CHAPTER 5 RESPIRATORY EFFECTS

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Respiratory Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and respiratory effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P 3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. The evidence presented throughout this chapter support the following causality determinations. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determinations
Short-term exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Long-term exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Inadequate
UFP	Inadequate

5.1 Short-Term $PM_{2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA (U.S. EPA, 2009) concluded that a "causal relationship is likely to exist" between short-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[55] This conclusion was based mainly on epidemiologic evidence demonstrating associations between short-term $PM_{2.5}$ 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 $PM_{2.5}$-related associations were observed in epidemiologic studies. In addition, the 2009 PM ISA described epidemiologic evidence as consistently showing $PM_{2.5}$-associated increases in hospital

[55] As detailed in the Preface, risk estimates are for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations unless otherwise noted.

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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. Epidemiologic evidence was inconsistent for hospital admissions or ED visits for asthma but supported associations with increased respiratory symptoms and decreases in lung function in children with asthma. Studies examining copollutant models showed that $PM_{2.5}$ associations with respiratory effects were robust to inclusion of CO or SO_2 in the model, but often were attenuated with inclusion of O_3 or NO_2. Evidence supporting an independent effect of $PM_{2.5}$ exposure on the respiratory system was provided by animal toxicological studies of $PM_{2.5}$ concentrated ambient particles (CAPs) demonstrating changes in some pulmonary function parameters, as well as inflammation, oxidative stress, injury, enhanced allergic responses, and reduced host defenses. Many of these effects have been implicated in the pathophysiology for asthma exacerbation, COPD exacerbation, or respiratory infection. Some of these effects were also observed with diesel exhaust (DE) or woodsmoke exposures; however, there was no attempt to attribute the effect to the particulate or gaseous components of the mixture. In the few controlled human exposure studies conducted in individuals with asthma or COPD, $PM_{2.5}$ exposure mostly had no effect on respiratory symptoms, lung function, or pulmonary inflammation. Short-term $PM_{2.5}$ exposure was not clearly related to respiratory effects in healthy people. Evidence integrated across scientific disciplines linked respiratory effects to several $PM_{2.5}$ components such as elemental carbon/black carbon (EC/BC), organic carbon (OC), and metals and $PM_{2.5}$ sources such as wildfires and traffic. However, there were few studies on any given component or source, and disparate outcomes were examined across studies and disciplines, complicating the overall interpretation of results. As a result, the 2009 PM ISA did not make a conclusion with respect to PM sources and components specifically for respiratory effects, but broadly concluded that "many [components] of PM can be linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those components or sources that are more closely related to specific health outcomes" (U.S. EPA, 2009).

The following section on short-term $PM_{2.5}$ exposure and respiratory effects opens with a discussion of biological plausibility (Section 5.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. The organization of sections by outcome group aims to clearly characterize the extent of coherence among related endpoints (e.g., hospital admissions, symptoms, inflammation) and biological plausibility of $PM_{2.5}$ effects. These outcome groups include asthma exacerbation (Section 5.1.2), COPD exacerbation (Section 5.1.4), respiratory infection (Section 5.1.5), combinations of respiratory-related disease hospital admissions and ED visits (Section 5.1.6), and respiratory mortality (Section 5.1.9). New to this ISA are distinct discussions of allergy exacerbation (Section 5.1.3), respiratory effects in healthy populations (Section 5.1.7), and respiratory effects in populations with cardiovascular disease (Section 5.1.8). Section 5.1.10 comprises an integrated discussion of policy-relevant considerations across the epidemiologic studies evaluated within Section 5.1. The evaluation of whether there is evidence of differential associations by various $PM_{2.5}$ components and sources, compared to $PM_{2.5}$ mass, is detailed in Section 5.1.11.

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5.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from short-term exposure to $PM_{2.5}$. Figure 5-1 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.1.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{2.5}$ may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Evidence that short-term exposure to $PM_{2.5}$ may affect the respiratory tract generally informs two proposed pathways (Figure 5-1). The first pathway begins with injury, inflammation, and oxidative stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of injury and oxidative stress, but it can also lead to further oxidative stress and injury due to secondary production of ROS by inflammatory cells. The second pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow.

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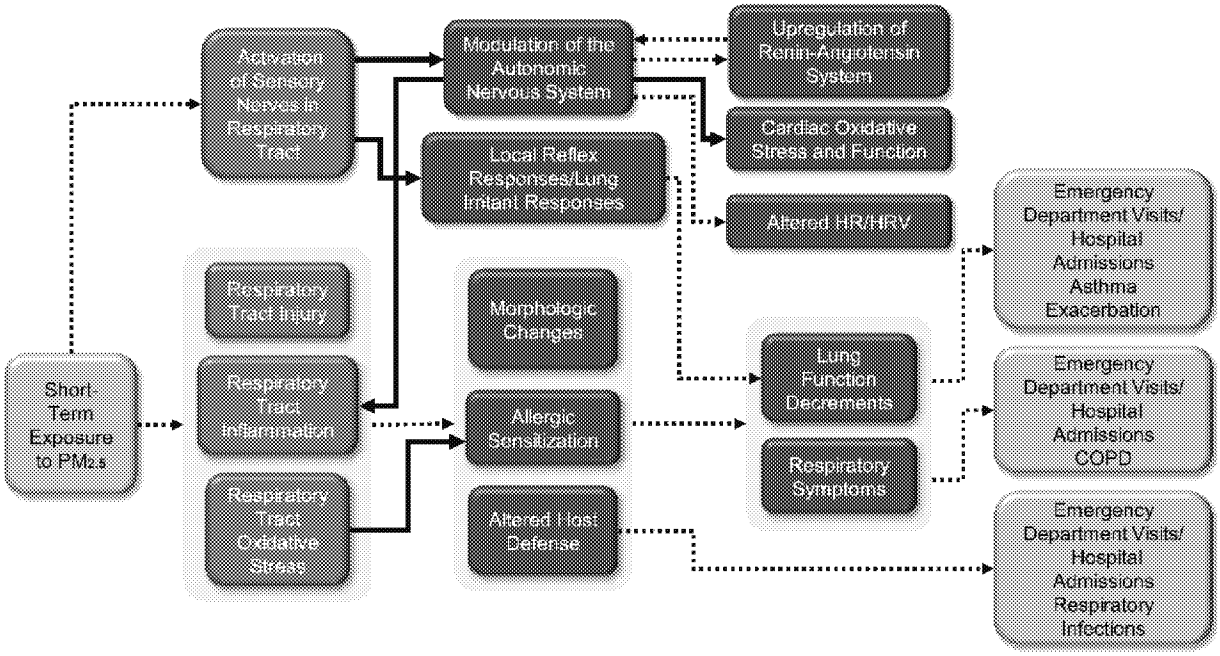

Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-1 Potential biological pathways for respiratory effects following short-term $PM_{2.5}$ exposure.

Injury, Inflammation, and Oxidative Stress

Regarding the first pathway, a large body of evidence from controlled human exposure (Section 5.1.7.2) and animal toxicological studies (Section 5.1.7.3 and Section 5.1.8) found injury, inflammation, and oxidative stress responses in healthy individuals and animals. These responses are highly variable. In studies involving concentrated ambient particles (CAPs) exposure, variability may be due to differences in concentration and sources of $PM_{2.5}$ present in the airshed. Multiday exposures generally resulted in more robust responses than exposures of a few hours. Some studies in humans and animals that examined markers in bronchoalveolar lavage fluid (BALF) found increased numbers of macrophages and neutrophils. Animal toxicological studies examining responses in lung tissue found markers of injury and oxidative stress, such as increased lung water and protein carbonyl content (Rhoden et al., 2004; Gurgueira et al., 2002), and markers of inflammation such as recruitment of macrophage populations (Xu et al., 2013). Other studies found evidence of mild morphologic changes, such as hyperplasia of the bronchoalveolar duct (Batalha et al., 2002) and changes in the mucus content of the nasal epithelium (Yoshizaki et al., 2016), that could be downstream effects of inflammation following

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inhalation of $PM_{2.5}$. Inflammation may lead to other downstream effects, such as lung function decrements. A decrease in maximal mid-expiratory flow coupled with a decrease in oxygen saturation, possibly indicating dysfunction of small peripheral airways, was observed in healthy humans following inhalation of $PM_{2.5}$ (Gong et al., 2005). It is not clear whether the decrement in lung function seen in this study was due to inflammation or to autonomic nervous system (ANS) responses, which are discussed below.

Some experimental evidence focuses on respiratory responses in specific disease states, such as asthma and COPD, in which inflammation is known to play an important role. In animal models of allergic airway disease, which share many phenotypic features with asthma in humans, short-term exposure to $PM_{2.5}$ led to morphologic changes due to allergic responses and airway remodeling (Section 5.1.2.4). These morphologic changes could lead to lung function decrements and respiratory symptoms, both of which are associated with $PM_{2.5}$ concentrations in epidemiologic panel studies of humans with asthma (Section 5.1.2.2 and Section 0). Further, evidence from epidemiologic panel studies in children with asthma linked $PM_{2.5}$ concentrations to the inflammatory marker leukotriene E4, asthma symptoms, medication use (Section 5.1.2.2 and Section 5.1.2.4) and decrements in lung function (Section 0). Overall, these results provide plausibility for epidemiologic findings of hospital admissions and ED visits for asthma (Section 5.1.2.1).

Injury and inflammatory responses to inhaled CAPs were more robust in animal models of COPD than in healthy animals (Saldiva et al., 2002; Kodavanti et al., 2000; Clarke et al., 1999). Lung function-related changes in oxygen saturation, FEV_1, and tidal volume were seen in controlled human exposure studies involving human subjects with COPD and in animal models of COPD following short-term exposure to $PM_{2.5}$ (Gong et al., 2005; Saldiva et al., 2002; Clarke et al., 1999) and provide plausibility for epidemiologic findings of exacerbation of COPD (Section 5.1.4). Whether these COPD-related changes in lung function were due to inflammation or to ANS responses, which are discussed below, is not clear.

In animal toxicological studies, inhalation of $PM_{2.5}$ resulted in additional effects on the immune system subsequent to respiratory tract inflammation and oxidative stress. Allergic sensitization occurred in one study using diesel exhaust particles (DEPs) (Whitekus et al., 2002). It was blocked by treatment with antioxidants (depicted by the solid line connecting oxidative stress and allergic sensitization in Figure 5-1), indicating a role for oxidative stress in mediating the response. Allergic sensitization is an early step in the development of an allergic phenotype, which could contribute to both lung function decrements and respiratory symptoms. Another study found altered macrophage function and increased susceptibility to an infectious following inhalation of CAPs (Zelikoff et al., 2003). This demonstration of impaired host defense provides plausibility for epidemiologic findings of respiratory infection (Section 5.2.6).

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Activation of Sensory Nerves

Regarding the second pathway, activation of sensory nerves, animal toxicological studies described in the previous ISA and later in this chapter demonstrated changes in respiratory rate and lung volumes (i.e., rapid, shallow breathing) (Section 5.1.7 and Section 5.1.8). These responses are characteristic of lung irritant responses. Activation of sensory nerves in the respiratory tract can trigger local reflex responses resulting in lung irritation. Evidence that lung irritant responses are mediated by parasympathetic pathways involving the vagus nerve is provided by a study in which DEPs were intra-tracheally instilled into a rodent (Mcqueen et al., 2007) (depicted as a solid line connecting activation of sensory nerves and local reflex responses in Figure 5-1). In this study, pretreatment with atropine, an inhibitor of parasympathetic pathways, and vagotomy, which involves severing of the vagus nerve, blocked the irritant response to DEP. Lung irritation serves as an adaptive response to a noxious chemical that can potentially decrease exposure to that chemical. While some studies in humans and animals involving inhalation of $PM_{2.5}$ found FEV_1 changes, it is not clear whether this effect was mediated by lung irritant responses or by inflammation.

Activation of sensory nerves in the respiratory tract can also transmit signals to regions of the central nervous system that regulate autonomic outflow and influence all the internal organs, including the heart. Involvement of specific receptors on the sensory nerves, the transient receptor potential (TRP) sensory nerve receptors, was demonstrated by (Ghelfi et al., 2008), since TRP antagonists blocked downstream effects of exposure to $PM_{2.5}$ on the heart (depicted by the solid line connecting activation of sensory nerves and cardiac oxidative stress and function in Figure 5-1). In this study, modulation of the ANS resulted in altered autonomic outflow, which was manifest as a change in heart rate (see Section 8.1.1 and Section 6.1.1).

Furthermore, studies suggest connections between $PM_{2.5}$-mediated modulation of the ANS and other effects. A study in mice found that short-term exposure to $PM_{2.5}$ increased sympathetic nervous system (SNS) activity, as indicated by increased norepinephrine levels in lung and brown adipose tissue (Chiarella et al., 2014). Furthermore, inhalation of $PM_{2.5}$ increased BALF cytokine levels, an effect which was enhanced by β_2 adrenergic receptor agonists, which mimic the actions of norepinephrine. Using knock-out mice lacking the β_2 adrenergic receptor specifically in alveolar macrophage, it was demonstrated that inhalation of $PM_{2.5}$ enhanced cytokine release from alveolar macrophages. This involvement of the SNS in $PM_{2.5}$-mediated inflammatory responses is depicted by the solid line connecting modulation of the ANS and respiratory tract inflammation in Figure 5-1. The SNS is one arm of the ANS (the other arm being the parasympathetic nervous system). This is likely to represent a positive feed-back mechanism by which ANS responses may enhance inflammation. Another study found upregulation of the renin-angiotensin system (RAS), as indicated by an increase in mRNA for angiotensin receptor Type 1 and angiotensin converting enzyme, in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion

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(Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term exposure to $PM_{2.5}$ may lead to respiratory health effects. One pathway involves respiratory tract injury, inflammation, and oxidative stress that may lead to morphologic changes and lung function decrements, which are linked to asthma and COPD exacerbations. Respiratory tract inflammation may also lead to altered host defense, which is linked to increased respiratory infections. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are linked to asthma and COPD exacerbations. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between exposure to $PM_{2.5}$ and both respiratory tract inflammation and lung function decrements. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.1.12).

5.1.2 Asthma Exacerbation

Asthma is a chronic inflammatory lung disease characterized by reversible airway obstruction and increased airway responsiveness. Exacerbation of disease is associated with symptoms such as wheeze, cough, chest tightness, and shortness of breath. Symptoms may be treated with asthma medication, and uncontrollable symptoms may lead to seeking medical treatment. Previous findings linking short-term $PM_{2.5}$ exposure to asthma exacerbation, particularly from epidemiologic studies of children, comprised one line of evidence informing the determination of a likely to be causal relationship with respiratory effects. Some incoherence was noted in the evidence for children with asthma in that $PM_{2.5}$ concentrations were associated with respiratory symptoms and lung function decrements but inconsistently and imprecisely associated with hospital admissions and ED visits for asthma. However, the main uncertainty was whether $PM_{2.5}$ exposure had an effect independent of correlated copollutants. In the few epidemiologic studies that examined copollutant confounding, $PM_{2.5}$ associations with asthma-related effects did not always persist in models that included O_3, NO_2, CO, or SO_2. Further, in the 2009 PM ISA, coherence between evidence for allergic responses and epidemiologic findings for asthma exacerbation was not assessed for short-term $PM_{2.5}$ exposure. In controlled human exposure and animal toxicological studies, short-term $PM_{2.5}$ exposure induced allergic inflammation, which is part of the pathophysiology for allergic asthma. Allergic asthma is the most common asthmatic phenotype in children, and allergic inflammation could link $PM_{2.5}$ exposure and asthma exacerbation.

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In characterizing the current state of the evidence, this section begins by considering the effects of short-term exposure to $PM_{2.5}$ on clinical indicators of asthma exacerbation (i.e., hospital admissions, ED visits, and physician visits for asthma) and then considers respiratory symptoms and asthma medication use in people with asthma. The evaluation follows with a consideration of the effects of short-term exposure to $PM_{2.5}$ on lung function, which may indicate airway obstruction and poorer control of asthma. The last section describes the evidence for subclinical effects such as pulmonary inflammation and oxidative stress resulting from short-term exposure to $PM_{2.5}$.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily epidemiologic studies that conducted time-series or case-crossover analyses examining asthma hospital admissions and ED visits.

5.1.2.1 Hospital Admissions and Emergency Department (ED) Visits

The 2009 PM ISA reported inconsistent evidence of associations between short-term increases in $PM_{2.5}$ concentration and hospital admissions and ED visits for asthma in children, but generally consistent positive associations in studies focusing on adults and people of all ages combined (U.S. EPA, 2009). However, the evaluation of results from studies conducted in populations of children is complicated by the difficulty in reliably diagnosing asthma in children <5 years of age because young children often have transient wheeze (NAEPP, 2007). The inclusion of children <5 years of age may add some uncertainty to the results of studies focusing on all children, but the few studies that presented results in children older than 5 years did indicate $PM_{2.5}$-associated increases in asthma hospital admissions and ED visits. The examination of potential copollutant confounding was not thoroughly considered by the studies evaluated in the 2009 PM ISA but provided some evidence that $PM_{2.5}$-asthma hospital admission and ED visit associations are robust to the inclusion of gaseous pollutants in copollutant models. Across studies, associations were observed for a range of lags, with evidence that risk estimates for asthma hospital admissions and ED visits increased in magnitude for longer or cumulative lags.

Asthma hospital admissions and ED visit studies are evaluated separately because only a small percentage of asthma ED visits result in a hospital admission. As a result, asthma ED visits may represent less severe outcomes compared to asthma hospital admissions. For each of the studies evaluated in this

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section, Table 5-1 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study. Other recent studies of asthma hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: (https:/hero.epa.gov/hero/particulate-matter).

Recent studies expand the evidence base from the 2009 PM ISA (U.S. EPA, 2009) with respect to the evaluation of asthma hospital admissions and further reinforce the results reported in studies that examined asthma ED visits. As summarized in Figure 5-2- and Figure 5-3, both studies of hospital admissions and ED visits report evidence of consistent positive associations when examining children and people of all ages, with inconsistent evidence of associations with short-term $PM_{2.5}$ exposure for older adults (i.e., generally >65 years of age). These results are further supported by meta-analyses that include studies reviewed in and published since the 2009 PM ISA (Fan et al., 2015; Zheng et al., 2015). The results from asthma hospital admission and ED visit studies are supported by a study focusing on asthma physician visits in Atlanta, for the initial time period of the study, but this pattern of associations was not observed for the later time period (Sinclair et al., 2010). However, it is important to note that the severity of a $PM_{2.5}$-related asthma exacerbation, personal behavior such as delaying a visit to the doctor for less severe symptoms, and insurance type (i.e., physician visits which often are ascertained for members of a managed care organization) may dictate whether an individual visits the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

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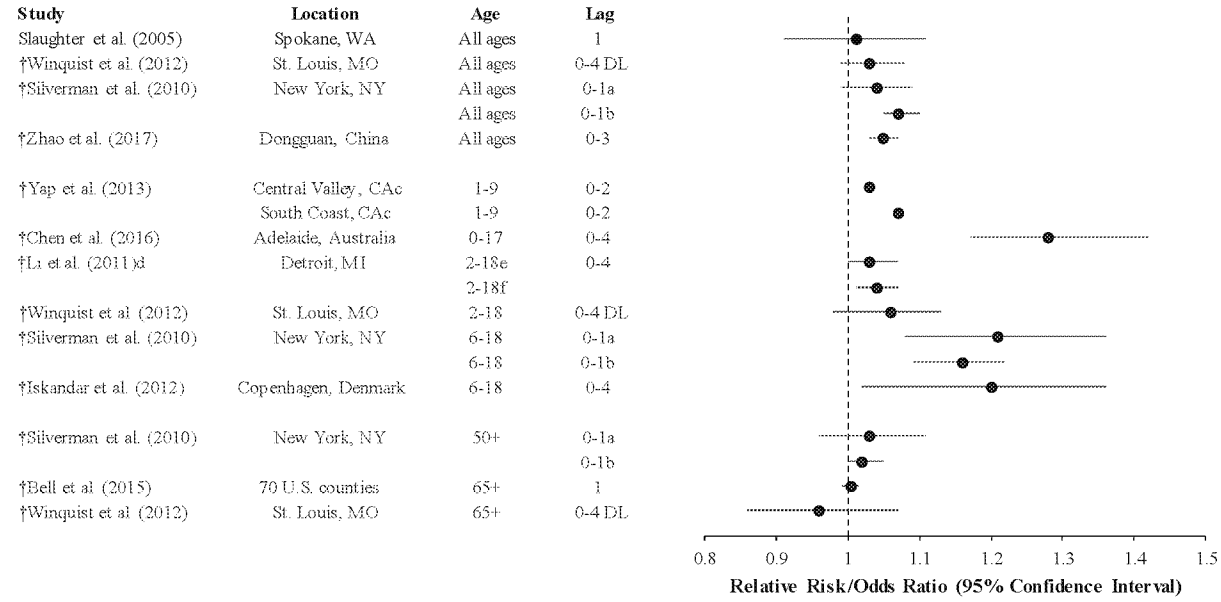

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = Intensive Care Unit (ICU) hospital admissions; b = non-ICU hospital admissions; c = values of confidence intervals not reported, but above the null; d = combination of hospital admissions and ED visits; e = time-series model results; f = case-crossover model results. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-2 Summary of associations between short-term $PM_{2.5}$ exposures and asthma hospital admissions for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

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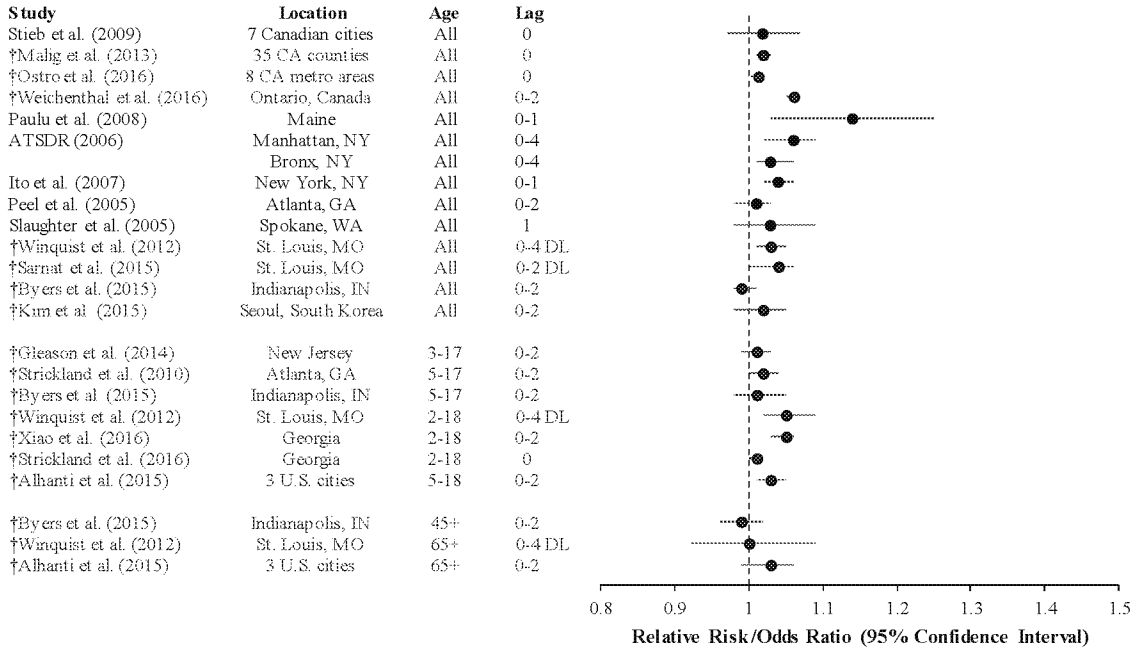

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. DL = distributed lag. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-3 Summary of associations from studies of short-term $PM_{2.5}$ exposures and asthma emergency department (ED) visits for a 10 μg/m³ increase in 24-hour average $PM_{2.5}$ concentrations.

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Table 5-1 Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
Hospital admissions				
†Yap et al. (2013) 12 counties, Central Valley and South Coast, CA 2000–2005 1–9 yr	Average of all monitors in each county	12.8–24.6	NR	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. counties 1999–2010 ≥65 yr	Average of all monitors in each county	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Hebbern and Cakmak (2015) 10 Canadian cities 1994–1997 All ages	Average of all monitors in each city	2.6–21.4	NR	Correlation (*r*): NA Copollutant models with: Pollen
†Silverman and Ito (2010) New York, NY 1999–2006 (warm season only) All ages, 6–18 yr, ≥50 yr	Average of 24 monitors	13[b]	75th: 21 90th: 29	Correlation (*r*): 0.59 O_3 Copollutant models with: O_3
†Liu et al. (2016) Greater Houston area, TX 2008–2013 All ages	Average of four monitors in one county, study area covers nine counties	12.0	90th: 18.5	Correlation (*r*): NA Copollutant models with: NA

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
†Kim et al. (2012) Denver, CO 2003–2007 All ages	One monitor	7.9	Max: 59.4	Correlation (*r*): 0.46 EC, 0.54, OC, 0.68 SO_4, 0.82, NO_3 Copollutant models with: NA
†Iskandar et al. (2012) Copenhagen, Denmark 2001–2008 0–18 yr	One monitor	10.3	75th: 11.8	Correlation (*r*): 0.33 NO_2, 0.33 NO_X, 0.85 PM_{10}, 0.26 UFP Copollutant models with: NO_2, NO_X, UFP
†Chen et al. (2016) Adelaide, Australia 2003–2013 0–17 yr	One monitor	7.8	75th: 9.1 Max: 61.2	Correlation (*r*): NA Copollutant models with: NA
†Cheng et al. (2015) Kaohshing, Taiwan 2006–2010 All ages	Six monitors averaged	45.9	75th: 61.9 Max: 144	Correlation (*r*): 0.69 $PM_{10-2.5}$, 0.40 O_3, 0.67 NO_2, 0.69 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2 (but all stratified by temperature)
†Zhao et al. (2016) Dongguan, China 2013–2015 All ages	Five monitors averaged	42.6	75th: 56.8 Max: 192.7	Correlation (*r*): 0.42 O_3, 0.80 NO_2, 0.81 CO, 0.25 SO_2 Copollutant models with: O_3, NO_2, SO_2

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
ED visits				
ATSDR (2006) Manhattan and Bronx, NY 1999–2000 All ages	One monitor per borough	24-h avg Manhattan: 16.7 Bronx: 15.0 1-h max Manhattan: 27.6 Bronx: 27.6	NR	Correlation (*r*): Bronx 24-h avg: 0.19 O_3, 0.61 NO_2, 0.45 SO_2, 0.19 pollen, 0.32 mold 1-h max: 0.35 O_3, 0.55 NO_2, 0.28 SO_2 Copollutant models with: O_3, NO_2, SO_2
Ito et al. (2007) New York, NY 1999–2002 All ages	Average of 30 monitors	15.1	75th: 19 95th: 32	Correlation (*r*): NA Copollutant models with: O_3, NO_2, CO, SO_2
Peel et al. (2005) Atlanta, GA 1998–2000 All ages	One monitor	19.2	90th: 32.3	Correlation (*r*): NA Copollutant models with: NA
Stieb et al. (2009) Seven Canadian cities 1992–2003, varies across cities All ages	One monitor to average of seven One monitor Halifax, Ottawa, Vancouver. Three Edmonton. Seven Montreal, Toronto.	Halifax: 9.8 Montreal: 8.6 Toronto: 9.1 Ottawa: 6.7 Edmonton: 8.5 Vancouver: 6.8	75th, Halifax: 11.3 Montreal: 10.9 Toronto: 11.9 Ottawa: 8.7 Edmonton: 10.9 Vancouver: 8.5	No copollutant model *r* = −0.05 to 0.62 O_3, 0.27–0.51 NO_2, 0.01–0.42 CO, 0.01–0.55 SO_2

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
Paulu and Smith (2008) Maine, whole state 2000–2003 (warm season only) All ages	Kriging of monitors Estimates for zip code centroid. Number monitors and method validation NR.	8–9[b]	Max across yr: 20 in 2000 to 42 in 2003	Does not persist with: O_3 *r* across yr = 0.76–0.87 O_3
†Alhanti et al. (2016) Three U.S. cities 1993–2009 5–18 yr, ≥65 yr	One monitor in each city	Atlanta: 14.1 St. Louis: 13.6 Dallas: 11.1	NR	Correlation (*r*): 0.57 O_3, 0.39 NO_2 Atlanta; 0.42 O_3, −0.15 NO_2 Dallas; 0.29 O_3, 0.29 NO_2 St. Louis Copollutant models with: NA
†Krall et al. (2016) Four U.S. cities 1999–2010 All ages	One monitor in each city	Atlanta: 15.6 St. Louis: 13.6 Dallas: 10.7 Birmingham: 17.0	NR	Correlation (*r*): NA Copollutant models with: NA
†Malig et al. (2013) 35 California counties 2005–2008 All ages	Nearest monitor within 20 km from population-weighted centroid of each patient's residential zip code	5.2–19.8	NR	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$
†Ostro et al. (2016) 2005–2009 Eight California metro areas All ages	Nearest monitor within 20 km from population-weighted centroid of each patient's residential zip code	16.5	NR	Correlation (*r*): NA Copollutant models with: NA

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
†Xiao et al. (2016) Georgia 2002–2008 2–18 yr	Combination of CMAQ model estimates and ground-based measurements at 12-km grid cells as detailed in Friberg et al. (2016); 10-fold cross validation, 76%; grid cells averaged over each zip code	13.2	75th: 16.1 Max: 86.4	Correlation (*r*): 0.61 O_3, 0.22 NO_2, 0.26 CO, 0.21 SO_2 Copollutant models with: NA
†Strickland et al. (2015) Georgia 2002–2010 2–18 yr	Satellite aerosol optical depth measurements at 1-km as detailed in Hu et al. (2014); R^2 ranged from 0.71 = 0.85; grid cells averaged over each zip code	12.9[b]	75th: 17.4 99th: 37.4	Correlation (*r*): NA Copollutant models with: NA
†Gleason et al. (2014) New Jersey, whole state 2004–2007 (warm season only) 3–17 yr	Fuse-CMAQ at 12-km grid cells assigned to geocoded address	NR	Max: 47.2	Correlation (*r*): <0.34 pollens, 0.56 O_3 Copollutant models with: Pollen
†Weichenthal et al. (2016) Ontario, Canada (15 cities) 2004–2011 All ages	Nearest monitor to population-weighted zip code centroid or single available monitor	7.1	Max: 56.8	Correlation (*r*): <0.42 NO_2 Copollutant models with: O_3, NO_2, oxidative potential

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
†Strickland et al. (2010) 1993–2004 Atlanta, GA 5–17 yr	Population-weighted average across monitors	16.4	NR	Correlation (*r*): Warm season = 0.50 O_3, 0.36 NO_2, 0.32 CO, 0.13 SO_2; cold season = −0.12 O_3, 0.37 NO_2, 0.38 CO, 0.00 SO_2. Copollutant models with: NA
†Sarnat et al. (2015) St. Louis, MO 2001–2003 All ages	One monitor	18.0	NR	Correlation (*r*): 0.25 CO, 0.35 NO_2, 0.08 SO_2, 0.23 O_3 Copollutant models with: NA
†Byers et al. (2015) Indianapolis, IN 2007–2011 All ages, 5–17 yr, ≥45 yr	Average of three monitors	13.4	NR	Correlation (*r*): 0.39 SO_2
†Kim et al. (2015)[c] Seoul, South Korea 2008–2011 All ages	Number of monitors not reported	24.8	75th: 30.8	Correlation (*r*): 0.02 O_3, 0.6 $PM_{10-2.5}$ Copollutant models with: NA

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
Physician visits				
†Sinclair et al. (2010) Atlanta, GA 1998–2002 All ages	One monitor	Overall: 17.1 Aug 1998–Aug 2000: 18.4 Sep 2000–Dec 2002: 16.2	NR	Correlation (*r*): Warm season = 0.63 O_3 Copollutant models with: NA
Hospital admissions and ED visits, separately				
Slaughter et al. (2005) Spokane, WA 1995–1999 All ages	One monitor	NR	90: 20.2	Correlation (*r*): 0.62 CO Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001–2007 All ages, 2–18 yr, ≥65 yr	One monitor	14.4	Max: 56.6	Correlation (*r*): 0.25 O_3 Copollutant models with: NA

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Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	Copollutant Examination
Hospital admissions and ED visits, combined				
†Li et al. (2011) Detroit, MI 2004–2006 2–18 yr	Average of four monitors	15.0	75th: 18.5 Max: 69.0	Correlation (*r*): Across monitors = 0.59, 0.64 NO_2, 0.53, 0.43 SO_2, 0.30, 0.41 CO Copollutant models with: NA

Avg = average, CMAQ = community multiscale air quality model, CO = carbon monoxide, ED = emergency department, max = maximum, NA = not available; NO_2 = nitrogen dioxide, NO_X = sum of NO_2 and nitric oxide, NR = not reported, O_3 = ozone, SO_2 = sulfur dioxide.

[a]All data are for 24-hour average unless otherwise specified

[b]Median concentration.

[c]$PM_{2.5}$ data only available for 1 year (2010).

†Studies published since the 2009 PM ISA.

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5.1.2.1.1 Hospital Admissions

Across recent studies, evidence supports an association between short-term $PM_{2.5}$ exposure and asthma hospital admissions, particularly in analyses of children and people of all ages (Figure 5-2). This evidence is supported by studies that examined associations with $PM_{2.5}$ 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 $PM_{2.5}$ exposure (CHAPTER 12). 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 $PM_{2.5}$ exposure and asthma hospital admissions in different age groups (i.e., people of all ages, children, and older adults). In New York City, 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 $PM_{2.5}$ 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 $PM_{2.5}$ (RR = 1.16 [95% CI: 1.10, 1.22]; lag 0−1). An elevated risk due to $PM_{2.5}$ exposure was also evident when examining both ICU and non-ICU admissions for children 6−18 years of age (Figure 5-2). 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. Winquist et al. (2012), 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 (Figure 5-2). 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 $PM_{2.5}$ exposure and asthma hospital admissions for people of all ages (quantitative results not presented). However, Liu et al. (2016) in a study conducted in the greater Houston area, did not report evidence of an association with $PM_{2.5}$ and unscheduled hospital admissions (quantitative results not presented). 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

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not differentiate amongst 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 $PM_{2.5}$ 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 (Figure 5-2).

5.1.2.1.2 Emergency Department (ED) Visits

Similar to hospital admission studies, recent ED visit studies provide evidence of generally consistent positive associations with short-term $PM_{2.5}$ exposures, particularly when examining children and people of all ages (Figure 5-3). However, compared to the hospital admission studies, the magnitude of the association tends to be smaller for ED visits. The evidence supporting an association between short-term $PM_{2.5}$ exposure and asthma ED visits is derived from studies conducted over an entire state, across multiple cities, or in individual cities. Additional studies focusing on exposure-related issues, such as exposure assignment (Sarnat et al., 2013b; Strickland et al., 2011) and air exchange rates (Sarnat et al., 2013a), have also focused on examining the relationship between short-term $PM_{2.5}$ exposure and asthma ED visits. They provide additional supporting evidence, but are characterized in CHAPTER 3 (Section 3.3.2.1 and Section 3.3.2.4.2).

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. Ostro et al. (2016) reported an OR = 1.01 (95% CI: 1.00, 1.02), and Malig et al. (2013) reported an OR = 1.02 (95% CI: 1.01, 1.03). These results are consistent with Weichenthal et al. (2016) in a study that encompassed Ontario, Canada that also reported a positive association with asthma ED visits for people of all ages but encompassed 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 $PM_{2.5}$ 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) report associations similar in magnitude to the multilocation studies, but with wider confidence intervals (Figure 5-3). However, Byers et al. (2015) did not report 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).

While a few of the studies that conducted analyses focusing on people of all ages also include analyses focusing on other age ranges including children (Byers et al., 2015; Winquist et al., 2012), several recent studies focus exclusively on the relationship between short-term $PM_{2.5}$ exposure and

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asthma ED visits in children. Both Winquist et al. (2012) and Byers et al. (2015) reported associations larger in magnitude in children compared to 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 (Figure 5-3), with ORs and RRs across studies ranging from 1.01–1.05. An additional multicity 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).

Most of studies that examined the association between short-term $PM_{2.5}$ exposure and asthma ED visits focused on analyses for people of all ages and/or children, with a more limited number of studies examining potential $PM_{2.5}$ effects in adults and older adults (Alhanti et al., 2016; Byers et al., 2015; Winquist et al., 2012). 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 (Figure 5-3). However, Alhanti et al. (2016) in three U.S. cities reported a RR = 1.03 (95% CI: 0.99, 1.06) at lag 0–2. Although Alhanti et al. (2016) included St. Louis, MO in the three U.S. cities examined, when examining city-specific results, the overall association is heavily influenced by Atlanta, GA with the St. Louis, MO result being consistent with that reported in Winquist et al. (2012).

5.1.2.1.3 Summary of Asthma Hospital Admissions and Emergency Department (ED) Visits

Building off the evidence detailed in the 2009 PM ISA (U.S. EPA, 2009), recent epidemiologic studies strengthen the evidence for a relationship between short-term $PM_{2.5}$ exposure and asthma-related hospital admissions and between short-term $PM_{2.5}$ exposure and ED visits in analyses of children and people of all ages. Evidence for a relationship in older adults continues to be inconsistent. The main results of studies detailed within this section are supported by analyses that examined specific policy-relevant issues as detailed in Section 5.1.10. Specifically, analyses of potential copollutant confounding provide evidence that $PM_{2.5}$ associations are relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$, but the evidence is more limited for $PM_{10-2.5}$ (Section 5.1.10). Although in some instances the results from copollutant models are attenuated, they remain positive overall. The associations observed across studies were found to be robust in sensitivity analyses that examined alternative model specifications to account for temporal trends as well as the potential confounding effects of weather.

Additionally, the overall body of evidence indicating a relationship between short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits is supported by studies that conducted analyses to further elucidate this relationship. Across studies that examined whether there was evidence of seasonal

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patterns, studies that divided the year into warm and cold season reported associations larger in magnitude for the warmer months. These results are supported by studies that examined all four seasons of the year, but they also indicate that effects may be strongest over more defined periods of the year (i.e., the spring) (Section 5.1.10.4.1). Additionally, examinations of the concentration-response (C-R) relationship provide some evidence for a linear relationship for short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cutpoint analyses that provide some potential indication for nonlinearity in the relationship between short-term $PM_{2.5}$ exposure and asthma hospital admission and ED visits (Section 5.1.10.6).

5.1.2.2 Respiratory Symptoms and Asthma Medication Use in Populations with Asthma

Studies evaluating the effects of short-term $PM_{2.5}$ exposure on respiratory symptoms and asthma medication use consisted solely of epidemiologic studies. Results will be discussed separately for children with asthma and for adults with asthma.

Children

Uncontrollable respiratory symptoms, such as cough, wheeze, sputum production, shortness of breath, and chest tightness, can lead people with asthma to seek medical care. Thus, along with medication use in children, studies examining the relation between $PM_{2.5}$ and increases in asthma symptoms may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.1.2.1. A limited number of panel studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provide evidence of an association between $PM_{2.5}$ 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 $PM_{2.5}$ and asthma severity were robust to the inclusion of CO in a copollutant model (Slaughter et al., 2003), while $PM_{2.5}$ 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 $PM_{2.5}$ and a composite index of multiple symptoms (Figure 5-4). In a panel study including 90 schoolchildren with asthma in Santiago, Chile, $PM_{2.5}$ 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 average $PM_{2.5}$. Similarly, among children at two schools in El Paso, TX, 5-day average $PM_{2.5}$ 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

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outdoor $PM_{2.5}$ concentration over time (Section 3.4.3.1). In contrast, students attending schools with varying nearby traffic levels were also examined in the Bronx, NY, though asthma symptoms were not associated with outdoor school or total personal $PM_{2.5}$ concentrations (Spira-Cohen et al., 2011). A low correlation between school and personal $PM_{2.5}$ concentrations ($r = 0.17$) and a reportedly high proportion of time spent indoors (89%), suggests that personal $PM_{2.5}$ 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 average $PM_{2.5}$ concentrations in a U.S. multicity study (O'Connor et al., 2008). Notably, confounding by meteorological factors is difficult to control with long averaging times. Study-specific details, including cohort descriptions and air quality characteristics are highlighted in Table 5-2.

In addition to respiratory symptoms, recent studies of medication use in children add to the limited evidence base, providing some additional evidence of $PM_{2.5}$-associated increases in the use of bronchodilators, which can provide quick relief from asthma symptoms (Figure 5-4). Panel studies of schoolchildren with asthma in Denver, CO (Rabinovitch et al., 2011) and Mexico City (Escamilla-Nuñez et al., 2008) observed associations between $PM_{2.5}$ concentrations and bronchodilator use. Escamilla-Nuñez et al. (2008) reported comparable associations using lag 0 and 5-day average $PM_{2.5}$, while Rabinovitch et al. (2011) observed associations that were stronger in magnitude when estimated using 2-day moving average $PM_{2.5}$ compared to single-day lags. In contrast, $PM_{2.5}$ concentrations were associated with decreased bronchodilator use in a panel study in Santiago, Chile (Prieto-Parra et al., 2017).

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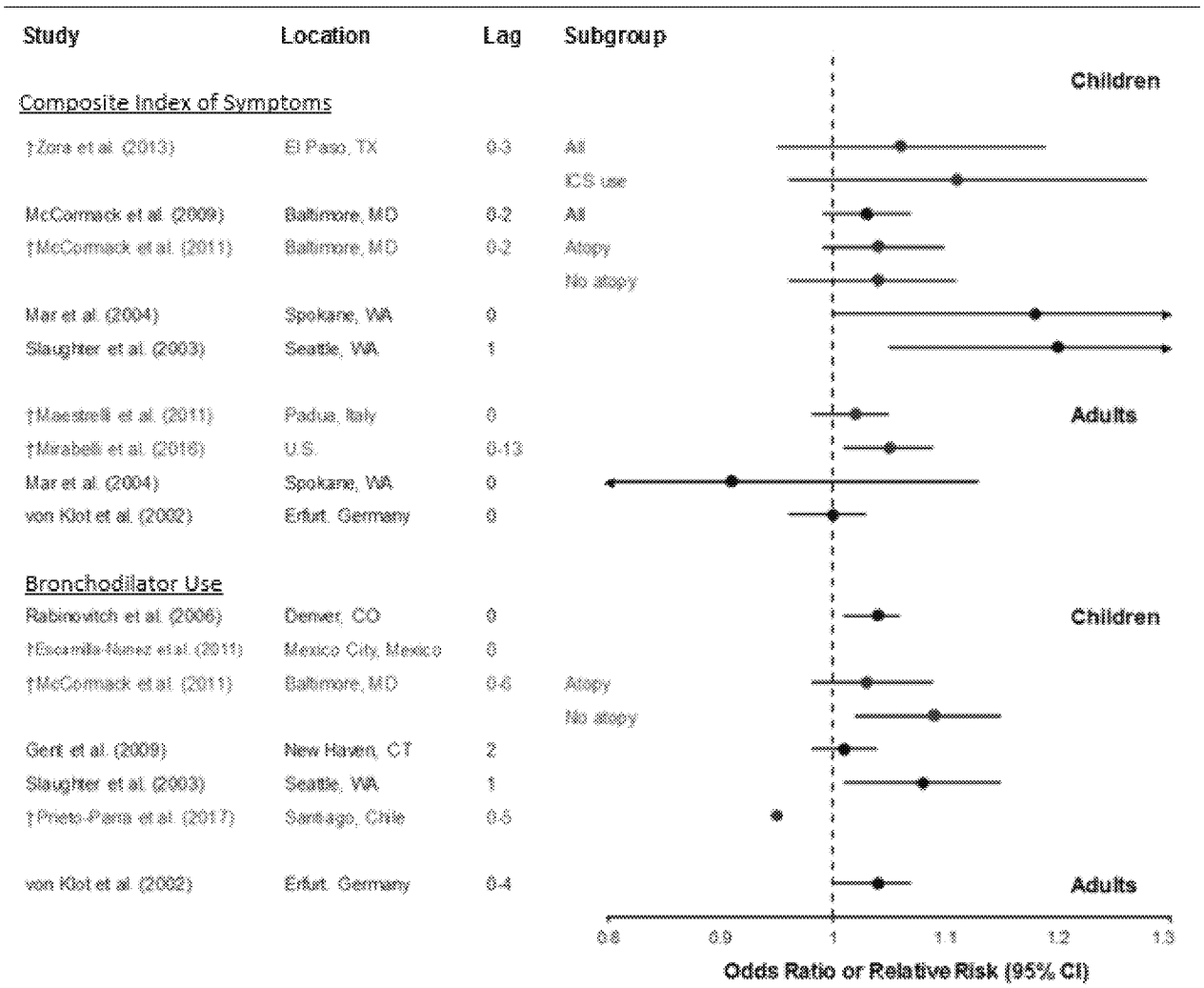

Note: †Studies published since the 2009 PM ISA. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$. CI = confidence interval, ICS = inhaled corticosteroid. Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-4 Summary of associations between short-term $PM_{2.5}$ exposures and respiratory symptoms and medication use in populations with asthma.

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Table 5-2 Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms and medication use in children with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Spira-Cohen et al. (2011) Bronx, NY 2002–2005	N = 40, ages 10–12 yr 78% with rescue inhaler use Daily diary for 1 mo No information on participation rate 89% time spent indoors	School outdoor and total personal 24-h avg *r* = 0.17 school and personal children walk to school	Mean School: 14.3 Total personal: 24.1	Correlation (*r*): NA Copollutant models with: NA
†Zora et al. (2013) El Paso, TX Mar–Jun 2010	N = 36, ages 6–11 yr 33% ICS use, 47% atopy Weekly measures for 13 weeks 95% follow-up participation	School outdoor 96-h avg Two schools: High and low traffic area *r* = 0.89 between schools, 0.91 between monitors, 0.73–0.86 school and monitor	Mean, max School 1: 13.8, 24.9 School 2: 9.9, 18.5	Correlation (*r*): (School 1, School 2) −0.33, −0.19 NO_2; −0.02, 0.25 benzene; 0.10, 0.33 toluene; 0.47, 0.28 O_3 Copollutant models with: NA
†Rabinovitch et al. (2011); Rabinovitch et al. (2006) Denver, CO 2002–2005	N = 82 (3-yr study), 73 (2-yr study) 65–86% moderate/severe asthma, 82–90% ICS use Daily measures for 4–7 mo No information on participation rate	One monitor 24-h avg, 10-h avg (12–11 a.m.), 1-h max (12–11 a.m.) 4.3 km from school *r* = 0.92 monitor and school	Mean, max for yr 1–3 24-h avg: 6.5–8.2, 20.5–23.7 10-h avg: 7.4–9.1, 22.7–30.2 1-h max: 16.8–22.9, 39–52 (95th)	Correlation (*r*): NA Copollutant models with: NA
†Escamilla-Nuñez et al. (2008) Mexico City, Mexico 2003–2005	N = 147, ages 9–14 yr 43% persistent asthma, 89% atopy Daily diary for mean 22 weeks 94% follow-up participation	One monitor 24-h avg Within 5 km of school or home *r* = 0.77 monitor and school	Mean: 27.8	Correlation (*r*): 0.62 NO_2, 0.54 O_3 Copollutant models with: NA

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Table 5-2 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms and medication use in children with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Prieto-Parra et al. (2017) Santiago, Chile May–Sep 2010–2011	N = 89, ages 6–14 yr 50% mild asthma, 53% ICS use, 64% atopy Daily diary for 3 mo 79% follow-up participation	One monitor Most homes within 3 km	Mean:30	Correlation (*r*): NA Copollutant models with: PM_{10}, NO_2, O_3, SO_2, K, Mo, Pb, S, Se, and V
†Mann et al. (2010) Fresno, Clovis, CA 2000–2005	N = 280, mean (SD) age 8.1 (1.7) 25% moderate/severe asthma, 38% ICS use, 63% atopy Daily diary for 2 weeks, every 3 mo 89% participation from enrolled	One monitor 24-h avg Within 20 km of home	Median: 18.7 75th: 32.0 Max: 137	Correlation (*r*): 0.63 NO_2, −0.45 O_3, −0.23 $PM_{10-2.5}$, 0.76 EC Copollutant models with: $PM_{10-2.5}$
Gent et al. (2009) New Haven, CT 2000–2004	N = 149, ages 4–12 yr 33% moderate/severe asthma Daily diary for mean 313 days No information on participation	One monitor 24-h avg Near highway, 0.9–27 km from homes (mean 10 km)	Mean: 17.0	Correlation (*r*): NA Copollutant models with: NA
Slaughter et al. (2003) Seattle, WA Years NR	N = 133, ages 5–12 yr 100% mild/moderate asthma Daily diary for 28–112 days No information on participation	Three monitors averaged 24-h avg	NR	Correlation (*r*): 0.82 CO Copollutant models with: CO
Mar et al. (2004) Spokane, WA 1997–1999	N = 9, ages 7–12 yr 100% regular medication use Daily diary for mean 580 days No information on participation	One monitor	Means 1997: 11.0 1998: 10.3 1999: 8.1	Correlation (*r*): 0.61 PM_{10}, 0.92 PM_1, 0.28 $PM_{10-2.5}$ Copollutant models with: NA

Avg = average, CO = carbon monoxide, ICS = inhaled corticosteroid use, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm; *r* = correlation coefficient; RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

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Recent evidence of associations from studies that measured $PM_{2.5}$ concentrations outside of children's schools, representing exposure where children spend a large part of their day, increases confidence in the associations observed. Additionally, recruitment mostly occurred at schools; thus, the study populations were likely representative of the general population of children with asthma. The representativeness of results is also supported by the high follow-up participation rates (79–95%; Table 5-2). Meanwhile, potential copollutant confounding remains a source of uncertainty given the lack of studies that report copollutant models. In limited copollutant results described in the 2009 PM ISA (U.S. EPA, 2009), $PM_{2.5}$ associations appeared robust to adjustments for CO, but not O_3, despite high copollutant correlation ($r > 0.7$) (Gent et al., 2003; Slaughter et al., 2003). Recent studies show moderate correlations ($0.4 < r < 0.7$) for $PM_{2.5}$ with O_3 and NO_2 (Table 5-2), though only a single study presented copollutant models. The association between $PM_{2.5}$ and asthma control in schoolchildren was attenuated but still positive with adjustment for NO_2, O_3, benzene, or toluene, which were all weakly to moderately correlated ($r < 0.5$) with $PM_{2.5}$ (Zora et al., 2013). Further discussion of copollutant confounding is provided in Section 5.1.10.1.

Adults

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) reported inconsistent evidence of an association between $PM_{2.5}$ and respiratory symptoms and medication use in adults with asthma. Recent studies provide limited evidence of association between $PM_{2.5}$ and respiratory symptoms or markers for medication use in adults with asthma (Figure 5-4). A U.S.-wide cross-sectional analysis indicates increases in any asthma symptom with increases in county-average $PM_{2.5}$ concentrations modeled by CMAQ (Mirabelli et al., 2016). Analysis of the concentration-response relationship isolates the association to lower concentrations, ranging from 4.0 to 7.1 $\mu g/m^3$. However, this study is limited by its cross-sectional design, and residual confounding may arise from the 14-day $PM_{2.5}$ averaging time and lack of consideration of confounding by community-level SES. A recent study in Milan, Italy measured levels of the beta-agonist salbutamol in untreated wastewater samples to estimate the daily population-level use of short-acting beta-antagonists (Fattore et al., 2016). Single-day $PM_{2.5}$ lags, ranging from 0 to 10 days, were associated with increases in daily defined doses of short-acting beta-antagonists, with associations that were strongest in magnitude at lags 7 and 8 (RR = 1.07 [95% CI: 1.02, 1.12]). The validity and reliability of wastewater levels of medication as an indicator for medication use is untested, but previous results show increases in self-reported beta-agonist and ICS use with increases in $PM_{2.5}$ concentrations averaged over 5 days (von Klot et al., 2002). Other recent studies of associations between personal exposure to $PM_{2.5}$ and respiratory symptoms, examined in aggregate or individually, are limited by simple correlation analyses on observations (Larsson et al., 2010) or by temporal mismatch between 2-day $PM_{2.5}$ exposure and 4-week symptom interval (Maestrelli et al., 2011).

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5.1.2.3 Lung Function Changes in Populations with Asthma

Studies evaluating the effects of short-term $PM_{2.5}$ exposure on lung function consisted solely of epidemiologic studies. Results will be discussed separately for children with asthma and for adults with asthma. Some studies in adults employed scripted exposures to further inform the relationship between short-term $PM_{2.5}$ exposure and lung function. Scripted studies measuring personal ambient $PM_{2.5}$ exposures are designed to minimize uncertainty in the $PM_{2.5}$ exposure metric by always measuring $PM_{2.5}$ at the site of exposure, ensuring exposure to sources of $PM_{2.5}$ and measuring outcomes at well-defined lags after exposure.

Children

Lung function metrics can indicate airway obstruction, which is the defining characteristic of asthma. Further, specific lung function metrics, such as FEV_1, have been shown to have prognostic value for asthma exacerbation (Pijnenburg et al., 2015), such that $PM_{2.5}$-related decrements in lung function may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.1.2.1. In the 2009 PM ISA (U.S. EPA, 2009), several panel studies of children with asthma provide generally consistent evidence of an association between short-term $PM_{2.5}$ concentrations and decreased FEV_1. $PM_{2.5}$ exposure in particular microenvironments was also associated with lung function decrements in studies examined in the 2009 PM ISA. In Seattle, decrements in some measures of lung function (PEF, MEF, FEV_1) were associated with $PM_{2.5}$ concentrations (Allen et al., 2008; Trenga et al., 2006). Based on the ratio of personal to ambient sulfur concentrations, total personal $PM_{2.5}$ exposure was partitioned into ambient-generated and nonambient-generated fractions. Only the ambient-generated $PM_{2.5}$ was associated with lung function decrements (FEV_1, PEF, MEF) (Allen et al., 2008). $PM_{2.5}$ 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). Notably, there was a lack of studies that examined potential confounding by copollutants, raising uncertainties about the independence of the observed associations.

Several recent studies continue to provide evidence of an association between short-term $PM_{2.5}$ exposure and FEV_1 decrements in children with asthma. As in studies of respiratory symptoms in children with asthma (Section 5.1.2.2), lung function studies followed children with asthma in an array of cities in the U.S., Canada, and Asia (Table 5-3) that are similar to the locations of studies that examined asthma hospital admissions and ED visits (Section 5.1.2.1). In Riverside and Whittier, CA, personal $PM_{2.5}$ and monitor $PM_{2.5}$ concentrations were associated with decreased FEV_1 (Delfino et al., 2008). Associations were strongest in magnitude for personal $PM_{2.5}$ exposures, particularly those for 1 and 8-hour max concentrations, suggesting that peak exposures in a certain microenvironment may have increased relevance to lung function. Similarly, among children attending two schools with varying nearby traffic levels in the Bronx, NY, Spira-Cohen et al. (2011) reported decrements in FEV_1 in relation to personal

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$PM_{2.5}$ concentrations averaged in the 12 hours prior to spirometry. The authors did not observe a similar association with $PM_{2.5}$ exposure estimated from monitors outside of the schools. In Windsor, Canada, in another panel of schoolchildren with asthma, Dales et al. (2009) observed associations between 24-hour average $PM_{2.5}$ concentrations and nighttime FEV_1 decrements, as well as 12-hour average $PM_{2.5}$ and diurnal FEV_1. $PM_{2.5}$ exposure was estimated from a city monitor, though most panel subjects reportedly lived within 10 km downwind of the monitor. In contrast with evidence of a relationship between FEV_1 and short-term exposure to $PM_{2.5}$, Smargiassi et al. (2014) reported that lung function was not associated with personal $PM_{2.5}$ in a panel study following 72 children with asthma for 10 consecutive days in Montreal, Canada.

Within studies that compared multiple exposure assignment methods, FEV_1 decrements were larger in relation to $PM_{2.5}$ exposure estimated from personal samplers compared to fixed-site monitors (Spira-Cohen et al., 2011; Delfino et al., 2008). This is generally consistent with evidence from the 2009 PM ISA (U.S. EPA, 2009) and potentially indicates reduced exposure measurement error in the personal exposure measures. The errors and uncertainties related to various exposure assignment methods (Section 3.3.5), and the relation between personal and ambient concentrations (Section 3.4.1.3) are discussed in further detail in CHAPTER 3. These results for personal exposure also provide some indication that $PM_{2.5}$ exposure in microenvironments may have an independent effect on lung function. However, uncertainties remain regarding the independent effect of $PM_{2.5}$ given the limited number of studies that examine potential copollutant confounding and the general limitations of copollutant models. A single recent study examined copollutant models, reporting diurnal and nighttime FEV_1 associations with $PM_{2.5}$ that were robust to adjustment for O_3 (Dales et al., 2009). Nighttime FEV_1 associations were also generally unchanged in models including NO_2 or SO_2, while diurnal FEV_1 decrements were attenuated, but still negative. Notably, the correlation between $PM_{2.5}$ and O_3 ($r = 0.26$) was much lower than $PM_{2.5}$-NO_2 ($r = 0.68$) and $PM_{2.5}$-SO_2 ($r = 0.43$) correlations. Further discussion of copollutant confounding is provided in Section 5.1.10.1.

A few recent studies also examine other lung function metrics. In the study of schoolchildren in New York, discussed previously, Spira-Cohen et al. (2011) observed an association between 12-hour average personal $PM_{2.5}$ exposure and PEF decrements. As with the examination of FEV_1, the authors did not observe an association with $PM_{2.5}$ at school-site monitors. In a panel study of children receiving long-term in-hospital care in Yotsukaido, Japan, $PM_{2.5}$ concentrations averaged over the 24 hours prior to spirometry were associated with both morning and evening PEF decrements (Yamazaki et al., 2011). Given the severity of asthma in this population, the results might not be applicable to the general population with asthma. PEF decrements were also associated with 24-hour average $PM_{2.5}$ concentrations in a panel of schoolchildren in Seoul, South Korea (Hong et al., 2010). While the authors examined several single-day lags, ranging from 0 to 4 days, they only observed an association at lag 0. As discussed previously, Smargiassi et al. (2014) reported that personal $PM_{2.5}$ exposure was not related to an array of lung function metrics, including FVC and $FEF_{25-75\%}$.

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In summary, recent studies add to the existing evidence linking short-term $PM_{2.5}$ exposure to decrements in FEV_1 in children with asthma. While the previously existing evidence base for $PM_{2.5}$-related decrements in PEF is less consistent than that for FEV_1, a few recent studies provide generally consistent evidence indicating an association. Importantly, uncertainty regarding potential copollutant confounding remains.

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Table 5-3 Epidemiologic studies of $PM_{2.5}$ and lung function in populations with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Children				
†Spira-Cohen et al. (2011) Bronx, NY 2002–2005	N = 40, ages 10–12 yr 78% rescue inhaler use Daily supervised measures—1 mo No information on participation rate 89% time spent indoors	School outdoor and total personal 12-h avg (9 a.m.–9 p.m.), 24-h avg *r* = 0.17 school and personal Most children walk to school	Mean School: 14.3 Total personal: 24.1	Correlation (*r*): NA Copollutant models with: NA
†Delfino et al. (2008) Riverside, Whittier, CA Jul–Dec 2003 and 2004	N = 53, ages 9–18 yr 100% mild/moderate persistent asthma, 62% controlled medication use Daily home measures—10 days No information on participation rate	One monitor and total personal 24-h avg, 1-h max, 8-h max Within 16 km of homes in Riverside, 8 km in Whittier. *r* = 0.60 personal-monitor 100% above limit of detection	Mean, max Monitor, 24-h avg: 23.3, 87.2 Total personal 24-h avg: 31.2, 180 1-h max: 90.1, 604 8-h max: 46.2, 241	Correlation (*r*): (personal, ambient) 0.22, 0.51 EC; 0.26, 0.62 OC; 0.38, 0.36 NO_2 Copollutant models with: NO_2
†Smargiassi et al. (2014) Montreal, Canada Oct 2009–Apr 2010	N = 72, ages 8–12 yr 43% ICS use, 68% atopic Daily supervised measures—10 days No information on participation rate	Total personal 24-h avg 12% below limit of detection	Mean: 9.6 75th: 11.7 Max: 100	Correlation (*r*): NA Copollutant models with: NA
†Jacobson et al. (2012) Alta Floresta, Brazil Aug–Dec 2006	N = 56, ages 8–15 yr 5% asthma medication use Daily supervised measures—4 mo 90% follow-up participation	School outdoor 24-h avg, 6-h avg (12–5:30 a.m. to 6–11:30 p.m.), 12-h avg (12–11:30 a.m. to 12–11:30 p.m.)		

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Table 5-3 (Continued): Epidemiologic studies of $PM_{2.5}$ and lung function in populations with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Allen et al. (2008); Trenga et al. (2006) Seattle, WA 1999–2002	N = 17, ages 6–13 yr Most mild persistent asthma, 65% asthma medication use Daily supervised measures—5-10 days, multiple sessions for some subjects No information on participation rate	Outdoor home, total personal, ambient 24-h avg Ambient estimated from personal to ambient sulfur ratio and outdoor home $PM_{2.5}$.	Mean median, 75th Outdoor home: 11.2, 14.7 Total personal: 11.3, 16.3 Ambient: 6.3, 7.6	Correlation (*r*): (home monitor, ambient monitor) 0.51, 0.56 NO_2; 0.70, 0.77 CO Copollutant models with: NA
Barraza-Villarreal et al. (2008) Mexico City, Mexico 2003–2005	N = 158, ages 6–14 yr 55% mild intermittent asthma, 6% ICS use, 89% atopy Supervised measures every 15 days-mean 22 weeks No information on participation rate	One monitor 8-h moving avg Within 5 km of school or home *r* = 0.77 monitor-school	8-h avg Mean: 28.9 Max: 103	Correlation (*r*): 0.46 O_3, 0.61 NO_2 Copollutant models with: O_3
O'Connor et al. (2008) Boston, MA; Bronx, Manhattan, NY; Chicago, IL; Dallas, TX; Tucson, AZ; Seattle, WA	N = 861, ages 5–12 yr 100% persistent asthma, 100% atopy, 12% ICS use Daily home measures—2 weeks every 2 mo for 2 yr 70% maximum measures obtained	Monitors averaged in city Number NR 24-h avg Within median 2.3 km of home	NR	Correlation (*r*): 0.59 NO_2, 0.37 SO_2, −0.02 O_3, 0.44 CO Copollutant models with: NA
†Dales et al. (2009) Windsor, Canada Oct–Dec 2005	N = 182, ages 9–14 yr 58% medication use Daily home measures—28 days No information on participation rate Mean 1.6 and 2.2 h/day outdoors	Two monitors averaged 24-h avg, 12-h avg (12–8 a.m., 8 a.m.–8 p.m.) 99% within 10 km of monitors	24-h avg Mean: 7.8 75th: 10.0	Correlation (*r*): −0.26 O_3, 0.68 NO_2, 0.43 SO_2 Copollutant models with: NO_2, SO_2, and O_3
†Yamazaki et al. (2011) Yotsukaido, Japan Oct–Dec 2000	N = 17, ages 8–15 yr Children in long-term hospital care 100% severe, 100% medication use, 100% atopy Daily supervised measures—2–3 mo No information on participation rate	One monitor next to hospital 24-h avg, 1-h avg	Mean 6–7 a.m.: 24.0 12–1 p.m.: 26.9 6–7 p.m.: 30.0	Correlation (*r*): (morning, noon, evening, night) −0.44, −0.24, −0.27, −0.40 O_3; 0.54, 0.78, 0.62, 0.56 Copollutant models with: O_3

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Table 5-3 (Continued): Epidemiologic studies of $PM_{2.5}$ and lung function in populations with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Hong et al. (2010) Seoul, South Korea May–Jun 2007	N = 18, mean (SD) age 9.3 (0.5) yr No information on asthma severity Daily home measures—1 mo No information on participation rate	Monitors in city, number NR 24-h avg	Mean: 36.2	Correlation (*r*): NA Copollutant models with: NA
Adults				
McCreanor et al. (2007) London, U.K. 2003–2005	N = 60, ages 19–55 yr 100% mild/moderate asthma, 100% AHR, 84% atopy Supervised measures—high and low traffic No information on participation rate	Personal ambient 2-h avg (10:30–12:30 a.m.) Scripted exposure walking on high-traffic road and in park, 3 weeks apart	Median, max High-traffic road: 28.3, 76.1 Park: 11.9, 55.9	Correlation (*r*): 0.62 UFP, 0.60 NO_2, 0.76 C, 0.73 EC Copollutant models with: NO_2
†Mirabelli et al. (2015) Atlanta, GA 2009–2011	N = 18, ages NR. Mean FEV_1: 100% predicted Supervised measures—pre- and post-commute, two exposures 93% completed 2nd commute	Personal in-vehicle 2-h avg (7–9 a.m.) Scripted exposure driving car on highway, median 17/13 weeks apart	Mean (SD) Asthma control > median: 23.8 (11.7) Asthma control < median: 21.5 (11.1)	Correlation (*r*): NA Copollutant models with: NA
†Maestrelli et al. (2011) Padua, Italy Years NR	N = 32, mean (SD) age 40 (7.5) yr 56% severe asthma, 91% atopy Supervised measures, six over 2 yr 76% with ≥ three measures	Total personal 24-h avg	NR	Correlation (*r*): NA Copollutant models with: NA

AHR = airway hyperresponsiveness, avg = average, BTEX = benzene, toluene, ethylbenzene, xylene, CO = carbon monoxide, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled corticosteroid use, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm; *r* = correlation coefficient; RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide, VOCs = volatile organic compounds.

†Studies published since the 2009 PM ISA.

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Adults

A single study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the association between short-term exposure to $PM_{2.5}$ and lung function in adults with asthma. In a panel of 60 adults with asthma in London, average $PM_{2.5}$ concentrations measured over a 2-hour outdoor walk was associated with decrements in FEV_1 and $MMEF_{25-75\%}$, but not FVC (McCreanor et al., 2007). Studies published since the completion of the 2009 PM ISA have been limited in number and results are inconsistent. Mirabelli et al. (2015) studied adults with asthma in Atlanta and reported decreased FEV_1 associated with 2-hour average personal $PM_{2.5}$ exposure measured 3 hours prior to spirometry. $PM_{2.5}$ concentrations were measured during scripted commutes through rush hour traffic, resulting in higher exposure levels. The observed associations were stronger in magnitude and more precise in participants with poorly controlled asthma. In contrast, in Padua, Italy, Maestrelli et al. (2011) tested the relationship between FEV_1 and 24-hour average personal $PM_{2.5}$ exposure the day before spirometry and reported no association in adults with asthma. This study was limited by a design that designated six single-day examination visits across a 2-year period, precluding the opportunity to examine alternative exposure lags. Additionally, low variability in personal $PM_{2.5}$ measurements may have contributed to the lack of an observed association.

5.1.2.3.1 Controlled Human Exposure Studies

Individuals with pre-existing airway diseases such as asthma, may suffer increased deleterious health effects from exposure to PM compared with individuals without pre-existing airway disease. Increased susceptibility of a $PM_{2.5}$-related health effect may be associated with specific mechanisms known to underlie the pathology of asthma, namely elevated inflammation and altered immune activity. However, there is little evidence from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that exposure to $PM_{2.5}$ results in decrements in lung function in individuals with asthma. Although a study evaluated in the 2009 PM ISA Petrovic et al. (2000) observed that a 2-hour exposure to $PM_{2.5}$ CAPs (92 $\mu g/m^3$) resulted in decreases in thoracic gas volume in healthy volunteers, other measures of lung function (spirometry, diffusing capacity, airway resistance) were unaffected. This general lack of effect of $PM_{2.5}$ exposure on lung function has also been shown in a study investigating the exposure of individuals with asthma to $PM_{2.5}$ CAPs (Gong et al., 2003). A recent study examining the respiratory effects of $PM_{2.5}$ on individuals with asthma has been conducted by (Urch et al., 2010) using a CAP facility for $PM_{2.5}$ located in downtown Toronto, Canada (study details in Table 5-4). Exposure to either $PM_{2.5}$ CAPs alone or in addition to O_3 was not observed to affect any measurement of pulmonary function, breathing parameters (tidal volume, breathing frequency, minute ventilation), or airway responsiveness (PC20), compared to filtered air control exposures. The lack of effect of $PM_{2.5}$ CAPs on respiratory function observed in Urch et al. (2010) is consistent with the results of previous controlled human exposure studies in which worsening of pulmonary function was not observed.

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Table 5-4 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and lung function in individuals with asthma.

Study	Study Design	Disease Status; n; Sex	Exposure Details (Concentration; Duration; Comparison Group	Endpoints Measured
Urch et al. (2010)	Blinded randomized block design	Healthy nonsmokers (13) and individuals with asthma (10); n = 23; 11 M, 12 F	$PM_{2.5}$ CAPs only: 64 ± 3 or 140 ± 6 μg/m^3 $PM_{2.5}$ CAPs + O_3: 68 ± 5 or 142 ± 7 μg/m^3 $PM_{2.5}$ + 119 ± 1 ppb O_3 Comparison group for both groups was filtered air; all exposures were for 2 h carried out at rest	Spirometry (pre-, 10-min, and 20-h post-exposure): Flow-volume, DLCO, MV, VT

CAPs = concentrated ambient particles; DLCO = diffusion capacity for CO; MV = minute volume; VT = tidal volume.

5.1.2.3.2 Animal Toxicological Studies

The 2009 ISA for PM (U.S. EPA, 2009) evaluated a limited number of inhalation studies examining pulmonary function in animal models of allergic airway disease, which share phenotypic features with asthma in humans. One study reported increased airway responsiveness to methacholine, as indicated by Penh, following short-term exposure to DE. However, this study did not distinguish between effects due to particles and gases in the mixture. No additional studies have become available since that time. In many animal studies, changes in ventilatory patterns are assessed using whole-body plethysmography, for which measurements are reported as Penh. Some investigators consider Penh solely an indicator of altered ventilatory timing (see Section 5.1.7.4) in the absence of other measurements to confirm changes in airway responsiveness.

5.1.2.3.3 Summary of Lung Function in Populations with Asthma

Overall, panel studies in children with asthma find generally consistent evidence of associations between short-term $PM_{2.5}$ exposure and lung function decrements. 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 $PM_{2.5}$ exposure. No studies have examined this endpoint in animal models of allergic disease, which share many phenotypic features with asthma in humans.

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5.1.2.4 Subclinical Effects Underlying Asthma Exacerbation

Studies evaluating the effects of short-term $PM_{2.5}$ exposure on subclinical effects consisted solely of epidemiologic studies. Results are discussed separately for children with asthma and adults with asthma. Some studies in adults employed scripted exposures to further inform this relationship. Scripted studies measuring personal ambient $PM_{2.5}$ exposures are designed to minimize uncertainty in the $PM_{2.5}$ exposure metric by always measuring $PM_{2.5}$ at the site of exposure, ensuring exposure to sources of $PM_{2.5}$ and measuring outcomes at well-defined lags after exposure.

Children

Evidence described in the preceding sections for $PM_{2.5}$-related increases in asthma hospital admissions, asthma ED visits, and respiratory symptoms and lung function in children with asthma indicates a potential link between $PM_{2.5}$ exposure and asthma exacerbation. The 2009 PM ISA (U.S. EPA, 2009) also described generally consistent epidemiologic evidence linking increases in pulmonary inflammation in children with asthma to short-term personal $PM_{2.5}$ exposure and ambient $PM_{2.5}$ concentrations. Most studies examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation. The relevance of eNO to asthma exacerbation is well supported. Levels of eNO have been associated with eosinophil counts (Brody et al., 2013), which mediate inflammation in allergic asthma. Further, eNO is higher in people with asthma and increases during acute exacerbation (Soto-Ramos et al., 2013; Kharitonov and Barnes, 2000). In the U.S., associations between short-term $PM_{2.5}$ exposure and eNO were observed in panel studies of children with asthma in southern California (Delfino et al., 2006) and Seattle (Allen et al., 2008; Koenig et al., 2005). In Seattle, total personal $PM_{2.5}$ exposure was partitioned into ambient-generated and nonambient-generated fractions based on the ratio of personal to ambient sulfur concentrations. Only the ambient-generated $PM_{2.5}$ was associated with pulmonary inflammation (Allen et al., 2008). Associations were also observed in most (Liu et al., 2009; Murata et al., 2007; Fischer et al., 2002), but not all (Holguin et al., 2007), studies of children outside of the U.S.

Several recent studies provide less consistent evidence of an association between short-term $PM_{2.5}$ exposure and pulmonary inflammation in children with asthma (Figure 5-5). Study-specific details, including cohort descriptions and air quality characteristics are highlighted in Table 5-5. Among children at four schools in the neighboring cities of El Paso, TX and Ciudad Juarez, Mexico, eNO was associated with 48-hour average outdoor $PM_{2.5}$ (Sarnat et al., 2012). Notably, the observed association was largely driven by results from children in one school (Ciudad Juarez) with the highest mean $PM_{2.5}$ concentrations. While Sarnat et al. (2012) reported a small, imprecise association between 2-day average outdoor $PM_{2.5}$ concentration and eNO in El Paso, a follow-up study of children in the same schools in El Paso observed null associations for 4-day average outdoor $PM_{2.5}$ concentrations (Greenwald et al., 2013). Ambient $PM_{2.5}$ concentrations across the two studies were similar (Table 5-5). A reanalysis of Delfino et al. (2006) confirmed that eNO was not associated with $PM_{2.5}$ concentrations measured at fixed-site monitors within 12 km of subjects' residences in a panel study of children with asthma in southern California (Delfino et

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al., 2013). However, Delfino et al. (2006) did report an association with personal $PM_{2.5}$ in the initial study. In contrast to evidence of an association between personal $PM_{2.5}$ exposure an eNO, Maikawa et al. (2016) observed a negative association between previous-day personal $PM_{2.5}$ exposures and eNO in 62 children with asthma in Montreal, Canada.

Other recent studies that used fixed-site monitors to estimate short-term $PM_{2.5}$ concentrations reported more consistent evidence of an association between $PM_{2.5}$ and pulmonary inflammation in children with asthma. Panel studies of children in Beijing, China (Lin et al., 2011) and southern California (Berhane et al., 2011) reported eNO associations with 24-hour average $PM_{2.5}$ concentrations on the same day of examination and 7-day average concentrations prior to examination, respectively. Additionally, a panel study of schoolchildren with asthma in Denver, CO (Rabinovitch et al., 2011) indicated a $PM_{2.5}$ association with increases in urinary leukotriene E4, a cytokine involved in inflammation that is found to increase during asthma exacerbation. Results were similar by asthma severity, but varied across years, with the $PM_{2.5}$-associated increases in urinary leukotriene E4 limited to 2 of the first 3 study years. Only some children overlapped across years, and $PM_{2.5}$ concentrations were slightly higher in Year 3 (Rabinovitch et al., 2011).

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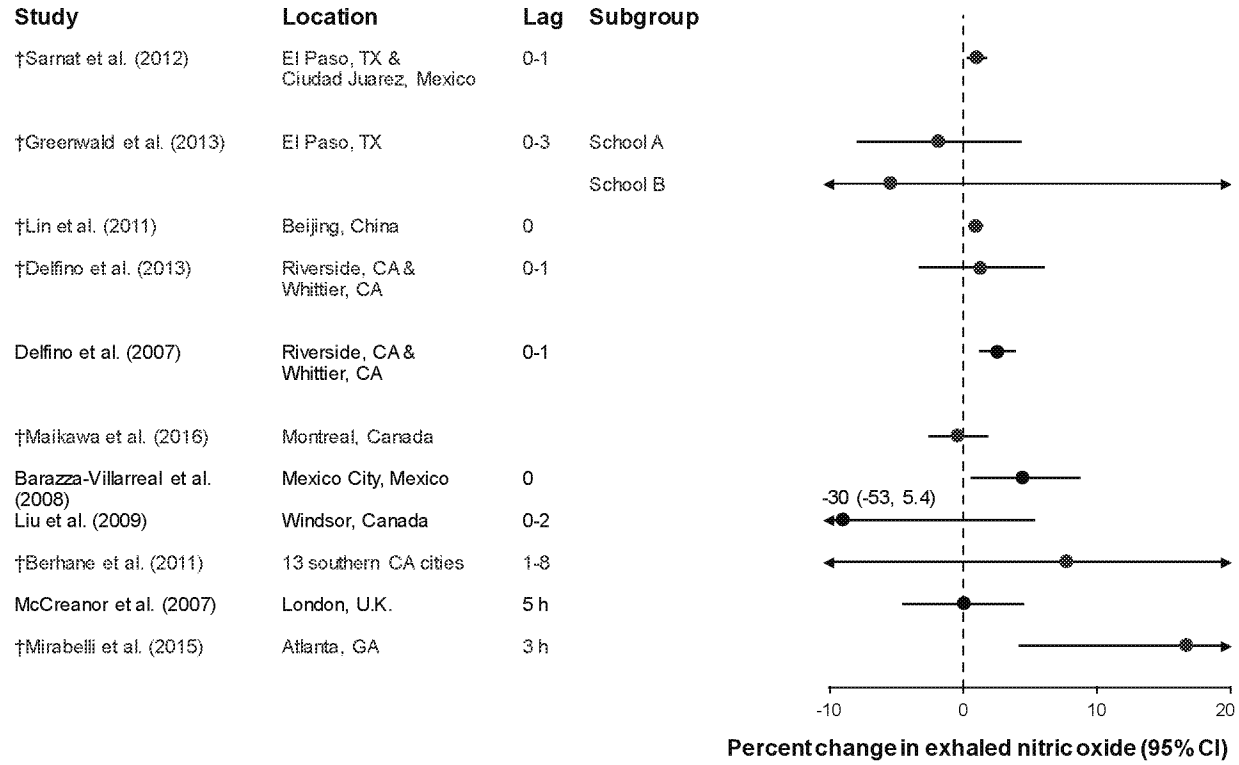

CI = confidence interval.

Note: Studies in red with a dagger are recent studies. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$. Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-5 Summary of associations between short-term $PM_{2.5}$ exposures and exhaled nitric oxide in populations with asthma.

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Table 5-5 Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Children				
†Sarnat et al. (2012) El Paso, TX; Ciudad Juarez, Mexico Jan−May 2008	N = 58 (14−15/school), ages 6−12 yr 33% ICS use, 41% hay fever Weekly eNO—16 weeks Mean 14 measures/subject, 787 total No information on participation rate	School outdoor 48-h avg Schools A and B: Low and high traffic Mean distance home—school: 3.2 km *r* = 0.71−0.93 school-school (within city), 0.91 school-monitor, 0.73−0.86 school-monitor	Mean outdoor Ciudad Juarez A: 31 Ciudad Juarez B: 20 El Paso A: 8.8 El Paso B: 15.6	Correlation (*r*): (across schools) 0.00, 0.05, −0.39, −0.28 NO_2 Copollutant models with: O_3 and NO_2
†Greenwald et al. (2013) El Paso, TX Mar−Jun 2010	N = 38, mean age 10 yr 55% ICS use Weekly eNO—13 weeks 536 total measures No information on participation rate	School outdoor 96-h avg School A and B: Low and high traffic *r* = 0.89 school-school, 0.91 monitor-monitor, 0.73−0.86 school-monitor (Zora et al., 2013)	Mean (SD) outdoor School A: 9.9 School B: 13.8	Correlation (*r*): 0.20 NO_2, 0.30 BTEX, 0.44 cleaning product VOCs, 0.37 SO_2 Copollutant models with: NA
†Lin et al. (2011); Zhu (2013) Beijing, China Jun, Sep, Dec 2007 and Jun, Sep 2008	N = 8, ages 9−12 yr Daily eNO—10 days, 5 periods 1,581 total measures No information on participation rate	One monitor, 0.65 km from school 24-h avg *r* = 0.56 school-monitor	Mean across periods 212, 96.0, 144, 183, 46.4 Max overall: 311	Correlation (*r*): 0.30 NO_2 Copollutant models with: NO_2, SO_2, and CO
†Delfino et al. (2013)	N = 45, ages 9−18 yr 100% persistent asthma, 64% ICS use Daily eNO—10 days	One monitor per city 24-h avg Within 12 km of Riverside homes, 5 km of Whittier homes	Mean: 23.2 Max: 87.2	Correlation (*r*): 0.31 NO_2, 0.39 O_3 Copollutant models with: NA

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Table 5-5 (Continued): Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Delfino et al. (2006) Riverside, CA Aug–Dec 2003 Whittier, CA Jul–Nov 2004	Number measures NR No information on participation rate	Total personal, One monitor per city 24-h avg, 1-h max *r* = 0.91 monitor-outdoor home. Riverside, *r* = 0.77 personal-home, 0.64 monitor-personal.	Mean, max Total personal, 24-h avg Riverside: 32.8, 98 Whittier: 36.2, 197 Total personal, 1-h max Riverside: 37.9, 432 Whittier: 93.6, 573 Monitor, 24-h avg Riverside: 36.6, 87 Whittier: 18, 77	Correlation (*r*): (personal, monitor) 0.33, 0.25 NO_2 Copollutant models with: NO_2
†Maikawa et al. (2016) Montreal, Canada Oct 2009–Apr 2010	N = 62, ages 8–12 yr 15% severe asthma, 24% ICS use, 44% atopy Daily eNO—10 days Median three measures/subject	Total personal 24-h avg 60% samples had insufficient mass	Mean: 19.3 Max: 101	Correlation (*r*): 0.00 O_3 Copollutant models with: O_3
Allen et al. (2008); Mar et al. (2005) Seattle, WA 1999–2002	N = 17, ages 6–13 yr Most mild persistent asthma, 65% asthma medication use Daily eNO—5–10 days, multiple periods 6–20 measures/subject, 226 total No information on participation rate	Home outdoor, total personal, ambient 24-h avg Ambient estimated from personal to ambient sulfur ratio and outdoor home $PM_{2.5}$.	Mean/median, 75th Outdoor home: 11.2, 14.7 Total personal: 11.3, 16.3 Ambient: 6.3, 7.6	Correlation (*r*): NA Copollutant models with: NA
†Rabinovitch et al. (2011); Rabinovitch et al. (2006) Denver, CO 2002–2005	N = 82 (3-yr study), 73 (2-yr study) 65–86% moderate/severe asthma, 82–90% ICS use Daily urinary LTE4—up to 8 days, two periods per yr Median 11–13 measures/subject Yr 1–3 No information on participation rate	One monitor 24-h avg, 10-h avg (12–11 a.m.), 1-h max (12–11 a.m.) 4.3 km from school *r* = 0.92 monitor and school	Mean, max for Yr 1–3 24-h avg: 6.5–8.2, 20.5–23.7 10-h avg: 7.4–9.1, 22.7–30.2 1-h max: 16.8–22.9,39–52 (95th)	Correlation (*r*): NA Copollutant models with: NA

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Table 5-5 (Continued): Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Barraza-Villarreal et al. (2008) Mexico City, Mexico 2003–2005	N = 158, ages 6–14 yr 55% mild intermittent asthma, 6% ICS use, 89% atopy eNO, nasal lavage IL—8 every 15 days-mean 22 weeks 702 total measures No information on participation rate	One monitor 8-h avg Within 5 km of school or home *r* = 0.77 monitor-school	Mean: 28.9 Max: 103	Correlation (*r*): 0.46 O_3, 0.61 NO_2 Copollutant models with: O_3
Liu et al. (2009); Liu (2013) Windsor, Canada Oct–Dec 2005	N = 182, ages 9–14 yr 37% ICS use Weekly eNO, TBARS—4 weeks 672 total measures No information on participation rate	Two monitors averaged 24-h avg 99% homes within 10 km	Median (IQR): 6.5 (6.0) 95th: 19.0	Correlation (*r*): −0.41 O_3, 0.71 NO_2, 0.56 SO_2 Copollutant models with: O_3, NO_2, and SO_2
†Berhane et al. (2011) 13 southern California cities 2004–2005	N = 169, ages 6–9 yr One eNO measure, cross-sectional No information on participation rate	One monitor per community 24-h avg	NR	Correlation (*r*): (warm season, cold season) 0.61, −0.05 O_3; 0.47, 0.65 NO_2 Copollutant models with: NA
Adults				
McCreanor et al. (2007) London, U.K. 2003–2005	N = 60, ages 19–55 yr 100% mild/moderate asthma, 100% AHR, 84% atopy 2 eNO measures—high and low traffic No information on participation rate	Personal ambient 2-h avg (10:30–12:30 a.m.) Scripted exposure walking on high-traffic road and in park, 3 weeks apart	Median, max High-traffic road: 28.3, 76.1 Park: 11.9, 55.9	Correlation (*r*): 0.60 NO_2, 0.76 CO Copollutant models with: NO_2
†Mirabelli et al. (2015) Atlanta, GA 2009–2011	N = 18, ages NR. Mean FEV_1: 100% predicted Two measures—pre- and post-commute, Two periods 93% completed 2nd commute	Personal in-vehicle 2-h avg (7–9 a.m.) Scripted exposure driving car on highway, median 17/13 weeks apart	Mean Asthma control > median: 23.8 Asthma control < median: 21.5	Correlation (*r*): NA Copollutant models with: NA

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Table 5-5 (Continued): Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Maestrelli et al. (2011) Padua, Italy Years NR	N = 32, mean (SD) age 40 (7.5) yr 56% severe asthma, 69% ICS use, 91% atopy Six eNO measures over 2 yr 166 total measures No information on participation rate	Total personal 24-h avg	NR	Correlation (*r*): NA Copollutant models with: NA

AHR = airway hyperresponsiveness, avg = average, BTEX = benzene, toluene, ethylbenzene, xylene, CO = carbon monoxide, eNO = exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled corticosteroid use, IL-8 = interleukin-8, IQR = interquartile range, LTE4 = leukotriene E4, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm; *r* = correlation coefficient; SD = standard deviation, SO_2 = sulfur dioxide, TBARS = thiobarbituric acid reactive substances, VOCs = volatile organic compounds.

†Studies published since the 2009 PM ISA.

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The inconsistency in recent findings, as related to the 2009 PM ISA, is not explained by lower $PM_{2.5}$ concentrations in recent studies (Table 5-5) but may be influenced by location-specific differences in PM sources, study populations, or building infiltration characteristics (Section 3.4). Studies evaluated in the 2009 PM ISA observed associations in locations representing a wide range of $PM_{2.5}$ concentrations. Additionally, a strength of previously reviewed studies of pulmonary inflammation is examination of the hourly lag structure of $PM_{2.5}$ associations. Most (Rabinovitch et al., 2006; Mar et al., 2005) results indicated an increase in inflammation with increases in $PM_{2.5}$ concentrations averaged over the preceding 1 to 11 hours. Associations were also observed with 1-hour or 8-hour max $PM_{2.5}$ that were larger in magnitude than those for 24-hour average $PM_{2.5}$ (Delfino et al., 2006; Rabinovitch et al., 2006). Other results indicate that $PM_{2.5}$ exposure may have a rapid and transient effect on pulmonary inflammation in people with asthma. For Seattle, WA and Riverside and Whittier, CA, distributed lag models show an increase in eNO with the 1-hour average $PM_{2.5}$ concentration up to 5 or 10 hours prior but not with longer lags of 24–48 hours (Delfino et al., 2006; Mar et al., 2005). This may suggest that some recent studies have examined exposure windows that were too long to detect an association, though Berhane et al. (2011) observed eNO associations with cumulative average $PM_{2.5}$ up to 30 days.

Additionally, recent studies of pulmonary inflammation do not establish an independent association with $PM_{2.5}$ exposure. A recent study presents $PM_{2.5}$ associations that are attenuated, but still positive in copollutant models with NO_2, SO_2, or CO (Lin et al., 2011). In a study evaluated in the 2009 PM ISA, personal $PM_{2.5}$ associations with eNO were robust to NO_2 adjustment (Delfino et al., 2006). The result for personal exposure supports an association with $PM_{2.5}$ that is independent of NO_2 exposure based on comparable exposure measurement error and low correlation ($r = 0.30$). However, the limited number of studies examining additional copollutants, in addition to some inconsistency in the observed associations in recent studies, leaves uncertainty as to whether $PM_{2.5}$ exposure leads to an increase in pulmonary inflammation in children with asthma. Further discussion of copollutant confounding is provided in Section 5.1.10.1.

Adults

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided contrasting evidence of an association between short-term exposure to $PM_{2.5}$ and lung function in adults with asthma. In a panel of 60 adults with asthma in London, average $PM_{2.5}$ concentrations measured over a 2-hour outdoor walk was not associated with eNO measurements taken 3 to 7 hours post-exposure (McCreanor et al., 2007). In contrast, in a panel of older adults in Seattle, $PM_{2.5}$ concentrations measured outside of residences were associated with eNO in subjects with asthma. Recent studies are limited in number and results are also inconsistent (Figure 5-5). Mirabelli et al. (2015) studied adults with asthma in Atlanta and reported increased in eNO associated with 2-hour average personal $PM_{2.5}$ exposure measured 0, 1, 2, and 3 hours prior to spirometry. $PM_{2.5}$ concentrations were measured during scripted commutes through rush hour traffic, resulting in higher exposure levels. The observed associations were stronger in magnitude in

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participants with poorly controlled asthma. In contrast, in Padua, Italy, Maestrelli et al. (2011) tested the relationship between eNO and 24-hour average personal $PM_{2.5}$ exposure the day before spirometry and reported negative associations in adults with asthma. This study was limited by a design that designated six single-day examination visits across a 2-year period, precluding the opportunity to examine alternative exposure lags.

5.1.2.4.1 Controlled Human Exposure Studies

There were no studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that specifically investigated the association between PM2.5 CAPs exposure and subclinical effects underlying asthma exacerbation. Recently, Urch et al. (2010) investigated the respiratory effects of short-term exposure to PM2.5 on individuals with asthma by using a CAP facility for PM2.5 located in downtown Toronto, Canada (study details in Table 5-6) and found little change in sputum total cell counts, neutrophils, or macrophages when compared to pre-exposure levels.

Table 5-6 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and subclinical effects underlying asthma exacerbation.

Study	Study Design	Disease Status; n; Sex	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Urch et al. (2010)	Blinded randomized block design	Healthy nonsmokers (13) and individuals with asthma (10); n = 23; 11 M, 12 F	$PM_{2.5}$ CAPs only: 64 ± 3 or 140 ± 6 μg/m^3 $PM_{2.5}$ CAPs + O_3: 68 ± 5 or 142 ± 7 μg/m^3 $PM_{2.5}$ + 119 ± 1 ppb O_3 Comparison group for both groups was filtered air; all exposures were for 2 h carried out at rest	Sputum (pre- and 3- and 20-hour post-exposure): IL-6, IL-8, and IL-10, TNF-α, leukotriene-B, differential cell counts Venous blood (pre-, 10-min, and 3- and 20-h post-exposure): IL-6, TNF-α

CAPs = concentrated ambient particles; IL-6 = Interleukin-6; IL-8 = Interleukin-8; IL-10 = Interleukin-10; O_3 = ozone; TNF-α = tumor necrosis factor α.

5.1.2.4.2 Animal Toxicological Studies

Animal toxicological studies have focused on exacerbation of asthma in the context of allergic airway disease. Allergic airway disease (asthma, rhinitis, etc.) is a type of immune hypersensitivity that is mediated by immunoglobulin E (IgE). Development of allergic airway disease requires sensitization (immunization) that requires, presentation of a foreign antigen by antigen-presenting cells (dendritic cells

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and macrophage subsets) to T-lymphocytes, the activation and clonal expansion of B-cells, and finally production of antigen-specific antibody (IgE) that binds to the antigen. Secondary exposure of previously sensitized individuals to the antigen (challenge, or elicitation phase), will activate IgE-mediated pathways that result in eosinophil recruitment, mucus production, and reactive airways.

The 2009 PM ISA (U.S. EPA, 2009) reviewed the evidence that exposure to $PM_{2.5}$ exacerbated allergic responses in laboratory rodents with pre-existing allergic airway disease. Several studies involved multiday exposures of ovalbumin (OVA)-sensitized and challenged Brown Norway rats to $PM_{2.5}$ CAPs. Increased nasal and airway mucosubstances, pulmonary inflammation, and retention of anthropogenic trace elements (La, V, Mn, S) in lung tissue were observed following 4–5 days of exposure to $PM_{2.5}$ CAPs in Detroit, MI (Harkema et al., 2004; Morishita et al., 2004). A 13-day exposure to $PM_{2.5}$ CAPs in Grand Rapids, MI resulted in no changes in BALF cells or gene expression in the whole lung (Heidenfelder et al., 2009). However, enhanced OVA-specific IgE and Muc5AC responses to ovalbumin (OVA) were observed. In addition, $PM_{2.5}$ CAPs exposure resulted in enhanced allergic bronchiolitis and alveolitis, as well as in epithelial hypertrophy and mucus cell metaplasia, which are characteristic of airway epithelial remodeling. Another study showed that enhancement of allergic responses in mice depended on proximity to the PM source following multiday exposure to roadway $PM_{2.5}$ CAPs in Los Angeles (Kleinman et al., 2005). Additionally, a single acute exposure to reaerosolized diesel exhaust particles (DEP) resulted in dose-dependent increases in levels of the Th2 cytokine IL-4 in BALF in allergic mice (Farraj et al., 2006a, b).

Recently, Harkema et al. (2009) extended their field studies in Detroit to determine if $PM_{2.5}$ CAPs inhalation would modify the allergic responses during the process of allergen challenge of sensitized rats. Ovalbumin-sensitized Brown Norway rats that were exposed to Detroit summertime $PM_{2.5}$ CAPs for the same 3 consecutive days of intra-nasal OVA challenge had increased lavaged total protein, secreted mucosubstances (Muc5AC), and numbers of lymphocytes and eosinophils compared to filtered air-exposed, allergic rats ($p < 0.05$). $PM_{2.5}$ CAPs exposure did not increase OVA-specific IgE levels in BALF above that seen in response to OVA alone. Decreases in pulmonary gene expression of TNFα, IL-10, and IFNγ (putative Th1 mediators) were also detected in $PM_{2.5}$ CAPs-exposed, OVA-challenged rats ($p \leq 0.05$). Using the same exposure protocol but in different rats and on different days when $PM_{2.5}$ CAPs concentration was lower; inflammation responses were unaffected by $PM_{2.5}$ CAPs exposure. In addition to having greater $PM_{2.5}$ CAPs concentration the first exposure study consisted of $PM_{2.5}$ that had more iron, sulfate, nitrate, and PAH content than during the second exposure study. Additional study details, for this recent study and a related one, are found in Table 5-7.

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Table 5-7 Study-specific details from animal toxicologic studies of subclinical effects underlying asthma exacerbation.

Study/Study Population	Pollutant	Exposure	Endpoints
Harkema et al. (2009) Species: Rat Sex: Male Strain: Brown Norway Age/weight: 10−12 weeks	$PM_{2.5}$ CAPs Detroit, MI (urban residential) Particle size: 0.66−0.79 μm Control: Filtered air	Route: Whole-body inhalation exposure Dose/concentration: Period 1: 596 μg/m³ Period 2: 356 μg/m³ Duration: 8 h/day, 3 days, two exposure periods in July Time to analysis: 24 h All animals sensitized to OVA. $PM_{2.5}$ CAPs inhalation during OVA challenge	Histopathology of nose and lung—light microscopy, airway labelling index BALF cells Gene expression-cytokines and Muc5AC
Wagner et al. (2012) Species: Rat Strain: Brown Norway Sex: Male Age/weight: 10−12 weeks	$PM_{2.5}$ CAPs Urban Grand Rapids, MI Urban Detroit, MI Particle sizes: $PM_{2.5}$ Control: HEPA-filtered control air	Route: Whole-body inhalation Dose/concentration (D) Detroit 542 μg/m³ (GR) Grand Rapids 519 μg/m³ Dose/concentration 8 h × 1 day; begun 30 min after intra-nasal OVA challenge Duration of exposure: 8 h Time to analysis: 16 h post exposure	PM characterization Histopathology—lung BALF cells Lung injury—BALF protein BALF-Muc5AC content

BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; Muc5AC = Mucin 5AC, oligomeric mucus/gel-forming; OVA = ovalbumin.

Morphologic responses to short-term $PM_{2.5}$ CAPs exposure was also examined by (Harkema et al., 2009). Both the nose and the lung were evaluated for histologic changes and epithelial cell proliferation. No additional effect on OVA-induced allergic rhinitis was seen in the animals exposed to $PM_{2.5}$ CAPs. However, exposure to $PM_{2.5}$ CAPs resulted in a greater severity of allergic bronchiolitis and alveolitis in OVA-sensitized and challenged rats. More severe mucus cell metaplasia was found, as evidenced by increased amounts of intra-epithelial mucosubstances in conducting airways ($p \leq 0.05$). Epithelial cell proliferation, as measured by labelling index in the airways, was not altered by $PM_{2.5}$ CAPs exposure. When the same exposure protocol was used but in different rats and on different days when $PM_{2.5}$ CAPs concentration was considerably lower, morphologic responses were unaffected by $PM_{2.5}$ CAPs exposure.

The OVA-allergic Brown Norway rat model was also used to compare the effects of $PM_{2.5}$ CAPs exposure that were derived from two dissimilar urban airsheds in Grand Rapids or Detroit MI (Wagner et

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al., 2012). Ovalbumin-sensitized rats were challenged with intra-nasal OVA and 30 minutes later breathed similar concentrations of $PM_{2.5}$ CAPs for 8 hours. Exposure to Detroit $PM_{2.5}$ CAPs, which were characterized by high sulfates and local industrial emissions (high Pb, Zn, and V content), enhanced eosinophilic inflammation ($p < 0.05$), mucus hypersecretion ($p < 0.05$), and mucous cell metaplasia. However, the opposite responses were seen when allergic rats inhaled Grand Rapids $PM_{2.5}$ CAPs, which were dominated by a large spike in morning traffic emissions (NO_2, CO, EC), but had low sulfates throughout the 8-hour exposure. Allergen-induced increases in airway eosinophils ($p < 0.05$), mucus hypersecretion ($p < 0.05$), and mucous cells were reversed in rats exposed to Grand Rapids $PM_{2.5}$ CAPs.

In summary, several studies provide evidence that exposure to $PM_{2.5}$ CAPs and DEP exacerbates allergic responses. In addition, one study found that $PM_{2.5}$ CAPs exposure resulted in an inhibition of allergic responses. These disparate findings may be due to source-related differences in the composition of $PM_{2.5}$ CAP due to different locations where the CAPs were collected.

5.1.2.4.3 Summary of Subclinical Effects Underlying Asthma Exacerbation

Overall, panel studies in children with asthma provide some evidence of associations between short-term $PM_{2.5}$ exposure and inflammatory markers although uncertainty regarding potential copollutant confounding remains. Results were more consistent with shorter lag times. Evidence is mainly negative in panel studies and controlled human exposure studies involving adults with asthma. Further, several studies found that short-term $PM_{2.5}$ exposure led to allergic inflammation and airway remodeling in animal models of allergic disease, which share many phenotypic features with asthma in humans. However, in studies of $PM_{2.5}$ CAPs, the response was dependent on concentration and source profile of the airshed.

5.1.2.5 Summary of Asthma Exacerbations

Recent epidemiologic studies strengthen the evidence for a relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation in children. In particular, recent studies add evidence supporting associations between short-term $PM_{2.5}$ concentration and asthma hospital admissions, ED visits, and physician visits in children. Additional evidence of $PM_{2.5}$-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 $PM_{2.5}$ concentration observed associations with asthma-related effects. Evidence for a relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation in adults continues to be inconsistent.

Evidence from experimental studies provides biological plausibility for associations seen in epidemiologic studies between short-term $PM_{2.5}$ exposure and asthma exacerbation. Although controlled

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human exposure studies were inconsistent in showing effects on lung function and pulmonary inflammation in individuals with asthma, animal toxicological studies demonstrated allergic inflammation, enhanced serum IgE, and airway remodeling in animal models of allergic airway disease. These changes may lead to lung function decrements and respiratory symptoms, which were observed in epidemiology studies in relation to $PM_{2.5}$ exposure (Figure 5-1).

Across the indicators of asthma exacerbation, associations continue to be observed with 24-hour average $PM_{2.5}$ concentrations from the same day, from the few preceding days, or averaged over a few days (Section 5.1.10). Evidence does not clearly point to a stronger effect for a particular exposure lag. Recent epidemiologic studies add evidence from copollutant models that show that $PM_{2.5}$ associations are independent of a copollutant among NO_2, CO, and O_3. Based on more limited investigation, there is evidence that $PM_{2.5}$ associations may be modified by these copollutants and aeroallergens. Other copollutants largely are unexamined. While there are some results from copollutant models based on personal exposure measurements that may have less differential exposure measurement error, scarce application of copollutant models limits the ability to analyze potential for confounding. Thus, as in the 2009 ISA for PM (U.S. EPA, 2009), uncertainty remains in distinguishing an independent effect of $PM_{2.5}$ exposure on asthma exacerbation.

5.1.3 Allergy Exacerbation

Animal toxicological studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provided evidence that $PM_{2.5}$ can facilitate delivery of allergenic material to the airways, promote allergic sensitization, and exacerbate allergic responses. Meanwhile, epidemiologic evidence was limited, with a single study reporting an association between short-term $PM_{2.5}$ concentrations and hospital admissions for allergic rhinitis in children in Turkey (Tecer et al., 2008). Recent evidence that $PM_{2.5}$ exposure enhances allergic inflammation in animal models of allergic airway disease, described in Section 5.1.2.4, not only supports $PM_{2.5}$-related asthma exacerbation but also indicates that $PM_{2.5}$ 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 $PM_{2.5}$ exposure to allergy exacerbation in children or adults. Recent studies examined an array of outcomes, including allergy symptoms, and lung function changes and pulmonary inflammation in populations with allergies. Notably, lung function can decrease during an allergy exacerbation due to airway obstruction caused by Th2 cytokine mediated inflammation, making lung function and pulmonary inflammation relevant markers of allergy exacerbation.

While Tecer et al. (2008) found evidence of an association between short-term $PM_{2.5}$ concentrations and allergic rhinitis hospitalizations in children, Villeneuve et al. (2006) did not observe an association between short-term $PM_{2.5}$ and physician visits for allergic rhinitis in individuals 65 years of age and older in Toronto. The authors examined single-day lags ranging from 0 to 7 days and reported mostly null associations, with some small positive and negative associations depending on the lag day.

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The comparative results of the studies may be indicative of age-related differences in allergic rhinitis sensitivity to $PM_{2.5}$, but differences in study design and location make it difficult to draw conclusions. Other recent studies examined the relationship between short-term exposure to $PM_{2.5}$ and skin allergies, including urticaria (Kousha and Valacchi, 2015) and atopic dermatitis symptoms (Song et al., 2011). Kousha and Valacchi (2015) monitored ED visits for urticaria in relations to short-term $PM_{2.5}$ concentrations in Windsor, Ontario. The authors only analyzed single-day lags, ranging from 0 to 7 days prior to ED visits, and reported associations at lags 1 (OR = 1.07 [95% CI: 0.99, 1. 16]), 2 (1.14 [1.04, 1. 22]), and 3 (1.07 [0.99, 1. 16]), with generally null results at other examined lag times. However, there are uncertainties in the urticaria results, because over 67% of the days included in the study period had less than two reported ED visits. Meanwhile, in a study of schoolchildren with atopic dermatitis in South Korea, $PM_{2.5}$ measured on the school rooftop was not associated with self-reported symptoms of itchy skin (Song et al., 2011).

As mentioned previously, lung function changes and pulmonary inflammation in populations with allergies may serve as markers of allergy exacerbation. In Mexico City, Barraza-Villarreal et al. (2008) examined the association between short-term $PM_{2.5}$ concentrations and several lung function and pulmonary inflammation metrics in schoolchildren with and without asthma. The authors reported that 72% of the 50 subjects without asthma were atopic, leading them to repeat the analysis in a subgroup of atopic children. In the subgroup analysis, $PM_{2.5}$ concentrations were positively associated with FeNO, a measure of airway inflammation, but no quantitative results were presented. The authors presumably did not observe similar associations with the other metrics examined in the main analysis, including IL-8, FEV_1, FVC, and FEV_{25-75}.

In summary, recent animal toxicological studies expand the existing evidence base, providing additional support for the biological plausibility of $PM_{2.5}$-related allergy exacerbation. In contrast, a limited number of epidemiologic studies provide inconsistent evidence of an association across multiple endpoints, including a variety of allergic symptoms, and lung function changes and pulmonary inflammation in people with existing allergies.

5.1.4 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by destruction of alveolar tissue, airway remodeling, and airflow limitation. Reduced airflow is associated with decreased lung function, and clinical symptoms demonstrating exacerbation of COPD include cough, dyspnea, sputum production, and shortness of breath. Severe exacerbation can lead to ED visits or hospital admissions. The epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided evidence of consistent positive associations between short-term $PM_{2.5}$ exposure and increases in hospital admissions and ED visits for COPD. Experimental studies evaluated in the 2009 PM ISA and the 2004 PM AQCD (U.S. EPA, 2004) provide biological plausibility for effects seen in epidemiologic studies. A

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limited number of controlled human exposure and animal toxicological studies demonstrated changes in lung function-related parameters, as well as lung injury and inflammation. Recent studies of the relationship between short-term $PM_{2.5}$ exposure and COPD exacerbation mainly examine hospital admissions and ED visits and are generally consistent in showing associations with $PM_{2.5}$. A small body of studies expand the evidence base and show associations with respiratory symptoms and pulmonary inflammation in adults with COPD, in some cases with measures of personal $PM_{2.5}$. Results for lung function changes are inconsistent. Thus, there is variable coherence among various endpoints linked to COPD exacerbation.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and COPD exacerbation, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on COPD hospital admissions and ED visits.

5.1.4.1 Hospital Admissions and Emergency Department (ED) Visits

Associations between short-term exposure to $PM_{2.5}$ and hospital admissions and ED visits for COPD were generally positive among the multicity and single-city studies conducted in the U.S. and Canada and evaluated in the 2009 PM ISA (U.S. EPA, 2009). Multicity studies reviewed in the 2009 PM ISA examining $PM_{2.5}$ and hospital admissions for COPD reported both null [a Canadian study, (Stieb et al., 2009)] and positive [a U.S. study, (Dominici et al., 2006)] associations between COPD hospital admissions and $PM_{2.5}$. The results from multicity studies were supported by single-city studies conducted in the U.S. and Canada that reported positive associations between short-term exposure to $PM_{2.5}$ and hospital admissions and ED visits for COPD.

Recent studies examining associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions and ED visits generally support the positive associations reported in the 2009 PM ISA. These recent studies report positive associations across both multi- and single-city studies, especially for hospital admissions in populations 65 and older (see Figure 5-6, Table 5-8). However, most of the recent studies that examine short-term $PM_{2.5}$ exposure and COPD ED visits consist of single-city studies.

For each of the studies evaluated in this section, Table 5-8 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants

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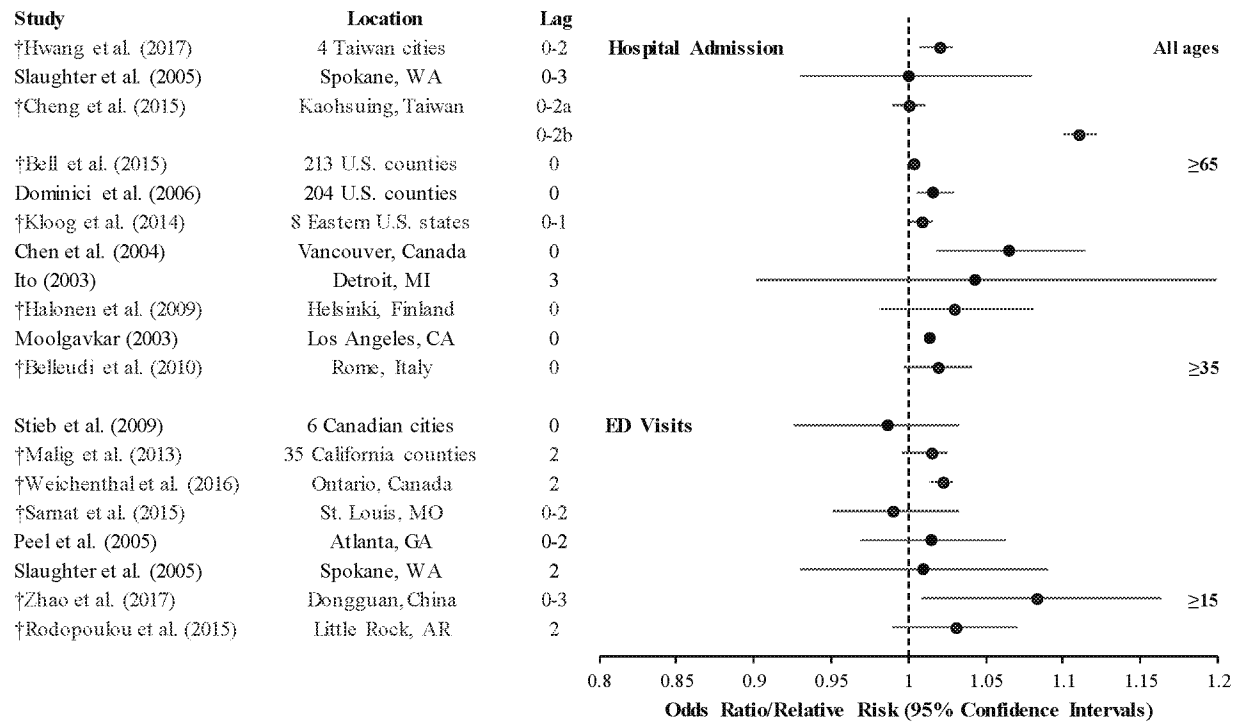
examined in each COPD hospital admission and ED visit study. Other recent studies of COPD hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and, therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-6 Summary of associations between short-term $PM_{2.5}$ exposures and chronic obstructive pulmonary disease (COPD) hospital admissions and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

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Table 5-8 Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Hospital admissions				
†Bell et al. (2015) 213 U.S. counties 1999–2010 Older adults ≥65 yr	Monitors in county averaged Number per county NR	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Correlations (*r*): NA Copollutant models with: NA
Dominici et al. (2006) 204 U.S. counties †Peng et al. (2009b) 94 U.S. counties 1999–2002 Older adults ≥65 yr	Monitors in county averaged Number per county NR	13.4	75th: 15.2	Correlations (*r*): NA Copollutant models with: NA
†Kloog et al. (2014) New York, New Jersey, Pennsylvania, Maryland, Delaware, Virginia, West Virginia, Washington, DC 2000–2006 Older adults ≥65 yr	Satellite-monitor hybrid model	Urban: 12.8 Rural: 11.5	75th Urban: 16.7 Rural: 14.2 Max Urban: 96.1 Rural: 95.9	Correlations (*r*): NA Copollutant models with: NA
Chen et al. (2004) Vancouver, Canada 1995–1999 Older adults ≥65 yr	NR	7.7	75th: 9.0 Max: 32	Correlations (*r*): NA Copollutant models with: O_3, NO_2, CO, SO_2

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Table 5-8 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Ito (2003) Detroit, MI 1992–1994 Older adults, age NR	One monitor in Windsor, Ontario	18	75th: 21 95th: 42	Correlations (*r*): NA Copollutant models with: NA
†Halonen et al. (2009a) Helsinki, Finland 1998–2004 Older adults ≥65 yr	Two monitors	Median: 8.8	75th: 11.0 Max: 41.5	Correlation (*r*): 0.43 O_3. Copollutant models with: O_3
Moolgavkar (2003) Los Angeles, CA 1987–1995 All adults	Monitors in city Number of monitors NR	NR	NR	Correlation (*r*): NA Copollutant models with: CO, SO_2, NO_2.
†Kim et al. (2012) Denver, CO 2003–2007 All adults	One monitor	8.0	Max: 59.4	Correlation (*r*): 0.30 O_3, 0.26 NO_2, 0.23 CO, 0.23 SO_2 Copollutant models with: NA
†Liu et al. (2016) Greater Houston area, TX 2008–2013 All adults	Four monitors averaged from one county	12.0	90th: 18.5	Correlations (*r*): NA Copollutant models with: NA
†Cheng et al. (2015) Kaohshing, Taiwan 2006–2010 All adults	Six monitors averaged	Median: 44.3	75th: 61.9 Max: 144	Correlation (*r*): 0.42 O_3, 0.80 NO_2, 0.81 CO, 0.25 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2

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Table 5-8 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Zhao et al. (2016) Dongguan, China 2013–2015 All adults	Five monitors averaged	42.6	75th: 56.8 Max: 193	Correlation (*r*): 0.40 O_3, 0.67 NO_2, 0.69 SO_2 Copollutant models with: O_3, SO_2, NO_2
†Belleudi et al. (2010) Rome, Italy 2001–2005	One monitor, 2 km from city center	22.8		Correlation (*r*): 0.84 PM_{10} Copollutant models with: NA
ED visits				
†Weichenthal et al. (2016) 15 cities Ontario, Canada 2004–2011 All ages	Nearest monitor to population-weighted zip code centroid or single available monitor	7.1	Max: 56.8	Correlation (*r*): <0.42 NO_2 Copollutant models with: O_3
†Sarnat et al. (2015) St. Louis, MO (eight Missouri counties, eight Illinois counties) 2001–2003 All adults	One monitor	18.0	75th: 22.7 Max: 48.7	Correlation (*r*): 0.23 O_3, 0.35 NO_2, 0.25 CO, 0.08 SO_2. Copollutant models with: NA
†Krall et al. (2016) Atlanta, GA, 1999–2009 Birmingham, AL, 2004–2010 St. Louis, MO, 2001–2007 Dallas, TX, 2006–2009 All adults	One monitor, each city	Atlanta: 15.6 Birmingham: 17.0 St. Louis: 13.6 Dallas: 10.7	NR	Correlation (*r*): 0.57 O_3, 0.39 NO_2 Atlanta, 0.42 O_3, −0.15 NO_2 Dallas, 0.29 O_3, 0.29 NO_2 St. Louis. Copollutant models with: NA

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Table 5-8 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998–2000 All adults	One monitor	19.2	90th: 32.3	Correlations (*r*): NA Copollutant models with: NA
†Rodopoulou et al. (2015) Little Rock, AR 2002–2012 Adults >15 yr	One monitor	12.4	75th: 15.6	Correlation (*r*): 0.33 O_3 Copollutant models with: O_3
†Malig et al. (2013); †Ostro et al. (2016) 35 or 8 California counties 2005–2008 All adults	Nearest monitor	35 counties: 5.2–19.8 8 counties: 16.5 overall	NR	Correlations (*r*): NA Copollutant models with: NA
Stieb et al. (2009) Halifax, Montreal, Toronto, Ottawa, Edmonton, Vancouver, Canada 1992–2003 across cities All adults	One monitor Halifax, Ottawa, Vancouver; three Edmonton; seven Montreal, Toronto	Halifax: 9.8 Montreal: 8.6 Toronto: 9.1 Ottawa: 6.7 Edmonton: 8.5 Vancouver: 6.8	75th, Halifax: 11.3 Montreal: 10.9 Toronto: 11.9 Ottawa: 8.7 Edmonton: 10.9 Vancouver: 8.5	Correlation (*r*): −0.05 to 0.62 O_3, 0.27–0.51 NO_2, 0.01–0.42 CO, 0.01–0.55 SO_2. Copollutant models with: NA
Hospital admissions and ED visits				
Slaughter et al. (2005) Spokane, WA 1995–1999	One monitor	NR	90th: 20.2	Correlation (*r*): 0.62 CO Copollutant models with: NA

Avg = average, CO = carbon monoxide, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; R^2 = coefficient of determination, RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

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5.1.4.1.1 Hospital Admissions

Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions in individuals 65 years and older. In a multicity study conducted in the Mid-Atlantic region of the U.S., Kloog et al. (2014) examined associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions by assigning exposure using a novel prediction model that combined land use regression with surface measurements of $PM_{2.5}$ concentration and satellite aerosol optical depth, which was also employed in a previous study conducted in New England (Kloog et al., 2012). The authors reported a 0.91% (95% CI: 0.18, 1.64) increase in COPD hospital admissions at model lag 0−1 days.

Bell et al. (2015) also examined COPD hospital admissions in adults ages 65 and older in a multicounty time-series analysis conducted in 213 U.S. counties. However, unlike Kloog et al. (2014), where exposures were assigned using model predictions, Bell et al. (2015) assigned exposures through $PM_{2.5}$ data retrieved from ambient monitors in each county. The authors reported a 0.34% (95% CI: −0.05, 0.74) increase in COPD hospital admissions at lag 0, which is smaller in magnitude than the association observed in Kloog et al. (2014), but may reflect the different exposure assignment approaches (Section 3.4.4.1). 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 $PM_{2.5}$ and hospital admissions for COPD. Kim et al. (2012) found no evidence of an association with COPD hospital admissions in Denver, Colorado (quantitative results not reported). Several single-city international studies examined the association with COPD hospital admissions and support the evidence reported in the U.S. multicity studies. A single-city study conducted in Rome, Italy focusing on adults aged 35 years and older investigated the association between $PM_{2.5}$ and COPD hospital admissions in a case-crossover analysis (Belleudi et al., 2010). Effects were assessed at several single- (0−6) and multiday lags (0−1, 0−2, 0−5 and 0−6 days). The association for $PM_{2.5}$ at a 0-day lag was positive but with wide confidence intervals (1.88% [95% CI: −0.27, 4.09]). The evidence observed using a shorter distributed lag is consistent with the lag structure of associations observed in the other COPD hospital admission studies, although in many instances the lags examined were selected a priori. In a similar fashion, 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 to other studies. Cheng et al. (2015), examining hospital admissions in a case-crossover study in Kaohsiung, Taiwan, found no association between $PM_{2.5}$ at a 0−2-day lag (RR 1.00, 95% CI: 0.98, 1.03).

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5.1.4.1.2 Emergency Department (ED) Visits

Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and COPD ED visits. In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term $PM_{2.5}$ 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 $PM_{10-2.5}$, the $PM_{2.5}$ association was relatively unchanged (1.58% [95% CI: 0.56, 2.62]) [Malig et al. (2013) and supplemental data file available on HERO]. 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 $PM_{2.5}$-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 $PM_{2.5}$ 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. The authors used 3-day unconstrained distributed lag models (i.e., lag 0−2) to allow for comparison of relationships among the multiple components and outcomes with potentially different lag structures. There was no evidence of an association between $PM_{2.5}$ and COPD ED visits (RR: 0.99 [95% CI: 0.95, 1.03]).

5.1.4.1.3 Summary of Chronic Obstructive Pulmonary Disease (COPD) Hospital Admissions and Emergency Department (ED) Visits

Consistent with the 2009 PM ISA (U.S. EPA, 2009), several recent studies examined COPD hospital admissions and ED visits and report generally positive associations with $PM_{2.5}$, with more recent multicity studies focusing on hospital admissions for older individuals (i.e., 65 years of age and older). Recent multicity studies conducted in the U.S., as well as single-city studies, that focused on individuals 65 years of age and older reported positive associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions. Associations of short-term $PM_{2.5}$ exposure and ED visits, although generally positive, were less precise due to most studies being conducted in individual cities. The results from the studies evaluated in this section are supported by a recent meta-analysis of 12 studies, some of which were reviewed in the 2009 PM ISA that reported a 3.1% (95% CI: 1.6,4.6) increase in COPD hospital admissions (Li et al., 2015a). As detailed in Section 5.1.10.1, the assessment of potential copollutant confounding in studies of COPD hospital admissions and ED visits was limited, but provided evidence that associations were relatively unchanged in copollutant models. Additionally, although not extensively examined, studies generally provide evidence of larger associations in the cold or winter season compared

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to warmer months (Section 5.1.10.4.1). However, it should be noted studies that examined seasonal patterns of associations did not examine potential copollutant confounding by season.

5.1.4.2 Respiratory Symptoms and Medication Use

A single study reviewed in the 2009 PM ISA (U.S. EPA, 2009) examined respiratory symptoms and medication use in adults with COPD and observed inconsistent evidence of an association with $PM_{2.5}$ across three single-day lags (Silkoff et al., 2005). A limited number of recent studies available for review followed populations comprised of adults with moderate or severe COPD. The results were not entirely consistent, though there was some evidence to indicate associations between $PM_{2.5}$ concentrations and increases in respiratory symptoms in adults with COPD. Study-specific details, air quality characteristics, and select results from these studies are highlighted in Table 5-9. Wu et al. (2016) examined the self-reported occurrence of several respiratory symptoms in relation to short-term $PM_{2.5}$ concentrations in a panel study of 23 adults in Beijing. The authors reported associations between most multiday (2−7) average $PM_{2.5}$ concentrations and sore throat, cough, sputum, wheeze, and dyspnea symptoms. Similarly, in a panel of 29 adults in Mexico City, total personal $PM_{2.5}$ exposure was associated with cough and phlegm, though not wheeze (Cortez-Lugo et al., 2015). A notable limitation of the study was 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, $PM_{2.5}$ was associated with a decrease in COPD exacerbations, defined as a worsening of respiratory symptoms (Devries et al., 2016). Studies accounted for potential confounding by temperature, season, and time trend and also adjusted for subject characteristics such as COPD severity, race, atopic status, and comorbidity. Few studies examined any copollutants. Associations of $PM_{2.5}$ concentrations with wheeze and dyspnea persisted with adjustment for NO_2 or SO_2 in (Wu et al., 2016). However, correlations for $PM_{2.5}$ with NO_2 and SO_2 were high (r = 0.80, 0.68).

5.1.4.3 Lung Function Changes in Adults with Chronic Obstructive Pulmonary Disease (COPD)

5.1.4.3.1 Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), results from a limited number of epidemiologic studies indicated an association between PM and decreased FEV_1 in adults with COPD (Trenga et al., 2006; Ebelt et al., 2005). A few recent studies also evaluated lung function changes in populations with COPD and the results were inconsistent (Table 5-9). Recent studies used trained technicians to measure lung function, but the frequency of measurements varied from daily (Hsu et al., 2011) to less than once per week (Cortez-Lugo et al., 2015). Total personal $PM_{2.5}$ exposure was associated with decreased PEF in adults with COPD in Mexico City, who spent more than 90% of their time indoors (Cortez-Lugo et al.,

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2015). As discussed previously, there was high loss to follow-up in this study. Associations were observed with 2-day average exposures lagged 2 or 3 days but not 0 or 1 days. In a small panel study of adults with COPD in New York City, ambient $PM_{2.5}$ concentrations were associated with decreases in PEF at lag 1, but increases in PEF at lag 0 (Hsu et al., 2011). Given the short sampling period (12 days) and relatively small sample size (nine participants), the interpretability of the results is limited.

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Table 5-9 Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms, lung function, and pulmonary inflammation in adults with chronic obstructive pulmonary disease.

Study	Study Population	Exposure Assessment Concentration µg/m³	Single Pollutant Effect Estimate 95% CI[a]	$PM_{2.5}$ Copollutant Model Results and Correlations
†Chi et al. (2016) Southwestern Taiwan 2014–2016	N = 19, 68% severe COPD Questionnaire every 2 mo for 1 yr 73% follow-up participation	Home outdoor Three measures for 1-min Mean: 120	Score for $PM_{2.5}$ >35 vs. ≤35 µg/m³ Wheeze: 1.46, $p < 0.01$ Phlegm: −0.22, $p > 0.05$ Dyspnea: 0.84, $p > 0.05$ Activity limitation: −0.84, $p > 0.05$	Correlation (r): NA Copollutant models with: NA
†Cortez-Lugo et al. (2015) Mexico City, Mexico Years NR	N = 29, mean 37% predicted FEV_1 Daily diary for three 12-day periods Recruited from clinic 62% completed two or three sessions 90% time spent indoors	Total personal 2-day avg Mean: 39	Phlegm, lag 2: 1.23 (0.98, 1.54) Cough, lag 2: 1.33 (1.05, 1.69) Nighttime PEF (L/min) Lag 1: 0.16 (−2.3, 2.6) Lag 2: −3.0 (−5.7, −0.3)	Correlation (r): NA Copollutant models with: NA
†Devries et al. (2016) Worcester, MA 2011–2012	N = 168, 68% severe COPD Calls to nurse on symptom onset Recruited from clinic No information on participation rate	Three monitors averaged Mean: 8.6 Max: 37.0	Any symptom, lag 1: 0.54 (0.28, 1.10)	Correlation (r): (seasonal range) 0.41–0.83 NO_2, 0.30–0.79 SO_2 Copollutant models with: NO_2 and SO_2
†Wu et al. (2016) Beijing, China Jan–Apr, Aug–Sep 2014	N = 23, 81% moderate/severe COPD Daily diary for 11–81 days 5–21 weekly eNO measures Recruited from clinic 96% completed one or two test periods	One monitor 1.6–8.8 km from homes 24-h avg Median, 75th Period 1: 96.5, 149 Period 2: 65.5, 92.0	Dyspnea, lag 0–4: 1.20 (1.10, 1.29) Sputum, lag 0–4: 1.06 (1.0, 1.13) Cough, lag 0–4: 1.05 (0.99, 1.14) eNO, lag 0–4: 1.7% (0.6, 2.8)	Correlation (r): 0.80 NO_2, 0.68 SO_2, 0.84 PM_{10} Copollutant models with: NO_2, SO_2, and PM_{10}

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Table 5-9 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms, lung function, and pulmonary inflammation in adults with chronic obstructive pulmonary disease.

Study	Study Population	Exposure Assessment Concentration µg/m³	Single Pollutant Effect Estimate 95% CI[a]	$PM_{2.5}$ Copollutant Model Results and Correlations
Trenga et al. (2006) Seattle, WA 1999–2002	N = 24, mean 56% predicted FEV_1 Daily FEV_1 for 36 sessions, 5–10 days each Supervised spirometry Recruited from clinics, senior centers, retirement homes	Total personal, fixed-site monitor, and home outdoor 24-h avg Medians, 75th Total personal: 11.3, 16 Monitor: 11.2, 16.9 Home outdoor: 9.6, 14.8	Change in FEV_1 (ml), lag 1 Total personal: −19 (−74, 36) Fixed-site monitor: −71 (−118, −23) Home outdoor: −45 (−103, 12)	Correlation (*r*): NA Copollutant models with: NA
Ebelt et al. (2005) Vancouver, Canada 1998	N = 16, light/moderate COPD 5–7 FEV_1 measures, every 1.5 week Supervised spirometry No information on participation rate	Personal exposure, five monitors 24-h avg Ambient exposure estimated from total personal SO_4^{2-}, air infiltration, time-activity Mean, max Total personal: 18.5, 90.9 Ambient exposure: 7.9, 21.3 Monitor: 11.4, 28.7	Change in FEV_1 (ml), lag 0 Total personal: −0.39 (−14, 14) Ambient exposure: −66 (−124, −13) Monitor: −27 (−88, 34)	Correlation (*r*): NA Copollutant models with: NA
†Hsu et al. (2011) New York, NY Nov 2002–Mar 2003	N = 9 Recruited from clinics Daily FEV_1 and PEF for 12 days Supervised spirometry No information on participation rate	One monitor within 4.8 km of home 24-h avg Concentrations NR	New York: Negative association of PEF with $PM_{2.5}$ at monitor at lag 1 but positive association of PEF with $PM_{2.5}$ at monitor at lag 0	Correlation (*r*): NA Copollutant models with: NA

Avg = average, COPD = chronic obstructive pulmonary disease, eNO = exhaled nitric oxide, IQR = interquartile range, FEV_1 = forced expiratory volume in 1 second, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, PEF = peak expiratory flow, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; R^2 = coefficient of determination, RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide, SO_4^{2-} = sulfate.

[a]Unless otherwise specified, effect estimates are standardized to a 10 µg/m³ increase in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.

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5.1.4.3.2 Controlled Human Exposure Studies

Two studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provide limited evidence for decreased lung function among subjects with COPD exposed to $PM_{2.5}$ (Gong et al., 2005; Gong et al., 2004). Gong et al. (2004) reported decreases in oxygen saturation among elderly COPD patients, although results were more consistent in elderly subjects without COPD; the authors reported no effects on spirometric measures of lung function. The association between $PM_{2.5}$ and decreased oxygen saturation in COPD patients was confirmed in Gong et al. (2005).

5.1.4.4 Subclinical Effects Underlying Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

5.1.4.4.1 Epidemiologic Studies

A limited number of studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) reported evidence of an association between short-term $PM_{2.5}$ concentrations and pulmonary inflammation in adults with COPD. Studies examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation, a key characteristic of COPD. Additionally, there is evidence that eNO increases during acute COPD exacerbation (Perng and Chen, 2017). Small panel studies of older adults in Steubenville, OH (Adamkiewicz et al., 2004) and Seattle, WA, (Jansen et al., 2005) reported increases in eNO associated with 24-hour average $PM_{2.5}$ concentrations measured at a single fixed-site monitor or outside of participants residences, respectively.

Information from the few available recent studies continues to support a relationship between $PM_{2.5}$ and increases in pulmonary inflammation in adults with COPD. Recent studies evaluated panels of older adults with COPD in Shanghai (Chen et al., 2015b) and Beijing, China (Wu et al., 2016). In both studies, $PM_{2.5}$ was measured at a single fixed-site monitor located within 4 km (Chen et al., 2015b) or 1.6–8.8 km (Wu et al., 2016) of subjects' residences, but information on the variability in $PM_{2.5}$ concentrations in the study areas was not reported. Chen et al. (2015b) observed eNO increases consistent with increases in $PM_{2.5}$ concentrations at 7–12-hour, 13–24-hour, 1-, 2-, and 3–7-day lags. Supporting these findings, the authors also reported associations between $PM_{2.5}$ and decreased methylation of the inducible nitric oxide synthase gene promoter that demonstrated the largest decrements at lag 0–6 hour. Lower methylation is associated with increased gene expression of inducible nitric oxide synthase which mediates production of nitric oxide. Wu et al. (2016) did not examine hourly lags but reported associations between eNO and cumulative average $PM_{2.5}$ concentrations ranging from 1 to 7 days. eNO associations were robust to adjustment for NO_2 but attenuated and no longer positive in two-pollutant models including SO_2 (Wu et al., 2016). However, there were high correlations of $PM_{2.5}$ with NO_2 and

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SO_2 (r = 0.80, 0.68). While these studies provide additional support to the previously limited evidence of an association between $PM_{2.5}$ exposure and pulmonary inflammation in adults with COPD, uncertainties remain in attributing the observed increases in pulmonary inflammation to $PM_{2.5}$ exposure, similar to findings for other indicators of COPD exacerbation.

5.1.4.4.2 Controlled Human Exposure Studies

In the 2009 PM ISA (U.S. EPA, 2009), a limited number of studies investigated $PM_{2.5}$-induced health effects in adults with COPD. (Gong et al., 2004) and Gong et al. (2005) found a decrease in columnar epithelia cells ($p < 0.01$) following short-term exposure to $PM_{2.5}$. This effect was more pronounced in healthy subjects compared to those with COPD.

5.1.4.4.3 Animal Toxicological Studies

While no additional toxicological studies on the effects of PM on COPD have become available in recent years, the 2004 PM AQCD (U.S. EPA, 2004) reported several studies which examined the effects of multiday exposure to $PM_{2.5}$ CAPs in rats with experimentally induced bronchitis, an animal model of COPD. Changes in tidal volume, BALF injury markers (protein, albumin, and N-acetyl glutaminidase), and numbers of BALF neutrophils and lymphocytes were greater in bronchitic rats compared to nonbronchitic rats exposed to $PM_{2.5}$ CAPs from Boston (Saldiva et al., 2002; Clarke et al., 1999) and Research Triangle Park, NC (Kodavanti et al., 2000).

5.1.4.5 Summary of Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Recent studies generally support an association between short-term increases in $PM_{2.5}$ concentration and exacerbation of COPD. Recent studies expand on the array of COPD-related outcomes and add coherence for the observations of $PM_{2.5}$-related increases in COPD-related hospital admissions and ED visits. Overall, evidence links short-term $PM_{2.5}$ exposure to COPD hospital admissions and ED visits. These findings are supported by recent observations of $PM_{2.5}$-related pulmonary inflammation; evidence for $PM_{2.5}$-related symptoms and decreases in lung function is less consistent. A strength of these studies is their assessment of personal $PM_{2.5}$ exposures. Overall, copollutant confounding was not adequately examined. Thus, it is unclear the extent to which the results can be attributed specifically to $PM_{2.5}$ exposure. However, experimental studies in individuals with COPD and in an animal model of COPD support an independent effect of short-term $PM_{2.5}$ 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 $PM_{2.5}$ CAPs exposure and provide biological plausibility for the findings of epidemiologic studies (Figure 5-1).

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5.1.5 Respiratory Infection

The respiratory tract is protected from exogenous pathogens by lung host defenses that include mucociliary clearance, pathogen detoxification, and clearance by alveolar macrophages, as well as innate and adaptive immunity. Impairment of these defense mechanisms can increase the risk of respiratory infection. The 2009 PM ISA (U.S. EPA, 2009) described evidence supporting $PM_{2.5}$-related respiratory infection but there was uncertainty due to a small evidence base relative to those for other respiratory effects. Previous epidemiologic studies consistently observed associations between $PM_{2.5}$ concentrations and hospital admissions or ED visits for indices aggregating various respiratory infections, particularly in U.S. and European cities. Findings from a limited number of studies also supported associations with pneumonia. In the 2004 PM AQCD and the 2009 PM ISA, controlled human exposure studies were not available to assess coherence, but an animal toxicological study demonstrated increased susceptibility to pneumonia infection and altered macrophage function following exposure to $PM_{2.5}$. Hospital admissions and ED visits comprise most of the epidemiologic evidence of respiratory infections and consistently indicate associations for $PM_{2.5}$ concentrations with multiple respiratory infections grouped together but not individually with pneumonia. Interpretation of the evidence, however, is complicated by the variety of respiratory infection outcomes examined.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and respiratory effects, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on respiratory infection hospital admissions and ED visits.

5.1.5.1 Hospital Admissions and Emergency Department (ED) Visits

Associations between short-term $PM_{2.5}$ exposure and hospital admissions and between short-term $PM_{2.5}$ exposure and ED visits for respiratory infections were consistently observed among multicity studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), although the type of respiratory infection examined varied across the studies (i.e., acute bronchitis, bronchiolitis, and pneumonia). Several multicity studies reported associations between short-term $PM_{2.5}$ exposure and pneumonia and acute bronchitis in children. The overall evidence base examining short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for respiratory infections expanded considerably since the 2009 PM ISA. These recent studies

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report generally positive associations between $PM_{2.5}$ and hospital admissions and ED visits for pneumonia, ear infections, and all respiratory infections grouped together (see Figure 5-7, Table 5-10). As in the 2009 PM ISA, respiratory infections when combined capture a range of outcomes (pneumonia, ear infections, bronchiolitis, sinusitis), with studies primarily focusing on children.

For each of the studies evaluated in this section, Table 5-10 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each respiratory infection hospital admission and ED visit study. Other recent studies of respiratory infection hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: https://hero.epa.gov/hero/particulate-matter.

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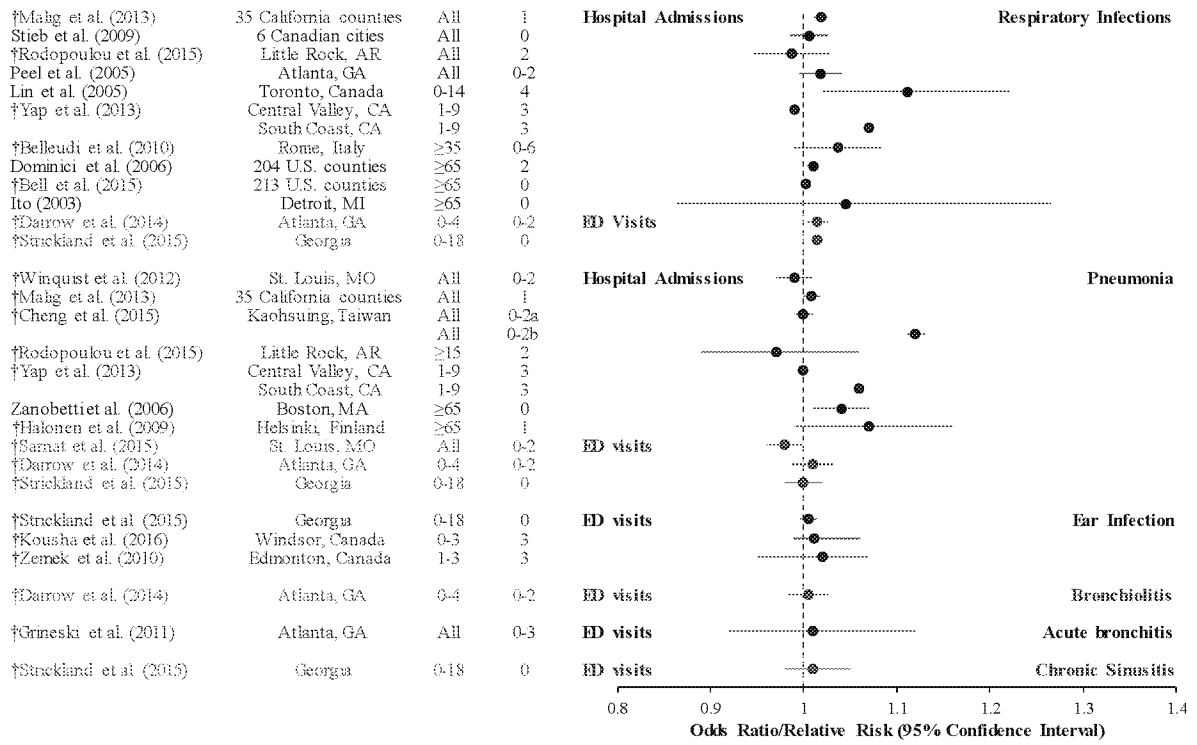

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-7 Summary of associations between short-term $PM_{2.5}$ exposures and respiratory infection hospital admissions and emergency department (ED) visits for a 10 μg/m³ increase in 24-hour average $PM_{2.5}$ concentrations.

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Table 5-10 Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Children					
Lin et al. (2005) Toronto, Canada 1998–2001	Four monitors averaged	Hospital admissions URI + LRI	9.6	75th: 12.3 Max: 50.5	Correlation (*r*): 0.56 O_3, 0.48 NO_2, 0.10 CO, 0.47 SO_2 Copollutant models with: NA
†Yap et al. (2013) 12 counties, Central Valley and South Coast, CA 2000–2005	Monitors in county averaged Number per county NR. 73 monitors total in state.	Hospital admissions ARI and pneumonia	12.8 Sacramento to 24.6 Riverside	NR	Correlation (*r*): 0.25 O_3. Copollutant models with: NA
†Darrow et al. (2014) Atlanta, GA 1993–2010	11 monitors combined for each census tract	ED visits URI and pneumonia	14.1	75th: 17.8 95th: 27.4 Max: 75.2	Correlation (*r*): 0.30 O_3, 0.41 NO_2, 0.45 CO Copollutant models with: NA
†Xiao et al. (2016); †Strickland et al. (2015) Georgia, whole state 2002–2008 or 2010	Fuse-CMAQ; satellite-monitor model	ED visits URI, pneumonia, ear infection, chronic sinusitis	Fuse-CMAQ Mean 13.2 Satellite-monitor Median State: 12.9 Large urban: 13.0 Nonurban: 12.9	Fuse-CMAQ 75th: 16.1 Max: 86.4 Satellite-monitor State 75th: 17.4 99th: 37.4	Correlation (*r*): 0.61 O_3, 0.22 NO_2, 0.26 CO, 0.21 SO_2 Copollutant models with: NA
†Zemek et al. (2010) Edmonton, Canada 1999–2002	Three monitors averaged	ED visits Ear infection	8.5	75th: 10.9	Correlation (*r*): NA Copollutant models with: NA

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Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Kousha and Castner (2016) Windsor, Canada 2004–2010	Monitors in city Number N	ED visits Ear infection	4.7	NR	Copollutant correlation (*r*): NA Copollutant models with: NA
Older adults					
Dominici et al. (2006) 204 U.S. counties 1999–2002	Monitors in county averaged Number per county NR	Hospital admissions URI + LRI	13.4	75th: 15.2	Copollutant correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. counties 1999–2010	Monitors in county averaged Number per county NR	Hospital admissions URI + LRI	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Copollutant correlation (*r*): NA Copollutant models with: NA
Ito (2003) Detroit, MI 1992–1994	One monitor Sited in Windsor, Ontario	Hospital admissions Type of infection NR	18	75th: 21 95th: 42	Copollutant correlation (*r*): NA Copollutant models with: NA
Zanobetti and Schwartz (2006) Boston, MA 1995–1999	One monitor Data missing for 1998	Hospital admissions Pneumonia	Median: 11.1	75th: 16.1 95th: 26.3	Correlation (*r*): 0.20 O_3, 0.55, NO_2, 0.52 CO Copollutant models with: NA
†Halonen et al. (2009b) Helsinki, Finland 1998–2004		Hospital admissions Pneumonia	Median: 9.5	75th: 11.7 Max: 69.5	Correlation (*r*) = 0.39 NO_2, 0.30 CO Copollutant models with: NO_2, CO
All adults					

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Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Halonen et al. (2009a) Helsinki, Finland 1998–2004	Two monitors	Hospital admissions Pneumonia	Median: 8.8	75th: 11.0 Max: 41.5	Correlation (*r*): 0.43 O_3. Copollutant models with: O_3
†Rodopoulou et al. (2015) Little Rock, AR 2002–2012	One monitor	ED visits ARI and pneumonia	12.4	75th: 15.6	Correlation (*r*): 0.33 O_3 Copollutant models with: O_3
†Liu et al. (2016) Greater Houston area, TX 2008–2013 Mostly adults (92%)	Four monitors averaged	Hospital admissions Pneumonia	12.0	90th: 18.5	Copollutant correlation (*r*): NA Copollutant models with: NA
†Belleudi et al. (2010) Rome, Italy 2001–2005	One monitor	Hospital admissions LRI	22.8	75th: 27.8	Correlation (*r*): 0.84 PM_{10} Copollutant models with: NA
†Sarnat et al. (2015) St. Louis, MO (eight Missouri counties, eight Illinois counties) 2001–2003 All adults	One monitor	ED visits Pneumonia	18.0	75th: 22.7 Max: 48.7	Correlation (*r*): 0.23 O_3, 0.35 NO_2, 0.25 CO, 0.08 SO_2 Copollutant models with: NA
All ages					
†Krall et al. (2016) Atlanta, GA, 1999–2009 Birmingham, AL, 2004–2010 St. Louis, MO, 2001–2007 Dallas, TX, 2006–2009	One monitor in each city	ED visits URI and pneumonia	Atlanta: 15.6 Birmingham: 17.0 St. Louis: 13.6 Dallas: 10.7	NR	Correlation (*r*): 0.57 O_3, 0.39 NO_2 Atlanta, 0.42 O_3, −0.15 NO_2 Dallas, 0.29 O_3, 0.29 NO_2 St. Louis. Copollutant models with: NA

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Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998–2000	One monitor	ED visits URI and pneumonia	19.2	90th: 32.3	Copollutant correlation (*r*): NA Copollutant models with: NA
†Malig et al. (2013) 35 California counties, 2005–2008 †Ostro et al. (2016) Eight California counties, 2005–2008	Nearest monitor Monitor within 25 or 20 km of population-weighted zip code centroid	ED visits ARI and pneumonia	35 counties: 5.2 to 19.8 8 counties: 16.5 overall	NR	Copollutant correlation (*r*): NA Copollutant models with: NA
Stieb et al. (2009) Halifax, Montreal, Toronto, Ottawa, Edmonton, Vancouver, Canada 1992–2003 across cities	One monitor	ED visits URI + LRI	6.7–9.8	75th 8.7–11.9	Correlation (*r*): −0.05 to 0.62 O_3, 0.27–0.51 NO_2, 0.01–0.42 CO, 0.01–0.55 SO_2. Copollutant models with: NA
Host et al. (2008) Paris, Le Havre, Toulouse, Rouen, Marseille, Lille, France, 2000–2003	Seven monitors	Hospital admissions URI + LRI	13.8–18.8	95th 26.3–33.0	Copollutant correlation (*r*): NA Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001–2007	One monitor	Hospital admissions and ED visits Pneumonia	14.4	Max: 56.6	Correlation (*r*): 0.25 O_3 Copollutant models with: NA
†Kim et al. (2012) Denver, CO 2003–2007	One monitor	ED visits Pneumonia	8.0	Max: 59.4	Correlation (*r*): 0.30 O_3, 0.26 NO_2, 0.23 CO, 0.23 SO_2 Copollutant models with: NA
†Cheng et al. (2015) Kaohsiung, Taiwan 2006–2010	Six monitors averaged	Hospital admissions Pneumonia	Median: 44.3	75th: 61.9 Max: 144	Correlation (*r*): 0.42 O_3, 0.80 NO_2, 0.81 CO, 0.25 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2

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Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Grineski et al. (2011) El Paso, TX 2000–2003	Two monitors averaged	Hospital admissions Acute bronchitis	12.8	75th: 15.6 95th: 26.6 Max: 119.1	Copollutant correlation (*r*): NA Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001–2007	Two monitors averaged	Hospital admissions and ED visits	14.4	Max: 56.6	Correlation (*r*): 0.25 O_3 Copollutant models with: NA
†Sinclair et al. (2010) Atlanta, GA 1998–2002	One monitor	Outpatient visits for acute respiratory illness	17.1	NR	Copollutant correlation (*r*): NA Copollutant models with: NA

ARI = acute respiratory infection, avg = average, CMAQ = community multiscale air quality, CO = carbon monoxide, ED = emergency department, IDW = inverse distance weighted, IQR = interquartile range, LRI = lower respiratory infection, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, R^2 = coefficient of determination, SD = standard deviation, SO_2 = sulfur dioxide, URI = upper respiratory infection.

†Studies published since the 2009 PM ISA.

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5.1.5.1.1 Hospital Admissions

Studies examined the association between short-term $PM_{2.5}$ exposure and hospital admissions for a variety of respiratory infections. Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and hospital admissions for respiratory infections in children age 1 to 9 years (Yap et al., 2013) and in individuals 65 years of age and older (Bell et al., 2015). Yap et al. (2013) evaluated pediatric (children ages 1 to 9 years) hospital admissions for respiratory conditions associated with $PM_{2.5}$ exposures in 12 California counties. For acute respiratory infections, including pneumonia, relative risks (RR) ranged from 1.03 to 1.07 in Los Angeles, Riverside, San Bernardino, and San Diego counties at lags 0–2 days. The association for combined respiratory infection hospital admissions was significantly higher in the south coast than the central valley (RR 1.07 vs. 0.99); confidence intervals were not reported. In addition to this evidence for pediatric infections, in a multicounty time-series analysis of adults conducted in 213 U.S. counties Bell et al. (2015) reported a 0.21% (95% CI: −0.07, 0.49) increase in combined respiratory tract infection hospital admissions among adults aged 65 and older at lag 0.

In addition to the multicity studies presented above, several single-city studies were conducted in the U.S. and internationally that examined respiratory infection hospital admissions. Grineski et al. (2011) primarily focused on examining the effect of dust and low wind events on asthma and acute bronchitis hospital admissions in El Paso, TX. The authors reported imprecise associations with $PM_{2.5}$ and acute bronchitis hospital admissions across both single and multiday lags with an OR = 1.01 (95% CI: 0.92, 1.12) at lag 0–3 days. By contrast, in Denver, CO, Kim et al. (2012) reported no association between $PM_{2.5}$ and pneumonia hospital admissions at any lag when examining a distributed lag model of 0–14 days (quantitative results not presented). Winquist et al. (2012) conducted a study in the St. Louis-MO metropolitan area to evaluate the impact of the type of health care visit on the association with short-term air pollution exposures, including $PM_{2.5}$. This study compared four visit types including ED visits, hospital admissions, hospital admissions that came through the ED, and nonelective hospital admissions. The authors found that compared with ED visits patients, hospital admission patients tended to be older, had evidence of greater severity for some outcomes, and had a different mix of specific outcomes. For pneumonia, associations with $PM_{2.5}$ were positive only among the 2–18-year-old group for ED visits, nonelective hospital admissions, and hospital admissions through ED types of visits. The only positive association was observed for hospital admissions through ED visits (0.43% [95% CI: −0.56, 0.68] at lag 0–4 days. In Rome, Italy, Belleudi et al. (2010) reported evidence of an association between $PM_{2.5}$ and lower respiratory tract infection hospital admissions among adults aged 35 years and older (3.62% [95% CI: −0.96, 8.42]; lag 0–6 DL).

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5.1.5.1.2 Emergency Department (ED) Visits

Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and respiratory infection-related ED visits. In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term $PM_{2.5}$ 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 $PM_{2.5}$ 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.

The evidence for associations with ED visits from single-city studies also expanded considerably since the 2009 PM ISA (U.S. EPA, 2009). Winquist et al. (2012) observed a positive association for hospital admissions through ED visits, can be compared to a more recent study conducted in the same St. Louis Missouri-Illinois (MO-IL) metropolitan area. However, unlike Winquist et al. (2012), Sarnat et al. (2015) found no evidence of an associations between $PM_{2.5}$ and pneumonia ED visits (RR = 0.98 [95% CI: 0.96, 1.00]) at lag 0−2 days.

Several studies investigated the associations between $PM_{2.5}$ 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 $PM_{2.5}$ and pediatric (ages 0−4) ED visits for respiratory infections, including bronchitis and bronchiolitis, pneumonia, and upper respiratory infection (URI). Daily concentrations of ambient air pollution from several networks of ambient monitors were combined using population-weighting. Pneumonia ED visits were positively associated with $PM_{2.5}$ (for children aged 0−4 years, RR = 1.01 [95% CI: 0.99, 1.03]). $PM_{2.5}$ at lag 0−2 days was not associated with an increase in ED visits for bronchiolitis and bronchitis, although some of the point estimates in the children aged 1−4 years were positive, but uncertain for URI and pneumonia. In the same location, Strickland et al. (2015) examined children ages 0−18 years old between 2002−2010 in a case-crossover study using predicted daily $PM_{2.5}$ concentrations from a two-stage spatiotemporal model with geographical weighting. 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) amongst 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).

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5.1.5.2 Outpatient and Physician Visit Studies

A study conducted in Atlanta, GA, Sinclair et al. (2010) examined the association between air pollution and several respiratory-related outpatient visits, including upper and lower respiratory infections. The authors separated the analysis into two consecutive time periods to compare the air pollutant concentrations and relationships for acute respiratory visits for the 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 and Inhalation Epidemiology Study (ARIES) (September 2000–December 2002). Across the two-time periods, 24-hour average $PM_{2.5}$ concentrations were lower in the 28-month versus the 25-month time-period (16.2 vs. 18.4 μg/m^3, respectively). A comparison of the two-time periods indicated that associations for $PM_{2.5}$ tended to be larger in the earlier 25-month period compared to the later 28-month period. The highest association with LRI was observed for lag 3–5 in the 25-month time-period (RR: 1.071 [95% CI: 1.003, 1.144]). For URI in the 25-month period, the association was positive at lag 0–2 days (RR: 1.015 [95% CI: 0.990, 1.040]). It should be noted that the severity of a $PM_{2.5}$-related respiratory outcome, personal behavior such as delaying a visit to the doctor for less severe symptoms, and insurance type (i.e., physician visits which often are ascertained for members of a managed care organization) may dictate whether individuals visit the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

5.1.5.3 Subclinical Effects Underlying Respiratory Infection

Subclinical effects have been investigated solely in animal toxicological studies. As described in the 2004 PM AQCD (U.S. EPA, 2004), Zelikoff et al. (2003) showed that exposure to $PM_{2.5}$ CAPs in New York City resulted in altered macrophage function in rats. In addition, a greater bacterial burden was found when infection with *S. pneumoniae* was followed 48 hours later by $PM_{2.5}$ CAPs exposure. However, when $PM_{2.5}$ CAPs exposure preceded *S. pneumoniae* infection, it had little effect on bacterial burden. Studies described in the 2009 PM ISA (U.S. EPA, 2009) demonstrated altered susceptibility to infectious agents following exposure to whole motor vehicle exhaust and effects due to metal-enriched particles (i.e., ROFA). Recent studies of respiratory-related infection did not examine the effects of $PM_{2.5}$ CAPs or seek to distinguish between the effect of gaseous and particulate components in a mixture.

5.1.5.4 Summary of Respiratory Infection

The body of evidence for associations between short-term exposure to $PM_{2.5}$ and respiratory infection is comprised mainly of studies of hospital admissions and ED visits. These studies increased in number since the last review. However, because of variability in the type of respiratory infection outcome examined, the overall interpretation of findings is more complicated. Associations reported in single-city

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studies were often imprecise, with confidence intervals crossing the null. A few recent single-city studies reported positive associations for acute bronchitis hospital admissions and respiratory tract infection hospital admissions. In several multicity studies, one conducted in the U.S. and one in or Canada, studying $PM_{2.5}$ and hospital admissions for respiratory infections, both reported positive associations. Most single-city studies in the U.S. consistently reported positive associations for pneumonia (adults and children, ages 0–4), but this effect was not observed for bronchiolitis and bronchitis in children ages 0–4. In contrast, a study of acute respiratory infection ED visits reported no evidence of an association with $PM_{2.5}$. However, a single-city U.S. study reported positive associations with outpatient visits for lower and upper respiratory tract infections. Moreover, these studies generally provide inconsistent evidence for seasonal patterns in the strength of association. A single experimental study in animals, demonstrating altered macrophage function and increased susceptibility to pneumonia in response to $PM_{2.5}$ CAPs exposure, supports findings of epidemiologic studies.

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

In addition to individual respiratory diseases, epidemiologic studies examined respiratory diseases in aggregate where, in some cases, the aggregate represented all respiratory diseases while, in others, a specific combination of respiratory diseases was represented (e.g., COPD, asthma and respiratory infections). In the 2009 PM ISA (U.S. EPA, 2009) there was a small number of studies that examined short-term $PM_{2.5}$ exposure and all respiratory-related diseases in the context of hospital admissions and ED visits. These studies generally encompassed single-city studies and reported evidence of consistent, positive associations when examining effects in children, people of all ages, adults, and older adults (i.e., ≥65 years of age) at lags within the range of 0 to 2 days. However, across these studies the evaluation of potential copollutant confounding was limited to analyses of $PM_{10-2.5}$, with no evaluation of gaseous pollutants. When interpreting these results, it is often difficult to determine if the associations observed indicate that $PM_{2.5}$ may affect the spectrum of respiratory diseases or reflects the evidence supporting associations with specific respiratory diseases, such as asthma.

Studies published since the completion of the 2009 PM ISA (U.S. EPA, 2009) report generally consistent, positive associations across studies of hospital admissions and ED visits for all age ranges, particularly in multicity studies (Figure 5-8). Among studies that examined both combinations of respiratory diseases grouped together and individual respiratory diseases, as detailed in previous sections within this chapter, most observed positive $PM_{2.5}$ associations with asthma (Section 5.1.2), respiratory infection (Section 5.1.5), or both, with results for COPD (Section 5.1.4) being more variable. However, some studies show associations with all three respiratory diseases. For studies that did not observe $PM_{2.5}$-related increases in hospital admissions or ED visits for all respiratory-related diseases, associations were often observed for individual respiratory diseases within the same study, for example asthma [e.g., Yap et al. (2013)]. Similar to the individual respiratory diseases discussed earlier within this

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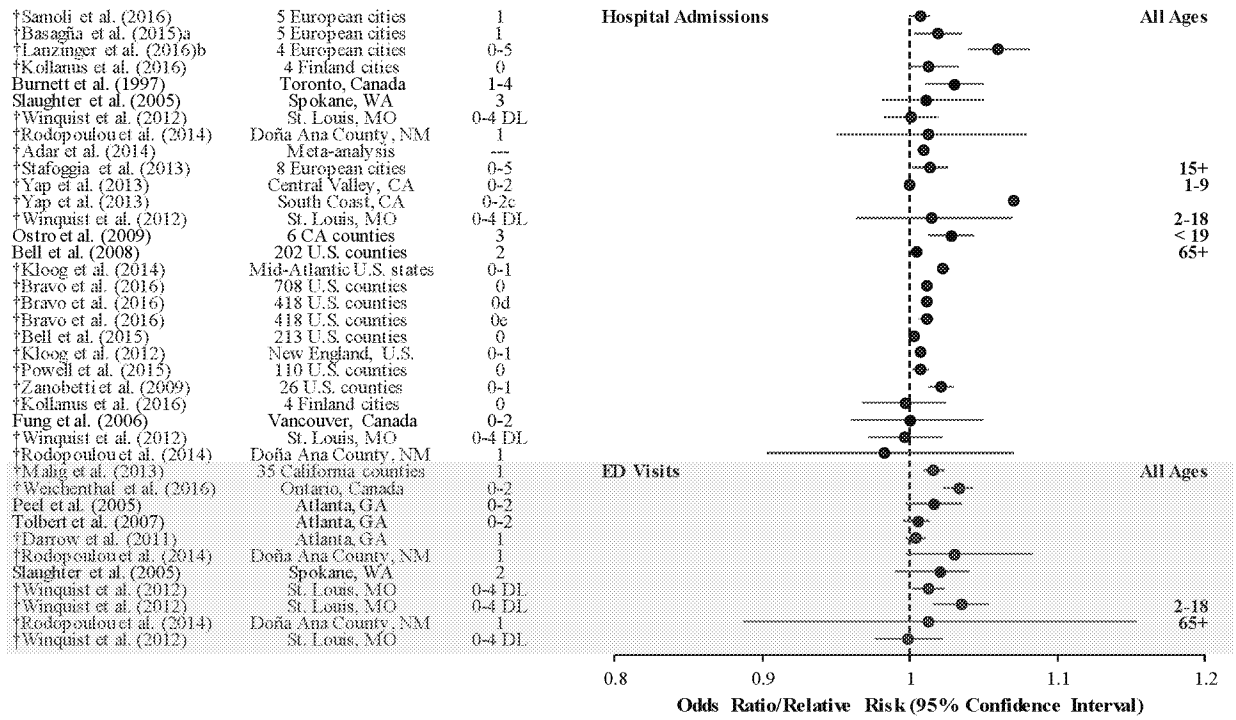
chapter, positive associations with respiratory-related diseases are more consistently observed among children and when examining people of all ages. However, recent studies further expand analyses with older adults, with multicity studies conducted in the U.S. providing evidence of consistent, positive associations between short-term $PM_{2.5}$ exposure and respiratory-related diseases.



DL = distributed lag.

Note: †Studies published since the 2009 PM ISA. Black text: U.S. and Canadian studies included in the 2009 PM ISA. a = five European cities as part of the MED-PARTICLES project; b = only four of the five cities had $PM_{2.5}$ data; c = quantitative data for confidence intervals not reported, but above the null; d = monitoring data result; e = downscaler CMAQ, only counties and days with monitoring data. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-8 Summary of associations from studies of short-term $PM_{2.5}$ exposure and respiratory-related hospital admission and emergency department (ED) visits for a 10 μg/m³ increase in 24-hour average $PM_{2.5}$ concentrations.

Consistent with earlier sections, the focus of this section is on those studies that address uncertainties and limitations in the evidence for association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions and ED visits identified at the completion of the 2009 PM ISA (U.S. EPA, 2009). For each of the studies that evaluated hospital admissions and ED visits for combinations of respiratory-related diseases, Table 5-11 presents the air quality characteristics of each

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city, or across all cities, the exposure assignment approach used, and information on copollutants examined. Other recent studies of hospital admissions and ED visits for respiratory-related diseases that did not address uncertainties and limitations in the evidence previously identified are not the focus of this evaluation. Additionally, many of these other studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these other studies can be found in HERO: https://hero.epa.gov/hero/particulate-matter.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and respiratory effects, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within this section consist only of epidemiologic studies that conducted time-series or case-crossover analyses focusing on combinations of respiratory-related ED visits and hospital admissions.

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Table 5-11 Epidemiologic studies of $PM_{2.5}$ and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Hospital admissions					
Bell et al. (2008) 202 U.S. counties 1999–2005 ≥65 yr	Average of all monitors in each county	490–492; 464–466; 480–487	NR	NR	Correlation (*r*): NA Copollutant models with: NA
Bell et al. (2009a) 168 U.S. counties 1999–2005 ≥65 yr	Average of all monitors in each county	490–492; 464–466; 480–487	NR	NR	Correlation (*r*): NA Copollutant models with: NA
Ostro et al. (2009) Six California counties 2000–2003 <19 yr	Average of all monitors in each county	460–519	19.4	NR	Correlation (*r*): NA Copollutant models with: NA
Fung et al. (2006) Vancouver, Canada 1995–1999 ≥65 yr	Average of all monitors	460–519	7.7	Max: 32	Correlation (*r*): −0.03 O_3, 0.36 NO_2, 0.23 CO, 0.42 SO_2 Copollutant models with: NA
Burnett et al. (1997) Toronto, Canada 1992–1994, summers only All ages	One monitor	464–466; 490; 480–486; 491–494, 496	16.8	75th: 23 95th: 40 Max: 66	Correlation (*r*): 0.32 O_3, 0.45 NO_2, 0.42 CO, 0.49 SO_2 Copollutant models with: O_3, CO, NO_2, SO_2

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Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Powell et al. (2015) 119 U.S. counties 1999–2010 ≥65 yr	Average of all monitors in each county	464–466, 480–487; 490–492	12.1[a]	75: 14.2	Correlation (*r*): NA Copollutant models with: NA
†Bravo et al. (2017) 708 U.S. counties, Eastern 2/3rd of U.S. 2002–2006 ≥65 yr	Average of all monitors within a county County-level population-weighted average of $PM_{2.5}$ concentrations predicted by downscaler CMAQ at census tract centroids Same as (2), but only for counties and days with monitoring data	464–466, 480–487; 490–492	Monitors: 12.5 Downscaler CMAQ: 12.6 Downscaler CMAQ Subset: 12.6	NR	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. counties 1999–2010 ≥65 yr	Average of all monitors in each county	464–466, 480–487; 490–492; 493	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Zanobetti et al. (2009) 26 U.S. counties 2000–2003 ≥65 yr	Average of all monitors in each county	460–519	15.3	NR	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2014) Three Connecticut and one Massachusetts counties 2000–2004 ≥65 yr	One monitor in each of three counties, two averaged in one Connecticut county	464–466, 480–487; 490–492	14.0	NR	Correlation (*r*): NA Copollutant models with: NA

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Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Kloog et al. (2012) New England, U.S. 2000–2006 ≥65 yr	Predicted daily concentrations to 10 km² grid cells based on AOD observation data and 78 monitoring sites code as detailed in Kloog et al. (2011), R^2 = 0.81, then matched to zip codes	460–519	9.6	75th: 11.7 Max: 71.6	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2014)[c] Mid-Atlantic States, U.S. 2000–2006 ≥65 yr	Predicted daily concentrations to 10-km² grid cells based on AOD observation data and 78 monitoring sites code as detailed in Kloog et al. (2011), R^2 = 0.81, then matched to zip codes	460–519	11.9	75th: 14.7 Max: 95.9	Correlation (*r*): NA Copollutant models with: NA
†Yap et al. (2013) 12 counties, Central Valley and South Coast, CA 2000–2005 1–9 yr	Average of all monitors in each county	460–466, 480–486; 493	12.8–24.6	NR	Correlation (*r*): NA Copollutant models with: NA
†Samoli et al. (2016a) Five European cities 2001–2011 All ages	Average of all monitors in each city	466, 480–487; 490–492, 494, 496; 493	7.8–22.7	NR	Correlation (*r*): NA Copollutant models with: NA
†Lanzinger et al. (2016b)[d] Four European cities (UFIREG) 2011–2014 All ages	Average of all monitors in each city	J00–J99	14.9–20.7	Max: 78.8–114.8	Correlation (*r*): 0.55–0.73 NO_2, 0.41–0.61 $PM_{10-2.5}$, 0.25–0.37 UFP, 0.49–0.50 PNC Copollutant models with: NA

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Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Basagaña et al. (2015) Five European cities (MED-PARTICLES) 2001–2010 All ages	One monitor in each city	460–519, J00–J99	16.0–27.6	NR	Correlation (*r*): NR Copollutant models with: NR
†Stafoggia et al. (2013) Eight European cities (MED-PARTICLES) 2003–2013 ≥15 yr	Average of all monitors in each city	460–519	17.2–34.4	NR	Correlation (*r*): >0.60 with NO_2 Copollutant models with: O_3, NO_2, $PM_{10-2.5}$
†Jones et al. (2015) New York State 2000–2005 All ages	Fused-CMAQ[b] to 12-km² grid cells, geocoded addresses to each grid cell	491, 492, 493, 496	8.0	75th: 11.1 Max: 69.5	Correlation (*r*): −0.34–0.59 O_3 Copollutant models with: NA
†Kim et al. (2012) Denver, CO 2003–2007 All ages	One monitor	480–486; 490–493, 496	7.9	Max: 59.4	Correlation (*r*): 0.68 SO_4^{2-}, 0.82 NO_3^- Copollutant models with: NA
†Kollanus et al. (2016) Helsinki, Finland 2001–2010 All ages	One urban background monitor and one regional background monitor	J00–J99	8.6	75th: 10.8 Max: 54.1	Correlation (*r*): NA Copollutant models with: NA

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Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
ED visits					
Peel et al. (2005) Atlanta, GA 1993–2000 All ages	One monitor	460–466, 477; 480–486; 491, 492, 496; 493, 786.09	19.2	90th: 32.3	Correlation (*r*): 0.55–0.68, CO, NO_2 Copollutant models with: NA
Tolbert et al. (2007) Atlanta, GA 1993–2004 All ages	One monitor	460–465, 460.0, 477; 480–486; 491, 492, 496; 493, 786.07, 786.09; 466.1, 466.11, 466.19	17.1	75th: 21.9 90th: 28.8 Max: 65.8	Correlation (*r*): 0.62 O_3, 0.47 NO_2, 0.47 CO, 0.17 SO_2, 0.47 $PM_{10-2.5}$ Copollutant models with: NA
†Malig et al. (2013) 35 California counties 2005–2008 All ages	Nearest monitor within 20 km from population-weighted centroid of each patient's residential zip code	460–519	5.2–19.8	NR	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$
†Krall et al. (2016) Four U.S. cities 1999–2010	One monitor in each city	460–465, 466.0, 477; 480–486; 491–493, 496, 786.07	Atlanta: 15.6 St. Louis: 13.6 Dallas: 10.7 Birmingham: 17.0	NR	Correlation (*r*): NA Copollutant models with: NA
†Darrow et al. (2011) Atlanta, GA 1998–2004 All ages	One monitor 24-h avg, 1-h max, commute (7–10 a.m.), daytime (8 a.m.–7 p.m.), nighttime (12–7 a.m.)	460–466, 477; 480–486; 491–493, 496, 786.09	24-h avg: 16 1-h max: 29 Commute: 17 Daytime: 15 Nighttime: 17	75th, Max: 24-h avg: 21, 72 1-h max: 36, 188 Commute: 21, 76 Daytime: 19, 71 Nighttime: 14, 88	Correlation (*r*): 24-h avg: 0.46 O_3, 0.52 NO_2, 0.45 CO. Similar for 1-h max, higher for nighttime, lower for daytime and commute. Copollutant models with: NA

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Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Weichenthal et al. (2016) Ontario, Canada (15 cities) 2004–2011 All ages	Nearest monitor to population-weighted zip code centroid or single available monitor	J00–J99	7.1	Max: 56.8	Correlation (*r*): <0.42 NO_2 Copollutant models with: O_3, NO_2, oxidative potential
Hospital admissions and ED visits, separately					
Slaughter et al. (2005) Spokane, WA 1995–1999 All ages	One monitor	464–466, 490; 480–487; 491–494, 496	NR	90: 20.2	Correlation (*r*): 0.62 CO; 0.31 $PM_{10-2.5}$ Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001–2007 All ages	One monitor	460–465, 466.0, 466.1, 466.11, 466.19, 477, 480–486, 491–493, 496, 786.07	14.4	75th: 22.7 Max: 48.7	Correlation (*r*): 0.25 O_3 Copollutant models with: NA
†Rodopoulou et al. (2014) Doña Ana County, NM 2007–2010 ≥18 yr	Three monitors	460–465, 466, 480–486, 490–493, 496	10.9	75th: 13 Max: 55.6	Correlation (*r*): −0.05 O_3 Copollutant models with: NA

CMAQ = Community Multi-Scale Air Quality model; MED-PARTICLES = particles size and composition in Mediterranean countries: Geographical variability and short-term health effects; UFIREG = Ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy.

[a]Median concentration.

[b]CMAQ predictions bias corrected using monitored data.

[c]$PM_{2.5}$ concentrations are for lag 0–1 day.

[d]Only four of the five cities had $PM_{2.5}$ data.

†Studies published since the 2009 PM ISA.

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5.1.6.1 Hospital Admissions

Recent studies that examined the association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions build upon the evidence detailed in the 2009 PM ISA (U.S. EPA, 2009), particularly the examination of effects in older adults (i.e., ≥65 years of age). Multicity studies conducted in Europe (Lanzinger et al., 2016b; Samoli et al., 2016a; Basagaña et al., 2015) and Finland (Kollanus et al., 2016) that examined people of all ages provide evidence of consistent, positive associations that are similar in magnitude to those reported in the U.S. and Canadian studies evaluated in the 2009 ISA (Figure 5-8). The results from analyses of people of all ages are further supported by Stafoggia et al. (2013) in a study of eight southern European cities that reported a 1.36% (95% CI: 0.23, 2.49) increase in hospital admissions at lag 0–5 days, as well as a meta-analysis conducted by Adar et al. (2014) (RR = 1.01 [95% CI: 1.00, 1.02]). However, single-city studies conducted in St. Louis, MO (Winquist et al., 2012) and Doña Ana County, NM (Rodopoulou et al., 2014), do not provide consistent evidence of an association with respiratory-related diseases in all ages analyses.

Studies that examined the relationship between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions in children are limited in number, but generally report associations that are similar in magnitude to previous studies. An exception is the study conducted by Yap et al. (2013) in 12 California counties focusing on children 1 to 9 years of age where there was no evidence of an association in the central valley counties (RR = 1.0), but a positive association in the south coast counties was seen (RR = 1.07) at lag 0–2 days. Winquist et al. (2012) also reported a positive association for children in St. Louis, MO, but confidence intervals were wide (RR = 1.02 [95% CI: 0.96, 1.07]; lag 0–4 DL).

Most of the recent studies focusing on respiratory-related hospital admissions focus on older adults, and consisted mostly of multicity or entire state analysis conducted in the U.S. These recent multicity studies report evidence of consistent, positive associations, except the study by Kollanus et al. (2016) in four cities in Finland (Figure 5-8). The associations reported across the U.S. for multicity studies are based on a variety of exposure assignment approaches (see Table 5-11), all of which resulted in associations that are similar in magnitude. In a multicounty time-series analysis conducted in 213 U.S. counties from 1999–2010, Bell et al. (2015) observed a 0.25% (95% CI: 0.01, 0.48) increase in all respiratory hospital admissions at lag 0 among adults aged 65 years and older. In a similar study of 110 U.S. counties, Powell et al. (2015) reported results consistent with Bell et al. (2015) (0.67% [95% CI: 0.14, 1.2]; lag 0). Bell et al. (2014), also examined single-day lags, but in four counties in Connecticut and Massachusetts, and reported evidence of positive associations across lags of 0 to 2 days, albeit with wide confidence intervals (quantitative results not presented). Additional evidence of a positive association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions is provided by Zanobetti et al. (2009) in an analysis of 26 U.S. counties where a 2.1% (95% CI: 1.2, 3.0) increase in hospital admissions was reported at lag 0–1. The results from the epidemiologic studies that rely on

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community-based monitors are supported by a series of studies that used a combination of monitored, modeled, and in some cases satellite-based $PM_{2.5}$ concentrations. In a multicity study conducted in the New England region of the U.S., Kloog et al. (2012) assessed exposure using a novel prediction model that combined land use regression with surface $PM_{2.5}$ measurements from satellite aerosol optical depth. The authors observed a 0.70% (95% CI: 0.35, 1.05) increase in respiratory-related hospital admissions for a 0−1-day lag. In a sensitivity analysis using monitor-based exposure assessment in the time-series analysis, Kloog et al. (2012) reported similar results (1.51% [95% CI: 0.42, 1.65]), but with slightly larger confidence intervals. Kloog et al. (2014) built upon the exposure assessment used in Kloog et al. (2012) in a study conducted in the Mid-Atlantic region of the U.S. The authors reported a 2.2% (95% CI: 1.9, 2.6) increase in respiratory-related hospital admissions at lag 0−1 day. The results of Kloog et al. (2012) and Kloog et al. (2014) are supported by Bravo et al. (2017) in a study of 708 U.S. counties. The authors examined associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions using three different exposure assessment approaches: (1) a population-weighted average of $PM_{2.5}$ concentration computed in 708 U.S. counties using a downscaled CMAQ model (Section 3.3.2.4.3); (2) a population-weighted average of downscaled CMAQ-simulated $PM_{2.5}$ concentrations computed in the 418 U.S. counties that have monitoring data; and (3) $PM_{2.5}$ concentrations from the 418 U.S. counties with fixed-site monitors. Across these three exposure assignment approaches, the authors reported a relatively consistent percent increase in hospital admissions at lag 0: (1) 1.16% (95% CI: 0.88, 1.45); (2) 1.11 (95% CI: 0.66, 1.56); and (3) 1.10% (95% CI: 0.70, 1.50).

5.1.6.2 Emergency Department (ED) Visits

Compared to studies that examined hospital admissions for respiratory-related diseases, fewer studies focused on ED visits, with the majority examining associations with short-term $PM_{2.5}$ exposure in analyses of all ages. Additionally, a recent study examined associations with PM size fractions smaller than 2.5 μm, but larger than UFP (i.e., number concentration [NC] and surface area concentration [SC] for particles 100−300 nm), which also supports the positive associations with respiratory-related ED visits observed for $PM_{2.5}$ (Leitte et al., 2011). Whereas, many hospital admission studies were conducted over multiple cities or entire states, the ED visit studies are mostly limited to individual cities.

Malig et al. (2013), in a study of 35 California counties, reported a 1.6% (95% CI: 0.98, 2.27) increase in respiratory-related ED visits at lag 1. Building on the previous studies conducted in Atlanta, GA (Tolbert et al., 2007; Peel et al., 2005), Darrow et al. (2011) also examined associations between short-term $PM_{2.5}$ exposures and respiratory-related ED visits, reporting an association similar in magnitude to the previous studies (0.4% [95% CI: −0.2, 1.0]; lag 1). Additionally, Krall et al. (2016) in a study of four U.S. cities (i.e., Atlanta, Birmingham, St. Louis, and Dallas) reported positive associations for each city at lag 0 (quantitative results not presented). Single-city studies conducted in Canada and the U.S. report associations that overall are consistently positive and generally similar in magnitude to Malig et al. (2013) (Figure 5-8). Across the studies evaluated, only Winquist et al. (2012) examined associations

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with respiratory related ED visits in children (i.e., 2–18 years of age) in St. Louis, MO, and reported an association larger in magnitude (RR = 1.03 [95% CI: 1.02, 1.05]; lag 0–4 DL) compared to that observed when examining people of all ages (RR = 1.01 [95% CI: 1.0, 1.02]; lag 0–4 DL). Of the few studies that examined effects in older adults (Rodopoulou et al., 2014; Winquist et al., 2012), there was no evidence of an association between short-term $PM_{2.5}$ exposure and respiratory-related ED visits.

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

Recent epidemiologic studies that examined short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases generally support the results from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009). Across studies, there is evidence of generally consistent, positive associations among children, with a growing body of evidence, primarily from multicity U.S.-based studies of older adults (Figure 5-8). Additional studies focusing on people of all ages, also provide evidence supporting an association with $PM_{2.5}$, with most of the studies conducted in individual cities.

The main results of studies detailed within this section are supported by analyses that examined specific policy-relevant issues as detailed in Section 5.1.10. Compared to the 2009 PM ISA (U.S. EPA, 2009), recent studies provide a more extensive examination of potential copollutant confounding, but overall the assessment is limited to only a few studies. These studies demonstrate that associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions and ED visits are relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$ (Section 5.1.10.1). In addition to copollutant confounding, several studies examined the influence of alternative model specifications on the $PM_{2.5}$ association with respiratory-related hospital admissions and ED visits and found that associations remained relatively unchanged when accounting for temporal trends and weather covariates using different specifications (Section 0). Analyses that focused on whether there are differences by season provide some evidence that $PM_{2.5}$ associations are larger in magnitude during the warmer months, but some studies reported larger associations during the colder months (Section 5.1.10.4.1). The difference in associations by season could reflect geographic variability that continues to be observed in multicity studies. However, to date it remains unclear what factors contribute to the observed geographic variability in $PM_{2.5}$ associations with respiratory-related diseases (Bell et al., 2009a).

While studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) tended to support $PM_{2.5}$ associations within the first few days after exposure (i.e., lag 0 to 3 days), recent studies support that evidence and provide initial evidence indicating that $PM_{2.5}$ effects may be more prolonged, ranging from 0–5 days (Section 5.1.10.3). To date, there are very few studies that have examined subdaily averaging times of $PM_{2.5}$ concentrations (Section 5.1.10.5). In terms of respiratory-related hospital admissions and ED visits, available evidence indicates that subdaily averaging times do not result in stronger associations with respiratory-related hospital admissions and ED visits compared to a 24-hour averaging time (Section 5.1.10.5). Lastly, recent evaluations of the C-R relationship between short-term $PM_{2.5}$ exposure

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and respiratory-related hospital admissions and ED visits provides evidence of a linear relationship, but this assessment is based on rather limited analyses that did not empirically evaluate alternatives to linearity (Section 5.1.10.6).

5.1.7 Respiratory Effects in Healthy Populations

The 2009 PM ISA (U.S. EPA, 2009) did not have a delineated discussion of respiratory effects in healthy populations, but relevant epidemiologic studies provided inconsistent evidence for $PM_{2.5}$-related decreases in lung function and increases in pulmonary inflammation, and no evidence for increases in respiratory symptoms in individuals with no underlying respiratory disease. Controlled human exposure studies evaluated in the 2009 PM ISA provided no evidence for changes in lung function and limited evidence for pulmonary inflammation, while animal toxicological studies more consistently provided evidence for $PM_{2.5}$ exposure-related effects.

To characterize the current state of the evidence, this section focuses on results specific to healthy populations. Some studies employed scripted exposures in an attempt to further inform the relationship between short-term $PM_{2.5}$ exposure and respiratory effects. Scripted studies measuring personal ambient $PM_{2.5}$ exposures are designed to minimize uncertainty in the $PM_{2.5}$ exposure metric by always measuring $PM_{2.5}$ at the site of exposure, ensuring exposure to sources of $PM_{2.5}$ and measuring outcomes at well-defined lags after exposure.

There are recent epidemiologic studies in populations with 13–28% prevalence of asthma, COPD, or atopy, some of which indicate $PM_{2.5}$-associated increases in respiratory effects. However, these studies are not evaluated in this section, as it is not known whether the results apply to the healthy portion of the population or are instead driven solely by an association in individuals with pre-existing respiratory conditions, these studies can be found in HERO (https://hero.epa.gov/hero/particulate-matter). Further, these studies do not provide additional insight on issues such as copollutant confounding, effects at low $PM_{2.5}$ exposure concentrations, or critical exposure periods.

5.1.7.1 Epidemiologic Studies

The 2009 PM ISA (U.S. EPA, 2009) evaluated a limited number of epidemiologic studies that examined respiratory effects in healthy populations. A study of adult school crossing guards in New Jersey observed decreases in lung function associated with 1-hour max $PM_{2.5}$ concentrations (Fan et al., 2008). In contrast, Holguin et al. (2007) did not observe an association between $PM_{2.5}$ and lung function or lung inflammation in a study of school children in Ciudad Juarez, Mexico. Several recent studies are available for evaluation, with most focusing on lung function changes and/or lung inflammation in healthy populations. Study-specific details, including cohort descriptions and air quality characteristics are highlighted in Table 5-2.

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Respiratory Symptoms

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, only a single recent study is available for review. In a study of school children in Santiago, Chile, 7-day average 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, NO2, SO2, or O3. However, copollutant correlations were not reported, limiting the interpretability of the copollutant models.

Lung Function Changes

The majority of recent studies on lung function changes in relation to $PM_{2.5}$ 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 $PM_{2.5}$ exposure and FEV_1 (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). In a study of adults commuting 2 hours through Atlanta traffic, Mirabelli et al. (2015) reported $PM_{2.5}$-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. Similar to the studies of scripted commutes through traffic, many of these quasi-experimental studies observed null associations between lung function and $PM_{2.5}$ (Kubesch et al., 2015; Mirowsky et al., 2015; Strak et al., 2012). In contrast, Dales et al. (2013) observed decreases in FEV_1 and $FEF_{25-75\%}$ associated with 8-hour average $PM_{2.5}$ concentrations in Sault Ste. Marie, Canada. Associations were observed despite low mean concentrations of 8-hour average $PM_{2.5}$. Additionally, in Barcelona, Spain, Matt et al. (2016) reported that healthy adults experienced decreased FEV_1 associated with 2-hour average $PM_{2.5}$ immediately after exposure. Notably, $PM_{2.5}$ 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 PEF associated with decreased 24-hour average $PM_{2.5}$.

Studies of lung function in healthy children were limited in number. School-children in an agricultural area of Brazil experienced decreases in PEF in association with $PM_{2.5}$ concentrations measured outside of school, 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 average $PM_{2.5}$ was associated with a small, imprecise decrease in PEFR in schoolchildren at lags 0 and 3, but no other lags

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up to 4 days. The location of the monitors relative to the school was not specified, so it is not clear to what degree exposure measurement error might have impacted the results (Section 3.4.2.2).

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. As such, 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 $PM_{2.5}$ exposure and subclinical respiratory effects (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). Mirabelli et al. (2015) observed associations between eNO and $PM_{2.5}$ concentrations during a 2-hour scripted commute through Atlanta traffic. The authors reported $PM_{2.5}$-related increases in eNO levels 0, 1, 2, and 3 hours post-commute. A similar $PM_{2.5}$-related increase in eNO was reported in a group of adults cycling alongside high- and low-traffic roads in Ottawa, Canada (Weichenthal et al., 2011). The observed associations with personal $PM_{2.5}$ concentrations were strongest 2 hours after cycling. Conversely, $PM_{2.5}$ was associated with a decrease in eNO in a study of adults commuting 2 hours by either car, bus, or bike in the Netherlands (Zuurbier et al., 2011b). However, the authors also noted that personal ambient $PM_{2.5}$ was associated with a decrease in Clara cell secretory protein (CC16), a pulmonary biomarker that is often decreased in subjects with lung epithelial damage.

Studies utilizing quasi-experimental designs were less consistent, despite similarly high mean concentrations of $PM_{2.5}$. In New York, $PM_{2.5}$ 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 $PM_{2.5}$ in studies where 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 $PM_{2.5}$ 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 average $PM_{2.5}$ at two schools in Umea, Sweden. $PM_{2.5}$ was measured at monitors located within 1.5 km of the two schools. Although copollutant models were not examined, $PM_{2.5}$ was weakly correlated with NO_X and only moderately correlated with O_3.

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Table 5-12 Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in μg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
Exposure interventions				
†Hao et al. (2017) Shanghai and Shandong, China 2012	N = 42, ages 50−61 yr 9-day relocation from higher to lower air pollution city Outcomes every other day	Total personal 24-h avg Mean (SD) Shanghai: 95.1 Shandong: 187	Per 10 μg/m³ decrease FEV_1: 9.0 (3.6, 14.4) mL PEF: 33.2 (4.8, 61.5) mL/sec	Correlation (*r*): NA Copollutant models with: NO_2
Scripted outdoor exposures				
†Mirabelli et al. (2015) Atlanta, GA 2009−2011	N = 21, ages NR Morning commute on highway Two times each, 75 observations Outcomes 0, 1, 2, 3 h after	Personal in-vehicle 2-h avg (7−9 a.m.) Mean: 28.8	Per 20.9 μg/m³ eNO, 0 h: 2.4% (−3.3, 8.5) FEV_1 percent predicted, 0 h: −0.42% (−2.2, 1.3)	Correlation (*r*): NA Copollutant models with: NA
†Mirowsky et al. (2015) New York, Sterling Forest NY; Nutley, NJ Jun−Sep, 2011−2012	N = 26, ages 18−33 yr Walking on highway bridge, no-truck highway, forest One time each, 70 observations Outcomes 0, 24 h after	Personal ambient 2-h avg Mean, max Bridge: 31, 45 No-truck highway: 21, 50 Forest: 13, 24	Increment NR eNO, 0 h: −0.38% (−1.6, 0.31) eNO, 24 h: 0.87% (−0.09, 1.8)	Correlation (*r*): 0.66 PM_{10}, 0.29 EC, 0.38 BC, 0.4 OC, 0.39 O_3 Copollutant models with: NA
†Dales et al. (2013) Sault Ste Marie, Canada May−Aug 2010	N = 61, mean (SD) age 24 (6) yr Near steel plant, college campus five times each Outcomes 0 h after	Personal ambient 8-h avg Mean (SD) Steel plant: 12.8 College campus: 11.6	Per 9 μg/m³ FEV_1: −0.42% (−0.83, 0) $FEF_{25-75\%}$: −0.92% (−1.7, −0.12)	Correlation (*r*): NA Copollutant models with: NA

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Table 5-12 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in μg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
†Weichenthal et al. (2011) Ottawa, Canada May–Sep 2010	N = 42, ages 19–58 yr Cycling on high- and low-traffic road One time each, 118 observations Outcomes 0, 1, 2, 3 h after	Personal ambient 1-h avg Mean, max High-traffic road: 12.2, 34 Low-traffic road: 8.1, 26	Per 8.7 μg/m³ 1-h post-exposure FEV_1: −16 (−90, 58) ml 2-h post-exposure eNO: 1.1 (0.08, 2.2) ppb	Correlation (*r*): (high traffic, low traffic) 0.06, −0.22 UFP; 0.32, 0.24 BC; 0.75, 0.59 CO; −0.30, −0.04 SO_2; 0.31, 0.45 NO_2; 0.58, 0.36 O_3 Copollutant models with: NA
†Strak et al. (2012); †Steenhof et al. (2013) Utrecht, the Netherlands Mar–Oct 2009	N = 31, ages 19–26 yr Free-flowing traffic road, stop-and-go traffic road, urban site, farm, underground train station One time each, with exercise Outcomes 0, 2, 22 h after	Personal ambient 5-h avg Geometric mean, max 39, 167	Per 11.5 μg/m³ FVC: 0.08%, $p > 0.10$ eNO: 0.17%, $p > 0.10$ For outdoor sites only Nasal lavage IL-6: 16%, $p < 0.05$	Correlation (*r*): −0.65 O_3, 0.21 NO_2, 0.31 NO_X Copollutant models with: O_3, SO_2, NO_X
†Zuurbier et al. (2011b); †Zuurbier et al. (2011a) Arnhem, the Netherlands Jun 2007–Jun 2008	N = 34, ages 23–55 yr Commute in car, bus, bike One time each, 352 observations Outcomes 0, 6 h after	Personal ambient 2-h avg Mean, max Diesel bus: 39.1, 324 Diesel car: 58.1, 358 Gas car: 68.1, 403 Bike, high traffic: 49.8, 219 Bike, low traffic: 65.2, 241	Per 68.1 μg/m³, 6 h post-exposure FEV_1: 0.02% (−0.41, 0.45) MMEF: 0.60% (−0.73, 1.9) eNO: −2.5% (−5.9, 1.1) CC16: −1.3% (−6.8, 0.3)	Correlation (*r*): NA Copollutant models with: NO_2
†Matt et al. (2016) Nov 2013–Mar 2014	N = 30, ages 19–57 yr Bridge over high-traffic road, seaside park One time each, with exercise and rest Outcomes 0, 7 h after	Personal ambient 2-h avg Mean, 95th High-traffic: 82, 92 Seaside Park: 39, 48	Per 1 μg/m³, 0-h post-exposure FEV_1: −0.55 (−1.4, 0.31) mL PEF: −0.06 (−0.32, 0.21) L/min Per 1 μg/m³, 7-h post-exposure FEV_1: 0.43 (−0.52, 1.4) mL PEF: 0.15 (−0.05, 0.35) L/min	Correlation (*r*): −0.04 high-traffic, 0.7 seaside park NO_X Copollutant models with: NA

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Table 5-12 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in µg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
†Kubesch et al. (2015) Barcelona, Spain Feb–Nov 2011	N = 28, ages 18–60 yr Bridge over high-traffic road, marketplace One time each, with exercise and rest Outcomes 0, 3, 6 h after	Personal ambient 2-h avg Mean, 95th High-traffic: 80.8, 88.6 Marketplace: 30.0, 37.7	Per IQR (NR) FEV_1: 0.00 (−0.02, 0.02) mL $FEF_{25-75\%}$: −0.05 (−0.11, 0) mL eNO: 0.40 (−0.53, 1.3) ppb	Correlation (*r*): 0.91 NO_X Copollutant models with: NA
Fan et al. (2008) Patterson, NJ Feb–May 2005	N = 11, mean (SD) age 61 (14) yr Crossing guards at work Three work shifts, 27 observations Outcomes 0 h after	Personal ambient Mean (SD), max difference from 24-h avg 1-h avg: 35.2, 87 1-h max: 71.3, 278	Increment NR FEV_1, 1-h avg: 20 (−58, 98) mL FEV_1, 1-h max: −130 (−287, 27) mL	Correlation (*r*): NA Copollutant models with: NA
General community exposures				
Holguin et al. (2007) Ciudad Juarez, Mexico 2002–2003	N = 99, ages 6–12 yr Biweekly measures for 4 mo	Outdoor school Children live 0.2–0.7 km 24-h avg Mean: 17.5	No quantitative results	Correlation (*r*): 0.30 NO_2, 0.49 EC Copollutant models with: NA
†Carlsen et al. (2016) Umea, Vasterbotten, Sweden Apr–Jun 2011	N = 95, ages 11–12 yr Two measures/week for 2 mo 973 observations	Monitors within 1.5 km of schools 24-h avg Mean: 5.6 Max: 16.7	Per 10 µg/m³ eNO (ppb) Lag 0: 1.9 (−5.8, 10) Lag 0–1: 5.4 (−3.1, 13)	Correlation (*r*): 0.01 $PM_{10-2.5}$, 0.36 NO_2, 0.42 O_3 Copollutant models with: NA
†Jacobson et al. (2012) Alta Floresta, Brazil Aug–Dec 2006	N = 224, ages 8–15 yr Daily measures for 4 mo	School outdoor 24-h avg, 6-h avg (12–6 a.m.), 12-h avg (12 a.m.–noon) Mean, 90th for 24-h avg 24.4, 44.1	Per 10 µg/m³ PEF (L/min) 24-h avg: −0.38 (−0.63, −0.13) 6-h avg: −0.36 (−0.66, −0.06) 12-h avg: −0.31 (−0.65, 0.02)	Correlation (*r*): NA Copollutant models with: NA

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Table 5-12 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in µg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
†Prieto-Parra et al. (2017) Santiago, Chile May–Sep 2010–2011	N = 83, ages 6–14 yr Daily measures for 3 mo Mean observations: 100 yr 1, 80 yr 2	One monitor Most children live within 3 km Mean: 30	OR per 10 µg/m³, lag 0–6 Cough: 1.22 (CI NR) Three symptom index: 1.28	Correlation (*r*): NA Copollutant models with: PM_{10}, NO_2, O_3, SO_2, K, Mo, Pb, S, Se, and V
†Hong et al. (2010) Seoul, South Korea May–Jun 2007	N = 92, mean (SD) age 9 (0.5) yr Daily measures for 1 mo	Monitors in city, number NR 24-h avg Mean: 36.2	No quantitative results	Correlation (*r*): NA Copollutant models with: NA

Avg = average, CC16 = club cell protein, CI = confidence interval, CO = carbon monoxide, eNO = exhaled nitric oxide, $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of forced vital capacity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NO_X = sum of NO_2 and nitric oxide, NR = not reported, O_3 = ozone, PEF = peak expiratory flow, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

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5.1.7.2 Controlled Human Exposure Studies

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided little evidence that exposure to $PM_{2.5}$ results in decrements in lung function in healthy populations. Although Petrovic et al. (2000) observed that a 2-hour exposure to $PM_{2.5}$ (92 μg/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 $PM_{2.5}$ on lung function was demonstrated in several studies investigating the exposure of healthy volunteers to $PM_{2.5}$ 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 $PM_{2.5}$ CAPs collected from Chapel Hill, NC. The authors reported no changes in multiple markers of lung function (including FVC, FEV_1, and FEF_{25-75}) or in the marker for diffusion capacity DLCO at 1 and 18 hours post exposure (study details in Table 5-13).

The 2009 PM ISA (U.S. EPA, 2009) provided limited evidence that exposure to $PM_{2.5}$ resulted in subclinical or inflammatory effects in healthy populations. Ghio et al. (2000) reported an increase in airway and alveolar neutrophils following exposure to $PM_{2.5}$ 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 (Y-CT et al., 2003). Recently, the healthy population respiratory response to $PM_{2.5}$ has been further examined by Behbod et al. (2013) and Huang et al. (2012). These studies involved exposure to $PM_{2.5}$ CAPs at either approximately 250 μg/m^3 (Behbod et al., 2013) or 90 μg/m^3 for approximately 2 hours (Huang et al., 2012) (additional study details are in Table 5-13). Multiple markers of airway inflammation were measured. Behbod et al. (2013) reported that relative to filtered air, no significant airway (sputum) responses were observed in subjects exposed to Toronto, Ontario $PM_{2.5}$ CAPs. Exposures to relatively lower levels of $PM_{2.5}$ CAPs (approximately 90 μg/m^3) (Huang et al., 2012) corroborated the effects seen in the higher exposure study (Behbod et al., 2013) in that exposure to Chapel Hill NC $PM_{2.5}$ CAPs had no effect on IL-6, IL-8, or α1-antitrypsin in the bronchoalveolar lavage of exposed healthy subjects, although changes in blood parameters were observed (see Section 6.1.11).

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Table 5-13 Study-specific details from controlled human exposure studies of short-term $PM_{2.5}$ exposure and respiratory effects in healthy populations.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Behbod et al. (2013)	Double-blind, randomized cross-over block design	Healthy nonsmokers; n = 35; 11 M, 12 F (18−60 yr)	234.7 μg/m³ $PM_{2.5}$ CAPs, Toronto, ON. (IQR: 52.4 μg/m³) for 130 min (120-min exposure + 10 min to complete tests) at rest. Comparison groups were either (1) filtered air or (2) medical air; a minimum 2-week washout period was used between exposures.	Sputum (pre- and 24-hour post-exposure): Total cell and neutrophil counts
Huang et al. (2012)	Not specifically stated	Healthy nonsmokers; n = 23; 15 M, 8 F (20−36 yr)	89.5 ± 10.7 μg/m³ $PM_{2.5}$ CAPs or 73.4 ± 9.9 μg/m³ $PM_{2.5}$ CAPs + 0.5 ppm NO_2 for 2 h, Chapel Hill, NC. During exposure, subjects completed four cycles of 15 min each rest or exercise. Comparison group was clean air.	Lung function BAL (18-h post-exposure): IL-6, IL-8, α1-antitrypsin, LDH, differential leucocyte counts

BAL = bronchoalveolar lavage; CAPs = concentrated ambient particles; IL-6 = interleukin-6; IL-8 = interleukin-8; IQR = interquartile range; LDH = lactate dehydrogenase; NO_2 = nitrogen dioxide.

5.1.7.3 Animal Toxicological Studies

Lung Function

The 2004 PM AQCD (U.S. EPA, 2004)and the 2009 PM ISA (U.S. EPA, 2009) reported several animal toxicological studies that measured pulmonary function following single or multiday exposure to $PM_{2.5}$ CAPs. Decreased breathing frequency (or respiratory rate) was observed in dogs exposed to $PM_{2.5}$ CAPs in Boston 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 $PM_{2.5}$ CAPs in Boston (Clarke et al., 1999) but not in New York City (Gordon et al., 2000). Increases in inspiratory and expiratory times were not seen in Wistar Kyoto rats exposed to $PM_{2.5}$ CAPs in Research Triangle Park, NC (Kodavanti et al., 2005). Results of these studies, showing changes in

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breathing frequency and depth of breathing, indicate that short-term $PM_{2.5}$ exposure stimulated lung irritant responses through the activation of sensory nerves and local reflexes.

Recently, Diaz et al. (2013) evaluated the effects of exposure to $PM_{2.5}$ 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 ($p < 0.05$). This breathing pattern, as well as the observed decrease in expiratory flow at 50% (EF_{50}) ($p = 0.01$), provide evidence of an irritative respiratory response. A 2-day exposure to a secondary organic aerosol formed from photochemical oxidation of primary tunnel gases (SOA) resulted in increases in pauses, including Penh ($p \leq 0.05$). A 4-day exposure to SOA decreased several parameters including frequency, tidal volume, minute volume, EF_{50}, and Vi, an indicator of respiratory drive ($p < 0.05$). A 4-day exposure to photochemically aged primary particles plus SOA (P + SOA) produced the largest change in breathing parameters including decreased volumes, flow, respiratory drive, and respiratory effort ($p < 0.05$). This pattern is reflective of rapid shallow breathing and suggests an irritative respiratory response with an additional effect at the thoracic level. Additional study details for this study, and other recent toxicological studies, are found in Table 5-14.

The effect of social stress on pulmonary function was examined in older Sprague Dawley rats exposed to $PM_{2.5}$ CAPs in Boston (Clougherty et al., 2010). In stressed animals, $PM_{2.5}$ 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, $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ CAPs in Sao Paulo, Brazil. Tracheal rings from male mice that were exposed to $PM_{2.5}$ CAPs were hyporesponsive to methacholine, a bronchoconstrictor, compared to tracheal rings from male mice exposed to ambient air ($p < 0.05$). Tracheal rings from diestrus female mice that were exposed to $PM_{2.5}$ 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 ($p < 0.05$).

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Table 5-14 Study-specific details from animal toxicologic studies of short-term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Amatullah et al. (2012) Species: Mouse Sex: Female Strain: BALB/c Age/weight: 6−8 weeks, 18 g	$PM_{2.5}$ CAPs Toronto Particle size: $PM_{0.15-2.5}$ Control: HEPA filtered air	Route: Nose-only inhalation Dose/concentration: $PM_{0.5-2.5}$ 254 µg/m³ Duration: 4 h Time to analysis: At end of exposure Modifier: Baseline ECG	Pulmonary function BALF Cells
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	$PM_{2.5}$ CAPs Mexico City Particle size: $PM_{2.5}$ Control: Filtered air	Route: Inhalation Dose/concentration: $PM_{2.5}$ 178 µg/m³ Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene expression and protein levels—lung tissue IL-6, components of the RAS and kallikrein-kinin endocrine system-heme oxygenase-1
Budinger et al. (2011) Species: Mouse Sex: Male Strain: C57BL/6 wild type and IL-6 knockouts Age/weight: 8−12 weeks	$PM_{2.5}$ CAPs Chicago, IL Particle size: $PM_{2.5}$ Control: Filtered ambient air	Route: Whole-body inhalation Dose/concentration: 88.5 ± 13.4 µg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue-protein level and gene expression of inflammatory mediators Plasma—biomarkers of coagulation
Chiarella et al. (2014) Species: Mouse Sex: Male Strain: C57BL/6 wild type and Adrβ knockouts Age/weight: 8−12 weeks	$PM_{2.5}$ CAPs Chicago, IL Particle size: $PM_{2.5}$ Control: Filtered ambient air	Route: Whole-body inhalation Dose/concentration: 109.1 ± 6.1 µg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue—IL-6, norepinephrine Brown adipose tissue—norepinephrine
Clougherty et al. (2010) Species: Rat Sex: Male Age/weight: 12 weeks	$PM_{2.5}$ CAPs Boston Particle size: PM ≤ 2.5 µm Control: Filtered air	Route: Whole-body inhalation Dose/concentration: 374 µg/m³ With large variance Duration: 10 days, 5 h/day Time to analysis: Respiratory data was collected during exposure at 10 min. intervals using Buxco Coexposure: Stress	Pulmonary function • Peak inspiratory flow • Minute volume • Breathing frequency • Inspiratory time • Expiratory time • Expiratory flows • Tidal volume

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Table 5-14 (Continued): Study specific details from animal toxicologic studies of short term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Diaz et al. (2013) Species: Rat Sex: Male Strain: Sprague-Dawley Age/weight: 250−300 g	Roadway tunnel particles (gases removed by denuder) Primary particles (P) Primary particles and secondary aerosol (P-SOA) Secondary organic aerosol (SOA) Particle size: PM < 2.5 µm Control-Filtered air (oxidizable gases, VOC and particles removed)	Route: Whole-body Inhalation Dose/concentration: P-47.5 µg/m^3 P + SOA-50 µg/m^3 SOA- 48.7 µg/m^3 Duration: 2−4 days, 5 h/day Time to analysis: 24 h or 48 h Coexposure: NO: P- 71.2 ppb P + SOA- 2.1 ppb SOA- 27.1 ppb NO_X: P- 92.6 ppb P + SOA- 37.5 ppb SOA- 56.9 ppb	BALF Cells Lung function • Tidal volume • Minute Volume • Expiratory time • Inspiratory time • Expiratory flow at 50% (flow) • Pause • Enhanced pause • End expiratory pause • End inspiratory pause • Peak of inspiratory flow • Inspiratory time
Kim et al. (2016b) Species: Mouse Strain: Balb/c Sex: Male Age/weight: 6−10 weeks	DEP (NIST SRM) Particle size: Not reported	Route: Inhalation Dose/concentration: 2 mg/m^3 Duration: 1 h/day for 5 days Time to analysis: 9 days	Middle ear: Gene expression microarray and pathway analysis
Mauderly et al. (2011) Species: Mouse/Rat Sex: Male and female Strain: Mouse Age/weight: C57BL/6 (10−13 weeks) A/J (5−8 weeks) BALB/c (3 weeks gestation, 4 weeks after birth) Strain: Rat F344 Age/weight: (7−9 weeks)	Simulated coal emissions low, medium, high doses and high dose filtered groups Particle size: Not reported in this publication. Likely PM < 2.5 Control: Clean air	Route: Whole-body Inhalation Dose/concentration: 1,000, 300, 100 µg/m^3 Duration: 6 mo or 1 week, 7 days/week, 6 h/day	BALF Cells/Cytokines (F344 rats) • MIP-2 • Leukocytes
Plummer et al. (2012) Species: Mouse Sex: Male Strain: C57BL/6 Age/weight: 12−14 weeks, 25−30 g	$PM_{2.5}$ CAPs from Fresno, (F, urban) or Westside (W, rural) locations in California, in two seasons (summer, winter) Particle size: $PM_{2.5}$ Control: Ambient air	Route: Whole-body inhalation Dose/concentration: F/Summer 284 µg/m^3, F/Winter 156 µg/m^3, W/Summer 126 µg/m^3, W/Winter 86 µg/m^3 Duration: 6 h/day for 10 days Time to analysis: 48 hr Note: Composition of $PM_{2.5}$ CAPs defined for organic/elemental carbon, nitriate, sulfate, ammonia, chloride	BALF cells Lung tissue Cytokine/Chemokine Histopathology—lung

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Table 5-14 (Continued): Study specific details from animal toxicologic studies of short term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Rohr et al. (2010) Species: Rat Strain: Spontaneously hypertensive (SH) Wistar Kyoto (WKY) Sex: Male Age/weight: 11−12 weeks	$PM_{2.5}$ CAPs residential urban Detroit, MI Particle size: $PM_{2.5}$ Control: HEPA-filtered clean air	Route: Whole-body inhalation Dose/concentration: 507 μg/m^3 Duration of exposure: 8 h, 13 consecutive days Time to analysis: 24 h	BALF cells Lung Injury • BALF protein content
Tyler et al. (2016) Species: Mouse Strain: C67BL/6 Age/weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 μm ± 1.3−1.6 μm Control: Filtered air	Route: Whole-body inhalation Dose/concentration: 315.3 ± 50.7 μg/m^3 Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages
Xu et al. (2013) Species: Mouse Strain: C57BL/6 Sex: Male Age/weight: 3 weeks	$PM_{2.5}$ CAPs Columbus, OH Particle size: ≤$PM_{2.5}$ Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 143.8 μg/m^3 Duration: 6 h/day, 5 days/week, 5, 14, 21 days Time to analysis: Immediately post-exposure	Immunohistochemistry—lung BALF cells—flow cytometry
Yoshizaki et al. (2016) Species: Mouse Sex: Male and female Strain: BALB/c Age/Weight: 21 days	$PM_{2.5}$ CAPs Sao Paulo, Brazil Particle size: $PM_{0.1-2.5}$ μm Control: Ambient air	Route: Whole-body Inhalation Dose/Concentration: Cumulative dose × time $PM_{2.5}$: 594 ± 77 μg/m^3 Duration: Multiday Coexposure: Other ambient pollutants and also PM_{10}	Gene expression and protein levels—nasal epithelium AhR, estrogen receptor, cytochrome P450 enzymes Immunohistochemistry—nasal epithelium mucus profile and mucus content
Yoshizaki et al. (2017) Species: Mouse Sex: Male and female (diestrus, proestrus, and estrus) Strain: BALB/c Age/Weight: 21 days	$PM_{2.5}$ CAPs Sao Paulo, Brazil Particle size: Control: Ambient air	Route: Whole-body Inhalation Dose/Concentration: Cumulative dose × time $PM_{2.5}$: 600 μg/m^3 Duration: Multiday Coexposure: Other ambient pollutants, PM_{10}	Ex vivo tracheal rings—reactivity to methacholine BALF cells and cytokines Lung Immunohistochemistry

Adrβ = beta adrenergic receptor; AhR = aryl hydrocarbon receptor; BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; DEP = diesel exhaust particles; ECG = electrocardiogram; HEPA = high-efficiency particulate absorber; IL-6 = interleukin-6; MIP-2 = macrophage inflammatory protein-2; NIST SRM = National Institute of Standards and Technology Standard Reference Material; NO = nitric oxide; NO_X = oxides of nitrogen; RAS = renin-angiotensin system; VOC = volatile organic carbon.

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Pulmonary Injury

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies examined pulmonary injury and altered lung barrier/secretory function in response to single or multiday exposure to $PM_{2.5}$ CAPs. While increased BALF protein and lung water content were observed in rats exposed to $PM_{2.5}$ CAPs in Boston (Gurgueira et al., 2002; Clarke et al., 1999), injury indices were not observed in rats exposed to $PM_{2.5}$ CAPs in New York City and Research Triangle Park, NC (Gordon et al., 2000; Kodavanti et al., 2000). Recently, Rohr et al. (2010) exposed Wistar Kyoto rats to residential urban $PM_{2.5}$ CAPs in Detroit, MI for 13 days and found increased BALF protein content ($p < 0.05$). Indices of injury (BALF protein and LDH activity) were not increased by any exposure to San Joaquin Valley $PM_{2.5}$ CAPs despite evidence of inflammation (Plummer et al., 2012). Additional study details are found in Table 5-14.

Pulmonary Oxidative Stress

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies examined oxidative stress in response to $PM_{2.5}$ exposure. Increased lung chemiluminescence, activities of MnSOD and catalase, TBARS, and protein carbonyl content were reported in rats exposed to $PM_{2.5}$ CAPs in Boston (Rhoden et al., 2004; Gurgueira et al., 2002). Pretreatment with the thiol antioxidant N-acetylcysteine blocked PM-mediated oxidative stress in Rhoden et al. (2004). In a recent study, tissue heme oxygenase-1 activity, an index of oxidative stress, was not increased by any exposure to San Joaquin Valley $PM_{2.5}$ CAPs (Plummer et al., 2012) despite evidence of inflammation (Table 5-14).

Pulmonary Inflammation

The 2004 PM AQCD (U.S. EPA, 2004) and 2009 PM ISA (U.S. EPA, 2009) reported several studies that examined the effect of single and multiday exposure to $PM_{2.5}$ on pulmonary inflammation. Exposure to $PM_{2.5}$ CAPS in Boston resulted in increased BALF neutrophils in dogs (exposed by tracheostomy) (Godleski et al., 2000) and increases in BALF neutrophils and lymphocytes in rats (Rhoden et al., 2004; Saldiva et al., 2002; Clarke et al., 1999), while BALF macrophages were decreased (Clarke et al., 1999). Godleski et al. (2002) found concentration-dependent increases in numbers of BALF neutrophils and increases in gene expression of inflammatory mediators following exposure to $PM_{2.5}$ CAPs in Boston. Increases in BALF total cells, neutrophils, and macrophages were also seen in rats exposed to $PM_{2.5}$ CAPs from Fresno, CA (Smith et al., 2003). Exposure of rats to $PM_{2.5}$ CAPs in New York City resulted in increased lavageable cells in one study (Zelikoff et al., 2003) and no increases in inflammatory cells in another (Gordon et al., 2000). Similarly, exposure to $PM_{2.5}$ CAPs in Research Triangle Park, NC had disparate effects in different studies (Kodavanti et al., 2005; Kodavanti et al., 2000). Other studies investigated the effects of exposure to traffic related air pollution, such as whole DE or GE or on-road highway aerosols, on pulmonary inflammation. However, these studies did not distinguish between effects of the gaseous or particulate parts of the mixture.

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Similarly, recent studies are not uniform in the observation of inflammation following inhalation exposure to $PM_{2.5}$. Amatullah et al. (2012) found no changes in BALF inflammatory cells immediately following a 4-hour exposure of BALB/c mice to $PM_{2.5}$ CAPs in Toronto (Table 5-14). No increases in BALF inflammatory cells were found in Wistar Kyoto rats exposed for 13 days to $PM_{2.5}$ CAPs in Detroit despite an increase in BALF protein, an index of lung injury (Rohr et al., 2010). In contrast, increases in lung tissue and BALF IL-6 were observed following multiday exposure of C57BL/6 mice to $PM_{2.5}$ CAPs in Chicago (Chiarella et al., 2014; Budinger et al., 2011), and Mexico City (Aztatzi-Aguilar et al., 2015). Budinger et al. (2011) also reported increases in BALF MCP-1 and TNF-α. In IL-6 knock-out mice, short-term $PM_{2.5}$ exposure failed to increase IL-6 levels, while the other two mediators were unaffected. In addition, upregulation of the IL-6 target genes surfactant protein B and tissue factor in lung tissue and thrombin-antithrombin complex in plasma was observed in wild-type, but not in IL-6 knock-out mice. These results demonstrate the involvement of lung IL-6 in mediating systemic increases in thrombin-antithrombin complex, a key mediator of thrombosis. Furthermore, increased numbers of neutrophils in the BALF were found in C57BL/6 mice exposed for 10 days to $PM_{2.5}$ CAPs in California ($p < 0.05$) (Plummer et al., 2012). In this latter study, $PM_{2.5}$ CAPs were collected during two seasons (summer and winter) from an urban (Fresno) and a rural site (Westside) near Fresno. While BALF neutrophils were increased in mice exposed to Westside summer and Westside winter $PM_{2.5}$ CAPs ($p < 0.05$), levels of KC, MCP-1 and IFN-γ were decreased in lung tissue from mice exposed to Fresno summer $PM_{2.5}$ CAPs ($p < 0.05$). This study demonstrates that urban and rural sites within the same airshed and season can have PM with differing ability to produce inflammation.

A time course study of pulmonary inflammation was conducted by Xu et al. (2013) in C57BL/6 mice exposed for 5, 14, and 21 days to $PM_{2.5}$ CAPs in Columbus, OH. No increases in numbers of macrophages or neutrophils were found in BALF. However, immunohistochemically staining of lung tissue showed increases in macrophages (using F4/80 + as the marker) at the three time points ($p < 0.05$), peaking at 5 days. No increases in neutrophils (using NIMPR14 as the marker) were seen in lung tissue. This study is unique in demonstrating early recruitment of macrophages to lung tissue in the absence of neutrophils and is indicative of innate immune system activation.

Other studies examined the effects of source-related $PM_{2.5}$ on pulmonary inflammation. Tyler et al. (2016) exposed C67BL/6 mice to resuspended DEP for 6 hours and found no increase in inflammatory cells or cytokines in the BALF and no increase in particle uptake in bronchial macrophages, despite inflammation in the hippocampus (Section 8.1.3). Diaz et al. (2013) exposed Sprague Dawley rats to three kinds of $PM_{2.5}$—primary particles that were obtained directly from a tunnel with roadway gases removed by a denuder (P), secondary organic aerosol formed from photochemical oxidation of the primary tunnel gases (SOA), and photochemically aged primary particles plus SOA (P + SOA). Lymphocytes in BALF increased following 1-day exposure to P ($p < 0.05$) and 2-day exposure to P + SOA ($p < 0.07$), while neutrophils in BALF increased after 2-day exposure to SOA ($p < 0.01$) and P + SOA ($p < 0.05$). Mauderly et al. (2011) exposed mice and rats for 1 week to simulated coal emissions with and without the addition

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of a particle filter. The increase in MIP-2 seen in the BALF of F344 ($p < 0.05$) was prevented by filtration, indicating that the particulate part of the mixture had a role in the pro-inflammatory response.

Two of the aforementioned studies investigated the relationship between pulmonary inflammation and neurohumoral or endocrine pathways. Chiarella et al. (2014) evaluated the role of the SNS in modulating inflammation following exposure to $PM_{2.5}$ using knock-out mice lacking the β_2-adrenergic receptor specifically on macrophages. While wild type C57BL/6 mice exposed for several days to $PM_{2.5}$ CAPs in Chicago had increased IL-6 mRNA and protein in BALF ($p < 0.05$), knock-out mice had a greatly diminished response ($p < 0.05$). This finding implicates agonists of the β_2-adrenergic receptor, i.e., catecholamines, as partly responsible for the effects of $PM_{2.5}$ on IL-6 through the stimulation of β_2-adrenergic receptors on lung macrophages. Supporting evidence was provided by the finding that treatment with an agonist of the β_2-adrenergic receptor enhanced IL-6 levels in the BALF of wild type mice exposed to $PM_{2.5}$ ($p < 0.05$) Additionally, levels of the catecholamine norepinephrine were increased in BALF and brown adipose tissue following $PM_{2.5}$ exposure ($p < 0.05$), indicative of increased sympathetic tone. Taken together, results of this study provide evidence that exposure to $PM_{2.5}$ activated the sympathetic nervous system, which enhanced the release of IL-6 from lung macrophages. Downstream effects of macrophage-derived IL-6 on thrombosis were also examined (see Section 6.1.12).

Aztatzi-Aguilar et al. (2015) evaluated the RAS and kallikrein-kinin endocrine system in the lung in Sprague Dawley rats exposed for several days to $PM_{2.5}$ CAPs in Mexico City. Increased protein expression of IL-6 in lung tissue ($p < 0.05$) was accompanied by increased expression of the angiotensin I receptor gene, reduced angiotensin I receptor protein levels, and increased angiotensin converting enzyme mRNA levels ($p < 0.05$). Protein levels of angiotensin converting enzyme and mRNA levels of angiotensin II receptor mRNA were not impacted. In addition, $PM_{2.5}$ CAPs exposure resulted in increased mRNA levels for kallikrein-1 enzyme ($p < 0.05$). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors The RAS mediates vasoconstriction and vascular oxidative stress and inflammation and is counterbalanced by the kallikrein-kinin endocrine system via bradykinin-mediated production of nitric oxide, an important vasodilator. The SNS is known to regulate the endocrine systems. Although not specifically examined in this study, $PM_{2.5}$ exposure-mediated activation of the SNS activation may link $PM_{2.5}$ exposure and the RAS.

Morphology

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies found that exposure to $PM_{2.5}$ CAPs in Boston, MA resulted in mild morphological changes in the lung including hyperplasia of the terminal bronchiolar and alveolar ductal epithelium and pulmonary arteriolar edema (Rhoden et al., 2004; Batalha et al., 2002; Saldiva et al., 2002). Recently, Yoshizaki et al. (2016) evaluated the effects of multiday exposure to Sao Paulo, Brazil $PM_{2.5}$ CAPs on nasal epithelium in male and female BALB/c mice. The influence of estrus cycle in female was also determined. $PM_{2.5}$ CAPs exposure resulted in an

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increase in acidic mucus content in males and a decrease in acidic mucus content in females ($p < 0.05$) (Table 5-14). $PM_{2.5}$ CAPs exposure had no effect on neutral mucus content in either male or female mice. In addition, estrus cycle had no effect on mucus content or response to $PM_{2.5}$ CAPs exposure. Upregulation of message and protein levels of estrogen, aryl hydrocarbon receptors, and cytochrome P450 proteins was examined in nasal epithelium. $PM_{2.5}$ CAPs exposure resulted in decreased mRNA levels of estrogen receptor β2 and cytochrome 1b1 in female mice ($p < 0.01$). Female rats in diestrus, but not estrus or proestrus, exhibited decreased mRNA levels of estrogen receptor β2, cytochrome 1b1, and cytochrome 1a2 ($p < 0.05$). Estrogen receptor protein levels were decreased in nasal epithelium and aryl hydrocarbon receptor protein levels were increased in submucosal gland by $PM_{2.5}$ CAPs exposure in female mice ($p < 0.05$). Only female rats in estrus not diestrus or proestrus) exhibited these changes ($p < 0.05$).

Allergic Sensitization

The 2009 PM ISA (U.S. EPA, 2009) described numerous studies demonstrating the adjuvant potential of PM. While most of these studies involved intra-nasal or other noninhalation routes of exposure, one inhalation study demonstrated a strong adjuvant effect of PM (Whitekus et al., 2002). In this study, mice were exposed to resuspended DEP and subsequently challenged with OVA. OVA-specific IgG1 and IgE were enhanced by DEP exposure in the absence of general markers of inflammation. This effect, as well as DEP-mediated lipid peroxidation and protein oxidation, was blocked by pretreatment with the thiol antioxidants N-acetylcysteine and bucillamine. These results indicate that oxidative stress played a role in DEP-mediated allergic sensitization. Recent studies that have become available since the last review, while supportive of the adjuvant potential of $PM_{2.5}$, involve noninhalation routes of exposure (i.e., subcutaneous, intra-peritoneal and oropharyngeal aspiration).

Pathways Related to Otitis Media

Kim et al. (2016b) conducted a transcriptomic analysis in the middle ear following exposure to DEP (Table 5-14). BALB/c mice were exposed to resuspended DEP for several days and gene expression microarray and pathway analysis were performed on tissue collected 9 days later. In the middle ear, numerous genes were upregulated or downregulated because of DEP exposure. Pathway analysis identified several of these genes as potential biomarkers for DEP-related otitis media including cholinergic receptor muscarinic 1, erythropoietin, son of sevenless homolog 1, estrogen receptor 1, cluster of differentiation 4, and interferon α 1.

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5.1.7.4 Summary of Respiratory Effects in Healthy Populations

Similar to results described in the 2009 PM ISA (U.S. EPA, 2009), evaluation of the current epidemiologic evidence indicates that short-term $PM_{2.5}$ 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 $PM_{2.5}$-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 $PM_{2.5}$ exposure leads to overt and persistent respiratory effects in healthy populations or is related to such effects across a wide range of $PM_{2.5}$ concentrations.

Controlled human exposure and animal toxicological studies also examined pulmonary function and inflammation responses to short-term exposure to $PM_{2.5}$ CAPs. While evidence from controlled human exposure studies was inconsistent, animal toxicological studies clearly demonstrated changes in pulmonary function and inflammation. Recent evidence supports the previously observed involvement of lung irritant responses in mediating the changes in respiratory function, such as rapid shallow breathing, seen following exposure to $PM_{2.5}$. BALF cellular infiltrates are commonly found following exposure to $PM_{2.5}$ and appear to primarily involve recruitment of macrophages and neutrophils into the airways. In addition, several studies implicate changes in various cytokines in BALF and lung tissue. Increases in numbers of specific macrophages in lung tissue provides evidence for the activation of innate immunity over several days to several weeks. Pulmonary injury and oxidative stress responses were inconsistent. However, a study evaluated in the 2009 PM ISA demonstrated oxidative stress-mediated allergic sensitization due to inhalation of $PM_{2.5}$. Different regions of the respiratory tract are impacted by short-term $PM_{2.5}$ exposure with morphologic changes observed in the terminal bronchiolar and alveolar regions and changes in mucus profile found in in nasal epithelium. A mechanistic study shows involvement of the SNS in augmenting macrophage-mediated inflammatory effects following exposure to $PM_{2.5}$. In addition, the RAS and kallikrein-kinin endocrine system in the lung were impacted by short-term exposure to $PM_{2.5}$.

Variability in results observed in controlled human exposure and animal toxicological studies could be due to the time points assessed (too long after exposure), the nature of the exposures (dose, particle composition), the sensitivity of the model (species, strain, age, predisposing factors) and the sensitivity of the measurements used. When $PM_{2.5}$ CAPs are used, the composition of the PM, which is related to source and season, could add to this variability. Finally, whether the exposure was a single time or repeated could have a large effect. Repeated exposures, even those less than 30 days, may trigger adaptive physiologic and cellular responses that are not present for very short term single exposure studies, such as single acute exposures.

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5.1.8 Respiratory Effects in Populations with Cardiovascular Disease

Given the prevalence of cardiovascular disease in the general population and the inter-relationships between the cardiovascular and respiratory systems, numerous animal toxicological studies have been conducted in animal models of cardiovascular disease. Many of these studies were evaluated in the 2004 PM AQCD and the 2009 PM ISA (U.S. EPA, 2009). Pulmonary function responses were examined following single and multiday exposure of hypertensive rats to $PM_{2.5}$ CAPs from New York, Research Triangle Park, NC, Taiwan, and Boston, MA (Kodavanti et al., 2005; Lei et al., 2004; Nadziejko et al., 2002; Godleski et al., 2000). Alterations in tidal volume and breathing frequency were found, indicating the involvement of lung irritant receptors and the triggering of local reflexes in the response to short-term $PM_{2.5}$ exposure. Multiday exposure of SH rats to $PM_{2.5}$ CAPs in the Netherlands altered levels of BALF CC16 in a concentration-dependent manner (Kooter et al., 2006). CC16 is a secretory product of nonciliated bronchiolar Club cells and is a marker of injury and thought to contribute to the control of inflammation. However, there was no evidence of pulmonary injury (as assessed by BALF LDH levels) in this study or another study involving $PM_{2.5}$ CAPs in Research Triangle Park, NC (Kodavanti et al., 2005). Kooter et al. (2006) also found that a multiday exposure of SH rats to $PM_{2.5}$ CAPs in the Netherlands increased levels of heme oxygenase-1, an indicator of oxidative stress. Several studies in hypertensive rats evaluated pulmonary inflammation following exposure to $PM_{2.5}$ CAPs. While some studies found increased numbers of inflammatory cells in BALF (and even a correlation between $PM_{2.5}$ CAPs concentrations and numbers of neutrophils) (Cassee et al., 2005; Lei et al., 2004), others did not (Kooter et al., 2006; Kodavanti et al., 2005). Campen et al. (2006) found a concentration-dependent effect on inflammation in $PM_{2.5}$ exposed-ApoE knockout mice, a model of atherosclerosis.

A few recent studies add to this evidence base (Table 5-15). Rohr et al. (2010) exposed SH rats to $PM_{2.5}$ CAPs in Detroit and found no evidence of lung injury as assessed by BALF protein levels. Farraj et al. (2015) studied the effect of a 4-hour exposure of SH rats to $PM_{2.5}$ CAPs in two seasons, summer and winter, in Research Triangle Park, NC. Activities of LDH, glutathione S transferase, and CuZn SOD, indicators of injury and oxidative stress, were decreased by exposure to summer $PM_{2.5}$ CAPs but not winter $PM_{2.5}$ CAPs ($p \leq 0.05$). $PM_{2.5}$ CAPs concentration was higher in summer than in winter, but metal exposure concentrations were roughly equivalent. Concomitant exposure to 200 ppb O_3 appeared to have little additional effect on these parameters. No effects on inflammation were found by Rohr et al. (2010) or Farraj et al. (2015). Furthermore, Tyler et al. (2016) conducted an inhalation exposure of ApoE knockout mice to resuspended DEP and found no increase in inflammatory cells or cytokines in the BALF and no increase in particle uptake in bronchial macrophages, despite inflammatory effects in the hippocampus (Section 8.1.3). Overall, short-term $PM_{2.5}$ exposure results in pulmonary effects in some studies but not others. The most consistent evidence is for changes in pulmonary function.

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Table 5-15 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and respiratory effects in models of cardiovascular disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Farraj et al. (2015) Species: Rat Sex: Male Strain: SH Age/Weight: 12 weeks	$PM_{2.5}$ CAPs Research Triangle Park, NC Particle size: 324 nm summer, 125 nm winter Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 85-170 µg/m^3 Duration: 4 h Time to analysis: 24 hr Modifier: Telemeter implanted, summer and winter	Lung Injury—BALF LDH activity Inflammation—BALF cells BALF antioxidant enzymes—GST and CuZn SOD
Rohr et al. (2010) Species: Rat Strain: Spontaneously hypertensive (SH) Wistar Kyoto (WKY) Sex: Male Age/Weight: 11−12 weeks	$PM_{2.5}$ CAPs residential urban Detroit, MI Particle sizes: $PM_{2.5}$	Route: Whole-body inhalation Dose/Concentration: 507 µg/m^3 Duration of exposure: 8 h, 13 consecutive days Time to analysis: 24 h	BALF cells Lung Injury • BALF protein content
Tyler et al. (2016) Species: Mouse Strain: ApoE knockout Age/Weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 µm ± 1.3−1.6 µm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 300 µg/m^3 Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = Apolipoprotein E; BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; CuZn SOD = copper, zinc superoxide dismutase; GST = glutathione S transferase; LDH = lactate dehydrogenase; SH = spontaneously hypertensive.

5.1.9 Respiratory Mortality

Studies that examine the association between short-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for $PM_{2.5}$-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. The multicity epidemiologic studies evaluated in the 2009 PM ISA provided evidence of consistent positive associations, ranging from 1.0−2.2% for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations, between short-term $PM_{2.5}$ exposure and respiratory mortality (U.S. EPA, 2009). However, compared to associations between short-term $PM_{2.5}$ exposure and cardiovascular and total (nonaccidental) mortality, confidence intervals were larger due to respiratory mortality comprising a smaller percentage of all mortalities. Across studies, the $PM_{2.5}$ 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

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single-city studies suggested that the $PM_{2.5}$-respiratory mortality relationship was not confounded by gaseous copollutants. Additionally, there was limited coherence across epidemiologic and controlled human exposure studies, which complicated the interpretation of the associations observed for short-term $PM_{2.5}$ exposure and respiratory mortality.

Recent multicity epidemiologic studies along with meta-analyses provide additional evidence of generally consistent positive associations between short-term $PM_{2.5}$ exposure and respiratory mortality (Figure 11-2). In addition to providing evidence that supports the rather immediate timing of respiratory mortality effects (i.e., lag 0 to 1 days), some recent studies also provide initial evidence that respiratory mortality effects due to short-term $PM_{2.5}$ exposure may be more prolonged (i.e., lags >2 days). Unlike the studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), some recent studies have also further evaluated the $PM_{2.5}$-respiratory mortality relationship by examining cause-specific respiratory mortality outcomes (i.e., COPD, pneumonia, and LRTI) (Samoli et al., 2014; Janssen et al., 2013). 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.

Evidence to further characterize the $PM_{2.5}$-respiratory mortality relationship is also provided by recent epidemiologic studies. Overall, these studies continue to support a relationship between $PM_{2.5}$ and respiratory mortality and provide additional evidence that: gaseous pollutants do not confound the $PM_{2.5}$-respiratory mortality relationship; $PM_{2.5}$ effects on respiratory mortality may not be limited to the first few days after exposure; the magnitude of the association tends to be largest during warmer months; and there is inconsistent evidence that temperature extremes modify associations between short-term $PM_{2.5}$ exposure and respiratory mortality (see Section 5.1.10).

5.1.10 Policy-Relevant Considerations

Epidemiologic studies that examined short-term $PM_{2.5}$ exposure and respiratory-related effects often conduct additional analyses to assess whether the associations observed are due to chance, confounding, or other biases. Within this section, evidence is evaluated across epidemiologic studies to further assess the association between short-term $PM_{2.5}$ exposure and respiratory-related effects, focusing specifically on those analyses that address policy-relevant issues: copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on respiratory-related ED visits and hospital admissions and respiratory mortality. Studies examining additional endpoints, such as subclinical markers of a PM-related respiratory

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effect (e.g., lung function, inflammation, etc.), may also examine some of these issues, but are not the focus of this evaluation.

5.1.10.1 Examination of Potential Copollutant Confounding

The potential confounding effect of copollutants is a previously identified source of uncertainty in the examination of the relationship between short-term $PM_{2.5}$ exposure and respiratory effects, and thus requires careful consideration particularly with respect to whether the magnitude and direction of $PM_{2.5}$ risk estimates change in copollutant models. Compared to the evidence available at the completion of the 2009 PM ISA, many recent studies conducted analyses that inform whether the relationship between short-term $PM_{2.5}$ exposures and respiratory-related effects, specifically hospital admissions, ED visits, and respiratory mortality, may be confounded by copollutants. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 (Figure 5-9), NO_2, (Figure 5-10), SO_2 (Figure 5-11), CO (Figure 5-12) and $PM_{10-2.5}$ (Figure 5-13). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of coexposures to correlated copollutants. Generally, these studies provide evidence that the association between short-term $PM_{2.5}$ exposures and respiratory health outcomes is robust to the inclusion of copollutants in a statistical model. This evidence provides support for an independent association between $PM_{2.5}$ concentrations and respiratory-related effects.

Building off studies evaluated in the 2009 PM ISA, recent studies that examined the potential confounding effects of O_3 on associations between short-term $PM_{2.5}$ exposure and respiratory-related outcomes continue to report correlations between O_3 and $PM_{2.5}$ ranging from low (<0.4) to high (>0.7). Across the respiratory-related outcomes examined, where positive associations with $PM_{2.5}$ were reported in single-pollutant models, associations were often attenuated in copollutant models, but remained positive. The most extensive evaluation of potential copollutant confounding was for studies focusing on asthma hospital admissions and ED visits, where recent studies report results that are consistent with those observed in studies evaluated in the 2009 PM ISA (Figure 5-9). Additionally, recent evidence provides additional support for positive $PM_{2.5}$ associations with hospital admissions and ED visits for all respiratory diseases as well as initial evidence indicating that $PM_{2.5}$ associations with respiratory mortality are relatively unchanged in copollutant models with O_3. While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were generally persistent, although in some cases attenuated, in copollutant models with O_3. Individual panel study results from copollutant models with O_3 are discussed within the relevant endpoint sections (Section 5.1.2.2, Section 0, and Section 5.1.7.1).

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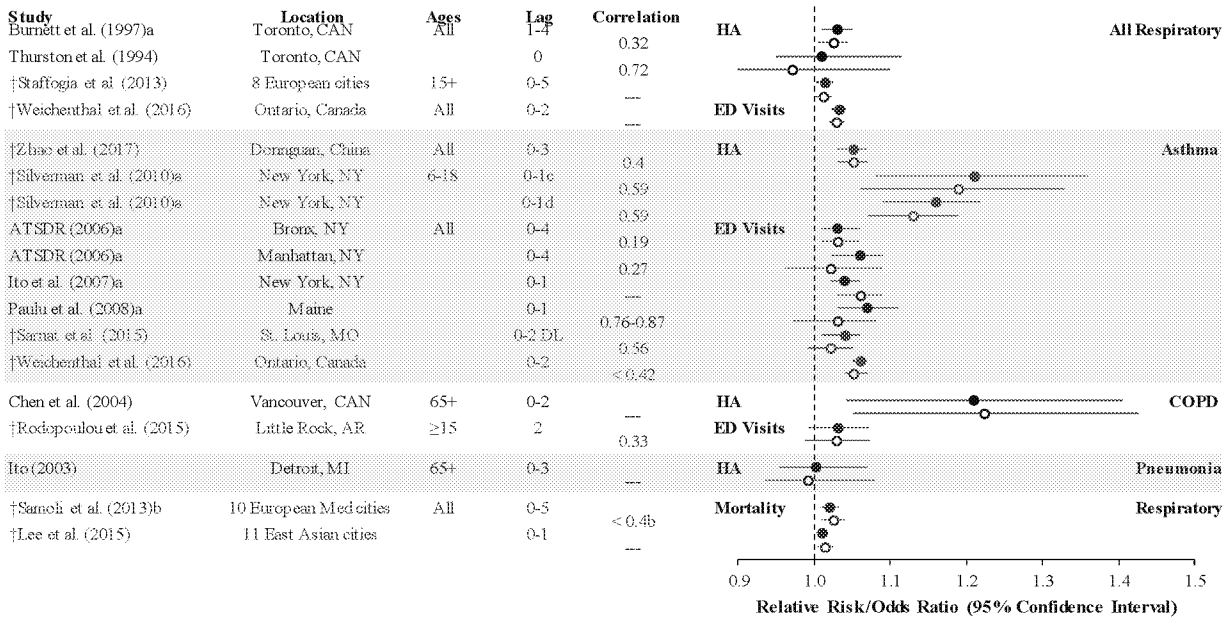

DL = distributed lag model.

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0–5 days; c = Intensive Care Unit (ICU) admissions; [d] = non-ICU admissions. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-9 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with ozone (O_3) for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Across studies, $PM_{2.5}$ associations with respiratory-related outcomes remain positive, although in some cases attenuated, in copollutant models with NO_2. Generally, $PM_{2.5}$ was reported to be low to moderately correlated with NO_2 ($r < 0.7$). Similar to the evaluation of copollutant models with O_3, most of the evidence with respect to potential copollutant confounding by NO_2 is from studies examining asthma hospital admissions and ED visits with recent studies supporting the results from studies evaluated in the 2009 PM ISA. Recent studies also build on the initial evidence reported in the 2009 PM ISA that $PM_{2.5}$ associations are robust to control for NO_2 in studies examining hospital admissions and ED visits for all respiratory diseases and provide initial evidence that $PM_{2.5}$ associations with respiratory mortality are also robust (Figure 5-10). While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were persistent, although in some cases attenuated, in copollutant models with NO_2. Individual panel study results from copollutant models with NO_2 are discussed within the relevant endpoint sections (Section 5.1.2.2, Section 0, Section 5.1.2.4, Section 5.1.4.2, Section 5.1.4.4, and Section 5.1.7.1).

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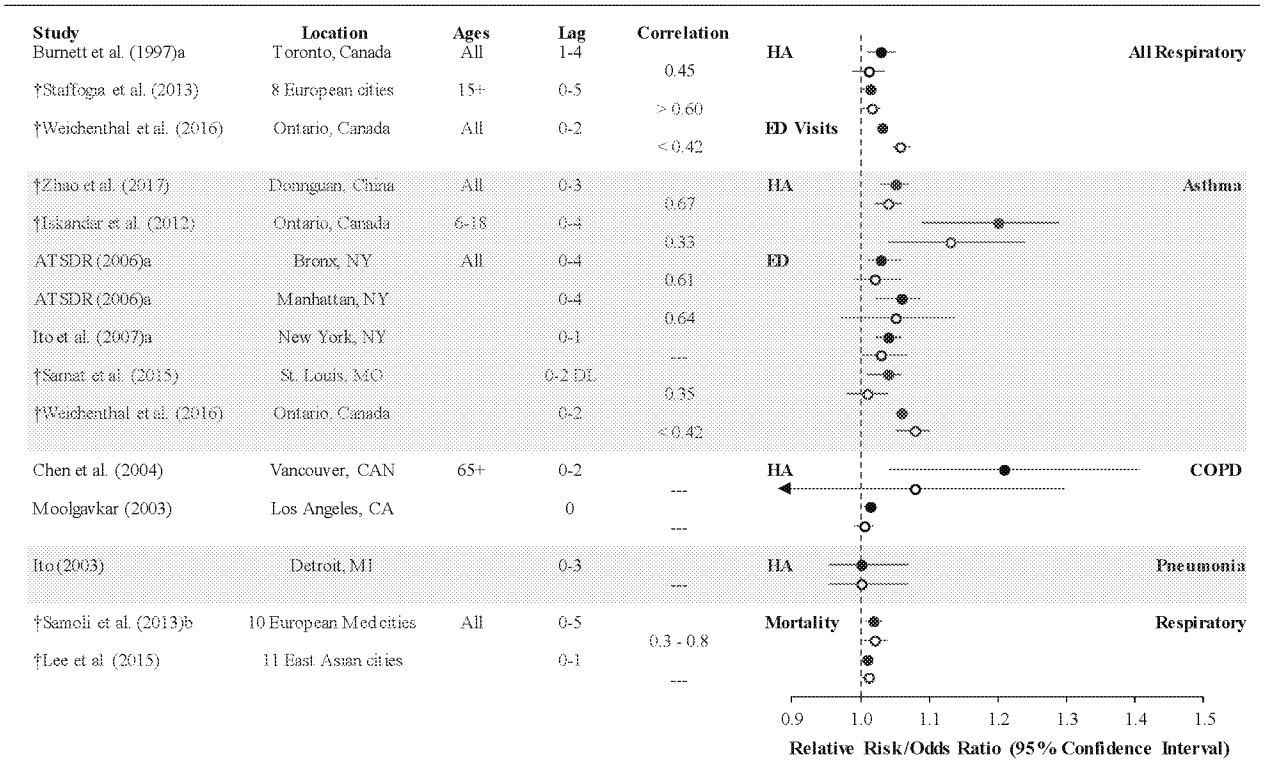

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0−5 days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-10 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with NO_2 for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

The examination of potential copollutant confounding by SO_2 on the relationship between short-term $PM_{2.5}$ exposure and respiratory-related outcomes is similar to that observed for O_3 and NO_2, with most of the evidence from studies examining asthma hospital admissions and ED visits (Figure 5-11). Across studies, correlations between $PM_{2.5}$ and SO_2 were primarily <0.5. Most of the studies that examined copollutant models with SO_2 were evaluated in the 2009 PM ISA, but recent studies add to the evidence base for asthma hospital admissions and ED visits further demonstrating that associations are relatively unchanged in copollutant models with SO_2, while also providing new evidence for respiratory mortality. While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were generally persistent, although in some cases attenuated, in copollutant models with SO_2. Individual panel study results from copollutant models with SO_2 are discussed within the relevant endpoint sections (Section 0, Section 5.1.2.4, Section 5.1.4.2, Section 5.1.4.4, and Section 5.1.7.1).

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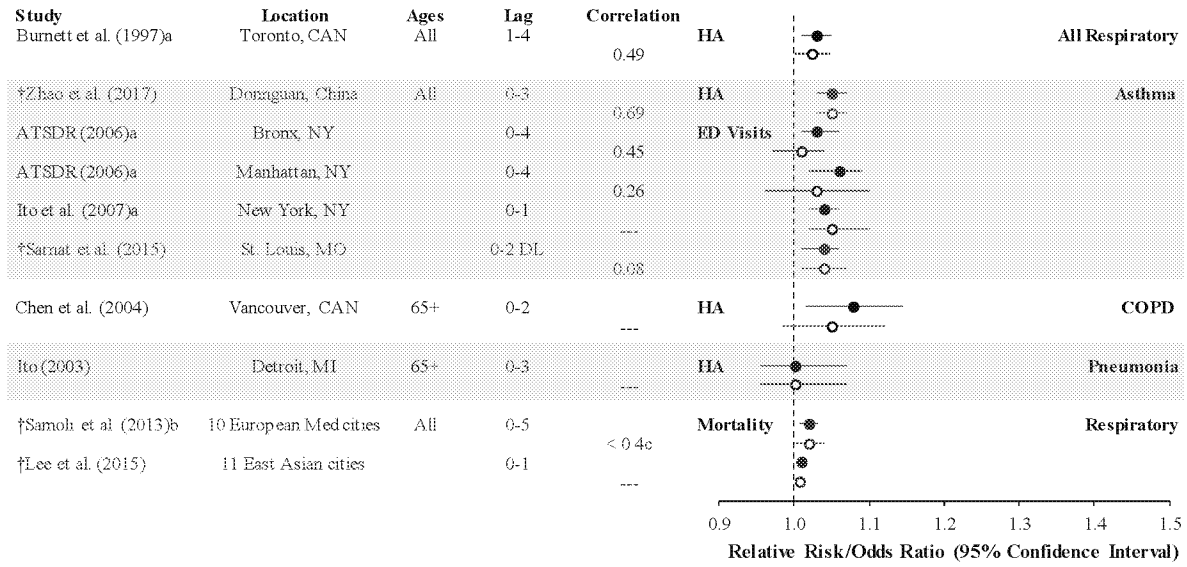

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0–5 days; c = correlations were <0.4 in all cities except Milan and Turin where it was ~0.6. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-11 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with sulfur dioxide (SO_2) for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Compared to O_3, NO_2, and SO_2 the assessment of potential copollutant confounding by CO has not been extensively examined in recent studies (Figure 5-12). However, across the studies evaluated in the 2009 PM ISA, along with the recent study conducted by Sarnat et al. (2015) examining asthma ED visits, evidence indicates that in studies that observed positive associations with $PM_{2.5}$, the association was relatively unchanged in copollutant models with CO.

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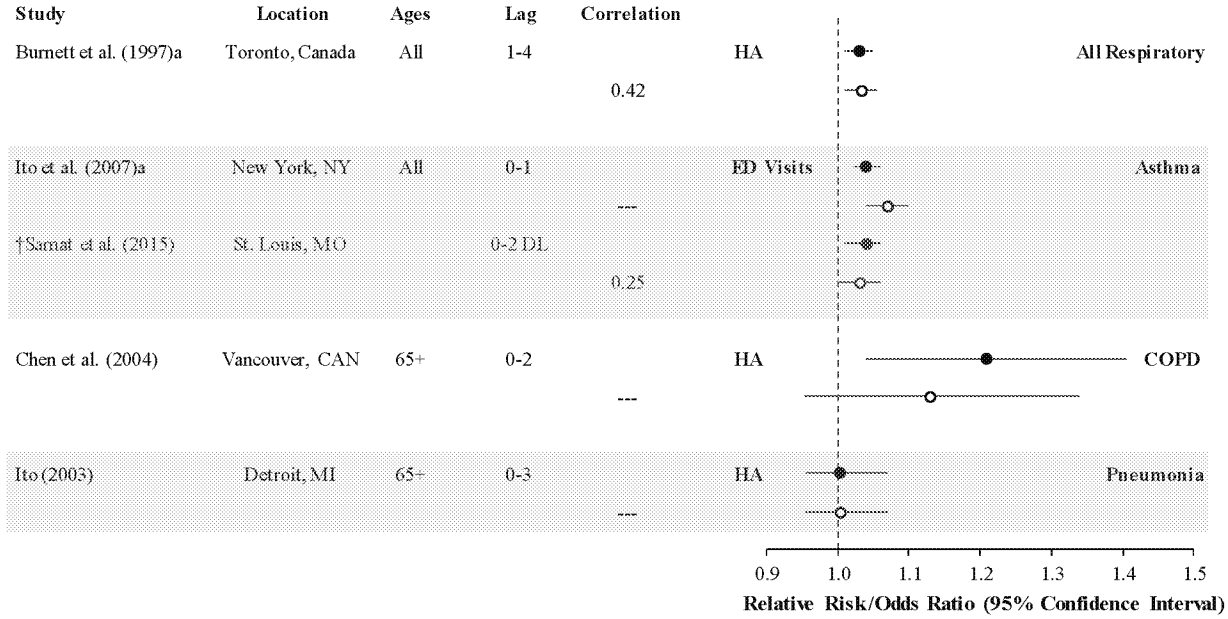

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analyses for warm season only. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-12 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with carbon monoxide (CO) for a 10 μg/m³ increase in 24-hour average $PM_{2.5}$ concentrations.

Recent studies also greatly expand upon the examination of potential copollutant confounding by $PM_{10-2.5}$ (Figure 5-13). Across the studies evaluated, correlations between $PM_{2.5}$ and $PM_{10-2.5}$ were primarily low ($r < 0.4$). $PM_{2.5}$ associations for all respiratory-related outcomes are generally unchanged in models that adjust for $PM_{10-2.5}$. However, an uncertainty across studies that examined either single- or copollutant models that include $PM_{10-2.5}$ is the variety of methods employed to estimate $PM_{10-2.5}$ concentrations and the potential measurement error associated with each method (Section 2.5.1.2.3 and Section 3.3.1.1).

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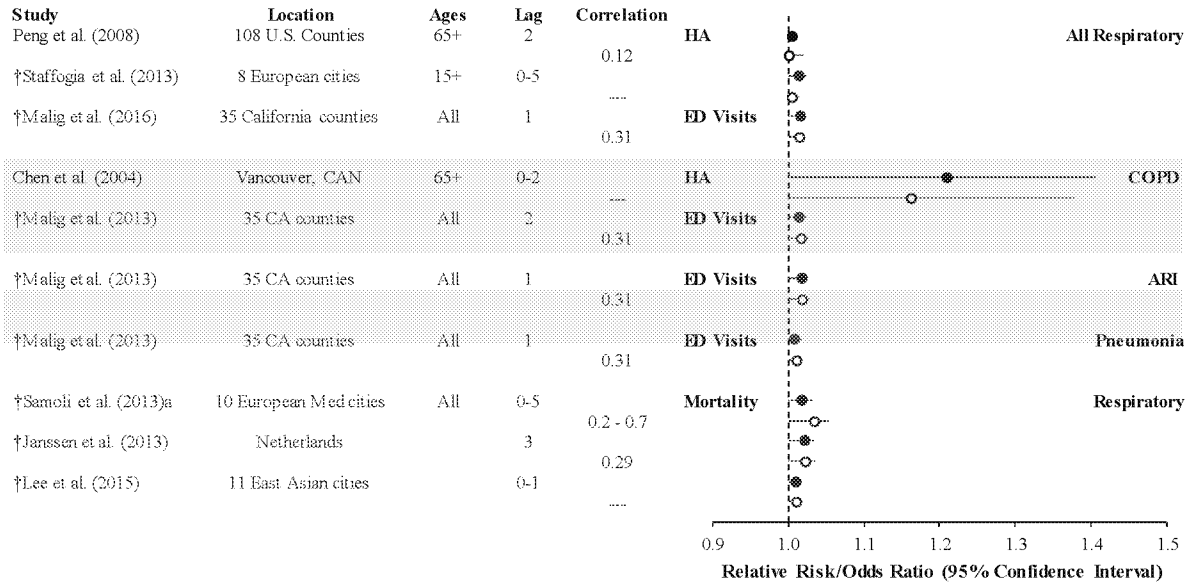

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analysis only conducted for lag 0–5. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-13 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with $PM_{10-2.5}$ for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

In conclusion, since the 2009 PM ISA, there has been growth in the number of studies that examined potential confounding of the relationship between short-term $PM_{2.5}$ exposure and respiratory-related outcomes by copollutants. These recent studies provide additional evidence supporting that $PM_{2.5}$ associations are relatively unchanged, although in some instances attenuated as well as increased, in copollutant models with gaseous and particle pollutants.

5.1.10.1.1 $PM_{2.5}$ within the Multipollutant Mixture

Although copollutant models are important in assessing potential copollutant confounding, it is well known that collinearity between pollutants can result in unstable estimates and that air masses are not limited to just two pollutants (Dominici et al., 2010). Therefore, in addition to copollutant models, studies that examine multipollutant exposures can provide additional information on the role of $PM_{2.5}$ within the complex air pollution mixture.

Analyses of pollutant mixtures, which use an array of statistical methods and pollutant combinations, for respiratory-related effects have focused on asthma ED visits. These studies indicate

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increases in asthma ED visits when ambient concentrations of $PM_{2.5}$ and a copollutant(s) are simultaneously high, but do not clearly show a larger increase than with $PM_{2.5}$ alone. In analyses conducted in Atlanta (Winquist et al., 2014a) and then subsequently for the entire state of Georgia (Xiao et al., 2016), $PM_{2.5}$ was a priori grouped with the other criteria pollutants (i.e., O_3, CO, NO_2, and SO_2) to examine their joint effect on pediatric asthma ED visits. In both studies, $PM_{2.5}$ was associated with pediatric asthma ED visits in single-pollutant models. However, in Xiao et al. (2016) joint effect models were relatively similar to the single-pollutant model, but in Winquist et al. (2014a) the joint effect model results were much larger (quantitative results only presented for warm season, no interaction model) (Table 5-16). Instead of defining air pollution mixtures a priori, other analyses examined whether there were groups of days with similar pollution profiles, specifically days representative of high and low air pollution exposures based on quartiles of $PM_{2.5}$, NO_2, CO, and O_3 concentrations using a classification and regression tree (C&RT) approach. This approach was used to examine associations between high and low air pollution days and asthma in Atlanta, GA; St. Louis, MO; and Dallas, TX. In Atlanta, GA. Gass et al. (2014) reported that RRs with $PM_{2.5}$ were largest in magnitude for days when $PM_{2.5}$ concentrations were in the highest quartile, while NO_2 was in the lowest two quartiles, as well as days when both NO_2 and $PM_{2.5}$ were in higher quartiles. Gass et al. (2015) expanded the analysis of Gass et al. (2014) to include Atlanta, GA; St. Louis, MO; and Dallas, TX. The authors observed that pollution profiles varied across cities resulting in the overall quartiles of pollutant concentrations for a particular mixture sometimes differing from the distribution of concentrations within an individual city. For example, $PM_{2.5}$ concentrations were in the 4th quartile for one city, but the overall mixture across cities showed that $PM_{2.5}$ concentrations were in the 1st quartile. Gass et al. (2015) reported evidence of mixtures with high $PM_{2.5}$ concentrations having the association largest in magnitude, but associations were similar in magnitude in instances when $PM_{2.5}$ concentrations were in the lowest quartile. While the other multipollutant studies focused on examining combinations of pollutants at different parts of the individual pollutant concentration distribution, Toti et al. (2016) in Houston, TX focused on pollutant concentrations on same and successive days that are in the 4th quartile of each pollutant concentration distribution. Across the different combinations, as well as those that included $PM_{2.5}$, the authors reported ORs that were relatively similar in magnitude. In contrast with U.S. cities, the association between asthma ED visits and an air quality health index (AQHI), which combines $PM_{2.5}$, NO_2, and O_3 based on mortality risk, in Windsor, ON, appears to be influenced by either $PM_{2.5}$ or O_3, depending on the lag (Szyszkowicz and Kousha, 2014). The OR for the AQHI was similar to that of O_3 at lag 0 and that of $PM_{2.5}$ at lags 4 and 5 (Table 5-16). Whereas the previous studies evaluated focused on multipollutant mixtures, Weichenthal et al. (2016) examined whether there was evidence of effect modification of the $PM_{2.5}$-asthma ED visit association in 15 Ontario cities. The authors observed that the $PM_{2.5}$ association increased with increasing city-level oxidative potential of $PM_{2.5}$, NO_2, and O_3 combined (Weichenthal et al., 2016).

In summary, the studies that examined multipollutant mixtures that include $PM_{2.5}$ indicate that mixtures encompassing days with high $PM_{2.5}$ concentrations are often those mixtures with the highest risk estimates. Additionally, when comparing single-pollutant $PM_{2.5}$ results with those based on mixtures, the

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1 risk estimate associated with the mixture is relatively similar and, in some cases, larger than that observed
2 for $PM_{2.5}$.

Table 5-16 Combined influence of $PM_{2.5}$ and copollutants on emergency department (ED) visits for asthma.

Study	$PM_{2.5}$ Single-Pollutant OR RR 95% CI	Combined OR or RR (95% CI)
†Xiao et al. (2016) Georgia, 2002–2008	Per 6.9 μg/m^3 1.03 (1.02, 1.04); lag 0–2	Joint Effect Model, Criteria Pollutants Combination (O_3, CO, NO_2, SO_2, and $PM_{2.5}$); lag 0–2 per IQR increase in each pollutant No interactions: 1.03 (1.01, 1.05) Interactions: 1.06 (1.02, 1.09)
†Winquist et al. (2014a) Atlanta, GA, 1998–2004	Per 9.2 μg/m^3, warm season 1.04 (1.02, 1.07)	Joint Effect Model, Criteria Pollutant Combination (O_3, CO, NO_2, SO_2, and $PM_{2.5}$) Warm season, no interactions: 1.13 (1.06, 1.21)
†Gass et al. (2014) Atlanta, GA, 1999–2009	NR	C&RT to group days by $PM_{2.5}$, NO_2, O_3 and CO quartiles Q1 $PM_{2.5}$, NO_2, CO, and O_3: 1.0 (reference) Q4 $PM_{2.5}$, Q1–4 O_3, Q1 or 2 NO_2, Q1–4 CO: 1.10 (1.05, 1.16) Q4 $PM_{2.5}$, Q1–3 O_3, Q3 NO_2, Q1–4 CO: 1.08 (1.01, 1.15) Q1 $PM_{2.5}$, Q1–4 O_3, Q3 or 4 NO_2, Q1–4 CO: 1.08 (1.03, 1.14)
†Gass et al. (2015) Atlanta, GA, 1999–2009 St. Louis, MO, 2001–2007 Dallas, TX, 2006–2008	NR	C&RT to group days by $PM_{2.5}$, NO_2 and O_3 quartiles Q1 $PM_{2.5}$, NO_2, and O_3: 1.0 (reference) Q4 $PM_{2.5}$, Q3 O_3, Q1 or 2 NO_2: 1.07 (1.03, 1.12) Q1 $PM_{2.5}$, Q3 O_3, Q3 or 4 NO_2: 1.04 (0.99, 1.08) Q1–4 $PM_{2.5}$, Q4 O_3, Q3 NO_2: 1.05 (1.01, 1.09)
†Toti et al. (2016) Houston, TX, 2006–2012	NR	Association rule mining to estimate ORs for all $PM_{2.5}$, O_3, NO_2, SO_2, CO and lag 0 to 4-day combinations and identify unique, statistically significant ORs. Q1–3 of each pollutant in combination: 1.0 (reference) Q4 $PM_{2.5}$ lag 0 and Q4 O_3 lag 0: 1.20 (1.02, 1.41) Q4 $PM_{2.5}$ lag 0, Q4 NO_2 lag 0 and Q4 O_3 lag 2: 1.33 (1.00, 1.65)
†Szyszkowicz and Kousha (2014) Windsor, ON, Canada 2004–2010	Per IQR (not reported) increase Lag 0: 1.02 (0.97, 1.06) Lag 3: 1.03 (0.99, 1.08) Lag 4: 1.05 (1.01, 1.09)	AQHI combining $PM_{2.5}$, O_3 and NO_2 (per 1 unit) Lag 0: 1.03 (0.99, 1.07) Lag 3: 1.02 (0.98, 1.06) Lag 4: 1.04 (1.01, 1.08)

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Table 5-16 (Continued): Combined influence of $PM_{2.5}$ and copollutants on emergency department (ED) visits for asthma.

Study	$PM_{2.5}$ Single-Pollutant OR RR 95% CI	Combined OR or RR (95% CI)
†Weichenthal et al. (2016) 15 cities Ontario, Canada 2004–2011	Lag 0–2 avg, per 10 μg/m^3 1.06 (1.05, 1.07)	Effect modification by oxidative potential of $PM_{2.5}$, NO_2 and O_3 Q1: 1.02 (0.99, 1.04) Q2: 1.06 (1.00, 1.13) Q3: 1.08 (0.97, 1.19) Q4: 1.10 (1.05, 1.15)

AQHI = air quality health index, C&RT = classification and regression tree, CO = carbon monoxide, NO_2 = nitrogen dioxide, O_3 = ozone, OR = odds ratio, RR = relative risk, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

5.1.10.2 Model Specification

An underlying uncertainty in the interpretation of epidemiologic study results is the difference in the magnitude and precision, and sometimes direction, of risk estimates across studies. It has remained difficult to elucidate why there are differences in risk estimates, but it is often thought to reflect the different statistical models used in each study. However, it has also been hypothesized that other factors may also be contributing to these observed differences such as differences in $PM_{2.5}$ composition or demographics between study locations (e.g., Section 11.6.3).

Recent epidemiologic studies have conducted sensitivity analyses to assess whether $PM_{2.5}$ associations with respiratory-related outcomes are dependent on the statistical model employed, in an attempt to reduce potential biases in observed associations. Such sensitivity analyses assess the influence of alternative model specifications, such as increasing degrees of freedom (df) to account for temporal trends, or the inclusion of alternative weather covariates. Collectively, recent studies that examined model specification provide evidence that $PM_{2.5}$ associations are generally robust to increasing the df per year to account for temporal trends, but in some cases attenuation of the association was observed when these additional df were included. Additionally, studies reported that $PM_{2.5}$ associations are relatively unchanged regardless of the weather covariates included in statistical models (i.e., different weather variables or lag days and df specified for the weather variables). Collectively, these studies reduce the uncertainty associated with the differences in the magnitude and direction of risk estimates in epidemiologic studies potentially resulting from the different statistical models employed across studies.

Several studies examined different approaches to control for seasonality or temporal trends by either increasing or decreasing the df/year used in studies of short-term $PM_{2.5}$ exposure and respiratory-related effects. $PM_{2.5}$-associated increases in asthma hospital admissions and ED visits were consistently observed when different df/year were used to account for temporal trends. For example, studies conducted in several U.S. cities reported that $PM_{2.5}$ associations remained robust to alternative

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