single-day lags 0−2 days and ED visits due to acute respiratory infection (RR: 1.007 [95% CI: 1, 1.01]). However, the authors reported positive associations between PM10₋2.5 and COPD ED visits at lag 2 days (0.67% [95% CI: −0.04, 1.38]). This study also reported a very weak association between short-term PM10₋2.5 exposures at single-day lags 0−2 days for pneumonia visits RR of 1.006 (95% CI: 0.99, 1.02).

In Atlanta, GA, Sinclair et al. (2010) compared air pollutant concentrations and relationships for acute respiratory visits for a 25-month time period examined in a previous study (August 1998−August 2000) and an additional 28-month time period of available data from the Atlanta Aerosol Research Inhalation Epidemiology Study (ARIES; September 2000−December 2002). The researchers found positive associations for upper and lower respiratory infections for the 25-month time frame.

Other recent multicity studies (Lanzinger et al., 2016b; Samoli et al., 2016a; Powell et al., 2015; Stafoggia et al., 2013) and single-city studies (Rodopoulou et al., 2014; Alessandrini et al., 2013; Atkinson et al., 2010) conducted in the U.S. and Europe showed positive associations between short-term PM10₋2.5 exposure and respiratory-related hospital admissions, particularly in analyses of people of all ages. In a limited assessment of potential copollutant confounding, associations were often attenuated, but

remained positive in copollutant models with PM$_{2.5}$, NO$_2$, and O$_3$ (Powell et al., 2015; Alessandrini et al., 2013; Stafoggia et al., 2013). The positive associations reported across these studies is supported by a meta-analysis focusing on PM$_{10-2.5}$ and respiratory hospital admissions that reported an RR of 1.01 [95% CI: 1.00, 1.02; Adar et al. (2014)]. Additional analyses conducted by Adar et al. (2014) to assess potential copollutant confounding by PM$_{2.5}$ did not observe a consistent pattern in PM$_{10-2.5}$ associations as the correlation with PM$_{2.5}$ increased or when evaluating studies that examined associations with both PM$_{2.5}$ and PM$_{10-2.5}$.

Additional single-city studies conducted in London, U.K. (Atkinson et al., 2010) and Rome, Italy, (Alessandrini et al., 2013) also contribute to the total body of evidence for respiratory-related hospital admissions. Atkinson et al. (2010), when examining a number of urban particles, examined associations with PM$_{10-2.5}$ and across single-day lags ranging from 0 to 6 days. The authors reported evidence of a positive association at lag 1 in an all age analysis. Alessandrini et al. (2013) examined the role of Saharan dust on the relationship between short-term PM$_{10-2.5}$ exposure and respiratory-related hospital admissions. Across the entire study duration, the authors reported a 4.4% increase (95% CI: −0.53, 9.60) in hospital admissions at lag 0−5 days. However, when differentiating between Saharan and non-Saharan dust days, Alessandrini et al. (2013) observed that the overall association reported was primarily attributed to the Saharan dust days (13.5%) compared to the non-Saharan dust days (−0.30%).

Asthma Exacerbation

Recent studies that examine the association between short-term PM$_{10-2.5}$ exposure and asthma hospital admissions were conducted in Taiwan (Cheng et al., 2015) and China (Zhao et al., 2016). Cheng et al. (2015) focused on whether the association between short-term PM$_{10-2.5}$ exposure and asthma hospital admissions varied if the mean temperature of each day was above or below 25°C. The authors reported positive associations similar in magnitude for both temperature ranges (>25°C: RR: 1.02 [95% CI: 1.00, 1.05]; <25°C: RR: 1.04 [95% CI: 1.01, 1.07]). Zhao et al. (2016) also reported evidence of a positive association with PM$_{10-2.5}$ that was similar in magnitude (5.5% [95% CI: 1.0, 10.2]; lag 0−3). Both Cheng et al. (2015) and Zhao et al. (2016) examined potential copollutant confounding with gaseous pollutants (i.e., NO$_2$, SO$_2$, O$_3$, and CO). In both studies, moderate ($r > 0.4$ and $r < 0.8$) to low correlations ($r < 0.4$) were reported between PM$_{10-2.5}$ and all pollutants. In Cheng et al. (2015), the results from copollutant analysis were similar to those reported in the single-pollutant analyses (>25°C: single pollutant, RR = 1.02, copollutant, RR = 1.01 to 1.02; <25°C: single pollutant, RR = 1.04, copollutant RR = 1.02 to 1.04). Zhao et al. (2016) also reported that results remained relatively unchanged in copollutant models with SO$_2$ and O$_3$, but the association with NO$_2$ was attenuated and uncertain (1.8% [95% CI: −2.9, 6.8]).

Recent U.S. studies of ED visits provide evidence of a positive association between asthma ED visits and PM$_{10-2.5}$. Malig et al. (2013), in a study of 35 California counties, observed positive associations across single-day lags ranging from 0 to 2 days, with the strongest association in terms of magnitude and precision at lag 2 (3.3% [95% CI: 2.0, 4.6]) in an analysis of people of all ages. This result was found to persist when excluding extreme (i.e., highest 5%) PM$_{10-2.5}$ concentrations. Additionally, Malig et al. (2013) provided some evidence that the association between asthma ED visits and PM$_{10-2.5}$ is larger in magnitude in the warm months. The all-year results of Malig et al. (2013) are supported by Strickland et al. (2010) in a study conducted in Atlanta, GA that focused on pediatric asthma ED visits where the authors reported an RR of 1.06 (95% CI: 1.02, 1.1) for a 0−2-day lag. However, when examining seasonal associations, the authors reported evidence that contradicts Malig et al. (2013), with associations being larger in magnitude in the cold months (RR: 1.07 [95% CI: 1.02, 1.13]) compared to the warm months (RR:

1.04 [95% CI: 0.99, 1.10]). Of the ED visit studies only, Malig et al. (2013) examined potential copollutant confounding with PM2.5 and reported that results were robust to the inclusion of PM2.5 in the model (3.0% [95% CI: 1.8, 4.2], lag 2).

Studies examining the relation between PM10–2.5 and increases in asthma symptoms may provide support for the observed increases in asthma hospital admissions and ED visits in children. Mar et al. (2004) reported PM10–2.5-related increases across several self-reported symptoms in children, including wheeze, shortness of breath, cough, increased sputum, and runny nose. The authors did not observe associations in healthy adults. Evidence from a limited number of recent panel studies further supports an association between PM10–2.5 and respiratory symptoms in asthmatic children. Wheeze was associated with PM10–2.5 in a panel study of children in Fresno, CA (Mann et al., 2010). The reported association was observed with 3-day lag PM10–2.5 concentrations from a single monitor (OR: 1.07 [95% CI: 1.01, 1.14]), but the authors noted that the association was relatively stable across lags. Zora et al. (2013) measured the 4-day avg PM10–2.5 concentrations from the roof-tops of two schools in El Paso, TX and reported poorer asthma control scores with increased concentrations, which reflect symptoms and activity levels. Prieto-Parra et al. (2017) also observed associations between 7-day avg coarse PM and cough and wheeze in Santiago, Chile. Notably, the authors reported that PM10–2.5 was associated with decreased bronchodilator use (Prieto-Parra et al., 2017).

Cardiovascular Effects

Past epidemiologic studies reported associations between short-term PM10–2.5 exposure and cardiovascular effects including ischemic heart disease (IHD) hospitalizations, supraventricular ectopy, and changes in heart rate variability (HRV). In addition, dust storm events resulting in high concentrations of crustal material were linked to increases in cardiovascular disease emergency department (ED) visits and hospital admissions (U.S. EPA, 2019). The 2019 PM ISA concludes that short-term PM10–2.5 exposure and cardiovascular effects is "suggestive of a causal relationship". Recent studies address the potential exposure measurement error in previous epidemiologic studies because of the methods used to estimate PM10–2.5 concentrations. In addition, there was limited evidence of cardiovascular effects from the few experimental studies that examined short-term PM10–2.5 exposures, recent studies expand on this (U.S. EPA, 2019). Below are the findings of the most recent studies.

Ischemic Heart Disease (IHD) and Myocardial Infarction

Several recent studies provide additional evidence for a positive association between short-term PM10–2.5 exposure and IHD ED visits and hospital admissions. Specifically, PM10–2.5 exposure was associated with IHD hospital admissions among U.S. Medicare beneficiaries in a multicity MCAPS study (Powell et al., 2015), as well as in single-city studies of IHD hospital admissions in Hong Kong, China and Kaohsiung, Taiwan (Chen et al., 2015b; Qiu et al., 2013). In the MCAPS study, PM10–2.5 exposure was associated with a 0.74% (95% CI: 0.29, 1.20) increase in hospital admissions for IHD on the same day (Powell et al., 2015). The association was unchanged in copollutant models adjusting for PM2.5. Qiu et al. (2013) also observed a positive association, which persisted but lost precision after adjustment for PM2.5. In Kaohsiung, Taiwan, Chen et al. (2015b) considered nearly 23,000 hospital admissions for IHD and reported positive associations on cool and warm days. The observed associations were generally robust to adjustment for NO_2, SO_2, CO, and O_3 in copollutant models. One additional important uncertainty across the available studies remains exposure measurement error for PM10–2.5. All studies used an indirect

measure of PM10₋2.5 (the difference between county-or area-averaged PM10 and PM2.5 measurements or the difference between concentrations measured at single PM10 and PM2.5 monitors).

Heart Failure and Impaired Heart Function

In a 110-county national Medicare cohort (MCAPS) study, Powell et al. (2015) reported a 0.40% (95% CI: −0.06, 0.87) increase in heart failure hospitalizations associated with PM10₋2.5 concentrations on the same day (measured by the difference of collocated PM10 and PM2.5 monitors). The association was attenuated in magnitude and precision, but still positive, in a two-pollutant model adjusting for PM2.5.

Powell et al. (2015) also found a positive association between PM10₋2.5 and arrhythmia-related hospital admissions (ERR: 0.94% [95% CI: 0.40, 1.48] associated with PM10₋2.5 concentrations on the same day, measured by the difference of collocated PM10 and PM2.5 monitors). In a much smaller study in Taipei, Taiwan, Chen et al. (2015b) also observed positive associations between PM10₋2.5 (measured by the difference of collocated PM10 and PM2.5 monitors) and CHF hospitalizations on both warm and cold days, and arrhythmia-related hospital admissions (ERR: 0.94% [95% CI: 0.40, 1.48]. The associations were robust in copollutant models adjusting for SO₂ and were attenuated, but still positive, in two-pollutant models adjusting for NO₂, CO, and O₃.

Cerebrovascular Disease (CBVD) and Stroke

A limited number of recent studies provide inconsistent evidence regarding the presence of an association between short-term PM10₋2.5 exposure and ED visits and hospital admissions for CBVD. Studies in Rome, Italy (Alessandrini et al., 2013) and Kaohsiung, Taiwan (Chen et al., 2015b) reported some evidence of an association between short-term PM10₋2.5 concentrations and ED visits and hospital admissions for CBVD. Alessandrini et al. (2013) considered 26,557 hospital admissions for CBVD in the context of Saharan dust outbreaks and observed a 1.6% (95% CI: −0.6, 3.8) increase in risk of hospital admissions associated with PM10₋2.5 concentrations measured on the same day. The association was larger in magnitude, but less precise (i.e., wide 95% CIs) on days with high Saharan dust levels, although effect measure modification by Saharan dust level was not statistically significant. Chen et al. (2015b) also evaluated approximately 25,000 hospitalizations for CBVD and reported associations with PM10₋2.5 concentrations on both warm and cool days, with a larger magnitude association observed on warm days. The observed association on warm days was robust to adjustment for SO₂ and O₃ and attenuated, but still positive, after adjustment for NO₂ and CO in copollutant models. Additional studies conducted in China reported inconsistent evidence of an association (Huang et al., 2016; Qiu et al., 2013). Huang et al. (2016) reported a positive association between PM10₋2.5 concentrations and stroke ED visits (lag 0) when adjusted for CO or NO₂ in Beijing, China. Additionally, when examining ischemic and hemorrhagic stroke subtypes, Huang et al. (2016) observed positive associations at lag 0, while associations were attenuated but still positive, or null, at longer lag periods (lag 1 to lag 3). Furthermore, the authors also reported consistently stronger associations across lag periods for ED visits on days when the temperature was greater than 13.5°C. In contrast to the studies in Rome, Kaohsiung, and Beijing, a study of over 100,000 ED visits in Hong Kong, China reported a null association between CBVD hospital admissions and PM10₋2.5 concentrations (Qiu et al., 2013).

Blood Pressure and Hypertension

An epidemiologic panel study (Zhao et al., 2015) and a few CHE studies (Byrd et al., 2016; Bellavia et al., 2013; Brook et al., 2014) provide some evidence of an effect of short-term PM10₋2.5 exposure on measurements of blood pressure. In addition, an animal toxicological study (Aztatzi-Aguilar et al., 2015)

also reported that short-term exposure to PM10-2.5 could result in changes in the blood pressure regulating renin-angiotensin system at the mRNA level. These recent studies provide additional evidence that short-term exposure to PM10-2.5 may result in changes in BP.

Combinations of Cardiovascular-Related Emergency Department (ED) Visits and Hospital Admissions

Many epidemiologic studies consider the composite endpoint of ED visits and hospital admissions for all cardiovascular diseases, including diseases of the circulatory system.

In 108 U.S. counties with collocated PM10 and PM2.5 monitors, Peng et al. (2008) reported a 0.8% (95% CI: 0.6, 1.0) increase in risk of CVD hospital admissions among Medicare beneficiaries associated with PM10-2.5 concentrations on the same day. A positive association was also observed in six French cities, but the association was much less precise (Host et al., 2008). Tolbert et al. (2007) did not find evidence of an association between PM10-2.5 exposure and CVD ED visits and hospital admissions in Atlanta, GA.

Several recent multicity studies provide evidence of an association between PM10-2.5 concentrations and cardiovascular-related hospital admissions. In the U.S. MCAPS study, Powell et al. (2015) observed increases in same-day (lag 0) PM10-2.5 concentrations were associated with a 0.69% (95% CI: 0.45, 0.92) higher rate of cardiovascular-related hospital admissions among Medicare beneficiaries. The association was diminished when longer lag periods were evaluated and was unchanged after adjustment for PM2.5 in copollutant models. The MED-PARTICLES study reported a similar positive association between PM10-2.5 concentrations (lag 0–1) and cardiovascular-related hospital admissions in eight southern European cities (Stafoggia et al., 2013). As in the findings from the U.S. MCAPS study, the association was not present at longer lags (0–5 and 2–5). The observed association was attenuated but still positive in copollutant models adjusted for PM2.5 and NO_2. Conversely, in a study of five cities in central and eastern Europe, Lanzinger et al. (2016b) reported a positive association with a wide confidence interval for PM10-2.5 concentrations averaged over a longer lag period (0–5), although no evidence of an association at a shorter lag period (0–1).

Results from single-city studies have shown less consistent evidence for the relationship between short-term PM10-2.5 exposure and cardiovascular-related ED visits and hospital admissions. In Rome Italy, Alessandrini et al. (2013) considered 26,557 hospital admissions for CVD in the context of Saharan dust outbreaks and observed a 3.6% (95% CI: 1.5, 5.9) increase in risk of hospitalization at lag 0–1. There was no evidence of effect modification by Saharan dust level. In another European study, Atkinson et al. (2010) reported a null association between PM10-2.5 exposure and cardiovascular-related hospital admissions in London, England. In Doña Ana County, NM, Rodopoulou et al. (2014) reported a positive association with ED visits (RR: 1.015 [95% CI: 0.993, 1.039], lag 1). A study in Hong Kong, China considered PM10-2.5 concentrations in relation to cardiac diseases (Qiu et al., 2013). Qiu et al. (2013) observed a positive association, but the association attenuated to the null after adjustment for PM2.5.

Cardiovascular Mortality

Across past studies there was evidence of consistent positive associations with cardiovascular mortality even though studies used a variety of approaches to estimate PM10-2.5 concentrations. Overall, there was a limited evaluation of the potential confounding effects of gaseous pollutants and the influence of model specification on the associations observed.

Recent multicity epidemiologic studies provide additional evidence of consistent positive associations between short-term PM10-2.5 exposure and cardiovascular mortality with the majority of evidence at lags 0-1 days. Recent studies have also further evaluated the PM10-2.5-cardiovascular mortality relationship by examining cause-specific cardiovascular mortality outcomes [e.g., stroke, heart failure, IHD;(Samoli et al., 2014; Pascal et al., 2014), but overall, these studies are still limited in number.

Controlled Human Exposure Studies of Heart Rate (HR) and Heart Rate Variability (HRV)
Results from a CHE study provides limited evidence that rural (Brook et al., 2014), but not urban (Byrd et al., 2016) PM10-2.5 may alter HR and HRV.

Systemic Inflammation and Oxidative Stress
Systemic inflammation and oxidative stress have been linked to some cardiovascular-related outcomes. Behbod et al. (2013) reported increased leukocytes and neutrophils at 24 hours, but not 3-hours postexposure to urban PM10-2.5 ($p < 0.05$). They also reported that increases in accompanying ambient endotoxin were associated with the increases in leukocytes. However, no changes in the inflammatory markers IL-6 or hs-CRP were reported.

Coagulation
Coagulation refers to the process by which blood changes from a liquid to a semi-solid state to form a clot. Increases in coagulation factors (e.g., fibrinogen) or decreases in anticoagulation factors can promote clot formation, and thus, increase the potential for an MI and perhaps, an embolism (U.S. EPA, 2019). Graff et al. (2009) reported a ~33% decrease in the clot dissolving protein tPA 20 hours postexposure per 10-μg/m^3 increase in PM10-2.5 concentration ($p = 0.01$). However, levels of other clotting-related proteins were unchanged in response to PM10-2.5 exposure. In a quasi-experimental study of 31 healthy volunteers in Utrecht assigned to different exposure locations, PM10-2.5 was associated with a 0.22% increase in vWF (95% CI: 0.02, 0.41; per 13.50 μg/m^3) but not fibrinogen or platelet counts (Strak et al., 2013a). Another study examined associations between PM10-2.5 in a panel of 52 older adult participants with ischemic heart disease and found positive associations between fibrinogen levels and 1-day lag of ambient PM10-2.5 (Huttunen et al., 2012). Null associations were observed between short-term exposures to PM10-2.5 and an array of circulating markers of coagulation among people with diabetes and short-term exposure to PM10-2.5 (Wang et al., 2015).

Nervous System Effects

There are a very limited number of studies looking at nervous system effects and short-term exposure to PM10-2.5. The evidence base consists of a limited number of experimental studies without supporting epidemiologic studies. The toxicological study examined the potential for inhalation of PM10-2.5 to affect the nervous system and found altered gene expression in the brain (Ljubimova et al., 2013). The controlled human exposure study indicated activation of the HPA stress axis in relation to short-term exposure to PM10-2.5 (Liu et al., 2017).

Ultra-Fine Particles (UFP)

Respiratory Effects

There are a limited number of studies examining short-term exposure to UFPs and respiratory effects but enough to be suggestive of a causal relationship. Past epidemiologic evidence indicated associations with combined respiratory-related diseases, respiratory infection, and asthma exacerbation. In addition, personal ambient UFP exposure from time spent in high-and low-traffic areas were associated with lung function decrements in adults with asthma. Older experimental studies provided limited coherence with epidemiologic findings for asthma exacerbation. Recent studies add to this evidence base and support epidemiologic evidence for asthma exacerbation and combined respiratory-related diseases but do not rule out chance, confounding, and other biases. Several animal toxicological studies showing effects related to allergic asthma provide biological plausibility (U.S. EPA, 2019).

For asthma exacerbation, there is some epidemiologic evidence that is not entirely consistent. Associations persisted in one epidemiologic study with adjustment for NO_2, but not in another. Additional supporting evidence, showing decrements in lung function and enhancement of allergic inflammation and other allergic responses, is provided by a controlled human exposure study in adults with asthma and by animal toxicological studies in an animal model of allergic airway disease. For combined respiratory-related diseases, recent findings add consistency for hospital admissions and ED visits and indicate lung function changes among adults with asthma or COPD. Uncertainty remains regarding the representativeness of UFP concentrations as a surrogate for exposure and for copollutant confounding, which limits inference about an independent effect of UFP. Additionally, there remains limited information on the spatial and temporal variability of UFP concentrations (U.S. EPA, 2019).

Asthma Exacerbation

Older studies of hospital admissions, ED visits (Andersen et al., 2008b; Halonen et al., 2008), and physician visits (Sinclair and Tolsma, 2004) reported evidence of associations across a range of lags, as well as for different UFP concentration metrics (i.e., number concentration [NC] and surface area [SA]). In panel studies of asthma symptoms in adults with asthma, supporting evidence of asthma exacerbation was observed across size fractions from NC_{10-100} to $NC_{500-2,500}$ (Mar et al., 2004; von Klot et al., 2002). Supporting evidence was also provided by a study of lung function in adults with asthma in which NC_{10-100} was associated with decrements in FEV_1, FVC, FEF_{25-75}, but not with increases in eNO after walking on a high-traffic road or in a park (McCreanor et al., 2007). This study of scripted exposure minimized uncertainty in the UFP exposure metric by measuring personal ambient UFP at the site of exposure. The evidence across studies was not entirely consistent, as associations between UFP exposure and ED visits for asthma were not observed in the Atlanta, GA-based SOPHIA study (Peel et al., 2005). Additionally, the overall interpretation of results from epidemiologic studies that examined UFP exposures, including those focusing on asthma exacerbation, is complicated by the spatial variability in UFP concentrations, the correlation between UFPs and other traffic-related pollutants, and the various size fractions and concentration metrics used as UFP exposure surrogates.

A few recent epidemiologic studies provide support for associations between increases in short-term UFP concentrations exposure and asthma exacerbation but is not entirely consistent. The supporting evidence comes from an array of outcomes related to asthma exacerbation, including hospital admissions, ED visits, and physician visits for asthma-to-asthma symptoms and medication use. Additional evidence from

studies in adults with asthma using personal ambient UFP exposures via scripted exposures in high-traffic locations is more consistent for lung function decrements than pulmonary inflammation. The relatively small body of recent studies of asthma hospital admissions, ED visits, and physician visits examined a range of UFP size fractions, which complicates the interpretation of results across studies. Several studies examined NC_{10-100} exposure among older children (>3 years), in whom the ascertainment of asthma is more reliable (U.S. EPA, 2019). Samoli et al. (2016a) reported no association with asthma hospital admissions in a study of five European cities. In contrast, Iskandar et al. (2012) reported an association with NC_{10-700} in a study conducted in Copenhagen, Denmark. Across studies, a similar array of lags was examined, and no particular lag was identified as having a stronger association with asthma hospital admissions, but many results support associations with UFP concentrations with a lag of 1 to 5 days or averaged over 3 to 6 days (U.S. EPA, 2019). While the examination of the relationship between short-term UFP exposure and asthma hospital admissions focused on studies that examined daily changes in UFP concentrations and hospital admissions (e.g., time-series, case-crossover analyses), the assessment of the relationship with ED visits was limited to a study that focused on asthma exacerbations that led to an ED visit (Evans et al., 2014). In a group of children with asthma enrolled in the School-Based Asthma Therapy trial, Evans et al. (2014) examined whether exposure to traffic-related pollutants, including UFPs, resulted in an asthma exacerbation that ld to an ED visit over multiday averages up to 0–7 days. There was some evidence of an association for lag 0–3 days (OR: 1.3 [95% CI: 0.90, 1.8] for a 2,088 increase in UFPs per cm^3); however, the association was more evident in children receiving preventative medication at school compared to at home. A recent study examined the association between UFP exposure and lung function and subclinical effects in adults with asthma. In this panel study of 18 adults in Atlanta, GA, NC_{total} was associated with increased eNO and decreased FEV_1 (Mirabelli et al., 2015). Personal NC_{total} was measured during two morning commutes through rush-hour traffic, resulting in higher exposure levels. The observed associations with FEV_1 were consistent across spirometry test conducted 0, 1, 2, and 3 hours post commute, while increased eNO was only associated with UFP exposure in adults with below-median asthma control.

Only one controlled study investigated the effects of short-term UFP exposure and respiratory effects in individuals with asthma. In this study, Gong et al. (2008) reported decreases in pulmonary function (oxygen saturation and FEV_1) following a 2-hour exposure to 100 $\mu g/m^3$ UFP CAPs (less than 0.18 μm aerodynamic diameter).

In animal studies Kleinman et al. (2005) found that a multiday exposure to roadway UFP CAPs in Los Angeles, CA enhanced allergic responses in OVA-sensitized and challenged BALB/c mice, and that this effect was dependent on proximity to the PM source. Recently, Li et al. (2010) extended these observations in OVA-sensitized and challenged BALB/c mice. The results demonstrate that short-term UFP exposure exacerbated the effects of allergen and suggest the involvement of Th2 and Th17 helper cells in the response. Pulmonary histopathology revealed that UFP inhalation during the OVA challenge extended allergic inflammation to more distal regions of the lung (i.e., the proximal alveolar duct and adjacent alveolar parenchyma). Their small size may have allowed UFPs to evade phagocytosis and deposit in the deep lung due to diffusion, as well as to stick to the airway walls due to Van der Waal's forces. The oxidative potential of urban UFP (Li et al., 2009) may have also contributed to inflammatory responses. It should be noted that in the recent study by Li et al. (2010), PM and allergens were coinstilled during sensitization prior to the inhalation challenge. This study design more clearly demonstrates the exacerbation of allergic responses than adjuvant activity. Short-term exposure to UFP may also promote

allergic sensitization and additional experiments employing different study designs are needed to show this effect.

Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

There are a few recent studies of UFP exposure and COPD exacerbation, but the evidence base remains small and does not clearly support a relationship. This applies to COPD hospital admissions and ED visits, which can result from uncontrollable respiratory symptoms that are hallmarks of COPD, exacerbation such as cough, sputum production, and shortness of breath.

Recent studies examine COPD hospital admissions in Europe and observe an association in Rome, Italy (Belleudi et al., 2010) but not a multicity study that includes Rome [Samoli et al. (2016a). Additionally, in a study conducted in Helsinki, Finland, Halonen et al. (2009b) reported an association between COPD hospital admissions in the nucleation mode (<0.03 μm), with an 0.8% (95% CI: −2.28, 3.97) increase in hospital admissions for a 3,583-count increase in the nucleation mode, and a 0.82% (95% CI: −1.51, 3.20) increase in hospital admissions for a 2,467-count increase in the Aitken mode (0.03−0.1 μm; lag 3). Among adults with COPD in Erfurt, Germany, NC_{10-100} was not associated with blood levels of the proinflammatory cells neutrophils and eosinophils or most markers of blood coagulation that are linked to cardiovascular effects rather than COPD (Bruske et al., 2010; Hildebrandt et al., 2009).

Respiratory Related Issues

The available evidence suggests small associations between UFPs and respiratory infections, although the distinct size fractions under analysis in each study make cross-study comparisons difficult. The limited evidence from previous and recent studies does not clearly link short-term UFP exposure to increases in respiratory infection, based largely on hospital admissions, ED visits, and physician visits for URI, pneumonia, or LRI, which combines pneumonia and bronchitis (U.S. EPA, 2019).

The evidence more consistently links increases in UFP concentration to increases in respiratory-related diseases broadly than to asthma, COPD, or respiratory infections. Recent findings not only add consistency for hospital admissions or ED visits, but they also indicate lung function changes among adults with asthma or COPD (U.S. EPA, 2019).

There is considerable variation across studies in the size fractions examined and in the fraction most strongly associated with hospital admissions and ED visits for respiratory-related diseases Associations were consistently observed for NC up to 100 nm (Lanzinger et al., 2016b; Samoli et al., 2016b; Leitte et al., 2011; Andersen et al., 2008b; Halonen et al., 2008). In Beijing, China, associations were observed with UFP NC and SC (Leitte et al., 2011). In contrast, hospital admissions and ED visits for respiratory-related diseases are inconsistently associated with size fractions with upper bounds less than 50 nm (Leitte et al., 2011; Halonen et al., 2008).

A few recent epidemiologic studies focusing on individuals with a combination of respiratory-related diseases that also examined associations with UFP concentrations provide evidence that supports an association with respiratory-related hospital admissions and ED visits. For adults with asthma and COPD in four European cities (Helsinki, Finland; Athens, Greece; Amsterdam, the Netherlands; Birmingham, U.K.), NC_{total} measured outside the home but not at a monitor in the city was associated with lung function decrements (de Hartog et al., 2010). Additionally, within the UFIREG study in Augsburg, Germany, NC_{total} was found to be highly correlated across four traffic and nontraffic sites [r = 0.77−0.95; Lanzinger et al. (2016b) and Cyrys et al. (2008)].

Respiratory Effects in Healthy Populations

Evidence linking short-term UFP exposure and respiratory effects in healthy populations is inconsistent or minimal in epidemiologic studies and controlled human exposure studies. Animal toxicological studies found pulmonary oxidative stress following short-term UFP exposure, but inconsistent evidence of pulmonary inflammation and no evidence of changes in lung function. The studies are discussed below.

Lung Function

An association between UFPs and wheeze was reported in a study of infants (Andersen et al., 2008a), in whom wheeze is common and transient. Several recent studies have employed scripted exposures to further inform the relationship between UFPs and respiratory effects in healthy populations. Scripted studies measuring personal ambient UFP exposures are designed to minimize uncertainty in the UFP exposure metric by always measuring UFPs at the site of exposure, ensuring exposure to sources of UFPs, such as traffic, and measuring outcomes at well-defined lags after exposure. A limitation of recent scripted exposure studies is that outcome assessment is only performed up to 6 hours after exposure, such that scripted studies do not inform understanding of the persistence of effects (U.S. EPA, 2019).

In these recent studies, increases in personal ambient UFP exposure were inconsistently associated with decreases in lung function and increases in markers of pulmonary inflammation in healthy adults (Weichenthal et al., 2011; Zuurbier et al., 2011b; Zuurbier et al., 2011b; Matt et al., 2016; Kubesch et al., 2015; Steenhof et al., 2013; Strak et al., 2012; Dales et al. (2013). Some studies provided evidence of transient respiratory effects associated with UFP exposure. Strak et al. (2012) reported decreases in FVC and FEV_1, and increases in eNO immediately after exposure, but not 6 or 18 hours later. Similarly, Matt et al. (2016) observed UFP-related FEV_1 decrements immediately after exposure that were positive 7-hours postexposure. Other studies observed associations with several lung function metrics, including FEV_1, FEV_1:FVC, FEF_{25-75}, total lung capacity (TLC), and residual volume [RV; Dales et al. (2013)] immediately after exposure, and PEF 2 and 6 hours after exposure (Zuurbier et al., 2011b). Notably, many studies that reported some evidence of associations had inconsistent results across an array of lung function metrics (Matt et al., 2016; Strak et al., 2012; Zuurbier et al., 2011b). Similarly, some studies reported UFP associations with lung function and eNO, but not other subclinical pulmonary effects, including nasal lavage levels of the proinflammatory cytokine IL-6 (Steenhof et al., 2013; Strak et al., 2012) or plasma CC16 levels (Zuurbier et al., 2011a), an indicator of decreased lung epithelial barrier function. Additional studies did not observe any associations between UFP concentrations and lung function or pulmonary inflammation in healthy populations up to 7 hours after exposure (Kubesch et al., 2015; Weichenthal et al., 2011; Strak et al., 2010). While respiratory symptoms are frequently studied in populations with pre-existing respiratory conditions, such as asthma or COPD, the outcome is less often examined in healthy populations. As such, no recent studies of UFP exposure evaluate respiratory symptoms or medication use in healthy populations.

In addition to major uncertainties regarding the spatial variability in UFP and the various size fractions and concentration metrics used as UFP exposure surrogates, the ability to attribute inconsistently observed associations to UFP exposure in the presence of moderately to highly correlated traffic-related copollutants (r = 0.50−0.70) remains limited. Only Strak et al. (2012)_examined models with these copollutants. The authors reported that UFP associations observed immediately after exposure persisted in copollutant models including EC, Fe, Cu, NO_2, or NO_x, but results may be unreliable for models with moderately to highly correlated pollutants.

Respiratory Tract Oxidative Stress

Two recent studies examined this endpoint. Seagrave et al. (2008) exposed rats to UFP (count median diameter 15–20 nm, mass median diameter 150 nm) and found increased lung tissue chemiluminescence. Recently, oxidative stress in olfactory epithelium, as well as olfactory bulb and other brain regions, was examined in mice exposed to resuspended urban UFP [Cheng et al. (2016). A single 5-hour exposure to UFP resulted in enhanced markers of oxidative stress in olfactory epithelium, but not olfactory bulb, cerebellum, or cerebral cortex. Multiple exposures over 3 weeks also increased oxidative stress markers in olfactory epithelium, as well as decreased levels of a protein expressed by olfactory sensory nerves, and increased levels of apoptosis-related proteins.

Respiratory Tract Inflammation

Inflammation was observed in two animal studies measuring effects in lung tissue. Cheng et al. (2016) found inflammatory responses in olfactory epithelium, as well as olfactory bulb and other brain regions, in C57BL/6J mice exposed to resuspended urban UFP. The number of IBA-1 positive-macrophages, an indicator of inflammation, increased in olfactory epithelial turbinates and in the olfactory bulb after 5-hours of exposure to UFP ($p < 0.05$). In addition, Aztatzi-Aguilar et al. (2015) found increased levels of IL-6 in lung tissue in Sprague-Dawley rats exposed to UFP CAPs in Mexico City for several days ($p < 0.05$). Aztatzi-Aguilar et al. (2015) also found that short-term UFP CAPs exposure had several effects on the two counterbalancing endocrine systems—the RAS and the kallikrein-kinin system in the lung ($p < 0.05$). These effects included upregulation of genes encoding angiotensin 1 receptor and angiotensin converting enzyme and reduced levels of reduced angiotensin 1 receptor protein. Levels of angiotensin converting enzyme and angiotensin 2 receptor mRNA were not impacted. The RAS plays an important role in pulmonary and systemic vasculature, with binding of angiotensin to the angiotensin 1 receptor mediating vasoconstriction and oxidative stress. In addition, short-term UFP CAPs exposure resulted in upregulation of the gene encoding kallikrein-1 ($p < 0.05$). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors. Bradykinin receptors are involved in the regulation of nitric oxide which mediates vasodilation.

Respiratory Effects in Population with COPD

Kooter et al. (2006) found that a multiday exposure of SH rats to UFP-enriched CAPs in the Netherlands decreased CC16 in BALF. CC16 is a secretory product of nonciliated bronchiolar club cells and is thought to contribute to control of inflammation. Recently, Tyler et al. (2016) exposed C57BL/7 and ApoE knockout mice for 6-hour to UFP generated from motor vehicle exhaust. No increases in BALF inflammatory cells were observed. However, increases in TNF-α levels in BALF and particle uptake into bronchial macrophages were found in ApoE knockout ($p < 0.001$) but not in C57BL/6 mice. Effects were also seen in the hippocampus.

Respiratory Mortality

The assessment of the relationship between short-term UFP exposure and respiratory mortality is limited to studies conducted in Europe (Stafoggia et al., 2017; Lanzinger et al., 2016a; Samoli et al., 2016b) and China (Leitte et al., 2012). Across studies of respiratory mortality, NC was used to examine associations with respiratory mortality. Both Lanzinger et al. (2016a), in a study of five central European cities as part of the UFIREG project, and Leitte et al. (2012), in Beijing, China, reported generally positive associations that were imprecise across each of the UFP size distributions examined, while Samoli et al. (2016b) did not report any evidence of an association with respiratory mortality. Although there is some evidence of

a positive association between short-term UFP exposure and respiratory mortality, within each study only a single monitor was used to estimate exposure to UFPs.

Cardiovascular Effects

A small number of epidemiologic panel studies have observed positive associations between short-term exposure to UFPs and measures of HRV and markers of coagulation ((Hampel et al., 2014; Weichenthal et al.,2014a; Bartell et al., 2013; Rich et al., 2012; Schneider et al., 2010). did not However Strak et al. (2013) did not report UFP-related effects. There is evidence from a single CHE study indicating decreases in the anticoagulant proteins plasminogen and thrombomodulin in individuals with metabolic syndrome (Devlin et al.; 2014).

Metabolic Effects

A recent longitudinal analysis of the data from the HNR study found an association of 28-day avg accumulation mode UFP (NC) exposure with increased blood glucose (0.64 mg/dL [95% CI: 0.07, 1.21] per IQR increase) and increased HbA1c [0.03% (0.01, 0.05) per IQR increase; Lucht et al. (2018a)]. Uncharacterized temporal and spatial variability in the exposure concentration is an uncertainty for this study because a 28-day avg exposure was estimated for 1-km^2 grid cells, not the participants' residence.

Nervous System Effects

There is limited evidence of a relationship between exposure to ultrafine particles (UFP) and nervous system effects. An experimental study demonstrated that inhalation of UFP CAPs enhanced pro-inflammatory responses in the brains of mice that had been sensitized and challenged with ovalbumin (Campbell et al., 2005). Nonallergic mice were not tested. In addition, experimental studies in rodents previously found that inhaled laboratory-generated UFP can translocate from the olfactory epithelium to the olfactory bulb via the axons of olfactory sensory neurons (Elder et al., 2006; Oberdörster et al., 2004). Furthermore, magnetite UFP (10–150 nm), likely derived from combustion sources, has recently been found in frontal tissue from brains of humans (Maher et al., 2016). These findings suggest that ambient UFP may reach the brain via olfactory transport; however, other routes of translocation have not been ruled out. Several recent experimental studies and an epidemiologic study of cognition in older adults add to the evidence base and are discussed below.

Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA) Stress Axis

A controlled human exposure study examined the effects of a 130-minute exposure to UFP CAPs on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). An association between exposure to UFP CAPs and an increase in urinary vanillylmandelic acid, a stress-related biomarker, was observed at 1-hour postexposure ($p < 0.1$) but was not statistically significant. Vanillylmandelic acid is the primary metabolite resulting from the breakdown of the stress hormones epinephrine and norepinephrine. Its presence in urine indicated that exposure to UFP CAPs led to secretion of epinephrine and/or norepinephrine into the blood by the adrenal medulla subsequent to activation of the HPA stress axis.

Allen et al. (2014b) reported changes in neurotransmitters in adult mice exposed for 4 days to UFP CAPs beginning at PND 56. Brain tissue was analyzed at 9 months. Neurotransmitters were altered by exposure to CAPs in a sex-and brain region-specific manner. Most notably, exposure resulted in decreased norepinephrine in the hypothalamus of male mice and increased norepinephrine in the midbrain of female mice ($p < 0.05$). Allen et al. (2014b) also examined serum corticosterone levels in male and female mice exposed to UFP CAPS. Blood samples were collected at PND 60 and at about 6 months of age. At both time points, exposure decreased serum corticosterone levels in males ($p < 0.05$) but had no effect in females.

Brain inflammation and Oxidative Stress

Cheng et al. (2016) examined the effects of exposure to UFP on inflammatory and oxidative stress responses in olfactory epithelium, olfactory bulb, cerebral cortex, and cerebellum. Ambient UFP was collected near a freeway in Los Angeles, CA and re-aerosolized in order to expose C57BL/6J mice for 5, 20, and 45 hours over 3 weeks. Increases in oxidative stress markers were seen after 5 and 45 hrs hours of exposure in olfactory epithelium ($p < 0.05$), but not in the other regions. This study demonstrated rapid responses to inhaled UFP in olfactory epithelium, and to a lesser extent, in olfactory bulb. Responses to UFP inhalation in cerebral cortex and cerebellum required longer exposures. This delay suggests a role for systemic inflammation, rather than particle translocation, in mediating the effects of UFP in these brain regions. Decreased olfactory marker protein and increased markers of apoptosis suggest an impact of UFP exposure on olfactory sensory neurons.

In addition, Allen et al. (2014b) and Ljubimova et al. (2013) reported changes in brain tissue with UFP exposure. Tyler et al. (2016) reported changes in inflammatory markers in the hippocampal tissue.

Cognitive and Behavioral

Wang et al. (2014) examined the association of UFP (2-week avg concentration) with depressive symptoms among older adults in the MOBILIZE study and reported findings that did support an effect of UFP on increased CESD-R score .16 (OR: 1.04 [95% CI: 0.68,1.57]).

In an animal toxicological study, Allen et al. (2013) investigated behavioral effects of short-term exposure to UFP CAPs. Exposure to UFP CAPs resulted in changes in mean wait time/fixed ratio completion time ($p < 0.05$), one of the behaviors related to delay of reward. Locomotor activity was evaluated and was not altered by exposure to UFP CAPs.

Long-term Effects of PM Exposure

PM2.5

Respiratory Effects

The 2019 PM ISA concluded that a likely to be causal relationship exists between long-term PM2.5 exposure and respiratory effects (U.S. EPA, 2019). Recent evidence continues to link long-term exposure to PM2.5 and reduced lung development in children and supports PM2.5-related acceleration of lung function decline in adults. The recent body of literature enhances the limited evidence base, providing further evidence that long-term exposure to PM2.5 is associated with asthma development in children and COPD development in adults. Epidemiologic evidence for the development of allergic disease,

respiratory infection, and severity of disease is inconsistent. Recent animal toxicological studies provide evidence for respiratory effects in healthy populations and animal models of cardiovascular disease, including pulmonary oxidative stress and inflammation. Studies focusing on the nasal airways find inflammation and morphologic changes. The epidemiologic literature provides evidence for respiratory mortality in relationship to long-term PM2.5 exposure and examines the relationship between the decline in PM2.5 levels and metrics of respiratory health. Findings that improved respiratory health in children are linked to decreased PM2.5 concentrations add to the evidence base linking long-term PM2.5 exposure and respiratory effects. However, uncertainty with respect to copollutant confounding remains (U.S. EPA, 2019).

Lung Development

Epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) indicated that long-term exposure to PM2.5 is associated with decrements in lung development in school children. Key evidence informing the relationship came from analyses of the Children's Health Study (CHS), a prospective cohort study of children in 12 southern California communities. Two studies of this cohort that were reviewed in the 2004 PM AQCD (U.S. EPA, 2004) observed decrements in annual pulmonary growth rates for all the examined lung function measures (FVC, FEV_1, MMEF, and FEF_{75}) in relation to long-term in PM2.5 exposure (Gauderman et al., 2002; Gauderman et al., 2000). Gauderman et al. (2000) examined lung function growth over a 4-year period for three age cohorts within CHS, including 4th, 7th, and 10th graders. The authors consistently reported the strongest associations in magnitude and precision in 4th graders and the weakest associations in 10th graders for all lung development metrics. Gauderman et al. (2004) followed children for 8 years and reported that PM-related deficits in average lung development between ages 10 and 18 years resulted in clinically important deficits in attained lung function at age 18 years (Gauderman et al., 2004).

Recent data from studies based in the U.S. and Asia continue to provide evidence for PM2.5-related decrements in lung development in children (U.S. EPA, 2019). Like the results from Gauderman et al. (2004), a small prebirth cohort study in Massachusetts (Rice et al., 2015b) and an ESCAPE analysis of multiple European cohorts (Gehring et al., 2013) observed increased odds of clinically low FEV_1 and FVC measurements in relation to long-term PM2.5 exposure. Eenhuizen et al. (2013) reported increases in interrupter resistance technique (R_{int}) consistent with long-term PM2.5 exposure estimated outside participants' birth addresses. Higher R_{int} was associated with lower FEV_1 levels at age 8 years, suggesting that R_{int} may be a predictor of later lung function. The CHS is further evaluated in recent studies that provide supporting evidence in multiple cohorts recruited in 1993 and 1996 and followed through 2007 (Gauderman et al., 2015; Breton et al., 2011). Recent results from the CHS not only corroborate previous results, but they also indicate improvements in lung development in association with declining PM2.5 concentrations (Gauderman et al., 2015). Results from the CHS indicate that long-term PM2.5 exposure may affect lung development during adolescence (age 10–18 years), a period of rapid, nonlinear growth (Wang et al., 1993). Associations during adolescence also are supported in a multicity cohort in Taiwan (Hwang et al., 2015). However, mean PM2.5 concentrations in this study were notably higher than those in the CHS studies. As examined in a limited number of recent studies, evidence is less clear for effects during the linear growth period of preadolescence. PM2.5 was associated with reduced lung development in a cohort in China that included children ages 6–12 years at baseline (Roy et al., 2012). However, no association was observed between PM2.5 and lung development in the PIAMA cohort between ages 8 and 12 years (Gehring et al., 2015a). Information on critical periods of exposure is limited, as most studies

examined concurrent exposure. In the PIAMA cohort, lung development was not associated with PM2.5 exposure estimated for the concurrent period or birth year (Gehring et al., 2015a).

Several studies of pulmonary function in children provide information on potential copollutant confounding through the evaluation of two-pollutant models. These studies add to the strength of the evidence by establishing a PM2.5 relationship with observed lung function decrements that is generally unchanged in models with other pollutants. PM2.5 correlations with NO_2 ranged from 0.25 to 0.75, across studies. In studies that reported higher correlations (r = 0.75), associations between PM2.5 and lung decrements were attenuated but still negative in copollutant models adjusting for NO_2 (Wang et al., 2015b; Gehring et al., 2013). Meanwhile, in studies with low PM2.5-NO_2 correlations (r = 0.25–0.33), associations were relatively unchanged in copollutant models (Chen et al., 2015a; Hwang et al., 2015). Hwang et al. (2015) and Chen et al. (2015a) also reported declines in lung function that persisted in copollutant models adjusting for CO, O_3, and SO_2. However, these studies of school children in Taiwan lack generalizability given PM2.5 concentrations that are much higher than studies in North America and Europe.

Lung function generally peaks in adults around the age of 25, and then slowly declines throughout adulthood (Götschi et al., 2008). In addition to studies of lung function in children, some studies have investigated whether long-term PM2.5 exposure accelerates the rate of decline in lung function as adults age. A longitudinal study of adults from 10 European countries found that annual PM2.5 concentrations were not associated with lung function decrements measured from two spirometry tests taken approximately 10 years apart (Götschi et al., 2008). However, PM2.5 exposures were estimated at the end of the study period, which may have introduced bias if the pattern of spatial variability of PM2.5 concentrations did not remain constant across cities over the 10-year study period. In contrast, cross-sectional studies reported associations between annual average PM2.5 and mean lung function (Schikowski et al., 2005; Ackermann-Liebrich et al., 1997). A limited number of recent longitudinal and cross-sectional studies in the U.S. and Europe have reported more consistent evidence that PM2.5 is associated with decreased lung function parameters in adults. As with past studies, lung function in these cohorts was assessed either as a measure of lung function decline over time or cross-sectionally as a single measure in time. These cross-sectional measurements are generally less informative than longitudinal studies because they do not establish a temporal relationship between the exposure and outcome of interest.

The Framingham Heart Study examined the association between long-term exposure to PM2.5 and longitudinal decline in lung function over a 15-year period (Rice et al., 2015a). Rice et al. (2015a) reported a 5.25 mL/year (95% CI: 0.5, 10.5) faster rate of decline in FEV_1 and a 5 mL/year (95% CI: −0.25, 10.25) faster decline in FVC per 5-$\mu g/m^3$ increase in annual average PM2.5 concentrations in the index year. The authors also observed PM2.5 associations with cross-sectional FEV_1 and FVC measures but did not observe evidence of associations with FEV_1:FVC in longitudinal or cross-sectional analyses. In an ESCAPE project analysis of five European cohorts, Adam et al. (2015) also reported evidence of an association between long-term exposure to PM2.5 and lung function in adults. Supporting evidence of a longitudinal association between PM2.5 concentrations and lung function in adults, Boogaard et al. (2013) examined traffic policy-related reductions in air pollution and found improvements in lung function associated with declining PM2.5 concentrations.

In the Multi-Ethnic Study of Atherosclerosis (MESA), the association between long-term exposure to PM2.5 and lung function was examined cross-sectionally (Adar et al., 2015). PM2.5 was estimated using

area-specific prediction models based on pollution measurements at the community or residential level in a subset of participants (MESA Air), which were incorporated with local geographic, meteorological, and emission data into a hierarchical spatiotemporal model to predict long-term exposure outside of participants' homes. PM2.5 levels 1 year prior to baseline exam and 20-year avg exposures were estimated, and both were negatively associated with FEV_1 and FVC and with higher odds of airflow limitation. Similar to the Framingham Heart Study (Rice et al., 2015a), the authors found null associations between long-term exposure to PM2.5 and FEV_1:FVC (Adar et al., 2015).

Development of Asthma

In a birth cohort study in the Netherlands, early-life PM2.5 exposure was associated with doctor-diagnosed asthma at age 4 years (Brauer et al., 2007). In the southern California Children's Health Study (CHS), PM2.5 was examined in relation to the association between lung function and asthma incidence. The protective association between lung function and new onset asthma observed in the overall population was not present in high PM2.5 communities (Islam et al., 2007).

The recent body of literature enhances the limited evidence base, providing further evidence that long-term exposure to PM2.5 is associated with asthma development in children. The strongest evidence supporting the relationship between long-term exposure to PM2.5 and childhood asthma comes from several recent prospective and retrospective cohort studies conducted in North America and Europe (U.S. EPA, 2019). Longitudinal epidemiologic studies, which follow subjects over time, can better characterize the temporal sequence between PM2.5 exposures and the incidence of asthma by ascertaining the first record of a physician diagnosis. In this regard, longitudinal studies distinguish between asthma onset and asthma exacerbation. In most studies, asthma incidence was ascertained through validated questionnaires that asked parents about the child ever having a physician diagnosis of asthma at baseline, and, at each follow-up, questions about a diagnosis of asthma in the intervening period. In other studies, asthma was assessed by pediatric allergist evaluation (Carlsten et al., 2011) and primary care physician diagnosis or hospitalization due to asthma (Tétreault et al., 2016a; Clark et al., 2010).

Most recent asthma incidence studies focused on birth year as the period of potentially heightened sensitivity to PM2.5 exposure and examine asthma incidence across varying follow-up times. The association between birth-year PM2.5 exposure and diagnosis of asthma at age 7 years was examined in a birth cohort of children at high-risk for asthma (n = 186) in Vancouver, Canada (Carlsten et al., 2011). The smaller sample size compared to other recent studies is balanced by using a high-risk cohort, which results in a higher proportion of cases compared to general population studies. Despite low mean outdoor PM2.5 concentrations at birth residences (5.6 µg/m3), Carlsten et al. (2011) observed that PM2.5 was associated with increased odds of asthma diagnosis (OR: 4.0 [95% CI: 1.4, 11.5]). In a larger study with relatively low mean PM2.5 concentrations (9.9 µg/m3; max: 14.9), Tétreault et al. (2016a) reported a positive and precise association between PM2.5 and onset of asthma in an administrative cohort study of over 1 million children (HR: 1.23 [95% CI: 1.21 to 1.24]). Other studies conducted at higher PM2.5 concentrations also reported generally positive associations between PM2.5 and asthma incidence (U.S. EPA, 2019). A pooled retrospective case-control analysis of minority children provided an exception to the generally consistent evidence of an association (Nishimura et al., 2013). However, the study had low statistical power due to missing PM2.5 concentration measurements for some regions.

Several studies examined alternate exposure windows to assess other periods of potential sensitivity to PM exposure in the development of asthma. Two studies of the PIAMA cohort in the Netherlands (Yang

et al., 2016; Gehring et al., 2015a) and one pooled analysis of four European birth cohorts (Gehring et al., 2015b) observed that asthma incidence was associated with PM2.5 concentrations outside birth residences, and reported attenuated but still positive associations with PM2.5 concentrations at the address of the participant at the time of follow-up. An earlier PIAMA study stratified by participants who had and had not moved from their birth address (movers vs. nonmovers) and observed associations between PM2.5 and incident asthma that were slightly stronger in magnitude in nonmovers (OR: 1.6 [95% CI: 1.1, 2.3]) than movers [OR: 1.3 (95% CI: 0.97, 1.8); Gehring et al. (2010)]. While the difference in ORs is not large, the stratified results may suggest continued sensitivity to PM2.5 exposure later in life. In a nested case-control study in British Columbia, Clark et al. (2010) examined asthma incidence at ages 3–4 years in association with PM2.5 concentrations in both the prenatal period and first year of life. The authors reported similar asthma-PM2.5 associations for prenatal and first year of life exposures.

Recent studies of asthma prevalence generally provide supporting evidence for an association with PM2.5 (Gehring et al., 2015b; Hasunuma et al., 2014; MacIntyre et al., 2014a; Mölter et al., 2014), although some did not (Fuertes et al., 2013b; Akinbami et al., 2010). Supporting evidence was also reported in studies examining PM2.5 and wheeze, a common symptom of asthma. Repeated wheeze in 2-year-olds was prospectively studied in a pregnancy cohort of women (n = 708) receiving care at Brigham and Women's Hospital in Boston, MA (Chiu et al., 2014). Prenatal PM2.5 exposure was associated with increased odds of repeated wheeze at age 2 years (OR: 2.0 [95% CI: 1.2, 3.4] for above median vs. below median PM2.5 concentrations). In the larger PIAMA cohort study, Gehring et al. (2010) observed increased odds of parental-reported prevalent wheeze during the first 8 years of life associated with long-term PM2.5 concentration (OR: 1.3 [95% CI: 1.1, 1.6]).

Contrary to this recent evidence supporting the presence of an association in children, the results for adult populations have been largely inconsistent (U.S. EPA, 2019).

Subclinical effects underlying the development of asthma, including airway inflammation and airway hyperresponsiveness, have been examined in both epidemiologic studies and animal toxicological studies.

In a cross-sectional analysis of school children in Windsor, Ontario Dales et al. (2008) observed an increase in airway inflammation (as measured by exhaled nitric oxide [eNO]) corresponding to an increase in annual PM2.5 concentrations. Several studies reported subclinical effects underlying the development of asthma following long-term exposure to DE or woodsmoke (U.S. EPA, 2009). However, these studies did not distinguish between effects due to gases or particles in the mixture.

Recently, a longitudinal study of the CHS cohort reported that, in models adjusted for short-term PM2.5 exposure, annual PM2.5 concentrations were associated with a 10.3 ppb (95% CI: 3.0, 17.6) increase in FeNO (Berhane et al., 2014). Results from a prior CHS analysis (Bastain et al., 2011) showed that elevated eNO was associated with increased risk of new onset asthma. However, potential copollutant confounding was not examined in either study. Thus, there are a limited number of epidemiologic studies providing evidence for subclinical effects underlying the development of asthma in association with long-term exposure to PM2.5.

Recently, a study evaluating the effects of PM2.5 on the development of asthma has become available. Kim et al. (2016a) exposed BALB/c mice to nebulized DEPs for 4, 8, and 12 weeks and found increased BALF levels of the Th2 cytokines IL-5 (8 and 12 weeks) and IL-13 (4 and 12 weeks; $p < 0.05$). Because these

mice were naïve and not sensitized or challenged with allergens, this result provides evidence that PM2.5 can induce an immune phenotype in the absence of an allergen.

Development of Allergic Disease

Epidemiologic studies examining a range of allergic indicators found a mix of positive and null associations with long-term exposure to PM2.5. While several studies reported PM2.5 associations with hay fever/allergic rhinitis, indoor and outdoor allergic sensitization, and/or eczema, there was comparable evidence of null associations across the same endpoints (U.S. EPA, 2019). Recent studies encompass two main indicators of allergic disease: hay fever/allergic rhinitis diagnosis (Gruzieva et al., 2014; Gehring et al., 2010; Weir et al., 2013), and allergic sensitization (Gehring et al., 2010; Gehring et al., 2015b; Fuertes et al., 2013a; Wang et al. (2015a). In addition, a single recent animal toxicological study provided evidence that long-term PM2.5 exposure can promote the development of a Th2 phenotype (Kim et al., 2016a).

Development of Chronic Obstructive Pulmonary Disease (COPD)

Recent large cohort studies examined the association between long-term PM2.5 and COPD development. In a study of COPD incidence in the U.K., a dispersion model was used to assign annual-average PM2.5 exposure to nearest postal code centroid for each patient (Atkinson et al., 2015). The authors reported that PM2.5 was associated with higher odds of first COPD hospitalization (OR: 1.14 [95% CI: 0.96, 1.36]), but not for COPD diagnosis from a general practitioner (OR: 0.98 [95% CI: 0.84, 1.16]). Hospital admissions records may represent more severe cases of COPD, which may explain the difference in effect estimates. The COPD hospitalization results persisted in two-pollutant models with SO_2, NO_2, and O_3 ($r < 0.5$ for all pollutants). Similarly, 5-year avg PM2.5 was associated with an increase, with wide confidence intervals, in the risk of hospitalization due to COPD (RR: 1.06 [95% CI: 0.93, 1.20]) in a large population-based cohort in metropolitan Vancouver (Gan et al., 2013). The study was limited to participants who had no previous record of COPD diagnosis, but hospitalization records were analyzed only for a few years prior. Thus, the hospitalization could reflect exacerbation of a previously diagnosed disease, rather than COPD onset. In a large cohort study of chronic disease prevalence in women living in Ontario, Canada, To et al. (2015) assigned PM2.5 exposure at a postal code level using satellite-based AOD observation data. The authors reported that the incidence and prevalence of COPD were associated with 8-year avg PM2.5 concentrations. Contrasting evidence was observed in an ESCAPE project pooled analysis of four European cohorts (Schikowski et al., 2014). COPD was defined using prebronchodilator FEV_1:FVC below the lower limit of normal (LLN) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition (FEV_1:FVC < 0.70).

A limited number of studies examined specific forms of COPD, including emphysema and chronic bronchitis. As discussed in the 2009 PM ISA (U.S. EPA, 2009), McConnell et al. (2003) reported associations between annual and 4-year avg PM2.5 and bronchitic symptoms in a prospective study of children in 12 CHS communities. A recent pooled analysis of five European cohorts also examined chronic bronchitis in relation to PM2.5 (Cai et al., 2014). Annual average PM2.5 concentrations were not associated with chronic bronchitis in the overall population (OR: 0.90 [95% CI: 0.74, 1.09]), but were associated with chronic bronchitis in a subanalysis of nonsmokers (OR: 1.28 [95% CI: 0.95, 1.72]). A

U.S. cross-sectional study using data from the National Health Interview Survey (NHIS) also observed an association between PM2.5 concentrations in the past year and the odds of chronic bronchitis [OR: 1.08 (95% CI: 0.94, 1.24); Nachman and Parker (2012)]. The association between emphysema and exposure to PM2.5 was examined cross sectionally in the MESA study (Adar et al., 2015). PM concentrations 1 year

prior to baseline exam and 20-year avg exposures were estimated. Percent emphysema, determined from CT scans, was positively associated with both 1-and 20-year avg PM2.5.

Recent studies provide some evidence that long-term PM2.5 exposure may be associated with development of COPD in adults, but uncertainties remain. Notably, studies of COPD hospitalization may reflect exacerbation of previously diagnosed disease rather than disease onset. Additionally, hospitalizations may represent severe cases of COPD and may not account for the potential effect of short-term exposures leading to these acute events. There is also a lack of available studies that examine potential copollutant confounding (U.S. EPA, 2019). However, one study observed that PM2.5 was associated with first-time COPD hospitalization independent of gaseous pollutants (Atkinson et al., 2015). Overall, a limited number of studies also provide evidence of an association between long-term exposure to PM2.5 and chronic bronchitis, a specific form of COPD.

Respiratory Infection

Results from epidemiologic studies indicate an association between PM and respiratory infection. The association between infant bronchiolitis and long-term PM2.5 exposure was examined in three large cohorts (Karr et al., 2009b; Karr et al., 2009a; Karr et al., 2007). A prominent respiratory infection in infancy, bronchiolitis is primarily caused by the respiratory syncytial virus (RSV) and results in inflammation of the bronchioles. Karr et al. (2009b) examined infant bronchiolitis hospitalization in a birth registry cohort in the Puget Sound region of Washington. Two similar studies also examined infant bronchiolitis in the Georgia Air Basin of British Columbia (Karr et al., 2009a) and the South Coast Air Basin of California (Karr et al., 2007). Each nested case-control study examined cumulative lifetime exposure to PM2.5 in relation to bronchiolitis incidence in the first year of life. The results were inconsistent across studies. Karr et al. (2009b) reported that PM2.5 concentrations were associated with RSV bronchiolitis, but not all bronchiolitis, which includes bronchiolitis due to other infectious agents. However, in a model examining effect modification, Karr et al. (2009b) reported an association with all bronchiolitis for infants living within 5 km of a fixed-site monitor. Karr et al. (2007) observed a 4% increase in the odds of bronchiolitis hospitalization in the first year of life in relation to cumulative lifetime PM2.5 exposure (95% CI: 2, 7). The association with PM2.5 was robust to the inclusion of O_3 in a copollutant model (4% [95% CI: 2, 7]; $r = -0.24$). In contrast to evidence observed in Washington (Karr et al., 2009b) and California (Karr et al., 2007), Karr et al. (2009a) reported null associations between lifetime PM2.5 exposure and infant bronchiolitis in British Columbia.

A limited number of studies evaluated other respiratory infection endpoints in infants or adults. MacIntyre et al. (2014b) examined parental-reported pneumonia, otitis media, and croup in an ESCAPE project pooled analysis of 10 European cohorts. PM2.5 estimated outside birth residence was associated with an imprecise increase in odds of pneumonia in the first 36 months of life across all cohorts (OR: 2.58 [95% CI: 0.91, 7.27]). The association with PM2.5 was attenuated, but still positive, in a two-pollutant model adjusting for NO_2 (OR: 1.91 [95% CI: 0.56, 6.57]; $r = 0.42-0.8$). A sensitivity analysis looking at alternative outcome windows showed the strongest association between long-term PM2.5 and pneumonia diagnosed in the first year of life. Associations were null or negative for croup and otitis media. In a case-control study in Ontario, Canada, Neupane et al. (2010) assessed the risk of hospitalization for community-acquired pneumonia in adults 65 years of age or older in relation to long-term exposure to PM2.5.

In summary, recent epidemiologic studies do not indicate a clear relationship between long-term PM2.5 exposures and respiratory infection in infants or adults. While the limited number of studies reviewed

generally reported associations between PM2.5 and at least some of the examined respiratory infection outcomes, there was limited overlap in endpoints across studies.

Severity of Respiratory Disease

Two older cohort studies have provided evidence of an association between long-term PM2.5 concentrations and increased severity of respiratory disease (U.S. EPA, 2009) A limited number of recent epidemiologic studies showed an association between long-term exposure to PM2.5 and severity demonstrated by increased risk of asthma hospitalizations and ED visits in children. A recent study also provided evidence of a similar association in adults. However, potential confounding by short-term exposures remains an uncertainty in ascertaining the independent effect of long-term PM2.5 exposure (U.S. EPA, 2019). One recent animal toxicological study evaluated the exacerbation of asthma in an animal model of allergic airway disease (Farraj et al.; 2010).

Subclinical Effects in Healthy Populations

Several older studies evaluated the effects of long-term exposure to PM2.5 on subclinical effects in healthy populations. These studies provided evidence of pulmonary injury, inflammation, oxidative stress, and morphological alterations following long-term exposure to DE, GE, and woodsmoke (U.S. EPA, 2009). While most studies made no effort to distinguish between effects due to gases or particles in the mixture, one study examined the effects of particle filtration. Injury and inflammatory responses to DE were diminished as a result of particle filtration, indicating that PM played a role in the responses. Recent studies and one older study provided evidence for several subclinical effects potentially underlying the development of respiratory disease following long-term PM2.5 exposure in healthy animal models. These include pulmonary injury, oxidative stress, inflammation, and altered morphology. In particular, increases in tissue and BALF expression of antioxidant genes and proteins and increases in BALF levels of oxidized phospholipids were found. Upregulation of cytokines in the lungs and infiltration of inflammatory cells, including lymphocytes, monocytes, and specific T-cells subtypes consistent with a Th1 proinflammatory response, were also observed. In addition, long-term PM2.5 exposure resulted in increased collagen deposition, an early step in the development of lung fibrosis, and upregulation of the RAS. While the above-mentioned studies focused on the lower airways, changes to the upper airways were also demonstrated. Two studies found evidence of oxidative stress, injury, inflammation, and morphologic changes in nasal mucosa resulting from long-term exposure to PM2.5 (U.S. EPA, 2019).

Respiratory Mortality

Evidence from past studies investigating respiratory mortality provided limited and inconsistent evidence for a respiratory effect related to long-term PM2.5 exposure. This included evidence from two large, multicity U.S. studies: the American Cancer Society (ACS) cohort (Pope III et al., 2004) and the Harvard Six Cities cohort (Laden et al., 2006). Several recent analyses further evaluated the associations of long-term PM2.5 exposures with risk of respiratory mortality based on the original ACS study (Pope et al., 1995), adding details about deaths due to respiratory disease (including COPD), and extending the follow-up period for the ACS to 22 years (1982–2004). In particular, Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term PM2.5 exposure and respiratory disease and COPD. The results of these extended analyses demonstrated positive associations with respiratory disease and COPD mortality, which had not been previously evaluated among the ACS cohort. Similarly, Lepeule et al. (2012) reported the results of an extended analysis of the

Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009. This was the first time that COPD mortality was evaluated among the Harvard Six Cities cohort; the relative risk was positive, but imprecise due to the smaller number of COPD deaths compared to deaths from other causes.

Several additional U.S. cohort studies evaluated the association between long-term PM2.5 exposure and respiratory mortality. In a nationwide cohort of older Americans, Thurston et al. (2016) used monthly estimates of PM2.5 concentration to assign annual mean concentrations to participants in the NIH-AARP cohort study and observed a positive association with respiratory mortality. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) examined the association between PM2.5 and mortality among female public-school teachers and observed positive associations between long-term PM2.5 exposure and respiratory mortality. In a reanalysis of the cohort with refined exposure assessment, Ostro et al. (2015) used a chemical transport model (CTM) to predict PM2.5 concentrations with a 4-km spatial resolution, observing a null association between PM2.5 exposure and respiratory mortality. Hart et al. (2011) examined the association between residential exposure to PM2.5 estimated from a single year of monitoring data (2000) and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS). The results for respiratory mortality were like those reported by Lipsett et al. (2011) for respiratory mortality. The results for COPD mortality were null for the cohort and positive, although imprecise for a sensitivity analysis excluding long-haul drivers.

Cardiovascular Effects

The 2019 PM ISA confirms a causal relationship between long-term effects of PM2.5 and cardiovascular effects. Studies of mortality from cardiovascular causes provided the strongest evidence in support of this conclusion. One large prospective study of postmenopausal women reported an increased risk of cardiovascular events, including CHD and stroke, in association with long-term exposure to PM 2.5 (Miller et al., 2007). Recent studies of long-term exposure to PM2.5 and cardiovascular mortality continue to provide strong evidence of a causal relationship between long-term exposure to PM2.5 and cardiovascular effects. Results from recent U.S. and Canadian cohort studies demonstrate consistent, positive associations between long-term PM2.5 exposure and cardiovascular mortality. Overall, the studies reporting positive associations examined the relationship at varying spatial scales and employed different exposure assessment and statistical methods. The studies were conducted in locations where mean annual average concentrations ranged from 4.08–17.9 µg/m3. Numerous U.S. and Canadian cohort studies conducted in locations where the long-term PM2.5 concentration are less than 13 µg/m3 added to the strong evidence base describing the relationship between long-term PM2.5 and cardiovascular mortality, and specifically IHD- and stroke-related mortality. Overall, these recent cardiovascular mortality studies reported positive associations at varying spatial scales and across different exposure assessment and statistical methods. The associations between long-term PM2.5 exposure and cardiovascular mortality generally persisted in models that were adjusted for ozone, NO_2, PM10‑2.5, or SO_2, and most analyses of the C-R function supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of PM2.5 (U.S. EPA, 2021).

Cardiovascular Heart Disease (CHD), Stroke, and Myocardial Infarction (MI)
The body of literature examining the relationship between long-term PM2.5 exposure and cardiovascular morbidity has greatly expanded, with positive associations reported in several cohorts. The findings from the WHI cohort of postmenopausal women (Miller et al., 2007), reporting associations of long-term PM2.5

and coronary events, were strengthened through a subsequent analysis, which considered potential confounding and modification by SES and applied enhanced exposure assessment methods (Chi et al., 2016a). However, analyses of the NHS and CTS, which are both cohorts of women and include extensive data on covariates (i.e., hormone use, menopausal status, and SES), were not entirely consistent with the WHI findings. Although the NHS cohort is comparable to WHI in that it is made of predominantly postmenopausal women, no associations with CHD or stroke were observed in this population (Hart et al., 2015b). An association with stroke, but not CHD, that was stronger among postmenopausal women was observed in the CTS (Lipsett et al., 2011). In a recent study, Rhinehart et al. (2020) estimated the association of annual average PM2.5 concentration within 300 meters of the residence with stroke in a prospective analysis of residents of Allegheny County Pennsylvania who were diagnosed with atrial fibrillation but had no history of stroke. This study reported a positive association (HR: 1.62 [95% CI: 11 1.00, 2.55]). As opposed to examining annual or 24-month average PM2.5 exposures, Shin et al. (2019) estimated the association between 5-year PM2.5 concentration and incident cases of stroke in a prospective analysis of the Canadian ONPHEC study and reported a positive association (HR: 1.05 [95% CI: 1.03, 14 1.07]).

Several studies conducted among cardiovascular disease patient populations generally reported positive associations with MI (Hartiala et al., 2016; Tonne et al., 2015; Koton et al., 2013), and a sensitivity analysis of the NHS restricted to women with diabetes detected a positive association with CHD. Although the evidence is not consistent across the populations studied, heterogeneity is expected when the methods, or the underlying distribution of covariates vary across studies (Higgins, 2008).

Recent analyses of the Canadian Ontario Population Health and Environment Cohort (ONPHEC) also add to the available evidence on the relationship between long-term PM2.5 exposure and cardiovascular effects. ONPHEC includes more than 5 million Canadian-born adults (35–85 years old at enrollment in 1996) who were registered with the provincial health service and had resided in Ontario for ≥5 years. In a prospective analysis, Bai et al. (2019) estimated the association between 3-year average PM2.5 concentrations and incident cases of acute MI. The study reported a positive association (HR: 1.07 7 [95% CI: 1.06, 1.09]). In addition, stratified analyses showed patterns of associations that indicated stronger effect estimates in the youngest (35–44 years) and oldest (75–85 years) age groups.

Chen et al. (2020) also analyzed data from the ONPHEC study but examined the association of annual average PM2.5 in the previous year with the incidence of acute MI. The authors conducted single pollutant analyses. In addition to conducting single-pollutant analyses, the authors introduced a new approach to assess whether the association of PM2.5 with acute MI varied depending on the proportion of PM2.5 attributed to selected components (i.e., sulphate, nitrate, ammonium, black carbon, organic matter, mineral dust, and sea salt). The study found that the model that adjusted for the proportion of each of the seven selected components was a better predictor of acute MI. In addition, Chen et al. (2020) reported that acute MI associations increased by an average of 10% when compared to single-pollutant results across each of the five regions of Ontario when using the component proportion adjusted approach. Overall, the component adjusted model provided some support that variability in the proportion of individual components that comprise PM2.5, could explain regional variability in risk estimates.

Elliott et al. (2020) examined the interaction between 24-month PM2.5 concentration and physical activity in association with MI among women enrolled in the Nurses' Health Study (NHS). Unlike an earlier analysis of this cohort that examined IHD (Hart et al., 2015b), the authors found a positive association of PM2.5

with MI (HR: 1.06 [95% CI: 1.00, 1.12]), although no statistical evidence of an interaction with physical activity was observed. In the previous analysis of the NHS cohort, Hart et al. (2015b) reported no association between long-term PM2.5 exposure and incident CHD (HR: 1.01 [95% CI: 0.96, 1.07]), although a positive association with IHD was observed among women with diabetes (HR: 1.10 [95% CI: 0.99, 1.21]). Weaver et al. (2019) studied cardiac catheterization patients residing in three counties in NC to determine the association of annual average PM2.5 concentration with MI, coronary artery disease (CAD), and hypertension. Among the objectives of this study was to understand the effect of sociodemographic characteristics on associations by assigning study participants to clusters based on the census block group of their residence that indicated specific sets of sociodemographic characteristics. Positive associations of annual average PM2.5 concentration with both CAD and MI were observed. The association with MI was observed across all sociodemographic clusters (OR for all 6 clusters: 3.57 [95% CI: 2.10, 5.77]). The association with CAD was also observed across all clusters (OR: 1.40 [95% CI: 0.90, 2.19]) but was largely driven by one cluster (OR: 2.01 [95% CI: 1.00, 3.86]), which was urban and characterized by low poverty, low unemployment, and composed of relatively highly educated residents with managerial jobs. In another study, Loop et al. (2018) conducted an analysis of the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, a nationwide study which oversampled participants from states in the southern U.S. where there is known to be an increased risk of stroke. Participants who were free from CHD at baseline were followed for an average of 6 years. Loop et al. (2018) reported an inverse association between annual average PM2.5 concentration at baseline and non-fatal MI (HR: 0.74 15 [95% CI: 0.56, 0.98]). Loop et al. (2018) also examined associations for total CHD, i.e., CHD deaths and non-fatal MI cases combined, and reported no evidence of an association (HR: 0.89 [95% CI: 0.71, 1.11]).

Atherosclerosis

Longitudinal change in measures of atherosclerosis in relation to long-term exposure to PM2.5 add to the collective evidence base (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). Coronary artery calcium (CAC) scoring, also called a coronary calcium scan, is a test that measures the amount of calcium in the walls of the heart's arteries. Deposits of calcium in the coronary arteries are a sign that there may also be a buildup of plaque—a waxy substance that can harden over time and narrow or block the arteries (called atherosclerosis). Kaufman et al. (2016) reported an association of PM2.5 with CAC among middle to older aged adults in the MESA study, while Dorans et al. (2016) reported no association in the Framingham Heart Study. Following the analysis by Kaufman et al. (2016), Keller et al. (2018) estimated the association of PM2.5 concentration (i.e., multi-year average during the study period, 2000–2012) with CAC progression among participants in MESA air residing in Baltimore, MD. The authors also assessed whether this association was modified by membership in clusters with different traffic related air pollution (TRAP) component profiles. The authors reported a 23.0 Agatston unit per year increase (95% CI :14.2, 31.7) among participants overall. Keller et al. (2018) also reported a larger magnitude association with CAC progression (42.6 Agatston unit per year increase [95% CI: 25.7, 59.4]) in the cold season among those belonging to a cluster that was characterized as downtown with above average ratios of ultrafine and accumulation mode particles relative to NO_X. Among women enrolled in the Study of Women's Health Across the Nation (SWAN), a cohort of U.S. women transitioning through menopause, Duan et al. (2019a) estimated the association of 5-year average PM2.5 concentration with carotid intima-media thickness test (cIMT). cIMT is a measure used to diagnose the extent of carotid atherosclerotic vascular disease. The study reported a 27.95 μm (95% CI: −2.90, 58.75) thicker mean cIMT in association with 5-year mean PM2.5 concentration in adjusted models. PM2.5 was also associated with

an increase in increased mean inter-adventitial diameter (IAD), which is a marker of vascular remodeling and aging as well as a predictor of cardiovascular events, of 105.90 (95% CI: −63.00, 274.80). No association was reported with plaque presence (OR: 0.90 [95% CI: 0.50, 1.61]) or plaque severity index (plaque index 0–2, OR: 1.05 [95% CI: 0.53, 8.95] and plaque index >2, OR: 0.62 [95% CI: 0.25, 1.47]) in the SWAN study. In an analysis of a subset of SWAN participants (Pittsburgh and Chicago only), Duan et al. (2019b) estimated the association of the same measures of atherosclerosis as Duan et al. (2019a) with annual average PM2.5 concentration reporting a 11.25 μm per year increase (95% CI: −3.05, 25.60) in mean cIMT. The authors also reported associations with plaque presence (OR: 2.10 [95% CI: 0.66, 6.63]) and plaque index progression (OR: 2.70 [95% CI: 0.77, 9.24]).

Heart Failure

A small number of epidemiologic studies also report positive associations between long-term PM2.5 exposure and heart failure (Aaron et al., 2016; D'Souza et al., 2017; Ohlwein et al. 2016), blood pressure (Chan et al., 2015; Hicken et al., 2013), and hypertension (Zhang et al., 2016; Coogan et al., 2016, To et al., 2015; Babisch et al., 2014; Fuks et al., 2014; Johnson and Parker, 2009). A recent study examining the association between long-term PM2.5 exposure and HF was conducted among participants in the Canadian ONPHEC study. In this prospective analysis, Bai et al. (2019) examined the relationship between 3-year moving average PM2.5 concentration with new cases of CHF. A positive association was reported, overall (HR: 1.07 [95% CI: 1.06, 1.07]).

These heart failure studies agree with animal toxicological studies demonstrating decreased cardiac contractility and function and increased coronary artery wall thickness following long-term PM2.5 exposure (U.S. EPA, 2019). Similarly, a limited number of animal toxicological studies demonstrating a relationship between long-term exposure to PM2.5 and consistent increases in BP in rats and mice are coherent with epidemiologic studies reporting positive associations between long-term exposure to PM2.5 and hypertension (Aztatzi-Aguilar et al., 2016; Ying et al., 2015; Wold et al., 2012).

Systemic Inflammation, Coagulation, and Endothelial Dysfunction

Longitudinal epidemiologic analyses also support the observation of positive associations with markers of systemic inflammation, coagulation, and endothelial dysfunction. These results are in coherence with animal toxicological studies generally reporting increased markers of systemic inflammation and oxidative stress, as well as with toxicological studies generally demonstrating endothelial dysfunction as evidenced by reduced vasodilation in response to acetylcholine (U.S. EPA, 2019).

Mortality

There is also consistent evidence from multiple epidemiologic studies that long-term exposure to PM2.5 is associated with mortality from cardiovascular causes. Associations with CHD, stroke, and atherosclerosis progression were observed in several additional epidemiologic studies, providing coherence with the mortality findings. Results from copollutant models generally support the independence of the PM2.5 associations. Additional evidence of the direct effect of PM2.5 on the cardiovascular system is provided by experimental studies in animals, which in part, demonstrate biologically plausible pathways by which long-term inhalation exposure to PM2.5 could potentially result in outcomes such as CHD, stroke, CHF, and cardiovascular mortality (U.S. EPA, 2019).

The evidence from several multicity U.S. studies, including the American Cancer Society (ACS) cohort (Pope III et al., 2004), the Harvard Six Cities cohort (Laden et al., 2006), the Women's Health Initiative [WHI; Miller et al. (2007)], and the Seventh-Day Adventist (AHSMOG) cohort (Chen et al., 2005) provide

the strongest evidence. These studies continue to provide strong support for the relationship between long-term exposure to PM2.5 and cardiovascular mortality. In addition, extended analyses of the ACS and Harvard Six Cities studies, as well as results from recent cohort studies contribute to the body of evidence for this relationship.

Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term PM2.5 exposure and cardiovascular, ischemic heart disease, heart failure and cardiac arrest, cerebrovascular disease, and hypertensive disease. The results of these extended analyses were consistent with previous results from the ACS cohort for cardiovascular and ischemic heart disease. In addition, these extended analyses provide associations for causes of death that had previously not been evaluated among the ACS cohort. Positive associations were observed with heart failure and cardiac arrest, cerebrovascular disease, and hypertensive disorder. Lepeule et al. (2012) reported the results of an extended analysis of the Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009, and the strong association with cardiovascular mortality persisted.

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health and Environment Cohort (CanCHEC). These studies evaluated the relationship between long-term PM2.5 exposure and CVD (including IHD, CBVD, and circulatory) mortality. The study authors observed positive associations between CVD mortality and long-term PM2.5 exposure, with similar estimates for satellite-derived estimates and ground monitor estimates. The strongest association was for IHD mortality and the weakest was for cerebrovascular mortality. Chen et al. (2016) limited their analyses to CanCHEC participants residing in Ontario who had experienced an acute myocardial infarction and observed positive associations with CVD and IHD deaths, as well as deaths due to subsequent acute myocardial infarctions. Crouse et al. (2015) extended the follow-up period of the CanCHEC to include 5 additional years (1991–2006) and observed positive associations for cardiovascular mortality, with the strongest association observed between long-term exposure to PM2.5 and mortality due to diabetes, followed by IHD. The association for cerebrovascular mortality was just below the null value. The general pattern and magnitude of these associations were generally unchanged in cumulative risk models that include O_3 and/or NO_2. Weichenthal et al. (2016a) evaluated the subset of the CanCHEC living within 5 km of a ground monitor (n = 193,300) and observed associations with IHD mortality that were close to the null value.

Several recent U.S. cohort studies examined the association between long-term PM2.5 exposure and cardiovascular mortality. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) observed positive associations between long-term PM2.5 exposure and IHD and cerebrovascular mortality, with the strongest association observed with IHD (HR: 1.70 [95% CI: 1.51, 1.91]). Analyses restricted to postmenopausal women yielded results like those for all subjects. Puett et al. (2009) examined the association between long-term PM2.5 exposure and all-cause mortality among a cohort of female nurses in the Nurses' Health Study. The authors observed positive associations with CHD mortality (HR: 1.42 [95% CI: 1.03, 1.94]). Using a design like that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term PM2.5 exposure and mortality among men enrolled in the Health Professionals Follow-Up Study cohort. Near null associations were observed for CHD mortality in this cohort. Hart et al. (2011) examined the association between residential exposure to PM2.5 and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS) and observed a modest positive association with cardiovascular mortality.

Recent studies also indicate that the combination of cardiovascular disease and diabetes together has a greater mortality risk than cardiovascular mortality alone and that cardiovascular diseases such as heart failure or previous MI may increase the risk of PM2.5-related all-cause mortality (Ward-Caviness et al., 2020; Malik et al., 2019).

Metabolic Effects

Positive associations between long-term exposure to PM2.5 and diabetes-related mortality were observed in well-established cohorts in the U.S. and Canada. Recent analyses from these two well-established cohorts (the ACS and CanCHEC cohorts) have included this outcome. Pope et al. (2014), Turner et al. (2016), and Jerrett et al. (2016) all used the extended follow-up period of the ACS (1982–2004) to examine the associations between long-term PM2.5 exposure and mortality due to diabetes. Pope et al. (2014) and Turner et al. (2016) assigned exposure using an LUR-BME model and observed positive associations with deaths due to diabetes. Jerrett et al. (2016) assigned PM2.5 exposure using six different methods and observed positive associations with diabetes mortality for each one, though the precision of the association varied across exposure assessment methods. The most precise estimate was observed for the monitor-LUR hybrid model (HR: 1.09 [95% CI: 1.03, 1.17]), and was similar in magnitude to the associations observed by Pope et al. (2014) and Turner et al. (2016).

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health and Environment Cohort (CanCHEC) and evaluated the relationship between long-term PM2.5 exposure and metabolic disease mortality. These studies either examined deaths due to diabetes or the combination of circulatory disease and diabetes in their evaluation of metabolic disease. The authors observed positive associations between diabetes mortality and long-term PM2.5 exposure, with similar estimates for satellite-derived estimates and ground monitor estimates (Crouse et al., 2016; Crouse et al., 2015; Brook et al., 2013a). The hazard ratios remained positive but were less consistent in magnitude for circulatory disease and diabetes deaths combined (Weichenthal et al., 2016; Crouse et al., 2015). Pinault et al. (2016) linked a subset of participants from the CanCHEC cohort to the Canadian Community Health Survey, which allowed them to include an expanded set of individual-level covariates in their analyses. Among the nearly 300,000 participants included in the study, the authors observed positive associations with combined circulatory and diabetes mortality (HR: 1.21 [95% CI: 1.10, 1.33]) similar in magnitude to those observed for diabetes mortality in the larger cohort (Crouse et al., 2016; Crouse et al., 2015).

The mortality findings are supported by epidemiologic and experimental studies reporting effects on glucose and insulin homeostasis, as well as other indicators of metabolic function (e.g., inflammation and liver function). Findings from epidemiologic studies of metabolic disease were not entirely consistent and consideration of copollutant confounding was limited; however, some well-conducted studies reported positive associations of long-term exposure to PM2.5 with metabolic syndrome and its components (e.g., increased blood glucose, insulin resistance, and dyslipidemia) and the incidence of diabetes (U.S. EPA, 2019).

Nervous System Effects

There is evidence from animal toxicological studies demonstrating a link between long-term PM2.5 exposure-mediated activation of the SNS and downstream cardiovascular effects. In addition, evidence

for neuroinflammation and downstream consequences is well substantiated and coherent across experimental animal and epidemiologic studies. Specifically, toxicological studies in adult animals demonstrate neuroinflammation, neurodegeneration, indicators of Alzheimer's disease, impaired learning and memory, and altered behavior. Epidemiologic studies provide support, reporting changes in brain morphology (i.e., neurodegeneration), cognitive decrements, and dementia in adult populations (U.S. EPA, 2019).

Reproductive and Developmental Effects

Male Reproduction

Effects of PM2.5 exposure on sperm have been studied in both the animal toxicological and the epidemiologic literature. The strongest effects in the epidemiologic literature come from studies of PM2.5 associated with impaired sperm motility. The toxicological literature also shows PM2.5-dependent effects on sperm, including impaired spermatogenesis and spermiation. Other studies from epidemiologic literature on sperm morphology have shown inconsistent results (U.S. EPA, 2019).

In the studies of sperm parameters, there is some evidence for decreased motility (Hammoud et al., 2009), including after adjustment for some copollutants [i.e., NO_x, $_{CO}$; Radwan et al. (2015)]. Evidence for association with abnormal morphology is inconsistent, with one study finding higher percent abnormal sperm with higher PM2.5 levels (Radwan et al., 2015) and a U.S. study reporting no evidence of associations between PM2.5 exposure and sperm morphology (Hansen et al., 2010). Among participants in the National Social Life, Health, and Aging Project (NSHAP), Tallon et al. (2017) observed positive associations between exposure to annual PM2.5 concentrations and erectile dysfunction in men aged 57–85 years (OR: 1.26 [95% CI: 0.81, 1.96]). Effect estimates were similar in magnitude and precision when PM2.5 concentrations were averaged over 1, 2, 3, 4, 5, 6, or 7 years. In summary, there are some associations between PM2.5 exposure and some sperm parameters, although the number of studies is limited.

In recent work, spermatogenesis was affected in adult animals after prenatal and/or early postnatal exposure of mice to PM2.5 (ambient air vs. filtered air) from high traffic areas of São Paulo, Brazil. Pires et al. (2011) assessed germ cell count, rates of proliferation and apoptosis, spermatid retention, and spermatogenic cycle timing. When compared to any other single exposure or the control animals, pre-and postnatal exposure caused significantly higher spermatid head retention at stages VIII–XII, a marker of defective spermiation (p = 0.004). No significant changes were detected in Leydig cell, Sertoli cell, spermatogonia, spermatocyte, or round spermatid numbers, or germ cell proliferation, apoptosis, or frequency of spermatogenic stages.

Female Reproduction

Studies of female reproduction in association with PM2.5 exposure include examinations of estrus, ovulation, reproduction, and fertility. In rodents, ovulation and estrus are affected by PM2.5 exposure. In the epidemiologic literature, results on human fertility and fecundity in association with PM2.5 exposure is limited, but evidence from in vitro fertilization (IVF) shows a modest association of PM2.5 concentrations with decreased odds of becoming pregnant. The toxicological evidence provides biological plausibility to these outcomes and shows multiple sensitive windows for PM exposure's effects (U.S. EPA, 2019).

Several recent epidemiologic studies examined the association between exposure to air pollutants and the reproductive function or fertility. Gametes (i.e., ova and sperm) may receive higher exposures while outside of the human body, as occurs with assisted reproduction. A recent study estimated daily concentrations of criteria pollutants at residential addresses of women undergoing their first IVF cycle and at their IVF labs from 2000 to 2007 in the northeastern U.S. (Legro et al., 2010). Increasing PM2.5 concentration estimated at the patient's address during ovulation induction (short-term exposure, ~12 days) was associated with a decreased odds of achieving pregnancy (determined by serum pregnancy test; OR: 0.90 [95% CI: 0.82, 0.99]) or an intrauterine pregnancy (determined by ultrasound; OR: 0.90 [95% CI: 0.82, 0.99]). These authors observed generally null associations with odds of a live birth after pregnancy was established when PM2.5 concentrations were averaged over several exposure periods during pregnancy. The results of this study indicate that short-term PM2.5 exposure during ovulation was detrimental and reduced the likelihood of becoming pregnant. Among the general population in the Czech Republic, increased PM2.5 exposure in the 30 days before initiation of unprotected intercourse also was associated with reduced fecundability [fecundability ratio: 0.93 (95% CI: 0.88, 0.98); Slama et al. (2013)].

In an analysis of the Nurses' Health Study II, Mahalingaiah et al. (2016) observed null associations with infertility and long-term PM2.5 exposure. They also found no evidence of association with endometriosis, a condition potentially linked to infertility [i.e., attempting to get pregnant for at least one year without success; Mahalingaiah et al. (2014)]. A cross-sectional study in Spain also reported null associations with fertility rates based on the number of live births per 1,000 women aged 15–44 years (Nieuwenhuijsen et al., 2014), while a study of almost 2,000 couples in the Czech Republic found increased PM2.5 exposure in the 60 days before initiation of unprotected intercourse was associated with reduced fecundity (Slama et al., 2013). Slama et al. (2013) also examined exposure in the 30 days post-conception as a negative control and observed no evidence of association between PM2.5 and fecundity in this period, providing greater certainty for the observed effect of PM2.5 exposure on fecundity in their study.

Examination of a cohort from Orange and Los Angeles counties in California revealed that the direction of the association between a composite outcome of gestational hypertensive disorders and PM2.5 changed based on how concentrations were determined, either using the CALINE4 model (positive association; OR: 1.47 [95% CI: 1.24, 1.68]) or the nearest monitor [negative association; OR: 0.90 (95% CI: 0.53, 1.54); Wu et al. (2009) and Wu et al. (2011)]. A cohort study conducted across the U.S. reported no evidence of association with preeclampsia for women with or without asthma (Mendola et al., 2016b). A study of around 3,500 women in Washington State observed no associations between preeclampsia and exposure to PM2.5 in the 7 months following conception (Rudra et al., 2011). While a study of a larger cohort from Jacksonville, FL, using monitors within 20 km for assignment and with similar average PM2.5 concentrations, reported positive odds ratios with any hypertensive disorder and PM2.5 exposure in the 1st and 2nd trimesters [OR: 1.09 (95% CI: 0.99, 1.20); OR: 1.24 (95% CI: 1.11, 1.39), respectively; Xu et al. (2014)]. Two meta-analyses have estimated positive odds ratios (ORs: 1.15–1.47) for PM2.5 and preeclampsia, however both studies had large heterogeneity scores, and therefore a combined effect may be inappropriate (Hu et al., 2014; Pedersen et al., 2014).

Several studies evaluated the association between short-and long-term PM2.5 exposure and gestational hypertension. Two long-term exposure studies of blood pressure reported inconsistent effects, with a Pittsburgh, PA study observing null associations (Lee et al., 2012b) and a Polish study reporting positive associations between 2nd trimester PM2.5 exposure and blood pressure measured in the 3rd trimester (Jedrychowski et al., 2012). In addition, a study that evaluated short-term PM2.5 exposure and blood

pressure observed higher blood pressure associated with increased PM2.5 0–4 hours before delivery in women with gestational hypertension and preeclampsia, but not in normotensive women or women with chronic hypertension (Männistö et al., 2014).

All the recent studies of gestational diabetes were conducted in areas with average PM2.5 concentrations less than 12 μg/m^3 and provide limited evidence for an association between PM2.5 exposure and gestational diabetes. In a nationwide cohort, Robledo et al. (2015) reported null associations with PM2.5 exposure in the preconception period (OR: 0.97 [95% CI: 0.94, 1.02]) and 1st trimester (OR: 0.98 [95% CI: 0.94, 1.03]). In a Florida-based study, Hu et al. (2015) observed similar results after adjusting for ozone for the 1st trimester, and also observed increased odds of gestational diabetes with 2nd trimester exposures. Both studies were large, with hundreds of thousands of women in each. In a study of around 2,000 women that compared exposure assignment with monitor values to that with satellite-derived concentrations, Fleisch et al. (2014) observed positive associations with impaired glucose tolerance and PM2.5 exposure in the 2nd trimester, but null associations with gestational diabetes. In a larger cohort using only satellite-derived concentrations, Fleisch et al. (2016) again observed no evidence of an association between PM2.5 in the 1st or 2nd trimesters and gestational diabetes.

In other outcomes related to pregnancy, PM2.5 exposure has been associated with increased odds of high C-reactive protein (Lee et al., 2011b) and altered umbilical cord lymphocyte distributions (Herr et al., 2010), both potentially linked to inflammatory mechanisms for PM, and decreased placental gene expression potentially related to neurodevelopment (Saenen et al., 2015). Recently, PM2.5 exposures have also been found to be associated with placental stress measures and intrauterine inflammation (Nachman et al., 2016; Saenen et al., 2016), along with fetal metabolic and fetal thyroid function (Janssen et al., 2016; Lavigne et al., 2016a).

Past studies provided some evidence of changes in placental vascularity with PM2.5 exposure, including PM2.5-dependent decreased placental weight (GD 17) with decreased blood vessel diameter on the maternal side of the placenta and increased capillary surface area on the fetal side of the placenta (Veras et al., 2008). Recent studies continue to show effects on the placenta in response to PM2.5 exposure. Blum et al. (2017) exposed pregnant B6C3F1 hybrid mice to Sterling Forest PM2.5 CAPs 6 hours/day and found that placental weight was significantly decreased with 3rd trimester PM2.5 exposure and significantly increased with PM exposure over the entire pregnancy ($p < 0.05$); placental weight was not affected by 1st or 2nd trimester PM2.5 exposure. The effect of PM2.5 exposure on placental inflammation was investigated in rats following a 1-hour daily exposure to São Paulo PM2.5 CAPs before and during pregnancy (de Melo et al., 2015). Results indicated placental inflammation after PM exposure. More recent work has evaluated the effects of PM2.5 on the mouse umbilical cord structural anatomy, microscopic vascular morphology, and markers of oxidative stress (Veras et al., 2012).

Birth outcomes

Studies on fetal growth, birth weight, preterm birth, and preterm rupture of membranes show positive associations with PM2.5 exposure in some animal toxicological and epidemiologic studies (U.S. EPA, 2019).

Many recent studies evaluate the association between PM2.5 exposure and birth weight, including studies of low birth weight (LBW) and birth weight as a continuous measure (Ha et al., 2017; Cândido da Silva et al., 2014; Dadvand et al., 2014; Ha et al., 2014; Harris et al., 2014; Hyder et al., 2014; Laurent et al., 2014; Dadvand et al., 2013b; Pedersen et al., 2013; Trasande et al., 2013; Ebisu and Bell, 2012; Salihu et al.,

2012; Morello-Frosch et al., 2010). But others report null or negative effect estimates (Ha et al., 2017; Lavigne et al., 2016b; Brown et al., 2015; Stieb et al., 2015; Fleischer, 2014; Fleischer et al., 2014; Gray et al., 2014; Vinikoor-Imler et al., 2014; Laurent et al., 2013; Madsen et al., 2010; Brauer et al., 2008; Parker and Woodruff, 2008). Similar results are reported for studies that examine change in the continuous measure of birth weight, with some reporting associations between PM2.5 exposure and decreases in birth weight (Erickson et al., 2016; Tu et al., 2016; Stieb et al., 2015; Gehring et al., 2014; Hyder et al., 2014; Pedersen et al., 2013; Kloog et al., 2012; Darrow et al., 2011; Gehring et al., 2011; Gray et al., 2011; Gray et al., 2010; Morello-Frosch et al., 2010), and others reporting null associations or showing increases in birth weight (Tu et al., 2016; Fleisch et al., 2015; Lakshmanan et al., 2015; Hannam et al., 2014; Vinikoor-Imler et al., 2014; Laurent et al., 2013; Geer et al., 2012; Darrow et al., 2011; Gehring et al., 2011; Bell et al., 2010; Jedrychowski et al., 2010; Madsen et al., 2010; Slama et al., 2010; Parker and Woodruff, 2008).

The number of studies evaluating the relationship between PM2.5 exposure and pre-term birth (PTB) has grown considerably in the last decade, and the majority of recent studies report positive associations between PM2.5 exposure and PTB, frequently for exposures averaged over the entire pregnancy period (Defranco et al., 2016; Hao et al., 2016; Laurent et al., 2016; Lavigne et al., 2016b; Mendola et al., 2016a; Pereira et al., 2015; Ha et al., 2014; Padula et al., 2014; Pereira et al., 2014a; Chang et al., 2013; Lee et al., 2013; Kloog et al., 2012; Salihu et al., 2012; Warren et al., 2012; Gehring et al., 2011; Wilhelm et al., 2011; Wu et al., 2011; Wu et al., 2009; Brauer et al., 2008). However, several recent studies report null (Giorgis-Allemand et al., 2017; Mendola et al., 2016a; Hannam et al., 2014; Hyder et al., 2014; Pereira et al., 2014a; Salihu et al., 2012; Gehring et al., 2011; Rudra et al., 2011; Darrow et al., 2009) or negative (Johnson et al., 2016; Mendola et al., 2016a; Stieb et al., 2015; Pereira et al., 2014a) effect estimates.

Recent studies have evaluated the relationship between both short-and long-term PM2.5 exposure and premature rupture of the membranes (PROM). Effect estimates are inconsistent across recent studies of PROM for long-term PM2.5 exposure. An Australian cohort reported elevated ORs with exposure to PM2.5 in the 2nd and 3rd trimesters (Pereira et al., 2014b). A U.S. cohort reported relative risks below the null for both PROM and preterm PROM (Wallace et al., 2016), and a small Rochester, NY cohort (n = 3,264) followed over multiple pregnancies reported null associations (Pereira et al., 2015).

In studies of fetal mortality occurring after 20 weeks of gestation, recent studies generally report positive associations, although timing of exposure varies across studies (Defranco et al., 2015; Green et al., 2015; Faiz et al., 2012). Defranco et al. (2015) reported positive associations with high PM2.5 exposure (defined as above mean plus IQR) in entire pregnancy and 3rd trimester, but not 1st or 2nd trimesters. Green et al. (2015) observed positive associations with entire pregnancy exposures (OR: 1.03 [95% CI: 0.99, 1.06]), although these associations were attenuated after adjustment for NO_2 (OR: 0.98 [95% CI: 0.93, 1.05]), and stratification by California air basin resulted in associations with higher magnitudes (e.g., Sacramento Valley OR: 1.16 [95% CI: 1.00, 1.35]; San Francisco Bay OR: 1.15 [95% CI: 0.97, 1.36]). In a New Jersey study, Faiz et al. (2012) observed positive associations in all trimesters, although slightly stronger ones in the 1st and 2nd trimesters. In a study of short-term exposures, Faiz et al. (2013) reported a positive association with stillbirth and PM2.5 exposure averaged over the 2 previous days, although associations were attenuated to the null after copollutant adjustment (i.e., NO_2, SO_2). Arroyo et al. (2016) also reported a positive association with short-term PM2.5 exposure in Gestation Week 31 and late fetal death (less than 24 hours after birth) (U.S. EPA, 2018).

Two studies of post-neonatal infant mortality reported positive associations for all-cause mortality, respiratory related mortality, and sudden infant death syndrome [SIDS; Son et al. (2011) and Woodruff et al. (2008)]. In the U.S.-based study, the association for respiratory-related mortality (OR: 1.08 [95% CI: 0.97, 1.20]) remained positive but was attenuated after adjusting for CO (OR: 1.04 [95% CI: 0.92, 1.17]) and other gaseous pollutants (i.e., SO_2, and O_3), while the association for SIDS moved away from the null after adjusting for CO in copollutant models (Woodruff et al., 2008). In a case-crossover study, Yorifuji et al. (2016) reported associations between same day PM2.5 and post-neonatal death and all-cause deaths, as well as deaths related to respiratory, SIDS, and birth defects.

The toxicological evidence gives biological plausibility to these outcomes and shows multiple sensitive windows for PM exposure's effect on preterm birth and low birth weight (U.S. EPA, 2019).

Cancer

Past epidemiologic studies evaluating PM2.5 and lung cancer incidence or cancers of other organs and systems generally did not show evidence of an association. Previous toxicological studies did not focus on exposures to specific PM size fractions, but rather investigated the effects of exposures to total ambient PM, or other source-based PM such as wood smoke. Collectively, results of in vitro studies were consistent with the larger body of evidence demonstrating that ambient PM and PM from specific combustion sources are mutagenic and genotoxic. However, animal inhalation studies found no evidence of tumor formation in response to chronic exposures, except for one study demonstrating enhanced formation of urethane-induced tumors. In addition, a small number of studies provided preliminary evidence that PM exposure can lead to changes in methylation of DNA, which may also contribute to biological events related to cancer (U.S. EPA, 2019)

Recent studies address several uncertainties and limitations with respect to the role of PM2.5 exposure in the development of cancer. Evidence from experimental and epidemiologic studies demonstrate that PM2.5 exposure can lead to a range of effects indicative of mutagenicity (Lemos et al., 2016; Traversi et al., 2014; de Rainho et al., 2013; Rainho et al., 2013; Lemos et al., 2012; Singla et al., 2012; Traversi et al., 2011; Kawanaka et al., 2008; Traversi et al., 2008), genotoxicity, and carcinogenicity, as well as epigenetic effects (U.S. EPA, 2019).

In vitro toxicological studies demonstrate that damage to DNA bases and DNA strands can occur after exposure to PM2.5 in these systems and that production of reactive oxygen species (ROS) may contribute to that damage. An animal inhalation study (Soberanes et al., 2012) and a controlled human exposure study (Liu et al., 2015) also provide evidence of oxidative DNA damage. These findings are supported by epidemiologic studies that demonstrate DNA damage in association with PM2.5 concentrations (Chu et al., 2015; Ma et al., 2015). In addition, epidemiologic studies indicate a larger percentage of B[a]P-like DNA adducts in people exposed to higher PM2.5 concentrations (Li et al., 2014; Rossner et al., 2013b).

An animal toxicological study involving inhalation of PM2.5 CAPs (Chicago) found promoter methylation of the tumor suppressor gene *p16* and upregulation of methylation enzymes in lung tissue (Soberanes et al., 2012). An in vitro experiment in the same study found similar results, as well as evidence for oxidative stress contributing to the effects. Other evidence from animal toxicological studies includes methylation of *p16* and the repetitive line element LINE-1 in blood and lung tissue in association with PM2.5 concentrations in a field study conducted in China (Ding et al., 2016) and upregulation of noncoding mRNA in an in vitro study involving PM2.5 collected in Lebanon (Borgie et al., 2015b).

Recent epidemiologic studies of ambient and personal PM2.5 concentrations generally reported some evidence of a change in DNA methylation. In studies examining both global methylation as well as methylation of specific genomic sites (i.e., CpG sites, LINE-1, Alu, SATα, and NBL2), there was evidence indicating hypomethylation in response to PM2.5 exposure (Panni et al., 2016; Guo et al., 2014; De Prins et al., 2013; Madrigano et al., 2011). However, there was also evidence of hypermethylation in some instances (Panni et al., 2016). A recent study in a cohort of mother-child pairs in Belgium also noted associations with PM2.5 concentrations and changes in global DNA methylation (Janssen et al., 2013). Collectively, studies of PM2.5 exposure and DNA methylation provide some evidence of epigenetic effects, but the broad number of biomarkers and measures of DNA methylation examined complicate the overall interpretation of results across studies. These cellular and molecular changes are supported by epidemiologic evidence demonstrating consistent positive associations between long-term PM2.5 exposure and lung cancer mortality and incidence.

Lung cancer

There has been a dramatic increase in the number of studies that examined the relationship between long-term PM2.5 exposure and lung cancer mortality and incidence using both previously examined cohorts as well as new cohorts in the past decade. Collectively, these studies provide evidence of generally consistent, positive associations with both lung cancer mortality and incidence (U.S. EPA, 2019). These associations were observed across studies that adjusted for smoking status and exposure to secondhand smoke (SHS) as well as those studies that had no direct measures of smoking status or used proxy measures to adjust for smoking.

In studies that conducted analyses on never smokers almost all the studies, except a few conducted in Canada (Tomczak et al., 2016; Hystad et al., 2013) provided evidence of consistent positive associations. The positive associations for lung cancer in never smokers were confirmed by Turner et al. (2011) in a study of only never smokers in the ACS-CPS II cohort. The limited number of studies that examined potential copollutant confounding reported that PM2.5-lung cancer mortality and incidence associations remained relatively unchanged, specifically for O_3, with less evidence for other pollutants (U.S. EPA, 2019).

In recent meta-analyses of PM2.5 and lung cancer risk Chen et al. (2015), Yang et al. (2015), Cui et al. (2014) and Hamra et al., 2014 found positive associations. Although the criteria for study inclusion varied across each of these meta-analyses they all reported evidence of a positive association between long-term PM2.5 exposure and lung cancer risk.

Liver Cancer

Recent studies conducted in Taiwan (Pan et al., 2016) and Europe (Pedersen et al., 2017) have examined the relationship between long-term PM2.5 exposure and liver cancer incidence. Within the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) cohort in Taiwan, Pan et al. (2016) examined long-term PM2.5 exposure based on 4-year avg concentrations and liver cancer incidence on both the main islands and Penghu islets. Additionally, the authors examined whether there was evidence of a direct or indirect effect of long-term PM2.5 exposure on serum alanine transaminase (ALT) levels, which is a marker of chronic liver tissue inflammation, and subsequently liver cancer incidence. During the course of the study, new cases of liver cancer were identified during follow-up by pathological examination. Between the two locations, the distribution of PM2.5 concentrations varied dramatically. Pan et al. (2016) reported an HR of 1.22 (95% CI: 1.02, 1.47) on the Penghu islets and HR of 1.21 (95% CI: 0.95, 1.52) on the main islands. In the mediation analysis, there was evidence of an

indirect effect of long-term PM2.5 exposure on liver cancer incidence through elevated ALT levels, as well as some evidence of a potential direct effect. Focusing on the two cohorts conducted in Denmark and Italy that reported PM2.5 concentrations, the authors reported a positive association with new liver cancer cases diagnosed during follow-up (HR: 1.34 [95% CI: 0.76, 2.35]), but the 95% confidence intervals were large (Pedersen et al., 2017).

Multiple Cancers

Although most of the studies that examine long-term PM2.5 exposure and cancer focused on specific cancer types, a few studies examined a few different cancer types. In a study conducted in Hong Kong, Wong et al. (2016) examined mortality attributed to a variety of cancers. Within this study, PM2.5 concentrations were much higher (mean = 33.7 $\mu g/m^3$) than in the other studies evaluated in this section. Across mortality outcomes attributed to cancer types, the authors observed strong positive associations (i.e., in terms of magnitude and precision) for all malignant, all digestive organs, and female genital cancers with HRs ranging from 1.10 to 1.32. There was no evidence of an association for male genital, urinary, or lymphohematopoietic cancer mortality.

Heck et al. (2013) and Lavigne et al. (2017) examined incident childhood cancers in California and Ontario, Canada, respectively. Heck et al. (2013) in a case-control study, examined associations between PM2.5 exposure during the entire pregnancy and childhood cancer (ages <6 years). There was not clear evidence of an association between PM2.5 and cancer risk for any of the cancer sites except for retinoblastoma (OR: 1.33 [95% CI: 1.06, 1.67]; n = 87). Lavigne et al. (2017) also examined multiple childhood cancers, but included cancer diagnoses up to age 14 years. In addition to examining exposures during the entire pregnancy, the authors also examined trimester specific exposures as well as those during the first year of life. Focusing on cancers with greater than 200 cases during the study period (i.e., acute lymphoblastic leukemia, astrocytoma, and Wilms tumor) the authors reported evidence of a number of positive associations across trimesters, the entire pregnancy, and the first year of life for each of these cancers, but 95% confidence intervals were large for all except astrocytoma (HR: 1.80 [95% CI: 1.09, 2.92] for the 1st trimester and HR: 1.68 [95% CI: 1.00, 2.89] for the entire pregnancy). These results are inconsistent with Heck et al. (2013), which also examined astrocytoma and found no evidence of an association with PM2.5 exposure during the entire pregnancy

PM10-2.5

Respiratory Effects

A limited number of recent epidemiology studies expand the evidence base for decrements in lung function, the development of asthma, and respiratory infection in children as discussed below. Uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding.

Recent analyses of European birth cohorts have observed consistent associations between PM10-2.5 and an array of lung function metrics. In the PIAMA cohort, PM10-2.5 estimated at children's current addresses was associated with decreases in FEV_1, FVC, and FEF_{25-75} measures collected at age 8 and 12 years (Gehring et al., 2015a). Similarly, in an ESCAPE project analysis of five European cohorts, PM10-2.5 estimates at both birth address and current address were negatively associated with FEV_1 measured at ages 6 and 8 years, but the effect was stronger when current address was used in the exposure assignment (Gehring

et al., 2013). PM10-2.5 at current address was also associated with higher odds of FEV$_1$ <85% of predicted values (OR: 1.81 [95% CI: 0.94, 3.47]), a clinically significant indicator of impaired lung function.

Cross-sectional studies of school children in 24 Taiwanese provinces (Chen et al., 2015a) and 9–10-year-olds participating in the Child Heart and Health Study in England (Barone-Adesi et al., 2015) provided inconsistent evidence of an association between PM10-2.5 and lung function. While Chen et al. (2015a) reported reductions of 102 mL (95% CI: 16, 189 mL) in FEV$_1$ and 121 mL (95% CI: 15, 227 mL) in FVC per 5-μg/m^3 increase in PM10-2.5 over the past 2 months, Barone-Adesi et al. (2015) did not observe any associations between annual PM10-2.5 exposure and the same lung function metrics. Additionally, it is unclear whether Chen et al. (2015a) estimated PM10-2.5 using collocated PM10 and PM2.5 monitors.

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term exposure to PM10-2.5 on pulmonary function in adults. Results for the various indices of pulmonary function were inconsistent among adults participating in the ESCAPE project (Adam et al., 2015). PM10-2.5 was associated with decrements in FEV$_1$ and FVC in a cross-sectional analysis, but an increase in FEV$_1$ in longitudinal analyses. Due to the strengths of a longitudinal study design compared to a cross-sectional design, it's possible that the negative association may have been the result of unmeasured confounding in the cross-sectional analysis.

A few recent studies report associations between PM10-2.5 and asthma incidence. In the PIAMA cohort in the Netherlands (Gehring et al., 2015a) and a pooled analysis of four European birth cohorts (Gehring et al., 2015b), asthma incidence was associated with PM10-2.5 concentrations outside birth residences. The associations were attenuated, but still positive when PM10-2.5 concentrations were assigned at the address of the participant at the time of follow-up. This indicates the potential importance of early-life exposures.

Studies examining asthma prevalence in children reported contrasting evidence. The Gehring et al. (2015b) pooled analysis, discussed above, observed inconsistent evidence of an association across cohorts, and reported a null association in a meta-analysis combining results from all cohorts. Another ESCAPE project analysis of five European birth cohorts estimated PM10-2.5 at participants' birth addresses and addresses at age 4 and 8 years (Mölter et al., 2014). Birth and current address PM10-2.5 were not associated with higher odds of prevalent asthma at age 4 years. However, PM10-2.5 estimated at both birth and current address was associated with an increase in odds of asthma by age 8 years. Contrary to the results for asthma incidence, the association was higher in magnitude and more precise when asthma prevalence was related to current address PM10-2.5 concentrations (OR: 1.16 [95% CI: 0.93, 1.44]) rather than birth address exposure (1.10 [0.72, 1.69]).

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term PM10-2.5 exposure in adults. An ESCAPE project analysis also examined associations between PM10-2.5 and incident asthma (Jacquemin et al., 2015). In a meta-analysis of all cohorts, annual PM10-2.5 was not associated with higher odds of incident asthma (OR: 0.99 [95% CI: 0.87, 1.14]).

Recently, an ESCAPE project study examined respiratory infections in relation to PM10-2.5 (MacIntyre et al., 2014b). PM10-2.5 estimated at birth residence was associated with an imprecise increase in odds of pneumonia in the first 36 months of life (OR: 1.24 [95% CI: 1.03, 1.5] per 5-μg/m^3 increase) but was not associated with increased odds of otitis media or croup. A sensitivity analysis looking at alternative

outcome windows showed the strongest association between long-term PM10-2.5 and pneumonia diagnosed in the first year of life (OR: 1.46 [95% CI: 1.11, 1.92]). The association between PM10-2.5 and pneumonia at 36 months was attenuated, but still positive in a two-pollutant model adjusting for NO_2 (1.13 [0.72, 1.76]; r = 0.34–0.93).

An animal toxicological study examined the potential for inhalation of PM10-2.5 to affect the respiratory system and found upregulation of the RAS and a dampening of oxidative stress and inflammation in the lung (Aztatzi-Aguilar et al., 2015). Several animal toxicological studies involving noninhalation routes of exposure found allergic inflammation and airway remodeling, which provides biological plausibility for the development of asthma (Liu et al., 2014; He et al., 2013a; He et al., 2013b).

Cardiovascular Effects

The evidence relating long-term exposure to PM10-2.5 to cardiovascular mortality remains limited. Overall, there is no consistent pattern of associations for cardiovascular mortality (U.S. EPA, 2019). In the instances where positive associations were observed for long-term PM10-2.5 exposure and mortality, and PM2.5 copollutant model results were reported, the PM10-2.5 effect estimates were often attenuated but still positive after adjusting for PM2.5. The epidemiologic studies examining the relationship between PM10-2.5 and other cardiovascular outcomes including myocardial infarction (MI) and stroke, atherosclerosis, venous thromboembolism (VTE), and blood pressure has grown (U.S. EPA, 2019). Some studies report positive associations with these outcomes. Specifically, single pollutant associations of long-term exposure to PM10-2.5 with ischemic heart disease (IHD) were observed in three studies (Hart et al., 2015b; Cesaroni et al., 2014; Tonne et al. (2015)] while no association was observed in another study after adjusting for PM2.5 in copollutant models (Puett et al., 2011). After adjusting for noise, Hoffmann et al. (2015) reported an inverse association with IHD in another study. Evidence of an association between long-term exposure to PM10-2.5 and stroke was similarly inconsistent with a positive association observed one study (Hart et al., 2015b) and little evidence of an effect two others (Puett et al., 2011; Stafoggia et al., 2014). An association between long-term PM2.5 exposure and pulmonary embolism was reported (Pun et al., 2015). An inconsistent pattern of results relating to the effect of PM10-2.5 on increased blood pressure and hypertension was reported in a limited number of studies (Chen et al., 2015a; Fuks et al., 2014). To date the studies that have examined the relationship between long-term PM10-2.5 exposure and mortality have used the difference method to derive concentrations for PM10-2.5, contributing to the uncertainty associated with these effect estimates.

There are individual epidemiologic studies that report positive associations with cardiovascular morbidity and mortality outcomes, but the evidence was not entirely consistent (U.S. EPA, 2019). Associations are sometimes attenuated in copollutant models and there is uncertainty stemming from the use of the subtraction method to estimate exposure.

Puett et al. (2009) examined the association between long-term PM10-2.5 exposure and CHD mortality among a cohort of female nurses in the Nurses' Health Study from 13 states in the Northeast and Midwest from 1992 through 2002. Spatiotemporal models were used to assign exposure to PM2.5 and PM10 and the PM10-2.5 concentrations were derived via subtraction. The authors observed positive associations with CHD mortality, although the associations were attenuated to below the null value in copollutant models that include PM2.5. Using a design like that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term PM10-2.5 (derived by subtraction of PM2.5 from PM10) exposure and

CHD mortality among men enrolled in the Health Professionals cohort. Near null associations were observed for CHD mortality in this cohort.

A pooled-analysis of the European ESCAPE cohort combined data from 22 existing cohort studies and evaluated the association between long-term PM10-2.5 exposure and cardiovascular mortality (Beelen et al., 2014). The authors observed a near-null association between long-term PM10-2.5 exposure and cardiovascular mortality (Beelen et al., 2014). The strongest association was observed for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.17 [95% CI: 0.90, 1.52]), although copollutant models with PM2.5 were not reported for this comparison. Using the same exposure models used for the pooled cohort study, Dehbi et al. (2016) assigned PM10-2.5 exposure to two British cohort studies that were pooled together to examine CVD mortality. The British cohorts included follow-up between 1989 and 2015, although PM10-2.5 exposure estimates were available for 2010–2011. The authors observed a negative association when exposure was considered on the continuous scale, but positive associations for each quartile when exposure was categorized. However, the confidence intervals were wide and overlapping for all of the results, and the inconsistency may indicate generally null results, but instability in the model. In a separate European cohort, Bentayeb et al. (2015) used the CHIMERE chemical transport model to estimate PM10 and PM2.5, and then subtracted to estimate long-term PM10-2.5 exposure. The authors observed positive association with cardiovascular mortality.

Metabolic Effects

A high-quality epidemiologic study reported an association between long-term PM10-2.5 exposure and incident diabetes (Puett et al., 2011). In addition, effects on glucose (Teichert et al., 2013) or insulin (Wolf et al., 2016) were observed in cross-sectional studies of glucose and insulin homeostasis conducted in European cohorts. Limited biological plausibility is derived from the potential for deposition of PM10-2.5 to modulate the ANS, the immune system, or disrupt glucose, lipid, and insulin homeostasis (U.S. EPA, 2019).

Nervous System Effects

Several recent epidemiologic studies report the association of long-term exposure to PM10-2.5 with cognitive and behavioral effects in adults, but not with neurodevelopmental effects in children. Among women enrolled in the NHS, Weuve et al. (2012) reported faster cognitive decline in association with increased PM10-2.5 exposure. The magnitude of the change between successive 2-year outcome measurement (β = −0.018 [95% CI: −0.035, −0.002]) persisted after adjustment for potential confounders (i.e., age, education, physical activity, alcohol consumption.). The correlation between long-term PM2.5 and PM10-2.5 concentrations was low (spearman correlation 0.20). Notably, the association with cognitive decline remained after additional adjustment for cardiovascular risk factors and SES. In another analysis of the NHS cohort, Power et al. (2015) observed a small positive association between high anxiety and the annual average concentration of PM10-2.5 (OR: 1.03 [95% CI: 0.99, 1.06]). Associations generally weakened with shorter averaging times in this study. A large imprecise association between long-term exposure to PM10-2.5 and mild cognitive impairment (MCI) was observed in a cross-sectional analysis of the HNR study [OR: 1.69 (95% CI: 0.90, 3.18); Tzivian et al. (2016)]. The association was stronger when MCI was defined to identify cases of amnestic MCI (i.e., objective impairment in at least one memory domain).

In a prospective study of children born in Rome and followed through age 7 years when the WISC-III was administered to measure cognitive function, Porta et al. (2015) reported small (relative to the size of the confidence interval), imprecise associations between PM10‑2.5 and decrement on FSIQ in fully adjusted models (β = −1.10 [95% CI: −2.80, 0.50]). A slightly larger decrease was observed on the Performance IQ subtest. Raz et al. (2015) reported little evidence association between PM10‑2.5 and ASD in a case-control study nested within the NHS cohort (e.g., OR: 1.07 [95% CI: 0.92, 1.24] 3rd trimester exposure, which was the strongest association). Findings from the Guxens et al. (2014) analysis of six European cohorts did not support a strong association with reduced general cognition or global psychomotor development (coefficient: 0.59 [95% CI: −0.99, 2.17] and coefficient: -0.42 [95% CI: −1.28, 0.45], respectively).

Reproductive and Developmental Effects

Infant respiratory mortality and decreased birth weight have the strongest evidence, reporting positive associations. Birth weight is associated with PM10‑2.5 exposure with reports of decreased birth weight with PM10‑2.5 exposure and increased odds of having a low-birth-weight baby with PM10‑2.5 exposure. Both a study in Seoul, South Korea and a study in Tokyo, Japan found increased infant mortality due to respiratory causes using coarse PM exposure from monitors (Yorifuji et al., 2016; Son et al., 2011). For exposures during the postnatal period, Peel et al. (2011) observed no associations between coarse PM and infant apnea and bradycardia. Salihu et al. (2012) observed elevated ORs for low birth weight, and Ebisu et al. (2016) observed small decreases in birth weight with increases in PM10‑2.5, including with adjustment for PM2.5.

Preterm birth is associated with increasing PM10‑2.5 exposure as is infertility. In a cross-sectional study in Barcelona, Spain, Nieuwenhuijsen et al. (2014) reported lower birth rates with increases in PM10‑2.5 from a land use regression model. In examinations of the Nurses' Health Study, Mahalingaiah et al. (2014) and Mahalingaiah et al. (2016) observed increased incident infertility and reduced endometriosis associated with increased PM10‑2.5 concentrations from a spatiotemporal model.

Inconsistent evidence is seen with studies of birth defects and studies of preterm birth with the literature being comprised of studies with positive associations as well as null findings. A study of birth defects found both positive and negative associations with coarse PM exposure (Schembari et al., 2014).

A Barcelona cohort study found positive associations with preeclampsia (Dadvand et al., 2013a).

Cancer

Cytogenetic effects, such as micronuclei formation and chromosomal aberrations, are biomarkers of genotoxicity (Demarini, 2013). Micronuclei are nuclei formed because of chromosomal damage, while chromosomal aberrations are modifications of the normal chromosome complement (Demetriou et al., 2012). Epidemiologic studies provide supportive evidence of micronuclei formation in association with PM10‑2.5 exposure (O'Callaghan-Gordo et al., 2015).

Evidence that PM10‑2.5 exposure induces mutagenicity, DNA damage, oxidative DNA damage, and oxidative stress is provided by a limited number of in vitro animal toxicological studies and a single controlled human exposure study (U.S. EPA, 2019). Liu et al. (2015) found a rapid, but transient increase, which was not statistically significant, in a urine biomarker of oxidative DNA damage following an approximately 2-hour exposure of human subjects to PM10‑2.5. The tissue source of this marker cannot

be discerned so it is unclear where in the body the DNA damage occurred. Additionally, an epidemiologic study reported evidence of increased micronuclei formation in relation to PM10-2.5 exposure (O'Callaghan-Gordo et al., 2015).

Overall, there is limited evidence of a positive association between long-term PM10-2.5 exposure and lung cancer incidence, with no studies examining lung cancer mortality (Raaschou-Nielsen et al., 2013 and Puett et al., 2014). A few recent studies have examined associations between long-term PM10-2.5 exposure and cancer incidence and mortality beyond the respiratory system. This includes individual studies examining breast cancer (Hart et al., 2016) and liver cancer (Pedersen et al., 2017) that reported positive associations, (HR: 1.03 [95% CI: 0.96, 1.10]) and (HR ranging from 1.26–1.86 depending on the ESCAPE cohort), respectively, but with large 95% confidence intervals.

Mortality

The evidence from recent multicity studies of short-term PM2.5 exposures and mortality demonstrate consistent positive associations with total (nonaccidental) mortality, with increases ranging from 0.25% (Chen et al., 2011) to 1.70% (Pascal et al., 2014) at lags of 0 to 2 days in single-pollutant models. However, across studies different approaches have been employed to measure PM10-2.5 concentrations (i.e., directly measured from a dichotomous sampler, difference between PM10 and PM2.5 at collocated monitors, and difference of area-wide concentrations of PM10 and PM2.5), which have not been compared to determine if their spatial and temporal correlation are similar, contributing uncertainty to the comparison of results across studies. Recent studies expand the assessment of potential copollutant confounding of the PM10-2.5-mortality relationship and provide some evidence that PM10-2.5 associations remain positive in copollutant models, but there is some evidence that associations are attenuated (U.S. EPA, 2019).

In addition to examining potential copollutant confounding, a few studies also assessed whether statistical models adequately account for temporal trends and weather covariates. Initial evidence indicates that PM10-2.5 associations may be sensitive to model specification. An examination of whether associations vary by season and temperature provide some evidence that PM10-2.5-mortality associations are larger in magnitude during warmer temperatures and seasons, but this pattern was not evident across all studies. Overall, recent epidemiologic studies provide additional support of consistent positive associations between short-term PM10-2.5 exposure and total (nonaccidental) mortality, but there remains a large degree of uncertainty due to the various approaches used to measure PM10-2.5 concentrations (U.S. EPA, 2019).

Ultrafine Particles (UFP)

Respiratory Effects

Several recent studies have examined the effects of long-term UFP exposure on pulmonary oxidative stress and inflammation and results show injury, oxidative stress, DNA hypermethylation, and changes in the RAS, but no pulmonary inflammation (U.S. EPA, 2019). Zhang et al. (2012) collected ambient UFP near a Los Angeles, CA freeway. Exposure of C57BL/6J mice to the re-aerosolized UFP for 10 weeks resulted in increases in mRNA and protein levels of heme oxygenase-1, NADPH quinone oxidoreductase 1, γ-glutamyl cysteine ligase catalytic subunit, and γ-glutamyl cysteine synthetase modifier subunit in the lung (p < 0.05).

These are Phase II regulated detoxifying enzymes and are important in defense against oxidative stress. Young mice (3 months) had a more robust increase in gene expression and protein levels than older mice (18 months). Zhang et al. (2012) also found evidence of upregulation of Phase II enzymes in specific brain regions and the liver. In contrast, Aztatzi-Aguilar et al. (2015) found decreased lung tissue heme oxygenase-1 activity in Sprague-Dawley rats following 8-weeks exposure to Mexico City UFP CAPs (p < 0.05) and no change in γ-glutamyl cysteine ligase catalytic subunit was observed. Aztatzi-Aguilar et al. (2015) also found decreased protein levels of IL-6 in lung tissue (p < 0.05). Further, Tyler et al. (2016) exposed C57BL/7 and ApoE knockout mice to UFP generated from motor vehicle exhaust. A 30-day exposure resulted in no increase in inflammatory cells or cytokines in the BALF. Particle uptake into bronchial macrophages was increased in both C57BL/6 and ApoE knockout mice (p < 0.05). Effects were also seen in the hippocampus. Aztatzi-Aguilar et al. (2015) found that long-term UFP CAPs exposure had several effects on the RAS, including induced lung expression of the angiotensin 1 receptor gene, and increased angiotensin 1 receptor protein levels (p < 0.05). Protein levels and mRNA of angiotensin converting enzyme were not impacted. Components of the RAS play an important role in the pulmonary circulation. Overall, older and recent studies provide some limited evidence for pulmonary injury, DNA hypermethylation, and changes in the RAS, inconsistent evidence for pulmonary oxidative stress and no evidence for pulmonary inflammation.

Cardiovascular Effects

Studies have shown increased atherosclerotic plaque size in mice following long-term exposure to UFPs (Araujo et al., 2008; Aguilera et al., 2016). A small number of recent epidemiologic studies report positive associations between long-term exposure to UFPs and cIMT and markers of inflammation and coagulation (Viehmann et al.,2015; Aguilera et al., 2016). In addition, a single recent animal toxicological study reported evidence of impaired heart function, as well as changes in markers associated with systemic inflammation, oxidative stress, and the renin-angiotensin system following long-term UFP exposure (Aztatzi-Aguilar et al., 2015). However, the overall toxicological evidence base examining the effects of long-term UFP exposure on cardiovascular endpoints remains extremely limited, and thus, there is little biological plausibility for the effects observed in the epidemiologic studies mentioned above.

Metabolic Effects

In a recent longitudinal epidemiologic study, Lucht et al. (2018a) reported an increase in FBG (0.67 mg/dL 0.10 1.24) and HbA1c (0.09% [95% CI: 0.07, 0.11] per IQR increase) in association with 91-day avg exposure to accumulation mode UFP (NC). In addition, a toxicological study (Li et al., 2013) evaluated the effects of long-term UFP in mice. This study investigated the effects of long-term UFP exposure in an $Ldlr^{-/-}$ mouse model fed a high fat diet in the presence or absence of an apolipoprotein A-I mimetic peptide (D-4F). This genetic mouse model has a mutation in the low-density lipoprotein receptor and are prone to very high blood cholesterol levels when fed a high fat diet. While the investigators identified UFP effects such as increased triglyceride, decreased HDL, reduced HDL antioxidant index, increased oxidized lipid metabolites (HETEs and HODEs), increased serum amyloid A (SAA) and TNF-α, and increased area in atherosclerotic plaque lesions (all *p* < 0.05) that were improved by D-4F (a mimetic peptide of apolipoprotein A-I made of D-amino acids) administration, the authors did not include wild-type controls. Furthermore, there are inherent differences in cholesterol metabolism between mouse and human that render the mouse somewhat resistant to the development of atherosclerotic plaques. Specifically, mice

lack cholesterol ester transfer protein that shuttles cholesterol from HDL to LDL for reverse cholesterol transport; therefore, mice carry most of their cholesterol on HDL particles rather than, like human, on LDL particles (Getz and Reardon, 2012).

Nervous System Effects

Studies of long-term exposure of adult mice to UFP from traffic-dominated sources provide evidence of inflammation and oxidative stress in the whole brain, hippocampus, and cerebral cortex (Cacciottolo et al., 2017; Tyler et al., 2016; Zhang et al., 2012; Morgan et al., 2011; Kleinman et al., 2008). Astrocyte activation and altered glutamatergic functions were also seen in these studies. Neurodegeneration, as indicated by decreased neurite density and white matter, occurred in specific regions of the hippocampus in UFP-exposed mice (Cacciottolo et al., 2017). Many responses, including neurodegeneration, were greater in young compared with middle-aged mice. However, one of the measured behavioral effects was altered to a greater degree by UFP exposure in middle-aged mice compared with young mice (Cacciottolo et al., 2017). Pathologic changes characteristic of Alzheimer's disease (i.e., amyloid deposits and amyloid-β oligomers in the cortex) were seen in a mouse model of Alzheimer's disease, but not in wild type mice following exposure to UFP (Cacciottolo et al., 2017).

Prenatal exposure to UFP resulted in altered behavioral indices in adult male, but not female, mice (Davis et al., 2013). Postnatal exposure to UFP CAPs led to developmental neurotoxicity in a group of studies from the same laboratory (Allen et al., 2017; Allen et al., 2014b; Allen et al., 2014a; Allen et al., 2013). Activation of microglia and astrocytes, indicative of inflammation and injury, respectively, was observed along with alterations in brain morphology and neurotransmitters, and changes in serum corticosterone and behavior. Some effects were sex-specific, notably the persistent ventriculomegaly found in male mice (Allen et al., 2017; Allen et al., 2014a). Long-term exposure to UFP was associated with effects on cognitive development in children (Sunyer et al., 2015). However, uncertainties remain because of inadequate assessment of potential copollutant confounding, the spatial variation in UFP concentrations, and exposure measurement error.

Reproductive Effects

Toxicological studies of male reproductive function show increased testosterone, increased testicular cholesterol, and increased activation of biomarkers on testicular cholesterol biosynthesis pathway with UFP exposure in male rodents. The epidemiologic literature for pregnancy and birth outcomes shows positive associations of UFP with preterm birth and low birth weight. In the UFP toxicological literature, neurodevelopmental outcomes are well studied and report neurological associations from multiple studies evaluating outcomes including increased impulsivity, ventriculomegaly, glial activation, and neurotransmitter changes with UFP exposure (U.S. EPA, 2019).

Cancer

Experimental studies are few and consist of a few controlled human exposure studies and in vitro animal toxicological studies. UFP exhibits two key characteristics of carcinogens (Smith et al., 2016) by demonstrating genotoxic effects and oxidative stress in experimental studies. While there is some biological plausibility for exposure to UFP and cancer, there is a lack of epidemiologic evidence of cancer

incidence or mortality. Additionally, there is uncertainty in the spatial variability of long-term UFP exposures, which is compounded by the relatively sparse UFP monitoring data in the U.S (U.S. EPA, 2019).

Sensitive Populations for PM-Related Health Effects

Certain populations may be more sensitive to the health effects of particulate air pollution, and evidence to assess susceptibility comes from epidemiological, controlled human exposure, and toxicological studies of PM2.5 and PM10 exposures. The U.S. EPA 2019 ISA for PM concluded that there is adequate evidence supporting increased susceptibility to the effects of PM among children (for respiratory effects) and nonwhite populations. There is limited evidence from stratified analyses to inform increased risk in children compared to adults. However, evidence from studies of pediatric asthma and impaired lung development provide strong and consistent evidence that effects are observed in children (U.S. EPA, 2019). There is also evidence from multiple epidemiologic studies demonstrating higher PM2.5 exposure in nonwhite populations. Furthermore, there is consistent evidence from epidemiologic studies demonstrating increased risk for mortality and cardiovascular/respiratory morbidity in this group (U.S. EPA, 2019).

There is suggestive evidence for those with pre-existing conditions of cardiovascular disease, respiratory illness, and obesity, individuals with certain genetic polymorphisms that control antioxidant response, regulate enzyme activity, or regulate procoagulants older adults (for cardiovascular effects), individuals with lower socioeconomic status and smokers. In addition, there is some limited but inadequate evidence that additional factors may increase a person's susceptibility to PM health effects, including diabetes, age, gender, near road or urban residence, and diet. Table summarizes the U.S. EPA's 2019 ISA assessment of susceptibility factors for particulate matter.

TABLE I-6

SUMMARY OF EVIDENCE FOR POPULATIONS POTENTIALLY AT INCREASED RISK OF PM2.5-RELATED HEALTH EFFECTS.

Assessment of Evidence	Potential At Risk Factor
Adequate Evidence	Children (<18 years) Nonwhite populations
Suggestive Evidence	Pre-existing disease (cardiovascular diseases, respiratory illnesses, obesity Genetic factors Socioeconomic status (SES) Smoking
Inadequate Evidence	Diabetes Older adult Gender

	Near road urban residence
	Diet (Individuals with reduced fruit/vegetable intake, alcohol consumption, or elevated cholesterol)

Adapted From (U.S. EPA 2019) Table 12-3

Summary - Particulate Matter Health Effects

Several studies have found correlations between elevated ambient particulate matter levels and an increase in mortality rates, respiratory infections, number and severity of asthma attacks, COPD exacerbation, combined respiratory-diseases and number of hospital admissions in different parts of the United States and in various areas around the world. Higher levels of PM2.5 have also been related to increased mortality due to cardiovascular or respiratory diseases, hospital admissions for acute respiratory conditions, school absences, lost workdays, a decrease in respiratory function in children, and increased medication use in children and adults with asthma.

Long-term exposure to PM has been found to be associated with reduced lung function growth in children, changes in lung development, development of asthma in children, and increased risk of cardiovascular diseases in adults. In recent years, studies have reported an association between long-term exposure to PM2.5 and increased total mortality (reduction in life-span and increased mortality) from lung cancer.

The U.S. EPA, in its most recent review, has concluded that both short-term and long-term exposure to PM2.5 are causally related to cardiovascular effects and increased mortality risk. In addition, new evidence is suggestive of metabolic, nervous system, and reproductive and developmental effects for short-term and long-term exposure to PM2.5.

Young children, non-white populations, and to some degree people with pre-existing conditions of cardiovascular disease, respiratory illness, and obesity, individuals with certain genetic polymorphisms that control antioxidant response, regulate enzyme activity, or regulate procoagulants older adults (for cardiovascular effects), individuals with lower socioeconomic status and smokers, appear to be more susceptible to the effects of PM10 and PM2.5.

ESTIMATES OF THE HEALTH BURDEN OF OZONE AND PARTICULATE MATTER IN THE SOUTH COAST AIR BASIN

In terms of estimating health burdens of air pollution exposure, CARB has conducted analyses in the past estimating exposures and quantitative health effects from exposures to particulate matter as well as other pollutants. A recent assessment focused on premature mortality and PM2.5, and estimated the deaths associated with exposures above 5.8 μg/m^3, which is an estimate of background PM2.5 (California Air Resources Board 2010a). The analysis used the U.S. EPA's risk assessment methodology for calculating premature mortality and used ambient air quality measurements averaged over a three-year period of 2006-2008. An update to this analysis using ambient air quality data from 2009-2011 indicated that PM2.5-related premature deaths in California due to cardiopulmonary causes as 7,200 deaths per year with an uncertainty range of 5,600 – 8,700. Estimates were also made for the California Air Basins. For the South Coast Air Basin, the estimate was 4,000 cardiopulmonary deaths per year with an uncertainty

range of 3,200–4,900. These estimates were calculated using the associations of cardiopulmonary mortality and PM2.5 from the second exposure period from Krewski (Krewski et al. 2009).

Another analysis of health impacts in the South Coast was conducted as part of the Socioeconomic Report for the 2016 AQMP. Table I-7 reports the health effect estimates for each health endpoint by pollutant. In total, it was estimated that more than 1,400 premature deaths will be avoided in 2023, and more than 2,700 in 2031, or an average of about 1,500 avoided premature deaths per year, if air quality improves as estimated in the Final 2016 AQMP. Figure I-4 shows that mortality risks will be reduced in each of the four counties, with the largest number of avoided premature deaths concentrated in the densely populated Los Angeles County area. Morbidity incidence is also reduced because of the 2016 Plan. It is estimated that reductions in ozone and PM2.5 concentrations will result in about 2,500 fewer asthma-related emergency department visits. In addition, the number of hospital admissions from all endpoints considered (asthma, cardiovascular, respiratory, and ischemic stroke) are estimated to decrease by about 700 per year on average.

TABLE I-7

HEALTH EFFECT ESTIMATES

	2023	2031	Average Annual
Premature Deaths Avoided, All Cause			
Short-Term Ozone Exposure[1]	45	89	49
Long-Term PM2.5 Exposure	1,394	2,716	1,512
Short-Term PM2.5 Exposure[2]	100	194	108
Reduced Morbidity Incidence			
Short-Term Ozone Exposure[1]			
Emergency Room Visits, Asthma	2,209	4,154	2,350
Hospital Admissions (HA), All Respiratory	68	148	78
Hospital Admissions (HA), Asthma	64	119	68
Minor Restricted Activity Days[4]	327,312	610,075	346,679
School Loss Days, All Cause[4]	100,034	184,781	105,451
Long-Term PM2.5 Exposure			
Acute Bronchitis	1,039	1,890	1,087
Short-Term PM2.5 Exposure			
Acute Myocardial Infarction, Nonfatal	33	71	38
Asthma Exacerbation (Wheeze, Cough, Shortness of Breath)	23,321	42,780	24,495
Asthma, New Onset (Wheeze)	2,956	5,577	3,151
HA, All Cardiovascular (less Myocardial Infarctions)	164	337	183
HA, All Respiratory (less Asthma)[3]	136	290	155
HA, Ischemic Stroke	79	171	91
HA and ED Visits, Asthma	142	260	149
Lower Respiratory Symptoms	12,268	22,387	12,850
Upper Respiratory Symptoms	24,342	44,720	25,587
Minor Restricted Activity Days[4]	528,869	961,248	552,809
Work Loss Days[4]	91,689	166,826	95,892

* Each health effect represents the point estimate of a statistical distribution of potential outcomes. Please see Appendix 3-B where the 95-percent confidence intervals are reported. Health effects for other years during the period 2017 to 2031 were based on interpolated, as opposed to modeled, air quality changes. The study population of each C-R function utilized can be found in Appendix 3-B.

[1] Health effects of ozone exposure are quantified for the summer planning period only (i.e., May 1 to September 30). There are potentially more premature mortalities and morbidity conditions avoided outside the ozone peak season.

[2] Premature deaths avoided due to short-term exposure to PM2.5 are likely to partially overlap with those due to long-term PM2.5 exposure. Therefore, the total premature deaths associated with PM2.5 will be lower than simply summing across mortality effects from both short-term and long-term exposure (Industrial Economics and Thurston 2016a; Kunzli et al. 2001).

[3] This is the pooled estimate of two health endpoints: HA, Chronic Lung Disease (less Asthma) (18-64 years old) and HA, All Respiratory (65 or older).

[4] Expressed in person-days. Minor Restricted Activity Days (MRAD) refer to days when some normal activities are avoided due to illness.

(Taken from Socioeconomic Report of the 2016 AQMP)
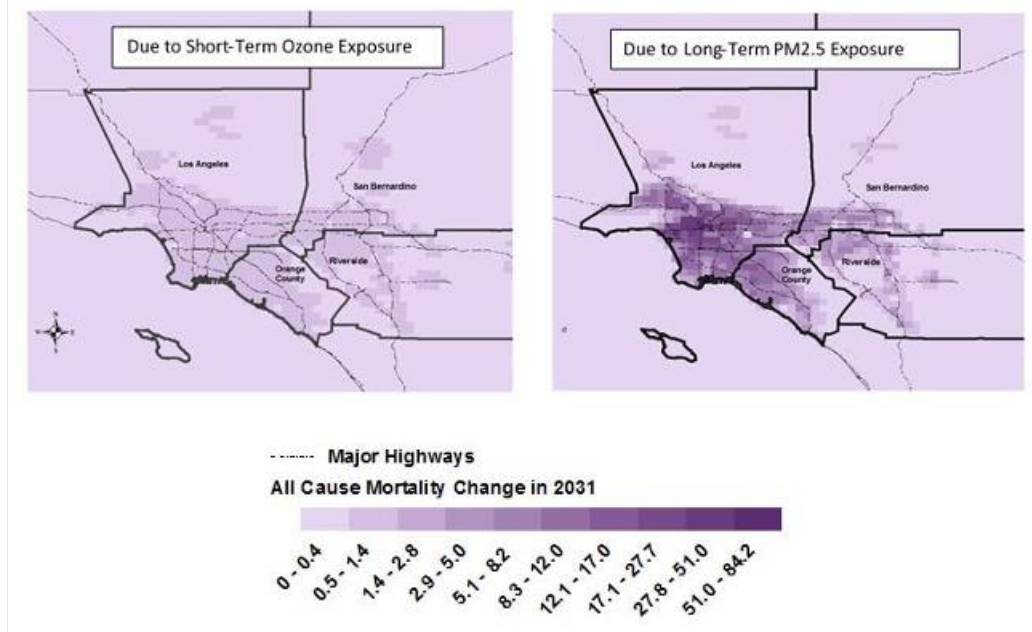
(Taken from Socioeconomic Report of the 2016 AQMP)

FIGURE I-4

SPATIAL DISTRIBUTION OF PREMATURE DEATHS AVOIDED (YEAR 2031)

After health effects are quantified, they are then translated into dollar values using two types of valuation methodologies. Monetized benefits associated with avoided premature deaths are monetized based on a population's willingness-to-pay (WTP) for a small reduction of mortality risk in a year and generally expressed as the "value of statistical life (VSL)."

The total monetized benefits of avoided premature deaths were derived by multiplying the number of premature mortalities reduced by the VSL. For morbidity effects, WTP was the preferred valuation method, but in many cases when such estimates are not yet available or reliable, cost of illness (COI) avoided were used to monetize morbidity risk reductions. Avoided COI is conceptually regarded as a conservative estimate of monetized health benefits, as it only accounts for avoided resource costs including direct medical costs and indirect productivity losses, but generally cannot fully account for the benefits of preventing pain and suffering associated with health-related issues. As shown in Table I-8, the overall quantifiable and monetized annual public health benefits are estimated to be $14.4 billion in 2023 and $30.9 billion in 2031 with an average annual benefit of $16.5 billion. About 99 percent of these benefits are attributable to mortality-related benefits, among which the avoided premature deaths due to reduced long-term exposure to PM2.5 were estimated to account for over 95 percent of total monetized public health benefits. The estimates were based on the VSL of $9.0 million and the assumption that the WTP for mortality risk reductions will increase as per-capita income grows; specifically, a one percent increase in income was assumed to raise VSL by 1.1 percent (i.e., an income elasticity of 1.1) (Industrial Economics and Robinson 2016a). These values correspond to a present value of quantified benefits of $173.2 billion at a four percent discount rate or $246.1 billion at a one percent discount rate, cumulatively from 2017 to 2031.

TABLE I-8

MONETIZED PUBLIC HEALTH BENEFITS (BILLIONS OF 2015 DOLLARS)

	Year 2023	Year 2031	Average Annual (2017-2031)	Present Value (2017-2031)
Mortality-related benefits	$14.2	$30.5	$16.2	$170.8
Short-Term Ozone Exposure	$0.5	$1.1	$0.6	$6.1
Long-Term PM2.5 Exposure	$13.7	$29.4	$15.7	$164.7
Morbidity-related benefits	$0.2	$0.4	$0.2	$2.4
Grand Total	$14.4	$30.9	$16.5	$173.2

Note:
1) Numbers may not sum up due to rounding, and the present value was calculated using a four-percent discount rate.
2) Premature deaths avoided due to short-term exposure to PM2.5 are monetized separately due to potentially double counting concerns with benefits associated with long-term exposure.
3) Health effects of the endpoint "Asthma, New Onset (Wheeze)" are not monetized, due to lack of a valuation method.
4) The monetized public health benefits reported in this table were estimated for the four-county region, which includes areas that are located outside the Basin. However, staff estimated that mortality-related benefits accrued to the areas within the Basin would account for 99 percent of the total. In other words, the difference is minimal between quantifying public health benefits for the Basin and for the four-county region.

(Taken from Socioeconomic Report of the 2016 AQMP)

As noted for Table I-8, the effects of reduced short-term PM2.5 exposure on mortality incidence likely overlap to some extent with those from long-term PM2.5 exposure. Thus, in these calculations the monetized value of these benefits from the total quantified public health benefits are excluded to avoid issues of double-counting. Based on the estimated avoided premature deaths of 100 and 194 on average in 2023 and 2031, respectively, the corresponding monetized benefits are $1.0 billion and $2.1 billion per year using the mid-point estimate of VSL. To see more on the socioeconomic analysis please refer to the 2016 AQMP Socioeconomic Report.

NITROGEN DIOXIDE

Nitrogen dioxide (NO_2) is a gaseous air pollutant that serves as an indicator of gaseous oxides of nitrogen, such as nitric oxide (NO) and other related compounds (NO_x). These gases can undergo photochemical reactions to form ground-level ozone and are important contributors to ozone pollution levels in the SCAB. Evidence of the health effects of NO_2 is derived from human and animal studies, which link NO_2 with respiratory effects such as decreased lung function and increases in airway responsiveness and pulmonary inflammation (U.S. EPA 2016). The U.S. EPA in 2010 retained the existing standards of 53 ppb for NO_2 averaged over one year and adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over one hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma based on controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies. The revised standard also requires additional monitoring for NO_2 near roadways.

In the most current U.S. EPA Integrated Science Assessment for Nitrogen Oxides (U.S. EPA 2016), the staff conclusion for causal relationships between exposures and health effects are shown in the following table.

TABLE I-9

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATION FOR HEALTH EFFECTS OF NITROGEN DIOXIDE

SHORT-TERM EXPOSURES	
Health Outcome	Causality Determination
Respiratory effects	Causal relationship
Cardiovascular and related metabolic effects	Suggestive of a causal relationship
Total mortality	Suggestive of a causal relationship
LONG-TERM EXPOSURES	
Health Outcome	Causality Determination
Respiratory effects	Likely to be a causal relationship
Cardiovascular and related metabolic effects	Suggestive of a causal relationship
Reproductive and developmental effects	Fertility, Reproduction, and Pregnancy: Inadequate to infer a causal relationship Birth Outcomes: Suggestive of a causal relationship Postnatal Development: Inadequate to infer a causal relationship
Total Mortality	Suggestive of a causal relationship
Cancer	Suggestive of a causal relationship

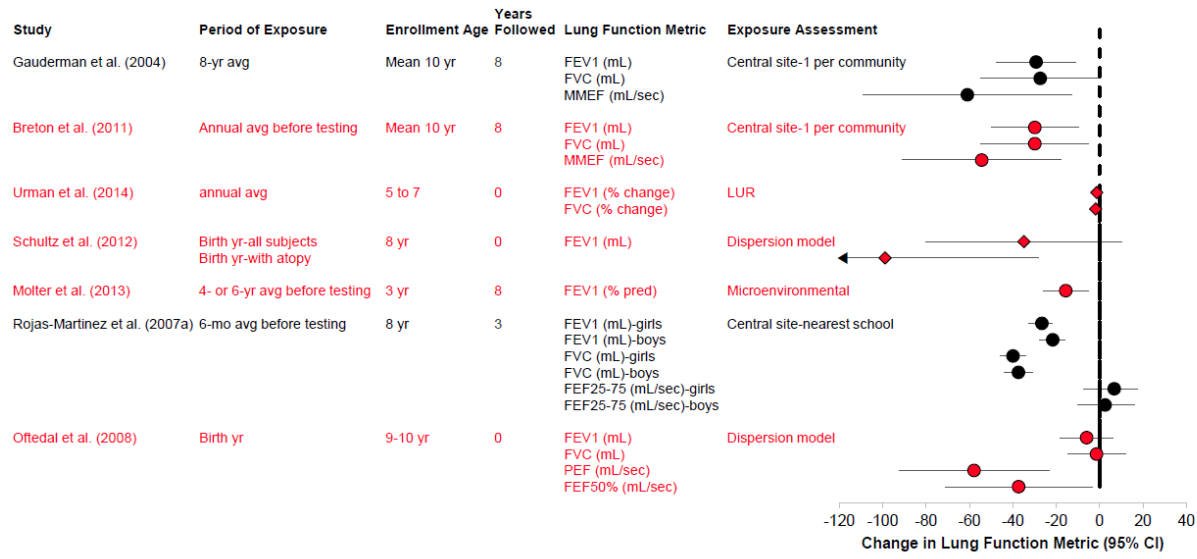(Taken from U.S. EPA (2016), Table ES-1)

No new U.S. EPA Integrated Science Assessment (ISA) for Nitrogen Oxides has been published since 2016. The last ISA pointed to a causal or likely causal relationship for respiratory effects. For non-respiratory outcomes, the U.S. EPA showed that the evidence for several short- and long-term outcomes is suggestive, but not sufficient to infer a causal relationship. Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional evidence is derived from animal studies. In the 2016 ISA, the U.S. EPA cited the coherence of the results from a variety of studies, and a plausible biological mechanism (whereby NO_2 reacts with the respiratory lining and forms secondary oxidation products that increase airway responsiveness and allergic inflammation) to support the determination of a causal relationship between short-term NO_2 exposures and asthma exacerbations ("asthma attacks"). The long-term link with respiratory outcomes was strengthened by recent experimental and epidemiological studies, and the strongest evidence available is from studies of asthma development.

Several studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, decreased lung function, pulmonary inflammation, increased emergency room visits for asthma, and cardiopulmonary mortality. However, since traffic exhaust is an important source of NO_2 and several other pollutants, such as particulate matter, exposure generally occurs in the presence of other pollutants, making it more difficult for these studies to distinguish the specific role of NO_2 in causing effects independent of other pollutants. However, studies linking NO_2 to asthma exacerbations and human experimental studies provided support for the U.S. EPA determination that this causal relationship exists for short-term NO_2 exposures independent of other traffic-related pollutants (U.S. EPA 2016). The report also concludes that epidemiological studies do not rule out the possible influence of other traffic-related pollutants on the observed health effects. A recent review of 67 relevant studies looked at current evidence on short-term effects (from several hours to 7 days) of exposure to NO_2 on asthma exacerbations, defined as emergency room visits (ERVs) and hospital admissions (HAs). 8- or 24-hour NO_2 levels correlated with asthma ERVs and hospitalization (Zheng et al., 2021).

The Children's Health Study in Southern California has evaluated a variety of health endpoints in relation to air pollution exposures, including lung function, lung development, school absences, and asthma. The study found associations between long-term exposure to air pollution, including NO_2, PM10, and PM2.5, and respiratory symptoms in asthmatic children (McConnell et al. 1999). Particles and NO_2 levels were correlated, and independent effects of individual pollutants could not be discerned. A subsequent analysis using more refined exposure estimation methods indicated consistent associations between long-term NO_2 exposures and respiratory symptoms in children with asthma (McConnell et al. 2003).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years, including children with no history of asthma. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated this may be a result of a package of pollutants from traffic sources (Gauderman et al. 2004).

A number of studies have since reported deficits in lung function associated with nitrogen oxides exposures. Examples are shown in Figure I-5.

Study	Period of Exposure	Enrollment Age	Years Followed	Lung Function Metric	Exposure Assessment
Gauderman et al. (2004)	8-yr avg	Mean 10 yr	8	FEV1 (mL) FVC (mL) MMEF (mL/sec)	Central site-1 per community
Breton et al. (2011)	Annual avg before testing	Mean 10 yr	8	FEV1 (mL) FVC (mL) MMEF (mL/sec)	Central site-1 per community
Urman et al. (2014)	annual avg	5 to 7	0	FEV1 (% change) FVC (% change)	LUR
Schultz et al. (2012)	Birth yr-all subjects Birth yr-with atopy	8 yr	0	FEV1 (mL)	Dispersion model
Molter et al. (2013)	4- or 6-yr avg before testing	3 yr	8	FEV1 (% pred)	Microenvironmental
Rojas-Martinez et al. (2007a)	6-mo avg before testing	8 yr	3	FEV1 (mL)-girls FEV1 (mL)-boys FVC (mL)-girls FVC (mL)-boys FEF25-75 (mL/sec)-girls FEF25-75 (mL/sec)-boys	Central site-nearest school
Oftedal et al. (2008)	Birth yr	9-10 yr	0	FEV1 (mL) FVC (mL) PEF (mL/sec) FEF50% (mL/sec)	Dispersion model

Change in Lung Function Metric (95% CI)

Note: Studies in red are recent studies. Studies in black were included in the 2008 ISA for Oxides of Nitrogen. Circles = NO_2; Diamonds = NO_X. All mean changes in this plot are standardized to a 10-ppb increase in NO_2 and a 20-ppb increase in NO_X concentration. Effect estimates from studies measuring NO_X in μg/m3 (Schultz et al., 2012) have not been standardized.

(Taken from U.S. EPA (2016), Figure 6-5)

FIGURE I-5

ASSOCIATIONS OF NITROGEN DIOXIDE (NO_2) OR THE SUM OF NITRIC OXIDE AND NO_2 (NO_X) WITH LUNG FUNCTION INDICES FROM PROSPECTIVE STUDIES OF CHILDREN

A follow-up report from the Children's Health Study has assessed whether improving air quality in Southern California over the past several decades has led to beneficial changes in health among children (Gauderman et al. 2015). It was reported that as the levels of nitrogen oxide and fine particulates came down as the result of air pollution emissions reductions, the deficits in lung function growth were also of a smaller magnitude. Such improvements were observed in children with asthma as well as in those without asthma. These results indicate that improvements in air quality are associated with improvements in children's health.

In recent years, the most compelling evidence of long-term effects of NO_2 has been from prospective cohort studies that link NO_2 exposures to the development of asthma, primarily in children. The U.S. EPA included several recent studies in their review, as shown in the Figure I-6. Most of these studies found that higher NO_2 exposures were linked to an increased risk or odds of developing asthma among children.
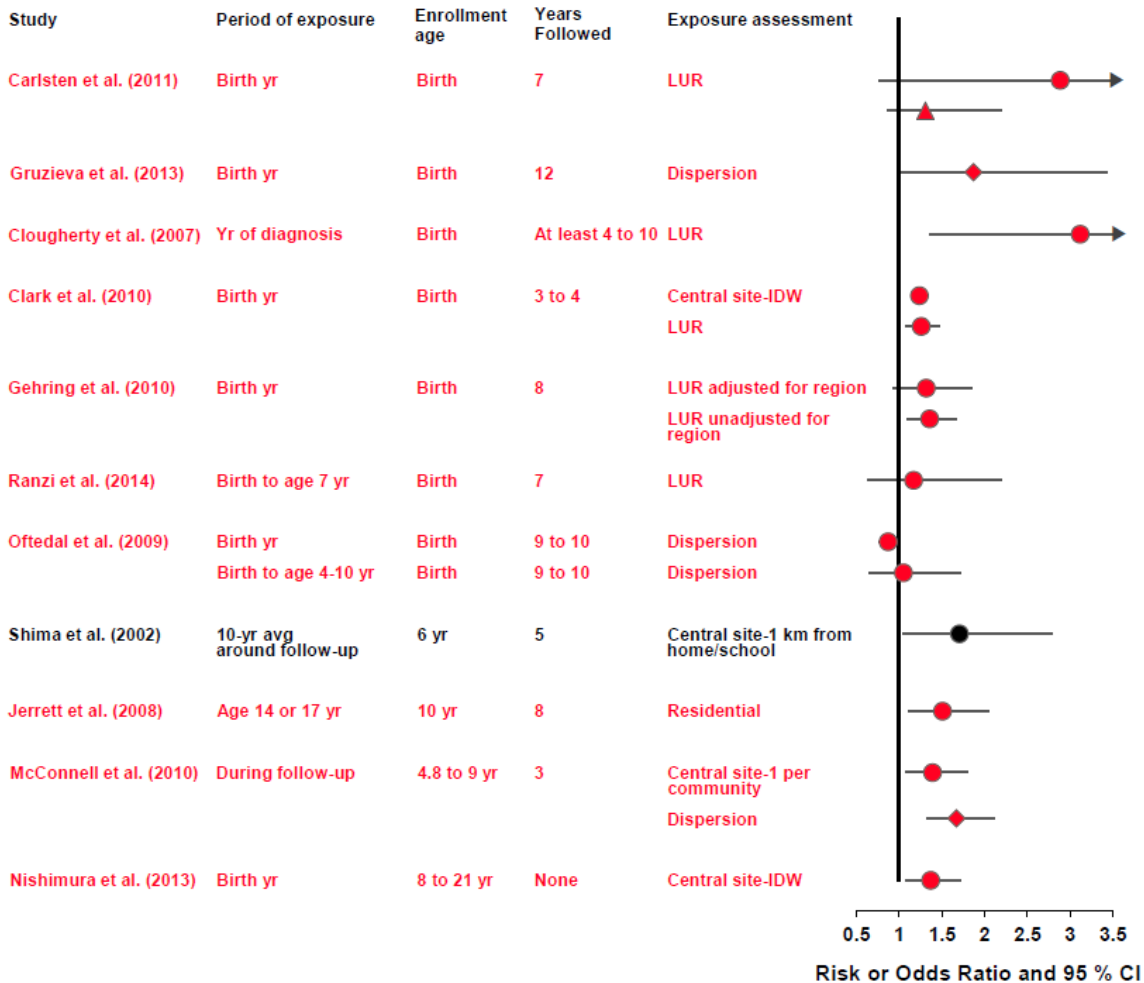
Effect estimates are standardized to a 10-ppb increase in NO₂, with the exception of Gruzieva et al. (2013) who examined NOₓ in µg/m3 and Oftedal et al (2009) who did not report increments for the effect estimates for the birth to age 4 years or birth to age 10 years exposure periods. Note: Black symbols = studies evaluated in the 2008 Integrated Science Assessment for Oxides of Nitrogen; Red symbols = recent studies. Circles=NO₂; triangles=NO; diamonds=NOₓ.

(Taken from (U.S. EPA 2016), Figure 6-1)

FIGURE I-6

ASSOCIATIONS OF AMBIENT NITROGEN DIOXIDE (NO₂) CONCENTRATIONS WITH ASTHMA INCIDENCE IN LONGITUDINAL COHORT STUDIES OF CHILDREN

Among the studies of childhood asthma incidence reviewed in the 2016 U.S. EPA ISA for Oxides of Nitrogen, two studies were conducted in Southern California. Both studies were based on the Children's Health Study cohort, but one study used a smaller subset of the cohort and estimated NO₂ exposures using monitors at the children's homes (Jerrett et al. 2008). The second study examined over 2000 children and used data from air monitoring stations as well as modeled NO₂ levels to estimate exposures (McConnell et al. 2010). Both studies found a positive association between NO₂ exposures and the onset of asthma in these children, however, because NO₂ is often strongly correlated with PM2.5 and other components of traffic-related air pollution, it is possible that the effects observed are due to some other

component of traffic exhaust for which NO_2 serves as a proxy measure. The consistency of the effects found linking NO_2 exposure and asthma development in children, the use of prospective longitudinal study designs following children for several years, and the use of several different methods to estimate exposures are noted strengths of such studies. Experimental studies have found that NO_2 exposures increase responsiveness of airways, pulmonary inflammation, and oxidative stress, and can lead to the development of allergic responses. These biological responses provide evidence of a plausible mechanism for NO_2 to cause asthma.

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (airway responsiveness) or after inhaled allergens (U.S. EPA 2016). Effects were observed among adult volunteers with asthma when exposed to 100 ppb NO_2 for 60 minutes and to 200-300 ppb for 30 minutes, with approximately 70 percent of study participants experiencing an increase in airway responsiveness. A similar response was reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm), although these changes in healthy adults are likely of little or no clinical significance. Increased airway responsiveness among people with asthma can lead to worse symptoms and reduced lung function. Mixed results have been reported from controlled human exposure studies of people with chronic obstructive lung disease, with some studies reporting no change in symptom score while other studies reporting increased symptom scores when participants were exposed to NO_2 while exercising (U.S. EPA 2016).

A recent random-effect meta-analyses were performed on examining exposure to nitrogen oxide (NOx) and its association with chronic obstructive pulmonary disease (COPD). The study reported consistent evidence of the potential positive association between NO_2 and COPD risk (Zhang et al., 2018)

Short-term controlled studies of rats exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory responses that can lead to liver damage and reduced hepatic function. Rodent models exposed to NO_2 repeatedly for 4 to 14 days demonstrated increased airway responsiveness with high levels of exposure (4000 ppb). Animal studies also provide evidence that NO_2 exposures have negative effects on the immune system, and therefore increase the host's susceptibility to respiratory infections. Epidemiological studies showing associations between NO_2 levels and hospital admissions for respiratory infections also support such a link (U.S. EPA 2016).

Several epidemiological studies conducted in California have examined associations between NO_2 exposures and other health effects, including some recent studies evaluating cardiovascular effects (Coogan et al. 2012; Bartell et al. 2013; Wittkopp et al. 2013), mortality (Lipsett et al. 2011; Bartell et al. 2013; Jerrett et al. 2013), birth outcomes (Ghosh et al. 2012; Laurent et al. 2014; Padula et al. 2014; Ritz et al. 2014; Green et al. 2015), and cancer (Ghosh et al. 2013). A recent meta-analysis of thirty-eight case-crossover studies and 48 time-series studies showed that NO_2 was significantly associated with ischemic heart disease (IHD) morbidity (pooled odds ratio from case-crossover studies: 1.074 95% CI 1.0521.097; pooled relative risk from time-series studies: 1.022 95% CI 1.016–1.029 per 10 ppb (Steib et al., 2020).

Another recent meta-analysis of all available epidemiologic studies evaluating the associations between long-term exposure to NO_2 with all-cause, cardiovascular, and respiratory mortality provided robust epidemiological evidence that long-term exposure to NO_2, is associated with a higher risk of all-cause, cardiovascular, and respiratory mortality. Their search criteria pulled up 1349 unique studies, of which 34 studies met the inclusion criteria (Huang et. al, 2021). In another meta-analysis that quantitatively assessed time-series studies of daily NO_2 and mortality and hospital admissions and controlled for

particulate matter (PM) determined whether or to what extent the NO$_2$ associations are independent of PM. Time-series studies—published in peer-reviewed journals worldwide, up to May 2011—that reported both single-pollutant and two-pollutant model estimates for NO$_2$ and PM were included. 60 eligible studies were identified, and meta-analysis was conducted on 23 outcomes. Two-pollutant model study estimates generally showed that the NO$_2$ associations were independent of PM mass. For all-cause mortality, a 10 μg/m3 increase in 24-hour NO$_2$ was associated with a 0.78% (95% CI 0.47% to 1.09%) increase in the risk of death, which reduced to 0.60% (0.33% to 0.87%) after control for PM. Heterogeneity between geographical region-specific estimates was removed by control for PM (I2 from 66.9% to 0%). Estimates of PM and daily mortality assembled from the same studies were greatly attenuated after control for NO$_2$: from 0.51% (0.29% to 0.74%) to 0.18% (−0.11% to 0.47%) per 10 μg/m3 PM10 and 0.74% (0.34% to 1.14%) to 0.54% (−0.25% to 1.34%) for PM2.5.

The latest assessment by the U.S. EPA assesses evidence that is suggestive of a causal relationship for some of these mentioned endpoints or inadequate to infer a causal relationship for other endpoints (U.S. EPA 2016). In addition, some of the newer outcomes evaluated in relation to NO$_2$ exposures include neurological outcomes such as Parkinson's disease (Ritz et al. 2016), Alzheimer's disease (Oudin et al. 2016), and autism (Beccerra et al. 2013; Volk et al., 2013; Flores-Pajot et al., 2016) well as metabolic diseases such as diabetes and obesity (Becerra et al. 2013; Volk et al. 2013, Marie-ClaireFlores-Pajot., 2016). Keramatina et al., (2016) show a weak association between exposure to NO$_2$ in ambient air and breast cancer at the individual level and a significant association at the aggregate level. However, many of these studies use NO$_2$ exposures as a proxy measure for traffic-related air pollutants, and do not aim to identify a specific pollutant within the mix of pollutants from this source. Thus, there is uncertainty on whether NO$_2$ exposure has independent relationships with non-respiratory related health effects, or whether NO$_2$ is simply a marker of near-road air pollution exposure, which includes a mixture of air pollutants, including some air toxics.

Examples of studies reporting an association of mortality with short-term NO$_2$ exposures are shown in the figure below.
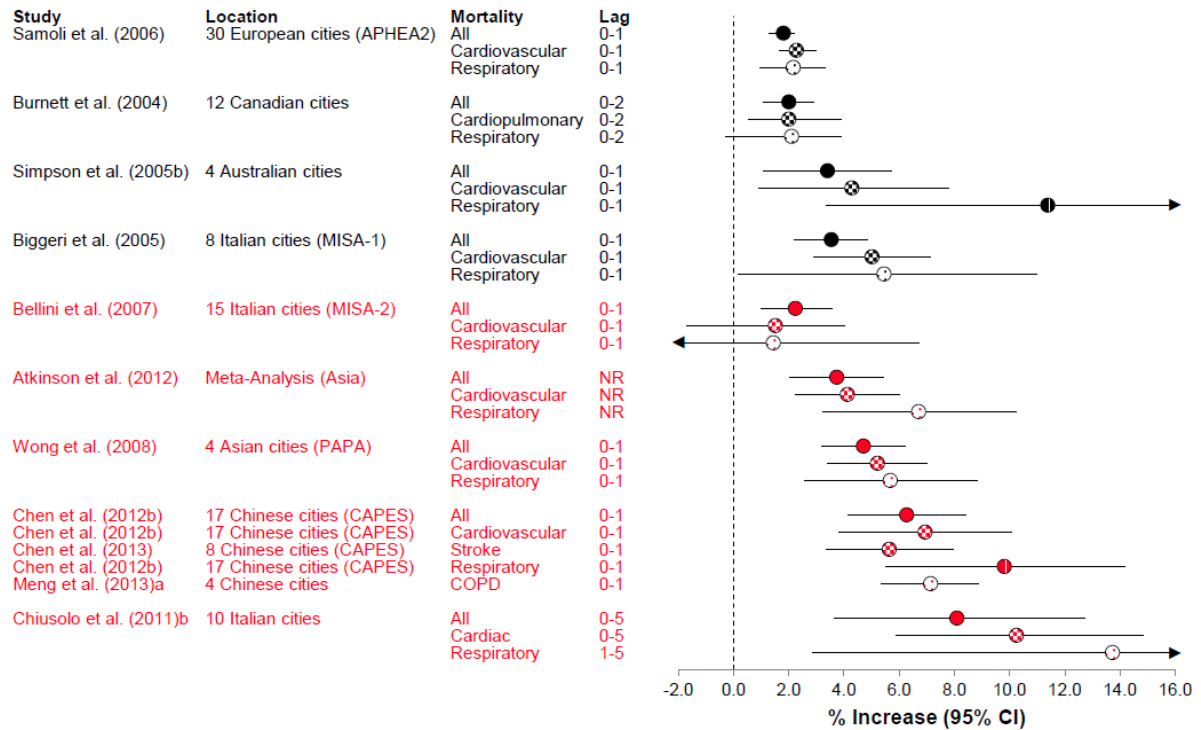
Note: Black symbols = multicity studies evaluated in the 2008 Integrated Science Assessment for Oxides of Nitrogen; Red symbols = recent studies. Filled circle = total mortality; Crosshatch = cardiovascular mortality; Vertical lines = respiratory mortality.
(Taken from U.S. EPA (2016), Figure 5-23)

FIGURE I-7

PERCENTAGE INCREASE IN TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY FROM MULTI-CITY STUDIES FOR A 20-PPB INCREASE IN 24-HOUR AVERAGE OR 30-PPB INCREASE IN ONE-HOUR MAXIMUM NITROGEN DIOXIDE CONCENTRATIONS

SULFUR DIOXIDE

Sulfur dioxide (SO_2) is a gaseous air pollutant that has been linked to a variety of respiratory effects, such as decreased lung function and increased airway resistance. Controlled laboratory studies involving human volunteers have clearly identified asthmatics as a very sensitive group to the effects of ambient SO_2 exposures. Healthy subjects have failed to demonstrate any short-term respiratory functional changes at exposure levels up to 1.0 ppm over 1-3 hours. In exercising asthmatics, brief exposure (5-10 minutes) to SO_2 at levels between 0.2-0.6 ppm can result in increases in airway resistance and decreases in breathing capacity. The response to SO_2 inhalation is observable within two minutes of exposure, increases further with continuing exposure up to five minutes, then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks (U.S. EPA 2008). In 2010, the U.S. EPA SO_2 air quality standard was set at 75 ppb (0.075 ppm) averaged over one hour to protect against acute asthma attacks in sensitive individuals.

Strong evidence indicates that there is a causal relationship between short-term SO_2 exposure and respiratory effects, as mentioned particularly for respiratory effects in the at-risk population of individuals with asthma. There is limited support for a relationship between short-term SO_2 exposure and other respiratory effects, including exacerbation of COPD, allergy exacerbation, respiratory infection, respiratory effects in healthy populations, and respiratory mortality (U.S. EPA 2017).

The EPA assessment based on the 2017 Integrated Science Assessment for Sulfur Oxides is shown in the table below (U.S. EPA 2017). This ISA evaluated evidence assessing links to mortality and cardiovascular, respiratory, carcinogenic, and reproductive effects (Brunekreef et al. 2009; Hart et al. 2011; Pascal et al. 2013; Chen et al. 2014; Gianicolo et al. 2014; Milojevic et al. 2014; Moridi et al. 2014; Stingone et al. 2014; Straney et al. 2014; Wang et al. 2014; Winquist et al. 2014; Yang et al. 2014; Ancona et al. 2015; Green et al. 2015; Rich et al. 2015; Shah et al. 2015; Yorifuji et al. 2015).

Below you will find the studies that support the EPA determinations.

TABLE I-10

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATIONS FOR HEALTH EFFECTS OF SULFUR OXIDES

SHORT-TERM EXPOSURES	
Health Outcome	Causality Determination
Respiratory morbidity	Causal relationship
Cardiovascular morbidity	Inadequate to infer a causal relationship
Mortality	Suggestive of a causal relationship
LONG-TERM EXPOSURES	
Health Outcome	Causality Determination
Respiratory morbidity	Suggestive of a causal relationship
Carcinogenic effects	Inadequate to infer a causal relationship

Prenatal and neonatal outcomes	Inadequate to infer a causal relationship
Mortality	Inadequate to infer a causal relationship

(Taken from U.S. EPA (2017), ES-1)

Respiratory Effects

Short-term Effects

Asthma Exacerbation

A causal relationship between short-term SO_2 exposure and respiratory effects is primarily supported by evidence from controlled human exposure studies of respiratory effects in adults with asthma. These studies consistently demonstrated that the majority of individuals with asthma experience a moderate or greater decrement in lung function, as defined by a ≥100% increase in sRaw or ≥15% decrease in FEV_1 (U.S. EPA, 2017). This decrement is frequently accompanied by respiratory symptoms following exposures of 5−10 minutes, with elevated ventilation rates at concentrations of 0.4−0.6 ppm (Johns et al., 2010; Linn et al., 1990; Linn et al., 1988; Balmes et al., 1987; Linn et al., 1987; Horstman et al., 1986; Linn et al., 1983b). A fraction of the population with asthma (~5−30%) has also been observed to have decrements in lung function at lower SO_2 concentrations (0.2−0.3 ppm) (Linn et al., 1990; Linn et al., 1988; Linn et al., 1987; Bethel et al., 1985). Although the degree of lung function decrements is considered moderate, they are less likely to be accompanied by respiratory symptoms at these lower concentrations (Linn et al., 1990; Linn et al., 1988; Linn et al., 1987; Roger et al., 1985; Linn et al., 1983b). A group of responders (defined as having ≥15% decrease in FEV_1 after exposure to 0.6 or 1.0 ppm SO_2) showed statistically significant decrements in FEV_1 following 5−10-minute exposure to 0.3 ppm SO_2 (Johns et al., 2010). A study in the Los Angeles area found that higher ambient SO_2 levels were associated with increased odds of asthma symptoms among Hispanic children with asthma (Delfino et al. 2003).

While SO_2-induced respiratory effects have been examined in individuals classified as having mild and moderate asthma, these individuals are relatively healthy. Thus, extrapolating to individuals with severe asthma is difficult because such individuals cannot be tested in an exposure chamber due to the severity of their disease. Therefore, it is unknown whether people with severe asthma are at increased risk of having respiratory effects due to short-term SO_2 exposure. The same may be said about children with asthma. There are no laboratory studies of children exposed to SO_2, but several studies have assessed airway responsiveness of children and adults exposed to the bronchoconstrictive stimuli methacholine. Based largely on those studies, school-aged children (~5−11 years of age), particularly boys and perhaps obese children, might be expected to have greater responses (i.e., larger decrements in lung function) following exposure to SO_2 than adolescents and adults. The coherence of the epidemiologic findings is supporting evidence for a causal relationship. Epidemiologic evidence for lung function changes in adults and children with asthma is inconsistent. However, short-term increases in ambient SO_2 concentration are associated with increases in asthma hospital admissions and ED visits among all ages, children (i.e., < 18 years of age) and older adults (i.e., 65 years of age and older), as well as asthma symptoms in children (Velická et al., 2015; SpiraCohen et al., 2011). Epidemiologic associations between short-term increases in ambient SO_2 concentration and respiratory mortality provide support for a potential continuum of effects between respiratory morbidity and respiratory mortality (U.S. EPA, 2017).

Most epidemiologic studies indicating associations between short-term SO$_2$ exposures and asthma exacerbation assigned exposure using SO$_2$ concentrations measured at fixed-site monitors. The use of fixed-site monitors to assign exposure, particularly to 1-h max SO$_2$, may introduce exposure measurement error if the spatiotemporal variability in SO$_2$ concentrations is not captured. The studies did not statistically correct for measurement error. A few recent results reduce the uncertainty with SO$_2$ measured or modeled at or near children's school or home (Velická et al., 2015; Spira-Cohen et al., 2011). Additional uncertainty exists regarding potential copollutant confounding. In many studies, SO$_2$ was moderately to highly correlated with PM2.5, larger sized PM, EC/BC, NO$_2$, and VOCs (r = 0.4–0.9). The few available results show association with sulfate. A small number of studies examined copollutant models. Some associations were relatively unchanged in magnitude after adjustment for a copollutant; others did not persist. However, inference from copollutant models is limited given potential differences in exposure measurement error for SO$_2$ compared to NO$_2$, CO, PM, and O$_3$ and in some studies, high copollutant correlations. Copollutant interactions are not well studied. Some controlled human exposure studies demonstrate increased asthma-related effects with coexposure to SO$_2$ and NO$_2$ or O$_3$. Limited epidemiologic evidence shows increased asthma-related effects with joint increases in SO$_2$ and copollutants but does not clearly show a joint association that is greater than a single-pollutant association. There is supportive evidence for a relationship between short-term SO$_2$ exposure and both airway responsiveness and pulmonary inflammation (U.S. EPA, 2017). Limited epidemiologic evidence points to an association with increased airway hyperresponsiveness (AHR) in a population of adults with asthma and a high prevalence of atopy (Taggart et al., 1996). Gong et al. (2001) demonstrated an increase in airway eosinophils in adults with asthma 2 hours after a 10-minute exposure to 0.75 ppm SO$_2$. This effect, along with bronchoconstriction, was attenuated by pretreatment with a leukotriene receptor antagonist. Other pharmacologic studies have demonstrated that inflammatory mediators play an important role in SO$_2$ exposure-induced bronchoconstriction in people with asthma. Further support for an important role of airway inflammation, including allergic inflammation, is provided by animal toxicological studies of repeated SO$_2$ exposure in allergic animals that are used to model the asthmatic phenotype (Li et al., 2014; Li et al., 2007). In addition, repeated exposure of naive animals promoted allergic sensitization and enhanced allergic inflammation (Park et al., 2001; Riedel et al., 1988). Increases in bronchial obstruction also observed in these studies suggest that SO$_2$ exposure increased airway responsiveness in the animals subsequently made allergic to ovalbumin. These latter studies point to a possible increased sensitivity to allergens following SO$_2$ exposure.

Other Respiratory Effects

Epidemiologic studies demonstrate some associations of ambient SO$_2$ concentrations with hospital admissions and ED visits for all respiratory causes combined (U.S. EPA, 2017). While these results suggest that the respiratory effects of short-term SO$_2$ exposure could extend beyond exacerbation of asthma, evidence across disciplines is inconsistent and/or lacks biological plausibility for conditions such as allergy exacerbation, COPD exacerbation, and respiratory infection. Where epidemiologic associations were found, potential copollutant confounding is uncertain. For COPD exacerbation, a controlled human exposure study demonstrated no effect of SO$_2$ exposure (Linn et al., 1985a), and epidemiologic associations are inconsistent for lung function (Peacock et al., 2011; Harre et al., 1997), respiratory symptoms s (Wu et al., 2016; Peacock et al., 2011), hospital admissions (Qiu et al., 2013b, Ko et al., 2007a, Wong et al., 2009) and ED visits (Peel et al., 2005; Stieb et al. 2009); Arbex et al., 2009). Some evidence supports SO$_2$-associated increases in hospital admissions and ED visits due to respiratory infections (Mehta et al. 2013; Ségala et al., 2008; Steib et al., 2009). However, the lack of multiple studies examining

the same respiratory infection outcome, inconsistent findings for self-reported infections in children, and the lack of evidence from controlled human exposure and animal toxicological studies produces uncertainty as to whether a relationship exists (U.S. EPA, 2017).

Controlled human exposure studies in healthy individuals provide evidence for transient decreases in lung function with ≥1 ppm SO_2 exposures for 5–10 minutes under exercising or a forced oral breathing condition with no evidence for increased respiratory symptoms (Dales et al., 2013). Epidemiologic evidence is inconsistent for SO_2 associations with lung function, respiratory symptoms, and pulmonary inflammation in healthy children and adults (U.S. EPA 2017).

Long Term Effects

Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects, based on the evidence across disciplines for development of asthma in children (U.S. EPA 2017).

A limited number of longitudinal epidemiologic studies report associations between asthma incidence among children and long-term SO_2 exposures (Nishimura et al., 2013; Clark et al., 2010). The evidence from longitudinal studies is coherent with animal toxicological evidence of allergic sensitization, airway remodeling, and increased airway responsiveness (Song et al., 2012; Li et al., 2007; Li et al., 2014; Riedel et al., 1988; Park et al., 2001), which are key events (or endpoints) in the proposed mode of action for the development of asthma. The animal toxicological evidence provides support for an independent effect of SO_2 and a possible relationship between long-term exposure to SO_2 and the development of asthma in children. Some evidence of a link between long-term exposure to SO_2 and respiratory symptoms and/or respiratory allergies among children further supports this relationship (Hart et al., 2011; Nafstad et al., 2004; Elliot et al., 2007; Cao et al., 2011; Carey et al. 2013; Dong et al. 2012; Katanoda et al., 2011). The potential for SO_2 to serve as an indicator for other pollutants or mixture related to PM is an uncertainty that applies to the body of epidemiologic evidence across the respiratory effects examined (U.S. EPA, 2017).

Cardiovascular Effects

Short-term Effects

Overall, the most recent EPA ISA (2017) stated that the available evidence is inadequate to infer a causal relationship between short-term exposure to SO_2 and cardiovascular health effects. Nonetheless, multiple epidemiologic studies report positive associations between short-term ambient SO_2 concentrations and cardiovascular outcomes, such as cardiovascular mortality, myocardial infarction and ischemic heart disease, and aggregated cardiovascular outcomes; however, substantial uncertainties remain regarding exposure measurement error and copollutant confounding. Specifically, the majority of studies reporting positive associations evaluated averaged SO_2 concentrations over multiple monitors and used a 24-h avg exposure metric, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (U.S. EPA, 2017).

Recent epidemiologic studies of specific cardiovascular outcomes add to the overall evidence for the effect of short-term SO_2 exposure on the cardiovascular system with a number of these studies evaluating

effects related to triggering a myocardial infarction (MI). Several recent epidemiologic studies of MI hospitalizations and ED visits consistently report associations in single pollutant models but associations are not always robust in copollutant models indicating that the associations may be due to confounding (Hsieh et al., 2010; Cheng et al., 2009; Ballester et al., 2006). The small number of studies based on clinical MI data, rather than hospitalizations, report inconsistent evidence regarding associations between ambient SO_2 concentrations and risk of MI (Milojevic et al., 2014; Turin et al., 2012; Bhaskaran et al., 2011). One study that examined the association of hourly ambient SO_2 concentrations prior to MI onset reported no association, although there was some evidence of a positive association in a sensitivity analysis of older adults (Bhaskaran et al., 2011). Although Chuang et al. (2008) reported an association between short-term SO_2 exposure and ST-segment changes, a nonspecific marker of myocardial ischemia, in patients with a history of coronary heart disease that generally remained unchanged after additional control for PM2.5 and BC in copollutant models; the evidence overall, was not generally consistent.

Some associations between short-term SO_2 exposure and markers of ventricular repolarization abnormalities that are risk factors for arrhythmia have been observed (Baja et al., 2010; Henneberger et al., 2005). Consistently positive associations have been reported in epidemiologic studies of short-term SO_2 exposure and cardiovascular mortality (U.S. EPA, 2017). Few experimental studies have evaluated the effects of SO_2 exposure on the cardiovascular system. The strongest evidence comes from controlled human exposure studies, for which copollutant confounding is not a concern, that short-term exposure to SO_2 can affect the autonomic nervous system of healthy adults and adults with asthma (Routledge et al., 2006; Tunnicliffe et al., 2001). These studies report changes in heart rate (HR) and heart rate variability (HRV) following SO_2 exposure in adults, which is indicative of potential cardiovascular effects being mediated by the neural reflex pathway; however, these changes were not reported in animal studies, nor did epidemiological evidence support the presence of associations, particularly after adjusting for copollutant confounding (U.S. EPA, 2017). Animal studies also provide limited evidence for the role of systemic oxidative stress as a key event in a proposed mode action. In particular, studies observed changes in sulfhemoglobin (Baskurt, 1988). In addition, studies of long-term exposure found lipid peroxidation in the brain (Qin et al., 2012), and mitochondrial changes in the heart and brain (Qin et al., 2016; Qin et al., 2012).

Despite numerous additional epidemiologic studies reporting positive associations between short-term SO_2 exposure and cardiovascular effects, a key uncertainty is the potential for confounding by other pollutants, specifically those from a common source that are highly correlated with SO_2. Those studies that do examine associations with SO_2 adjusted for PM, NO_2, or other correlated pollutants report that, in general, associations were either attenuated or no longer present after controlling for potential copollutant confounding (Hsieh et al., 2010; Cheng et al., 2009; Ballester et al., 2006). A limited number of studies examined copollutant confounding on the SO_2-cardiovascular mortality relationship, which included analyses on stroke mortality, and provided evidence that the SO_2 association was reduced in copollutant models with NO_2 and PM10 (Chen et al., 2013; Chen et al., 2012b; Kan et al., 2010).

Long-term Effects

Although a number of epidemiologic studies report positive associations between long-term exposure to SO_2 concentrations and cardiovascular disease and stroke, the evidence for any one outcome is limited and inconsistent (U.S. EPA, 2017).

Reproductive and Developmental Effects

There are several recent well-designed, well-conducted studies that indicate an association between SO_2 and reproductive and developmental health outcomes, including fetal growth metrics, preterm birth, birth weight, and fetal and infant mortality. For example, several high quality studies reported positive associations between SO_2 exposures during pregnancy and fetal growth metrics (Le et al., 2012; Rich et al., 2009; Brauer et al., 2008; Liu et al., 2003), preterm birth (Mendola et al., 2016a; Le et al., 2012; Zhao et al., 2011; Sagiv et al., 2005; Liu et al., 2003), birth weight (Ebisu and Bell, 2012; Darrow et al., 2011; Morello-Frosch et al., 2010; Liu et al., 2003), and fetal and infant mortality (Faiz et al., 2012; Hwang et al., 2011; Woodruff et al., 2008). However, a number of uncertainties are associated with the observed relationship between exposure to SO_2 and birth outcomes, such as timing of exposure windows, exposure error, and spatial and temporal heterogeneity. Few studies have examined other health outcomes, such as fertility, effects on pregnancy (e.g., pre-eclampsia, gestational diabetes), and developmental effects, and there is little coherence or consistency among epidemiologic and toxicological studies for these outcomes. Based on the EPA ISA for Sulfur Oxides (2017) the evidence is inadequate to infer a causal relationship between exposure to SO_2 and reproductive and developmental outcomes.

Mortality

Short-term

Recent multicity studies provide consistent evidence of positive associations between short-term SO_2 exposures and total mortality (See Table I-11), however key uncertainties and data gaps still remain, like copollutant confounding, and limited spatial and temporal variability. Recent multicity studies evaluated have further informed key uncertainties and data gaps in the SO_2-mortality relationship including confounding, modification of the SO_2-mortality relationship, potential seasonal differences in SO_2-mortality associations, and the shape of the SO_2-mortality C-R relationship (U.S. EPA, 2017).

TABLE I-11

AIR QUALITY CHARACTERISTICS OF MULTICITY STUDIES AND META-ANALYSES

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
North America						
Dominici et al. (2003)	72 U.S. cities (NMMAPS)[a]	1987–1994	Total	24-h avg	0.4–14.2	---
Burnett et al. (2004)	12 Canadian cities	1981–1999	Total cardiovascular respiratory	24-h avg	0.9–9.6	---
†Moolgavkar et al. (2013)	85 U.S. cities (NMMAPS)[b]	1987–2000	Total	24-h avg	---	---
Europe						
Katsouyanni et al. (1997)	12 European cities (APHEA-1)	1980–1992	Total	24-h avg	5.0–28.2[c]	90th: 17.2–111.8
Biggeri et al. (2005)	Eight Italian cities (MISA-1)	1990–1999	Total cardiovascular respiratory	24-h avg	2.5–15.6	95th: 6.0–50.1 Max: 7.1–111.0
Hoek (2003)	Netherlands	1986–1994	Total cardiovascular respiratory	24-h avg	3.5–5.6	---
†Berglind et al. (2009)	Five European cities[d]	1992–2002	Total	24-h avg	1.0–1.6[c]	---
†Bellini et al. (2007)	15 Italian cities (MISA-2)	1996–2002	Total cardiovascular respiratory	24-h avg	---	---

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
Asia						
†Kan et al. (2010); Wong et al. (2008b); Wong et al. (2010)	Four Asian cities (PAPA)	1996–2004[e]	Total cardiovascular respiratory	24-h avg	5.0–17.1	75th: 6.0–21.5 Max: 23.4–71.7
†Chen et al. (2012b)	17 Chinese cities (CAPES)	1996–2010[f]	Total cardiovascular respiratory	24-h avg	6.1–38.2	75th: 6.5–56.1 Max: 25.2–298.5
†Chen et al. (2013)	Eight Chinese cities	1996–2008[f]	Stroke	24-h avg	6.1–32.1	---
†Meng et al. (2013)	Four Chinese cities	1996–2008[g]	COPD	24-h avg	6.8–19.1	---
Meta-analyses						
Stieb et al. (2003)	Meta-analysis	1958–1999[b]	Total	24-h avg	0.7–75.2	---
HEI (2004)	Meta-analysis (South Korea, China, Taiwan, India, Singapore, Thailand, Japan)	1980–2003[h]	Total	24-h avg	~10->200	---
†Atkinson et al. (2012)	Meta-analysis (Asia)	1980–2007[i]	Total cardiovascular respiratory COPD	24-h avg	---	---
†Shah et al. (2015)	Meta-analysis	1948–Jan 2014	Stroke	NR	6.2[j]	Max: 30.2

(Table taken from U.S. EPA (2017) Table 5-39)

Long-term

Several longitudinal cohort studies have been conducted in the U.S. and have found small, statistically significant positive associations between long-term exposure to SO_2 and total mortality (Hart et al., 2011; Lipfert et al., 2009; Pope et al., 2002; Krewski et al., 2000). The body of evidence is smaller and less consistent when these studies examine cause-specific mortality, although Hart et al. (2011) observed positive, yet imprecise associations (i.e., wide 95% confidence intervals) with respiratory, lung cancer, and cardiovascular mortality.

A prospective cohort study, the Harvard Six Cities study, looked at the effects of air pollution with the focus on PM components in six U.S. cities and provided limited evidence for an association between

mortality and exposure to SO_2. Dockery et al. (1993) reported that lung cancer and cardiopulmonary mortality were more strongly associated with the concentrations of inhalable and fine PM and sulfate particles than with the levels of TSP, SO_2, NO_2, or acidity of the aerosol. Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities study and examined associations between gaseous pollutants (i.e., O_3, NO_2, SO_2, and CO) and mortality, observing positive associations between SO_2 and total mortality and cardiopulmonary deaths. In this data set SO_2 was highly correlated with PM2.5 ($r = 0.85$), sulfate ($r = 0.85$), and NO_2 ($r = 0.84$), making it difficult to attribute the observed associations to an independent effect of SO_2.

Pope et al. (1995) investigated associations between long-term exposure to PM and the mortality outcomes in the American Cancer Society (ACS) cohort and provides limited evidence for an association between exposure to SO_2 and mortality. Ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through 1989. Gaseous pollutants were not analyzed in the original analysis. Extensive reanalysis of the ACS data, augmented with additional gaseous pollutants data, showed positive associations between mortality and SO_2, but not for the other gaseous pollutants (Jerrett et al., 2003; Krewski et al., 2000). Lipfert et al. (2000) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid-1970s and were followed up for about 21 years (up to 1996) and provides scant evidence for an association between exposure to SO_2 and mortality.

Abbey et al. (1999) investigated associations of long-term ambient concentrations of PM10, sulfate, SO_2, O_3, and NO_2 with mortality in a cohort of 6,338 nonsmoking California Seventh-Day Adventists. Monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to ZIP codes according to home or work location of study participants, cumulated, and then averaged over time. They reported associations between PM10 and total mortality for males and nonmalignant respiratory mortality for both sexes. SO_2 was positively associated with total mortality for males but not for females. Generally, null associations were observed for cardiopulmonary deaths and respiratory mortality for both males and females.

Cancer

Recent studies include evidence on lung cancer as well as other cancer types. Although some studies of SO_2 concentrations and lung cancer mortality have reported null results, other studies that included various cofounders and copollutants reported positive associations. Positive associations were also observed in a study of SO_2 concentrations and bladder cancer mortality but not in ecological studies of bladder cancer incidence. Limited supportive evidence for mode of action is available from genotoxicity and mutagenicity studies, but animal toxicological studies provide no coherence with epidemiologic findings (U.S. EPA, 2017).

Based on a level determined necessary to protect the most sensitive individuals, the California Air Resources Board (CARB) in 1976 adopted a standard of 25 $\mu g/m^3$ (24-hour average) for sulfates. There is no federal air quality standard for sulfates.

CARBON MONOXIDE

Carbon monoxide (CO) is emitted from virtually all sources of incomplete combustion, including internal combustion engines, fires, improperly adjusted gas and oil appliances, water heaters, and ovens, and by tobacco smoking. The formation of carboxyhemoglobin by the binding of CO to circulating hemoglobin reduces the O2-carrying capacity of blood. The resulting reduction in oxygen supply in the bloodstream is responsible for the toxic effects of CO, which are typically manifested in the oxygen-sensitive organ systems. The effects have been studied in controlled laboratory environments involving exposure of humans and animals to CO, as well as in population-based studies of ambient CO exposure effects. People with deficient blood supply to the heart (ischemic heart disease) are known to be susceptible to the effects of CO. Protection of this group is the basis of the existing National Ambient Air Quality Standards for CO at 35 ppm for one hour and 9 ppm averaged over eight hours. The health effects of ambient CO were reviewed by the U.S. EPA in 2010, with the strongest evidence supporting a likely causal link between short-term CO exposures and cardiovascular outcomes, although studies have linked both short-term and long-term CO exposures to several other health outcomes (Table I-12) (U.S. EPA 2010).

TABLE I-12

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATIONS FOR HEALTH EFFECTS OF CARBON MONOXIDE

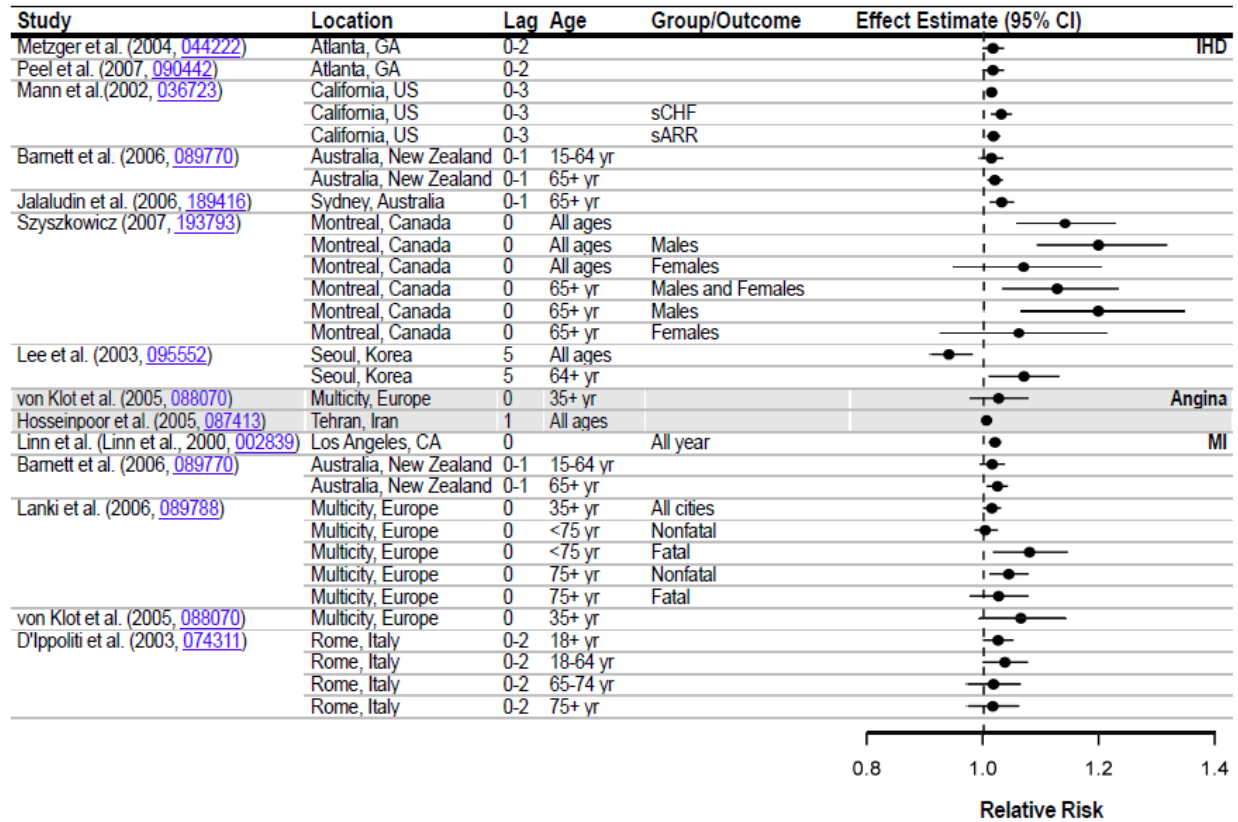| SHORT-TERM EXPOSURES	
Health Outcome	Causality Determination
Cardiovascular morbidity	Likely to be a causal relationship
Central nervous system	Suggestive of a causal relationship
Respiratory morbidity	Suggestive of a causal relationship
Mortality	Suggestive of a causal relationship
LONG-TERM EXPOSURES	
Health Outcome	Causality Determination
Cardiovascular morbidity	Inadequate to infer a causal relationship
Central nervous system	Suggestive of a causal relationship
Birth outcomes and developmental effects	Suggestive of a causal relationship
Respiratory morbidity	Inadequate to infer a causal relationship
Mortality	Not likely to be a causal relationship

(Taken from U.S. EPA (2010) Table 2-1)

Inhaled CO has no known direct toxic effect on lungs but rather exerts its effects by interfering with oxygen transport—through the formation of carboxyhemoglobin (COHb, a chemical complex of CO and

hemoglobin), which reduces the amount of oxygen the blood can carry to the tissues. Exposure to CO is often evaluated in terms of COHb levels in blood, measured as percentage of total hemoglobin bound to CO. Endogenous COHb is estimated to be <1 percent in healthy individuals, but COHb levels are sensitive to health status and metabolic state, with higher levels among smokers and persons with inflammatory diseases. Estimates based on a large prospective study of adults conducted in the 1970s showed a dose-response relationship between the average number of cigarettes smoked per day and the COHb concentrations (never smokers: 1.59±1.72 percent, former smokers: 1.96±1.87 percent, 1-5 cigarettes/day: 2.31±1.94 percent, 6–14 cigarettes/day: 4.39±2.48 percent, 15–24 cigarettes/day: 5.68±2.64 percent, >=25 cigarettes/day: 6.02±2.86 percent) (Hart et al. 2006).

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5 percent COHb levels exhibited reduced duration of maximal exercise performance due to the inability to deliver sufficient oxygen to the heart and other muscles. Studies involving subjects with coronary artery disease who engaged in exercise during CO exposures have shown that COHb levels as low as 2.4 percent can lead to earlier onset of electrocardiograph changes indicative of deficiency of oxygen supply to the heart. Other effects of inadequate oxygen delivery to the body tissues include earlier onset of chest pain, increase in the duration of chest pain, headache, confusion and drowsiness (U.S. EPA 2000).

A number of epidemiological studies have found associations between short-term ambient CO levels and increased hospital admissions and emergency department visits for ischemic heart disease, including myocardial infarction (U.S. EPA 2010). In a recent review and meta-analysis Lee et al. (2020) showed that myocardial infarction was associated with exposure to ambient carbon monoxide.

In studies reporting results stratified by age and sex, larger effects were generally observed among older adults and among males. Examples of such studies, including information on number of days of lag time between exposure and hospital admissions for key cardiovascular outcomes, are shown in the figure below.

Study	Location	Lag	Age	Group/Outcome	Effect Estimate (95% CI)
Metzger et al. (2004, 044222)	Atlanta, GA	0-2			IHD
Peel et al. (2007, 090442)	Atlanta, GA	0-2			
Mann et al.(2002, 036723)	California, US	0-3			
	California, US	0-3		sCHF	
	California, US	0-3		sARR	
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr		
	Australia, New Zealand	0-1	65+ yr		
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1	65+ yr		
Szyszkowicz (2007, 193793)	Montreal, Canada	0	All ages		
	Montreal, Canada	0	All ages	Males	
	Montreal, Canada	0	All ages	Females	
	Montreal, Canada	0	65+ yr	Males and Females	
	Montreal, Canada	0	65+ yr	Males	
	Montreal, Canada	0	65+ yr	Females	
Lee et al. (2003, 095552)	Seoul, Korea	5	All ages		
	Seoul, Korea	5	64+ yr		
von Klot et al. (2005, 088070)	Multicity, Europe	0	35+ yr		Angina
Hosseinpoor et al. (2005, 087413)	Tehran, Iran	1	All ages		
Linn et al. (Linn et al., 2000, 002839)	Los Angeles, CA	0		All year	MI
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr		
	Australia, New Zealand	0-1	65+ yr		
Lanki et al. (2006, 089788)	Multicity, Europe	0	35+ yr	All cities	
	Multicity, Europe	0	<75 yr	Nonfatal	
	Multicity, Europe	0	<75 yr	Fatal	
	Multicity, Europe	0	75+ yr	Nonfatal	
	Multicity, Europe	0	75+ yr	Fatal	
von Klot et al. (2005, 088070)	Multicity, Europe	0	35+ yr		
D'Ippoliti et al. (2003, 074311)	Rome, Italy	0-2	18+ yr		
	Rome, Italy	0-2	18-64 yr		
	Rome, Italy	0-2	65-74 yr		
	Rome, Italy	0-2	75+ yr		

Relative Risk: 0.8 — 1.0 — 1.2 — 1.4

Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h average CO concentrations. Lag time is the time between the exposure and the outcome measured. The closed circle on the diagram indicates the effect estimate, while the bar indicates the 95 percent confidence interval.

(Taken from U.S. EPA (2010), Figure 5-2)

FIGURE I-8

EFFECT ESTIMATES (95 PERCENT CONFIDENCE INTERVALS) ASSOCIATED WITH HOSPITAL ADMISSIONS FOR VARIOUS FORMS OF HEART DISEASE.

In addition to observed physiological effects and cardiovascular effects, CO can modify electron transport in nerve cells, resulting in behavioral, neurological, and developmental toxicological consequences (Kleinmann, 2020). Looking at mortality, a time-series analysis in 272 major cities in China from January, 2013, to December, 2015 Liu et al.(2018), found an association between short-term exposure to ambient carbon monoxide and increased cardiovascular disease mortality, especially coronary heart disease mortality.

Recent studies are also showing more respiratory effects from CO exposure. Zhoa et. al (2016) found an association with ambient CO and alleviated respiratory inflammation in healthy young adults. In another recent study by Zhao et al., (2019) that looked at ambient CO and hospital outpatient visits for respiratory diseases in Dongguan, China, the authors found that short-term exposure to ambient CO was associated with increased risk of outpatient visits for respiratory diseases and emergency department visits for respiratory diseases overall and visits for asthma (Zhao et al., 2019).

Research studies have also evaluated ambient CO exposures in relation to reproductive health outcomes. Epidemiological studies conducted in Southern California have reported an association between CO exposure during pregnancy and increases in pre-term births (Ritz et al. 2000; Wilhelm et al. 2005; Ritz et al. 2007). The increases in the pre-term births were also associated with PM10 or PM2.5 levels. There are very few studies examining CO exposure and birth defects, but one Southern California study found increased risks for cardiac-related birth defects with carbon monoxide exposure in the second month of pregnancy (Ritz et al. 2002). Some recent epidemiological studies in pregnant women show that odds ratios for cardiac ventricular septal defects increased in a dose-responsive fashion with increasing CO exposure (Kleinman, 2020). Toxicological studies in laboratory animals with higher than ambient levels of CO have also reported decrements in birth weight and prenatal growth, as well as impaired neurobehavior in the offspring of exposed animals (U.S. EPA 2010). Reductions in birth weight and impaired neurobehavioral development have been observed in animals chronically exposed to CO resulting in COHb levels like those observed in smokers (Kleinmann, 2020). The U.S. EPA concluded in their most recent review that the evidence linking long-term CO exposures with reproductive health outcomes was suggestive of a causal relationship.

The population groups affected by CO exposure are people with cardiovascular diseases, people with anemia and other blood disorders, and people with chronic lung disease.

LEAD

Lead (Pb) is a toxic air contaminant that is recognized to exert an array of deleterious effects on multiple organ systems. There are serveral potential public health effects at low level exposures, and there is no recognized lower threshold for health effects (U.S. EPA 2013a). The health implications are generally indexed by blood lead levels which are related to lead exposures both from inhalation as well as from ingestion. Effects include impacts on population IQ as well as heart disease and kidney disease. The initial air quality standard for lead was established by U.S. EPA in 1978 at a level of 1.5 µg /m^3 averaged over a calendar quarter. U.S. EPA revised the NAAQS for lead in 2008 to a level of 0.15 µg/m^3 averaged over a rolling three-month period to protect against lead toxicity.

The U.S. EPA reviewed the health effects of ambient lead exposures in conjunction with an Integrated Science Assessment and a review of the NAAQS for lead in 2015 and 2013 (U.S. EPA 2013a; U.S. EPA 2015c). Lead can accumulate and be stored in the bone, and this lead in bone can be released into the blood when the bone is metabolized, which happens naturally and continuously. Blood lead is the most common measure of lead exposure, and it represents recent exposure and may be an indicator of total body burden of lead (U.S. EPA 2013a). The following table gives the summary of causality conclusions from the U.S. EPA review, which illustrates the wide range of health effects associated with lead exposure.

TABLE I-13

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATIONS FOR HEALTH EFFECTS OF LEAD

HEALTH OUTCOME	CAUSALITY DETERMINATION
Children - Nervous System Effects	
Cognitive Function Decrements	Causal relationship
Externalizing Behaviors: Attention, Impulsivity and Hyperactivity	Causal relationship
Externalizing Behaviors: Conduct Disorders in Children and Young Adults	Likely to be a causal relationship
Internalizing Behaviors	Likely to be a causal relationship
Auditory Function Decrements	Likely to be a causal relationship
Visual Function Decrements	Inadequate to infer a causal relationship
Motor Function Deficits	Likely to be a causal relationship
Adults – Nervous System Effects	
Cognitive Function Decrements	Likely to be a causal relationship
Psychopathological Effects	Likely to be a causal relationship
Cardiovascular effects	
Hypertension	Causal relationship
Subclinical Atherosclerosis	Suggestive of a causal relationship
Coronary Heart Disease	Causal relationship
Cerebrovascular Disease	Inadequate to infer a causal relationship
Renal Effects	
Reduced Kidney Function	Suggestive of a causal relationship
Immune System Effects	
Atopic and Inflammatory Response	Likely to be a causal relationship
Decreased Host Resistance	Likely to be a causal relationship
Autoimmunity	Inadequate to infer a causal relationship
Hemotologic Effects	
Decreased Red Blood Cell Survival and Function	Causal relationship

TABLE I-13

SUMMARY OF U.S. EPA'S CAUSAL DETERMINATIONS FOR HEALTH EFFECTS OF LEAD (CONTINUED)

Altered Heme Synthesis	Causal relationship
Reproductive and Developmental Effects	
Development	Causal relationship
Birth Outcomes (low birth weight, spontaneous abortion)	Suggestive of a causal relationship
Male Reproductive Function	Causal relationship
Female Reproductive Function	Suggestive of a causal relationship
Cancer	
Cancer	Likely to be a causal relationship

(Taken from U.S. EPA (2013a) Table ES-1)

Children appear to be sensitive to the neurological toxicity of lead, with effects observed at blood lead concentration ranges of 2–8 µg/dL. No clear threshold has been established for such effects. According to the U.S. EPA review, the most important effects observed are neurotoxic effects in children and cardiovascular effects in adults. The effects in children include impacts on intellectual attainment and school performance. Figure I-9 provides a summary of the lowest levels of blood lead that have been associated with certain neurological, hematological and immune effects in children.

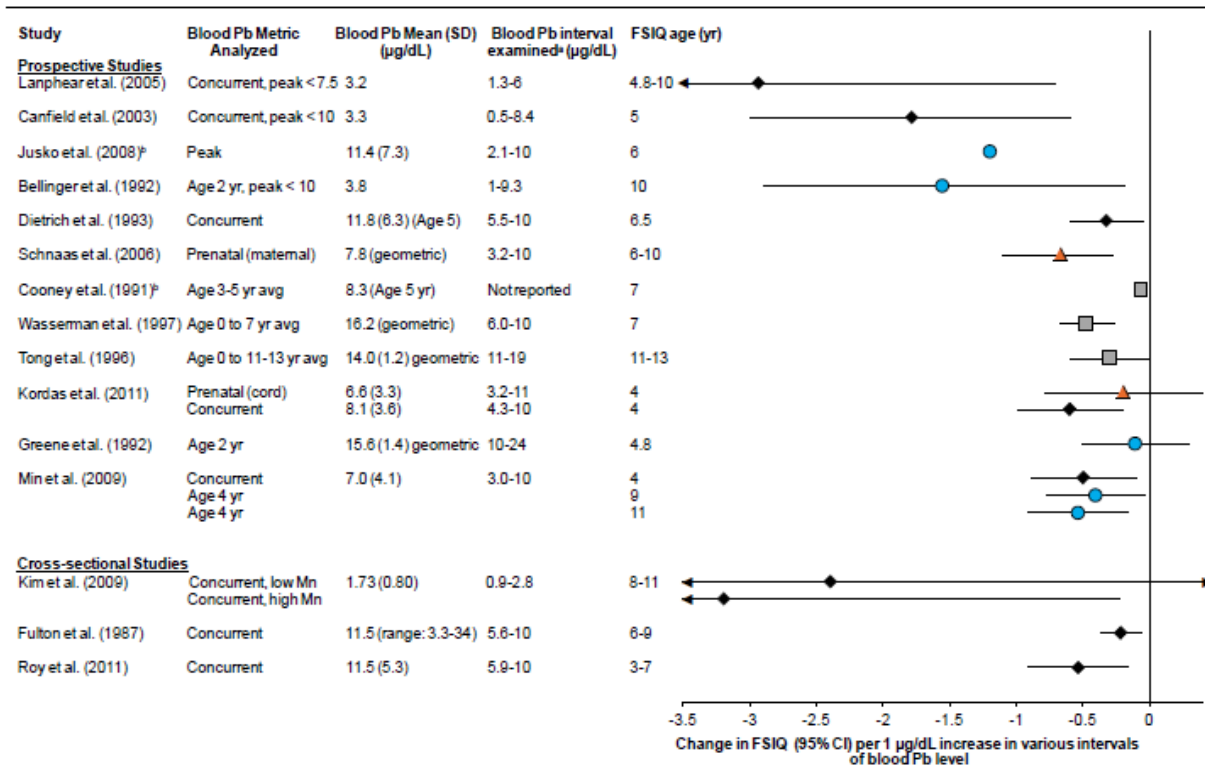| Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Immune Effects
30 µg/dL		Increased urinary δ-aminolevulinic acid	
15 µg/dL	Behavioral disturbances (e.g., inattention, delinquency) Altered electrophysiological responses	Erythrocyte protoporphyrin (EP) elevation	
10 µg/dL	Effects on neuromotor function CNS cognitive effects (e.g., IQ deficits)	Inhibition of δ-aminolevulinic acid dehydratase (ALAD) | Pyrimidine-5′-nuclotidase (Py5N) activity inhibition	Effects on humoral (↑ serum IgE) and cell-mediated (↓ T-cell abundance) immunity
5 µg/dL	↓	↓	
	(???)	(???)	
0 µg/dL			

Note: Arrows depict cases where weight of overall evidence strongly substantiates likely occurrence of type of effect in association with blood-Pb concentrations in range of 5-10 µg/dL, or possibly lower, as implied by (???). Although no evident threshold has yet been clearly established for those effects, the existence of such effects at still lower blood-Pb levels cannot be ruled out based on available data.

Source: Adapted/updated from Table 1-17 of U.S. Environmental Protection Agency (1986a).

(From (U.S. EPA 2007), Table 3-1)

FIGURE I-9

SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN CHILDREN

Figures I-10 and I-11, taken from the U.S. EPA review (U.S. EPA 2007), depict the health effects of lead in relation to blood levels. In the figure, the question marks indicate that there are no demonstrated threshold blood lead levels for health effects. The Centers for Disease Control (CDC) has recently revised their lead hazard information and replaced their level of concern for adverse effects of 10 µg/dL blood lead level with a childhood blood lead level reference value of 5 µg/dL to identify children and environments associated with lead-exposure hazards (Centers for Disease Control and Prevention 2016).

Figure I-10 provides a summary of the lowest levels of blood lead that have been associated with key health effects in adults. For adults, evidence supports a causal relationship between lead and increased blood pressure and hypertension, as well as coronary heart disease (myocardial infarction, ischemic heart disease, and heart rate variability). Other health effects among adults are also relatively high on the causal scale, including neurological, hematological, and renal effects. Disorders of various body systems and the role of inflammation due to lead exposure has been shown in various recent studies. These studies indicate that lead exposure may cause respiratory, neurologic, digestive, cardiovascular and urinary diseases. The increased inflammatory cells and mediators due to lead exposure including cytokines and chemokines due to lead exposure may cause these various organ disorders (Boskabady et al., 2018).

Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Cardiovascular Effects	Renal Effects
30 µg/dL	Peripheral sensory nerve impairment	Erythrocyte protoporphyrin (EP) elevation in males		Impaired Renal Tubular Function
20 µg/dL	Cognitive impairment			
15 µg/dL	Postural sway	Erythrocyte protoporphyrin (EP) elevation in females		
		Increased urinary δ-aminolevulinic acid		
10 µg/dL		Inhibition of δ-aminolevulinic acid dehydratase (ALAD)	Elevated blood pressure	
5 µg/dL			(???)	Elevated serum creatine (↓ creatine clearance)
0 µg/dL				

Note: Arrows depict cases where weight of overall evidence strongly substantiates likely occurrence of type of effect in association with blood-Pb concentrations in range of 5-10 µg/dL, or possibly lower, as implied by (???). Although no evident threshold has yet been clearly established for those effects, the existence of such effects at still lower blood-Pb levels cannot be ruled out based on available data.

Source: Adapted/updated from Table 1-16 of U.S. Environmental Protection Agency (1986a).

(Taken from U.S. EPA (2007), Table 3-2)

FIGURE I-10

SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN ADULTS

In its most recent review of lead health effects, the U.S. EPA confirmed its previous conclusion regarding the cognitive decline in children as the most sensitive adverse effect associated with lead exposures. The effects as measured by a reduction in IQ from a number of studies are shown in the following figure. According to the review, the currently available evidence supports a median estimate of -1.75 IQ points for a change of 1 µg/dL blood lead to describe the neurocognitive impacts on young children (U.S. EPA 2015c).

Study	Blood Pb Metric Analyzed	Blood Pb Mean (SD) (µg/dL)	Blood Pb interval examined[a] (µg/dL)	FSIQ age (yr)
Prospective Studies				
Lanphear et al. (2005)	Concurrent, peak <7.5	3.2	1.3-6	4.8-10
Canfield et al. (2003)	Concurrent, peak <10	3.3	0.5-8.4	5
Jusko et al. (2008)[b]	Peak	11.4 (7.3)	2.1-10	6
Bellinger et al. (1992)	Age 2 yr, peak < 10	3.8	1-9.3	10
Dietrich et al. (1993)	Concurrent	11.8 (6.3) (Age 5)	5.5-10	6.5
Schnaas et al. (2006)	Prenatal (maternal)	7.8 (geometric)	3.2-10	6-10
Cooney et al. (1991)[b]	Age 3-5 yr avg	8.3 (Age 5 yr)	Not reported	7
Wasserman et al. (1997)	Age 0 to 7 yr avg	16.2 (geometric)	6.0-10	7
Tong et al. (1996)	Age 0 to 11-13 yr avg	14.0 (1.2) geometric	11-19	11-13
Kordas et al. (2011)	Prenatal (cord)	6.6 (3.3)	3.2-11	4
	Concurrent	8.1 (3.6)	4.3-10	4
Greene et al. (1992)	Age 2 yr	15.6 (1.4) geometric	10-24	4.8
Min et al. (2009)	Concurrent	7.0 (4.1)	3.0-10	4
	Age 4 yr			9
	Age 4 yr			11
Cross-sectional Studies				
Kim et al. (2009)	Concurrent, low Mn	1.73 (0.80)	0.9-2.8	8-11
	Concurrent, high Mn			
Fulton et al. (1987)	Concurrent	11.5 (range: 3.3-34)	5.6-10	6-9
Roy et al. (2011)	Concurrent	11.5 (5.3)	5.9-10	3-7

[a]See Table 4-3 for explanation of the blood Pb level interval examined. Effect estimates were calculated for the lowest range examined in the study or the 10th percentile of blood Pb level to a blood Pb level of 10 µg/dL.
[b]Sufficient data were not available to calculate 95% CI.

Note: Mn = manganese. Results are presented for most of the cohorts examined in the literature and generally are grouped according to strength of study design, representativeness of the study population characteristics and blood Pb levels examined, and extent of consideration for potential confounding. There is not necessarily a continuum of decreasing strength across studies. Results usually are presented for the oldest age examined in cohorts. Multiple results from a cohort are grouped together. To facilitate comparisons among effect estimates across studies with different distributions of blood Pb levels and model structures (e.g., linear, log-linear), effect estimates are standardized to a 1 µg/dL increase for the lowest range of blood Pb levels examined in the study or the interval from the 10th percentile of blood Pb level to 10 µg/dL. For populations with 10th percentiles near or above 10 µg/dL, the effect estimate was calculated for the 10th to 90th percentile of blood Pb level. The percentiles are estimated using various methods and are only approximate values. Effect estimates are assumed to be linear within the blood Pb level interval evaluated. The various tests used to measure FSIQ are scored on a similar scale (approximately 40-160 FSIQ points). Black diamonds, blue circles, orange triangles, and gray squares represent effect estimates for concurrent, earlier childhood, prenatal, and lifetime average blood Pb levels, respectively. The horizontal lines associated with point estimates represent 95% confidence intervals (CI).

(Taken from U.S. EPA (2013a), Figure 4-2)

FIGURE I-11

ASSOCIATIONS OF BLOOD PB LEVELS WITH FULL-SCALE IQ (FSIQ) IN CHILDREN

TOXIC AIR CONTAMINANTS

Toxic air contaminants are pollutants for which there generally are no ambient air quality standards. The Toxic Air Contaminant Identification and Control Act (AB 1807, Tanner, 1983) created California's first program to reduce exposures to air toxics by requiring CARB to adopt Air Toxics Control measures. Air Districts must either enforce these measures or adopt their own equally or more stringent measures. The Air Toxics "Hot Spots" Information and Assessment Act (AB 2588, Connelly, 1987) supplements the earlier program by requiring air toxics inventories for certain facilities, notification of people's exposure to significant health risks, and facility plans to reduce these risks. Under California's Air Toxics Program, the Office of Environmental Health Hazard Assessment (OEHHA) assesses the health effects of substances that may pose a risk of adverse health effects, and CARB assesses the potential for humans to be exposed to these substances. These effects are usually an increased risk for cancer, adverse birth outcomes, or respiratory effects. After review by the state Scientific Review Panel, CARB holds a public hearing on whether to formally list substances that may pose a significant risk to public health as a Toxic Air Contaminant. Air toxics include many different types of chemicals, and the discussion here will not address all air toxics in a comprehensive manner. However, this section will discuss very briefly diesel particulate matter and volatile organic compounds (VOCs), because diesel particulate matter is the most significant contributor to cancer risk in the South Coast Air Basin, and because some VOCs are air toxics, and are part of the control measures proposed in the current Air Quality Management Plan.

DIESEL PARTICULATE MATTER

The California Air Resources Board listed diesel particulate matter as a Toxic Air Contaminant in 1998, based on the determination that it was a human carcinogen (California Air Resources Board 2010b). The International Agency for Research on Cancer, an arm of the World Health Organization, classified diesel exhaust as probably carcinogenic to humans in 1989 (International Agency for Research on Cancer 1989). More recently, IARC convened an international panel of scientists to review the published literature since the initial classification regarding the carcinogenicity of diesel combustion emissions. The panel concluded that diesel exhaust is a substance that causes lung cancer in humans (International Agency for Research on Cancer 2012b).

OEHHA also establishes potency factors for air toxics that are carcinogenic. The potency factors can be used to estimate the additional cancer risk from ambient levels of toxics. This estimate represents the chance of contracting cancer in an individual over a lifetime exposure to a given level of an air toxic and is usually expressed in terms of additional cancer cases per million people exposed.

South Coast AQMD conducted studies on the ambient concentrations and estimated the potential health risks from air toxics (South Coast Air Quality Management District 2000; South Coast Air Quality Management District 2008; South Coast Air Quality Management District 2015; South Coast Air Quality Management District 2021). In the latest South Coast AQMD Multiple Air Toxics Exposure Study, MATES V, a one-year monitoring program was undertaken at 10 sites throughout the SCAB over the time period 2018 – 2019 (South Coast Air Quality Management District 2021). Over 90 substances were measured, which included the toxics that contributed the most to health risks in the Basin.

The levels of air toxics continued to decline compared to previous MATES iterations with the air toxics cancer risk at the MATES V monitoring locations ranging from 585 to 842 per million. This risk refers to the expected number of additional cancers over a 70-year lifetime in a population of one million individuals if they were continuously exposed to these levels for 30 years. In contrast to past MATES iterations where only exposure via inhalation was considered, this analysis considers additional exposure pathways. This approach is consistent with how cancer risks are estimated under South Coast AQMD's programs such as permitting, Air Toxics Hot Spots (AB2588), and California Environmental Quality Act (CEQA).

As in previous MATES iterations, diesel PM is the largest contributor to overall air toxics cancer risk, contributing approximately 50% of the cancer risk. However, the average levels of diesel PM in MATES V are 53% lower at the 10 monitoring sites compared to MATES IV and 86% lower since MATES II based on monitored data. Based on other South Coast AQMD analyses of projected diesel PM emissions in future years, significant decreases in diesel PM health impacts are expected within the next 5-10 years. These reductions reflect recent and continued efforts by the District, CARB and U.S. EPA that reduce diesel PM emissions, especially from mobile sources.

Although direct PM2.5 emissions from diesel engines represent a small portion of overall PM2.5 exposure, PM2.5 health effects are important in understanding diesel particulate matter effects. The most noteworthy PM2.5 health effect is the association between both short-term (24hour) and long-term PM2.5 exposure and premature mortality, especially from cardiovascular causes. These causal associations were reaffirmed in the 2019 ISA. It is also important to note that NO_x emissions from diesel engines also eventually lead to PM2.5 formation in the atmosphere and represent a larger component of PM2.5 exposure (South Coast Air Quality Management District 2013a; Harley 2014).

VOLATILE ORGANIC COMPOUNDS

VOCs are a class of air pollutants that undergo photochemical reactions in the air to form ozone. It should be noted that there are no state or national ambient air quality standards for VOCs because they are not classified as criteria pollutants. VOCs are regulated, however, because limiting VOC emissions reduces the rate of photochemical reactions that contribute to the formation of ozone.

VOCs are also transformed into organic aerosols in the atmosphere, contributing to higher PM and lower visibility levels. In addition, VOCs that have toxic properties are also regulated as air toxics. Chapter 3 of the draft 2022 AQMP presents data on VOC sources and emissions in the South Coast Air Basin.

Some examples of VOCs that are known to cause health effects include benzene, toluene, ethylbenzene and xylenes (abbreviated BTEX), 1,3-butadiene, formaldehyde, and perchloroethylene. Several of these VOCs are carcinogenic. Based on the MATES V analysis, carbonyl species, such as formaldehyde and acetaldehyde, contribute to 10% of the air toxics cancer risk, compared to only 4% in MATES IV. However, the modeling results showed that formaldehyde and acetaldehyde primarily came from secondary formation rather than direct emissions during this time period. Benzene, 1,3- Butadiene, and Carbonyls together make up approximately 25% of the cancer risk in the SCAB.

Not all carcinogenic VOCs are known to cause the same types of cancers, although several are associated with blood cancers. For example, the cancers most closely associated with long-term benzene exposure

are leukemias. Formaldehyde is linked to nasopharyngeal cancer and leukemias, while 1,3-butadiene causes cancers in both the blood and lymphatic systems (International Agency for Research on Cancer 2012a).

Many VOCs can also cause non-cancer health effects. Additional information about the various health effects associated with the specific air toxics can be found on the Air Chemicals website (https://oehha.ca.gov/air/chemicals) developed by the Office of Environmental Health Hazard Assessment. For non-cancer health outcomes, OEHHA has developed acute and chronic Reference Exposure Levels (RELs). RELs are concentrations in the air below which adverse health effects are not likely to occur. Acute RELs refer to short-term exposures, generally of one-hour duration. Chronic RELs refer to long-term exposures of several years. OEHHA has also established eight-hour RELs for several substances. The ratio of ambient concentration to the appropriate REL can be used to calculate a Hazard Index (HI). A Hazard Index of less than one would not be expected to result in adverse effects (Dodge et al. 2015).

In general, concentrations of most air toxics were substantially lower in MATES V compared to previous MATES. The measurements indicate that chronic non-cancer health impacts have decreased significantly since MATES III, however, the chronic HIs have remained similar at the fixed monitoring locations since MATES IV. In the MATES V assessment of chronic non-cancer health risks, the monitored air toxics levels were found to be below the chronic RELs. In other words, the general levels of air toxics in the SCAB are not expected to cause adverse non-cancer health effects. Importantly, the MATES V monitoring network was designed to characterize the air toxics exposures in the basin overall. Given that ambient monitoring is necessarily conducted at a limited number of locations, and modeling is limited to a spatial resolution of 2km, there may be higher exposures not captured by the fixed-site monitoring. Communities with environmental justice concerns often have higher exposures that might not be captured in the spatial resolution of 2km. In 2017, Assembly Bill (AB) 617 was signed into law to address air quality disparities in EJ communities across the state. Among the many AB 617 program elements that aim to bring air quality benefits to EJ communities, one part of the program involves the designation of specific communities for the development of community plans. MATES V study included local-scale studies in 6 such communities very close to known industrial sources or large mobile source facilities, with a focus on ultrafine particles and diesel PM emissions. Details of these study results can be found in the MATES V final report (South Coast Air Quality Management District 2021). Between MATES IV and MATES V, air toxics cancer risk decreased by 57% in EJ communities overall compared to a 52% reduction in non-EJ communities. Importantly, although air toxics cancer risks have decreased overall, and especially decreased substantially in EJ communities, people living in EJ communities in the SCAB continue to experience higher air toxics cancer risks compared to those in non-EJ communities.

ODORS

Environmental odors are recognized as having the potential to cause health effects and/or quality of life impacts. The theory of "miasma" dates back to Hippocrates in ancient Greek times, and related bad odors to disease.   The health effects of environmental odors can vary widely, and depend on the compound causing the odor, the level of the compound, as well as the sensitivity and physiological responses of the person detecting the odor.

Different levels of odor exposure can cause a range of responses and health effects, and the science of odor as a potential health issue was summarized previously by Schiffman and Williams (Schiffman et al. 2005b). There are two key nerves in the nasal cavity involved in odor effects: the olfactory nerve provides the sense of smell, while the trigeminal nerve provides the sense of irritation. At very low levels, an odor can be detected (i.e. odor threshold), and at slightly higher levels, an odor can be recognized and identified. At levels higher than detection or recognition levels, an odor can cause annoyance or intolerance, and at even higher levels, an odor can cause irritation or possible toxicity, if the odor is caused by a compound that is also an air toxic (Schiffman et al. 2005b).

Schiffman and Williams proposed three mechanisms of action for odor symptoms (Schiffman et al. 2005b). In the first mechanism, an odor substance can be at the level that can produce irritation, which triggers the trigeminal nerve. This mechanism is considered a toxic effect because symptoms appear when the chemical concentration is at or above the irritation level; here, the odor serves only as the marker of the toxic effect. In the second mechanism, the odor compound is below the irritation level but above odor detection thresholds, which can result in odor annoyance. This mechanism is relatively common among environmental odors, and has been studied in communities exposed to odors from landfills, hazardous waste sites or concentrated animal feeding operations (CAFO's) (Shusterman et al. 1991; Schiffman et al. 2005a; Heaney et al. 2011; Schinasi et al. 2011; Blanes-Vidal et al. 2012; Hooiveld et al. 2015). In this mechanism, the health effect is not a toxicological effect, and the dose does not necessarily correlate well with the effect in these instances. Genetic factors, previous exposure ("learning"), and beliefs about the safety of the odor may play important roles in these odors causing health symptoms (Shusterman 2001). The third proposed mechanism is when an odor substance is present along with a co-pollutant or endotoxin that is capable of producing health effects. In this mechanism, the effect is also a toxic effect, but the odor serves as a marker of the presence of a mixture that includes a toxic compound; if the co-pollutant were not present, no health effect would be expected in this scenario.

Individual characteristics can play important roles in altering an individual's response to an odor. Factors that can influence odor perception include age, genetics, gender, medical history (including mental health, neurological conditions, and other health conditions), health-related behaviors (tobacco, alcohol), and occupational and environmental factors (Greenberg et al. 2013; Wilson et al. 2014; Agency for Toxic Substances and Disease Registry 2016). Additionally, an individual's cognitive associations with the odor prior to an exposure can result in increased reporting of health-related symptoms after exposure (Shusterman et al. 1991; Shusterman 2001; Greenberg et al. 2013). Common symptoms associated with environmental odor exposures include headache, nasal congestion, eye, nose and throat irritation, hoarseness or sore throat, cough, chest tightness, shortness of breath, wheezing heart palpitations, nausea, drowsiness, and mental depression (Agency for Toxic Substances and Disease Registry 2016). If the concentrations of the odor compound are below irritation levels, then the symptoms are not expected

to persist once the person is no longer exposed; however, being exposed to odor levels at or above irritation levels for longer periods of time may cause symptoms that persist after moving out of the exposure area (Agency for Toxic Substances and Disease Registry 2016).

CONCLUSIONS

A large body of scientific evidence shows that the adverse impacts of air pollution on human and animal health are clear. A considerable number of population-based and laboratory studies have established a link between air pollution and increased morbidity and, in some instances, premature mortality. Importantly, the health effects of air pollution extend beyond respiratory effects, and there is substantial evidence that air pollution (including particulate matter and ozone) exposures cause cardiovascular morbidity and mortality. Some air pollutants, such as diesel PM, lead, and several other air toxics, have been linked to increased cancer risk. Health studies have also identified populations who may be more susceptible to the adverse effects of air pollution, such as children, older adults, low SES communities, people with certain pre-existing health conditions, and people with certain genetic factors. Understanding the impacts of air pollution on these more susceptible populations can help inform policies that better protect public health, for example, in setting standards for criteria air pollutants, and in the development of methods to evaluate air toxics health risks. Continued research on the effects of specific PM constituents and ultrafine particles will be important in furthering the understanding of how these pollutants affect human health.

As the scientific methods for the study of air pollution health effects have progressed over the past decades, adverse effects have been shown to occur at lower levels of exposure. For some pollutants, no clear thresholds for effects have been demonstrated. The new findings have, in turn, led to the revision and lowering of National Ambient Air Quality Standards (NAAQS) which, in the judgment of the Administrator of the U.S. EPA, are necessary to protect public health. Chapter 8 of the Draft 2022 AQMP provides an overview of the extensive, multi-year, public process involved in setting federal air quality standards. Assessments of the scientific evidence from health studies is an important part of the process and has helped inform revisions to the federal air pollution standards (U.S. EPA, Process of Reviewing the National Ambient Air Quality Standards). Figures I-12 and I-13 are meant to convey some of the historical context to recent revisions to the NAAQS for ozone and for particulate matter, regarding key developments in the understanding of the health effects of these pollutants.
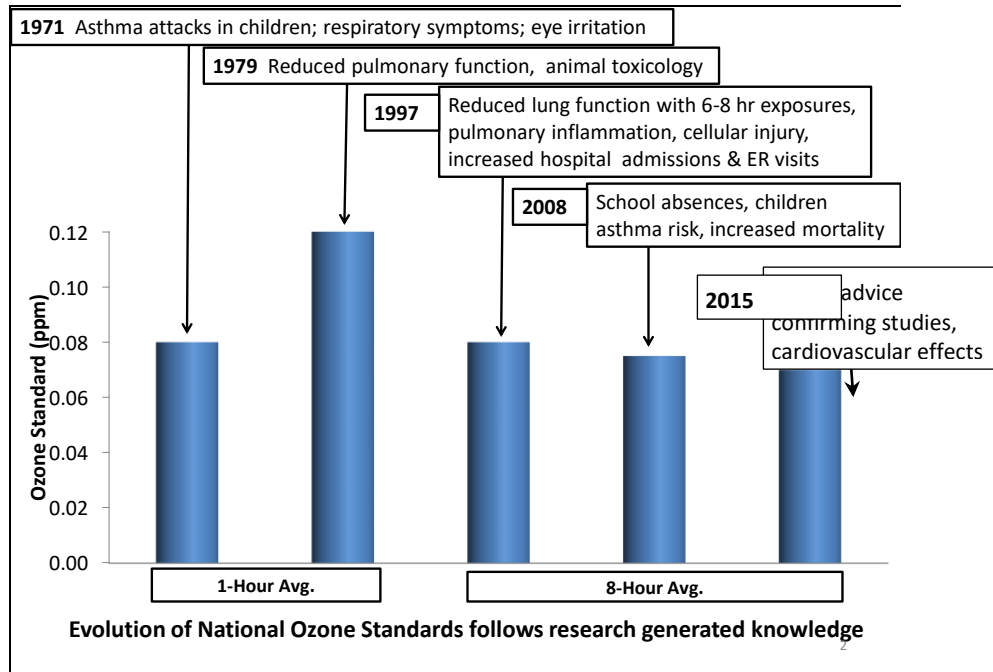
FIGURE I-12

HISTORICAL CONTEXT TO REVISIONS OF NAAQS FOR OZONE
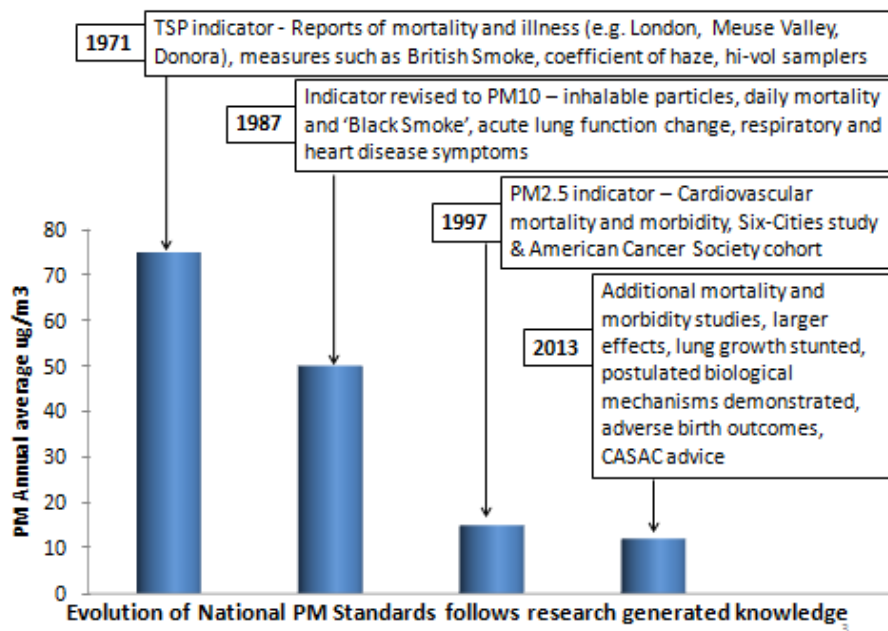
FIGURE I- 13

HISTORICAL CONTEXT TO REVISIONS OF NAAQS FOR PM

RECENT RESEARCH AND UPCOMING TOPICS

Wildfires

Wildfires have been increasing in frequency in the western United States (US) with the recent fire seasons experiencing some of the worst wildfires in terms of suppression costs and air pollution that the western US has seen. Although growing evidence suggests respiratory exacerbations from elevated fine particulate matter (PM2.5) during wildfires, significantly less is known about the impacts on human health of ozone (O_3) that may also be increased due to wildfires. Reid et al. (2019) showed that during the active fire periods, PM2.5 was significantly associated with exacerbations of asthma and chronic obstructive pulmonary disease (COPD) and these effects remained after controlling for O_3. However, effect estimates of O_3 during the fire period were non-significant for respiratory hospitalizations but were significant for ED visits for asthma (RR = 1.05 and 95% CI = (1.022, 1.078) for a 10 ppb increase in O_3). In mutually-adjusted models, the significant findings for PM2.5 remained whereas the associations with O_3 were confounded. Adjusted for O_3, the RR for asthma ED visits associated with a 10 µg/m3 increase in PM2.5 was 1.112 and 95% CI = (1.087, 1.138). The significant findings for PM2.5 but not for O_3 in mutually-adjusted models is likely because PM2.5 levels during these fires exceeded the 24-hour National Ambient Air Quality Standard (NAAQS) of 35 µg/m3 for 4976 ZIP-code days and reached levels up to 6.073 times the NAAQS, whereas our estimated O_3 levels during the fire period only occasionally exceeded the NAAQS of 70 ppb with low exceedance levels.

COVID

Various regions of California have experienced many wildfires in 2020, at the same time the state has been experiencing many cases of and deaths from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Meo et al., aimed to investigate the relationship of wildfire allied pollutants, including particulate matter (PM2.5), carbon monoxide (CO), and Ozone (O_3) with the dynamics of new daily cases and deaths due to SARS-COV 2 infection in 10 counties, which were affected by wildfire in California. The data recorded from the date of the appearance of first case of (SARS-CoV-2) in California region to the onset of wildfire, and from the onset of wildfire to September 22, 2020. After the wildfire, the PM2.5 concentration increased by 220.71%; O_3 by 19.56%; and the CO concentration increased by 151.05%. After the wildfire, the numbers of cases and deaths due to COVID-19 both increased respectively by 56.9% and 148.2%. The California wildfire caused an increase in ambient concentrations of toxic pollutants which were temporally associated with an increase in the incidence and mortality of COVID-19 (Meo et al., 2021).

Another recent study's findings support a relation between long-term ambient air pollution exposure (particulate matter <2.5 µm (PM2.5) and <10 µm (PM10), nitrogen dioxide (NO_2), and ozone (O_3)) and COVID-19 mortality. Communities with historically high pollution levels might be at higher risk of COVID-19 mortality (Garcia et al., 2022).

References

Aaron, CP; Chervona, Y; Kawut, SM; Diez Roux, AV; Shen, M; Bluemke, DA; Van Hee, VC; Kaufman, JD; Barr, RG. (2016). Particulate matter exposure and cardiopulmonary differences in the multi-ethnic study of atherosclerosis. Environ Health Perspect 124: 1166-1173. http://dx.doi.org/10.1289/ehp.1409451.

Abbey, DE; Nishino, N; McDonnell, WF; Burchette, RJ; Knutsen, SF; Beeson, WL; Yang, JX. (1999). Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159: 373-382. http://dx.doi.org/10.1164/ajrccm.159.2.9806020

Ackermann-Liebrich, U; Leuenberger, P; Schwartz, J; et al. (1997). Lung function and long term exposure to air pollutants in Switzerland. Am J Respir Crit Care Med 155: 122-129. http://dx.doi.org/10.1164/ajrccm.155.1.9001300.

Adar, SD; Filigrana, PA; Clements, N; Peel, JL. (2014). Ambient coarse particulate matter and human health: A systematic review and meta-analysis [Review]. Curr Environ Health Rep 1: 258-274. http://dx.doi.org/10.1007/s40572-014-0022-z.

Adar, SD; Kaufman, JD; Diez-Roux, AV; et al. (2015). Air pollution and percent emphysema identified by computed tomography in the multi-ethnic study of atherosclerosis. Environ Health Perspect 123: 144-151. http://dx.doi.org/10.1289/ehp.1307951.

Adam, M; Schikowski, T; Carsin, AE; et al. (2015). Adult lung function and long-term air pollution exposure. ESCAPE: A multicentre cohort study and meta-analysis. Eur Respir J 45: 38-50. http://dx.doi.org/10.1183/09031936.00130014.

Adams, WC. (2006). Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square- wave and triangular profiles on pulmonary responses. Inhal Toxicol 18: 127-136. http://dx.doi.org/10.1080/08958370500306107

Agency for Toxic Substances and Disease Registry. (2016, February 29, 2016). "Frequently Asked Questions (FAQ)." Retrieved November 18, 2016, from https://www.atsdr.cdc.gov/odors/faqs.html.

Aguilera, I; Dratva, J; Caviezel, S; et al. (2016). Particulate matter and subclinical atherosclerosis: associations between different particle sizes and sources with carotid intima-media thickness in the SAPALDIA study. Environ Health Perspect 124: 1700- 1706. http://dx.doi.org/10.1289/EHP161.

Akinbami, L. J., C. D. Lynch, J. D. Parker and T. J. Woodruff (2010). "The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004." Environ Res 110(3): 294-301.

Alberti, KG; Eckel, RH; Grundy, SM; Zimmet, PZ; Cleeman, JI; Donato, KA; Fruchart, JC; James, WP; Loria, CM; Smith, SC. (2009). Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity Circulation 120: 1640-1645. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192644

Alessandrini, ER; Stafoggia, M; Faustini, A; Gobbi, GP; Forastiere, F. (2013). Saharan dust and the association between particulate matter and daily hospitalisations in Rome, Italy. Occup Environ Med 70: 432-434. http://dx.doi.org/10.1136/oemed-2012-101182.

Alexeeff, SE; Litonjua, AA; Suh, H; Sparrow, D; Vokonas, PS; Schwartz, J. (2007). Ozone exposure and lung function: Effect modified by obesity and airways hyperresponsiveness in the VA Normative Aging Study. Chest 132: 1890-1897. http://dx.doi.org/10.1378/chest.07-1126

Alexis, N. E. and C. Carlsten (2014). "Interplay of air pollution and asthma immunopathogenesis: a focused review of diesel exhaust and ozone." Int Immunopharmacol 23(1): 347-355.

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: 180-188. http://dx.doi.org/10.1038/jes.2015.57.

Allen, JL; Conrad, K; Oberdoerster, G; Johnston, CJ; Sleezer, B; Cory-Slechta, DA. (2013). Developmental exposure to concentrated ambient particles and preference for immediate reward in mice. Environ Health Perspect 121: 32-38. http://dx.doi.org/10.1289/ehp.1205505.

Allen, JL; Liu, X; Pelkowski, S; et al. (2014a). Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ Health Perspect 122: 939-945. http://dx.doi.org/10.1289/ehp.1307984.

Allen, JL; Liu, X; Weston, D; Conrad, K; Oberdoerster, G; Cory-Slechta, DA. (2014b). Consequences of developmental exposure to concentrated ambient ultrafine particle air pollution combined with the adult paraquat and maneb model of the Parkinson's disease phenotype in male mice. Neurotoxicology 41: 80-88. http://dx.doi.org/10.1016/j.neuro.2014.01.004.

Allen, RW; Mar, T; Koenig, J; Liu, LJ; Gould, T; Simpson, C; Larson, T. (2008). Changes in lung function and airway inflammation among asthmatic children residing in a woodsmoke-impacted urban area. Inhal Toxicol 20: 423-433. http://dx.doi.org/10.1080/08958370801903826.

Amatullah, H; North, ML; Akhtar, US; Rastogi, N; Urch, B; Silverman, FS; Chow, CW; Evans, GJ; Scott, JA. (2012). Comparative cardiopulmonary effects of size-fractioned airborne particulate matter. Inhal Toxicol 24: 161-171. http://dx.doi.org/10.3109/08958378.2011.650235.

American Thoracic Society (1996a). "Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society." Am J Respir Crit Care Med 153(1): 3-50.

American Thoracic Society (1996b). "Health effects of outdoor air pollution. Part 2. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society." Am J Respir Crit Care Med 153(2): 477-498.

Ancona, C; Badaloni, C; Mataloni, F; Bolignano, A; Bucci, S; Cesaroni, G; Sozzi, R; Davoli, M; Forastiere, F. (2015). Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models. Environ Res 137: 467-474.

Andersen, ZJ; Loft, S; Ketzel, M; Stage, M; Scheike, T; Hermansen, MN; Bisgaard, H. (2008a). Ambient air pollution triggers wheezing symptoms in infants. Thorax 63: 710-716. http://dx.doi.org/10.1136/thx.2007.085480.

Andersen, ZJ; Wahlin, P; Raaschou-Nielsen, O; Ketzel, M; Scheike, T; Loft, S. (2008b). Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. Occup Environ Med 65: 458-466. http://dx.doi.org/10.1136/oem.2007.033290.

Aragon, MJ; Chrobak, I; Brower, J; Roldan, L; Fredenburgh, LE; Mcdonald, JD; Campen, MJ. (2015).

Inflammatory and vasoactive effects of serum following inhalation of varied complex mixtures. Cardiovasc Toxicol 16: 163-171. http://dx.doi.org/10.1007/s12012-015-9325-z.

Araujo, JA; Barajas, B; Kleinman, M; et al. (2008). Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. Circ Res 102: 589-596. http://dx.doi.org/10.1161/circresaha.107.164970.

Arbex, MA; de Souza Conceição, GM; Cendon, SP;; et al. (2009). Urban air pollution and chronic obstructive pulmonary disease- related emergency department visits. J Epidemiol Community Health 63: 777-783. http://dx.doi.org/10.1136/jech.2008.078360

Arjomandi, M; Balmes, JR; Frampton, MW; et al. (2018). Respiratory responses to ozone exposure: the multicenter ozone study in older subjects (moses). Am J Respir Crit Care Med 197: 13191327. http://dx.doi.org/10.1164/rccm.201708-1613OC

Arjomandi, M; Wong, H; Donde, A; Frelinger, J; Dalton, S; Ching, W; Power, K; Balmes, JR. (2015). Exposure to medium and high ambient levels of ozone causes adverse systemic inflammatory and cardiac autonomic effects. Am J Physiol Heart Circ Physiol 308: H1499-1509. http://dx.doi.org/10.1152/ajpheart.00849.2014

Arroyo, V; Díaz, J; Carmona, R; Ortiz, C; Linares, C. (2016). Impact of air pollution and temperature on adverse birth outcomes: Madrid, 2001-2009. Environ Pollut 218: 1154-1161. http://dx.doi.org/10.1016/j.envpol.2016.08.069.

Assibey-Mensah, V; Liu, K; Thurston, SW; et al. (2015). Impact of the 2008 Beijing Olympics on the risk of pregnancy complications. Arch Environ Occup Health 71: 208-215. http://dx.doi.org/10.1080/19338244.2015.1058236

Atkinson, RW; Carey, IM; Kent, AJ; van Staa, TP; Anderson, HR; Cook, DG. (2013). Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24: 44- 53. http://dx.doi.org/10.1097/EDE.0b013e318276ccb8

Atkinson, RW; Carey, IM; Kent, AJ; van Staa, TP; Anderson, HR; Cook, DG. (2015). Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occup Environ Med 72: 42-48. http://dx.doi.org/10.1136/oemed-2014-102266.

Atkinson, RW; Fuller, GW; Anderson, HR; Harrison, RM; Armstrong, B. (2010). Urban ambient particle metrics and health: A time-series analysis. Epidemiology 21: 501-511. http://dx.doi.org/10.1097/EDE.0b013e3181debc88.

Avol, EL; Trim, SC; Little, DE; Spier, CE; Smith, MN; Peng, RC; Linn, WS; Hackney, JD; Gross, KB; D'Arcy, JB; et al. (1990). Ozone exposure and lung function in children attending a southern California summer camp. In Proceedings of the 83rd A&WMA Annual Meeting. Pittsburgh, PA: Air & Waste Management Association.

Aztatzi-Aguilar, OG; Uribe-Ramírez, M; Arias-Montaño, JA; Barbier, O; De Vizcaya-Ruiz, A. (2015). Acute and subchronic exposure to air particulate matter induces expression of angiotensin and bradykinin-related genes in the lungs and heart: Angiotensin-II type-I receptor as a molecular target of particulate matter exposure. Part Fibre Toxicol 12: 17. http://dx.doi.org/10.1186/s12989-015-0094-4.

Aztatzi-Aguilar, OG; Uribe-Ramírez, M; Narváez-Morales, J; De Vizcaya-Ruiz, A; Barbier, O. (2016). Early kidney damage induced by subchronic exposure to PM2.5 in rats. Part Fibre Toxicol 13: 68. http://dx.doi.org/10.1186/s12989-016-0179-8.

Babisch, W; Wolf, K; Petz, M; Heinrich, J; Cyrys, J; Peters, A. (2014). Associations between traffic noise, particulate air pollution, hypertension, and isolated systolic hypertension in adults: the KORA study. Environ Health Perspect 122: 492-498. http://dx.doi.org/10.1289/ehp.1306981.

Bao, A; Liang, L; Li, F; Zhang, M; Zhou, X. (2013). Effects of acute ozone exposure on lung peak allergic inflammation of mice. Front Biosci 18: 838-851. http://dx.doi.org/10.2741/4147

Badaloni, C; Ranucci, A; Cesaroni, G; et al. (2013). Air pollution and childhood leukaemia: a nationwide case-control study in Italy. Occup Environ Med 70: 876-883. http://dx.doi.org/10.1136/oemed- 2013-101604

Bai, L; Shin, S; Burnett, RT; et al. (2019). Exposure to ambient air pollution and the incidence of congestive failure and acute myocardial infarction: A population-based study of 5.1 million Canadian adults living in Ontario. Environ Int 132: 105004. http://dx.doi.org/10.1016/j.envint.2019.105004

Balasubramanian, P; Sirivelu, MP; Weiss, KA; et al. (2013). Differential effects of inhalation exposure to PM2.5 on hypothalamic monoamines and corticotrophin releasing hormone in lean and obese rats. Neurotoxicology 36: 106-111. http://dx.doi.org/10.1016/j.neuro.2012.02.016.

Ballester, F; Rodriguez, P; Iniguez, C; et al. (2006). Air pollution and cardiovascular admisisons association in Spain: Results within the EMECAS project. J Epidemiol Community Health 60: 328-336. http://dx.doi.org/10.1136/jech.2005.037978

Balmes, JR; Fine, JM; Sheppard, D. (1987). Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am J Respir Crit Care Med 136: 1117-1121. http://dx.doi.org/10.1164/ajrccm/136.5.1117

Barnett, AG; Williams, GM; Schwartz, J; Best, TL; Neller, AH; Petroeschevsky, AL; Simpson, RW. (2006). The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. Environ Health Perspect 114: 1018-1023. http://dx.doi.org/10.1289/ehp.8674.

Barraza-Villarreal, A; Sunyer, J; Hernandez-Cadena, L; et al. (2008). Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. Environ Health Perspect 116: 832-838. http://dx.doi.org/10.1289/ehp.10926

Bartell, SM; Longhurst, J; Tjoa, T; Sioutas, C; Delfino, RJ. (2013). Particulate air pollution, ambulatory heart rate variability, and cardiac arrhythmia in retirement community residents with coronary artery disease.

Environ Health Perspect 121: 1135-1141. http://dx.doi.org/10.1289/ehp.1205914.

Bartoli, ML; Vagaggini, B; Malagrino, L; Bacci, E; Cianchetti, S; Dente, FL; Novelli, F; Costa, F; Paggiaro, P. (2013). Baseline airway inflammation may be a determinant of the response to ozone exposure in asthmatic patients. Inhal Toxicol 25: 127-133. http://dx.doi.org/10.3109/08958378.2013.763313

Barone-Adesi, F; Dent, JE; Dajnak, D; Beevers, S; Anderson, HR; Kelly, FJ; Cook, DG; Whincup, PH. (2015).

Long-term exposure to primary traffic pollutants and lung function in children: cross-sectional study and meta-analysis. PLoS ONE 10: e0142565. http://dx.doi.org/10.1371/journal.pone.0142565.

Basagaña, X; Jacquemin, B; Karanasiou, A; et al. (2015). Short- term effects of particulate matter constituents on daily hospitalizations and mortality in five South-European cities: Results from the MED-PARTICLES project. Environ Int 75: 151-158. http://dx.doi.org/10.1016/j.envint.2014.11.011.

Bass, V; Gordon, CJ; Jarema, KA; et al. (2013). Ozone induces glucose intolerance and systemic metabolic effects in young and aged brown Norway rats. Toxicol Appl Pharmacol 273: 551-560. http://dx.doi.org/10.1016/j.taap.2013.09.029

Baskurt, OK. (1988). Acute hematologic and hemorheologic effects of sulfur dioxide inhalation. Arch Environ Occup Health 43: 344-348. http://dx.doi.org/10.1080/00039896.1988.9934946

Bastain, T; Islam, T; Berhane, K; et al. (2011). Exhaled nitric oxide, susceptibility and new-onset asthma in the Children's Health Study. Eur Respir J 37: 523-531. http://dx.doi.org/10.1183/09031936.00021210.

Basu, R., M. Harris, L. Sie, B. Malig, R. Broadwin and R. Green (2014). "Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California." Environ Res 128: 42-51.

Basu, R. and J. M. Samet (2002). "Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence." Epidemiol Rev 24(2): 190-202.

Basu, R., T. J. Woodruff, J. D. Parker, L. Saulnier and K. C. Schoendorf (2004). "Comparing exposure metrics in the relationship between PM2.5 and birth weight in California." J Expo Anal Environ Epidemiol 14(5): 391-396.

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: 380-386. http://dx.doi.org/10.1289/ehp.1205827

Beelen, R.; G. Hoek P. A.; van den Brandt, R. A.; et al. (2008). "Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study)." Environmental Health Perspectives 116(2): 196-202.

Beelen, R; Stafoggia, M; Raaschou-Nielsen, O; et al.(2014). Long-term exposure to air pollution and cardiovascular mortality: An analysis of 22 European cohorts. Epidemiology 25: 368-378. http://dx.doi.org/10.1097/EDE.0000000000000076.

Behbod, B; Urch, B; Speck, M; Scott, JA; Liu, L; Poon, R; Coull, B; Schwartz, J; Koutrakis, P; Silverman, F; Gold, DR. (2013). Endotoxin in concentrated coarse and fine ambient particles induces acute systemic inflammation in controlled human exposures. Occup Environ Med 70: 761-767. http://dx.doi.org/10.1136/oemed-2013-101498.

Bell, ML; Belanger, K. (2012). Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures [Review]. J Expo Sci Environ Epidemiol 22: 429-438. http://dx.doi.org/10.1038/jes.2012.42.

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: 884-891. http://dx.doi.org/10.1097/EDE.0b013e3181f2f405.

Bell, ML; Ebisu, K; Peng, RD; Walker, J; Samet, JM; Zeger, SL; Dominic, F. (2008). Seasonal and regional short-term effects of fine particles on hospital admissions in 202 U.S. counties, 1999-2005. Am J Epidemiol 168: 1301-1310. http://dx.doi.org/10.1093/aje/kwn252.

Bell, ML; Son, JY; Peng, RD; Wang, Y; Dominici, F. (2015). Brief report: Ambient PM2.5 and risk of hospital admissions: do risks differ for men and women? Epidemiology 26: 575-579. http://dx.doi.org/10.1097/EDE.0000000000000310.

Bell, M. L., A. Zanobetti and F. Dominici (2014). "Who is more affected by ozone pollution? A systematic review and meta-analysis." Am J Epidemiol 180(1): 15-28.

Bellavia, A; Urch, B; Speck, et al. (2013). DNA hypomethylation, ambient particulate matter, and increased blood pressure: Findings from controlled human exposure experiments. J Am Heart Assoc 2: e000212. http://dx.doi.org/10.1161/JAHA.113.000212.

Belleudi, V; Faustini, A; Stafoggia, M; Cattani, G; Marconi, A; Perucci, CA; Forastiere, F. (2010). Impact of fine and ultrafine particles on emergency hospital admissions for cardiac and respiratory diseases.

Epidemiology 21: 414-423. http://dx.doi.org/10.1097/EDE.0b013e3181d5c021.

Benjamin, EJ; Wolf, PA; D'Agostino, RB; Silbershatz, H; Kannel, WB; Levy, D. (1998). Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98: 946-952.

Bennett, WD; Ivins, S; Alexis, NE; Wu, J; Bromberg, PA; Brar, SS; Travlos, G; London, SJ. (2016). Effect of obesity on acute ozone-induced changes in airway function, reactivity, and inflammation in adult females. PLoS ONE 11: e0160030. http://dx.doi.org/10.1371/journal.pone.0160030

Bentayeb, M; Wagner, V; Stempfelet, et al. (2015). Association between long-term exposure to air pollution and mortality in France: A 25-year follow-up study. Environ Int 85: 5-14. http://dx.doi.org/10.1016/j.envint.2015.08.006

Berhane, K; Chang, CC; McConnell, R; et al. (2016). Association of changes in air quality with bronchitic symptoms in children in California, 1993-2012. JAMA 315: 1491-1501. http://dx.doi.org/10.1001/jama.2016.3444

Berhane, K; Zhang, Y; Salam, MT; Eckel, SP; Linn, WS; Rappaport, EB; Bastain, TM; Lurmann, F; Gilliland, FD. (2014). Longitudinal effects of air pollution on exhaled nitric oxide: the Children's Health Study. Occup Environ Med 71: 507-513. http://dx.doi.org/10.1136/oemed-2013-101874.

Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation. 1992 Jan;85(1):164-71. doi: 10.1161/01.cir.85.1.164. PMID: 1728446.

Biller, H; Holz, O; Windt, H; Koch, W; Müller, M; Jörres, RA; Krug, N; Hohlfeld, JM. (2011). Breath profiles by electronic nose correlate with systemic markers but not ozone response. Respir Med 105: 1352-1363. http://dx.doi.org/10.1016/j.rmed.2011.03.002

Biller, H., Holz, O., Windt, H., Koch, W., Müller, M., Jörres, R. A., Krug, N., & Hohlfeld, J. M. (2011). Breath profiles by electronic nose correlate with systemic markers but not ozone response. Respiratory Medicine, 105(9), 1352–1363. https://doi.org/10.1016/j.rmed.2011.03.002

Bhaskaran, K; Hajat, S; Armstrong, B; Haines, A; Herrett, E; Wilkinson, P; Smeeth, L. (2011). The effects of hourly differences in air pollution on the risk of myocardial infarction: case crossover analysis of the MINAP database. B M J 343: d5531. http://dx.doi.org/10.1136/bmj.d5531

Blanes-Vidal, V., H. Suh, E. S. Nadimi, P. Lofstrom, T. Ellermann, H. V. Andersen and J. Schwartz (2012). "Residential exposure to outdoor air pollution from livestock operations and perceived annoyance among citizens." Environ Int 40: 44-50.

Blum, JL; Chen, L-C; Zelikoff, JT. (2017). Exposure to ambient particulate matter during specific gestational periods produces adverse obstetric consequences in mice. Environ Health Perspect 125: 077020. http://dx.doi.org/10.1289/EHP1029.

Boogaard, H; Fischer, PH; Janssen, NA; et al. (2013). Respiratory effects of a reduction in outdoor air pollution concentrations. Epidemiology 24: 753-761. http://dx.doi.org/10.1097/EDE.0b013e31829e1639.

Borgie, M; Dagher, Z; Ledoux, F; et al. (2015a). Comparison between ultrafine and fine particulate matter collected in Lebanon: Chemical characterization, in vitro cytotoxic effects and metabolizing enzymes gene expression in human bronchial epithelial cells. Environ Pollut 205: 250-260. http://dx.doi.org/10.1016/j.envpol.2015.05.027.

Brauer, M; Hoek, G; Smit, HA; de Jongste, JC; Gerritsen, J; Postma, DS; Kerkhof, M; Brunekreef, B. (2007). Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J 29: 879-888. http://dx.doi.org/10.1183/09031936.00083406.

Borgie, M; Ledoux, F; Verdin, A; Cazier, F; Greige, H; Shirali, P; Courcot, D; Dagher, Z. (2015b). Genotoxic and epigenotoxic effects of fine particulate matter from rural and urban sites in Lebanon on human bronchial epithelial cells. Environ Res 136C: 352-362. http://dx.doi.org/10.1016/j.envres.2014.10.010.

Bosson, J. A., Blomberg, A., Stenfors, N., Helleday, R., Kelly, F. J., Behndig, A. F., & Mudway, I. S. (2013). Peripheral blood neutrophilia as a biomarker of ozone-induced pulmonary inflammation. PLoS ONE, 8(12). https://doi.org/10.1371/journal.pone.0081816

Boskabady, M., Marefati, N., Farkhondeh, T., Shakeri, F., Farshbaf, A., & Boskabady, M. H. (2018). The effect of environmental lead exposure on human health and the contribution of inflammatory mechanisms, a review. Environment International, 120, 404–420. https://doi.org/10.1016/j.envint.2018.08.013

Brauer, M; Lencar, C; Tamburic, L; Koehoorn, M; Demers, P; Karr, C. (2008). A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect 116: 680-686. http://dx.doi.org/10.1289/ehp.10952.

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: 594-601. http://dx.doi.org/10.1289/EHP257.

Breton, CV; Salam, MT; Vora, H; Gauderman, WJ; Gilliland, FD. (2011). Genetic variation in the glutathione synthesis pathway, air pollution, and children's lung function growth. Am J Respir Crit Care Med 183: 243- 248. http://dx.doi.org/10.1164/rccm.201006-0849OC.

Breton, CV; Wang, X; Mack, WJ; et al. (2012). Childhood air pollutant exposure and carotid artery intima-media thickness in young adults. Circulation 126: 1614-1620. http://dx.doi.org/10.1161/CIRCULATIONAHA.112.096164

Brook, RD; Bard, RL; Kaplan, MJ; et al. (2013a). The effect of acute exposure to coarse particulate matter air pollution in a rural location on circulating endothelial progenitor cells: results from a randomized controlled study. Inhal Toxicol 25: 587-592. http://dx.doi.org/10.3109/08958378.2013.814733.

Brook, RD; Bard, RL; Morishita, M; et al. (2014). Hemodynamic, autonomic, and vascular effects of exposure to coarse particulate matter air pollution from a rural location. Environ Health Perspect 122: 624-630. http://dx.doi.org/10.1289/ehp.1306595.

Brook, R. D., & Kousha, T. (2015). Air pollution and emergency department visits for hypertension in Edmonton and Calgary, Canada: A case-crossover study. American Journal of Hypertension, 28(9), 1121–1126. https://doi.org/10.1093/ajh/hpu302

Brook, RD; Xu, X; Bard, RL; Dvonch, JT; Morishita, M; Kaciroti, N; Sun, Q; Harkema, J; Rajagopalan, S. (2013b). Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. Sci Total Environ 448: 66-71. http://dx.doi.org/10.1016/j.scitotenv.2012.07.034.

Brook, RD; Z. Sun; J. R. Brook; et al. (2016). "Extreme Air Pollution Conditions Adversely Affect Blood Pressure and Insulin Resistance: The Air Pollution and Cardiometabolic Disease Study." Hypertension 67(1): 77-85.

Brown, JS; Bateson, TF; Mcdonnell, WF. (2008). Effects of exposure to 0.06 ppm ozone on FEV1 in humans: A secondary analysis of existing data. Environ Health Perspect 116: 1023-1026. http://dx.doi.org/10.1289/ehp.11396

Brown, JM; Harris, G; Pantea, C; Hwang, SA; Talbot, TO. (2015). Linking air pollution data and adverse birth outcomes: Environmental public health tracking in New York State. J Public Health Manag Pract 21: S68- S74. http://dx.doi.org/10.1097/PHH.0000000000000171.

Bruske, I; Hampel, R; Socher, MM; et al. (2010). Impact of ambient air pollution on the differential white blood cell count in patients with chronic pulmonary disease. Inhal Toxicol 22: 245-252. http://dx.doi.org/10.3109/08958370903207274.

Brunekreef, B; Beelen, R; Hoek, G; et al. (2009). Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: The NLCS-AIR Study. (139). Boston, MA: Health Effects Institute. http://www.n65.nl/NCLS-AIR-Study-2009.pdf

Burnett, RT; Brook, J; Dann, T; et al. (2000). Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol 12: 15-39. http://dx.doi.org/10.1080/08958370050164851

Burnett, R; Raizenne, M; Krewski, D. (1990). Acute health effects of transported air pollution: A study of children attending a residential summer camp. Can J Stat 18: 367-373. http://dx.doi.org/10.2307/3315843

Byers, N; Ritchey, M; Vaidyanathan, A; Brandt, AJ; Yip, F. (2015). Short-term effects of ambient air pollutants on asthma-related emergency department visits in Indianapolis, Indiana, 2007-2011. J Asthma 53: 1-8. http://dx.doi.org/10.3109/02770903.2015.1091006.

Byrd, JB; Morishita, M; Bard, RL; Das, R; Wang, L; Sun, Z; Spino, C; Harkema, J; Dvonch, JT; Rajagopalan, S; Brook, RD. (2016). Acute increase in blood pressure during inhalation of coarse particulate matter air pollution from an urban location. J Am Soc Hypertens 10: 133-139.e134. http://dx.doi.org/10.1016/j.jash.2015.11.015.

Cacciottolo, M., Wang, X., Driscoll, I., et al. (2017). Particulate Air Pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. Translational Psychiatry, 7(1). https://doi.org/10.1038/tp.2016.280

Cai, Y; Schikowski, T; Adam, M; et al. (2014). Cross-sectional associations between air pollution and chronic bronchitis: an ESCAPE meta-analysis across five cohorts [Review]. Thorax 69: 1005-1014. http://dx.doi.org/10.1136/thoraxjnl-2013-204352.

Cakmak, S; Hebbern, C; Pinault, L; Lavigne, E; Vanos, J; Crouse, DL; Tjepkema, M. (2018).

Associations between long-term PM2.5 and ozone exposure and mortality in the Canadian Census Health and Environment Cohort (CANCHEC), by spatial synoptic classification zone. Environ Int 111: 200-211. http://dx.doi.org/10.1016/j.envint.2017.11.030

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: 589-599. http://dx.doi.org/10.1016/j.envpol.2016.04.067

Cakmak, S; Kauri, L; Shutt, R; Liu, L; Green, MS; Mulholland, M; Stieb, D; Dales, R. (2014). The association between ambient air quality and cardiac rate and rhythm in ambulatory subjects. Environ Int 73: 365-371. http://dx.doi.org/10.1016/j.envint.2014.08.015.

California Air Resources Board. (2010a). "Estimate of Premature Deaths Associated with Fine Particle Pollution (PM2.5) in California Using a U.S. Environmental Protection Agency Methodology."

California Air Resources Board. (2010b, February 25, 2010). "Rulemaking Identification of Particulate Emissions from Diesel-Fueled Engines as a Toxic Air Contaminant."   Retrieved Oct 7, 2016, from https://www.arb.ca.gov/regact/diesltac/diesltac.htm.

California Air Resources Board and Office of Environmental Health Hazard Assessment. (2002). "Public Hearing to Consider Amendments to the Ambient Air Quality Standards for Particulate Matter and Sulfates."   California Environmental Protection Agency. from http://arbis.arb.ca.gov/research/aaqs/std-rs/pm-final/pm-final.htm.

California Air Resources Board and Office of Environmental Health Hazard Assessment. (2005). "Review of the California Ambient Air Quality Standard for Ozone."   California Air Resources Board and Office of Environmental Health Hazard Assessment. from http://www.arb.ca.gov/research/aaqs/ozone-rs/rev-staff/rev-staff.htm.

California Air Resources Board and Office of Environmental Health Hazard Assessment. (2007). "Review of the California Ambient Air Quality Standard for Nitrogen Dioxide."   California Air Resources Board and Office of Environmental Health Hazard Assessment. from http://www.arb.ca.gov/research/aaqs/no2-rs/no2-doc.htm

Campbell, A; Oldham, M; Becaria, A; Bondy, SC; Meacher, D; Sioutas, C; Misra, C; Mendez, LB; Kleinman,

M. (2005). Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology 26: 133-140. http://dx.doi.org/10.1016/j.neuro.2004.08.003.

Cândido da Silva, AM; Moi, GP; Mattos, IE; Hacon, S. (2014). Low birth weight at term and the presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based retrospective cohort study. BMC Pregnancy Childbirth 14: 309. http://dx.doi.org/10.1186/1471-2393-14-309.

Cao, J; Yang, C; Li, J; Chen, R; Chen, B; Gu, B; Kan, H. (2011). Association between long-term exposure to outdoor air pollution and mortality in China: A cohort study. J Hazard Mater 186: 1594-1600. http://dx.doi.org/10.1016/j.jhazmat.2010.12.036

Carey, IM; Atkinson, RW; Kent, AJ; van Staa, T; Cook, DG; Anderson, HR. (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187: 1226-1233. http://dx.doi.org/10.1164/rccm.201210-1758OC

Carlsen, HK; Boman, P; Björ, B; Olin, AC; Forsberg, B. (2016). Coarse fraction particle matter and exhaled nitric oxide in non-asthmatic children. Int J Environ Res Public Health 13. http://dx.doi.org/10.3390/ijerph13060621.

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: 291-295. http://dx.doi.org/10.1136/oem.2010.055152.

Carré, J; Gatimel, N; Moreau, J; Parinaud, J; Leandri, R. (2016). Influence of air quality on the results of in vitro fertilization attempts: A retrospective study. Eur J Obstet Gynecol Reprod Biol 210: 116-122. http://dx.doi.org/10.1016/j.ejogrb.2016.12.012

Centers for Disease Control and Prevention. (2016, March 15, 2016). "What Do Parents Need to Know to Protect Their Children?"   Retrieved May 31, 2016, from http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm.

Cesaroni, G; Forastiere, F; Stafoggia, M; et al. (2014). Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. BMJ 348: f7412.

Chan, SH; Van Hee, VC; Bergen, S; Szpiro, AA; Deroo, LA; London, SJ; Marshall, JD; Kaufman, JD; Sandler, DP. (2015). Long-term air pollution exposure and blood pressure in the Sister Study. Environ Health Perspect 123: 951-958. http://dx.doi.org/10.1289/ehp.1408125.

Chang, HH; Reich, BJ; Miranda, ML. (2013). A spatial time-to-event approach for estimating associations between air pollution and preterm birth. J R Stat Soc Ser C Appl Stat 62: 167-179. http://dx.doi.org/10.1111/j.1467-9876.2012.01056.x.

Chen, CH; Chan, CC; Chen, BY; Cheng, TJ; Leon Guo, Y. (2015a). Effects of particulate air pollution and ozone on lung function in non-asthmatic children. Environ Res 137: 40-48. http://dx.doi.org/10.1016/j.envres.2014.11.021.

Chen, H; Zhang, ZL; van Donkelaar, A; Bai, L; Martin, RV; Lavigne, E; Kwong, JC; Burnett, RT. (2020). Understanding the Joint Impacts of Fine Particulate Matter Concentration and Composition on the Incidence and Mortality of Cardiovascular Disease: A Component-Adjusted Approach. Environ Sci Technol 54: 4388-4399. http://dx.doi.org/10.1021/acs.est.9b06861

Chen, G; Wan, X; Yang, G; Zou, X. (2015). Traffic-related air pollution and lung cancer: A meta-analysis. 6: 307-318. http://dx.doi.org/10.1111/1759-7714.12185.

Chen, K; Glonek, G; Hansen, A; Williams, S; Tuke, J; Salter, A; Bi, P. (2016). The effects of air pollution on asthma hospital admissions in Adelaide, South Australia, 2003-2013: time-series and case-crossover analyses. Clin Exp Allergy 46: 1416-1430. http://dx.doi.org/10.1111/cea.12795.

Chen, LH; Knutsen, SF; Shavlik, D; Beeson, WL; Petersen, F; Ghamsary, M; Abbey, D. (2005). The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? Environ Health Perspect 113: 1723-1729. http://dx.doi.org/10.1289/ehp.8190.

Chen, R; Li, Y; Ma, Y; Pan, G; Zeng, G; Xu, X; Chen, B; Kan, H. (2011b). Coarse particles and mortality in three Chinese cities: the China Air Pollution and Health Effects Study (CAPES). Sci Total Environ 409: 4934-4938. http://dx.doi.org/10.1016/j.scitotenv.2011.08.058.

Chen, JC; Schwartz, J. (2009). Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology 30: 231-239. http://dx.doi.org/10.1016/j.neuro.2008.12.011

Chen, R; Huang, W; Wong, CM; Wang, Z; Thach, TQ; Chen, B; Kan, H. (2012b). Short-term exposure to sulfur dioxide and daily mortality in 17 Chinese cities: The China air pollution and health effects study (CAPES). Environ Res 118: 101-106. http://dx.doi.org/10.1016/j.envres.2012.07.003

Chen, R; Qiao, L; Li, H; Zhao, Y; Zhang, Y; Xu, W; Wang, C; Wang, H; Zhao, Z; Xu, X; Hu, H; Kan, H. (2015b). Fine particulate matter constituents, nitric oxide synthase DNA methylation and exhaled nitric oxide. Environ Sci Technol 49: 11859-11865. http://dx.doi.org/10.1021/acs.est.5b02527.

Chen, R; Zhang, Y; Yang, C; Zhao, Z; Xu, X; Kan, H. (2013). Acute effect of ambient air pollution on stroke mortality in the china air pollution and health effects study. Stroke 44: 954-960. http://dx.doi.org/10.1161/STROKEAHA.111.673442

Chen, YC; Weng, YH; Chiu, YW; Yang, CY. (2015b). Short-term effects of coarse particulate matter on hospital admissions for cardiovascular diseases: A case-crossover study in a tropical city. J Toxicol Environ Health A 78: 1-13. http://dx.doi.org/10.1080/15287394.2015.1083520.

Chen Z, Newgard CB, Kim JS, et al. Near-roadway air pollution exposure and altered fatty acid oxidation among adolescents and young adults - The interplay with obesity. Environ Int. 2019;130:104935. doi:10.1016/j.envint.2019.104935

Cheng, C., M. Campbell, Q. Li, et al. (2008). "Differential and combined impacts of extreme temperatures and air pollution on human mortality in south–central Canada. Part I: historical analysis." Air Qual Atmos Health 1: 209-222.

Cheng, H; Saffari, A; Sioutas, C; Forman, HJ; Morgan, TE; Finch, CE. (2016). Nano-scale particulate matter from urban traffic rapidly induces oxidative stress and inflammation in olfactory epithelium with concomitant effects on brain. Environ Health Perspect 124: 1537-1546. http://dx.doi.org/10.1289/EHP134.

Cheng, MF; Tsai, SS; Yang, CY. (2009). Air pollution and hospital admissions for myocardial infarction in a tropical city: Kaohsiung, Taiwan. J Toxicol Environ Health A 72: 1135-1140. http://dx.doi.org/10.1080/15287390903091756

Cheng, MH; Chiu, HF; Yang, CY. (2015). Coarse particulate air pollution associated with increased risk of hospital admissions for respiratory diseases in a tropical city, Kaohsiung, Taiwan. Int J Environ Res Public Health 12: 13053-13068. http://dx.doi.org/10.3390/ijerph121013053.

Chi, MC; Guo, SE; Hwang, SL; Chou, CT; Lin, CM; Lin, YC. (2016). Exposure to indoor particulate matter worsens the symptoms and acute exacerbations in chronic obstructive pulmonary disease patients of southwestern Taiwan: a pilot study. Int J Environ Res Public Health 14. http://dx.doi.org/10.3390/ijerph14010004.

Chi, GC; Hajat, A; Bird, CE; Cullen, MR; Griffin, BA; Miller, KA; Shih, RA; Stefanick, ML; Vedal, S; Whitsel, EA; Kaufman, JD. (2016a). Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. Environ Health Perspect 124: 1840-1847. http://dx.doi.org/10.1289/EHP199.

Chi, GC; Liu, Y; MacDonald, JW; Barr, RG; Donohue, KM; Hensley, MD; Hou, L; McCall, CE; Reynolds, LM; Siscovick, DS; Kaufman, JD. (2016b). Long-term outdoor air pollution and DNA methylation in circulating monocytes: results from the multi-ethnic study of atherosclerosis (MESA). Environ Health 15: 119. http://dx.doi.org/10.1186/s12940-016-0202-4.

Chiu, YHM; Coull, BA; Sternthal, MJ; Kloog, I; Schwartz, J; Cohen, S; Wright, RJ. (2014). Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. J Allergy Clin Immunol 133: 713-+. http://dx.doi.org/10.1016/j.jaci.2013.09.023.

Chu, M; Sun, C; Chen, W; et al. (2015). Personal exposure to PM2.5, genetic variants and DNA damage: A multi-center population-based study in Chinese. Toxicol Lett 235: 172-178. http://dx.doi.org/10.1016/j.toxlet.2015.04.007.

Chuang, KJ; Yan, YH; Chiu, SY; Cheng, TJ. (2011). Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. Occup Environ Med 68: 64-68. http://dx.doi.org/10.1136/oem.2009.052704

Clark, NA; Demers, PA; Karr, CJ; Koehoorn, M; Lencar, C; Tamburic, L; Brauer, M. (2010). Effect of early life exposure to air pollution on development of childhood asthma. Environ Health Perspect 118: 284-290. http://dx.doi.org/10.1289/ehp.0900916.

Clarke, RW; Catalano, PJ; Koutrakis, P; Krishna Murthy, GG; Sioutas, C; Paulauskis, J; Coull, B; Ferguson, S; Godleski, JJ. (1999). Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. Inhal Toxicol 11: 637-656. http://dx.doi.org/10.1080/089583799196781.

Cleary, EG; Cifuentes, M; Grinstein, G; Brugge, D; Shea, TB. (2018). Association of low-level ozone with cognitive decline in older adults. J Alzheimers Dis 61: 67-78. http://dx.doi.org/10.3233/JAD- 170658

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: 769-775. http://dx.doi.org/10.1289/ehp.0901631.

Cole-Hunter, T; de Nazelle, A; Donaire-Gonzalez, D; et al. (2018). Estimated effects of air pollution and space-time-activity on cardiopulmonary outcomes in healthy adults: A repeated measures study. Environ Int 111: 247-259. http://dx.doi.org/10.1016/j.envint.2017.11.024

Coogan, PF; White, LF; Yu, J; Brook, RD; Burnett, RT; Marshall, JD; Bethea, TN; Rosenberg, L; Jerrett, M. (2017). Long-term exposure to NO2 and ozone and hypertension incidence in the black women's health study. Am J Hypertens 30: 367-372. http://dx.doi.org/10.1093/ajh/hpw168

Coogan, P. F., L. F. White, M. Jerrett, R. D. Brook, J. G. Su, E. Seto, R. Burnett, J. R. Palmer and L. Rosenberg (2012). "Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles." Circulation 125(6): 767-772.

Cortez-Lugo, M; Ramirez-Aguilar, M; Perez-Padilla, R; Sansores-Martinez, R; Ramirez-Venegas, A; Barraza- Villarreal, A. (2015). Effect of personal exposure to PM2.5 on respiratory health in a Mexican panel of patients with COPD. Int J Environ Res Public Health 12: 10635-10647. http://dx.doi.org/10.3390/ijerph120910635.

Crouse, D; Philip, S; van Donkelaar, A; Martin, RV; Jessiman, B; Peters, PA; Weichenthal, S; Brook, J. R.; 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. http://dx.doi.org/10.1038/srep18916.

Crouse, DL; Peters, PA; Hystad, P; 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: 1180-1186. http://dx.doi.org/10.1289/ehp.1409276.

Cui, P; Huang, Y; Han, J; Song, F; Chen, K. (2014). Ambient particulate matter and lung cancer incidence and mortality: a meta-analysis of prospective studies. Eur J Public Health 25: 324-329. http://dx.doi.org/10.1093/eurpub/cku145.

Cyrys, J; Pitz, M; Heinrich, J; Wichmann, HE; Peters, A. (2008). Spatial and temporal variation of particle number concentration in Augsburg, Germany. Sci Total Environ 401: 168-175. http://dx.doi.org/10.1016/j.scitotenv.2008.03.043.

D'Souza, JC; Kawut, SM; Elkayam, LR; et al. (2017). Ambient coarse particulate matter and the right ventricle: The multi-ethnic study of atherosclerosis. Environ Health Perspect 125: 077019. http://dx.doi.org/10.1289/EHP658.

Dadvand, P; Figueras, F; Basagaña, X; et al. (2013a). Ambient air pollution and preeclampsia: A spatiotemporal analysis. Environ Health Perspect 121: 1365-1371. http://dx.doi.org/10.1289/ehp.1206430.

Dadvand, P; Ostro, B; Figueras, F; et al. (2014). Residential proximity to major roads and term low birth weight: The roles of air pollution, heat, noise, and road-adjacent trees. Epidemiology 25: 518- 525. http://dx.doi.org/10.1097/EDE.0000000000000107.

Dadvand, P; Parker, J; Bell, ML; et al. (2013b). Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity.Environ Health Perspect 121: 267-373. http://dx.doi.org/10.1289/ehp.1205575.

Dales, R; Kauri, LM; Cakmak, S; et al. (2013). Acute changes in lung function associated with proximity to a steel plant: A randomized study. Environ Int 55: 15-19. http://dx.doi.org/10.1016/j.envint.2013.01.014

Dales, R; Wheeler, A; Mahmud, M; Frescura, AM; Smith-Doiron, M; Nethery, E; Liu, L. (2008). The influence of living near roadways on spirometry and exhaled nitric oxide in elementary schoolchildren. Environ Health Perspect 116: 1423-1427. http://dx.doi.org/10.1289/ehp.10943.

Darrow, LA; Klein, M; Flanders, WD; Waller, LA; Correa, A; Marcus, M; Mulholland, JA; Russell, AG; Tolbert, PE. (2009). Ambient air pollution and preterm birth: A time-series analysis. Epidemiology 20: 689- 698. http://dx.doi.org/10.1097/EDE.0b013e3181a7128f.

Darrow, LA; Klein, M; Flanders, WD; Mulholland, JA; Tolbert, PE; Strickland, MJ. (2014). Air pollution and acute respiratory infections among children 0-4 years of age: an 18-year time-series study. Am J Epidemiol 180: 968-977. http://dx.doi.org/10.1093/aje/kwu234.

Darrow, LA; Klein, M; Strickland, MJ; Mulholland, JA; Tolbert, PE. (2011). Ambient air pollution and birth weight in full-term infants in Atlanta, 1994-2004. Environ Health Perspect 119: 731-737. http://dx.doi.org/10.1289/ehp.1002785.

Davel, AP; Lemos, M; Pastro, LM; Pedro, SC; de André, PA; Hebeda, C; Farsky, SH; Saldiva, PH; Rossoni, LV. (2012). Endothelial dysfunction in the pulmonary artery induced by concentrated fine particulate

matter exposure is associated with local but not systemic inflammation. Toxicology 295: 39-46. http://dx.doi.org/10.1016/j.tox.2012.02.004.

Davis, DA; Bortolato, M; Godar, SC; Sander, TK; Iwata, N; Pakbin, P; Shih, JC; Berhane, K; McConnell, R; Sioutas, C; Finch, CE; Morgan, TE. (2013). Prenatal exposure to urban air nanoparticles in mice causes altered neuronal differentiation and depression-like responses. PLoS ONE 8: e64128. http://dx.doi.org/10.1371/journal.pone.0064128.

de Hartog, JJ; Ayres, JG; Karakatsani, A; et al. (2010). Lung function and indicators of exposure to indoor and outdoor particulate matter among asthma and COPD patients. Occup Environ Med 67: 2-10. http://dx.doi.org/10.1136/oem.2008.040857.

de Melo, JO; Soto, SF; Katayama, IA; et al. (2015). Inhalation of fine particulate matter during pregnancy increased IL-4 cytokine levels in the fetal portion of the placenta. Toxicol Lett 232: 475-480. http://dx.doi.org/10.1016/j.toxlet.2014.12.001.

de Miguel-Díez, J., Jiménez-García, R., López de Andrés, A., et al. (2016). Analysis of environmental risk factors for pulmonary embolism: A case-crossover study (2001–2013). European Journal of Internal Medicine, 31, 55–61. https://doi.org/10.1016/j.ejim.2016.03.001

De Prins, S; Koppen, G; Jacobs, G; et al. (2013). Influence of ambient air pollution on global DNA methylation in healthy adults: a seasonal follow-up. Environ Int 59: 418-424. http://dx.doi.org/10.1016/j.envint.2013.07.007.

de Rainho, CR; Correa, SM; Mazzei, JL; Fortes Aiub, CA; Felzenszwalb, I. (2013). Genotoxicity of polycyclic aromatic hydrocarbons and nitro-derived in respirable airborne particulate matter collected from urban areas of Rio de Janeiro (Brazil). BioMed Res Int 2013: 765352. http://dx.doi.org/10.1155/2013/765352.

deSouza, P; Braun, D; Parks, RM; Schwartz, J; Dominici, F; Kioumourtzoglou, MA. (2021). Nationwide Study of Short-term Exposure to Fine Particulate Matter and Cardiovascular Hospitalizations Among Medicaid 22   Enrollees. Epidemiology 32: 6-13. http://dx.doi.org/10.1097/EDE.0000000000001265

Dehbi, HM; Blangiardo, M; Gulliver, J; Fecht, D; de Hoogh, K; Al-Kanaani, Z; Tillin, T; Hardy, R; Chaturvedi, N; Hansell, AL. (2016). Air pollution and cardiovascular mortality with over 25years follow-up: A combined analysis of two British cohorts. Environ Int 99: 275-281. http://dx.doi.org/10.1016/j.envint.2016.12.004.

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: e0120594. http://dx.doi.org/10.1371/journal.pone.0120594.

Devries, R; Kriebel, D; Sama, S. (2016). Low level air pollution and exacerbation of existing copd: a case crossover analysis. Environ Health 15: 98. http://dx.doi.org/10.1186/s12940-016-0179-z.

Defranco, E; Moravec, W; Xu, F; Hall, E; Hossain, M; Haynes, EN; Muglia, L; Chen, A. (2016). Exposure to airborne particulate matter during pregnancy is associated with preterm birth: a population-based cohort study. Environ Health 15: 6. http://dx.doi.org/10.1186/s12940-016-0094-3.

Delfino, RJ; Gillen, DL; Tjoa, T; Staimer, N; Polidori, A; Arhami, M; Sioutas, C; Longhurst, J. (2011). Electrocardiographic ST-segment depression and exposure to trafficrelated aerosols in elderly subjects

with coronary artery disease. Environ Health Perspect 119: 196-202. http://dx.doi.org/10.1289/ehp.1002372.

Delfino, R. J., H. Gong, Jr., W. S. Linn, E. D. Pellizzari and Y. Hu (2003). "Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants." Environ Health Perspect 111(4): 647-656.

Delfino, RJ; Staimer, N; Tjoa, T; Polidori, A; Arhami, M; Gillen, DL; Kleinman, MT; Vaziri, ND; Longhurst, J; Zaldivar, F; Sioutas, C. (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: 898-906. http://dx.doi.org/10.1289/ehp.11189.

Demarini, DM. (2013). Genotoxicity biomarkers associated with exposure to traffic and near-road atmospheres: a review [Review]. Mutagenesis 28: 485-505. http://dx.doi.org/10.1093/mutage/get042.

Demetriou, CA; Raaschou-Nielsen, O; Loft, S; Moller, P; Vermeulen, R; Palli, D; Chadeau-Hyam, M; Xun, W; Vineis, P. (2012). Biomarkers of ambient air pollution and lung cancer: a systematic review [Review]. Occup Environ Med 69: 619-627. http://dx.doi.org/10.1136/oemed-2011-100566.

Dennekamp, M., Akram, M., Abramson, M. J., Tonkin, A., Sim, M. R., Fridman, M., & Erbas, B. (2010). Outdoor air pollution as a trigger for out-of-hospital cardiac arrests. Epidemiology, 21(4), 494–500. https://doi.org/10.1097/ede.0b013e3181e093db

Devlin, RB; Smith, CB; Schmitt, MT; Rappold, AG; Hinderliter, A; Graff, D; Carraway, MS. (2014). Controlled exposure of humans with metabolic syndrome to concentrated ultrafine ambient particulate matter causes cardiovascular effects. Toxicol Sci 140: 61-72. http://dx.doi.org/10.1093/toxsci/kfu063.

Di, Q., Dai, L., Zanobetti, A., Wang, Y., Choirat, C., Dominici, F., & Schwartz, J. D. (2018). A nationwide case-crossover study on air pollution and mortality in the Medicare population. ISEE Conference Abstracts, 2017(1). doi:10.1289/isee.2017.2017-265

Di Mauro R, Cantarella G, Bernardini R, et al. The Biochemical and Pharmacological Properties of Ozone: The Smell of Protection in Acute and Chronic Diseases. Int J Mol Sci. 2019;20(3):634. Published 2019 Feb 1. doi:10.3390/ijms20030634

Diaz, EA; Chung, Y; Lamoureux, DP; Papapostolou, V; Lawrence, J; Long, MS; Mazzaro, V; Buonfiglio, H; Sato, R; Koutrakis, P; Godleski, JJ. (2013). Effects of fresh and aged traffic-related particles on breathing pattern, cellular responses, and oxidative stress. Air Qual Atmos Health 6: 431-444. http://dx.doi.org/10.1007/s11869-012-0179-2.

Dimakopoulou, K., Douros, J., Samoli, E., Karakatsani, A., Rodopoulou, S., Papakosta, D., . . . Katsouyanni, K. (2020). Long-term exposure to ozone and children's respiratory health: Results from the Respoze Study. Environmental Research, 182, 109002. doi:10.1016/j.envres.2019.109002

Dockery, DW; Pope, CA, III; 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: 1753-1759. http://dx.doi.org/10.1056/NEJM199312093292401

Dodge, D. E., and G. Harris. (2015). "The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments." Sacramento Office of Environmental Health Hazard Assessment. from http://oehha.ca.gov/media/downloads/crnr/2015guidancemanual.pdf.

Dominici, F; Peng, RD; Bell, ML; Pham, L; McDermott, A; Zeger, SL; Samet, JL. (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 295: 1127-1134. http://dx.doi.org/10.1001/jama.295.10.1127.

Dong, G; Qian, Z; Wang, J; Chen, W; Ma, W; Trevathan, E; Xaverius, PK; DeClue, R; Wiese, A; Langston, M; Liu, MM; Wang, D; Ren, W. (2013a). Associations between ambient air pollution and prevalence of stroke and cardiovascular diseases in 33 Chinese communities. Atmos Environ 77: 968-973. http://dx.doi.org/10.1016/j.atmosenv.2013.06.034

Dong, GH; Qian, ZM; Trevathan, E; Zeng, XW; Vaughn, MG; Wang, J; Zhao, Y; Liu, YQ; Ren, WH; Qin, XD. (2014). Air pollution associated hypertension and increased blood pressure may be reduced by breastfeeding in Chinese children: the Seven Northeastern Cities Chinese Children's Study. Int J Cardiol 176: 956-961. http://dx.doi.org/10.1016/j.ijcard.2014.08.099

Dong, GH; Qian, ZM; Xaverius, PK; Trevathan, E; Maalouf, S; Parker, J; Yang, L; Liu, MM; Wang, D; Ren, WH; Ma, W; Wang, J; Zelicoff, A; Fu, Q; Simckes, M. (2013b). Association between long-term air pollution and increased blood pressure and hypertension in China. Hypertension 61: 578-584. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.00003

Dong, GH; Zhang, P; Sun, B; Zhang, L; Chen, X; Ma, N; Yu, F; Guo, H; Huang, H; Lee, YL; Tang, N; Chen, J. (2012). Long-term exposure to ambient air pollution and respiratory disease mortality in Shenyang, China: A 12-year population-based retrospective cohort study. Respiration 84: 360-368. http://dx.doi.org/10.1159/000332930

Dorans, KS; Wilker, EH; Li, W; Rice, MB; Ljungman, PL; Schwartz, J; Coull, BA; Kloog, I; Koutrakis, P; D'Agostino, RB; Massaro, JM; Hoffmann, U; O'Donnell, CJ; Mittleman, MA. (2016). Residential proximity to major roads, exposure to fine particulate matter, and coronary artery calcium: The Framingham Heart Study. Arterioscler Thromb Vasc Biol 36: 1679-1685. 46 http://dx.doi.org/10.1161/ATVBAHA.116.307141

Duan, C; Talbott, E; Brooks, M; Park, SK; Broadwin, R; Matthews, K; Barinas-Mitchell, E. (2019a). Five-year exposure to PM2.5 and ozone and subclinical atherosclerosis in late midlife women: The Study of Women's Health Across the Nation. Int J Hyg Environ Health 222: 168-176. 50 http://dx.doi.org/10.1016/j.ijheh.2018.09.001

Duan, C; Talbott, EO; Broadwin, R; Brooks, M; Matthews, K; Barinas-Mitchell, E. (2019b). Residential exposure to PM2.5 and ozone and progression of subclinical atherosclerosis among women transitioning through menopause: The study of women's health across the nation. J Womens Health 28: 802-811. 54 http://dx.doi.org/10.1089/jwh.2018.7182

Dye, JA; Ledbetter, AD; Schladweiler, MC; Costa, DL; Kodavanti, UP. (2015). Whole body plethysmography reveals differential ventilatory responses to ozone in rat models of cardiovascular disease. Inhal Toxicol 27: 14-25. http://dx.doi.org/10.3109/08958378.2014.954167

Ebisu, K; Bell, ML. (2012). Airborne PM2.5 chemical components and low birth weight in the Northeastern and Mid-Atlantic regions of the United States. Environ Health Perspect 120: 1746-1752. http://dx.doi.org/10.1289/ehp.1104763.

Eckel, SP; Louis, TA; Chaves, PH; Fried, LP; Margolis, AH. (2012). Modification of the association between ambient air pollution and lung function by frailty status among older adults in the cardiovascular health study. Am J Epidemiol 176: 214-223. http://dx.doi.org/10.1093/aje/kws001

Eenhuizen, E; Gehring, U; Wijga, AH; Smit, HA; Fischer, PH; Brauer, M; Koppelman, GH; Kerkhof, M; de Jongste, JC; Brunekreef, B; Hoek, G. (2013). Traffic related air pollution is related to interrupter resistance in four-year old children. Eur Respir J 41: 1257-1263. http://dx.doi.org/10.1183/09031936.00020812.

Elder, A., Gelein, R., Silva, V., Feikert, T., Opanashuk, L., Carter, J., Potter, R., Maynard, A., Ito, Y., Finkelstein, J., & Oberdörster, G. (2006). Translocation of inhaled ultrafine manganese oxide particles to the CentralNervous system. Environmental Health Perspectives, 114(8), 1172–1178. https://doi.org/10.1289/ehp.9030

El Fakhri G, Kardan A, Sitek A, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with (82)Rb PET: comparison with (13)N-ammonia PET. J Nucl Med. 2009;50(7):1062-1071. doi:10.2967/jnumed.104.007831

Erickson, AC; Ostry, A; Chan, LHM; Arbour, L. (2016). The reduction of birth weight by fine particulate matter and its modification by maternal and neighbourhood-level factors: a multilevel analysis in British Columbia, Canada. Environ Health 15: 51. http://dx.doi.org/10.1186/s12940-016-0133-0.

Escamilla-Nuñez, MC; Barraza-Villarreal, A; Hernandez-Cadena, L; Moreno-Macias, H; Ramirez-Aguilar, M; Sienra-Monge, JJ; Cortez-Lugo, M; Texcalac, JL; del Rio-Navarro, B; Romieu, I. (2008). Traffic-related air pollution and respiratory symptoms among asthmatic children, resident in Mexico City: The EVA cohort study. Respir Res 9: 74. http://dx.doi.org/10.1186/1465-9921-9-74.

Elliott, EG; Laden, F; James, P; Rimm, EB; Rexrode, KM; Hart, JE. (2020). Interaction between Long-Term Exposure to Fine Particulate Matter and Physical Activity, and Risk of Cardiovascular Disease and Overall Mortality in US Women. Environ Health Perspect 128: 127012. http://dx.doi.org/10.1289/EHP7402

Elliott, P; Shaddick, G; Wakefield, JC; de Hoogh, C; Briggs, DJ. (2007). Long-term associations of outdoor air pollution with mortality in Great Britain. Thorax 62: 1088-1094. http://dx.doi.org/10.1136/thx.2006.076851

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: 11-19. http://dx.doi.org/10.1016/j.envres.2013.12.001.

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: 308-316. http://dx.doi.org/10.1093/aje/kws029.

Faiz, AS; Rhoads, GG; Demissie, K; Lin, Y; Kruse, L; Rich, DQ. (2013). Does ambient air pollution trigger stillbirth? Epidemiology 24: 538-544. http://dx.doi.org/10.1097/EDE.0b013e3182949ce5.

Fan, ZT; Meng, Q; Weisel, C; Laumbach, R; Ohman-Strickland, P; Shalat, S; Hernandez, MZ; Black, K. (2008). Acute exposure to elevated PM2.5 generated by traffic and cardiopulmonary health effects in healthy older adults. J Expo Sci Environ Epidemiol 19: 525-533. http://dx.doi.org/10.1038/jes.2008.46.

Farhat, J; Farhat, SC; Braga, AL; Cocuzza, M; Borba, EF; Bonfá, E; Silva, CA. (2016). Ozone decreases sperm quality in systemic lupus erythematosus patients. Revista Brasileira de Reumatologia 56: 212-219. http://dx.doi.org/10.1016/j.rbre.2015.08.005

Farraj, AK; Boykin, E; Ledbetter, A; Andrews, D; Gavett, SH. (2010). Increased lung resistance after diesel particulate and ozone co-exposure not associated with enhanced lung inflammation in allergic mice. Inhal Toxicol 22: 33-41. http://dx.doi.org/10.3109/08958370902862434.

Fauchier, L., Babuty, D., Melin, A., Bonnet, P., Cosnay, P., & Fauchier, J. P. (2004). Heart rate variability in severe right or left heart failure: The role of Pulmonary Hypertension and resistances. European Journal of Heart Failure, 6(2), 181–185. https://doi.org/10.1016/j.ejheart.2003.09.007

Finnbjornsdottir, R. G., Zoëga, H., Olafsson, O., Thorsteinsson, T., & Rafnsson, V. (2013). Association of air pollution and use of glyceryl trinitrate against angina pectoris: A population-based case-crossover study. Environmental Health, 12(1). https://doi.org/10.1186/1476-069x-12-38

Fleisch, AF; Gold, DR; Rifas-Shiman, SL; Koutrakis, P; Schwartz, JD; Kloog, I; Melly, S; Coull, BA; Zanobetti, A; Gillman, MW; Oken, E. (2014). Air pollution exposure and abnormal glucose tolerance during pregnancy: the project Viva cohort. Environ Health Perspect 122: 378-383. http://dx.doi.org/10.1289/ehp.1307065.

Fleisch, AF; Kloog, I; Luttmann-Gibson, H; Gold, DR; Oken, E; Schwartz, JD. (2016). Air pollution exposure and gestational diabetes mellitus among pregnant women in Massachusetts: a cohort study. Environ Health 15: 40. http://dx.doi.org/10.1186/s12940-016-0121-4.

Fleisch, AF; Rifas-Shiman, SL; Koutrakis, P; Schwartz, JD; Kloog, I; Melly, S; Coull, BA; Zanobetti, A; Gillman, MW; Gold, DR; Oken, E. (2015). Prenatal exposure to traffic pollution: associations with reduced fetal growth and rapid infant weight gain. Epidemiology 26: 43-50. http://dx.doi.org/10.1097/EDE.0000000000000203.

Fleischer. (2014). Erratum: Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health (EHP vol 122, pg 425, 2014). Environ Health Perspect 122: A151-A151. http://dx.doi.org/10.1289/ehp.122-A151.

Fleischer, NL; Merialdi, M; van Donkelaar, A; Vadillo-Ortega, F; Martin, RV; Betran, A; Souza, JP; O'Neill, MS. (2014). Outdoor Air Pollution, Preterm Birth, And Low Birth Weight: Analysis Of The World Health Organization Global Survey On Maternal And Perinatal Health. Environ Health Perspect 122: 425-430. http://dx.doi.org/10.1289/ehp.1306837.

Flores-Pajot, M.-C., Ofner, M., Do, M. T., Lavigne, E., & Villeneuve, P. J. (2016). Childhood autism spectrum disorders and exposure to nitrogen dioxide, and Particulate Matter Air Pollution: A Review and meta-analysis. Environmental Research, 151, 763–776. https://doi.org/10.1016/j.envres.2016.07.030

Fouladi F, Bailey MJ, Patterson WB, Sioda M, Blakley IC, Fodor AA, Jones RB, Chen Z, Kim JS, Lurmann F, Martino C, Knight R, Gilliland FD, Alderete TL. Air pollution exposure is associated with the gut

microbiome as revealed by shotgun metagenomic sequencing. Environ Int. 2020 May;138:105604. doi: 10.1016/j.envint.2020.105604. Epub 2020 Mar 2. PMID: 32135388; PMCID: PMC7181344.

Fry, RC; Rager, JE; Zhou, H; Zou, B; Brickey, JW; Ting, J; Lay, JC; Peden, DB; Alexis, NE. (2012). Individuals with increased inflammatory response to ozone demonstrate muted signaling of immune cell trafficking pathways. Respir Res 13: 89. http://dx.doi.org/10.1186/1465-9921-13-89

Frampton, MW; Pietropaoli, A; Dentler, M; Chalupa, D; Little, EL; Stewart, J; Frasier, L; Oakes, D; Wiltshire, J; Vora, R; Utell, MJ. (2015). Cardiovascular effects of ozone in healthy subjects with and without deletion of glutathione-S-transferase M1. Inhal Toxicol 27: 113-119. http://dx.doi.org/10.3109/08958378.2014.996272

Fuertes, E; Brauer, M; MacIntyre, E; et al. (2013a). Childhood allergic rhinitis, traffic-related air pollution, and variability in the GSTP1, TNF, TLR2, and TLR4 genes: Results from the TAG Study. J Allergy Clin Immunol 132: 342-352.e342. http://dx.doi.org/10.1016/j.jaci.2013.03.007.

Fuertes, E; Standl, M; Cyrys, J; Berdel, D; von Berg, A; Bauer, CP; Krämer, U; Sugiri, D; Lehmann, I; Koletzko, S; Carlsten, C; Brauer, M; Heinrich, J. (2013b). A longitudinal analysis of associations between traffic-related air pollution with asthma, allergies and sensitization in the GINIplus and LISAplus birth cohorts. Peer J 1: e193. http://dx.doi.org/10.7717/peerj.193.

Fuks, KB; Weinmayr, G; Foraster, M; et al. (2014). Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European study of cohorts for air pollution effects (ESCAPE) [Review]. Environ Health Perspect 122: 896-905. http://dx.doi.org/10.1289/ehp.1307725.

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: e004743. http://dx.doi.org/10.1136/bmjopen-2013-004743.

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: 721-727. http://dx.doi.org/10.1164/rccm.201211-2004OC.

Garcia, E; Berhane, KT; Islam, T; Mcconnell, R; Urman, R; Chen, Z; Gilliland, FD. (2019). Association of changes in air quality with incident asthma in children in California, 1993-2014. JAMA 321: 1906-1915. http://dx.doi.org/10.1001/jama.2019.5357

Garcia E, Marian B, Chen Z, et al. Long-term air pollution and COVID-19 mortality rates in California: Findings from the Spring/Summer and Winter surges of COVID-19. Environ Pollut. 2022;292(Pt B):118396. doi:10.1016/j.envpol.2021.118396

Gatto, NM; Henderson, VW; Hodis, HN; St John, JA; Lurmann, F; Chen, JC; Mack, WJ. (2014). Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology 40: 1-7. http://dx.doi.org/10.1016/j.neuro.2013.09.004

Gauderman, WJ; Avol, E; Gilliland, F; Vora, H; Thomas, D; Berhane, K; McConnell, R; Kuenzli, N; Lurmann, F; Rappaport, E; Margolis, H; Bates, D; Peters, J. (2004). The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 351: 1057-1067. http://dx.doi.org/10.1056/NEJMoa040610.

Gauderman, WJ; Gilliland, GF; Vora, H; Avol, E; Stram, D; McConnell, R; Thomas, D; Lurmann, F; Margolis, HG; Rappaport, EB; Berhane, K; Peters, JM. (2002). Association between air pollution and lung function growth in southern California children: results from a second cohort. Am J Respir Crit Care Med 166: 76-84. http://dx.doi.org/10.1164/rccm.2111021.

Gauderman, WJ; McConnell, R; Gilliland, F; London, S; Thomas, D; Avol, E; Vora, H; Berhane, K; Rappaport, EB; Lurmann, F; Margolis, HG; Peters, J. (2000). Association between air pollution and lung function growth in southern California children. Am J Respir Crit Care Med 162: 1383-1390. http://dx.doi.org/10.1164/ajrccm.162.4.9909096.

Gauderman, WJ; Urman, R; Avol, E; Berhane, K; McConnell, R; Rappaport, E; Chang, R; Lurmann, F; Gilliland, F. (2015). Association of improved air quality with lung development in children. N Engl J Med 372: 905-913. http://dx.doi.org/10.1056/NEJMoa1414123.

Geer, LA; Weedon, J; Bell, ML. (2012). Ambient air pollution and term birth weight in Texas from 1998 to 2004. J Air Waste Manag Assoc 62: 1285-1295. http://dx.doi.org/10.1080/10962247.2012.707632.

Gehring, U; Beelen, R; Eeftens, M; Hoek, G; de Hoogh, K; de Jongste, JC; Keuken, M; Koppelman, GH; Meliefste, K; Oldenwening, M; Postma, DS; van Rossem, L; Wang, M; Smit, HA; Brunekreef, B. (2015a). Particulate matter composition and respiratory health: the PIAMA Birth Cohort study. Epidemiology 26: 300-309. http://dx.doi.org/10.1097/EDE.0000000000000264.

Gehring, U; Gruzieva, O; Agius, RM; et al. (2013). Air pollution exposure and lung function in children: the ESCAPE project. Environ Health Perspect 121: 1357- 1364. http://dx.doi.org/10.1289/ehp.1306770.

Gehring, U; Tamburic, L; Sbihi, H; Davies, HW; Brauer, M. (2014). Impact of noise and air pollution on pregnancy outcomes. Epidemiology 25: 351-358. http://dx.doi.org/10.1097/EDE.0000000000000073.

Gehring, U; Wijga, AH; Brauer, M; Fischer, P; de Jongste, JC; Kerkhof, M; Oldenwening, M; Smit, HA; Brunekreef, B. (2010). Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 181: 596-603. http://dx.doi.org/10.1164/rccm.200906-0858OC.

Gehring, U; Wijga, AH; Fischer, P; de Jongste, JC; Kerkhof, M; Koppelman, GH; Smit, HA; Brunekreef, B. (2011). Traffic-related air pollution, preterm birth and term birth weight in the PIAMA birth cohort study. Environ Res 111: 125-135. http://dx.doi.org/10.1016/j.envres.2010.10.004.

Gehring, U; Wijga, AH; Hoek, G; et al.(2015b). Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study [Supplemental Data]. Lancet Respir Med 3: 933-942.http://dx.doi.org/10.1016/S2213-2600(15)004269.

Gent, JF; Triche, EW; Holford, TR; Belanger, K; Bracken, MB; Beckett, WS; Leaderer, BP. (2003). Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. JAMA 290: 1859- 1867. http://dx.doi.org/10.1001/jama.290.14.1859.

Getz, GS; Reardon, CA. (2012). Animal models of atherosclerosis [Review]. Arterioscler Thromb Vasc Biol 32: 1104-1115. http://dx.doi.org/10.1161/ATVBAHA.111.237693.

Ghio, AJ; Kim, C; Devlin, RB. (2000). Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am J Respir Crit Care Med 162: 981-988.

Ghio, AJ; Soukup, JM; Dailey, LA; Richards, JH; Duncan, KE; Lehmann, J. (2014). Iron decreases biological effects of ozone exposure. Inhal Toxicol 26: 391-399. http://dx.doi.org/10.3109/08958378.2014.908330

Ghosh, J. K., J. E. Heck, M. Cockburn, J. Su, M. Jerrett and B. Ritz (2013). "Prenatal exposure to traffic-related air pollution and risk of early childhood cancers." Am J Epidemiol 178(8): 1233-1239.

Ghosh, J. K., M. Wilhelm, J. Su, D. Goldberg, M. Cockburn, M. Jerrett and B. Ritz (2012). "Assessing the influence of traffic-related air pollution on risk of term low birth weight based on land-use-based regression models and measures of air toxics." Am J Epidemiol 175(12): 1262-1274.

Gianicolo, EAL; Mangia, C; Cervino, M; Bruni, A; Andreassi, MG; Latini, G. (2014). Congenital anomalies among live births in a high environmental risk area-A case-control study in Brindisi (southern Italy). Environ Res 128: 9-14. http://dx.doi.org/10.1016/j.envres.2013.11.002

Gilliland, F; Avol, E; McConnell, R; K, B; Gauderman, WJ; Lurmann, FW; Urnam, R; Change, R; Rappaport, EB; Howland, S. (2017). The effects of policy-driven air quality improvements on childrens respiratory health [HEI]. (Research Report 190). Boston, MA: Health Effects Institute. https://www.healtheffects.org/system/files/GillilandRR190.pdf

Gilliland, F. D., K. Berhane, E. B. Rappaport, D. C. Thomas, E. Avol, W. J. Gauderman, S. J. London, H. G. Margolis, R. McConnell, K. T. Islam and J. M. Peters (2001). "The effects of ambient air pollution on school absenteeism due to respiratory illnesses." Epidemiology 12(1): 43-54.

Giorgis-Allemand, L; Pedersen, M; Bernard, C; et al. (2017). The influence of meteorological factors and atmospheric pollutants on the risk of preterm birth. Am J Epidemiol 185: 247-258. http://dx.doi.org/10.1093/aje/kww141.

Gleason, JA; Fagliano, JA. (2015). Associations of daily pediatric asthma emergency department visits with air pollution in Newark, NJ: utilizing time-series and case-crossover study designs. J Asthma 52: 815-822.

Godleski, JJ; Verrier, RL; Koutrakis, P; Catalano, P; Coull, B; Reinisch, U; Lovett, EG; Lawrence, J; Murthy, GG; Wolfson, JM; Clarke, RW; Nearing, BD; Killingsworth, C. (2000). Mechanisms of morbidity and mortality from exposure to ambient air particles [Review]. Res Rep Health Eff Inst 91: 5-88; discussion 89- 103

Gong, H, Jr; Linn, WS; Clark, KW; Anderson, KR; Sioutas, C; Alexis, NE; Cascio, WE; Devlin, RB. (2008). Exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in Los Angeles. Inhal Toxicol 20: 533-545. http://dx.doi.org/10.1080/08958370801911340.

Gong, H, Jr; 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: 305-325. http://dx.doi.org/10.1080/08958370304455.

Gong, H, Jr; Linn, WS; Terrell, SL; Anderson, KR; Clark, KW. (2001). Anti-inflammatory and lung function effects of montelukast in asthmatic volunteers exposed to sulfur dioxide. Chest 119: 402-408. http://dx.doi.org/10.1378/chest.119.2.402

Gong, H, Jr; Sioutas, C; Linn, WS; Clark, KW; Terrell, SL; Terrell, LL; Anderson, KR; Kim, S; Chang, MC. (2000). Controlled human exposures to concentrated ambient fine particles in metropolitan Los Angeles:

methodology and preliminary health-effect findings. http://dx.doi.org/10.1080/0895-8378.1987.11463186.

Gong, H., Simmons, M. S., Linn, W. S., McDonnell, W. F., & Westerdahl, D. (1998). Relationship between acute ozone responsiveness and chronic loss of lung function in residents of a high-ozone community. Archives of Environmental Health: An International Journal, 53(5), 313–319. https://doi.org/10.1080/00039899809605715

Goodrich, AJ; Volk, HE; Tancredi, DJ; Mcconnell, R; Lurmann, FW; Hansen, RL; Schmidt, RJ. (2017). Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. Autism Res 11: 69-80. http://dx.doi.org/10.1002/aur.1885

Goodson, WH; Lowe, L; Carpenter, DO; et al. (2015). Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead [Review]. Carcinogenesis 36 Suppl 1: S254-S296. http://dx.doi.org/10.1093/carcin/bgv039.

Gordon, CJ; Jarema, KA; Lehmann, J. R.; Ledbetter, AD; Schladweiler, MC; Schmid, JE; Ward, WO; Kodavanti, UP; Nyska, A; Macphail, RC. (2013). Susceptibility of adult and senescent Brown Norway rats to repeated ozone exposure: an assessment of behavior, serum biochemistry and cardiopulmonary function. Inhal Toxicol 25: 141-159. http://dx.doi.org/10.3109/08958378.2013.764946

Gordon, T; Nadziejko, C; Chen, LC; Schlesinger, R. (2000). Effects of concentrated ambient particles in rats and hamsters: An exploratory study [HEI]. (Research Report 93). Cambridge, MA: Health Effects Institute. https://www.healtheffects.org/system/files/Gordon.pdf.

Gordon, CJ; Phillips, PM; Beasley, TE; Ledbetter, A; Aydin, C; Snow, SJ; Kodavanti, UP; Johnstone, AF. (2016a). Pulmonary sensitivity to ozone exposure in sedentary versus chronically trained, female rats. Inhal Toxicol 28: 293-302. http://dx.doi.org/10.3109/08958378.2016.1163441

Gordon, CJ; Phillips, PM; Johnstone, AFM; Beasley, TE; Ledbetter, AD; Schladweiler, MC; Snow, SJ; Kodavanti, UP. (2016b). Effect of high-fructose and high-fat diets on pulmonary sensitivity, motor activity, and body composition of brown Norway rats exposed to ozone. Inhal Toxicol 28: 203-215. http://dx.doi.org/10.3109/08958378.2015.1134730

Gordon, CJ; Phillips, PM; Ledbetter, A; Snow, SJ; Schladweiler, MC; Johnstone, AF; Kodavanti, UP. (2017b). Active vs. sedentary lifestyle from weaning to adulthood and susceptibility to ozone in rats. Am J Physiol Lung Cell Mol Physiol 312: L100-L109. http://dx.doi.org/10.1152/ajplung.00415.2016

Götschi, T; Sunyer, J; Chinn, S; de Marco, R; Forsberg, B; Gauderman, JW; Garcia-Esteban, R; Heinrich, J; Jacquemin, B; Jarvis, D; Ponzio, M; Villani, S; Künzli, N. (2008). Air pollution and lung function in the European Community Respiratory Health Survey. Int J Epidemiol 37: 1349-1358. http://dx.doi.org/10.1093/ije/dyn136.

Graff, D; Cascio, W; Rappold, A; Zhou, H; Huang, Y; Devlin, R. (2009). Exposure to concentrated coarse air pollution particles causes mild cardiopulmonary effects in healthy young adults. Environ Health Perspect 117: 1089-1094. http://dx.doi.org/10.1289/ehp0900558.

Gray, SC; Edwards, SE; Miranda, ML. (2010). Assessing exposure metrics for PM and birth weight models. J Expo Sci Environ Epidemiol 20: 469-477. http://dx.doi.org/10.1038/jes.2009.52.

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: 4. http://dx.doi.org/10.1186/1476- 069X-13-4.

Gray, SC; Gelfand, AE; Miranda, ML. (2011). Hierarchical spatial modeling of uncertainty in air pollution and birth weight study. Stat Med 30: 2187-2198. http://dx.doi.org/10.1002/sim.4234.

Green, R; Broadwin, R; Malig, B; Basu, R; Gold, EB; Qi, L; Sternfeld, B; Bromberger, JT; Greendale, GA; Kravitz, HM; Tomey, K; Matthews, K; Derby, C; Jackson, EA; Green, R; Ostro, B. (2015). Long-and short-term exposure to air pollution and inflammatory/hemostatic markers in midlife women. Epidemiology 27: 211- 7   220. http://dx.doi.org/10.1097/EDE.0000000000000421

Green, R; Broadwin, R; Malig, B; Basu, R; Gold, EB; Qi, L; Sternfeld, B; Bromberger, JT; Greendale, GA; Kravitz, HM; Tomey, K; Matthews, K; Derby, C; Jackson, EA; Green, R; Ostro, B. (2015). Long-and short-term exposure to air pollution and inflammatory/hemostatic markers in midlife women. Epidemiology 27: 211-220. http://dx.doi.org/10.1097/EDE.0000000000000421

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: 874-882. http://dx.doi.org/10.1093/aje/kwu460.

Greenberg, M. I., J. A. Curtis and D. Vearrier (2013). "The perception of odor is not a surrogate marker for chemical exposure: a review of factors influencing human odor perception." Clin Toxicol (Phila) 51(2): 70-76.

Greer, JR; Abbey, DE; Burchette, RJ. (1993). Asthma related to occupational and ambient air pollutants in nonsmokers. J Occup Environ Med 35: 909-915. http://dx.doi.org/10.1097/00043764- 199309000-00014

Gruzieva, O; Gehring, U; Aalberse, R; et al. (2014). Meta- analysis of air pollution exposure association withallergic sensitization in European birth cohorts. J Allergy Clin Immunol 133: 767 http://dx.doi.org/10.1016/j.jaci.2013.07.048.

Guarnieri, M. and J. R. Balmes (2014). "Outdoor air pollution and asthma." Lancet 383(9928): 1581-1592.

Guo, L; Byun, H; Zhong, J, ia; Motta, V; Barupal, J; Zheng, Y; Dou, C; Zhang, F; Mccracken, JP; Diaz, A; Marco, SG; Colicino, S; Schwartz, J; Wang, S; Hou, L; Baccarelli, AA. (2014). Effects of short-term exposure to inhalable particulate matter on DNA methylation of tandem repeats. Environ Mol Mutagen 55: 322-335. http://dx.doi.org/10.1002/em.21838.

Guo, Y; Zeng, H; Zheng, R; Li, S; Barnett, AG; Zhang, S; Zou, X; Huxley, R; Chen, W; Williams, G. (2016). The association between lung cancer incidence and ambient air pollution in China: A spatiotemporal analysis. Environ Res 144: 60-65. http://dx.doi.org/10.1016/j.envres.2015.11.004

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 134C: 198-204. http://dx.doi.org/10.1016/j.envres.2014.08.002

Ha, S; Zhu, Y; Liu, D; Sherman, S; Mendola, P. (2017). Ambient temperature and air quality in relation to small for gestational age and term low birthweight. Environ Res 155: 394-400. http://dx.doi.org/10.1016/j.envres.2017.02.021.

Haberzettl, P; Lee, J; Duggineni, D; McCracken, J; Bolanowski, D; O'Toole, TE; Bhatnagar, A; Conklin, DJ. (2012). Exposure to ambient air fine particulate matter prevents VEGF-induced mobilization of endothelial progenitor cells from the bone marrow. Environ Health Perspect 120: 848-856. http://dx.doi.org/10.1289/ehp.1104206.

Haberzettl, P; McCracken, JP; Bhatnagar, A; Conklin, DJ. (2016). Insulin sensitizers prevent fine particulate matter-induced vascular insulin resistance and changes in endothelial progenitor cell homeostasis. Am J Physiol Heart Circ Physiol 310: H1423-H1438. http://dx.doi.org/10.1152/ajpheart.00369.2015.

Hamra, GB; Guha, N; Cohen, A; Laden, F; Raaschou-Nielsen, O; Samet, JM; Vineis, P; Forastiere, F; Saldiva, P; Yorifuji, T; Loomis, D. (2014). Outdoor particulate matter exposure and lung cancer: A systematic review and meta-analysis [Review]. Environ Health Perspect 122: 906-911. http://dx.doi.org/10.1289/ehp.1408092.

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: 42. http://dx.doi.org/10.1186/1476-069X-8-42.

Halonen, JI; Lanki, T; Yli-Tuomi, T; Tiittanen, P; Kulmala, M; Pekkanen. (2009). Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among the elderly. Epidemiology 20: 143-153. http://dx.doi.org/10.1097/EDE.0b013e31818c7237.

Halonen, JI; Lanki, T; Yli-Tuomi, T; Kulmala, M; Tiittanen, P; Pekkanen, J. (2008). Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax 63: 635-641. http://dx.doi.org/10.1136/thx.2007.091371.

Halonen, JI; Lanki, T; Yli-Tuomi, T; Tiittanen, P; Kulmala, M; Pekkanen. (2009b). Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among the elderly. Epidemiology 20: 143-153. http://dx.doi.org/10.1097/EDE.0b013e31818c7237.

Hannam, K; Mcnamee, R; Baker, P; Sibley, C; Agius, R. (2014). Air pollution exposure and adverse pregnancy outcomes in a large UK birth cohort: use of a novel spatio-temporal modelling technique. Scand J Work Environ Health 40: 518-530. http://dx.doi.org/10.5271/sjweh.3423.

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: 203-209. http://dx.doi.org/10.1289/ehp.0901022.

Hansen, JS; Nørgaard, AW; Koponen, IK; Sørli, JB; Paidi, MD; Hansen, SW; Clausen, PA; Nielsen, GD; Wolkoff, P; Larsen, ST. (2016). Limonene and its ozone-initiated reaction products attenuate allergic lung inflammation in mice. J Immunotoxicol 13: 793-803. http://dx.doi.org/10.1080/1547691X.2016.1195462

Hao, H; Chang, HH; Holmes, HA; Mulholland, JA; Klein, M; Darrow, LA; Strickland, MJ. (2016). Air pollution and preterm birth in the U.S. state of Georgia (2002-2006): Associations with concentrations of 11 ambient air pollutants estimated by combining community multiscale air quality model (CMAQ) simulations with stationary monitor measurements. Environ Health Perspect 124: 875-880. http://dx.doi.org/10.1289/ehp.1409651.

Harley, R. (2014). "On-Road Measurement of Emissions from Heavy-Duty Diesel Trucks: Impacts of Fleet Turnover and ARB's Drayage Truck Regulation, Final Report." Sacramento, CA California Air Resources Board. Contract No. 09-340.

Harre, ESM; Price, PD; Ayrey, RB; Toop, LJ; Martin, IR; Town, GI. (1997). Respiratory effects of air pollution in chronic obstructive pulmonary disease: A three month prospective study. Thorax 52: 1040-1044. http://dx.doi.org/10.1136/thx.52.12.1040

Haro, R; Paz, C. (1993). Effects of ozone exposure during pregnancy on ontogeny of sleep in rats. Neurosci Lett 164: 67-70. http://dx.doi.org/10.1016/0304-3940(93)90859-J

Harris, G; Thompson, WD; Fitzgerald, E; Wartenberg, D. (2014). The association of PM2.5 with full term low birth weight at different spatial scales. Environ Res 134C: 427-434. http://dx.doi.org/10.1016/j.envres.2014.05.034.Hart, JE; Liao, X; Hong, B; Puett, RC; Yanosky, JD; Suh, H; Kioumourtzoglou, MA; Spiegelman, D; Laden, F. (2015a). The association of long-term exposure to PM2.5 on all-cause mortality in the Nurses' Health Study and the impact of measurement-error correction. Environ Health 14: 38. http://dx.doi.org/10.1186/s12940- 015-0027-6.

Hart, C. L., G. D. Smith, D. J. Hole, and V. M. Hawthorne (2006). "Carboxyhaemoglobin concentration, smoking habit, and mortality in 25 years in the Renfrew/Paisley prospective cohort study." Heart 92(3): 321-324.

Hart, JE; Garshick, E; Dockery, DW; Smith, TJ; Ryan, L; Laden, F. (2011). Long-term ambient multi-pollutant exposures and mortality. Am J Respir Crit Care Med 183: 73-78. http://dx.doi.org/10.1164/rccm.200912- 1903OC

Hart, JE; Puett, RC; Rexrode, KM; Albert, CM; Laden, F. (2015b). Effect modification of long-term air pollution exposures and the risk of incident cardiovascular disease in US women. J Am Heart Assoc 4. http://dx.doi.org/10.1161/JAHA.115.002301.

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. http://dx.doi.org/10.1161/JAHA.116.003947.

Hasunuma, H; Ishimaru, Y; Yoda, Y; Shima, M. (2014). Decline of ambient air pollution levels due to measures to control automobile emissions and effects on the prevalence of respiratory and allergic disorders among children in Japan. Environ Res 131: 111-118. http://dx.doi.org/10.1016/j.envres.2014.03.007.

Hatch, GE; Mckee, J; Brown, J; Mcdonnell, W; Seal, E; Soukup, J; Slade, R; Crissman, K; Devlin, R. (2013). Biomarkers of dose and effect of inhaled ozone in resting versus exercising human subjects: Comparison with resting rats. Biomarker Insights 8: 53-67. http://dx.doi.org/10.4137/BMI.S11102

Hatch, GE; Slade, R; Harris, LP; Mcdonnell, WF; Devlin, RB; Koren, HS; Costa, DL; Mckee, J. (1994). Ozone dose and effect in humans and rats: A comparison using oxygen-18 labeling and bronchoalveolar lavage. Am J Respir Crit Care Med 150: 676-683. http://dx.doi.org/10.1164/ajrccm.150.3.8087337

He, M; Ichinose, T; Song, Y; Yoshida, Y; Arashidani, K; Yoshida, S; Liu, B; Nishikawa, M; Takano, H; Sun, G. (2013a). Effects of two Asian sand dusts transported from the dust source regions of Inner Mongolia and northeast China on murine lung eosinophilia. Toxicol Appl Pharmacol 272: 647-655. http://dx.doi.org/10.1016/j.taap.2013.07.010.

He, M; Ichinose, T; Yoshida, S; Takano, H; Nishikawa, M; Mori, I; Sun, G; Shibamoto, T. (2012). Aggravating effects of Asian sand dust on lung eosinophilia in mice immunized beforehand by ovalbumin. Inhal Toxicol 24: 751-761. http://dx.doi.org/10.3109/08958378.2012.716870.

He, M; Ichinose, T; Yoshida, S; Takano, H; Nishikawa, M; Sun, G; Shibamoto, T. (2013b). Induction of immune tolerance and reduction of aggravated lung eosinophilia by co-exposure to Asian sand dust and ovalbumin for 14 weeks in mice. Allergy Asthma Clin Immunol 9: 19. http://dx.doi.org/10.1186/1710-1492-9-19.

He, F; Shaffer, M; Rodriguez-Colon, S; Yanosky, J; Bixler, E; Cascio, W; Liao, D. (2011). Acute effects of fine particulate air pollution on cardiac arrhythmia-The APACR Study. Environ Health Perspect 119: 927-932. http://dx.doi.org/10.1289/ehp.1002640.

Heaney, C. D., S. Wing, R. L. Campbell, D. Caldwell, B. Hopkins, D. Richardson and K. Yeatts (2011). "Relation between malodor, ambient hydrogen sulfide, and health in a community bordering a landfill." Environ Res 111(6): 847-852.

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: 1385-1391. http://dx.doi.org/10.1289/ehp.1306761.

Henneberger, A; Zareba, W; Ibald-Mulli, A; Rückerl, R; Cyrys, J; Couderc, JP; Mykins, B; Woelke, G; Wichmann, HE; Peters, A. (2005). Repolarization changes induced by air pollution in ischemic heart disease patients. Environ Health Perspect 113: 440-446. http://dx.doi.org/10.1289/ehp.7579

Henriquez, AR; Snow, SJ; Schladweiler, MC; Miller, CN; Dye, JA; Ledbetter, AD; Richards, JE; Mauge-Lewis, K; Mcgee, MA; Kodavanti, UP. (2017). Adrenergic and glucocorticoid receptor antagonists reduce ozone-induced lung injury and inflammation. Toxicol Appl Pharmacol 339: 161-171. http://dx.doi.org/10.1016/j.taap.2017.12.006

Herr, CE; Dostal, M; Ghosh, R; Ashwood, P; Lipsett, M; Pinkerton, KE; Sram, R; Hertz-Picciotto, I. (2010). Air pollution exposure during critical time periods in gestation and alterations in cord blood lymphocyte distribution: A cohort of livebirths. Environ Health 9: 46. http://dx.doi.org/10.1186/1476-069X-9-46.

Hildebrandt, K; Rückerl, R; Koenig, W; Schneider, A; Pitz, M; Heinrich, J; Marder, V; Frampton, M; Oberdörster, G; Wichmann, HE; Peters, A. (2009). Short-term effects of air pollution: A panel study of blood markers in patients with chronic pulmonary disease. Part Fibre Toxicol 6: 25. http://dx.doi.org/10.1186/1743- 8977-6-25.

Hicken, MT; Adar, SD; Diez Roux, AV; O'Neill, MS; Magzamen, S; Auchincloss, AH; Kaufman, JD. (2013). Do psychosocial stress and social disadvantage modify the association between air pollution and blood pressure?: the multi-ethnic study of atherosclerosis. Am J Epidemiol 178: 1550-1562. http://dx.doi.org/10.1093/aje/kwt190.

Higgins, JP. (2008). Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified [Comment]. Int J Epidemiol 37: 1158-1160. http://dx.doi.org/10.1093/ije/dyn204.

Higgins, ITT; D'Arcy, JB; Gibbons, DI; Avol, EL; Gross, KB. (1990). Effect of exposures to ambient ozone on ventilatory lung function in children. Am J Respir Crit Care Med 141: 1136-1146. http://dx.doi.org/10.1164/ajrccm/141.5_Pt_1.1136

Hoffmann, B; Weinmayr, G; Hennig, F; Fuks, K; Moebus, S; Weimar, C; Dragano, N; Hermann, DM; Kaelsch, H; Mahabadi, AA; Erbel, R; Joeckel, KH. (2015). Air quality, stroke, and coronary events results of the Heinz Nixdorf Recall study from the Ruhr region. Deutsches Ärzteblatt International 112: 195-U123. http://dx.doi.org/10.3238/arztebl.2015.0195.

Hoffmeyer, F; Sucker, K; Monsé, C; Berresheim, H; Rosenkranz, N; Jettkant, B; Beine, A; Brüning, T; Bünger, J. (2013). Relationship of pulmonary function response to ozone exposure and capsaicin cough sensitivity. Inhal Toxicol 25: 569-576. http://dx.doi.org/10.3109/08958378.2013.812699

Hooiveld, M., C. van Dijk, F. van der Sman-de Beer, L. A. Smit, M. Vogelaar, I. M. Wouters, D. J. Heederik and C. J. Yzermans (2015). "Odour annoyance in the neighborhood of livestock farming - perceived health and health care seeking behaviour." Ann Agric Environ Med 22(1): 55-61.

Hong, YC; Pan, XC; Kim, SY; Park, K; Park, EJ; Jin, X; Yi, SM; Kim, YH; Park, CH; Song, S; Kim, H. (2010). Asian Dust Storm and pulmonary function of school children in Seoul. Sci Total Environ 408: 754-759. http://dx.doi.org/10.1016/j.scitotenv.2009.11.015.

Holguin, F; Flores, S; Ross, Z; Cortez, M; Molina, M; Molina, L; Rincon, C; Jerrett, M; Berhane, K; Granados, A; Romieu, I. (2007). Traffic-related exposures, airway function, inflammation, and respiratory symptoms in children. Am J Respir Crit Care Med 176: 1236-1242. http://dx.doi.org/10.1164/rccm.200611-1616OC.

Horstman, DH; Ball, BA; Brown, J; Gerrity, T; Folinsbee, LJ. (1995). Comparison of pulmonary responses of asthmatic and nonasthmatic subjects performing light exercise while exposed to a low level of ozone. Toxicol Ind Health 11: 369-385. http://dx.doi.org/10.1177/074823379501100401

Horstman, DH; Folinsbee, LJ; Ives, PJ; Abdul-Salaam, S; Mcdonnell, WF. (1990). Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. Am J Respir Crit Care Med 142: 1158-1163. http://dx.doi.org/10.1164/ajrccm/142.5.1158

Horstman, D; Roger, LJ; Kehrl, H; Hazucha, M. (1986). Airway sensitivity of asthmatics to sulfur dioxide. Toxicol Ind Health 2: 289-298.

Host, S; Larrieu, S; Pascal, L; Blanchard, M; Declercq, C; Fabre, P; Jusot, JF; Chardon, B; Le Tertre, A; Wagner, V; Prouvost, H; Lefranc, A. (2008). Short-term associations between fine and coarse particles and hospital admissions for cardiorespiratory diseases in six French cities. Occup Environ Med 65: 544-551. http://dx.doi.org/10.1136/oem.2007.036194.

Hou, HY; Wang, D; Zou, XP; Yang, ZH; Li, TC; Chen, YQ. (2014). Does ambient air pollutants increase the risk of fetal loss? A case-control study. Arch Gynecol Obstet 289: 285-291. http://dx.doi.org/10.1007/s00404-013- 2962-1

Hsieh, YL; Yang, YH; Wu, TN; Yang, CY. (2010). Air pollution and hospital admissions for myocardial infarction in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A 73: 757-765. http://dx.doi.org/10.1080/15287391003684789

Hsu, WH; Hwang, SA; Kinney, PL; Lin, S. (2017). Seasonal and temperature modifications of the association between fine particulate air pollution and cardiovascular hospitalization in New York state. Sci Total Environ 578: 626-632. http://dx.doi.org/10.1016/j.scitotenv.2016.11.008.

Huang, YC; 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: 790-797. http://dx.doi.org/10.3109/08958378.2012.718809.

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: 853-859. http://dx.doi.org/10.1289/ehp.1408456.

Hu, H; Ha, S; Roth, J; Kearney, G; Talbott, EO; Xu, X. (2014). Ambient air pollution and hypertensive disorders of pregnancy: a systematic review and meta-analysis. Atmos Environ 97: 336-345. http://dx.doi.org/10.1016/j.atmosenv.2014.08.027.

Huang, YCT; Ghio, AJ; Stonehuerner, J; McGee, J; Carter, JD; Grambow, SC; Devlin, RB. (2003). The role of soluble components in ambient fine particles-induced changes in human lungs and blood. Inhal Toxicol 15: 327-342. http://dx.doi.org/10.1080/08958370304460.

Huang, S., Li, H., Wang, M., Qian, Y., Steenland, K., Caudle, W. M., Liu, Y., Sarnat, J., Papatheodorou, S., & Shi, L. (2021). Long-term exposure to nitrogen dioxide and mortality: A systematic review and meta-analysis. Science of The Total Environment, 776, 145968. https://doi.org/10.1016/j.scitotenv.2021.145968

Huttunen, K; Siponen, T; Salonen, I; et al. (2012). Low- level exposure to ambient particulate matter is associated with systemic inflammation in ischemic heart disease patients. Environ Res 116: 44-51. http://dx.doi.org/10.1016/j.envres.2012.04.004.

Hwang, BF; Chen, YH; Lin, YT; Wu, XT; Lee, YL. (2015). Relationship between exposure to fine particulates and ozone and reduced lung function in children. Environ Res 137: 382-390. http://dx.doi.org/10.1016/j.envres.2015.01.009.

Hwang, BF; Lee, YL; Jaakkola, JJ. (2011). Air pollution and stillbirth: A population-based case-control study in Taiwan. Environ Health Perspect 119: 1345-1349. http://dx.doi.org/10.1289/ehp.1003056

Hwang, SL; Lin, YC; Guo, SE; Chou, CT; Lin, CM; Chi, MC. (2017). Fine particulate matter on hospital admissions for acute exacerbation of chronic obstructive pulmonary disease in southwestern Taiwan during 2006-2012. Int J Environ Health Res 27: 95-105. http://dx.doi.org/10.1080/09603123.2017.1278748.

Hyder, A; Lee, H; Ebisu, K; Koutrakis, P; Belanger, K; Bell, M. (2014). PM2.5 exposure and birth outcomes use of satellite- and monitor-based data. Epidemiology 25: 58-67. http://dx.doi.org/10.1097/EDE.0000000000000027.

Hystad, P; Demers, PA; Johnson, KC; Brook, J; van Donkelaar, A; Lamsal, L; Martin, R; Brauer, M. (2012). Spatiotemporal air pollution exposure assessment for a Canadian population-based lung cancer case-control study. Environ Health 11: 22. http://dx.doi.org/10.1186/1476-069X-11-22.

Hystad, P; Demers, PA; Johnson, KC; Carpiano, RM; Brauer, M. (2013). Long-term residential exposure to air pollution and lung cancer risk. Epidemiology 24: 762-772. http://dx.doi.org/10.1097/EDE.0b013e3182949ae7.

International Agency for Research on Cancer. (1989). "Diesel and Gasoline Engines Exhaust and Some Nitroarenes." IARC Monographs of the Evaluation of Carcinogenic Risk to Humans Lyon, France International Agency for Research on Cancer. Volume 46.

International Agency for Research on Cancer. (2012a). "Chemical Agents and Related Occupations." IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Lyon, France International Agency for Research on Cancer. 100F, from http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php.

International Agency for Research on Cancer. (2012b). "Diesel and Gasoline Engines Exhaust and Some Nitroarenes." IARC Monographs of the Evaluation of Carcinogenic Risk to Humans Lyon, France International Agency for Research on Cancer. 105.

Iskandar, A; Andersen, ZJ; Bønnelykke, K; Ellermann, T; Andersen, KK; Bisgaard, H. (2012). Coarse and fine particles but not ultrafine particles in urban air trigger hospital admission for asthma in children. Thorax 67: 252-257. http://dx.doi.org/10.1136/thoraxjnl-2011-200324.

Islam, T., K. Berhane, R. McConnell, W. J. Gauderman, E. Avol, J. M. Peters and F. D. Gilliland (2009). "Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children." Thorax 64(3): 197-202.

Islam, T; Gauderman, WJ; Berhane, K; Mcconnell, R; Avol, E; Peters, JM; Gilliland, FD. (2007). The relationship between air pollution, lung function and asthma in adolescents. Thorax 62: 957-963. http://dx.doi.org/10.1136/thx.2007.078964.

Islam, T; Mcconnell, R; Gauderman, WJ; Avol, E; Peters, JM; Gilliland, FD. (2008). Ozone, oxidant defense genes and risk of asthma during adolescence. Am J Respir Crit Care Med 177: 388-395. http://dx.doi.org/10.1164/rccm.200706-863OC

Ito, K; Mathes, R; Ross, Z; Nádas, A; Thurston, G; Matte, T. (2011). Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. Environ Health Perspect 119: 467-473. http://dx.doi.org/10.1289/ehp.1002667.

Jacobson, LD; Hacon, SD; Castro, HA; Ignotti, E; Artaxo, P; Ponce de Leon, AC. (2012). Association between fine particulate matter and the peak expiratory flow of schoolchildren in the Brazilian subequatorial Amazon: A panel study. Environ Res 117: 27-35. http://dx.doi.org/10.1016/j.envres.2012.05.006.

Jacquemin, B., F. Kauffmann, I. Pin, N. Le Moual, J. Bousquet, F. Gormand, J. Just, R. Nadif, C. Pison, D. Vervloet, N. Kunzli and V. Siroux (2012). "Air pollution and asthma control in the Epidemiological study on the Genetics and Environment of Asthma." J Epidemiol Community Health 66(9): 796-802.

Jacquemin, B; Siroux, V; Sanchez, M; et al. (2015). Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). Environ Health Perspect 123: 613-621. http://dx.doi.org/10.1289/ehp.1408206.

Janssen, NAH; Fischer, P; Marra, M; Ameling, C; Cassee, FR. (2013). Short-term effects of PM2.5, PM10 and PM2.5-10 on daily mortality in the Netherlands. Sci Total Environ 463: 20-26. http://dx.doi.org/10.1016/j.scitotenv.2013.05.062.

Janssen, BG; Saenen, ND; Roels, HA; Madhloum, N; Gyselaers, W; Lefebvre, W; Penders, J; Vanpoucke, C; Vrijens, K; Nawrot, TS. (2016). Fetal thyroid function, birth weight, and in utero exposure to fine particle air pollution: A birth cohort study. Environ Health Perspect 125: 699-705. http://dx.doi.org/10.1289/EHP508.

Jedlinska-Krakowska, M; Bomba, G; Jakubowski, K; Rotkiewicz, T; Jana, B; Penkowskii, A. (2006a). Impact of oxidative stress and supplementation with vitamins E and C on testes morphology in rats. J Reprod Dev 52: 203-209.

Jedlinska-Krakowska, M; Gizejewski, Z; Dietrich, GJ; Jakubowski, K; Glogowski, J; Penkowski, A. (2006b). The effect of increased ozone concentrations in the air on selected aspects of rat reproduction. Pol J Vet Sci 9: 11-16.

Jedrychowski, W; Perera, F; Mrozek-Budzyn, D; Flak, E; Mroz, E; Sochacka-Tatara, E; Jacek, R; Kaim, I; Skolicki, Z; Spengler, JD. (2010). Higher fish consumption in pregnancy may confer protection against the harmful effect of prenatal exposure to fine particulate matter. Ann Nutr Metab 56: 119-126. http://dx.doi.org/10.1159/000275918.

Jedrychowski, WA; Perera, FP; Maugeri, U; Spengler, J; Mroz, E; Flak, E; Stigter, L; Majewska, R; Kaim, I; Sowa, A; Jacek, R. (2012). Prohypertensive effect of gestational personal exposure to fine particulate matter. prospective cohort study in non-smoking and non-obese pregnant women. Cardiovasc Toxicol 12: 216-225. http://dx.doi.org/10.1007/s12012-012-9157-z.

Jerrett, M; Brook, R; White, LF; Burnett, RT; Yu, J; Su, J; Seto, E; Marshall, J; Palmer, JR; Rosenberg, L; Coogan, PF. (2017). Ambient ozone and incident diabetes: A prospective analysis in a large cohort of African American women. Environ Int 102: 42-47. http://dx.doi.org/10.1016/j.envint.2016.12.011

Jerrett, M; Burnett, RT; Beckerman, BS; Turner, MC; Krewski, D; Thurston, G; Martin, RV; van Donkelaar, A; Hughes, E; Shi, Y; Gapstur, SM; Thun, MJ; Pope, CA, III. (2013). Spatial analysis   of air pollution and mortality in California. Am J Respir Crit Care Med 188: 593-599. http://dx.doi.org/10.1164/rccm.201303-0609OC

Jerrett, M; Burnett, RT; Pope, CA, III; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. (2009). Long-term ozone exposure and mortality. N Engl J Med 360: 1085-1095. http://dx.doi.org/10.1056/NEJMoa0803894

Jerrett, M., K. Shankardass, K. Berhane, et al. (2008). "Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement." Environ Health Perspect 116(10): 1433-1438.

Jerrett, M; Turner, MC; Beckerman, BS; et al. (2016). Comparing the health effects of ambient particulate matter estimated using ground-based versus remote sensing exposure estimates. Environ Health Perspect 125: 552-559. http://dx.doi.org/10.1289/EHP575.

Jhun, I; Fann, N; Zanobetti, A; Hubbell, B. (2014). Effect modification of ozone-related mortality risks by temperature in 97 US cities. Environ Int 73: 128-134. http://dx.doi.org/10.1016/j.envint.2014.07.009

Jo H, Eckel SP, Wang X, et al. Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. Environ Pollut. 2019;254(Pt A):113010. doi:10.1016/j.envpol.2019.113010

Johns, DO; Svendsgaard, D; Linn, WS. (2010). Analysis of the concentration-respiratory response among asthmatics following controlled short-term exposures to sulfur dioxide. Inhal Toxicol 22: 1184-1193. http://dx.doi.org/10.3109/08958378.2010.535220

Johnson, S; Bobb, JF; Ito, K; Savitz, DA; Elston, B; Shmool, JL; Dominici, F; Ross, Z; Clougherty, JE; Matte, T. (2016). Ambient fine particulate matter, nitrogen dioxide, and preterm birth in New York City. Environ Health Perspect 124: 1283-1290. http://dx.doi.org/10.1289/ehp.1510266.

Johnson, D; Parker, JD. (2009). Air pollution exposure and self-reported cardiovascular disease. Environ Res 109: 582-589. http://dx.doi.org/10.1016/j.envres.2009.01.001.

Johnston, R. A., J. P. Mizgerd, L. Flynt, L. J. Quinton, E. S. Williams and S. A. Shore (2007). "Type I interleukin-1 receptor is required for pulmonary responses to subacute ozone exposure in mice." Am J Respir Cell Mol Biol 37(4): 477-484.

Jung, CR; Lin, YT; Hwang, BF. (2013). Air pollution and newly diagnostic autism spectrum disorders: a population-based cohort study in taiwan. PLoS ONE 8: e75510. http://dx.doi.org/10.1371/journal.pone.0075510

Kan, H; Wong, CM; Vichit-Vadakan, N; Qian, Z. (2010). Short-term association between sulfur dioxide and daily mortality: The Public Health and Air Pollution in Asia (PAPA) study. Environ Res 110: 258-264. http://dx.doi.org/10.1016/j.envres.2010.01.006

Karr, CJ; Demers, PA; Koehoorn, MW; Lencar, CC; Tamburic, L; Brauer, M. (2009a). Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. Am J Respir Crit Care Med 180: 995-1001. http://dx.doi.org/10.1164/rccm.200901-0117OC.

Karr, CJ; Rudra, CB; Miller, KA; Gould, TR; Larson, T; Sathyanarayana, S; Koenig, JQ. (2009b). Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. Environ Res 109: 321-327. http://dx.doi.org/10.1016/j.envres.2008.11.006.

Karr, C., T. Lumley, A. Schreuder, R. Davis, T. Larson, B. Ritz and J. Kaufman (2007). "Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis." Am J Epidemiol 165(5): 553-560.

Kehrl, H. R., M. J. Hazucha, J. J. Solic and P. A. Bromberg (1985). "Responses of subjects with chronic obstructive pulmonary disease after exposures to 0.3 ppm ozone." American Review of Respiratory Disease 131(5): 719-724.

Katanoda, K; Sobue, T; Satoh, H; Tajima, K; Suzuki, T; Nakatsuka, H; Takezaki, T; Nakayama, T; Nitta, H; Tanabe, K; Tominaga, S. (2011). An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J Epidemiol 21: 132-143. http://dx.doi.org/10.2188/jea.JE20100098

Kaufman, JP; Adar, SD; Barr, RG; et al. (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. Lancet 388: 696-704. http://dx.doi.org/10.1016/S0140-6736(16)00378-0.

Kawanaka, Y; Matsumoto, E; Wang, N; Yun, S, -J; Sakamoto, K. (2008). Contribution of nitrated polycyclic aromatic hydrocarbons to the mutagenicity of ultrafine particles in the roadside atmosphere. Atmos Environ 42: 7423-7428. http://dx.doi.org/10.1016/j.atmosenv.2008.06.032.

Keller, JP; Larson, TV; Austin, E; Barr, RG; Sheppard, L; Vedal, S; Kaufman, JD; Szpiro, AA. (2018). Pollutant composition modification of the effect of air pollution on progression of coronary artery calcium: the Multi-Ethnic Study of Atherosclerosis. Environmental Epidemiology 2. 27 http://dx.doi.org/10.1097/EE9.0000000000000024

Kim, CS; Alexis, NE; Rappold, AG; Kehrl, H; Hazucha, MJ; Lay, JC; Schmitt, MT; Case, M; Devlin, RB; Peden, DB; Diaz-Sanchez, D. (2011). Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. Am J Respir Crit Care Med 183: 1215- 1221. http://dx.doi.org/10.1164/rccm.201011-1813OC

Kim, J; Kim, H; Kweon, J. (2015). Hourly differences in air pollution on the risk of asthma exacerbation. Environ Pollut 203: 15-21. http://dx.doi.org/10.1016/j.envpol.2015.03.040.

KIM JH, HONG YC. GSTM1, GSTT1, and GSTP1 polymorphisms and associations between air pollutants and markers of insulin resistance in elderly Koreans. Environ Health Perspect. 2012;120:1378–84.

Kim JS, Chen Z, Alderete TL, et al. Associations of air pollution, obesity and cardiometabolic health in young adults: The Meta-AIR study. Environ Int. 2019;133(Pt A):105180. doi:10.1016/j.envint.2019.105180

Kim, HJ; Kim, SY; Kwon, JY; Kim, YJ; Kang, SH; Jang, WH; Lee, JH; Seo, MW; Song, JJ; Seo, YR; Park, MK. (2016b). Identification of potential novel biomarkers and signaling pathways related to otitis media induced by diesel exhaust particles using transcriptomic analysis in an in vivo system. PLoS ONE 11: e0166044. http://dx.doi.org/10.1371/journal.pone.0166044.

Kim, H; Kim, J; Kim, S; Kang, SH; Kim, HJ; Kim, H; Heo, J; Yi, SM; Kim, K; Youn, TJ; Chae, IH. (2017). Cardiovascular effects of long-term exposure to air pollution: a population-based study with 900845person-years of follow-up. J Am Heart Assoc 6. http://dx.doi.org/10.1161/JAHA.117.007170

Kim, B; Lee, PH; Lee, S; Kim, YE; Shin, M; Kang, Y; Bae, SH; Kim, M; Rhim, T; Park, C; Jang, A. (2016a). Long-term effects of diesel exhaust particles on airway inflammation and remodeling in a mouse model. Allergy Asthma Immunol Res 8: 246-256. http://dx.doi.org/10.4168/aair.2016.8.3.246.

Kim, KN; Lee, H; Kim, JH; Jung, K; Lim, YH; Hong, YC. (2015). Physical activity- and alcohol-dependent association between air pollution exposure and elevated liver enzyme levels: An elderly panel study. 48: 151-169. http://dx.doi.org/10.3961/jpmph.15.014.

Kim, SY; Peel, JL; Hannigan, MP; Dutton, SJ; Sheppard, L; Clark, ML; Vedal, S. (2012). The temporal lag structure of short-term associations of fine particulate matter chemical constituents and cardiovascular and respiratory hospitalizations. Environ Health Perspect 120: 1094-1099. http://dx.doi.org/10.1289/ehp.1104721.

Kioumourtzoglou, MA; Power, MC; Hart, JE; Okereke, OI; Coull, BA; Laden, F; Weisskopf, MG. (2017). The association between air pollution and onset of depression among middle-aged and older women. Am J Epidemiol 185: 801-809. http://dx.doi.org/10.1093/aje/kww163

Kleinman, M. T., Araujo, J. A., Nel, A., Sioutas, C., Campbell, A., Cong, P. Q., Li, H., & Bondy, S. C. (2008). Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways. Toxicology Letters, 178(2), 127–130. https://doi.org/10.1016/j.toxlet.2008.03.001

Kleinman, M; Sioutas, C; Stram, D; Froines, J; Cho, A; Chakrabarti, B; Hamade, A; Meacher, D; Oldham, M. (2005). Inhalation of concentrated ambient particulate matter near a heavily trafficked road stimulates antigen-induced airway responses in mice. J Air Waste Manag Assoc 55: 1277-1288.

Kloog, I; Coull, BA; Zanobetti, A; Koutrakis, P; Schwartz, JD. (2012). Acute and chronic effects of particles on hospital admissions in New-England. PLoS ONE 7: e34664. http://dx.doi.org/10.1371/journal.pone.0034664.

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: 40. http://dx.doi.org/10.1186/1476-069X-11-40.

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: e88578. http://dx.doi.org/10.1371/journal.pone.0088578.

Kodavanti, UP; Schladweiler, MC; Ledbetter, AD; McGee, JK; Walsh, L; Gilmour, PS; Highfill, JW; Davies, D; Pinkerton, KE; Richards, JH; Crissman, K; Andrews, D; Costa, DL. (2005). Consistent pulmonary and systemic responses from inhalation of fine concentrated ambient particles: Roles of rat strains used and physicochemical properties. Environ Health Perspect 113: 1561-1568. http://dx.doi.org/10.1289/ehp.7868.

Kotecha D, New G, Flather MD, Eccleston D, Pepper J, Krum H. Five-minute heart rate variability can predict obstructive angiographic coronary disease. Heart. 2012 Mar;98(5):395-401. doi: 10.1136/heartjnl-2011-300033. Epub 2011 Nov 25. PMID: 22121069.

Koton, S; Molshatzki, N; Yuval, N; Myers, V; Broday, DM; Drory, Y; Steinberg, DM; Gerber, Y. (2013). Cumulative exposure to particulate matter air pollution and long-term post-myocardial infarction outcomes. 54 Prev Med 57: 339-344. http://dx.doi.org/10.1016/j.ypmed.2013.06.009

Kooter, IM; Boere, AJ; Fokkens, PH; Leseman, DL; Dormans, JA; Cassee, FR. (2006). Response of spontaneously hypertensive rats to inhalation of fine and ultrafine particles from traffic: experimental controlled study. Part Fibre Toxicol 15: 3-7. http://dx.doi.org/10.1186/1743-8977-3-7.

Kousha, T; Valacchi, G. (2015). The air quality health index and emergency department visits for urticaria in Windsor, Canada. J Toxicol Environ Health A 78: 524-533. http://dx.doi.org/10.1080/15287394.2014.991053.

Krall, JR; Chang, HH; Waller, LA; Mulholland, JA; Winquist, A; Talbott, EO; Rager, JR; Tolbert, PE; Sarnat, SE.(2018). A multicity study of air pollution and cardiorespiratory emergency department visits: Comparing approaches for combining estimates across cities. Environ Int 120: 312-320. 4 http://dx.doi.org/10.1016/j.envint.2018.07.033

Krall, JR; Mulholland, JA; Russell, AG; Balachandran, S; Winquist, A; Tolbert, PE; Waller, LA; Sarnat, SE. (2016). Associations between source-specific fine particulate matter and emergency department visits for respiratory disease in four U.S. cities. Environ Health Perspect 125: 97-103. http://dx.doi.org/10.1289/EHP271.

Kreit, JW; Gross, KB; Moore, TB; Lorenzen, TJ; D'Arcy, J; Eschenbacher, WL. (1989). Ozone- induced changes in pulmonary function and bronchial responsiveness in asthmatics. J Appl Physiol (1985) 66: 217-222.

Keramatinia, A., Hassanipour, S., Nazarzadeh, M., Wurtz, M., Monfared, A. B., Khayyamzadeh, M., Bidel, Z., Mhrvar, N., & Mosavi-Jarrahi, A. (2016). Correlation between nitrogen dioxide as an air pollution indicator and breast cancer: A systematic review and meta-analysis. Asian Pacific Journal of Cancer Prevention, 17(1), 419–424. https://doi.org/10.7314/apjcp.2016.17.1.419

Krewski, D; Burnett, RT; Goldberg, MS; Hoover, K; Siemiatycki, J; Jerrett, M; Abrahamowicz, M; White, WH. (2000). Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. Cambridge, MA: Health Effects Institute. http://pubs.healtheffects.org/view.php?id=6

Krewski, D; Jerrett, M; Burnett, RT; et al. (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality [HEI]. (HEI Research Report 140). Boston, MA: Health Effects Institute. https://www.healtheffects.org/system/files/Krewski140Statement.pdf

Kubesch, NJ; de Nazelle, A; Westerdahl, D; Martinez, D; Carrasco-Turigas, G; Bouso, L; Guerra, S; Nieuwenhuijsen, MJ. (2015). Respiratory and inflammatory responses to short-term exposure to traffic-related air pollution with and without moderate physical activity. Occup Environ Med 72: 284-293. http://dx.doi.org/10.1136/oemed-2014-102106.

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: e9096. http://dx.doi.org/10.1371/journal.pone.0009096.

Kurhanewicz, N; Mcintosh-Kastrinsky, R; Tong, H; Walsh, L; Farraj, A; 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: 54. http://dx.doi.org/10.1186/s12989- 014-0054-4.

Kwok, CS; Loke, YK; Hale, R; Potter, JF; Myint, PK. (2011). Atrial fibrillation and incidence of dementia: A systematic review and meta-analysis [Review]. Neurology 76: 914-922. http://dx.doi.org/10.1212/WNL.0b013e31820f2e38.

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: 667-672. http://dx.doi.org/10.1164/rccm.200503-443OC.

Lakshmanan, A; Chiu, YH; Coull, BA; Just, AC; Maxwell, SL; Schwartz, J; Gryparis, A; Kloog, I; Wright, RJ; Wright, RO. (2015). Associations between prenatal traffic-related air pollution exposure and birth weight: Modification by sex and maternal pre-pregnancy body mass index. Environ Res 137: 268-277. http://dx.doi.org/10.1016/j.envres.2014.10.035.

Lall, R; Ito, K; Thurston, G. (2011). Distributed lag analyses of daily hospital admissions and source-apportioned fine particle air pollution. Environ Health Perspect 119: 455-460. http://dx.doi.org/10.1289/ehp.1002638.

Lanzinger, S; Schneider, A; Breitner, S; Stafoggia, M; Erzen, I; Dostal, M; Pastorkova, A; Bastian, S; Cyrys, J; Zscheppang, A; Kolodnitska, T; Peters, A. (2016a). Associations between ultrafine and fine particles and mortality in five central European cities - Results from the UFIREG study. Environ Int 88: 44-52. http://dx.doi.org/10.1016/j.envint.2015.12.006.

Lanzinger, S; Schneider, A; Breitner, S; Stafoggia, M; Erzen, I; Dostal, M; Pastorkova, A; Bastian, S; Cyrys, J; Zscheppang, A; Kolodnitska, T; Peters, A. (2016b). Ultrafine and fine particles and hospital admissions in Central Europe, results from the UFIREG Study. Am J Respir Crit Care Med 194: 1233-1241. http://dx.doi.org/10.1164/rccm.201510-2042OC.

Laurent, O; Hu, J; Li, L; Cockburn, M; Escobedo, L; Kleeman, MJ; Wu, J. (2014). Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 20012008. Environ Res 134: 488-495. http://dx.doi.org/10.1016/j.envres.2014.05.003

Laurent, O., J. Hu, L. Li, M. Cockburn, L. Escobedo, M. J. Kleeman and J. Wu (2014). "Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008." Environ Res 134: 488-495.

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 92-93: 471-477. http://dx.doi.org/10.1016/j.envint.2016.04.034

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: 1479-1486. http://dx.doi.org/10.1289/ehp.1510133

Laurent, O; Wu, J; Li, L; Chung, J; Bartell, S. (2013). Investigating the association between birth weight and complementary air pollution metrics: a cohort study. Environ Health 12: 18. http://dx.doi.org/10.1186/1476-069X-12-18

Lavigne, E; Ashley-Martin, J; Dodds, L; et al. (2016a). Air pollution exposure during pregnancy and fetal markers of metabolic function: the MIREC Study. Am J Epidemiol 183: 842-851. http://dx.doi.org/10.1093/aje/kwv256.

Lavigne, É; Bélair, MA; Do, MT; et al. (2017). Maternal exposure to ambient air pollution and risk of early childhood cancers: A population-based study in Ontario, Canada. Environ Int 100: 139-147. http://dx.doi.org/10.1016/j.envint.2017.01.004.

Lavigne, E; Yasseen, AS; Stieb, DM; et al. (2016b). Ambient air pollution and adverse birth outcomes: Differences by maternal comorbidities. Environ Res 148: 457-466. http://dx.doi.org/10.1016/j.envres.2016.04.026.

Le, HQ; Batterman, SA; Wirth, JJ; Wahl, RL; Hoggatt, KJ; Sadeghnejad, A; Hultin, ML; Depa, M. (2012). Air pollutant exposure and preterm and term small-for-gestational-age births in Detroit, Michigan: Long-term trends and associations. Environ Int 44: 7-17. http://dx.doi.org/10.1016/j.envint.2012.01.003

Lee, K. K., & Mills, N. L. (2020). Early rule-out pathways for myocardial infarction: Is observational data enough? Heart, 106(20), 1545–1546. https://doi.org/10.1136/heartjnl-2020-317012

Lee, MS; Moon, KY; Bae, DJ; Park, MK; Jang, AS. (2013). The effects of pycnogenol on antioxidant enzymes in a mouse model of ozone exposure. 28: 216-223. http://dx.doi.org/10.3904/kjim.2013.28.2.216

Lee, Y. L., R. McConnell, K. Berhane and F. D. Gilliland (2009). "Ambient ozone modifies the effect of tumor necrosis factor G-308A on bronchitic symptoms among children with asthma." Allergy 64(9): 1342-1348.

Lee, PC; 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: 545-555. http://dx.doi.org/10.1007/s10995-012-1028-5.

Lee, PC; Talbott, EO; Roberts, JM; Catov, JM; Bilonick, RA; Stone, RA; Sharma, RK; Ritz, B. (2012b). Ambient air pollution exposure and blood pressure changes during pregnancy. Environ Res 117: 46-53. http://dx.doi.org/10.1016/j.envres.2012.05.011.

Lee, PC; Talbott, EO; Roberts, JM; Catov, JM; Sharma, RK; Ritz, B. (2011b). Particulate air pollution exposure and C-reactive protein during early pregnancy. Epidemiology 22: 524-531. http://dx.doi.org/10.1097/EDE.0b013e31821c6c58.

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: 1317-1324. http://dx.doi.org/10.1093/humrep/deq021

Leiser, CL; Smith, KR; Vanderslice, JA; Glotzbach, JP; Farrell, TW; Hanson, HA. (2019). Evaluation of the Sex-and-Age-Specific Effects of PM2.5 on Hospital Readmission in the Presence of the Competing Risk of Mortality in the Medicare Population of Utah 1999-2009. J Clin Med 8: 2114. 36 http://dx.doi.org/10.3390/jcm8122114

Leitte, A; Schlink, U; Herbarth, O; Wiedensohler, A; Pan, X; Hu, M; Richter, M; Wehner, B; Tuch, T; Wu, Z; Yang, M; Liu, L; Breitner, S; Cyrys, J; Peters, A; Wichmann, H; Franck, U. (2011). Size segregated particle

number concentrations and respiratory emergency room visits in Beijing, China. Environ Health Perspect 119: 508-513. http://dx.doi.org/10.1289/ehp.1002203.

Lemos, AT; Coronas, MV; Rocha, JA; Vargas, VM. (2012). Mutagenicity of particulate matter fractions in areas under the impact of urban and industrial activities. Chemosphere 89: 1126-1134. http://dx.doi.org/10.1016/j.chemosphere.2012.05.100.

Lemos, AT; Lemos, CT; Flores, AN; Pantoja, EO; Rocha, JA; Vargas, VM. (2016). Genotoxicity biomarkers for airborne particulate matter (PM2.5) in an area under petrochemical influence. Chemosphere 159: 610-618. http://dx.doi.org/10.1016/j.chemosphere.2016.05.087.

Leroy, P; Tham, A; Wong, H; Tenney, R; Chen, C; Stiner, R; Balmes, JR; Paquet, AC; Arjomandi, M. (2015). Inflammatory and repair pathways induced in human bronchoalveolar lavage cells with ozone inhalation. PLoS ONE 10: e0127283. http://dx.doi.org/10.1371/journal.pone.0127283

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: 965-970. http://dx.doi.org/10.1289/ehp.1104660.

Li, N; Harkema, JR; Lewandowski, RP; Wang, MY; Bramble, LA; Gookin, GR; Ning, Z; Kleinman, MT; Sioutas, C; Nel, AE. (2010). Ambient ultrafine particles provide a strong adjuvant effect in the secondary immune response: implication for traffic-related asthma flares. Am J Physiol Lung Cell Mol Physiol 299: L374-L383. http://dx.doi.org/10.1152/ajplung.00115.2010.

Li, N; Wang, M; Bramble, LA; Schmitz, DA; Schauer, JJ; Sioutas, C; Harkema, JR; Nel, AE. (2009). The adjuvant effect of ambient particulate matter is closely reflected by the particulate oxidant potential. Environ Health Perspect 117: 1116-1123. http://dx.doi.org/10.1289/ehp.0800319.

Li, P; Zhao, J; Gong, C; Bo, L; Xie, Y; Kan, H; Song, W. (2014). Association between individual PM2.5 exposure and DNA damage in traffic policemen. J Occup Environ Med 56: e98-e101. http://dx.doi.org/10.1097/JOM.0000000000000287.

Li, R; Meng, Z; Xie, J. (2007). Effects of sulfur dioxide on the expressions of MUC5AC and ICAM-1 in airway of asthmatic rats. Regul Toxicol Pharmacol 48: 284-291. http://dx.doi.org/10.1016/j.yrtph.2007.04.009

Li, R; Navab, M; Pakbin, P; Ning, Z; Navab, K; Hough, G; Morgan, TE; Finch, CE; Araujo, JA; Fogelman, AM; Sioutas, C; Hsiai, T. (2013). Ambient ultrafine particles alter lipid metabolism and HDL anti-oxidant capacity in LDLR-null mice. J Lipid Res 54: 1608-1615. http://dx.doi.org/10.1194/jlr.M035014.

Li, S; Batterman, S; Wasilevich, E; Wahl, R; Wirth, J; Su, FC; Mukherjee, B. (2011). Association of daily asthma emergency department visits and hospital admissions with ambient air pollutants among the pediatric Medicaid population in Detroit: Time-series and time-stratified case-crossover analyses with threshold effects. Environ Res 111: 1137-1147. http://dx.doi.org/10.1016/j.envres.2011.06.002.

Liao, D; Shaffer, ML; He, F; Rodriguez-Colon, S; Wu, R; Whitsel, EA; Bixler, EO; Cascio, WE. (2011). Fine particulate air pollution is associated with higher vulnerability to atrial fibrillation--the APACR study. J Toxicol Environ Health A 74: 693-705. http://dx.doi.org/10.1080/15287394.2011.556056.

Liu, C., Yin, P., Chen, R., Meng, X., Wang, L., Niu, Y., Lin, Z., Liu, Y., Liu, J., Qi, J., You, J., Kan, H., & Zhou, M. (2018). Ambient carbon monoxide and cardiovascular mortality: A nationwide time-series analysis in 272 cities in China. The Lancet Planetary Health, 2(1). https://doi.org/10.1016/s2542-5196(17)30181-x

Lim, YH; Kim, H; Kim, JH; Bae, S; Park, HY; Hong, YC. (2012). Air pollution and symptoms of depression in elderly adults. Environ Health Perspect 120: 1023-1028. http://dx.doi.org/10.1289/ehp.1104100

Link, MS; Luttmann-Gibson, H; Schwartz, J; Mittleman, MA; Wessler, B; Gold, DR; Dockery, DW; Laden, F. (2013). Acute exposure to air pollution triggers atrial fibrillation. J Am Coll Cardiol 62: 816-825. http://dx.doi.org/10.1016/j.jacc.2013.05.043.

Linn, WS; Avol, EL; Peng, RC; Shamoo, DA; Hackney, JD. (1987). Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. Am Rev Respir Dis 136: 1127-1134. http://dx.doi.org/10.1164/ajrccm/136.5.1127

Linn, WS; Avol, EL; Shamoo, DA; Peng, RC; Spier, CE; Smith, MN; Hackney, JD. (1988). Effect of metaproterenol sulfate on mild asthmatics' response to sulfur dioxide exposure and exercise. Arch Environ Occup Health 43: 399-406. http://dx.doi.org/10.1080/00039896.1988.9935858

Linn, W. S., D. A. Fischer, D. A. Medway, U. T. Anzar, C. E. Spier, L. M. Valencia, T. G. Venet and J. D. Hackney (1982). "Short-term respiratory effects of 0.12 ppm ozone exposure in volunteers with chronic obstructive pulmonary disease." American Review of Respiratory Disease 125(6): 658-663.

Linn, WS; Fischer, DA; Shamoo, DA; Spier, CE; Valencia, LM; Anzar, UT; Hackney, JD. (1985a). Controlled exposures of volunteers with chronic obstructive pulmonary disease to sulfur dioxide. Environ Res 37: 445- 451. http://dx.doi.org/10.1016/0013-9351(85)90126-4

Linn, WS; Shamoo, DA; Peng, RC; Clark, KW; Avol, EL; Hackney, JD. (1990). Responses to sulfur dioxide and exercise by medication-dependent asthmatics: Effect of varying medication levels. Arch Environ Occup Health 45: 24-30. http://dx.doi.org/10.1080/00039896.1990.9935920

Linn, WS; Shamoo, DA; Venet, TG; Bailey, RM; Wightman, LH; Hackney, JD. (1984b). Comparative effects of sulfur dioxide exposures at 5 degrees C and 22 degrees C in exercising asthmatics. Am Rev Respir Dis 129: 234-239.

Linn, W. S., D. A. Shamoo, T. G. Venet, C. E. Spier, L. M. Valencia, U. T. Anzar and J. D. Hackney (1983). "Response to ozone in volunteers with chronic obstructive pulmonary disease." Archives of Environmental and Occupational Health 38(5): 278-283.

Linn, WS; Venet, TG; Shamoo, DA; Valencia, LM; Anzar, UT; Spier, CE; Hackney, JD. (1983b). Respiratory effects of sulfur dioxide in heavily exercising asthmatics: A dose-response study. Am Rev Respir Dis 127: 278-283.

Lipfert, FW; Perry, HM, Jr; Miller, JP; Baty, JD; Wyzga, RE; Carmody, SE. (2000). The Washington University- EPRI veterans' cohort mortality study: Preliminary results. Inhal Toxicol 12: 41-73. http://dx.doi.org/10.1080/713856640

Lipfert, FW; Wyzga, RE; Baty, JD; Miller, JP. (2009). Air pollution and survival within the Washington University- EPRI veterans cohort: Risks based on modeled estimates of ambient levels of hazardous and

criteria air pollutants. J Air Waste Manag Assoc 59: 473-489. http://dx.doi.org/10.3155/1047-3289.59.4.473

Lippmann, M., & Leikauf, G. D. (2020). Chapter 12: Carbon Monoxide. In Environmental toxicants: Human exposures and their health effects. essay, Wiley.

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: 828-835. http://dx.doi.org/10.1164/rccm.201012-2082OC.

Liu, X; Bertazzon, S; Villeneuve, PJ; Johnson, M; et al. (2020). Temporal and spatial effect of air pollution on hospital admissions for myocardial infarction: a case-crossover study. CMAJ Open 8: E619-E626. http://dx.doi.org/10.9778/cmajo.20190160

Liu, B; Ichinose, T; He, M; Kobayashi, F; Maki, T; Yoshida, S; Yoshida, Y; Arashidani, K; Takano, H; Nishikawa, M; Sun, G; Shibamoto, T. (2014). Lung inflammation by fungus, Bjerkandera adusta isolated from Asian sand dust (ASD) aerosol and enhancement of ovalbumin-induced lung eosinophilia by ASD and the fungus in mice. Allergy Asthma Clin Immunol 10: 10. http://dx.doi.org/10.1186/1710-1492-10-10.

Liu, L; Urch, B; Poon, R; Szyszkowicz, M; Speck, M; Gold, DR; Wheeler, AJ; Scott, JA; Brook, JR; Thorne, PS; Silverman, FS. (2015). Effects of ambient coarse, fine, and ultrafine particles and their biological constituents on systemic biomarkers: A controlled human exposure study. Environ Health Perspect 123: 534- 540. http://dx.doi.org/10.1289/ehp.1408387.

Liu, S; Ganduglia, CM; Li, X; Delclos, GL; Franzini, L; Zhang, K. (2016). Short-term associations of fine particulate matter components and emergency hospital admissions among a privately insured population in Greater Houston. Atmos Environ 147: 369-375. http://dx.doi.org/10.1016/j.atmosenv.2016.10.021.

Liu, S; Krewski, D; Shi, Y; Chen, Y; Burnett, RT. (2003). Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect 111: 1773-1778.

Liu, Y; Zhou, Y; Ma, J; Bao, W; Li, J; Zhou, T; Cui, X; Peng, Z; Zhang, H; Feng, M; Yuan, Y; Chen, Y; Huang, X; Li, Y; Duan, Y; Shi, T; Jin, L; Wu, L. (2017). Inverse Association between Ambient Sulfur Dioxide Exposure and Semen Quality in Wuhan, China. Environ Sci Technol 51: 12806- 12814. http://dx.doi.org/10.1021/acs.est.7b03289

Loop, MS; McClure, LA; Levitan, EB; Al-Hamdan, MZ; Crosson, WL; Safford, MM. (2018). Fine particulate matter and incident coronary heart disease in the REGARDS cohort. Am Heart J 197: 94-102. 25 http://dx.doi.org/10.1016/j.ahj.2017.11.007

Lucht, SA; Hennig, F; Matthiessen, C; Ohlwein, S; Icks, A; Moebus, S; Jöckel, KH; Jakobs, H; Hoffmann, B. (2018a). Air pollution and glucose metabolism: An analysis in non-diabetic participants of the Heinz Nixdorf recall study. Environ Health Perspect 126. http://dx.doi.org/10.1289/EHP2561.

Ma, M; Li, S; Jin, H; Zhang, Y; Xu, J; Chen, D; Kuimin, C; Yuan, Z; Xiao, C. (2015). Characteristics and oxidative stress on rats and traffic policemen of ambient fine particulate matter from Shenyang. Sci Total Environ 526: 110-115. http://dx.doi.org/10.1016/j.scitotenv.2015.04.075.

MacIntyre, EA; Brauer, M; Melén, E; et al. (2014a). GSTP1 and TNF gene variants and associations between air pollution and incident childhood asthma: The traffic, asthma and genetics (TAG) study. Environ Health Perspect 122: 418-424. http://dx.doi.org/10.1289/ehp.1307459.

MacIntyre, EA; Gehring, U; Mölter, A; et al. (2014b). Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE Project. Environ Health Perspect 122: 107-113. http://dx.doi.org/10.1289/ehp.1306755.

MacIntyre, EA; Karr, CJ; Koehoorn, M; Demers, PA; Tamburic, L; Lencar, C; Brauer, M. (2011). Residential air pollution and otitis media during the first two years of life. Epidemiology 22: 81-89. http://dx.doi.org/10.1097/EDE.0b013e3181fdb60f

Madrigano, J; Baccarelli, A; Mittleman, MA; Wright, RO; Sparrow, D; Vokonas, PS; Tarantini, L; Schwartz, J. (2011). Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men. Environ Health Perspect 119: 977-982. http://dx.doi.org/10.1289/ehp.1002773.

Madrigano, J., Jack, D., Anderson, G.B. et al. Temperature, ozone, and mortality in urban and non-urban counties in the northeastern United States. Environ Health 14, 3 (2015). https://doi.org/10.1186/1476-069X-14-3

Madsen, C; Gehring, U; Walker, SE; Brunekreef, B; Stigum, H; Naess, O; Nafstad, P. (2010). Ambient air pollution exposure, residential mobility and term birth weight in Oslo, Norway. Environ Res 110: 363-371. http://dx.doi.org/10.1016/j.envres.2010.02.005.

Mahalingaiah, S; Hart, JE; Laden, F; Aschengrau, A; Missmer, SA. (2014). Air pollution exposures during adulthood and risk of endometriosis in the Nurses' Health Study II. Environ Health Perspect 122: 58-64. http://dx.doi.org/10.1289/ehp.1306627.

Mahalingaiah, S; Hart, JE; Laden, F; Farland, LV; Hewlett, MM; Chavarro, J; Aschengrau, A; Missmer, SA. (2016). Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. Hum Reprod 31: 638-647. http://dx.doi.org/10.1093/humrep/dev330.

Maher, B. A., Ahmed, I. A., Karloukovski, V., MacLaren, D. A., Foulds, P. G., Allsop, D., Mann, D. M., Torres-Jardón, R., & Calderon-Garciduenas, L. (2016). Magnetite pollution nanoparticles in the human brain. Proceedings of the National Academy of Sciences, 113(39), 10797–10801. https://doi.org/10.1073/pnas.1605941113

Malik, AO; Jones, PG; Chan, PS; Peri-Okonny, PA; Hejjaji, V; Spertus, JA. (2019). Association of long-term exposure to particulate matter and ozone with health status and mortality in patients after myocardial infarction. Circulation Cardiovascular Quality and Outcomes 12: e005598. 33 http://dx.doi.org/10.1161/CIRCOUTCOMES.119.005598

Malmqvist E, Larsson HE, Jönsson I, Rignell-Hydbom A, Ivarsson SA, Tinnerberg H, Stroh E, Rittner R, Jakobsson K, Swietlicki E, Rylander L. Maternal exposure to air pollution and type 1 diabetes--Accounting

for genetic factors. Environ Res. 2015 Jul;140:268-74. doi: 10.1016/j.envres.2015.03.024. Epub 2015 Apr 13. PMID: 25880886.

Mann, JK; Balmes, JR; Bruckner, TA; Mortimer, KM; Margolis, HG; Pratt, B; Hammond, SK; Lurmann, F; Tager, IB. (2010). Short-term effects of air pollution on wheeze in asthmatic children in Fresno, California. Environ Health Perspect 118: 1497-1502. http://dx.doi.org/10.1289/ehp.0901292.

Männistö, T; Mendola, P; Liu, D; Leishear, K; Sherman, S; Laughon, SK. (2014). Acute air pollution exposure and blood pressure at delivery among women with and without hypertension. Am J Hypertens 28: 58-72. http://dx.doi.org/10.1093/ajh/hpu077.

Mar, TF; Larson, TV; Stier, RA; Claiborn, C; Koenig, JQ. (2004). An analysis of the association between respiratory symptoms in subjects with asthma and daily air pollution in Spokane, Washington. Inhal Toxicol 16: 809-815. http://dx.doi.org/10.1080/08958370490506646.

Matt, F; Cole-Hunter, T; Donaire-Gonzalez, D; Kubesch, N; Martínez, D; Carrasco-Turigas, G; Nieuwenhuijsen, M. (2016). Acute respiratory response to traffic-related air pollution during physical activity performance. Environ Int 97: 45-55. http://dx.doi.org/10.1016/j.envint.2016.10.011.

Madden, MC; Stevens, T; Case, M; Schmitt, M; Diaz-Sanchez, D; Bassett, M; Montilla, TS; Berntsen, J; Devlin, RB. (2014). Diesel exhaust modulates ozone-induced lung function decrements in healthy human volunteers. Part Fibre Toxicol 11: 37. http://dx.doi.org/10.1186/s12989-014-0037-5

Madrigano, J; Jack, D; Anderson, GB; Bell, ML; Kinney, PL. (2015). Temperature, ozone, and mortality in urban and non-urban counties in the northeastern United States. Environ Health 14: 3. http://dx.doi.org/10.1186/1476-069X-14-3

Malig, BJ; Pearson, DL; Chang, Y; Broadwin, R; Basu, R; Green, RS; Ostro, B. (2016). A time- stratified case-crossover study of ambient ozone exposure and emergency department visits for specific respiratory diagnoses in California (2005-2008). Environ Health Perspect 124: 745-753. http://dx.doi.org/10.1289/ehp.1409495

McConnell, R., K. Berhane, F. Gilliland, S. J. London, H. Vora, E. Avol, W. J. Gauderman, H. G. Margolis, F. Lurmann, D. C. Thomas and J. M. Peters (1999). "Air pollution and bronchitic symptoms in Southern California children with asthma." Environ Health Perspect 107(9): 757-760.

Mcconnell, R; Berhane, K; Gilliland, F; London, SJ; Islam, T; Gauderman, WJ; Avol, E; Margolis, HG; Peters, JM. (2002). Asthma in exercising children exposed to ozone: A cohort study. Lancet 359: 386-391. http://dx.doi.org/10.1016/S0140-6736(02)07597-9

McConnell, R; Berhane, K; Gilliland, F; Molitor, J; Thomas, D; Lurmann, F; Avol, E; Gauderman, WJ; Peters, JM. (2003). Prospective study of air pollution and bronchitic symptoms in children with asthma. Am J Respir Crit Care Med 168: 790-797. http://dx.doi.org/10.1164/rccm.200304- 466OC

McConnell, R., T. Islam, K. Shankardass, M. Jerrett, F. Lurmann, F. Gilliland, J. Gauderman, E. Avol, N. Kunzli, L. Yao, J. Peters and K. Berhane (2010). "Childhood incident asthma and traffic-related air pollution at home and school." Environ Health Perspect 118(7): 1021-1026.

McCreanor, J; Cullinan, P; Nieuwenhuijsen, MJ; Stewart-Evans, J; Malliarou, E; Jarup, L; Harrington, R; Svartengren, M; Han, IK; Ohman-Strickland, P; Chung, KF; Zhang, J. (2007). Respiratory effects of

exposure to diesel traffic in persons with asthma. N Engl J Med 357: 2348-2358.
http://dx.doi.org/10.1056/NEJMoa071535.

McDonnell, WF; Abbey, DE; Nishino, N; Lebowitz, MD. (1999a). Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the Ahsmog study. Environ Res 80: 110-121. http://dx.doi.org/10.1006/enrs.1998.3894

McDonnell, WF; Stewart, PW; Smith, MV. (2010). Prediction of ozone-induced lung function responses in humans. Inhal Toxicol 22: 160-168. http://dx.doi.org/10.3109/08958370903089557

McDonnell, WF; Stewart, PW; Smith, MV. (2013). Ozone exposure-response model for lung function changes: An alternate variability structure. Inhal Toxicol 25: 348-353. http://dx.doi.org/10.3109/08958378.2013.790523

McDonnell, WF; Stewart, PW; Smith, MV; Pan, WK; Pan, J. (1999b). Ozone-induced respiratory symptoms: Exposure-response models and association with lung function. Eur Respir J 14: 845- 853. http://dx.doi.org/10.1034/j.1399-3003.1999.14d21.x

Mehta, S; Ngo, LH; Dzung, DV; Cohen, A; Thach, TQ; Dan, VX; Tuan, ND; Giang, LT. (2013). Air pollution and admissions for acute lower respiratory infections in young children of Ho Chi Minh City. Air Qual Atmos Health 6: 167-179. http://dx.doi.org/10.1007/s11869-011-0158-z

Mendola, P; Wallace, M; Hwang, BS; Liu, D; Robledo, C; Männistö, T; Sundaram, R; Sherman, S; Ying, Q; Grantz, KL. (2016a). Preterm birth and air pollution: Critical windows of exposure for women with asthma. J Allergy Clin Immunol 138: 432-440.e435. http://dx.doi.org/10.1016/j.jaci.2015.12.1309.

Mendola, P; Wallace, M; Liu, D; Robledo, C; Männistö, T; Grantz, KL. (2016b). Air pollution exposure and preeclampsia among US women with and without asthma. Environ Res 148: 248-255. http://dx.doi.org/10.1016/j.envres.2016.04.004.

Meng, YY; Rull, RP; Wilhelm, M; Lombardi, C; Balmes, J; Ritz, B. (2010). Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. J Epidemiol Community Health 64: 142-147. http://dx.doi.org/10.1136/jech.2008.083576

Meng, Y. Y., M. Wilhelm, R. P. Rull, P. English and B. Ritz (2007). "Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults." Ann Allergy Asthma Immunol 98(5): 455-463.

Meo, S. A., Abukhalaf, A. A., Alomar, A. A., Alessa, O. M., Sami, W., & Klonoff, D. C. (2021). Effect of environmental pollutants PM-2.5, carbon monoxide, and ozone on the incidence and mortality of SARS-COV-2 infection in ten wildfire affected counties in California. Science of The Total Environment, 757, 143948. doi:10.1016/j.scitotenv.2020.143948

Miller, CN; Dye, JA; Ledbetter, AD; et al. (2017). Uterine artery flow and offspring growth in long-evans rats following maternal exposure to ozone during implantation. Environ Health Perspect 125: 127005. http://dx.doi.org/10.1289/EHP2019

Miller, DB; Snow, SJ; Henriquez, A; Schladweiler, MC; Ledbetter, AD; Richards, JE; Andrews, DL; Kodavanti, UP. (2016). Systemic metabolic derangement, pulmonary effects, and insulin insufficiency following subchronic ozone exposure in rats. Toxicol Appl Pharmacol 306: 47-57. http://dx.doi.org/10.1016/j.taap.2016.06.027

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: 447-458. http://dx.doi.org/10.1056/NEJMoa054409.

Milojevic, A; Wilkinson, P; Armstrong, B; Bhaskaran, K; Smeeth, L; Hajat, S. (2014). Short-term effects of air pollution on a range of cardiovascular events in England and Wales: Case-crossover analysis of the MINAP database, hospital admissions and mortality. Heart 100: 1093-1098. http://dx.doi.org/10.1136/heartjnl- 2013-304963

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: 546-555. http://dx.doi.org/10.1097/EDE.0000000000000296.

Mirowsky, JE; Jin, L; Thurston, G; Lighthall, D; Tyner, T; Horton, L; Galdanes, K; Chillrud, S; Ross, J; Pinkerton, KE; Chen, LC; Lippmann, M; Gordon, T. (2015). In vitro and in vivo toxicity of urban and rural particulate matter from California. Atmos Environ 103: 256-262. http://dx.doi.org/10.1016/j.atmosenv.2014.12.051.

Mobasher, Z; Salam, MT; Goodwin, TM; Lurmann, F; Ingles, SA; Wilson, ML. (2013). Associations between ambient air pollution and hypertensive disorders of pregnancy. Environ Res 123: 9-16. http://dx.doi.org/10.1016/j.envres.2013.01.006

Mokoena, ML; Brink, CB; Harvey, BH; Oliver, DW. (2011). Appraisal of ozone as biologically active molecule and experimental tool in biomedical sciences. Med Chem Res 20: 1687-1695. http://dx.doi.org/10.1007/s00044-010-9493-0

Mokoena, ML; Harvey, BH; Viljoen, F; Ellis, SM; Brink, CB. (2015). Ozone exposure of Flinders Sensitive Line rats is a rodent translational model of neurobiological oxidative stress with relevance for depression and antidepressant response. Psychopharmacology 232: 2921-2938. http://dx.doi.org/10.1007/s00213-015-3928 8

Mölter, A; Simpson, A; Berdel, D; et al. (2014). A multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. Eur Respir J 45: 610-624. http://dx.doi.org/10.1183/09031936.00083614.

Morello-Frosch, R; Jesdale, BM; Sadd, JL; Pastor, M. (2010). Ambient air pollution exposure and full-term birth weight in California. Environ Health 9: 44. http://dx.doi.org/10.1186/1476-069X-9-44.

Moolgavkar, SH; Mcclellan, RO; Dewanji, A; Turim, J; Luebeck, EG; Edwards, M. (2013). Time- series analyses of air pollution and mortality in the United States: A subsampling approach. Environ Health Perspect 121: 73-78. http://dx.doi.org/10.1289/ehp.1104507

Moore, K., R. Neugebauer, F. Lurmann, J. Hall, V. Brajer, S. Alcorn and I. Tager (2008). "Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California." Environ Health Perspect 116(8): 1063-1070.

Moridi, M; Ziaei, S; Kazemnejad, A. (2014). Exposure to ambient air pollutants and spontaneous abortion. J Obstet Gynaecol Res 40: 743-748. http://dx.doi.org/10.1111/jog.12231

Morgan, T. E., Davis, D. A., Iwata, N., et al. (2011). Glutamatergic neurons in rodent models respond to Nanoscale Particulate Urban Air Pollutants in vivo and in vitro. Environmental Health Perspectives, 119(7), 1003–1009. https://doi.org/10.1289/ehp.1002973

Nachman, KE; Parker, JD. (2012). Exposures to fine particulate air pollution and respiratory outcomes in adults using two national datasets: a cross-sectional study. Environ Health 11: 25. http://dx.doi.org/10.1186/1476- 069X-11-25.

Nachman, RM; Mao, G; Zhang, X; et al. (2016). Intrauterine inflammation and maternal exposure to ambient PM2.5 during preconception and specific periods of pregnancy: the Boston Birth Cohort. Environ Health Perspect 124: 1608-1615. http://dx.doi.org/10.1289/EHP243.

Nafstad, P; Haheim, LL; Wisloff, T; Gram, F; Oftedal, B; Holme, I; Hjermann, I; Leren, P. (2004). Urban air pollution and mortality in a cohort of Norwegian men. Environ Health Perspect 112: 610-615.

Neophytou, AM; White, MJ; Oh, SS; et al. (2016). Air pollution and lung function in minority youth with asthma in the GALA II (Genesenvironments and admixture in Latino Americans) and SAGE II (Study of African Americans, asthma, genes, and environments) studies. Am J Respir Crit Care Med 193: 1271-1280. http://dx.doi.org/10.1164/rccm.201508-1706OC

Neupane, B., Jerrett, M., Burnett, R. T., 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. American Journal of Respiratory and Critical Care Medicine, 181(1), 47–53. https://doi.org/10.1164/rccm.200901-0160oc

Nieuwenhuijsen, MJ; Basagaña, X; Dadvand, P; Martinez, D; Cirach, M; Beelen, R; Jacquemin, B. (2014). Air pollution and human fertility rates. Environ Int 70: 9-14. http://dx.doi.org/10.1016/j.envint.2014.05.005.

Nikolov, MC; Coull, BA; Catalano, PJ; Diaz, E; Godleski, JJ. (2008). Statistical methods to evaluate health effects associated with major sources of air pollution: a case-study of breathing patterns during exposure to concentrated Boston air particles. J R Stat Soc Ser C Appl Stat 57: 357-378. http://dx.doi.org/10.1111/j.1467- 9876.2008.00618.x.

Nishimura, KK; Galanter, JM; Roth, LA; et al. (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: 309-318. http://dx.doi.org/10.1164/rccm.201302-0264OC.

Nobles, CJ; Schisterman, EF; Ha, S; Buck Louis, GM; Sherman, S; Mendola, P. (2018). Time-varying cycle average and daily variation in ambient air pollution and fecundability. Hum Reprod 33: 166-176. http://dx.doi.org/10.1093/humrep/dex341

Nuvolone, D., Petri, D., & Voller, F. (2017). The effects of ozone on human health. Environmental Science and Pollution Research, 25(9), 8074–8088. https://doi.org/10.1007/s11356-017-9239-3

O'Callaghan-Gordo, C; Fthenou, E; Pedersen, M; et al. (2015). Outdoor air pollution exposures and micronuclei frequencies in lymphocytes from pregnant women and newborns in Crete, Greece (Rhea cohort). Environ Res 143: 170-176. http://dx.doi.org/10.1016/j.envres.2015.10.011.

O'Connor, GT; Neas, L; Vaughn, B; Kattan, M; Mitchell, H; Crain, EF; Evans, R, III; Gruchalla, R; Morgan, W; Stout, J; Adams, GK; Lippmann, M. (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 121: 1133- 1139.e1131. http://dx.doi.org/10.1016/j.jaci.2008.02.020

O'Toole, TE; Hellmann, J; Wheat, L; Haberzettl, P; Lee, J; Conklin, DJ; Bhatnagar, A; Pope, CA. (2010). Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. Circ Res 107: 200-203. http://dx.doi.org/10.1161/CIRCRESAHA.110.222679.

Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., & Cox, C. (2004). Translocation of inhaled ultrafine particles to the brain. Inhalation Toxicology, 16(6-7), 437–445. https://doi.org/10.1080/08958370490439597

Ohlwein, S; Klümper, C; Vossoughi, M; Sugiri, D; Stolz, S; Vierkötter, A; Schikowski, T; Kara, K; Germing, A; Quass, U; Krämer, U; Hoffmann, B. (2016). Air pollution and diastolic function in elderly women - Results from the SALIA study cohort. Int J Hyg Environ Health 219: 356-363. http://dx.doi.org/10.1016/j.ijheh.2016.02.006.

Olsson, D; Mogren, I; Forsberg, B. (2013). Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. BMJ Open 3. http://dx.doi.org/10.1136/bmjopen-2012-001955

Olsson D, Johansson C, Forsberg B. Associations between Vehicle Exhaust Particles and Ozone at Home Address and Birth Weight. Int J Environ Res Public Health. 2020 May 28;17(11):3836. doi: 10.3390/ijerph17113836. PMID: 32481677; PMCID: PMC7312427.

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: 363-369. http://dx.doi.org/10.1289/ehp.0901181.

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: 450-459. http://dx.doi.org/10.1093/aje/kwv343.

Oudin, A., B. Forsberg, A. N. Adolfsson, N. Lind, L. Modig, M. Nordin, S. Nordin, R. Adolfsson and L. G. Nilsson (2016). "Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study." Environ Health Perspect 124(3): 306-312.

Padula, AM; Mortimer, KM; Tager, IB; Hammond, SK; Lurmann, FW; Yang, W; Stevenson, DK; Shaw, GM. (2014). Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. Ann Epidemiol 24: 888-895.e884. http://dx.doi.org/10.1016/j.annepidem.2014.10.004.

Paquette, M; Roy, D; Talajic, M; Newman, D; Couturier, A; Yang, C; Dorian, P. (2000). Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. Am J Cardiol 86: 764-768. http://dx.doi.org/10.1016/S0002-9149(00)01077-8.

Padula, AM; Tager, IB; Carmichael, SL; Hammond, SK; Lurmann, F; Shaw, GM. (2013a). The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. Am J Epidemiol 177: 1074-1085. http://dx.doi.org/10.1093/aje/kws367.

Padula, AM; Tager, IB; Carmichael, SL; Hammond, SK; Yang, W; Lurmann, F; Shaw, GM. (2013b). Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin Valley of California. Paediatr Perinat Epidemiol 27: 329-339. http://dx.doi.org/10.1111/ppe.12055.

Padula, AM; Tager, IB; Carmichael, SL; Hammond, SK; Yang, W; Lurmann, FW; Shaw, GM. (2013c). Traffic- related air pollution and selected birth defects in the San Joaquin Valley of California. Birth Defects Res A Clin Mol Teratol 97: 730-735. http://dx.doi.org/10.1002/bdra.23175.

Pan, WC; Wu, CD; Chen, MJ; Huang, YT; Chen, CJ; Su, HJ; Yang, HI. (2016). Fine particle pollution, alanine transaminase, and liver cancer: A Taiwanese prospective cohort study (REVEAL-HBV). J Natl Cancer Inst 108: djv341. http://dx.doi.org/10.1093/jnci/djv341.

Panni, T; Mehta, AJ; Schwartz, JD; Baccarelli, AA; Just, AC; Wolf, K; Wahl, S; Cyrys, J; Kunze, S; Strauch, K; Waldenberger, M; Peters, A. (2016). Genome-wide analysis of DNA methylation and fine particulate matter air pollution in three study populations: KORA F3, KORA F4, and the Normative Aging Study. Environ Health Perspect 124: 983-990. http://dx.doi.org/10.1289/ehp.1509966.

Park, JK; Kim, YK; Lee, SR; Cho, SH; Min, KU; Kim, YY. (2001). Repeated exposure to low levels of sulfur dioxide (SO2) enhances the development of ovalbumin-induced asthmatic reactions in guinea pigs. Ann Allergy Asthma Immunol 86: 62-67. http://dx.doi.org/10.1016/S1081-1206(10)62358-7

Parker, JD; Akinbami, LJ; Woodruff, TJ. (2009). Air pollution and childhood respiratory allergies in the United States. Environ Health Perspect 117: 140-147. http://dx.doi.org/10.1289/ehp.11497

Parker, JD; Woodruff, TJ. (2008). Influences of study design and location on the relationship between particulate matter air pollution and birthweight. Paediatr Perinat Epidemiol 22: 214-227. http://dx.doi.org/10.1111/j.1365-3016.2008.00931.x.

Pascal, L; Pascal, M; Stempfelet, M; Goria, S; Declercq, C. (2013). Ecological study on hospitalizations for cancer, cardiovascular, and respiratory diseases in the industrial area of Etang-de-Berre in the South of France. J Environ Public Health 2013: 328737. http://dx.doi.org/10.1155/2013/328737

Pascal, M; Falq, G; Wagner, V; Chatignoux, E; Corso, M; Blanchard, M; Host, S; Pascal, L; Larrieu, S. (2014). Short-term impacts of particulate matter (PM10, PM10-2.5, PM2.5) on mortality in nine French cities. Atmos Environ 95: 175-184. http://dx.doi.org/10.1016/j.atmosenv.2014.06.030.

Patterson, W. B., Glasson, J., Naik, N., Jones, R. B., Berger, P. K., Plows, J. F., . . . Alderete, T. L. (2021). Prenatal exposure to ambient air pollutants and early infant growth and adiposity in the southern California mother's milk study. Environmental Health, 20(1). doi:10.1186/s12940-021-00753-8

Peacock, JL; Anderson, HR; Bremner, SA; Marston, L; Seemungal, TA; Strachan, DP; Wedzicha, JA. (2011). Outdoor air pollution and respiratory health in patients with COPD. Thorax 66: 591-596. http://dx.doi.org/10.1136/thx.2010.155358

Pedersen, M; Andersen, ZJ; Stafoggia, M; et al. (2017). Ambient air pollution and primary liver cancer incidence in four European cohorts within the ESCAPE project. Environ Res 154: 226-233. http://dx.doi.org/10.1016/j.envres.2017.01.006.

Pedersen, M; Giorgis-Allemand, L; Bernard, C; et al. (2013). Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med 1: 695-704. http://dx.doi.org/10.1016/S2213-2600(13)70192-9.

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 [Review]. Hypertension 64: 494-500. http://dx.doi.org/10.1161/HYPERTENSIONAHA.114.03545.

Peel, JL; Klein, M; Flanders, WD; Mulholland, JA; Freed, G; Tolbert, PE. (2011). Ambient air pollution and apnea and bradycardia in high-risk infants on home monitors. Environ Health Perspect 119: 1321-1327. http://dx.doi.org/10.1289/ehp.1002739.

Peel, JL; Tolbert, PE; Klein, M; Metzger, KB; Flanders, WD; Todd, K; Mulholland, JA; Ryan, PB; Frumkin, H. (2005). Ambient air pollution and respiratory emergency department visits. Epidemiology 16: 164-174. http://dx.doi.org/10.1097/01.ede.0000152905.42113.db.

Penard-Morand, C; Charpin, D; Raherison, C; Kopferschmitt, C; Caillaud, D; Lavaud, F; Annesi- Maesano, I. (2005). Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. Clin Exp Allergy 35: 1279-1287. http://dx.doi.org/10.1111/j.1365-2222.2005.02336.x

Peng, R; Bell, M; Geyh, A; McDermott, A; Zeger, S; Samet, J; Dominici, F. (2009). Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. Environ Health Perspect 117: 957-963. http://dx.doi.org/10.1289/ehp.0800185.

Peng, C; Bind, MC; Colicino, E; et al. (2016). Particulate air pollution and fasting blood glucose in non-diabetic individuals: Associations and epigenetic mediation in the normative aging study, 2000-2011. Environ Health Perspect 124: 1715-1721. http://dx.doi.org/10.1289/EHP183.

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: 2172-2179. http://dx.doi.org/10.1001/jama.299.18.2172.

Peng, RD; Samoli, E; Pham, L; et al. (2013). Acute effects of ambient ozone on mortality in Europe and North America: results from the APHENA study. Air Qual Atmos Health 6: 445-453. http://dx.doi.org/10.1007/s11869-012-0180-9

Pereira, G; Belanger, K; Ebisu, K; Bell, ML. (2014a). Fine Particulate Matter And Risk Of Preterm Birth In Connecticut In 2000-2006: A Longitudinal Study. Am J Epidemiol 179: 67-74. http://dx.doi.org/10.1093/aje/kwt216.

Pereira, G; Bell, ML; Belanger, K; de Klerk, N. (2014b). Fine particulate matter and risk of preterm birth and pre-labor rupture of membranes in Perth, Western Australia 1997-2007: a longitudinal study. Environ Int 73: 143-149. http://dx.doi.org/10.1016/j.envint.2014.07.014.

Pereira, G; Bracken, MB; Bell, ML. (2016). Particulate air pollution, fetal growth and gestational length: The influence of residential mobility in pregnancy. Environ Res 147: 269-274. http://dx.doi.org/10.1016/j.envres.2016.02.001.

Pereira, G; Evans, KA; Rich, DQ; Bracken, MB; Bell, ML. (2015). Fine particulates, preterm birth, and membrane rupture in Rochester, NY. Epidemiology 27: 66-73. http://dx.doi.org/10.1097/EDE.0000000000000366.

Perepu, RSP; Dostal, DE; Garcia, C; Kennedy, RH; Sethi, R. (2012). Cardiac dysfunction subsequent to chronic ozone exposure in rats. Mol Cell Biochem 360: 339-345. http://dx.doi.org/10.1007/s11010-011-1073-1

Petrovic, S; Urch, B; Brook, J; et al. (2000). Cardiorespiratory effects of concentrated ambient PM25: A pilot study using controlled human exposures. Inhal Toxicol 1: 173-188. http://dx.doi.org/10.1080/089583700196482.

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: 18. http://dx.doi.org/10.1186/s12940-016-0111-6.

Pinto-Almazan, R; Rivas-Arancibia, S; Farfan-Garcia, ED; Rodriguez-Martinez, E; Guerra-Araiza, C. (2014). Neuroprotective effects of tibolone against oxidative stress induced by ozone exposure. Rev Neurol 58: 441-449.

Pires, A; Neves de Melo, E; Mauad, T; Hilario Nascimento Saldiva, P; de Siqueira Bueno, HM. (2011). Pre- and postnatal exposure to ambient levels of urban particulate matter (PM2.5) affects mice spermatogenesis. Inhal Toxicol 23: 237-245. http://dx.doi.org/10.3109/08958378.2011.563508.

Poloniecki, J. D., Atkinson, R. W., de Leon, A. P., & Anderson, H. R. (1997). Daily Time Series for Cardiovascular Hospital admissions and previous day's air pollution in London, UK. Occupational and Environmental Medicine, 54(8), 535–540. https://doi.org/10.1136/oem.54.8.535

Pope, CA; Turner, MC; Burnett, R; Jerrett, M; Gapstur, SM; Diver, WR; Krewski, D; Brook, RD. (2014). Relationships between fine particulate air pollution, cardiometabolic disorders and cardiovascular mortality. Circ Res 116: 108-U258. http://dx.doi.org/10.1161/CIRCRESAHA.116.305060.

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: 71-77. http://dx.doi.org/10.1161/01.cir.0000108927.80044.7f.

Pope, CA, III; 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: 1132-1141. http://dx.doi.org/10.1001/jama.287.9.1132

Pope, CA, III; 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: 669-674. http://dx.doi.org/10.1164/ajrccm/151.3_Pt_1.669

Porta, D., Narduzzi, S., Badaloni, C., Bucci, S., Cesaroni, G., Colelli, V., Davoli, M., Sunyer, J., Zirro, E., Schwartz, J., & Forastiere, F. (2015). Air pollution and cognitive development at age seven in a prospective Italian birth cohort. Epidemiology, 1. https://doi.org/10.1097/ede.0000000000000405

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: 1152-1158. http://dx.doi.org/10.1289/ehp.1408720.

Power, M. C., Kioumourtzoglou, M.-A., Hart, J. E., Okereke, O. I., Laden, F., & Weisskopf, M. G. (2015). The relation between past exposure to fine particulate air pollution and prevalent anxiety: Observational cohort study. BMJ. https://doi.org/10.1136/bmj.h1111

Prieto-Parra, L; Yohannessen, K; Brea, C; Vidal, D; Ubilla, CA; Ruiz-Rudolph, P. (2017). Air pollution, PM2.5 composition, source factors, and respiratory symptoms in asthmatic and nonasthmatic children in Santiago, Chile. Environ Int 101: 190-200. http://dx.doi.org/10.1016/j.envint.2017.01.021.

Puett, RC; Hart, JE; Suh, H; Mittleman, M; Laden, F. (2011). Particulate matter exposures, mortality and cardiovascular disease in the health professionals follow-up study. Environ Health Perspect 119: 1130-1135. http://dx.doi.org/10.1289/ehp.1002921.

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: 1697-1701. http://dx.doi.org/10.1289/ehp.0900572.

Pun, VC; Hart, JE; Kabrhel, C; Camargo, CA; 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: 1265-1270. http://dx.doi.org/10.1289/ehp.1408927.

Qin, G; Wang, J; Huo, Y; Yan, H; Jiang, C; Zhou, J; Wang, X; Sang, N. (2012). Sulfur dioxide inhalation stimulated mitochondrial biogenesis in rat brains. Toxicology 300: 67-74. http://dx.doi.org/10.1016/j.tox.2012.05.026

Qin, G; Wu, M; Wang, J; Xu, Z; Xia, J; Sang, N. (2016). Sulfur dioxide contributes to the cardiac and mitochondrial dysfunction in rats. Toxicol Sci 151: 334-346.

Qin, XD; Qian, Z; Vaughn, MG; Trevathan, E; Emo, B; Paul, G; Ren, WH; Hao, YT; Dong, GH. (2015). Gender-specific differences of interaction between obesity and air pollution on stroke and cardiovascular diseases in Chinese adults from a high pollution range area: A large population based cross sectional study. Sci Total Environ 529: 243-248. http://dx.doi.org/10.1016/j.scitotenv.2015.05.041

Qiu, H; Yu, ITS; Wang, X; Tian, L; Tse, LA; Wong, TW. (2013b). Season and humidity dependence of the effects of air pollution on COPD hospitalizations in Hong Kong. Atmos Environ 76: 74-80. http://dx.doi.org/10.1016/j.atmosenv.2012.07.026

Qiu, H; Yu, I; Wang, X; Tian, L; Tse, L; Wong, T. (2013). Differential effects of fine and coarse particles on daily emergency cardiovascular hospitalizations in Hong Kong. Atmos Environ 64: 296-302. http://dx.doi.org/10.1016/j.atmosenv.2012.09.060.

Raaschou-Nielsen, O; Andersen, ZJ; Beelen, R; et al. (2013). Air pollution and lung cancer incidence in 17 European cohorts: Prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol 14: 813- 822. http://dx.doi.org/10.1016/S1470-2045(13)70279-1.

Raaschou-Nielsen, O; Beelen, R; Wang, M; et al. (2016). Particulate matter air pollution components and risk for lung cancer. Environ Int 87: 66-73. http://dx.doi.org/10.1016/j.envint.2015.11.007.

Rabinovitch, N; Silveira, L; Gelfand, EW; Strand, M. (2011). The response of children with asthma to ambient particulate is modified by tobacco smoke exposure. Am J Respir Crit Care Med 184: 1350-1357. http://dx.doi.org/10.1164/rccm.201010-1706OC.

Rabinovitch, N; Strand, M; Gelfand, EW. (2006). Particulate levels are associated with early asthma worsening in children with persistent disease. Am J Respir Crit Care Med 173: 1098-1105. http://dx.doi.org/10.1164/rccm.200509-1393OC.

Radwan, M; Jurewicz, J; Polańska, K; Sobala, W; Radwan, P; Bochenek, M; Hanke, W. (2015). Exposure to ambient air pollution-does it affect semen quality and the level of reproductive hormones? Ann Hum Biol 43: 50-56. http://dx.doi.org/10.3109/03014460.2015.1013986.

Rajagopalan, S. (2012). Cardiovascular remodeling in response to long-term exposure to fine particulate matter air pollution. Circulation: Heart Failure 5: 452-461. http://dx.doi.org/10.1161/CIRCHEARTFAILURE.112.966580.

Rage, E; Jacquemin, B; Nadif, R; Oryszczyn, MP; Siroux, V; Aguilera, I; Kauffmann, F; Künzli, N. (2009). Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults. Allergy 64: 40-46. http://dx.doi.org/10.1111/j.1398-9995.2008.01800.x

Rainho, CR; Velho, AM; Corrêa, SM; Mazzei, JL; Aiub, CA; Felzenszwalb, I. (2013). Prediction of health risk due to polycyclic aromatic hydrocarbons present in urban air in Rio de Janeiro, Brazil. Genet Mol Res 12: 3992-4002. http://dx.doi.org/10.4238/2013.February.28.6.

Raizenne, ME; Burnett, RT; Stern, B; Franklin, CA; Spengler, JD. (1989). Acute lung function responses to ambient acid aerosol exposures in children. Environ Health Perspect 79: 179-185.

Ramadour, M; Burel, C; Lanteaume, A; Vervloet, D; Charpin, D; Brisse, F; Dutau, H; Charpin, D. (2000). Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous air pollutants. Allergy 55: 1163-1169. http://dx.doi.org/10.1034/j.1398-9995.2000.00637.x

Rappazzo KM, Nichols JL, Rice RB, Luben TJ. Ozone exposure during early pregnancy and preterm birth: A systematic review and meta-analysis. Environ Res. 2021 Jul;198:111317. doi: 10.1016/j.envres.2021.111317. Epub 2021 May 12. PMID: 33989623; PMCID: PMC8221456.

Ray, A., Huisman, M., Tamsma, J., Van Asten, J., Bingen, B., Broeders, E., . . . De Vries, L. (2009). The role of inflammation on atherosclerosis, intermediate and clinical cardiovascular endpoints in type 2 diabetes mellitus. European Journal of Internal Medicine, 20(3), 253-260. doi:10.1016/j.ejim.2008.07.008

Renzi, M; Cerza, F; Gariazzo, C; Agabiti, N; Cascini, S; Di Domenicantonio, R; Davoli, M; Forastiere, F; Cesaroni, G. (2017). Air pollution and occurrence of type 2 diabetes in a large cohort study. Environ Int 112: 68-76. http://dx.doi.org/10.1016/j.envint.2017.12.007

Rhinehart, ZJ; Kinnee, E; Essien, UR; Saul, M; Guhl, E; Clougherty, JE; Magnani, JW. (2020). Association of Fine Particulate Matter and Risk of Stroke in Patients With Atrial Fibrillation. JAMA Netw Open 3: e2011760. http://dx.doi.org/10.1001/jamanetworkopen.2020.11760

Rice, MB; Ljungman, PL; Wilker, EH; Gold, DR; Schwartz, JD; Koutrakis, P; Washko, GR; O'Connor, GT; Mittleman, MA. (2013). Short-term exposure to air pollution and lung function in the Framingham heart study. Am J Respir Crit Care Med 188: 1351-1357. http://dx.doi.org/10.1164/rccm.201308-1414OC

Rice, MB; Rifas-Shiman, SL; Litonjua, AA; et al. (2015b). Lifetime exposure to ambient pollution and lung function in children. Am J Respir Crit Care Med 193: 881-888. http://dx.doi.org/10.1164/rccm.201506-1058OC.

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: 488-496. http://dx.doi.org/10.1136/jech.2008.082792

Rich, DQ; Mittleman, MA; Link, MS; Schwartz, J; Luttmann-Gibson, H; Catalano, PJ; Speizer, FE; Gold, DR; Dockery, DW. (2006b). Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. Environ Health Perspect 114: 120-123. http://dx.doi.org/10.1289/ehp.8371.

Ritz, B., P. C. Lee, J. Hansen, C. F. Lassen, M. Ketzel, M. Sorensen and O. Raaschou-Nielsen (2016). "Traffic-Related Air Pollution and Parkinson's Disease in Denmark: A Case-Control Study." Environ Health Perspect 124(3): 351-356.

Reid CE, Brauer M, Johnston FH, Jerrett M, Balmes JR, Elliott CT. Critical Review of Health Impacts of Wildfire Smoke Exposure. Environ Health Perspect. 2016 Sep;124(9):1334-43. doi: 10.1289/ehp.1409277. Epub 2016 Apr 15. PMID: 27082891; PMCID: PMC5010409.

Riedel, F; Kramer, M; Scheibenbogen, C; Rieger, CHL. (1988). Effects of SO2 exposure on allergic sensitization in the guinea pig. J Allergy Clin Immunol 82: 527-534. http://dx.doi.org/10.1016/0091-6749(88)90961-X

Ritz, B., P. C. Lee, J. Hansen, C. F. Lassen, M. Ketzel, M. Sorensen and O. Raaschou-Nielsen (2016). "Traffic-Related Air Pollution and Parkinson's Disease in Denmark: A Case-Control Study." Environ Health Perspect 124(3): 351-356.

Ritz, B., J. Qiu, P. C. Lee, F. Lurmann, B. Penfold, R. Erin Weiss, R. McConnell, C. Arora, C. Hobel and M. Wilhelm (2014). "Prenatal air pollution exposure and ultrasound measures of fetal growth in Los Angeles, California." Environmental Research 130: 7-13.

Ritz, B., M. Wilhelm, K. J. Hoggatt and J. K. Ghosh (2007). "Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles." Am J Epidemiol 166(9): 1045-1052.

Ritz, B., M. Wilhelm and Y. Zhao (2006). "Air pollution and infant death in southern California, 1989-2000." Pediatrics 118(2): 493-502.

Ritz, B., F. Yu, G. Chapa and S. Fruin (2000). "Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993." Epidemiology 11(5): 502-511.

Ritz, B., F. Yu, S. Fruin, G. Chapa, G. M. Shaw and J. A. Harris (2002). "Ambient air pollution and risk of birth defects in Southern California." Am J Epidemiol 155(1): 17-25.

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: 316-322. http://dx.doi.org/10.1016/j.envres.2014.12.020.

Rodopoulou, S; Chalbot, MC; Samoli, E; Dubois, DW; Filippo, B; Kavouras, IG. (2014). Air pollution and hospital emergency room and admissions for cardiovascular and respiratory diseases in Doria Ana County, New Mexico. Environ Res 129: 39-46. http://dx.doi.org/10.1016/j.envres.2013.12.006.

Rodopoulou, S; Samoli, E; Chalbot, MG; Kavouras, IG. (2015). Air pollution and cardiovascular and respiratory emergency visits in Central Arkansas: A time-series analysis. Sci Total Environ 536: 872-879. http://dx.doi.org/10.1016/j.scitotenv.2015.06.056.

Romieu, I., N. Gouveia, L. A. Cifuentes, A. P. de Leon, W. Junger, J. Vera, V. Strappa, M. Hurtado-Diaz, V. Miranda-Soberanis, L. Rojas-Bracho, L. Carbajal-Arroyo and G. Tzintzun-Cervantes (2012). "Multicity study of air pollution and mortality in Latin America (the ESCALA study)." Res Rep Health Eff Inst(171): 5-86.

Rossner, P; Rossnerova, A; Spatova, M; Beskid, O; Uhlirova, K; Libalova, H; Solansky, I; Topinka, J; Sram, RJ. (2013a). Analysis of biomarkers in a Czech population exposed to heavy air pollution. Part II: chromosomal aberrations and oxidative stress. Mutagenesis 28: 97-106. http://dx.doi.org/10.1093/mutage/ges058.

Rossner, P; Rossnerova, A; Sram, RJ. (2011). Oxidative stress and chromosomal aberrations in an environmentally exposed population. Mutat Res 707: 34-41. http://dx.doi.org/10.1016/j.mrfmmm.2010.12.005.

Roy, A; Hu, W; Wei, F; Korn, L; Chapman, RS; Zhang, JJ. (2012). Ambient particulate matter and lung function growth in Chinese children. Epidemiology 23: 464-472. http://dx.doi.org/10.1097/EDE.0b013e31824cbd6d.

Rossner, P; Svecova, V; Schmuczerova, J; Milcova, A; Tabashidze, N; Topinka, J; Pastorkova, A; Sram, RJ. (2013b). Analysis of biomarkers in a Czech population exposed to heavy air pollution. Part I: bulky DNA adducts. Mutagenesis 28: 89-95. http://dx.doi.org/10.1093/mutage/ges057.

Routledge, HC; Manney, S; Harrison, RM; Ayres, JG; Townend, JN. (2006). Effect of inhaled sulphur dioxide and carbon particles on heart rate variability and markers of inflammation and coagulation in human subjects. Heart 92: 220-227. http://dx.doi.org/10.1136/hrt.2004.051672

Rowan, W. H., Campen, M. J., Wichers, L. B., & Watkinson, W. P. (2007). Heart rate variability in rodents: Uses and caveats in toxicological studies. Cardiovascular Toxicology, 7(1), 28–51. https://doi.org/10.1007/s12012-007-0004-6

Rudra, CB; Williams, MA; Sheppard, L; Koenig, JQ; Schiff, MA. (2011). Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in western Washington state. Environ Health Perspect 119: 886-892. http://dx.doi.org/10.1289/ehp.1002947.

Saenen, ND; Plusquin, M; Bijnens, E; Janssen, BG; Gyselaers, W; Cox, B; Fierens, F; Molenberghs, G; Penders, J; Vrijens, K; De Boever, P; Nawrot, T. (2015). In utero fine particle air pollution and placental expression of genes in the brain-derived neurotrophic factor signaling pathway: An ENVIRONAGE birth cohort study. Environ Health Perspect 123: 834-840. http://dx.doi.org/10.1289/ehp.1408549.

Saenen, ND; Vrijens, K; Janssen, BG; Madhloum, N; Peusens, M; Gyselaers, W; Vanpoucke, C; Lefebvre, W; Roels, HA; Nawrot, TS. (2016). Placental nitrosative stress and exposure to ambient air pollution during gestation: A population study. Am J Epidemiol 184: 442-449. http://dx.doi.org/10.1093/aje/kww007.

Sagiv, SK; Mendola, P; Loomis, D; Herring, AH; Neas, LM; Savitz, DA; Poole, C. (2005). A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997-2001. Environ Health Perspect 113: 602-606. http://dx.doi.org/10.1289/ehp.7646

Salam, MT; Islam, T; Gauderman, WJ; Gilliland, FD. (2009). Roles of arginase variants, atopy, and ozone in childhood asthma. J Allergy Clin Immunol 123: 596-602. http://dx.doi.org/10.1016/j.jaci.2008.12.020

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: 1679-1687. http://dx.doi.org/10.1007/s10995-011-0868-8.

Samoli, E; Andersen, ZJ; Katsouyanni, K; et al. (2016a). Exposure to ultrafine particles and respiratory hospitalisations in five European cities. Eur Respir J 48: 674- 682. http://dx.doi.org/10.1183/13993003.02108-2015.

Samoli, E; Atkinson, RW; Analitis, A; Fuller, GW; Beddows, D; Green, DC; Mudway, IS; Harrison, RM; Anderson, HR; Kelly, FJ. (2016b). Differential health effects of short-term exposure to source-specific particles in London, U.K. Environ Int 97: 246-253. http://dx.doi.org/10.1016/j.envint.2016.09.017.

Samoli, E; Stafoggia, M; Rodopoulou, S; et al. (2014). Which specific causes of death are associated with short term exposure to fine and coarse particles in Southern Europe ? Results from the MED-PARTICLES project. Environ Int 67: 54-61. http://dx.doi.org/10.1016/j.envint.2014.02.013.

Sarnat, SE; Winquist, A; Schauer, JJ; Turner, JR; Sarnat, JA. (2015). Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the St. Louis, Missouri-Illinois, metropolitan area. Environ Health Perspect 123: 437-444. http://dx.doi.org/10.1289/ehp.1307776.

Sarovar V, Malig BJ, Basu R. A case-crossover study of short-term air pollution exposure and the risk of stillbirth in California, 1999-2009. Environ Res. 2020 Dec;191:110103. doi: 10.1016/j.envres.2020.110103. Epub 2020 Aug 23. PMID: 32846172.

Schembari, A; Nieuwenhuijsen, MJ; Salvador, J; de Nazelle, A; Cirach, M; Dadvand, P; Beelen, R; Hoek, G; Basagaña, X; Vrijheid, M. (2014). Traffic-related air pollution and congenital anomalies in Barcelona. Environ Health Perspect 122: 317-323. http://dx.doi.org/10.1289/ehp.1306802.

Schelegle, ES; Morales, CA; Walby, WF; Marion, S; Allen, RP. (2009). 6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. Am J Respir Crit Care Med 180: 265-272. http://dx.doi.org/10.1164/rccm.200809-1484OC

Schelegle, ES; Walby, WF. (2012). Vagal afferents contribute to exacerbated airway responses following ozone and allergen challenge. Respir Physiol Neurobiol 181: 277-285. http://dx.doi.org/10.1016/j.resp.2012.04.003

Schiffman, S. S., C. E. Studwell, L. R. Landerman, K. Berman and J. S. Sundy (2005a). "Symptomatic effects of exposure to diluted air sampled from a swine confinement atmosphere on healthy human subjects." Environ Health Perspect 113(5): 567-576.

Schiffman, S. S. and C. M. Williams (2005b). "Science of odor as a potential health issue." J Environ Qual 34(1): 129-138.

Schinasi, L., R. A. Horton, V. T. Guidry, S. Wing, S. W. Marshall and K. B. Morland (2011). "Air pollution, lung function, and physical symptoms in communities near concentrated Swine feeding operations." Epidemiology 22(2): 208-215.

Schikowski, T; Adam, M; Marcon, A; et al. (2014). Association of ambient air pollution with the prevalence and incidence of COPD. Eur Respir J 44: 614-626. http://dx.doi.org/10.1183/09031936.00132213.

Schikowski, T; Sugiri, D; Ranft, U; Gehring, U; Heinrich, J; Wichmann, HE; Krämer, U. (2005). Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Respir Res 22: 152- 161. http://dx.doi.org/10.1186/1465-9921-6-152.

Schneider, A; Hampel, R; Ibald-Mulli, A; et al. (2010). Changes in deceleration capacity of heart rate and heart rate variability induced by ambient air pollution in individuals with coronary artery disease. Part Fibre Toxicol 7: 29. http://dx.doi.org/10.1186/1743-8977-7-29.

Shusterman, D. (2001). "Odor-associated health complaints: competing explanatory models." Chem Senses 26(3): 339-343.

Shusterman, D., J. Lipscomb, R. Neutra and K. Satin (1991). "Symptom prevalence and odor-worry interaction near hazardous waste sites." Environ Health Perspect 94: 25-30.

Seagrave, J; Campen, M; McDonald, J; Mauderly, J; Rohr, A. (2008). Oxidative stress, inflammation, and pulmonary function assessment in rats exposed to laboratory-generated pollutant mixtures. J Toxicol Environ Health A 71: 1352-1362. http://dx.doi.org/10.1080/15287390802271566.

Ségala, C; Poizeau, D; Mesbah, M; Willems, S; Maidenberg, M. (2008). Winter air pollution and infant bronchiolitis in Paris. Environ Res 106: 96-100. http://dx.doi.org/10.1016/j.envres.2007.05.003

Sethi, R; Manchanda, S; Perepu, RS; Kumar, A; Garcia, C; Kennedy, RH; Palakurthi, S; Dostal, D. (2012). Differential expression of caveolin-1 and caveolin-3: potential marker for cardiac toxicity subsequent to chronic ozone inhalation. Mol Cell Biochem 369: 9-15. http://dx.doi.org/10.1007/s11010-012-1363-2

Sienra-Monge, J. J., M. Ramirez-Aguilar, H. Moreno-Macias, et al. (2004). "Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone." Clinical and Experimental Immunology 138(2): 317-322.

Silverman, RA; Ito, K. (2010). Age-related association of fine particles and ozone with severe acute asthma in New York City. J Allergy Clin Immunol 125: 367-373. http://dx.doi.org/10.1016/j.jaci.2009.10.061.

Sinclair, AH; Edgerton, ES; Wyzga, R; Tolsma, D. (2010). A two-time-period comparison of the effects of ambient air pollution on outpatient visits for acute respiratory illnesses. J Air Waste Manag Assoc 60: 163- 175. http://dx.doi.org/10.3155/1047-3289.60.2.163.

Sinclair, AH; Tolsma, D. (2004). Associations and lags between air pollution and acute respiratory visits in an ambulatory care setting: 25-month results from the Aerosol Research and Inhalation Epidemiological Study. J Air Waste Manag Assoc 54: 1212-1218. http://dx.doi.org/10.1080/10473289.2004.10470979.

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 [Review]. B M J (Online) 350: h1295. http://dx.doi.org/10.1136/bmj.h1295

Shin, HH; Gogna, P; Maquiling, A; Parajuli, RP; Haque, L; Burr, B. (2021a). Comparison of hospitalization and mortality associated with short-term exposure to ambient ozone and PM2.5 in Canada. Chemosphere 265: 9128683. http://dx.doi.org/10.1016/j.chemosphere.2020.128683

Shin, HH; Parajuli, RP; Gogna, P; Maquiling, A; Dehghani, P. (2021b). Pollutant-sex specific differences in respiratory hospitalization and mortality risk attributable to short-term exposure to ambient air pollution. 12 Sci Total Environ 755: 143135. http://dx.doi.org/10.1016/j.scitotenv.2020.143135

Sharkhuu, T; Doerfler, DL; Copeland, C; Luebke, RW; Gilmour, MI. (2011). Effect of maternal exposure to ozone on reproductive outcome and immune, inflammatory, and allergic responses in the offspring. J Immunotoxicol 8: 183-194. http://dx.doi.org/10.3109/1547691X.2011.568978

Slama, R; Bottagisi, S; Solansky, I; Lepeule, J; Giorgis-Allemand, L; Sram, R. (2013). Short-term impact of atmospheric pollution on fecundability. Epidemiology 24: 871-879. http://dx.doi.org/10.1097/EDE.0b013e3182a702c5.

Slama, R; Darrow, L; Parker, J; et al. (2008). Meeting report: Atmospheric pollution and human reproduction. Environ Health Perspect 116: 791-798. http://dx.doi.org/10.1289/ehp.11074.

Slama, R; Gräbsch, C; Lepeule, J; Siroux, V; Cyrys, J; Sausenthaler, S; Herbarth, O; Bauer, M; Borte, M; Wichmann, HE; Heinrich, J. (2010). Maternal fine particulate matter exposure, polymorphism in xenobiotic- metabolizing genes and offspring birth weight. Reprod Toxicol 30: 600-612. http://dx.doi.org/10.1016/j.reprotox.2010.07.001.

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: 346-353. http://dx.doi.org/10.1016/S1081-1206(10)61681-X.

Smith, MT; Guyton, KZ; Gibbons, CF; et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis [Review]. Environ Health Perspect 124: 713-721. http://dx.doi.org/10.1289/ehp.1509912.

Smith, RB; Fecht, D; Gulliver, J; Beevers, SD; Dajnak, D; Blangiardo, M; Ghosh, RE; Hansell, AL; Kelly, FJ; Anderson, HR; Toledano, MB. (2017). Impact of London's road traffic air and noise pollution on birth

weight: retrospective population based cohort study. BMJ 359: j5299. http://dx.doi.org/10.1136/bmj.j5299

Smith, GS; Van Den Eeden, SK; Garcia, C; Shan, J; Baxter, R; Herring, AH; Richardson, DB; Van Rie, A; Emch, M; Gammon, MD. (2016). Air pollution and pulmonary tuberculosis: A nested case- control study among members of a northern california health plan. Environ Health Perspect 124: 761-768. http://dx.doi.org/10.1289/ehp.1408166

Snow, SJ; Gordon, CJ; Bass, VL; Schladweiler, MC; Ledbetter, AD; Jarema, KA; Phillips, PM; Johnstone, AF; Kodavanti, UP. (2016). Age-related differences in pulmonary effects of acute and subchronic episodic ozone exposures in Brown Norway rats. Inhal Toxicol 28: 313-323. http://dx.doi.org/10.3109/08958378.2016.1170910

Soberanes, S; Gonzalez, A; Urich, D; et al. (2012). Particulate matter Air Pollution induces hypermethylation of the p16 promoter Via a mitochondrial ROS-JNK-DNMT1 pathway. Sci Rep 2: 275. http://dx.doi.org/10.1038/srep00275.

Solic, J. J., M. J. Hazucha and P. A. Bromberg (1982). "The acute effects of 0.2 ppm ozone in patients with chronic obstructive pulmonary disease." American Review of Respiratory Disease 125(6): 664-669.

Son; J-Y; Bell, ML; Lee; J-T. (2011). Survival analysis of long-term exposure to different sizes of airborne particulate matter and risk of infant mortality using a birth cohort in Seoul, Korea. Environ Health Perspect 119: 725-730. http://dx.doi.org/10.1289/ehp.1002364.

Song, S; Lee, K; Lee, YM; Lee, JH; Lee, SI; Yu, SD; Paek, D. (2011). Acute health effects of urban fine and ultrafine particles on children with atopic dermatitis. Environ Res 111: 394-399. http://dx.doi.org/10.1016/j.envres.2010.10.010.

Song, A; Liao, Q; Li, J; Lin, F; Liu, E; Jiang, X; Deng, L. (2012). Chronic exposure to sulfur dioxide enhances airway hyperresponsiveness only in ovalbumin-sensitized rats. Toxicol Lett 214: 320-327. http://dx.doi.org/10.1016/j.toxlet.2012.09.010

South Coast Air Quality Management District. (1996). "1996 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/home/library/clean-air-plans/air-quality-mgt-plan/1997-aqmp.

South Coast Air Quality Management District. (2000). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-II)." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/home/library/air-quality-data-studies/health-studies/mates-ii.

South Coast Air Quality Management District. (2003). "2003 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2003-air-quality-management-plan/2003-aqmp-appendix-i.pdf?sfvrsn=2.

South Coast Air Quality Management District. (2007). "2007 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2007-air-quality-management-plan/2007-aqmp-appendix-i.pdf?sfvrsn=2.

South Coast Air Quality Management District. (2008). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-III)." Diamond Bar, CA South Coast Air Quality Management District from http://www.aqmd.gov/home/library/air-quality-data-studies/health-studies/mates-iii.

South Coast Air Quality Management District. (2012). "Socioeconomic Report for the 2012 AQMP." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2012-air-quality-management-plan/final-2012-aqmp-(february-2013)/final-socioeconomic-report-2012.pdf?sfvrsn=2.

South Coast Air Quality Management District. (2013a). "2012 Air Quality Management Plan." Diamond Bar, CA South Coast Air Quality Management District.

South Coast Air Quality Management District. (2013b). "2012 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2012-air-quality-management-plan/final-2012-aqmp-(february-2013)/appendix-i-final-2012.pdf.

South Coast Air Quality Management District. (2015). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-IV)." Diamond Bar, CA South Coast Air Quality Management District. From http://www.aqmd.gov/home/library/air-quality-data-studies/health-studies/mates-iv.

South Coast Air Quality Management District. (2021). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-V)." Diamond Bar, CA South Coast Air Quality Management District. from https://www.aqmd.gov/home/air-quality/air-quality-studies/health-studies/mates-v.

Spektor, DM; Lippmann, M. (1991). Health effects of ambient ozone on healthy children at a summer camp. In RL Berglund; DR Lawson; DJ McKee (Eds.), Tropospheric Ozone and the Environment: Papers from an International Conference; March 1990; Los Angeles, CA (pp. 83-89). Pittsburgh, PA: Air & Waste Management Association.

Spektor, DM; Lippmann, M; Lioy, PJ; Thurston, GD; Citak, K; James, DJ; Bock, N; Speizer, FE; Hayes, C. (1988). Effects of ambient ozone on respiratory function in active, normal children. Am Rev Respir Dis 137: 313-320. http://dx.doi.org/10.1164/ajrccm/137.2.313

Spiezia, L; Campello, E; Bon, M; Maggiolo, S; Pelizzaro, E; Simioni, P. (2014). Short-term exposure to high levels of air pollution as a risk factor for acute isolated pulmonary embolism. Thromb Res Suppl 134: 259-263. http://dx.doi.org/10.1016/j.thromres.2014.05.011

Spira-Cohen, A; Chen, LC; Kendall, M; Lall, R; Thurston, GD. (2011). Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. Environ Health Perspect 119: 559-565. http://dx.doi.org/10.1289/ehp.1002653

Stafoggia, M; Cesaroni, G; Peters, A; et al. (2014). Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. Environ Health Perspect 122: 919-925. http://dx.doi.org/10.1289/ehp.1307301.

Stafoggia, M; Samoli, E; Alessandrini, E; Cadum, E; Ostro, B; Berti, G; Faustini, A; Jacquemin, B; Linares, C; Pascal, M; Randi, G; Ranzi, A; Stivanello, E; Forastiere, F. (2013). Short-term associations between fine

and coarse particulate matter and hospitalizations in southern europe: Results from the MED-PARTICLES Project. Environ Health Perspect 121: 1026-1033. http://dx.doi.org/10.1289/ehp.1206151.Stafoggia, M;

Schneider, A; Cyrys, J; Samoli, E; et al. (2017). Association between short-term exposure to ultrafine particles and mortality in eight European urban areas. Epidemiology 28: 172-180. http://dx.doi.org/10.1097/EDE.0000000000000599.

Steenhof, M; Mudway, IS; Gosens, I; et al. (2013). Acute nasal pro-inflammatory response to air pollution depends on characteristics other than particle mass concentration or oxidative potential: The RAPTES project. Occup Environ Med 70: 341-348. http://dx.doi.org/10.1136/oemed-2012-100993.

Steurer MA, Baer RJ, Chambers CD, et al. (2021) Mortality and Major Neonatal Morbidity in Preterm Infants with Serious Congenital Heart Disease. J Pediatr. 2021 Dec;239:110-116.e3. doi: 10.1016/j.jpeds.2021.08.039. Epub 2021 Aug 26. PMID: 34454949.

Stieb, D. M., Berjawi, R., Emode, M., Zheng, C., Salama, D., Hocking, R., Lyrette, N., Matz, C., Lavigne, E., & Shin, H. H. (2021). Systematic Review and meta-analysis of cohort studies of long term outdoor nitrogen dioxide exposure and mortality. PLOS ONE, 16(2). https://doi.org/10.1371/journal.pone.0246451

Stieb, DM; Chen, L; Beckerman, BS; et al. (2015). Associations of pregnancy outcomes and PM2.5 in a national Canadian study. Environ Health Perspect 124: 243-249. http://dx.doi.org/10.1289/ehp.1408995.

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: 25. http://dx.doi.org/10.1186/1476-069X-8-25.

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: 25. http://dx.doi.org/10.1186/1476-069X-8-25

Stiegel, MA; Pleil, JD; Sobus, JR; Stevens, T; Madden, MC. (2017). Linking physiological parameters to perturbations in the human exposome: Environmental exposures modify blood pressure and lung function via inflammatory cytokine pathway. J Toxicol Environ Health A 80: 485-501. http://dx.doi.org/10.1080/15287394.2017.1330578

Stingone, JA; Luben, TJ; Daniels, JL; 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: 863-872. http://dx.doi.org/10.1289/ehp.1307289

Strak, M; Boogaard, H; Meliefste, K; Oldenwening, M; Zuurbier, M; Brunekreef, B; Hoek, G. (2010).

Respiratory health effects of ultrafine and fine particle exposure in cyclists. Occup Environ Med 67: 118-124. http://dx.doi.org/10.1136/oem.2009.046847.

Strak, M; Janssen, NA; Godri, KJ; et al. (2012). Respiratory health effects of airborne particulate matter: The role of particle size, composition and oxidative potential - The RAPTES project. Environ Health Perspect 120: 1183-1189. http://dx.doi.org/10.1289/ehp.1104389.

Strak, M; Hoek, G; Godri, KJ; et al. (2013a). Composition of PM affects acute vascular inflammatory and coagulative markers - The RAPTES project. PLoS ONE 8: e58944. http://dx.doi.org/10.1371/journal.pone.0058944.

Strak, M; Hoek, G; Steenhof, M; et al. (2013b). Components of ambient air pollution affect thrombin generation in healthy humans: The RAPTES project. Occup Environ Med 70: 332-340. http://dx.doi.org/10.1136/oemed-2012-100992.

Strand, M; Vedal, S; Rodes, C; Dutton, SJ; Gelfand, EW; Rabinovitch, N. (2006). Estimating effects of ambient PM2.5 exposure on health using PM2.5 component measurements and regression calibration. J Expo Sci Environ Epidemiol 16: 30-38. http://dx.doi.org/10.1038/sj.jea.7500434.

Straney, L; Finn, J; Dennekamp, M; Bremner, A; Tonkin, A; Jacobs, I. (2014). Evaluating the impact of air pollution on the incidence of out-of-hospital cardiac arrest in the Perth Metropolitan Region: 2000-2010. J Epidemiol Community Health 68: 6-12. http://dx.doi.org/10.1136/jech-2013-202955

Strickland, MJ; Darrow, LA; Klein, M; Flanders, WD; Sarnat, JA; Waller, LA; Sarnat, SE; Mulholland, JA; Tolbert, PE. (2010). Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Am J Respir Crit Care Med 182: 307-316. http://dx.doi.org/10.1164/rccm.200908- 1201OC.

Strickland, MJ; Hao, H; Hu, X; Chang, HH; Darrow, LA; Liu, Y. (2015). Pediatric emergency visits and short-term changes in PM2.5 concentrations in the U.S. state of Georgia. Environ Health Perspect 124: 690-696. http://dx.doi.org/10.1289/ehp.1509856.

Symanski, E; Mchugh, MK; Zhang, X; Craft, ES; Lai, D. (2016). Evaluating narrow windows of maternal exposure to ozone and preterm birth in a large urban area in Southeast Texas. J Expo Sci Environ Epidemiol 26: 167-172. http://dx.doi.org/10.1038/jes.2015.32

Taggart, SCO; Custovic, A; Francis, HC; Faragher, EB; Yates, CJ; Higgins, BG; Woodcock, A. (1996). Asthmatic bronchial hyperresponsiveness varies with ambient levels of summertime air pollution. Eur Respir J 9: 1146-1154. http://dx.doi.org/10.1183/09031936.96.09061146

Talbott, EO; Rager, J. R.; Benson, S; Ann Brink, L; Bilonick, RA; Wu, C. (2014). A case-crossover analysis of the impact of PM2.5 on cardiovascular disease hospitalizations for selected CDC tracking states. Environ Res 134C: 455-465. http://dx.doi.org/10.1016/j.envres.2014.06.018.

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: S29-S35. http://dx.doi.org/10.1038/sj.jes.7500625.

Tallon, LA; Manjourides, J; Pun, VC; Mittleman, MA; Kioumourtzoglou, MA; Coull, B; Suh, H. (2017). Erectile dysfunction and exposure to ambient Air pollution in a nationally representative cohort of older Men. Environ Health 16: 12. http://dx.doi.org/10.1186/s12940-017-0216-6

Tank, J; Biller, H; Heusser, K; Holz, O; Diedrich, A; Framke, T; Koch, A; Grosshennig, A; Koch, W; Krug, N; Jordan, J; Hohlfeld, JM. (2011). Effect of acute ozone induced airway inflammation on human sympathetic nerve traffic: a randomized, placebo controlled, crossover study. PLoS ONE 6: e18737. http://dx.doi.org/10.1371/journal.pone.0018737

Tecer, LH; Alagha, O; Karaca, F; Tuncel, G; Eldes, N. (2008). Particulate matter (PM2.5, PM10-2.5, and PM10) and childrens hospital admissions for asthma and respiratory diseases: a bidirectional case-crossover study. J Toxicol Environ Health A 71: 512-520. http://dx.doi.org/10.1080/15287390801907459.

Teichert, T; Vossoughi, M; Vierkötter, A; Sugiri, D; Schikowski, T; Schulte, T; Roden, M; Luckhaus, C; Herder, C; Krämer, U. (2013). Association between traffic-related air pollution, subclinical inflammation and impaired glucose metabolism: Results from the SALIA study. PLoS ONE 8: e83042. http://dx.doi.org/10.1371/journal.pone.0083042.

Tétreault, LF; Doucet, M; Gamache, P; Fournier, M; Brand, A; Kosatsky, T; Smargiassi, A. (2016a). Childhood exposure to ambient air pollutants and the onset of asthma: an administrative cohort study in Québec. Environ Health Perspect 124: 1276-1282. http://dx.doi.org/10.1289/ehp.1509838

Tétreault, LF; Doucet, M; Gamache, P; Fournier, M; Brand, A; Kosatsky, T; Smargiassi, A. (2016b). Severe and moderate asthma exacerbations in asthmatic children and exposure to ambient air pollutants. Int J Environ Res Public Health 13: 771. http://dx.doi.org/10.3390/ijerph13080771

Thomson, EM; Vladisavljevic, D; Mohottalage, S; Kumarathasan, P; Vincent, R. (2013). Mapping acute systemic effects of inhaled particulate matter and ozone: multiorgan gene expression and glucocorticoid activity. Toxicol Sci 135: 169-181. http://dx.doi.org/10.1093/toxsci/kft137

To, T; Zhu, J; Larsen, K; et al. (2016). Progression from asthma to chronic obstructive pulmonary disease (COPD): is air pollution a risk factor? Am J Respir Crit Care Med 194: 429-438. http://dx.doi.org/10.1164/rccm.201510- 1932OC

To, T; Zhu, J; Villeneuve, PJ; Simatovic, J; Feldman, L; Gao, C; Williams, D; Chen, H; Weichenthal, S; Wall, C; Miller, AB. (2015). Chronic disease prevalence in women and air pollution - A 30-year longitudinal cohort study. Environ Int 80: 26-32. http://dx.doi.org/10.1016/j.envint.2015.03.017.

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: 1958-1966. http://dx.doi.org/10.1002/ijc.30255.

Tonne, C; Halonen, JI; Beevers, SD; Dajnak, D; Gulliver, J; Kelly, FJ; Wilkinson, P; Anderson, HR. (2015). Long-term traffic air and noise pollution in relation to mortality and hospital readmission among myocardial infarction survivors. Int J Hyg Environ Health 219: 72-78. http://dx.doi.org/10.1016/j.ijheh.2015.09.003.

Trasande, L; Wong, K; Roy, A; Savitz, DA; Thurston, G. (2013). Exploring prenatal outdoor air pollution, birth outcomes and neonatal health care utilization in a nationally representative sample. J Expo Sci Environ Epidemiol 23: 315-321. http://dx.doi.org/10.1038/jes.2012.124.

Traversi, D; Cervella, P; Gilli, G. (2014). Evaluating the genotoxicity of urban PM2.5 using PCR-based methods in human lung cells and the Salmonella TA98 reverse test. Environ Sci Pollut Res Int 22: 1279-1289. http://dx.doi.org/10.1007/s11356-014-3435-1.

Traversi, D; Degan, R; De Marco, R; Gilli, G; Pignata, C; Ponzio, M; Rava, M; Sessarego, F; Villani, S; Bono,

R. (2008). Mutagenic properties of PM2.5 air pollution in the Padana Plain (Italy) before and in the course of XX Winter Olympic Games of Torino 2006. Environ Int 34: 966-970. http://dx.doi.org/10.1016/j.envint.2008.02.007.

Traversi, D; Schilirò, T; Degan, R; Pignata, C; Alessandria, L; Gilli, G. (2011). Involvement of nitro-compounds in the mutagenicity of urban Pm2.5 and Pm10 in Turin. Mutat Res 726: 54-59. http://dx.doi.org/10.1016/j.mrgentox.2011.09.002.

Trenga, CA; Sullivan, JH; Schildcrout, JS; Shepherd, KP; Shapiro, GG; Liu, LJ; Kaufman, JD; Koenig, JQ. (2006). Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. Chest 129: 1614-1622. http://dx.doi.org/10.1378/chest.129.6.1614.

Tu, J; Tu, W; Tedders, SH. (2016). Spatial variations in the associations of term birth weight with ambient air pollution in Georgia, USA. Environ Int 92-93: 146-156. http://dx.doi.org/10.1016/j.envint.2016.04.005.

Tunnicliffe, WS; Hilton, MF; Harrison, RM; Ayres, JG. (2001). The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. Eur Respir J 17: 604-608.

Turin, TC; Kita, Y; Rumana, N; Nakamura, Y; Ueda, K; Takashima, N; Sugihara, H; Morita, Y; Ichikawa, M; Hirose, K; Nitta, H; Okayama, A; Miura, K; Ueshima, H. (2012). Short-term exposure to air pollution and incidence of stroke and acute myocardial infarction in a Japanese population. Neuroepidemiology 38: 84- 92. http://dx.doi.org/10.1159/000335654

Turner, J; Hernandez, M; Snawder, JE; Handorean, A; McCabe, KM. (2015). A toxicology suite adapted for comparing parallel toxicity responses of model human lung cells to diesel exhaust particles and their extracts. Aerosol Sci Technol 49: 599-610. http://dx.doi.org/10.1080/02786826.2015.1053559.

Turner, MC; Cohen, A; Jerrett, M; Gapstur, SM; Diver, WR; Pope, CA; Krewski, D; Beckerman, BS; Samet, JM. (2014). Interactions between cigarette smoking and fine particulate matter in the risk of lung cancer mortality in cancer prevention study II. Am J Epidemiol 180: 1145-1149. http://dx.doi.org/10.1093/aje/kwu275.

Turner, MC; Jerrett, M; Pope, A, III; Krewski, D; Gapstur, SM; Diver, WR; Beckerman, BS; Marshall, JD; Su, J; Crouse, DL; Burnett, RT. (2016). Long-term ozone exposure and mortality in a large prospective study. Am J Respir Crit Care Med 193: 1134-1142. http://dx.doi.org/10.1164/rccm.201508-1633OC.

Turner, MC; Krewski, D; Pope, CA, III; 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: 1374-1381. http://dx.doi.org/10.1164/rccm.201106-1011OC.

Tyler, CR; Zychowski, KE; Sanchez, BN; Rivero, V; Lucas, S; Herbert, G; Liu, J; Irshad, H; McDonald, JD; Bleske, BE; Campen, MJ. (2016). Surface area-dependence of gas-particle interactions influences pulmonary and neuroinflammatory outcomes. Part Fibre Toxicol 13: 64. http://dx.doi.org/10.1186/s12989-016-0177-x.

Tzivian, L., Dlugaj, M., Winkler, A., et al. (2016). Long-term air pollution and traffic noise exposures and mild cognitive impairment in older adults: A cross-sectional analysis of the Heinz Nixdorf Recall Study. Environmental Health Perspectives, 124(9), 1361–1368. https://doi.org/10.1289/ehp.1509824

U.S. EPA (U.S. Environmental Protection Agency). (1996a). Air quality criteria for ozone and related photochemical oxidants [EPA Report]. (EPA/600/P-93/004AF). Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (2006). Air quality criteria for ozone and related photochemical oxidants [EPA Report]. (EPA/600/R-05/004AF). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923

U.S. EPA. (2007). "Review of the National Ambient Air Quality Standards for Lead: Policy Assessment of Scientific and Technical Information " Washington, DC U.S. Environmental Protection Agency. EPA-452/R-07-013.

U.S. EPA. (2008). "Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria (Final Report)." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-08/047F.

U.S. EPA (U.S. Environmental Protection Agency). (2009). Integrated science assessment for particulate matter [EPA Report]. (EPA/600/R-08/139F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546.

U.S. EPA. (2010). "Integrated Science Assessment for Carbon Monoxide (Final Report)." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-09/019F.

U.S. EPA. (2012). "Regulatory Impact Analysis related to the Proposed Revisions to the National Ambient Air Quality Standards for Particulate Matter " Washington, DC U.S. Environmental Protection Agency. EPA-452/R-12-003.

U.S. EPA (U.S. Environmental Protection Agency). (2013a). Integrated science assessment for ozone and related photochemical oxidants [EPA Report]. (EPA/600/R-10/076F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492

U.S. EPA (U.S. Environmental Protection Agency). (2015). Preamble to the integrated science assessments [EPA Report]. (EPA/600/R-15/067). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, RTP Division. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

U.S. EPA. (2015b). "National Ambient Air Quality Standards for Lead. Proposed Rule." Federal Register Washington, DC U.S. Environmental Protection Agency. Vol, 80, No. 2.

U.S. EPA. (2017). "Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria (Final Report)." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-17/451. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division.https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=338596

U.S. EPA (U.S. Environmental Protection Agency). (2019). Integrated science assessment for particulate matter [EPA Report]. (EPA/600/R-19/188). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534

U.S. EPA (U.S. Environmental Protection Agency). (2020). Integrated science assessment for ozone and related photochemical oxidants [EPA Report]. (EPA/600/R-20/012)Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division. https://cfpub.epa.gov/ncea/isa/recorddisplay.cfm?deid=348522

U.S. EPA (U.S. Environmental Protection Agency). (2021). Supplement to Integrated science assessment for particulate matter [EPA Report]. (EPA/600/R-21/198) Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. https://cfpub.epa.gov/ncea/isa/recorddisplay.cfm?deid=354490

Urman, R; McConnell, R; Islam, T; Avol, EL; Lurmann, FW; Vora, H; Linn, WS; Rappaport, EB; Gilliland, FD; Gauderman, WJ. (2014). Associations of children's lung function with ambient air pollution: Joint effects of regional and near-roadway pollutants. Thorax 69: 540-547. http://dx.doi.org/10.1136/thoraxjnl-2012-203159

Vanos, J. K., Hebbern, C., & Cakmak, S. (2014). Risk assessment for cardiovascular and respiratory mortality due to air pollution and synoptic meteorology in 10 Canadian cities. Environmental Pollution, 185, 322-332. doi:10.1016/j.envpol.2013.11.007

Vedal, S. (1997). "Ambient particles and health: lines that divide." J Air Waste Manag Assoc 47(5): 551-581.

Velická, H; Puklová, V; Keder, J; Brabec, M; Malý, M; Bobák, M; Kotlík, B; Jiřík, V; Janout, V; Kazmarová, H. (2015). Asthma exacerbations and symptom variability in children due to short-term ambient air pollution changes in Ostrava, Czech Republic. Cent Eur J Public Health 23: 292-298. http://dx.doi.org/10.21101/cejph.a4548

Vencloviene, J., Braziene, A., Dedele, A., Lopatiene, K., & Dobozinskas, P. (2017). Associations of short-term exposure to ambient air pollutants with emergency ambulance calls for the exacerbation of essential arterial hypertension. International Journal of Environmental Health Research, 27(6), 509–524. https://doi.org/10.1080/09603123.2017.1405246

Veras, MM; Damaceno-Rodrigues, NR; Caldini, EG; Maciel Ribeiro, AA; Mayhew, TM; Saldiva, PH; Dolhnikoff, M. (2008). Particulate urban air pollution affects the functional morphology of mouse placenta. Biol Reprod 79: 578-584. http://dx.doi.org/10.1095/biolreprod.108.069591.

Veras, MM; Guimaraes-Silva, RM; Caldini, EG; Saldiva, PHN; Dolhnikoff, M; Mayhew, TM. (2012). The effects of particulate ambient air pollution on the murine umbilical cord and its vessels: A quantitative morphological and immunohistochemical study. Reprod Toxicol 34: 598-606. http://dx.doi.org/10.1016/j.reprotox.2012.08.003.

Viehmann, A; Hertel, S; Fuks, K; Eisele, L; Moebus, S; Möhlenkamp, S; Nonnemacher, M; Jakobs, H; Erbel, R; Jöckel, KH; Hoffmann, B. (2015). Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. Occup Environ Med 72: 656-663. http://dx.doi.org/10.1136/oemed-2014-102800.

Vieira, JL; Guimaraes, GV; de Andre, PA; Cruz, FD; Nascimento Saldiva, PH; Bocchi, EA. (2016a). Respiratory filter reduces the cardiovascular effects associated with diesel exhaust exposure a

randomized, prospective, double-blind, controlled study of heart failure: the FILTER-HF trial. JACC: Heart Failure 4: 55-64. http://dx.doi.org/10.1016/j.jchf.2015.07.018.

Vieira, JL; Guimaraes, GV; de Andre, PA; Nascimento Saldiva, PH; Bocchi, EA. (2016b). Effects of reducing exposure to air pollution on submaximal cardiopulmonary test in patients with heart failure: Analysis of the randomized, double-blind and controlled FILTER-HF trial. Int J Cardiol 215: 92-97. http://dx.doi.org/10.1016/j.ijcard.2016.04.071.

Vinikoor-Imler, LC; Davis, JA; Meyer, RE; Messer, LC; Luben, TJ. (2014). Associations between prenatal exposure to air pollution, small for gestational age, and term low birthweight in a state- wide birth cohort. Environ Res 132: 132-139. http://dx.doi.org/10.1016/j.envres.2014.03.040

Villeneuve, P. J., Chen, L., Stieb, D., & Rowe, B. H. (2006). Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. European Journal of Epidemiology, 21(9), 689-700. doi:10.1007/s10654-006-9050-9

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: 696-701. http://dx.doi.org/10.1002/bdra.23159.

Vinikoor-Imler, LC; Davis, JA; Meyer, RE; Messer, LC; Luben, TJ. (2014). Associations between prenatal exposure to air pollution, small for gestational age, and term low birthweight in a state-wide birth cohort. Environ Res 132: 132-139. http://dx.doi.org/10.1016/j.envres.2014.03.040.

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. http://dx.doi.org/10.1016/j.envpol.2015.03.001.

Volk, HE; Lurmann, F; Penfold, B; Hertz-Picciotto, I; McConnell, R. (2013). Traffic-related air pollution, particulate matter, and autism. Arch Gen Psychiatry 70: 71-77. http://dx.doi.org/10.1001/jamapsychiatry.2013.266

von Klot, S; Wölke, G; Tuch, T; Heinrich, J; Dockery, DW; Schwartz, J; Kreyling, WG; Wichmann, HE; Peters, A. (2002). Increased asthma medication use in association with ambient fine and ultrafine particles. Eur Respir J 20: 691-702. http://dx.doi.org/10.1183/09031936.02.01402001.

Wallace, ME; Grantz, KL; Liu, D; Zhu, Y; Kim, SS; Mendola, P. (2016). Exposure to ambient air pollution and premature rupture of membranes. Am J Epidemiol 183: 1114-1121. http://dx.doi.org/10.1093/aje/kwv284.

Wang, C; Chen, R; Zhao, Z; Cai, J; Lu, J; Ha, S; Xu, X; Chen, X; Kan, H. (2015). Particulate air pollution and circulating biomarkers among type 2 diabetic mellitus patients: The roles of particle size and time windows of exposure. Environ Res 140: 112-118. http://dx.doi.org/10.1016/j.envres.2015.03.026.Wang, IJ; Tung, TH; Tang, CS; Zhao, ZH. (2015a). Allergens, air pollutants, and childhood allergic diseases. Int J Hyg Environ Health 219: 66-71. http://dx.doi.org/10.1016/j.ijheh.2015.09.001.

Wang, M; Gehring, U; Hoek, G; Keuken, M; Jonkers, S; Beelen, R; Eeftens, M; Postma, DS; Brunekreef, B. (2015b). Air pollution and lung function in Dutch children: a comparison of exposure estimates and

associations based on land use regression and dispersion exposure modeling approaches. Environ Health Perspect 123: 847-851. http://dx.doi.org/10.1289/ehp.1408541.

Wang, X; Dockery, DW; Wypij, D; Gold, DR; Speizer, FE; Ware, JH; Ferris, BG, Jr. (1993). Pulmonary function growth velocity in children 6 to 18 years of age. Am J Respir Crit Care Med 148: 1502-1508. http://dx.doi.org/10.1164/ajrccm/148.6_Pt_1.1502.

Ward-Caviness, CK; Weaver, AM; Buranosky, M; Pfaff, ER; Neas, LM; Devlin, RB; Schwartz, J; Di, Q; Cascio, WE; Diaz-Sanchez, D. (2020). Associations between long-term fine particulate matter exposure and mortality in heart failure patients. J Am Heart Assoc 9: e012517. 54 http://dx.doi.org/10.1161/JAHA.119.012517

Warren, J; Fuentes, M; Herring, A; Langlois, P. (2012). Spatial-temporal modeling of the association between air pollution exposure and preterm birth: Identifying critical windows of exposure. Biometrics 68: 1157-1167. http://dx.doi.org/10.1111/j.1541-0420.2012.01774.x.

Warren, JL; Stingone, JA; Herring, AH; Luben, TJ; Fuentes, M; Aylsworth, AS; Langlois, PH; Botto, LD; Correa, A; Olshan, AF; NBDPS. (2016). Bayesian multinomial probit modeling of daily windows of susceptibility for maternal PM2.5 exposure and congenital heart defects. Stat Med 35: 2786-2801. http://dx.doi.org/10.1002/sim.6891.

Weaver, AM; Mcguinn, L; Neas, L; et al. (2019). Neighborhood sociodemographic effects on the associations between long-term PM2.5 exposure and cardiovascular outcomes and diabetes. Environmental Epidemiology 3. http://dx.doi.org/10.1097/EE9.0000000000000038

Weaver, AM; Wang, Y; Wellenius, GA; Bidulescu, A; Sims, M; Vaidyanathan, A; Hickson, DA; Shimbo, D; Abdalla, M; Diaz, KM; Seals, SR. (2021). Long-term air pollution and blood pressure in an African American cohort: The Jackson Heart Study. Am J Prev Med 60: 397-405. 8 http://dx.doi.org/10.1016/j.amepre.2020.10.023

Wei, Y; Wang, Y; Di, Q; Choirat, C; Wang, Y; Koutrakis, P; Zanobetti, A; Dominici, F; Schwartz, JD. (2019). Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case crossover study. BMJ 367: l6258. http://dx.doi.org/10.1136/bmj.l6258

Wei, Y; Wang, Y; Wu, X; Di, Q; Shi, L; Koutrakis, P; Zanobetti, A; Dominici, F; Schwartz, JD. (2020). Causal effects of air pollution on mortality in Massachusetts. Am J Epidemiol 189: 1316–1323. http://dx.doi.org/10.1093/aje/kwaa098

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: 92-99. http://dx.doi.org/10.1016/j.envres.2015.12.013.

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: 70. http://dx.doi.org/10.1186/s12989-014-0070-4.

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: 1373-1378. http://dx.doi.org/10.1289/ehp.1003321.

Weichenthal, S; Lavigne, E; Evans, G; Pollitt, K; Burnett, RT. (2016b). Ambient PM2.5 and risk of emergency room visits for myocardial infarction: Impact of regional PM2.5 oxidative potential: A case-crossover study. Environ Health 15: 46. http://dx.doi.org/10.1186/s12940-016-0129-9.

Weichenthal, SA; Lavigne, E; Evans, GJ; Godri Pollitt, KJ; Burnett, RT. (2016c). PM2.5 and emergency room visits for respiratory illness: effect modification by oxidative potential. Am J Respir Crit Care Med 194: 577- 586. http://dx.doi.org/10.1164/rccm.201512-2434OC.

Weichenthal, S; Pinault, LL; Burnett, RT. (2017). Impact of oxidant gases on the relationship between outdoor fine particulate air pollution and nonaccidental, cardiovascular, and respiratory mortality. Sci Rep 7: 16401. http://dx.doi.org/10.1038/s41598-017-16770-y

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: 609-615. http://dx.doi.org/10.1289/ehp.1307277.

Weir, CH; Yeatts, KB; Sarnat, JA; Vizuete, W; Salo, PM; Jaramillo, R; Cohn, RD; Chu, H; Zeldin, DC; London, SJ. (2013). Nitrogen dioxide and allergic sensitization in the 2005-2006 National Health and Nutrition Examination Survey. Respir Med 107: 1763-1772. http://dx.doi.org/10.1016/j.rmed.2013.08.010

Wenten, M., W. J. Gauderman, K. Berhane, P. C. Lin, J. Peters and F. D. Gilliland (2009). "Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: an example of epistasis in gene-environment interactions." Am J Epidemiol 170(12): 1494-1501.

Weuve, J. (2012). Exposure to particulate air pollution and cognitive decline in older women. Archives of Internal Medicine, 172(3), 219. https://doi.org/10.1001/archinternmed.2011.683

White, LF; Jerrett, M; Yu, J; Marshall, JD; Rosenberg, L; Coogan, PF. (2016). Ambient air pollution and 16-year weight change in African-American women. Am J Prev Med 51: e99e105. http://dx.doi.org/10.1016/j.amepre.2016.03.007

Wilhelm, M. and B. Ritz (2005). "Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA." Environ Health Perspect 113(9): 1212-1221.

Wilhelm, M; Ghosh, JK; Su, J; Cockburn, M; Jerrett, M; Ritz, B. (2011). Traffic-related air toxics and preterm birth: a population-based case-control study in Los Angeles county, California. Environ Health 10: 89. http://dx.doi.org/10.1186/1476-069X-10-89.

Wilson, D. A., W. Xu, B. Sadrian, E. Courtiol, Y. Cohen and D. C. Barnes (2014). "Cortical odor processing in health and disease." Prog Brain Res 208: 275-305.

Winquist, A; Kirrane, E; Klein, M; Strickland, M; Darrow, LA; Sarnat, SE; Gass, K; Mulholland, J; Russell, A; Tolbert, P. (2014). Joint effects of ambient air pollutants on pediatric asthma emergency department visits

Winquist, A; Klein, M; Tolbert, P; Flanders, WD; Hess, J; Sarnat, SE. (2012). Comparison of emergency department and hospital admissions data for air pollution time-series studies. Environ Health 11: 70. http://dx.doi.org/10.1186/1476-069X-11-70.

Wittkopp, S., N. Staimer, T. Tjoa, D. Gillen, N. Daher, M. Shafer, J. J. Schauer, C. Sioutas and R. J. Delfino (2013). "Mitochondrial genetic background modifies the relationship between traffic-related air pollution exposure and systemic biomarkers of inflammation." PLoS ONE 8(5): e64444.

Woodruff, TJ; Darrow, LA; Parker, JD. (2008). Air pollution and postneonatal infant mortality in the United States, 1999-2002. Environ Health Perspect 116: 110-115. http://dx.doi.org/10.1289/ehp.10370.

Wolf, K; Popp, A; Schneider, A; Breitner, S; Hampel, R; Rathmann, W; Herder, C; Roden, M; Koenig, W; Meisinger, C; Peters, A. (2016). Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation and adipokines. Diabetes 65: 3314-3326. http://dx.doi.org/10.2337/db15-1567.

Wolkoff, P; Clausen, PA; Larsen, ST; Hammer, M; Nielsen, GD. (2012). Airway effects of repeated exposures to ozone-initiated limonene oxidation products as model of indoor air mixtures. Toxicol Lett 209: 166-172. http://dx.doi.org/10.1016/j.toxlet.2011.12.008

Wong, CM; Tsang, H; Lai, HK; Thomas, GN; Lam, KB; Chan, KP; Zheng, Q; Ayres, JG; Lee, SY; Lam, TH; Thach, TQ. (2016). Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol Biomarkers Prev 25: 839-845. http://dx.doi.org/10.1158/1055-9965.EPI-15-0626.

Wong, CM; Yang, L; Thach, TQ; Chau, PY; Chan, KP; Thomas, GN; Lam, TH; Wong, TW; Hedley, AJ; Peiris, JS. (2009). Modification by influenza on health effects of air pollution in Hong Kong. Environ Health Perspect 117: 248-253. http://dx.doi.org/10.1289/ehp.11605

Wood, AM; Harrison, RM; Semple, S; Ayres, JG; Stockley, RA. (2009). Outdoor air pollution is associated with disease severity in a1-antitrypsin deficiency. Eur Respir J 34: 346-353. http://dx.doi.org/10.1183/09031936.00087908

Woodruff, TJ; Darrow, LA; Parker, JD. (2008). Air pollution and postneonatal infant mortality in the United States, 1999-2002. Environ Health Perspect 116: 110-115. http://dx.doi.org/10.1289/ehp.10370

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: 17731779. http://dx.doi.org/10.1289/ehp.0800334.

Wu, J; Wilhelm, M; Chung, J; Ritz, B. (2011). Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res 111: 685-692. http://dx.doi.org/10.1016/j.envres.2011.03.008.

Wu, S; Ni, Y; Li, H; Pan, L; Yang, D; Baccarelli, AA; Deng, F; Chen, Y; Shima, M; Guo, X. (2016). Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China. Environ Int 94: 76-82. http://dx.doi.org/10.1016/j.envint.2016.05.004.

Wyatt, LH; Xi, YZ; Kshirsagar, A; Di, Q; Ward-Caviness, C; Wade, TJ; Cascio, WE; Rappold, AG. (2020c).Association of short-term exposure to ambient PM2.5 with hospital admissions and 30-day

readmissions in end-stage renal disease patients: population-based retrospective cohort study. BMJ Open 10: e041177. 45 http://dx.doi.org/10.1136/bmjopen-2020-041177

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: 115. http://dx.doi.org/10.1186/s12940-016-0196-y.

Xu, X; Ha, S; Kan, H; Hu, H; Curbow, BA; Lissaker, CTK. (2013). Health effects of air pollution on length of respiratory cancer survival. BMC Public Health 13: 800. http://dx.doi.org/10.1186/1471- 2458-13-800

Xu, X; Hu, H; Ha, S; Roth, J. (2014). Ambient air pollution and hypertensive disorder of pregnancy. J Epidemiol Community Health 68: 13-20. http://dx.doi.org/10.1136/jech-2013-202902.

Xu, X; Jiang, SY; Wang, T; Bai, Y; Zhong, M; Wang, A; Lippmann, M; Chen, L; Rajagopalan, S; Sun, Q. (2013). Inflammatory response to fine particulate air pollution exposure: Neutrophil versus monocyte. PLoS ONE 8: e71414. http://dx.doi.org/10.1371/journal.pone.0071414.

Yan, YH; Huang, CH; Chen, WJ; Wu, MF; Cheng, TJ. (2008). Effects of diesel exhaust particles on left ventricular function in isoproterenol-induced myocardial injury and healthy rats. Inhal Toxicol 20: 199-203. http://dx.doi.org/10.1080/08958370701861082.Yang, A; Janssen, NA; Brunekreef, B; Cassee, FR; Hoek, G; Gehring, U. (2016). Children's respiratory health and oxidative potential of PM2.5: the PIAMA birth cohort study. Occup Environ Med 73: 154-160. http://dx.doi.org/10.1136/oemed-2015-103175.

Yang, BY; Qian, ZM; Vaughn, MG; et al. (2017). Is prehypertension more strongly associated with long-term ambient air pollution exposure than hypertension? Findings from the 33 Communities Chinese Health Study. Environ Pollut 229: 696-704. http://dx.doi.org/10.1016/j.envpol.2017.07.016

Yang, BY; Qian, ZM; Li, S; Fan, S; Chen, G; Syberg, KM; Xian, H; Wang, SQ; Ma, H; Chen, DH; Yang, M; Liu, KK; Zeng, XW; Hu, LW; Guo, Y; Dong, GH. (2018). Long-term exposure to ambient air pollution (including PM1) and metabolic syndrome: The 33 Communities Chinese Health Study (33CCHS). Environ Res 164: 204-211. http://dx.doi.org/10.1016/j.envres.2018.02.029

Yang, WS; Zhao, H; Wang, X; Deng, Q; Fan, WY; Wang, L. (2015). An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. Eur J Cancer Prev 25: 163-172. http://dx.doi.org/10.1097/CEJ.0000000000000158.

Yaghjyan, L; Arao, R; Brokamp, C; O'Meara, ES; Sprague, BL; Ghita, G; Ryan, P. (2017). Association between air pollution and mammographic breast density in the Breast Cancer Surveillance Consortium. Breast Cancer Research 19: 36. http://dx.doi.org/10.1186/s13058-017- 0828-3

Yap, P; Gilbreath, S; Garcia, C; Jareen, N; Goodrich, B. (2013). The influence of socioeconomic markers on the association between fine particulate matter and hospital admissions for respiratory conditions among children. Am J Public Health 103: 695-702. http://dx.doi.org/10.2105/AJPH.2012.300945.

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: 15. http://dx.doi.org/10.1186/s12989-015-0092-6.

Yitshak Sade, M; Kloog, I; Liberty, IF; Schwartz, J; Novack, V. (2016). The association between air pollution exposure and glucose and lipids levels. J Clin Endocrinol Metab 101: 2460-2467. http://dx.doi.org/10.1210/jc.2016-1378.

Yorifuji, T; Kashima, S; Doi, H. (2016). Fine-particulate air pollution from diesel emission control and mortality rates in Tokyo: a quasi-experimental study. Epidemiology 27: 769-778. http://dx.doi.org/10.1097/EDE.0000000000000546.

Yorifuji, T; Kashima, S; Doi, H. (2016). Acute exposure to fine and coarse particulate matter and infant mortality in Tokyo, Japan (2002-2013). Sci Total Environ 551-552: 66-72. http://dx.doi.org/10.1016/j.scitotenv.2016.01.211.

Yoshizaki, K; Brito, JM; Silva, LF; Lino-Dos-Santos-Franco, A; Frias, DP; E Silva, RC; Amato-Lourenço, LF; Saldiva, PH; de Fátima Lopes Calvo Tibério, I; Mauad, T; Macchione, M. (2017). The effects of particulate matter on inflammation of respiratory system: Differences between male and female. Sci Total Environ 586: 284-295. http://dx.doi.org/10.1016/j.scitotenv.2017.01.221.

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: 201-207. http://dx.doi.org/10.1136/oemed- 2013-101526.

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: 58. http://dx.doi.org/10.1186/1476- 069X-8-58.

Zanobetti, A; Schwartz, J. (2011). Ozone and survival in four cohorts with potentially predisposing diseases. Am J Respir Crit Care Med 184: 836-841. http://dx.doi.org/10.1164/rccm.201102- 0227OC

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: 1414-1420. http://dx.doi.org/10.1289/EHP163.

Zhang, H; Liu, H; Davies, KJ; Sioutas, C; Finch, CE; Morgan, TE; Forman, HJ. (2012). Nrf2-regulated phase II enzymes are induced by chronic ambient nanoparticle exposure in young mice with age-related impairments. Free Radic Biol Med 52: 2038-2046. http://dx.doi.org/10.1016/j.freeradbiomed.2012.02.042.

Zhang, Z., Wang, J., & Lu, W. (2018). Exposure to Nitrogen Dioxide and chronic obstructive pulmonary disease (COPD) in adults: A systematic review and meta-analysis. Environmental Science and Pollution Research, 25(15), 15133–15145. https://doi.org/10.1007/s11356-018-1629-7

Zhang, Z; Whitsel, E; Quibrera, P; Smith, R; Liao, D; Anderson, G; Prineas, R. (2009). Ambient fine particulate matter exposure and myocardial ischemia in the Environmental Epidemiology of Arrhythmogenesis in the Women's Health Initiative (EEAWHI) study. Environ Health Perspect 117: 751-756. http://dx.doi.org/10.1289/ehp.0800046.

Zhao, A; Chen, R; Wang, C; Zhao, Z; Yang, C; Lu, J; Chen, X; Kan, H. (2015). Associations between size-fractionated particulate air pollution and blood pressure in a panel of type II diabetes mellitus patients. Environ Int 80: 19-25. http://dx.doi.org/10.1016/j.envint.2015.03.003.

Zhao, QG; Liang, ZJ; Tao, SJ; Zhu, JA; Du, YK. (2011). Effects of air pollution on neonatal prematurity in

Zhao, Y., Hu, J., Tan, Z., Liu, T., Zeng, W., Li, X., Huang, C., Wang, S., Huang, Z., & Ma, W. (2019). Ambient carbon monoxide and increased risk of daily hospital outpatient visits for respiratory diseases in Dongguan, China. Science of The Total Environment, 668, 254–260. https://doi.org/10.1016/j.scitotenv.2019.02.333

Zhou, P., Qian, Z., McMillin, S., Vaughn, M., Xie, Z., Xu, Y., Dong, G. (2021). Relationships between long-term ozone exposure and allergic rhinitis and bronchitic symptoms in Chinese children. Toxics, 9(9), 221. doi:10.3390/toxics9090221

Zhao, Y; Qian, Z; Wang, J; Vaughn, MG; Liu, Y; Ren, W; Dong, G. (2013). Does obesity amplify the association between ambient air pollution and increased blood pressure and hypertension in adults? Findings from the 33 Communities Chinese Health Study [Letter]. Int J Cardiol 168: E148-E150. http://dx.doi.org/10.1016/j.ijcard.2013.08.071

Zhao, Y; Wang, S; Lang, L; Huang, C; Ma, W; Lin, H. (2016). Ambient fine and coarse particulate matter pollution and respiratory morbidity in Dongguan, China. Environ Pollut 222: 126-131. http://dx.doi.org/10.1016/j.envpol.2016.12.070.

Zhao, Z., Chen, R., Lin, Z., Cai, J., Yang, Y., Yang, D., Norback, D., & Kan, H. (2016). Ambient carbon monoxide associated with alleviated respiratory inflammation in healthy young adults. Environmental Pollution, 208, 294–298. https://doi.org/10.1016/j.envpol.2015.07.029

Zheng, X.-yan, Orellano, P., Lin, H.-liang, Jiang, M., & Guan, W.-jie. (2021). Short-term exposure to ozone, nitrogen dioxide, and sulphur dioxide and emergency department visits and hospital admissions due to asthma: A systematic review and meta-analysis. Environment International, 150, 106435. https://doi.org/10.1016/j.envint.2021.106435

Zora, JE; Sarnat, SE; Raysoni, AU; Johnson, BA; Li, WW; Greenwald, R; Holguin, F; Stock, TH; Sarnat, JA. (2013). Associations between urban air pollution and pediatric asthma control in El Paso, Texas. Sci Total Environ 448: 56-65. http://dx.doi.org/10.1016/j.scitotenv.2012.11.067.

Zuurbier, M; Hoek, G; Oldenwening, M; Meliefste, K; Krop, E; van den Hazel, P; Brunekreef, B. (2011a). In- traffic air pollution exposure and CC16, blood coagulation, and inflammation markers in healthy adults. Environ Health Perspect 119: 1384-1389. http://dx.doi.org/10.1289/ehp.1003151.

Zuurbier, M; Hoek, G; Oldenwening, M; Meliefste, K; van den Hazel, P; Brunekreef, B. (2011b). Respiratory effects of commuters' exposure to air pollution in traffic. Epidemiology 22: 219-227. http://dx.doi.org/10.1097/EDE.0b013e3182093693.