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Provisional Assessment of Recent Studies on Health Effects of Particulate Matter Exposure

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EXECUTIVE SUMMARY

In the proposed rule on the National Ambient Air Quality Standards for particulate matter (PM), EPA committed to conduct a review and assessment of the numerous studies relevant to assessing the health effects of PM that were published too recently to be included in the 2009 PM Integrated Science Assessment (ISA). This report presents the findings of EPA's survey and provisional assessment of such studies. EPA has screened and surveyed the recent literature and developed a provisional assessment that places those studies of potentially greatest relevance to the current PM NAAQS review in the context of the findings of the 2009 PM ISA. The focus is on: (a) epidemiologic studies that used $PM_{2.5}$ (i.e., fine PM) or $PM_{10\text{-}2.5}$ (i.e., coarse PM) and were conducted in the U.S. or Canada, and (b) toxicological or epidemiologic studies that compared effects of PM from different sources, PM components, or size fractions. The provisional assessment is not intended to critically review individual studies or integrate the scientific findings to draw causal conclusions as is done for an ISA.

This survey and assessment finds that that the new studies expand the scientific information and provide important insights on the relationships between PM exposure and health effects of PM. However, the new information and findings do not materially change any of the broad scientific conclusions regarding the health effects of PM exposure made in the 2009 PM ISA. In brief, this report finds the following:

- Recent epidemiologic studies, most of which are extensions of earlier work, continue to support the conclusions of the 2009 PM ISA for *long-term exposure to $PM_{2.5}$* and mortality, cardiovascular effects, respiratory effects, and reproductive and developmental effects. Notably, updated findings from the Harvard Six Cities and American Cancer Society cohorts continue to observe an association between long-term $PM_{2.5}$ exposure and mortality, which supports the findings from previous studies conducted in these cohorts. Additionally, a new Canadian multicity study observed associations with mortality at long-term mean $PM_{2.5}$ concentrations below those reported in the PM ISA. Recent cause-specific mortality studies also provide more evidence for cardiovascular mortality associations, especially in women, and additional evidence for respiratory mortality including lung cancer. Studies of cardiovascular effects provide evidence of myocardial infarction, hypertension, diabetes, and stroke, especially among women, which is consistent with the conclusions of the 2009 PM ISA. Recent studies continue to demonstrate associations with respiratory morbidity including respiratory symptoms and hospital admissions, as well as incident asthma among children. Reproductive and developmental effects studies continue to provide evidence for associations between long-term exposure to $PM_{2.5}$ and reduced birth weight.
- Recent epidemiologic studies have also continued to report associations between *short-term exposure to $PM_{2.5}$* and mortality and morbidity health endpoints, which further

support the causality determinations presented in the 2009 PM ISA. These include multi- and single-city analyses that demonstrate consistent positive associations across all respiratory and cardiovascular hospital admissions and emergency department visits as well as cause-specific outcomes, particularly asthma. Although limited to single-city studies, recent studies continue to demonstrate associations between short-term fine PM exposures and nonaccidental and cardiovascular mortality. Additionally, new evidence for stroke which focuses on assigning exposure from the time of stroke onset, instead of entry to the hospital, provides new information regarding an uncertainty recognized in the PM ISA.

- New toxicological and epidemiologic studies have continued to link health outcomes with a range of *$PM_{2.5}$ sources and components.* Several new epidemiologic analyses continue to demonstrate health effects attributed to multiple sources and PM components including combustion activities (e.g., motor vehicle emissions, coal combustion, oil burning, power plants, and wood smoke/vegetative burning), crustal sources, and secondary sulfate. Toxicological studies examined various source categories and found that no source consistently showed the strongest association with cardiovascular health effects. Additionally, an examination of a number of $PM_{2.5}$ components found associations with various components and both cardiovascular and respiratory endpoints.
- Only a few recent epidemiologic studies have examined health effects of *short- and long-term exposures to coarse particles ($PM_{10-2.5}$).* A short-term exposure and respiratory emergency department visits (ED) visits study found a positive and significant association with pediatric asthma ED visits in Atlanta, GA. One long-term exposure and mortality study did not find any evidence of an association with all-cause mortality though there was a positive but not statistically significant association with coronary heart disease (CHD) mortality.

1. INTRODUCTION AND METHODOLOGY

EPA is currently in the final stages of the review of the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM). As described in more detail in the Federal Register Notice of EPA's proposed rule on the PM NAAQS (77 FR 38890), EPA has prepared the *Integrated Science Assessment for Particulate Matter* (hereafter 2009 PM ISA) which reviewed, summarized, and integrated the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare that may be expected from the presence of PM in the ambient air in varying quantities, as required by section 108 of the Clean Air Act (CAA) (U.S. EPA, 2009). As noted in the PM proposal,[1] EPA is aware that numerous studies potentially relevant to assessing the health effects of ambient PM have been published recently that were not included in the 2009 PM ISA (U.S. EPA, 2009). The proposal notice also indicates the Agency's intent to conduct a review and assessment of these new studies before a final decision is made on the PM NAAQS. The purpose of this report is to present the findings of EPA's survey and provisional assessment of potentially relevant recent studies on the health effects of PM exposure. This provisional assessment will inform a decision by the EPA Administrator to proceed with final rulemaking or to revise the ISA to include the new studies.

This provisional assessment is focused on those studies most important to the major conclusions presented in the 2009 PM ISA and most relevant to the considerations of the current review of the PM NAAQS. EPA, therefore, identified potentially relevant studies by applying the following selection criteria to those studies published through August 2012: (1) epidemiologic studies that used $PM_{2.5}$ (i.e., fine PM) or $PM_{10\text{-}2.5}$ (i.e., coarse PM) and were conducted in the U.S. or Canada, and (2) toxicological or epidemiologic studies that compared effects of PM from different sources, PM components, or size fractions. In addition, we considered studies identified by public comments submitted to the docket of the proposed rule. Studies that met these criteria were evaluated by EPA staff and their key findings were summarized. This preliminary assessment was then developed to place those new studies of potentially greatest relevance in the context of the findings of the 2009 PM ISA including a judgment as to whether the new studies materially change the major conclusions of the 2009 PM ISA. The provisional assessment presented here does not attempt to critically review individual studies or to provide the kind of full integration found in a typical ISA.

[1] As stated in the PM NAAQS proposal: "The EPA is aware that a number of new scientific studies on the health effects of PM have been published since the mid-2009 cutoff date for inclusion in the Integrated Science Assessment. As in the last PM NAAQS review, the EPA intends to conduct a provisional review and assessment of any significant new studies published since the close of the Integrated Science Assessment, including studies that may be submitted during the public comment period on this proposed rule in order to ensure that, before making a final decision, the Administrator is fully aware of the new science that has developed since 2009. In this provisional assessment, the EPA will examine these new studies in light of the literature evaluated in the Integrated Science Assessment. This provisional assessment and a summary of the key conclusions will be placed in the rulemaking docket." (77 FR 38899)

The literature search and submissions from public commenters found that more than 1,500 studies have been published since the ISA closed on the health effects of particulate matter. Application of the selection criteria resulted in a list of over 100 studies that are summarized in the main body of this report. Additional details of the air quality distributions observed in these studies can be found in the annex to this report. The most significant studies are discussed in the assessment, and where feasible, quantitative results are compared to those from the 2009 PM ISA. A comprehensive list of studies identified as being potentially relevant through the survey effort, including those studies not discussed in detail in this report can be found here: http://hero.epa.gov/pm . Studies not discussed in detail include controlled human exposure studies, and toxicological studies that examined health effects attributed to specific PM size fractions, as well as studies that focused on ultrafine particles.

The overview in the main body of this report is organized into three main sections:

(2.1) Epidemiologic studies on effects associated with long-term exposure to PM, focusing on U.S. and Canadian studies with measurements of $PM_{2.5}$ or $PM_{10-2.5}$; (2.2) Epidemiologic studies on effects associated with short-term PM exposure, again focusing on U.S. and Canadian studies with measurements of $PM_{2.5}$ or $PM_{10-2.5}$; and (2.3) Toxicological and epidemiologic studies that have evaluated health effects with exposure to PM components and PM from different sources. This last section includes results of studies that assessed the effects of a range of PM sources or components, including those using source apportionment methods or comparing effects for numerous PM components, and not on studies of individual components. Most studies have focused on components or sources of $PM_{2.5}$, but information related to sources of $PM_{10-2.5}$ was also included to the extent available. Unless otherwise noted, the majority of new studies included in this assessment did not examine the robustness of single-pollutant results in copollutants models.

2. OVERVIEW OF RECENT HEALTH STUDIES RESULTS

As stated in the 2009 PM ISA, EPA integrated the scientific evidence from toxicological, controlled human exposure, and epidemiologic studies in combination with evidence from atmospheric chemistry and exposure assessment studies and developed causal determinations for health outcomes categories (e.g., respiratory effects, cardiovascular effects, mortality, etc.) for different exposure durations (i.e., short- or long-term) and PM size fractions. Causal judgments drawn for short- and long-term exposure to $PM_{2.5}$ and short-term exposure to $PM_{10-2.5}$ are included in Table 2.1.

Table 2-1 Causal Determinations for Short-and Long-term Exposure to $PM_{2.5}$

Long-term Exposure to $PM_{2.5}$		
Size Fraction	**Outcome**	**Causality Determination**
$PM_{2.5}$	Cardiovascular Effects	Causal
	Respiratory Effects	Likely to be causal
	Mortality	Causal
	Reproductive and Developmental	Suggestive
	Cancer, Mutagenicity, and Genotoxicity	Suggestive

Short-term Exposure to $PM_{2.5}$		
Size Fraction	**Outcome**	**Causality Determination**
$PM_{2.5}$	Cardiovascular Effects	Causal
	Respiratory Effects	Likely to be causal
	Mortality	Causal

Short-term Exposure to $PM_{10-2.5}$		
Size Fraction	**Outcome**	**Causality Determination**
$PM_{10-2.5}$	Cardiovascular Effects	Suggestive
	Respiratory Effects	Suggestive
	Mortality	Suggestive

The following sections of this document summarize the scientific evidence published since the completion of the 2009 PM ISA for each of the health outcome categories presented in Table 2.1.

2.1. Epidemiologic Studies of Long-Term Exposure

The majority of the epidemiologic evidence evaluated in the 2009 PM ISA (U.S. EPA, 2009) focused on health effects of $PM_{2.5}$ exposure, with very limited evidence for health effects of

long-term exposure to $PM_{10-2.5}$. These studies demonstrated consistent positive associations between long-term $PM_{2.5}$ exposures and a variety of health effects (Chapter 7, (U.S. EPA, 2009)).

Sections 2.1.1 - 2.1.4 highlight results from epidemiologic studies of mortality, cardiovascular effects, respiratory effects, and reproductive and developmental effects, respectively, published since the completion of the 2009 PM ISA (U.S. EPA, 2009) because these were the health outcomes specifically taken into consideration in developing the proposed rule (77 FR 38890). Tables A.1 through A.5 (Appendix A) summarize the recent epidemiologic studies that evaluated relationships between health effects and long-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$. The discussions below emphasize results of studies conducted in the U.S. and Canada.

2.1.1. Mortality

Long-term exposure to $PM_{2.5}$

Summary of 2009 PM ISA Conclusions

The 2009 PM ISA synthesized the epidemiologic literature characterizing the association between long-term exposure to $PM_{2.5}$ and increased risk of mortality and concluded that "a causal relationship exists between long-term exposure to $PM_{2.5}$ and mortality" (See Section 7.6 of the 2009 PM ISA). Long-term mean[2] $PM_{2.5}$ concentrations ranged from 13.2 to 32.0 $\mu g/m^3$ during the study periods in the areas in which these studies, comprising the entire body of evidence reviewed in the 2009 ISA, were conducted. When evaluating cause-specific mortality, the strongest evidence contributing to this causal determination was observed for associations between $PM_{2.5}$ and cardiovascular mortality. Positive associations were also reported between $PM_{2.5}$ and lung cancer mortality. Both the Harvard Six Cities (Laden et al., 2006; Dockery et al., 1993) and the American Cancer Society (ACS) (Krewski, 2009; Pope III et al., 2004; Pope et al., 2002) studies continued to provide strong evidence for the associations between long-term exposure to $PM_{2.5}$ and cardiopulmonary disease (CPD) and ischemic heart disease (IHD) mortality. Additional evidence from a study that used the Women's Health Initiative (WHI) cohort (Miller et al., 2007) found a particularly strong association between long-term exposure to $PM_{2.5}$ and cardiovascular disease (CVD) mortality in post-menopausal women.

Recent Mortality Studies

Since the completion of the 2009 PM ISA (U.S. EPA, 2009), a number of studies have been published that examined the association between long-term exposure to $PM_{2.5}$ and all-cause mortality (See Figure 2.1) and cause-specific mortality (See Figures 2.2 and 2.3), including updated results for both the Harvard Six Cities and ACS cohorts. Lepeule et al. (2012) extended the analysis of the Harvard Six Cities cohort using 11 additional years of follow-up and $PM_{2.5}$

[2] For long-term exposure studies, the long-term mean $PM_{2.5}$ concentration refers to the average $PM_{2.5}$ concentrations reported across the entire study duration, which could equate to the monthly or annual $PM_{2.5}$ concentration averaged over many years.

monitoring data and explored a variety of issues that might affect the size and timing of the mortality effect. Generally, the authors observed results similar to those reported by Laden et al. (2006) for all-cause and cardiovascular mortality, though the central estimate was slightly diminished and had slightly narrower confidence intervals (all-cause mortality: RR=1.14 [95% CI: 1.07, 1.22][3] for Lepeule et al. (2012) versus RR=1.16 [95% CI: 1.07, 1.26] for Laden et al. (2006); cardiovascular mortality: RR=1.26 [95% CI: 1.14, 1.40] for Lepeule et al. (2012) versus RR=1.28 [95% CI: 1.13, 1.44] for Laden et al.(2006). The authors applied both spline and linear models to investigate the concentration-response relationship, and observed that for all-cause mortality, the model fit was better without the spline, indicating a no threshold, linear relationship with $PM_{2.5}$ down to the lowest observed concentration (i.e., 8 µg/m^3). Jerrett et al. (2009a) reanalyzed data from the ACS cohort, including data from 86 metropolitan statistical areas (MSAs) across the U.S with monitoring data for $PM_{2.5}$. The authors observed an association between $PM_{2.5}$ and all-cause mortality in single pollutant models (RR 1.048 [95% CI: 1.024, 1.071]) that increased in magnitude in a copollutant model adjusting for ozone (O_3) concentration (RR 1.080 [95% CI: 1.048, 1.113]). The associations were stronger when limited to mortality due to cardiovascular disease (CPD mortality: RR 1.129 [95% CI: 1.094, 1.071]; CVD mortality: RR 1.150 [95% CI: 1.111, 1.191]; IHD mortality: RR 1.211 [95% CI: 1.156, 1.268]); these associations also became stronger in copollutant models adjusting for O_3 concentration. No statistically significant association was observed between $PM_{2.5}$ and respiratory mortality in this re-analysis of the ACS cohort. In another analysis among the ACS cohort, McKean-Cowdin et al. (2009) examined the association between long-term exposure to $PM_{2.5}$ and brain cancer mortality. The authors observed no associations with brain cancer mortality.

[3] All effect estimates for associations between long-term exposure to $PM_{2.5}$ and mortality are presented for a 10 µg/m^3 increase in $PM_{2.5}$ concentration.

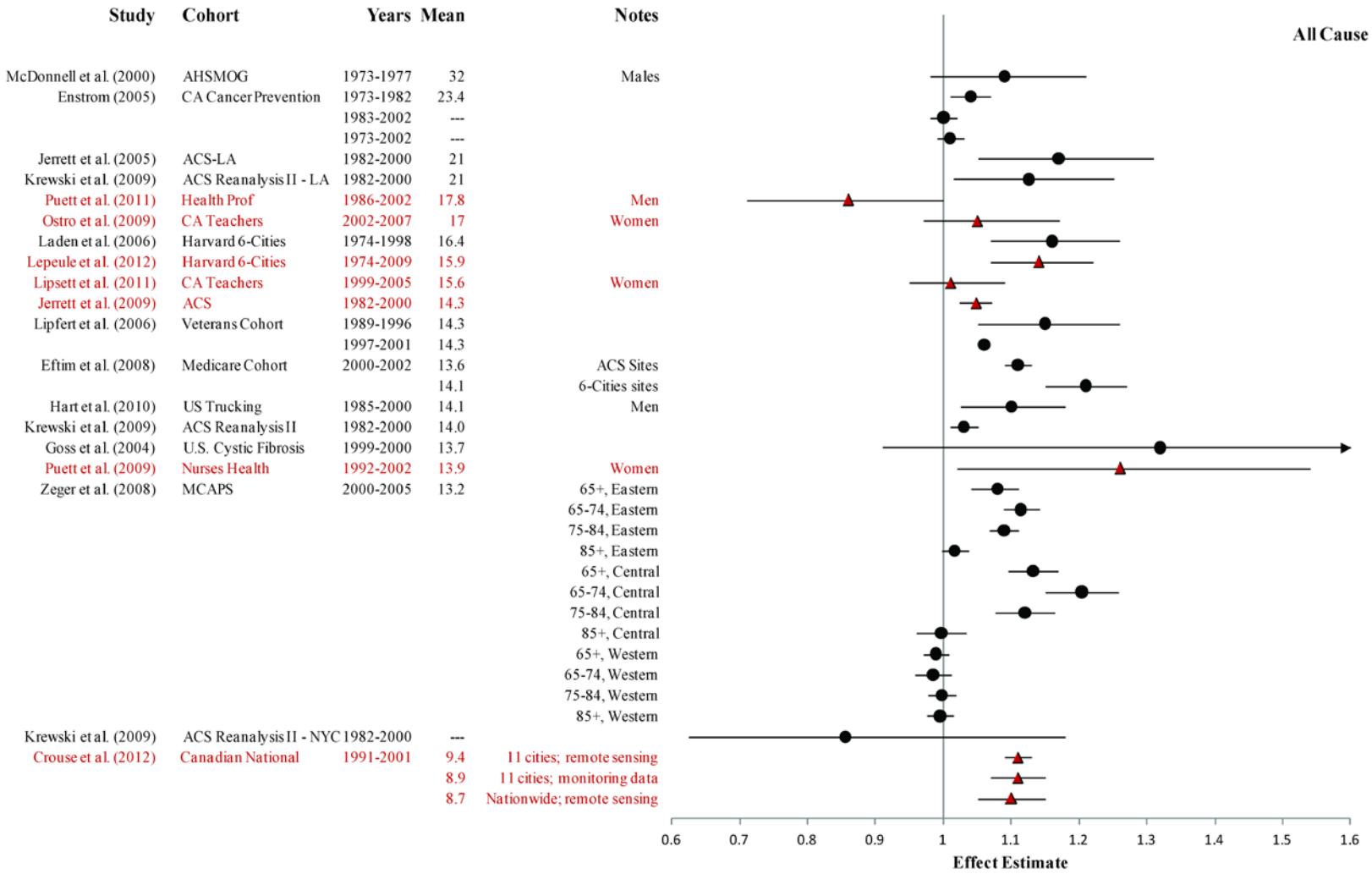
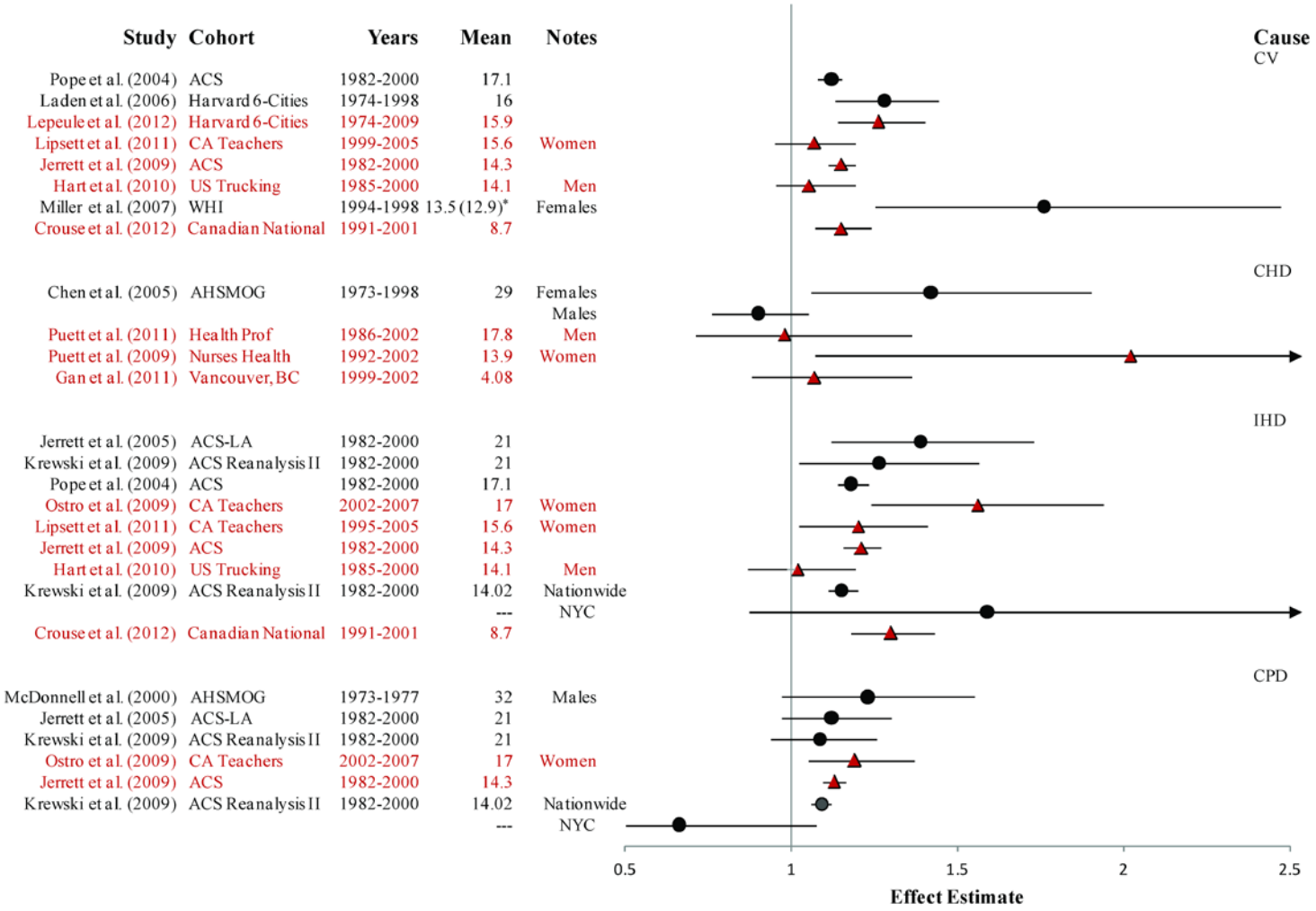


Figure 2.1 **All-cause mortality risk estimates, long-term exposure to $PM_{2.5}$ in recent cohort studies. Red text and triangles represent new studies published since the completion of the 2009 PM ISA.**



* Note: As discussed in Federal Register Notice of EPA's proposed rule on the PM NAAQS (77 FR at 38929 and 38934 n. 82). CV = cardiovascular disease, CHD = coronary heart disease, IHD = ischemic heart disease, CPD = cardiopulmonary disease.

Figure 2.2. Cardiovascular mortality risk estimates, long-term exposure to $PM_{2.5}$ in recent cohort studies. Red text and triangles represent new studies published since the completion of the 2009 PM ISA.

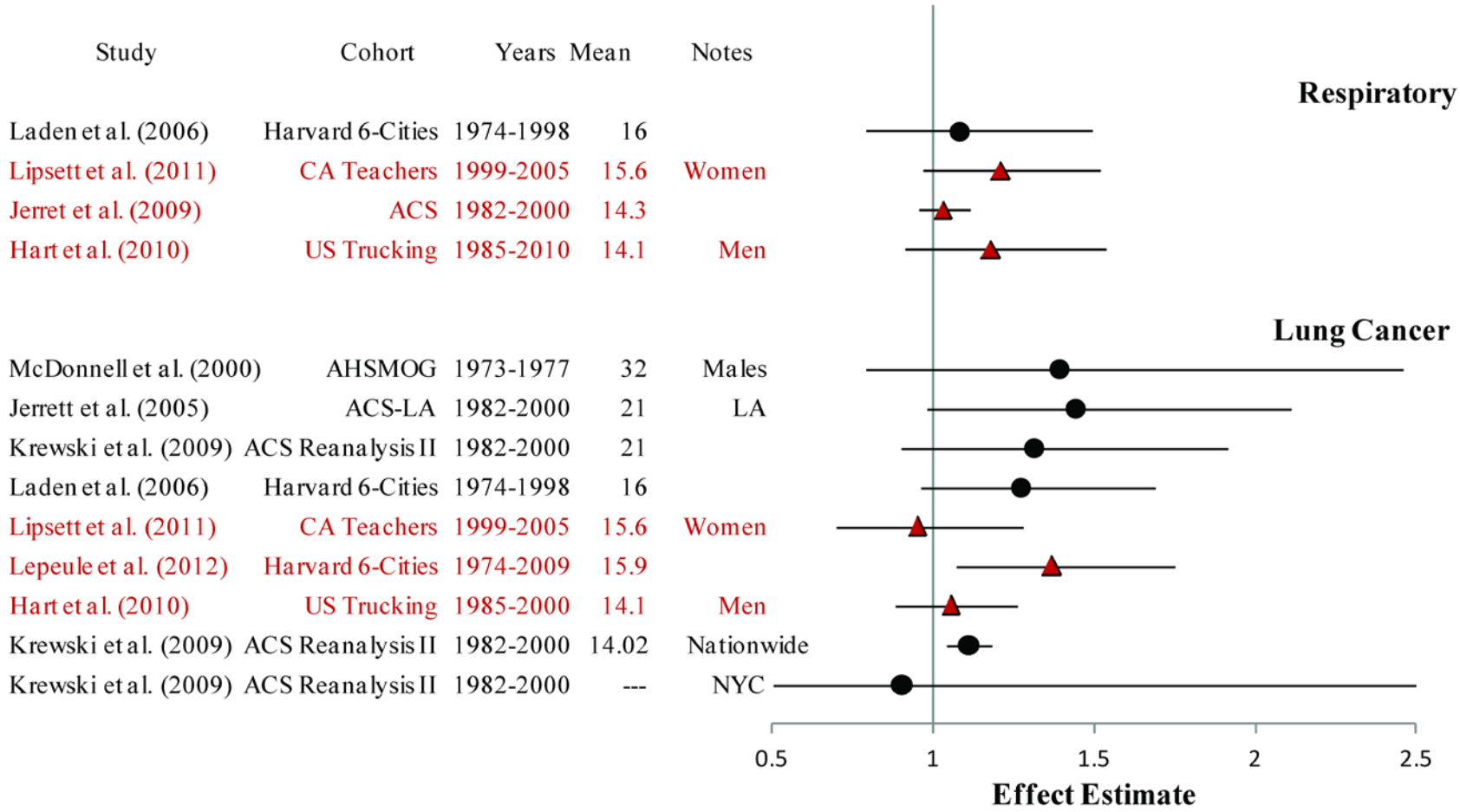


Figure 2.3 **Respiratory mortality risk estimates, long-term exposure to $PM_{2.5}$ in recent cohort studies. Red text and triangles represent new studies published since the completion of the 2009 PM ISA.**

In an update to a study by Janes et al. (2007), Greven et al. (2011) used data from a nationwide Medicare mortality cohort to develop a statistical approach for estimating the associations between monthly mean $PM_{2.5}$ concentrations averaged over the preceding 12 months and monthly mortality rates among subjects living within ZIP codes with a geographic centroid within a six mile radius of one of 814 monitoring stations from 2000 to 2006. The study authors decomposed the association between $PM_{2.5}$ and mortality into two components: (1) the association between the "national" trend in the monthly $PM_{2.5}$ concentrations averaged over the previous 12 months and the national average trend in monthly mortality rates (purely temporal association); and (2) the association between the "local" trend in the deviation in the community-specific trend from the national average trend of monthly averages of $PM_{2.5}$ and the deviation of the community-specific trends from the national average trend of mortality rates (residual spatio-temporal association). The authors posit that this second component provides evidence as to whether locations having steeper declines in $PM_{2.5}$ also have steeper declines in mortality relative to the national trend. The authors conclude that differences in effect estimates at these two spatiotemporal scales raise concerns about confounding bias in these analyses, with the association for the national trend more likely to be confounded than the association for the local trend. The authors observed no evidence for a "local" effect, but did observe evidence for a "national" effect. Similar to the study by Janes et al. (2007), Greven et al. (2011) eliminate all of the spatial variation in air pollution and mortality in their data set when estimating the "national" effect, focusing instead on sub-chronic (monthly) temporal differences in the data. As noted by the authors, this eliminates 90% of the variance in the data set used for these analyses that is attributable to spatial variability (Janes et al. (2007), Table 1). Only 5% of the variance in the data set used in these analyses is attributable to the space by time component, which was the focus of the papers by Janes et al. (2007) and Greven et al. (2011). Thus, while the results of the papers themselves provide evidence for an association between exposure to $PM_{2.5}$ and mortality, it is not possible to directly compare the results of these studies to the results of other cohort studies investigating the relationship between long-term exposure to $PM_{2.5}$ and mortality, which make use of spatial variability in air pollution and mortality data. As noted by Pope and Burnett (2007) and highlighted in the 2009 PM ISA (Section 7.6.1, (U.S. EPA, 2009)), the conclusions of Janes et al. (2007) "largely excludes the sources of variability that are exploited in those other [cohort] studies." These comments are also applicable to the study by Greven et al. (2011).

Crouse et al. (2012) conducted a nationwide study of the relationship between long-term exposure and $PM_{2.5}$ in Canada and provide new evidence for a positive association at relatively low concentrations of $PM_{2.5}$. The authors investigated the association between long-term exposure to ambient $PM_{2.5}$ and non-accidental mortality. The level of ambient $PM_{2.5}$ to which the study population was exposed was estimated from satellite observations and assigned to the cohort of 2.1 million Canadian adults that completed detailed census data in 1991. The study included deaths between 1991 and 2001. The authors observed a hazard ratio (HR) of 1.15 (95% CI: 1.13, 1.16) for non-accidental mortality. Using spatial random-effects models, the HR was slightly diminished (1.10 [95% CI: 1.05, 1.15]). The strongest association was observed for

deaths due to ischemic heart disease (HR: 1.31 [95% CI: 1.27, 1.35]). Using spatial random-effects models did not substantially change the association (HR: 1.30 [95% CI: 1.18, 1.43]). The associations between $PM_{2.5}$ and deaths due to CVD and circulatory diseases were similar in magnitude to that observed for non-accidental mortality. There was a weaker association with mortality due to cerebrovascular disease (CBD) (HR: 1.04 [95%CI; 0.99, 1.10]). Sensitivity analyses including 11 Canadian cities with ground-based $PM_{2.5}$ measurements produced similar associations to those observed in the full cohort that utilized satellite observations to estimate $PM_{2.5}$ exposure (See Figure 2.1).

A number of studies have looked at the association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality among different occupational cohorts. Hart et al. (2010) examined the association between residential exposure to $PM_{2.5}$ and mortality among men in the U.S. trucking industry. The authors observed a 10% (95% CI: 2.5, 18) increase in all-cause mortality. This association was stronger when the cohort was restricted to truck drivers that maintained local routes, and long haul drivers were excluded (15% increase [95% CI: 5.0, 26.6] for all-cause mortality; 59.7% increase [95% CI: 18.7, 114.9%] for respiratory mortality). The associations for other causes of death (i.e., lung cancer, CVD, IHD, chronic obstructive pulmonary disease [COPD]) were generally positive, but were not statistically significant. Puett et al. (2009) examined the relationship of long-term $PM_{2.5}$ exposures with all-cause mortality among women from the Nurses' Health Study. The authors found an increased risk of all-cause mortality (HR 1.26 [95% CI: 1.02, 1.54]) and coronary heart disease (CHD) mortality (HR 2.02, 95% CI: 1.07, 3.78) associated with long-term exposure to $PM_{2.5.}$ More recently, Puett et al. (2011) used the same spatiotemporal exposure estimation models to characterize the association between long-term exposure to $PM_{2.5}$ and mortality among male subjects in the Health Professionals Follow-up Study. In this cohort, long-term exposure to $PM_{2.5}$ was not associated with all-cause or CHD mortality. Ostro et al. (2010) examined the association between long-term exposures to $PM_{2.5}$ and all-cause, CPD, IHD and pulmonary disease mortality among the subjects from the California Teachers Study. No associations were observed between all-cause mortality and $PM_{2.5}$. There was a positive association between long-term exposure to $PM_{2.5}$ and CPD mortality (HR: 1.19 [95% CI: 1.05, 1.37]) and IHD mortality (HR: 1.56 [95% CI: 1.24, 1.94]). In a follow-up study, Lipsett et al. (2011) examined the associations between long-term exposure to $PM_{2.5}$ and all-cause and cause-specific mortality among the subjects in the California Teachers Study. The authors did not observe an association between long-term exposure to $PM_{2.5}$ and all-cause mortality in this cohort, but observed an association with IHD mortality (HR 1.20 [95% CI: 1.02, 1.41]). They also observed positive associations for respiratory mortality and CBD mortality, though these associations were not statistically significant.

In a single-city study conducted in Toronto, Ontario, Canada, Jerrett et al (2009b) examined the association between long-term exposure to $PM_{2.5}$ and all-cause mortality among subjects from a respiratory clinic. The authors observed positive, though not statistically significant associations with all-cause, circulatory or respiratory mortality. A limited number of deaths in the cohort and low variability in $PM_{2.5}$ concentrations (limiting the exposure contrast) led the authors to

conclude that "no definitive conclusions [could] be drawn about these associations with $PM_{2.5}$". In a single-city study conducted in Vancouver, British Columbia, Canada, Gan et al. (2011) conducted a population-based cohort study to evaluate the association between traffic-related pollutants and risk of mortality due to CHD. Land-use regression models were used to estimate exposure over a 5 year period (1994-1998) and the cohort was followed up for 4 years (1999-2002). Exposure to $PM_{2.5}$ was weakly associated with CHD mortality.

Recent studies that examined the association between long-term $PM_{2.5}$ exposure and mortality further support the conclusions of the 2009 PM ISA. The strongest evidence for mortality was from the Harvard Six Cities (Laden et al., 2006; Dockery et al., 1993) and American Cancer Society cohorts (Krewski, 2009; Pope III et al., 2004; Pope et al., 2002), which was supported by a number of other cohort studies. Updated results from the Harvard Six Cities (Lepeule et al., 2012) and American Cancer Society (Jerrett et al., 2009a) cohorts support the findings of the 2009 PM ISA, while a new Canadian multicity study (Crouse et al., 2012) observed associations below those reported in the PM ISA (i.e., < 10 $\mu g/m^3$). In the 2009 PM ISA, for cause-specific mortality, the strongest evidence was for cardiovascular-related mortality, particularly among post-menopausal women (Miller et al., 2007). Respiratory-related mortality was also observed, particularly for lung cancer mortality (Naess et al., 2007). Recent studies provide more evidence for strong associations with cardiovascular-related mortality among women (Lipsett et al., 2011; Puett et al., 2009) and additional evidence for respiratory mortality including lung cancer mortality (Lepeule et al., 2012).

Long-term exposure to $PM_{10-2.5}$

Summary of 2009 PM ISA Conclusions

The 2009 PM ISA synthesized the epidemiologic literature characterizing the association between long-term exposure to $PM_{10-2.5}$ and increased risk of mortality and concluded that the evidence was too limited to adequately characterize the associations for $PM_{10-2.5}$. The findings from the AHSMOG (Chen et al., 2005) and Veterans (Lipfert et al., 2006) cohort studies provided limited evidence for associations between long-term exposure to $PM_{10-2.5}$ and mortality in areas with mean concentrations in the range of 16 to 25 $\mu g/m^3$. Overall, the evidence was determined to be inadequate to determine if a causal relationship exists between long-term exposure to $PM_{10-2.5}$ and mortality (See Section 7.6 of the 2009 PM ISA). Recent studies published since the completion of the 2009 PM ISA are characterized in Table A.1.

Recent Mortality Studies

Since the completion of the 2009 PM ISA, Puett et al. (2009) examined the relationship of long-term exposure to $PM_{10-2.5}$ with all-cause and CHD mortality among women from the Nurses' Health Study. The authors did not find an association between $PM_{10-2.5}$ and the risk of all-cause mortality (HR 1.03 [95% CI: 0.89, 1.18]). The association between $PM_{10-2.5}$ and CHD mortality was positive, but not statistically significant (HR: 1.14 [95% CI: 0.73, 1.77]). More recently,

Puett et al. (2011) used the same spatiotemporal exposure estimation models to characterize the association between $PM_{10-2.5}$ and mortality among male subjects in the Health Professionals Follow-up Study. In this cohort, long-term exposure to $PM_{10-2.5}$ was not associated with all-cause or CHD mortality.

In summary, two new studies (Puett et al., 2011; Puett et al., 2009) evaluated the association between long-term exposure to $PM_{10-2.5}$ and mortality. The long-term mean $PM_{10-2.5}$ concentrations reported in these studies were lower than those reported in the 2009 PM ISA (7.7 and 10.1µg/m^3, respectively). These studies do not provide any additional evidence for an association between long-term exposure to $PM_{10-2.5}$ and mortality that would be sufficient to materially change conclusions made in the 2009 PM ISA.

2.1.2. Morbidity – Cardiovascular Effects

Summary of 2009 PM ISA Conclusions

The 2009 PM ISA concluded that "the evidence from epidemiologic and toxicological studies is sufficient to conclude that a causal relationship exists between long-term exposures to $PM_{2.5}$ and cardiovascular effects." The strongest evidence was provided by large, multicity, U.S.-based studies of cardiovascular mortality (See Section 7.2.10 of the 2009 PM ISA) with supporting evidence from a U.S.-based epidemiologic study (Miller et al. (2007)) that reported associations between $PM_{2.5}$ and incident stroke and myocardial infarction (MI) among post-menopausal women at mean $PM_{2.5}$ concentrations of 13.5 µg/m^3.[4]

Recent Cardiovascular Morbidity Studies

Several new studies of long-term exposure to $PM_{2.5}$ and cardiovascular disease were conducted since the completion of the 2009 PM ISA. In a study of male subjects enrolled in the Health Professionals Follow-Up Study, Puett et al. (2011) used spatiotemporal models to estimate exposure to $PM_{2.5}$ by combining data from available air monitoring networks with geographic information system (GIS) derived variables such as distance to roadway and elevation. The authors reported no association between long-term $PM_{2.5}$ and total CVD or ischemic stroke; however, in fully adjusted models (i.e. adjusted for covariates including body mass index (BMI), hypertension, hypercholesterolemia, diabetes, family history of MI, smoking physical activity, diet) elevated HRs for non-fatal MI and hemorrhagic stroke were observed (HR: 1.16 [95% CI: 0.81, 1.64] and 1.69 [95%CI: 0.59, 3.71])[5]. Associations of $PM_{2.5}$ with all-cause mortality and fatal CHD were not observed in this all male cohort. A cross-sectional study of male and female patients attending a pulmonary clinic after reporting respiratory complaints reported no associations of long-term $PM_{2.5}$ exposure with prevalent IHD, although an association with

[4] Listed as 12.9 µg/m^3 for the reasons stated in Federal Register Notice of EPA's proposed rule on the PM NAAQS (77 FR 38934 n. 82).
[5] All effect estimates for associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity are presented for a 10 µg/m^3 increase in $PM_{2.5}$ concentration.

nitrogen dioxide (NO_2) was reported (Beckerman et al., 2012). Interactions among exposures, risk factors and potential confounders were tested and no statistically significant effect modifiers were identified. A study using satellite derived aerosol optical depth (AOD) measurements to predict $PM_{2.5}$ concentrations, reported a 3.12% (95% CI: 0.30, 4.29) increase in cardiovascular hospital admission among older adults for an increase in long-term $PM_{2.5}$ exposure (Kloog et al., 2012a). A similar increase in risk was reported for stroke hospital admissions (3.49 [95% CI: 0.09, 5.18]).

The stronger evidence linking long-term $PM_{2.5}$ exposure with cardiovascular disease was apparent in studies of women as originally demonstrated in the 2009 PM ISA. In a study of female teachers residing in California, Lipsett et al. (2011) used concentration data from 1999-2000 and applied inverse distance weighted interpolation techniques to develop monthly $PM_{2.5}$ concentration surfaces from ambient monitor data. This study reported an increased risk for incident stroke (HR: 1.15 95% CI 1.00-1.33), which was highest among post-menopausal women, but no association between $PM_{2.5}$ and incident MI (HR: 0.99 95% CI 0.84-1.15). This study supports the findings of Miller et al. (2007) linking incident stroke to long-term $PM_{2.5}$ exposure among post-menopausal women; however, they also reported an association with incident MI. Coogan et al. (2012) followed African American women who ranged in age from 21 to 69 years at enrollment in the Black Women's Health Study for 10 years to investigate incident hypertension and diabetes in association with long-term exposure to $PM_{2.5}$. $PM_{2.5}$ concentrations were spatially interpolated using monitoring data from state and local stations in the Los Angeles basin for the year 2000. This study reported an increased risk of incident hypertension (IRR: 1.48 95%CI: 0.95-2.31) . This risk was attenuated, but remained positive in a copollutant model containing NO_2 (IRR: 1.32 95%CI: 0.84-2.05).

Several studies have been published from the Multi-Ethnic Study of Atherosclerosis (MESA) that was designed to inform on mechanistic pathways by which $PM_{2.5}$ exposure may act on the cardiovascular system. Long-term $PM_{2.5}$ exposure was associated with increased prevalent QT prolongation (OR: 1.6 95% CI: 1.2-2.2) and intraventricular conduction delay (OR: 1.7 95% CI 1.0-2.6) (Van Hee et al., 2011). In addition, both long- and short-term $PM_{2.5}$ exposure was associated with a narrowing of retinal vessel diameter (Adar et al., 2010). Reductions in flow-mediated dilation have been observed in association with short-term exposures to $PM_{2.5}$ (See Section 6.2.4 of the PM ISA); however, O'Neill et al. (2011) found no association of long-term $PM_{2.5}$ exposure with chronic arterial stiffness.

Generally, the results of recent studies are consistent with the evidence for an association between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity characterized in the 2009 PM ISA. Findings on incident stroke reported by Miller et al (2007) in a cohort of post-menopausal women are supported by a new study of female teachers (Lipsett et al., 2011), while a recent study of black women reports an association between $PM_{2.5}$ and incident hypertension (Coogan et al., 2012) at long-term mean $PM_{2.5}$ concentrations ranging from 15.6 – 21.5 $\mu g/m^3$ (Table A.3).

2.1.3. Morbidity – Respiratory Effects

Summary of 2009 PM ISA Conclusions

The epidemiologic evidence reviewed in the 2009 PM ISA demonstrated associations between long-term exposure to $PM_{2.5}$ and decrements in lung function growth, increased respiratory symptoms, and asthma development in study locations with mean $PM_{2.5}$ concentrations ranging from 13.8 to 30 $\mu g/m^3$ during the study periods (See Sections 7.3.1.1 and 7.3.2.1 of the 2009 PM ISA). These studies contributed to a body of evidence that was sufficient to conclude that "a causal relationship is likely to exist between long-term exposures to $PM_{2.5}$ and respiratory effects."

Recent Respiratory Morbidity Studies

Since the completion of the 2009 PM ISA, a number of studies have been published that examine the association between long-term exposure to $PM_{2.5}$ and respiratory outcomes (Table A.4). These recent studies are consistent with the associations observed for respiratory outcomes reported in the 2009 PM ISA and provide additional evidence for associations between long-term exposure to $PM_{2.5}$ and respiratory symptoms and asthma development. For example, in a recent prospective community intervention study in Libby, MT (Noonan et al., 2012) ambient $PM_{2.5}$ concentrations decreased by 26.7% over four winters following the replacement of over 1,100 wood stoves in the community with new lower emission wood stoves or other heating sources. This decrease in $PM_{2.5}$ concentrations was associated with decreases in reported wheeze and respiratory infections (including colds, bronchitis, influenza and throat infection) among school children. These results suggest that beneficial health impacts are associated with decreases in ambient $PM_{2.5}$ concentrations.

A number of other studies evaluated the association between long-term exposure to $PM_{2.5}$ and respiratory symptoms. Several nationwide U.S. studies that used data from the National Health Interview Survey reported associations between long-term exposure to $PM_{2.5}$ and respiratory symptoms among children (including respiratory allergy/hay fever (Parker et al., 2009), and respiratory allergy and frequent ear infections (Bhattacharyya and Shapiro, 2010) and adults (including asthma among African-Americans (Nachman and Parker, 2012); sinusitis (Nachman and Parker, 2012; Bhattacharyya, 2009); and hay fever (Bhattacharyya, 2009). Meng et al. (2010) examined long-term exposure to $PM_{2.5}$ in the San Joaquin Valley of California and weekly asthma symptoms among participants with physician-diagnosed asthma. They observed associations between annual average concentrations of $PM_{2.5}$ and frequent asthma symptoms. In a study conducted in New York City, Patel et al. (2009) examined long-term exposure to $PM_{2.5}$ and respiratory symptoms in children through 24 months of age. Long-term exposure to $PM_{2.5}$ was not associated with wheeze or cough in this study, though several $PM_{2.5}$ constituents were associated with wheeze and/or cough (see Section 2.4.2 for results on $PM_{2.5}$ constituents).

A substantial body of evidence exists that has evaluated short-term exposure to $PM_{2.5}$ and emergency department visits and hospitalizations for respiratory causes (See Section 2.2.2.1).

Several recent studies have evaluated the association between long-term exposure to $PM_{2.5}$ and respiratory hospitalizations. Karr et al. (2009a; 2009b) examined exposure to $PM_{2.5}$ averaged over an infant's lifetime (0-12 months) and did not observe an association between $PM_{2.5}$ and bronchiolitis hospitalizations in the Puget Sound Region of Washington (Karr et al., 2009a) or in the Georgia Air Basin of British Columbia, Canada (Karr et al., 2009b). Kloog et al. (2012a) investigated hospital admissions for all respiratory causes among residents of New England 65 years of age and older. The authors observed a 4.22% (95% CI 1.06, 4.75)[6] increase in respiratory hospital admissions associated with long-term $PM_{2.5}$ concentrations. Similarly, Neupane et al. (2010) restricted their analyses of pneumonia hospitalizations to those 65 years of age and older and found that long-term exposure to $PM_{2.5}$ was associated with hospitalization for community-acquired pneumonia (OR 13.64, 95% CI: 1.79, 101.01). Meng et al. (2010) examined long-term exposure to $PM_{2.5}$ in the San Joaquin Valley of California and asthma-related emergency department visits or hospitalizations (analyzed together) among participants with physician-diagnosed asthma. They observed associations between annual average concentrations of $PM_{2.5}$ and emergency department visits and hospitalizations.

The 2009 PM ISA identified a number of prospective cohort studies that provided evidence of an association between long-term exposure to $PM_{2.5}$ and the development of asthma. Recent studies contribute to this weight of evidence, reporting results that are consistent with those summarized in the 2009 PM ISA. Akinbami et al. (2010) conducted a nationwide U.S. study with data on children (ages 3-17 years) from the National Health Interview Survey and observed a positive association between county-wide annual average $PM_{2.5}$ concentration and current asthma (OR 1.43, 95% CI: 0.98, 2.10 comparing highest quartile of exposure to lowest) and/or a recent asthma attack (OR 1.30, 95% CI: 0.89, 1.90 comparing highest quartile of exposure to lowest). Two studies examining the relationship between long-term exposure to $PM_{2.5}$ and incident asthma were conducted in British Columbia, Canada. Carlsten et al. (2011) evaluated birth year exposure to $PM_{2.5}$ and physician-diagnosed asthma at age 7 and observed an association with an increased risk of incident asthma. Similarly, Clark et al. (2010) assigned exposure based on average $PM_{2.5}$ concentration during the first week of life and the association with incident asthma between ages 3 and 4. The authors did not observe an association between $PM_{2.5}$ and incident asthma. McConnell et al. (2010) characterized the relationship between childhood incident asthma and long-term exposure to $PM_{2.5}$ among the Southern California Children's Health Study participants. In this cohort, asthma-free kindergarten and first-grade children were followed up for three years and the authors observed a positive association (HR 1.34, 95% CI: 0.95, 1.90), though this association was diminished when the authors adjusted for traffic related pollution concentrations measured near the child's home and school.

[6] All effect estimates for associations between long-term exposure to $PM_{2.5}$ and respiratory morbidity are presented for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration.

In summary, the results of recent studies generally continue to demonstrate an association between long-term exposure to $PM_{2.5}$ and respiratory morbidity. Recent epidemiologic studies reported associations with respiratory symptoms and respiratory hospitalizations. New findings on incident asthma among children are consistently positive, though not statistically significant. These recent studies demonstrate associations at long-term mean $PM_{2.5}$ concentrations ranging from 9.7 to 27 $\mu g/m^3$ (Table A.4).

2.1.4. Morbidity – Reproductive and Developmental Effects

Summary of 2009 PM ISA Conclusions

The 2009 PM ISA synthesized the epidemiologic literature characterizing the association between long-term exposure to $PM_{2.5}$ and increased risk of reproductive and developmental effects and concluded that the evidence was suggestive of a causal relationship between long-term exposure to $PM_{2.5}$ and reproductive and developmental outcomes (See Section 7.4 of the 2009 PM ISA). The strongest evidence was for reduced birth weight and infant mortality, especially due to respiratory causes during the post-neonatal period. The mean $PM_{2.5}$ concentrations during the study periods ranged from 5.3 – 27.4 $\mu g/m^3$, with effects becoming more precise and consistently positive in locations with mean $PM_{2.5}$ concentrations of 15 $\mu g/m^3$ and above. The epidemiologic literature did not consistently report associations between long-term exposure to $PM_{2.5}$ and preterm birth, growth restriction, birth defects or decreased sperm quality.

Recent Reproductive and Developmental Outcome Studies

Since the completion of the 2009 PM ISA, a number of studies have been published that examine the association between long-term exposure to $PM_{2.5}$ and reproductive and developmental outcomes (Table A.5). These recent studies are consistent with the associations observed for reproductive and developmental outcomes reported in the 2009 PM ISA, within similar concentrations (long-term mean $PM_{2.5}$ concentrations ranging from 11.0 – 19.8 $\mu g/m^3$), and provide additional evidence for associations between long-term exposure to $PM_{2.5}$ and reduced birth weight (Ghosh et al., 2012; Kloog et al., 2012b; Kumar, 2012; Darrow et al., 2011b; Bell et al., 2010; Morello-Frosch et al., 2010; Salihu et al., In Press). Recent evidence remains inconsistent for the association between exposure to $PM_{2.5}$ and preterm birth, with some studies providing evidence for an association (Chang et al., 2012b; Wu et al., 2009), while others did not (Rudra et al., 2011; Darrow et al., 2009).

2.2. Epidemiologic Studies of Short-Term Exposure

The 2009 PM ISA included the results of many new epidemiologic studies reporting associations between short-term exposure to PM and a range of health outcomes. The epidemiologic evidence evaluated in the ISA contributed to the determination that there is sufficient evidence to conclude that "a causal relationship exists" between short-term $PM_{2.5}$ exposure and cardiovascular effects

and mortality, and a "likely to be causal relationship exists" between short-term $PM_{2.5}$ exposure and respiratory effects (Chapter 2, 2009 PM ISA). Additionally, the epidemiologic evidence contributed to a "suggestive" causal determination for short-term $PM_{10-2.5}$ exposure and cardiovascular and respiratory effects, and mortality (Chapter 2, 2009 PM ISA).

Sections 2.2.1 and 2.2.2 highlight results from recent epidemiologic studies. Tables A.6 through A.11 (Appendix A) summarize results of recent epidemiologic studies that evaluated relationships between health effects and short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$.

The 2009 PM ISA included a particular focus on results of multicity studies due to their evaluation of a wide range of PM exposures and large numbers of observations, which lead to generally more precise effects estimates than most smaller scale studies of single cities. The multicity studies also allowed investigation of homogeneity or heterogeneity of PM health relationships, evaluation of confounding by co-pollutants across communities with different air pollution mixtures, and assessment of potential effect modifiers. Since the completion of the 2009 PM ISA, numerous multicity analyses have been published that evaluate morbidity outcomes.

2.2.1. Mortality

Summary of 2009 PM ISA Conclusions

Overall, in the evaluation of multi- and single-city studies in the 2009 PM ISA and in the 2004 PM Air Quality Criteria Document (AQCD) (U.S. EPA, 2004) consistent positive associations were observed at mean 24-h average[7] $PM_{2.5}$ concentrations above 12.8 $\mu g/m^3$. This collective evidence contributed to the conclusion that "a causal relationship exists between short-term $PM_{2.5}$ exposure and mortality." Building on the evidence presented in the 2004 PM AQCD (U.S. EPA, 2004), multi- and single-city studies evaluated in the 2009 PM ISA reported consistent positive associations between short-term $PM_{10-2.5}$ exposure and mortality (Section 6.5.2.3, 2009 PM ISA).

Recent Mortality Studies

Several recent studies evaluated the effects of short-term exposure to $PM_{2.5}$ on mortality in single city analyses. No new multi-city studies have been published. Additionally, no new studies have been published that examined associations between short-term $PM_{10-2.5}$ exposure and mortality in the U.S. or Canada.

New studies have continued to report associations between $PM_{2.5}$ and mortality that are consistent with the conclusions of the 2009 PM ISA as shown in Figure 2.4. Two of these studies were conducted in New York City. Ito et al. (2011a) examined the relationship between short-term exposure to $PM_{2.5}$ and PM components and cardiovascular disease (CVD) mortality for the

[7] For short-term exposure studies the mean 24-h avg $PM_{2.5}$ concentration refers to the mean of all daily 24-h avg PM2.5 concentrations over the course of the study duration.

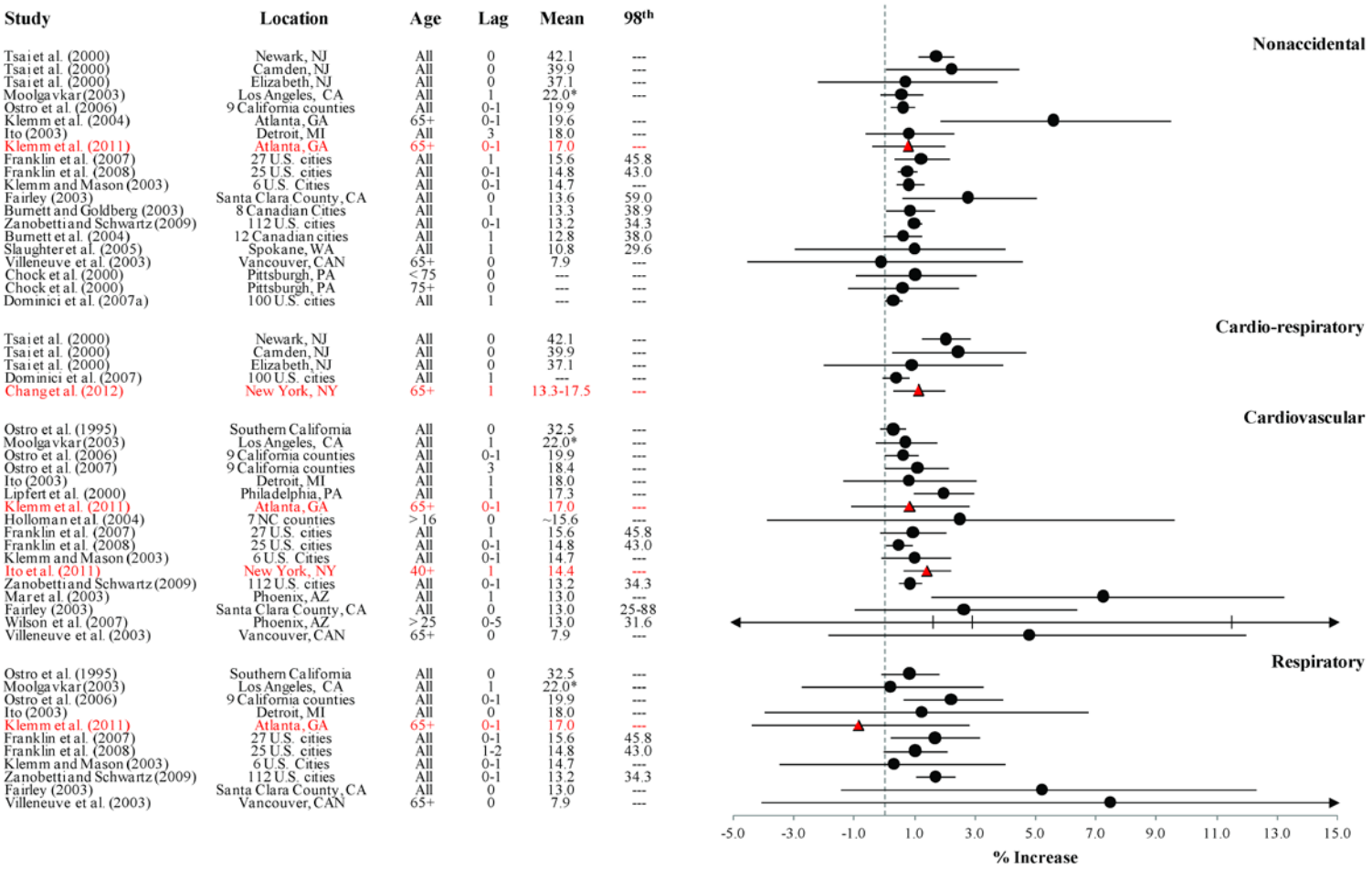
population ≥ 40 years old in New York City for the years 2000-2006. $PM_{2.5}$ was associated with CVD mortality at lag 1 in the all-year and cold season (October-March) analyses, but the strongest association with CVD mortality was observed during the warm season (April-September) at lag 0 and 1. Also in New York City, Chang et al. (2012a) used a novel approach to examine the relationship between short-term exposure to $PM_{2.5}$ concentrations and cardiorespiratory mortality. The authors used a spatio-temporal deterministic model that was bias-corrected with monitoring data to predict daily $PM_{2.5}$ concentrations. The authors developed a statistical model to consider personal exposure to $PM_{2.5}$ from outdoor sources to improve exposure assessment. Using data from 2001-2005, positive associations were observed for those greater than 65 years old. The model that accounted for personal exposure found a higher risk of mortality (2.32% [95% CI: 0.68, 3.94] at lag 1)[8] compared to a model that used only $PM_{2.5}$ concentrations (1.13% [95% CI: 0.27, 2.00]) suggesting that risk estimates derived using ambient concentrations as a proxy for exposure are biased towards the null.

Additional single-city analyses were conducted in Seattle, Detroit, and Atlanta. Zhou et al. (2011) conducted a study using daily $PM_{2.5}$ data collected in Seattle and Detroit to examine the effect of short-term $PM_{2.5}$ exposure on all-cause, cardiovascular, and respiratory mortality for the years 2002-2004. In a distributed lag model of 0-2 days, a strong association was observed between $PM_{2.5}$ and all-cause and cardiovascular mortality, with some evidence of an association with respiratory mortality in Detroit during the warm season (April-September) (quantitative results not presented). There was no evidence of an association with $PM_{2.5}$ and any mortality outcome in Seattle in the warm season. In the cold season (October-March), the strongest associations were for all-cause and cardiovascular mortality in Seattle, while there was no evidence of an association between $PM_{2.5}$ and any mortality outcome in Detroit. Interestingly the magnitude of the cardiovascular mortality association in Seattle in the cold season is larger than that in Detroit in the warm season even though mean $PM_{2.5}$ concentrations are lower, 11.4 $\mu g/m^3$ and 14.9 $\mu g/m^3$, respectively. Klemm et al. (2011) conducted an extended analysis of two previously published studies (Klemm et al., 2004; Klemm and Mason, 2000) that examined the effect of air pollution on mortality in Atlanta, GA. This analysis included an additional 7.5 years of data and expanded the study location to include two additional counties. Focusing on deaths in individuals 65 years of age and older, the authors found a positive association between short-term $PM_{2.5}$ exposure and nonaccidental (0.78% [95% CI: -0.43, 2.0]; lag 0-1 for a 10 $\mu g/m^3$ increase in 24-h avg $PM_{2.5}$ concentrations) and cardiovascular mortality (0.83% [95% CI: -1.1, 2.8]), but no evidence of an association with respiratory mortality (-0.86% [95% CI: -4.4, 2.8]).

In summary, multi- and single-city studies evaluated in the 2009 PM ISA provided evidence of consistent positive associations between short-term $PM_{2.5}$ exposure and nonaccidental, cardiovascular, and respiratory mortality. Relatively few mortality studies have been published in the U.S. and Canada since the completion of the 2009 PM ISA and they are limited to single-

[8] All effect estimates for associations between short-term exposure to $PM_{2.5}$ and mortality are presented for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration.

city studies. These studies continue to demonstrate evidence of positive associations between short-term $PM_{2.5}$ exposures and mortality in the same range of concentrations as those studies included in the 2009 PM ISA (i.e., mean 24-h avg concentrations of 12.8 $\mu g/m^3$ and above in the multi-city studies).



Note: Results presented from single-pollutant models for purposes of comparing results across studies that included different mixes of copollutants.

Figure 2.4 Percent increase in non-accidental and cause-specific mortality for a 10 μg/m^3 increase in 24-h average $PM_{2.5}$ concentrations in single-pollutant models from U.S. and Canadian studies. Red text and triangles represent recent studies published since the completion of the 2009 PM ISA.

2.2.2. Morbidity

2.2.2.1. Associations between Short-Term Exposures to PM and Respiratory Morbidity

Summary of 2009 PM ISA Conclusions

The association between short-term $PM_{2.5}$ exposure and respiratory-related emergency department (ED) visits, hospital admissions, and physician visits was evaluated in Section 6.3.8 of the 2009 PM ISA (U.S. EPA, 2009). The numerous multi- and single-city studies evaluated reported consistent positive associations with respiratory ED visits and hospital admissions for COPD, asthma, and respiratory infection in study areas with mean 24-h average $PM_{2.5}$ concentrations ranging from 6.1 – 22 $\mu g/m^3$. However, associations for asthma were imprecise and not consistently positive when limiting analyses to children. The evidence from respiratory-related emergency department (ED) visits, hospital admissions, and physician visits studies contributed to the conclusion that a "causal relationship is likely to exist between short-term exposures to $PM_{2.5}$ and respiratory effects."

Additional epidemiologic studies evaluated in the 2009 PM ISA examined associations between short-term $PM_{10-2.5}$ exposure and respiratory hospital admissions and ED visits. This limited number of studies demonstrated consistent positive associations with respiratory-related hospital admissions and ED visits with the strongest evidence in children. The evidence from these studies in combination with the evidence from toxicological and controlled human exposure studies led to the conclusion that the collective evidence across disciplines "is suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and respiratory effects."

Recent Respiratory Hospital Admission Studies

Within this section, respiratory-related hospital admissions and ED visit studies are discussed separately. This is because ED visits for respiratory-related outcomes often represent less serious, but more common health effects. Additionally, only a small percentage of respiratory-related ED visits result in a hospital admission. Therefore, it is important to discuss the evidence for each respiratory-related health outcome separately.

Respiratory-related Hospital Admissions

A number of studies published since the completion of the 2009 PM ISA conducted multicity or multi-location analyses to examine the association between short-term $PM_{2.5}$ exposures and respiratory hospital admissions. Figure 2.5 summarizes the evidence from single-pollutant models from studies evaluated in the 2009 PM ISA as well as recent studies published since its completion. Bell et al. (2012) represented a consolidated and more detailed account of a number of previous publications, of which most were discussed in the 2009 PM ISA (Bell et al., 2009a; Bell et al., 2009b; Bell et al., 2008; Bell et al., 2007). In an all-year analysis of 187 U.S. counties,

short-term exposure to $PM_{2.5}$ was positively associated with respiratory hospital admissions in individuals 65 years of age and older across lags of 0 to 2 days, with the strongest association at lag 2 (0.41% [95% CI: 0.09, 0.74])[9]. In seasonal analyses, the association at lag 2 was consistently positive across seasons, but the strongest association was at lag 0 (1.05% [95% CI: 0.29, 1.82]) in the winter season with the largest magnitude of an effect in the Northeast region. Of note the Northeast region comprised 53% of all counties included in the analysis. In an additional analysis using this data (Bell et al., 2009a), there was no evidence of a reduction in the association between $PM_{2.5}$ and respiratory hospital admissions when accounting for air conditioning use. In a multi-city study conducted in the New England region of the U.S., Kloog et al. (2012a) examined associations between short-term $PM_{2.5}$ exposure and respiratory hospital admissions in individuals 65 years of age and older. To estimate exposure the authors developed a novel prediction model that combined land use regression with physical measurements from satellite aerosol optical depth. The authors observed a 0.70% (95% CI: 0.35, 1.05) increase in respiratory hospital admissions for lags days 0-1. The results obtained using the novel approach presented (i.e., 0.70% increase in respiratory hospital admissions) were consistent with the percent increase in respiratory hospital admissions observed in a traditional time-series analysis (i.e., 1.51%).

In addition to the multicity studies presented above, a few single city studies were conducted in the U.S. that examined asthma and acute bronchitis. Silverman and Ito (2010) conducted a study to evaluate the effect of short-term $PM_{2.5}$ and O_3 exposure on asthma hospital admissions, both general and those that required a stay in the intensive care unit (ICU) in New York City. Analyses focused on four age groups (i.e., <6, 6-18, 19-49, and 50+) and were limited to the warm season (April-August). Positive associations were observed for each age group and for all ages combined when considering general asthma hospital admissions, with the strongest association for the age group 6-18 (15.5% [95% CI: 9.1, 22.0] at lag 0-1). When limiting the analysis to ICU asthma admissions, again the strongest association was for the age group 6-18 (21.1% [95% CI: 8.3, 35.5]). The observed associations remained robust in copollutant models with O_3. The authors also examined the shape of the concentration-response (C-R) relationship using linear, smooth functions, which allowed for a possible nonlinear relationship. This analysis found evidence that the linear fit is a reasonable approximation of the relationship between short-term $PM_{2.5}$ concentrations and asthma 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; however, since daily $PM_{2.5}$ data were available the authors also examined associations between short-term $PM_{2.5}$ exposures and each respiratory health effect. The authors found that $PM_{2.5}$ was positively, but weakly associated with asthma (OR=1.02 [95% CI: 0.96, 1.09]) and acute bronchitis (OR=1.01 [95% CI: 0.92, 1.12]) hospital admissions.

[9] All effect estimates for associations between short-term exposure to $PM_{2.5}$ and morbidity are presented for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration.

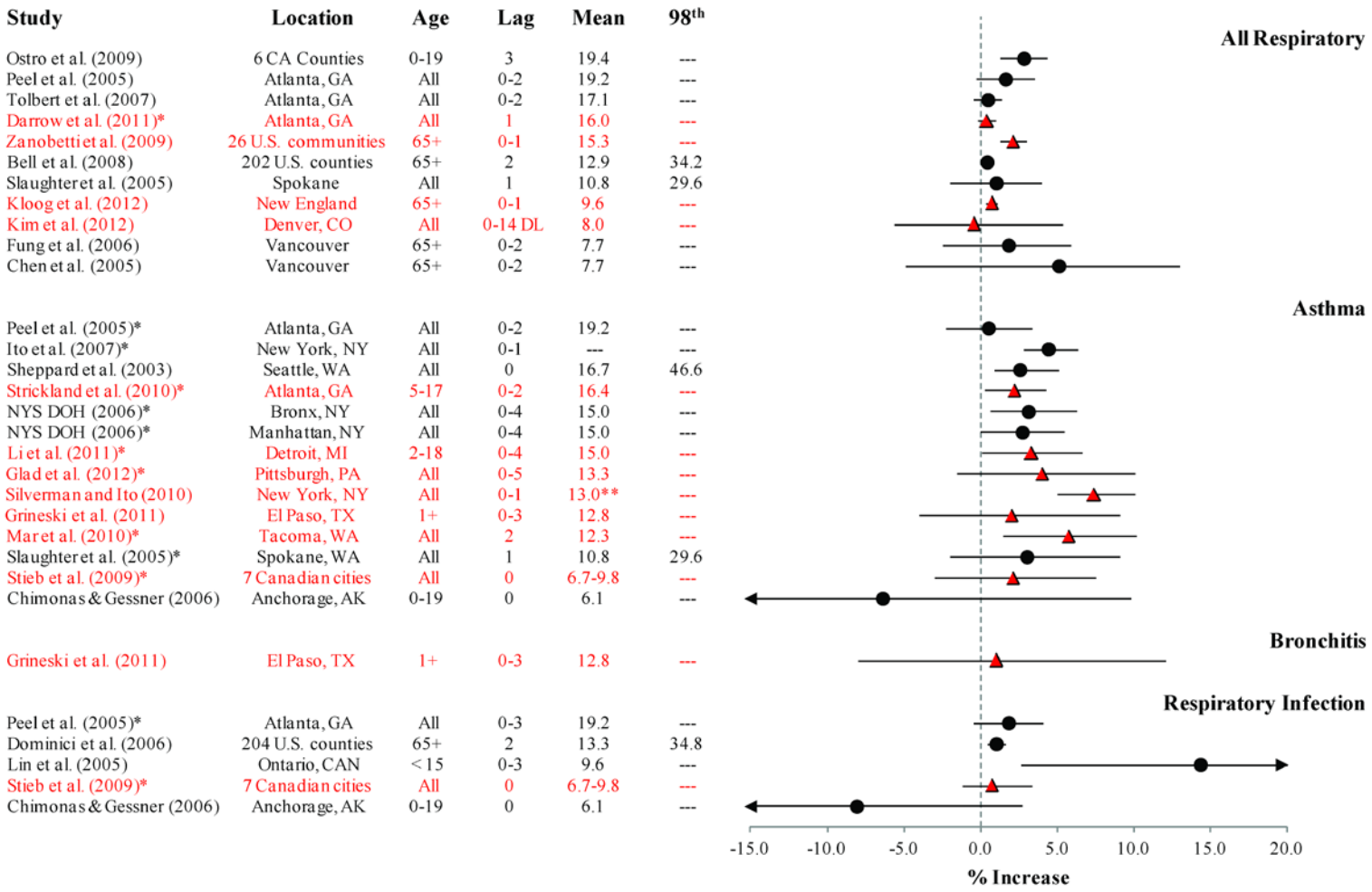
Recent Respiratory-related ED Visits Studies

Of the recent studies identified that focused on short-term exposures to $PM_{2.5}$ and respiratory-related ED visits the majority consisted of single-city studies. However, a couple large, multi-city studies were conducted in the U.S. and Canada. Zanobetti et al. (2009) examined the association between short-term $PM_{2.5}$ exposure and respiratory ED visits in individuals 65 years of age and older in 26 U.S. communities. In an all-year analysis, $PM_{2.5}$ was strongly associated with respiratory ED visits (2.1 [95% CI: 1.2, 3.0] at lag 0-1), while in seasonal analyses positive associations were observed across seasons with the strongest association in the spring (4.3% [95% CI: 2.2, 6.5]). Stieb at al. (2009) conducted a study in 7 Canadian cities to examine the effect of air pollution on ED visits for multiple respiratory-related health outcomes including asthma, COPD, and respiratory infection. The authors found no evidence of an association between short-term $PM_{2.5}$ exposure and COPD ED visits at any of the single-day lags examined. In all-year analyses, positive associations were observed for asthma with the magnitude of the association decreasing as lag day increased (i.e., the strongest association was observed at lag 0, 2.1% [95% CI: -3.0, 7.5]). However, in a warm season analysis (April-September), the magnitude of the association between $PM_{2.5}$ and asthma was nearly 4 times higher (9.3% [95% CI: 6.3, 12.5]).

A couple of single city studies were also conducted that examined all respiratory, multiple respiratory effects, or asthma ED visits. Darrow et al. (2011a) examined the association between short-term air pollution exposure and respiratory ED visits in Atlanta using various exposure metrics (i.e., 1-h max, 24-h avg, Commute (0700-1000, 1600-1900 hours), Day-time (0800-1900 hours), and Night-time (2400-0600 hours). $PM_{2.5}$ (lag 1) was positively associated with respiratory ED visits across exposure metrics, with the magnitude ranging from 0.2% to 0.4%. Kim et al. (2011) examined the associations between short-term $PM_{2.5}$ exposure and hospital admissions in Denver, CO. The authors found no evidence of an association with all respiratory (-0.44% [95% CI: -5.6, 5.4]), COPD or pneumonia hospital admissions (quantitative results only presented for all respiratory). However, there was evidence of a delayed effect of $PM_{2.5}$ on asthma hospital admissions with effects not occurring until approximately lag day 4.

A number of studies focused on ED visits and hospital admissions for asthma. Strickland et al. (2010)conducted an analysis in Atlanta using the same air quality data as Darrow et al. (2011a) to examine the association between air pollution and pediatric (ages 5-17) asthma ED visits. $PM_{2.5}$ was strongly associated with pediatric asthma ED visits in both all-year (2.2% [95% CI: 0.2, 4.2] at lag 0-2) and warm season (4.7% [95% CI: 1.7, 7.6]) analyses. The magnitude of the association was robust to the inclusion of O_3 in the model. An examination of the C-R relationship through a quintile analysis and a loess C-R analysis using lag 0-2 day $PM_{2.5}$ concentrations found evidence of increased risk of pediatric asthma ED visits down to relatively low ambient concentrations (i.e., mean 24-h avg concentrations < 14 $\mu g/m^3$). In Tacoma, WA, Mar et al. (2010) also examined the association between short-term $PM_{2.5}$ exposure and asthma ED visits. Individual lag days of 0 to 5 days were examined with the strongest association

occurring at lag 2 (5.7% [95% CI: 1.4, 10.1]). Li et al. (2011) examined the C-R relationship between short-term $PM_{2.5}$ exposures and asthma ED visits in children 2 to 18 years of age in Detroit. Associations were examined in both a time-series and time-stratified case-crossover study design assuming: (1) no deviation from linearity and (2) a change in linearity at 12 $\mu g/m^3$. In the analyses assuming linearity, similar effect estimates were observed in both models for a 0-4 day lag, (time series: RR=1.03 [95% CI: 1.00, 1.07]; case-crossover: OR=1.04 [95% CI: 1.01, 1.07]). In the models assuming a deviation from linearity at 12 $\mu g/m^3$, the authors reported slightly larger effect estimates, compared to the linear model, for asthma ED visits in the time-series (RR=1.07 [95% CI: 1.03, 1.11]; lag 0-4) and case-crossover analyses (OR=1.06 [95% CI: 1.03, 1.09]; lag 0-4), respectively. Glad et al. (2012) conducted a study in Pittsburgh, PA that found $PM_{2.5}$ to be positively associated with asthma ED visits in analyses of all ages and ages 18 to 64 for single lag days and the average of 0-5 days (i.e., all ages: OR=1.04 [95% CI: 0.98, 1.10] and 18 to 64: OR=1.053 [95% CI: 0.99, 1.12] at lag 0-5). Additionally, when stratifying by race there was some evidence for larger effects in African Americans compared to Caucasian Americans.



*Note: ED visit studies. ** Median concentration.

Figure 2.5 Percent increase in respiratory-related hospital admissions and ED visits for a 10 µg/m^3 increase in 24-h average $PM_{2.5}$ concentrations in single-pollutant models from U.S. and Canadian studies. Red text and triangles represent recent studies published since the completion of the 2009 PM ISA.

The 2009 PM ISA evaluated a number of multi- and single-city studies that found consistent positive associations with all and cause-specific respiratory hospital admissions and ED visits, specifically COPD and respiratory infections in study areas with mean 24-h $PM_{2.5}$ concentrations ranging from 6.1 – 22.0 $\mu g/m^3$. Additionally, there was evidence for asthma hospital admissions and ED visits, but the effects were not consistent in children. Recent multi- and single-city studies have continued to demonstrate consistent positive associations for all respiratory-related hospital admissions and ED visits, and provide additional evidence for increases in asthma hospital admissions and ED visits. The associations observed in the new studies occur in locations with mean concentrations similar (i.e., mean 24-h avg concentrations ranging from 6.7 – 16.4 $\mu g/m^3$) to those studies included in the 2009 PM ISA.

The 2009 PM ISA also found evidence that associations between short-term $PM_{10-2.5}$ exposures and respiratory-related hospital admissions and ED visits were strongest among children. A recent study by Strickland et al. (2010) that examined the association between short-term $PM_{10-2.5}$ exposure and pediatric asthma ED visits in Atlanta, GA further supports this conclusion. Positive associations were observed in both all-year (5.8% [95% CI: 1.9, 9.9] at lag 0-2) and seasonal analyses, with the strongest association in the cold season (7.0% [95% CI: 1.7, 12.7]). An examination of the C-R relationship in both quintile and smooth estimates of the concentration-response provided evidence of associations at relatively low ambient concentrations for all pollutants, including $PM_{10-2.5}$ (i.e., mean 24-h avg concentrations < ~12 $\mu g/m^3$)..

2.2.2.2. Associations between Short-Term Exposures to PM and Cardiovascular Morbidity

Summary of 2009 PM ISA Conclusions

The associations between short-term $PM_{2.5}$ exposure and cardiovascular-related hospital admissions and ED visits was evaluated in Section 6.2.10 of the 2009 PM ISA (U.S. EPA, 2009). Epidemiologic studies that examined the effect of $PM_{2.5}$ on cardiovascular ED visits and hospital admissions reported consistent positive associations (predominantly for IHD and congestive heart failure [CHF]) in study areas with mean 24-h average concentrations ranging from 7.0 – 18 $\mu g/m^3$. This evidence contributed to the conclusion that "a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects."

Epidemiologic studies of the association of short-term $PM_{10-2.5}$ exposure with cardiovascular hospital admissions and ED visits were also evaluated in the 2009 PM ISA, and the evidence from these studies contributed to the conclusion that the evidence "is suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and cardiovascular effects.

Recent Cardiovascular-related Hospital Admissions/ED Visits Studies

Recent multi-city and multi-location studies, as well as single-city studies, add to the collective body of evidence that examined associations between short-term $PM_{2.5}$ exposure and

cardiovascular-related hospital admissions and ED visits evaluated in the 2009 PM ISA. Figure 2.6 summarizes the results from single-pollutant models from studies evaluated in the 2009 PM ISA as well as recent studies published since its completion. No new studies have been published that examined the association between short-term $PM_{10-2.5}$ exposure and cardiovascular hospital admissions or ED visits in the U.S. or Canada.

In a recent Health Effects Institute (HEI) report, Bell et al. (2012) compiled findings from several multicity analyses of Medicare data (older adults, ≥ 65 years of age) for 204 counties across the U.S. (some analyses included fewer counties). Although additional detail is provided in the HEI report, these analyses were largely included in the 2009 PM ISA (Bell et al., 2008; Dominici et al., 2006). In an analysis using the same data, Bell et al. (Bell et al., 2009a) found a higher prevalence of central air conditioning was associated with a decrease in the risk of $PM_{2.5}$ - associated hospitalization for cardiovascular disease.

Recent studies are consistent with the evidence assessed in the 2009 PM ISA. In a time-series analysis of Medicare records for older adults ≥65 years of age in 26 US communities for 2000-2003, Zanobetti et al. (2009) reported increases in hospital admissions for all CVD (1.89% 95%CI: 1.34 to 2.45), MI (2.25% 95%CI: 1.10 to 3.42) and CHF (1.85% 95%CI: 1.19 to 2.51; lag 0-1). Although the largest excess risks were observed in the spring, statistically significant excess risks were also observed in the winter. In a time-series analysis of hospital admissions in seven Canadian cities, a 17% (95%CI: 0 to 37%) increase in hospital admissions for heart failure was observed at lag 0 (Stieb et al., 2009). Weak, nonsignificant associations were observed between $PM_{2.5}$ and dysrhythmia and MI hospitalizations.

In a study of emergency hospitalizations among New York City residents ≥ 40 years of age, Ito et al. (2011a) reported an excess risk of 1.0% (95% CI: 0.40, 1.6, lag 0). The excess risk was stronger in the cold season (1.1% [95% CI 0.2 to 2.0]). These results were not sensitive to the choice of method used to control temperature. Using a subset of these emergency hospitalization data, Mathes et al. (2011) defined two cardiovascular syndromes from a database containing text descriptions of the chief complaint reported by the patient upon admission to the hospital. This study reported that $PM_{2.5}$ was associated with both cardiac and more general cardiovascular syndromes. In case-crossover analysis of cardiovascular disease admissions across New York state from 2001 to 2005, Haley et al. (2009) found a 3.9% increase in heart failure admissions per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (lag 0-2). A case-crossover study of atrial fibrillation hospitalizations between 1993 and 2008 in Utah (Wasatch Front) reported consistently positive, but non-significant, associations across all lags examined in the study (lag 0 through 21 day moving average) (quantitative results not provided) (Bunch et al., 2011). Finally, a 1.03% (95% CI: 0.69, 1.34) increase in cardiovascular admissions was reported in a time-series study of hospitalizations across New England among older adults (65 years) with predicted PM2.5 concentrations using satellite-derived AOD measurements (Kloog et al., 2012b).

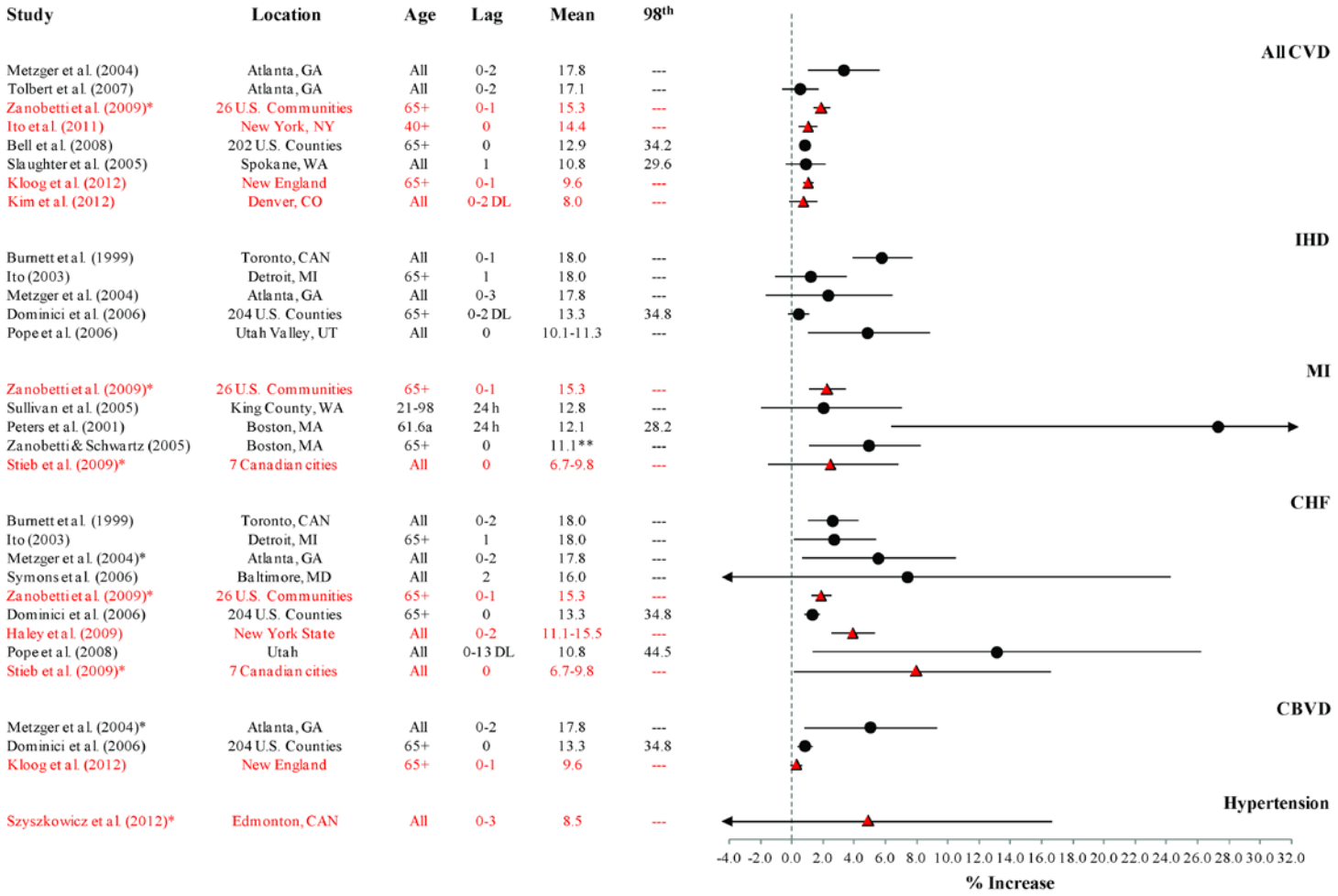
Acute Stroke

Wellenius et al. (2012) examined the association of $PM_{2.5}$ with neurologist-confirmed ischemic stroke in predominately white female patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) in Boston from 1999 to 2008. Time of stroke symptom onset (exact or estimated) was available for most patients included in the study. The OR of stroke onset was 1.30 (95% CI: 1.08 to 1.58) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ in the previous 24 hours. Authors report a 34% (95% CI: 13 to 58) higher risk of ischemic stroke during the previous 24 hours in an analysis comparing moderate $PM_{2.5}$ exposure ($\geq$15 $\mu g/m^3$) to good (<15 $\mu g/m^3$) exposure, as defined by EPA's Air Quality Index (AQI). These results were confirmed in an additional analysis conducted by Mostofsky et al. (2012) using a subset of the data (i.e., 2003-2008) used by Wellenius et al. (2012). Mostofsky et al. (2012) found a 22.7% (95% CI: 3.1, 47.0) increase in ischemic stroke onset for an increase in $PM_{2.5}$ over the previous 24 hours.

Out of Hospital Cardiac Arrests

The small number of studies of out-of-hospital cardiac arrest included in the 2009 PM ISA reported mixed results. A recent time series analysis of cardiac arrests in New York City reported an increased risk of 1.06 (95%CI 1.02, 1.10, lag 0-1) per 10 µg/m3 increase in $PM_{2.5}$ (Silverman et al., 2010). Case cross-over analysis of the same data produced a result that was similar in magnitude but did not reach statistical significance. The association with cardiac arrest was stronger in the warm season (1.09 95% CI: 1.03-1.15) compared to the cold season (1.01 95% CI 0.95 to 1.07).

In summary, the 2009 PM ISA found consistent positive associations between short-term $PM_{2.5}$ exposures and all and cause-specific cardiovascular hospital admissions and ED visits, specifically IHD and CHF in study areas with mean 24-h $PM_{2.5}$ concentrations ranging from 7.0 – 18.0 $\mu g/m^3$. New multi- and single-city studies further support associations with all cardiovascular hospital admissions and ED visits at mean 24-h $PM_{2.5}$ concentrations ranging from 6.7 – 15.3 $\mu g/m^3$. Additional support for associations between short-term $PM_{2.5}$ exposures and cardiovascular effects comes from a new study of stroke onset (Wellenius et al. (2012)).



* Note: ED visit studies. ** Median concentration. a = study only presented mean age of participants

Figure 2.6 Percent increase in cardiovascular-related hospital admissions and ED visits for a 10 μg/m^3 increase in 24-h average $PM_{2.5}$ concentrations in single-pollutant models from U.S. and Canadian studies. Red text and triangles represent recent studies published since the completion of the 2009 PM ISA.

2.3. Health Effects Related to Sources or Components of PM

Summary of 2009 PM ISA Conclusions

The 2009 PM ISA evaluated epidemiologic, toxicological, and controlled human exposure studies that examined health effects associated with ambient PM components and sources. These studies used a variety of quantitative methods and examined a broad set of PM components (Section 6.6), and found evidence of health effects from sources and components associated with a number of combustion activities (e.g., motor vehicle emissions, coal combustion, oil burning, power plants, and wood smoke/vegetative burning), crustal sources, and secondary sulfate. As a result, the ISA concluded that "the evidence is not yet sufficient to allow differentiation of those components or sources that are more closely related to specific health outcomes." These conclusions are consistent with those presented in the 2004 PM AQCD where the studies evaluated found evidence of health effects attributed to a number of source types, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning.

Recent Studies of Health Effects Related to Sources or Components of PM

Recent studies have continued to examine whether specific PM components or sources are more closely related to specific health outcomes. For the purposes of this provisional assessment of new literature published since the release of the 2009 PM ISA, emphasis has been placed on studies that investigated the health effects related to PM sources or comparisons of various PM components. To highlight the scientific content of the recent literature while focusing on key PM study categories, this section focuses on results of studies that evaluated the effects of a range of sources or components. Thus, the discussion includes: (1) recent epidemiologic studies using source apportionment; (2) epidemiologic evidence on effects with PM components; and (3) results of new toxicological studies using source apportionment with exposures to concentrated ambient particles (CAPs) to provide insight into potential effects related to PM from different sources, and comparative toxicology studies using fine PM components. In addition, numerous epidemiologic and/or toxicology studies have reported effects of several ultrafine PM as discussed in the 2009 PM ISA. Specific findings for ultrafine PM are not discussed in detail; instead, the available new studies are included in the reference list: http://hero.epa.gov/pm .

2.3.1. Epidemiologic Studies Using Source Apportionment

Lall et al. (2011) examined the association between source-specific daily $PM_{2.5}$ mass and component data and hospital admissions in New York City for the years 2001-2002. The use of daily data allowed for the examination of both single-day lags and a distributed lag. Source categories identified through positive matrix factorization included long-range transported sulfates, traffic, residual oil, steel metal works dust, and soil. In single-day lag models, total respiratory hospital admissions were positively associated with residual oil at lag 2, but the strongest associations were with steel metal works dust at lag 0 and 3. For cardiovascular hospital admissions the strongest associations were observed with traffic at lag 0 and residual oil

at lag 3. When examining associations between cause-specific cardiovascular and the traffic source category, the strongest associations were observed at lag 0 for total cardiovascular, heart failure, and stroke. For associations between cause-specific respiratory hospital admissions and the steel source category, pneumonia was associated with steel metal works dust at lag 3, while asthma was observed to have the largest magnitude of an association across all lags. The distributed lag model demonstrated a stronger association between traffic and cardiovascular hospital admissions and steel metal works dust and respiratory hospital admissions than the single-day lag models, indicating that single-day lags may underestimate the magnitude of associations. Finally, a sensitivity analysis using key tracers of each source (i.e., elemental carbon for traffic and manganese for steel metal works) found similar patterns of associations as the source-specific analyses.

2.3.2. Epidemiologic Studies on Effects of Fine PM Components and Sources

In addition to examining the association between short-term $PM_{2.5}$ exposures and mortality or hospital admissions and ED visits a number of studies also attempted to identify if an individual PM component or group of PM components could explain the observed association. The following section describes the results from these studies some of which have been aforementioned.

Short-term exposure to $PM_{2.5}$ components and sources and mortality

In addition to examining the association between short-term exposure to $PM_{2.5}$ and mortality, a few single-city studies also examined the effect of individual $PM_{2.5}$ components on mortality. Ito et al. (2011a) focused on key PM components (i.e., elemental carbon [EC], organic carbon [OC], sulfate [SO_4], nickel [Ni], vanadium [V], zinc [Zn], silicon [Si], selenium [Se], sodium [Na], and bromine [Br]) identified in previous source apportionment studies conducted in NYC. In all-year analyses, the strongest associations were observed at lag 1 for EC, OC, SO_4, Si, Se, and Br. In the warm season, strong associations were observed for secondary aerosols including OC and SO_4, Se, which is associated with transported coal emissions, EC, and Br. In the cold season, the components associated with residual oil burning, Ni, V, and Zn, all showed a similar pattern of associations, with the strongest effects at lag 3. Overall, the components representing regional transport showed a seasonal pattern of associations similar to those found with $PM_{2.5}$ mass, while associations were found throughout the year with EC and NO_2.

Zhou et al. (2011) examined the association between PM components with all-cause, cardiovascular, and respiratory mortality in seasonal analyses in Seattle and Detroit. The components selected for analysis represent the major emissions sources of the two cities: soil (aluminium [Al] and Si), smelter effluents (iron [Fe] and Zn), residual oil burning (Ni and V), coal burning (sulfur [S]), traffic (EC), sea salt (Na), and wood burning (potassium [K]). Daily component data was available in both cities, which allowed for the examination of a 0-2 day distributed lag. In Detroit, S was associated with all-cause and cardiovascular mortality and S

and Ni were moderately associated with respiratory mortality in the warm season. No components were positively associated with any mortality outcome in the cold season in Detroit. In Seattle, in the warm season no component was significantly associated with any mortality outcome, but Fe, K, and EC were positively associated with respiratory mortality. In the cold season, Al, K, Si, Zn, and EC were strongly associated with all-cause mortality, with the same components, minus Al, strongly associated with cardiovascular mortality. No components were associated with respiratory mortality in Seattle in the cold season. Overall, in Detroit the components associated with mortality are indicative of coal burning while in Seattle the components associated with mortality represent cold-season traffic and combustion sources, such as residual oil and wood burning.

In the study conducted by Klemm et al. (2011) in Atlanta, daily concentrations of the PM components EC, OC, nitrate [NO_3], and SO_4 were also available for the entire study duration. The authors found that EC, OC, and NO_3 were positively associated with nonaccidental mortality at lag 0-1 in individuals 65 years of age and older, with the strongest association for NO_3. In analyses of cause-specific mortality, a similar pattern of associations was observed for cardiovascular and respiratory mortality. SO_4 was not found to be associated with any of the mortality outcomes examined.

Respiratory-related Hospital Admissions and ED Visits

Recent multicity studies were identified that examined the effect of PM components on the relationship between short-term PM exposure and respiratory-related ED visits and hospital admissions. Zanobetti et al. (2009) conducted a second-stage analysis, using the same methodology as Franklin et al. (2008) (2009 PM ISA; p. 6-193-195) and examined whether season and community-specific long-term mean seasonal concentration ratios of PM components to $PM_{2.5}$ total mass modified the association between short-term $PM_{2.5}$ concentrations and respiratory ED visits. Of the components examined only Na^+ and Ni were found to modify the association between $PM_{2.5}$ and respiratory ED visits. Using a different approach, Levy et al. (2012) attempted to identify if some PM components are more toxic than others by focusing on the four components that dominate $PM_{2.5}$ mass and are highly correlated with $PM_{2.5}$ (i.e., EC, OC, SO_4, and NO_3). In a time-series analysis using Medicare data from 119 U.S. counties the authors examined the association between each component and respiratory hospital admissions across the U.S. and regionally (i.e., East and West). Of the components examined, only EC and OC were positively associated with respiratory hospital admissions.

A few single-city studies were also identified that examined associations between respiratory-related ED visits and hospital admissions and individual PM components. Strickland et al. (2010) focused on the PM components SO_4, EC, OC, and water-soluble metals. For each component positive associations were observed with pediatric asthma ED visits in all-year analyses. The strongest associations were observed in the warm season with the magnitude being similar across components. In addition, analyses including copollutant adjustment were conducted using warm

season data. Risk estimates for $PM_{2.5}$, EC, and SO_4 were attenuated, but remained positive when including O_3 in the model. In LOESS C-R analyses, there was evidence of a positive C-R relationship for each component. Kim et al. (2011) examined the lag structure of associations between the PM components EC, OC, SO_4, and NO_3 and respiratory hospital admissions. The authors focused on these components because they comprise the majority of $PM_{2.5}$ mass in Denver. Consistent with the $PM_{2.5}$ results, there was no evidence of an association with COPD or pneumonia and any of the components. For both all respiratory and asthma hospital admissions there was evidence of greater effects with EC and OC compared to SO_4 and NO_3, and additional evidence for delayed effects occurring 2 to 5 days after exposure.

Cardiovascular-related Hospital Admissions and ED Visits

The 2009 PM ISA included multicity analyses of the effect of $PM_{2.5}$ components on cardiovascular hospital admissions that reported associations between oil combustion and traffic-related $PM_{2.5}$ and CVD hospitalizations.

Two recent studies investigated the association of $PM_{2.5}$ components with cardiovascular hospital admissions. Using Medicare data from 26 US communities, Zanobetti et al. (2009) examined the modification of the associations of $PM_{2.5}$ with CVD, MI and CHF hospital admissions by season- and community-specific $PM_{2.5}$ composition. Authors estimated the relative contribution of specific components (EC, OC, SO_4, NO_3, Na, Ni, V, Zn, Si, Se, Br) by computing concentration ratios (i.e. component species as a proportion of $PM_{2.5}$ mass). In the second stage of a hierarchical model, season- and community-specific estimates of the association between $PM_{2.5}$ and CVD hospitalizations were regressed on the concentration ratios. The association of $PM_{2.5}$ with all CVD hospitalizations was significantly modified when the proportion of Br, Na^+, Ni, V and Al in $PM_{2.5}$ was high. The association of $PM_{2.5}$ with all MI hospitalizations was significantly modified when the proportion of arsenic [As], chromium [Cr], manganese [Mn], OC, Ni, K and Na^+ was high. Additional increases in CVD hospitalizations per interquartile range (IQR) increase in the proportion of the component ranged from 0.53% to 0.9% (larger, less precise increases were reported for MI). None of the components significantly modified the association of $PM_{2.5}$ with CHF admissions (i.e. p-value > 0.05). Ito et al. (2011b) conducted a time series analysis of the lag structure and seasonal patterns in the association between emergency hospitalization for CVD and $PM_{2.5}$ chemical components. Same day concentration of most components examined was associated with CVD hospitalizations (EC, OC, SO_4, NO_3, Na, Ni, V, Zn, Se, and Br). The association and lag structure of EC with CVD hospitalization was constant across season; associations of OC, SO_4, Ni, Zn, Si, Se and Br with CVD hospitalizations were strongest in the cold season.

An additional study (Mostofsky et al., 2012) examined different approaches to modeling the association between PM components and health outcomes using ischemic stroke onset as an example. The authors used three different models that included parameters for the following: (1) component concentration, (2) component concentration adjusted for total $PM_{2.5}$ mass, which

accounts for total $PM_{2.5}$ mass, and (3) component residuals, which eliminates confounding by total $PM_{2.5}$ mass. In model 1, positive associations were observed for a number of components including Al, calcium [Ca], Br, lead [Pb], Se, titanium [Ti], and Fe with the strongest associations for V, S, Ni, and black carbon [BC]. Models 2 and 3 resulted in relatively few components with positive associations, but the pattern of associations across pollutants was consistent between the two models with the strongest associations for V, Ni, and BC.

Long-term exposure to $PM_{2.5}$ components and mortality

Ostro et al. (2010) also examined the association between long-term exposures to $PM_{2.5}$ components (i.e., EC, OC, SO_4, NO_3, Fe, K, Si, Zn) and all-cause mortality among the subjects from the California Teachers Study. No associations were observed between all-cause mortality and any $PM_{2.5}$ component. In analyses of cause-specific mortality, Ostro et al. (2010) observed an association between long-term exposure to several $PM_{2.5}$ components and mortality from CPD, IHD and pulmonary disease. The authors observed positive associations of CPD and IHD mortality with each of the measured components, and between pulmonary mortality and SO_4 and NO_3. Of the components analyzed, there were positive associations with nitrate, sulfate and silicon for CPD mortality and all of the components were associated with mortality from IHD (See Table 2.2).

Table 2-2 Association between Mortality Outcomes and $PM_{2.5}$ Components using a 30-km Buffer (n=43,220) (Adapted from Ostro et al. [2011])

Component (IQR, $\mu g/m^3$)	All-Cause*	CPD*	IHD*	Pulmonary*
EC (0.65)	1.02 (0.93, 1.12)	1.07 (0.94, 1.22)	1.46 (1.17, 1.83)	0.88 (0.68, 1.15)
OC (0.84)	1.00 (0.95, 1.04)	1.04 (0.98, 1.11)	1.13 (1.01, 1.25)	0.95 (0.84, 1.06)
SO_4 (2.2)	1.06 (0.97, 1.16)	1.14 (1.01, 1.29)	1.48 (1.20, 1.82)	1.04 (0.82, 1.31)
NO_3 (3.2)	1.03 (0.98, 1.09)	1.11 (1.03, 1.19)	1.27 (1.12, 1.43)	1.04 (0.90, 1.20)
Fe (0.13)	1.01 (0.93, 1.11)	1.05 (0.93, 1.19)	1.39 (1.13, 1.72)	0.88 (0.69, 1.13)
K (0.07)	1.01 (0.94, 1.08)	1.06 (0.97, 1.17)	1.27 (1.07, 1.49)	0.90 (0.74, 1.09)
Si (0.03)	1.02 (0.99, 1.06)	1.05 (1.00, 1.10)	1.11 (1.02, 1.20)	0.98 (0.89, 1.08)
Zn (0.01)	1.03 (0.96, 1.11)	1.09 (0.98, 1.20)	1.33 (1.12, 1.58)	0.97 (0.79, 1.18)

*Hazard ratio and 95% confidence interval for an increase in $PM_{2.5}$ components equal to the interquartile range (IQR)

Source: Adapted from Ostro et al. (2011)

Long-term exposure to $PM_{2.5}$ components and sources and morbidity

In a study conducted in New York City, Patel et al. (2009) examined long-term exposure to $PM_{2.5}$ components (Ni, V, Zn, EC) and respiratory symptoms in children through 24 months of age. Positive associations were observed between Ni and wheeze, but not cough. No other

associations were observed between the other metals or EC and either wheeze or cough. $PM_{2.5}$ mass was not associated with wheeze and/or cough (see Section 2.1.3 for results on $PM_{2.5}$ mass).

Several recent studies have examined the association between exposure to $PM_{2.5}$ components and sources and birth outcomes, including birth weight and preterm birth. Studies examining birth weight and $PM_{2.5}$ components and sources found the strongest associations with metals/oil combustion (Bell et al., 2012; Darrow et al., 2011b; Bell et al., 2010) and elemental carbon/motor vehicles (Wilhelm et al., 2012; Darrow et al., 2011b; Bell et al., 2010). Similarly, when evaluating $PM_{2.5}$ components and preterm birth, the associations with metals, EC, OC and ammonium nitrate were strongest (Wilhelm et al., 2011; Darrow et al., 2009). Several $PM_{2.5}$ sources were associated with preterm birth, including biomass burning and diesel traffic (Wilhelm et al., 2011).

2.3.3. Toxicology Studies – Source Apportionment and Fine PM Components

The 2009 PM ISA examined health effects associated with exposure to ambient PM components and sources in animals. In vivo and in vitro studies reported a variety of sources and components were linked with cardiopulmonary effects; however, there was insufficient evidence overall to determine which sources or components were most closely related to the observed effects. Since the completion of the 2009 PM ISA, a small number of animal toxicology studies have continued to assess the role of PM sources and components on effects observed after exposure to $PM_{2.5}$.

2.3.3.1. Toxicology Studies Comparing Ambient Fine PM Sources and Components

Toxicology studies employing CAPs offer a relevant surrogate for atmospheric PM. Table 2.3 shows the endpoints that were associated with various source categories from rodents exposed to CAPs from four locations. These three studies compare electrocardiogram (ECG) responses during CAPs inhalation to $PM_{2.5}$ components associated with source factors (Kamal et al., 2011; Rohr et al., 2011; Chen et al., 2010).

Chen et al. (2010) compared subchronic CAPs inhalation exposures from two locations in New York, Sterling Forest (SF; undeveloped woodland park) and Manhattan in male hyperlipidemic mice. Using Manhattan CAPs (mean CAPs concentration, 122.9 ± 81.1 $\mu g/m^3$), heart rate (HR) decreased with increased current day CAPs mass at all lags and several measures of heart rate variability (HRV) increased with increased CAPs mass (i.e., standard deviation of the normal-to-normal intervals, SDNN; root mean square of the standard deviation of the normal-to-normal intervals, rMSSD; and frequency domain indices, high-frequency, HF, low-frequency, LF, and LF/HF ratio). Using SF CAPs (mean CAPs concentration, 133.3 ± 110.5 $\mu g/m^3$), CAPs mass was positively associated with HR, whereas HRV decreased with increased CAPs. Using Manhattan CAPs, ECG changes were associated with components related to residual oil combustion > long-range transport > traffic > iron/steel > incineration > soil. Using SF CAPs, ECG changes were associated with long-range transport > Ni refinery > soil > residual oil combustion/traffic. Chen et al. (2010) also performed single-element analysis and note that EC did not account for the

acute ECG changes associated with $PM_{2.5}$ and that Ni may have an effect in Manhattan but not SF.

Rohr et al. (2011) reported altered ECG responses in spontaneously hypertensive rats following CAPs inhalation exposures from Detroit, Michigan over 13 consecutive days in both the summer and winter. Source factors were identified using positive matrix factorization. In summer (time weighted average CAPs concentration, 518 $\mu g/m^3$), decreased HRV (SDNN) was associated with cement/lime, iron/steel, and gasoline/diesel factors, and less so with sludge incineration. In winter (time weighted average CAPs concentration, 357 $\mu g/m^3$); decreased HR was associated with sludge incineration, cement/lime, and coal/secondary sulfate factors.

Kamal et al. (2011) also identified source factors (via positive matrix factorization) associated with ECG alterations in hypertensive rats exposed for 13 days to CAPs (from Steubenville, OH; mean CAPs concentration 406 ± 266 $\mu g/m^3$). Statistically significant associations were found between acute cardiac responses and PM components linked with incineration, metal processing, mobile sources, and iron/steel production. The strength of the association with each source was dependent upon wind direction; however, incineration was consistently found to be associated with changes in HR and HRV. Several individual CAPs components were also associated with cardiovascular responses, S, SO_2, Pb, and oxides of nitrogen (NO_x).

Table 2-3 Concentrated Ambient Particles (CAPs): Sources and Associated Endpoints

Source Category	Elemental Loading	Endpoint Affected	Location	Exposure Duration	References
Metal processing	V, Cr, Ti, Mo, La, Ce	↑ HR ↓ SDNN	Steubenville, OH	13 days (s)	Kamal et al. (2011)
Incineration (including sludge)	Zn, Cd	↓ HR ↓ SDNN	Steubenville, OH	13 days (s)	Kamal et al. (2011)
	Zn, Ba, Mn, Sr, Sb	↓ HR (w) ↓ SDNN (s)	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
	Zn, Pb, Cu, Fe	ECG alterations	Manhattan, NY	6 months	Chen et al. (2010)
Pb	Pb, Cu	↓ HR	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
Iron/Steel manufacturing	Fe, Mn, Cu, EC, Pb	↓ HR ↑ rMSSD	Steubenville, OH	13 days (s)	Kamal et al. (2011)
	Mn, Fe	ECG alterations	Manhattan, NY	6 months	Chen et al. (2010)
	Fe, Mn, Cu	↑ rMSSD (w) ↓ SDNN (s)	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
Mobile/Traffic	Fe, Sb, As, K, CO	↓ SDNN ↑ rMSSD	Steubenville, OH	13 days (s)	Kamal et al. (2011)
	Fe, Ti, Zn	↓ SDNN (s) ↑ rMSSD (w)	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
	EC, NO_2, Si, Fe, Cu	ECG alterations	Manhattan, NY	6 months	Chen et al. (2010)
Coal and Secondary Sulfate	S, Se, Al, V, P	↓ HR ↑ rMSSD	Steubenville, OH	13 days (s)	Kamal et al. (2011)
	S, Se	↓ HR (w) ↑ rMSSD (w)	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
Oil refinery	La, Ce	↑ HR (w)	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
Cement/lime processing	Ca, Sr, Mg	↓ HR (w) ↓ SDNN (s)	Detroit, MI	13 days (s & w)	Rohr et al. (2011)
Residual oil combustion	V, Ni, EC, Fe	ECG alterations	Manhattan, NY	6 months	Chen et al. (2010)
Ni-refinery	Cr, Ni	ECG alterations	Sterling Forest, NY	6 months	Chen et al. (2010)
Soil	Al, Si, Ca, Fe	ECG alterations	Sterling Forest, NY Manhattan, NY	6 months	Chen et al. (2010)
Long range transport	S, Se, Br	ECG alterations	Sterling Forest, NY Manhattan, NY	6 months	Chen et al. (2010)

(w) winter season, (s) summer season, HR: heart rate, SDNN: standard deviation of the normal-to-normal intervals, rMSSD: root mean square of the standard deviation of the normal-to-normal intervals, Mo: molybdenum, La: lanthanum, Ce: cerium, Cd: cadmium, Ba: barium, Sr: strontium, Sb: antimony, Cu: copper, CO: carbon monoxide, P: phosphorus

Other studies have used regression and correlation approaches to estimate the relationship between various PM components and sources with health effects. Happo et al. (2010b) intratracheally instilled mice (10 mg/kg) with size-segregated ambient PM samples collected in six European cities over various seasons: Duisberg autumn, Prague winter, Amsterdam winter, Helsinki spring, Barcelona spring, Athens summer. PM exposure ($PM_{10-2.5}$ and $PM_{2.5-0.2}$) increased bronchoalveolar lavage fluid (BALF) total cell number and BALF protein concentration. No formal source apportionment was conducted, but oxidized organic compounds (e.g., dicarboxylic acids), transition metals (e.g., Fe and Cr), and source tracers for fuel oil combustion (i.e., Ni and V) were the most strongly correlated components of $PM_{2.5-0.2}$ contributing to the inflammatory response (i.e., BALF total cell number). These studies measured response to $PM_{10-2.5}$ and $PM_{2.5-0.2}$ PM samples, and generally report stronger inflammatory responses (e.g., BALF cytokines, cell number, and total protein) after exposure to coarse PM compared to fine. Source tracers for soil (K^+, magnesium [Mg^{2+}], Cu, manganese [Mn], Fe) and sea spray (Na^+, chlorine [Cl^-], and NO_3^-) found in $PM_{10-2.5}$ were the most strongly correlated with inflammatory response.

A few studies discuss how seasonal variation in PM components may affect PM-induced health effects. Happo et al. (2010a) intratracheally instilled mice (10 mg/kg) with size-fractionated ambient PM collected in Helsinki in the winter, spring, summer, and autumn. PM collected in the spring produced the highest relative inflammatory activity (i.e., total cell number, total protein, tissue necrosis factor alpha [TNF-α], interleukin-6 [IL-6], and keratinocyte-derived chemokine in BALF) when dose was adjusted to the PM per cubic meter of urban air, whereas the PM collected in the autumn produced the highest inflammation per equal mass dose. This difference was influenced by a greater PM mass concentration in urban air in the springtime. The overall inflammatory activity of PM decreased with particle size, such that $PM_{10-2.5}$ and $PM_{2.5-1}$ had a higher potency than $PM_{1-0.2}$ and $PM_{0.2}$. Components of road dust (Ca^{2+}, Fe, Mn, and Al) and trace metals (presumed to be the result of non-exhaust PM from traffic; Cu, Chromium [Cr], cobalt [Co]) were consistently correlated with BALF inflammatory response in $PM_{2.5-1}$. Resuspension of road dust was also strongly correlated with inflammatory responses to $PM_{10-2.5}$. Farina et al. (2011) treated mice (100 µg, intratracheal aerosolization) with size-fractionated ambient PM collected from Milano, Italy in summer and winter. A stronger inflammatory activity was generally observed after administration of summer PM_{10} and $PM_{2.5}$ than winter PM. PM_{10} exposure resulted in a higher TNF-α concentration (in BALF) compared to $PM_{2.5}$, and this was attributed to the greater endotoxin concentration and bacteria content of PM_{10}.

Additional studies assessed the differential responses of PM collected at different distances from a highway. Cho et al. (2009) found similar composition in size-fractionated ambient PM collected near (20 m) and far (275 m) from a road in Raleigh, NC; however, PM collected near-road was enriched with metals and a greater concentration of endotoxin. Coarse PM samples, but not fine PM samples, produced pulmonary inflammation (i.e., BALF, macrophage inflammatory protein 2 [MIP-2], TNF-α, IL-6) in exposed mice (25 and 100 µg) irrespective of distance collected from the road. Zhang et al. (2011) reported greater increases in protein and lactate

dehydrogenase [LDH] in BALF after instillation (7.5 mg/kg) of $PM_{2.5}$ collected near traffic compared to far from traffic in Beijing, China. Chemical analysis of the near-traffic PM revealed higher concentrations of polycyclic aromatic hydrocarbons [PAHs] and heavy metal elements (arsenic [As], Cd, Zn, S), but no statistical correlations were computed between these components and the health effects observed.

A number of studies have attempted to disentangle the role of PM and gaseous components in the health effects associated with ambient air pollution exposure by removing PM from the mixture using a high efficiency particle filter. A few recent studies report cardiovascular, respiratory, and reproductive effects after exposure to unfiltered (the whole mixture), but not filtered Sao Paulo urban air (20 m from road) (Pires et al., 2011; Matsumoto et al., 2010; Akinaga et al., 2009). These studies suggest that PM but not the gaseous components of the urban air play a role in these responses.

2.3.3.2. Toxicology Studies Comparing Source-Derived PM and Components

A number of studies attempted to characterize effects from ambient PM sources by exposing animals in the laboratory to PM derived from potential ambient sources (e.g., coal combustion, diesel).

A series of studies evaluated the health effects resulting from various coal-fired power plant emissions scenarios (Diaz et al., 2011; Godleski et al., 2011a; Godleski et al., 2011c; Godleski et al., 2011b; Lemos et al., 2011; Wellenius et al., 2011). Stack emissions were collected from three coal-fired power plants and various atmospheric transformations (e.g., oxidation, reaction with α-pinene, neutralization) were simulated to investigate the toxicity of primary and photochemically aged (secondary) particles. Particle mass concentrations varied from 43.8 to 257.1 $\mu g/m^3$ (Kang et al., 2011). Rats were exposed to these simulated emissions scenarios for 6 hours and demonstrated (1) increased BALF total cells, macrophages, and neutrophils (Godleski et al., 2011a); (2) moderately increased heart and lung reactive oxygen species (measured by in vivo chemiluminescence) (Lemos et al., 2011), 3) increased premature ventricular beat frequency, but no change in heart rate, HRV, or ECG intervals (Wellenius et al., 2011); and 4) breathing pattern changes (Diaz et al., 2011). Overall, specific PM components did not predict respiratory or cardiovascular effects observed after PM exposure as well as simulated atmospheric transformation scenarios.

Additionally, a few studies assessed respiratory, cardiovascular, and systemic effects following exposure to filtered and unfiltered simulated downwind coal combustion emissions (Barrett et al., 2011; Mauderly et al., 2011). Barrett et al. (2011) reported different respiratory effects after exposure to filtered and unfiltered emissions. Mauderly et al. (2011) found 17 out of 270 species-gender-time-outcome comparisons were affected by whole emissions and that PM participated in only 3 responses (liver weight, serum K^+, and MIP-2). The authors concluded that PM contributed to a few of the effects but that the pollutants responsible for the effects observed were not able to be identified.

Studies have also evaluated the role of PM in engine emissions on the progression of health effects. Tzamkiozis et al. (2010) instilled mice with PM collected from a gasoline Euro 3 car, a diesel Euro 2 car, and a diesel Euro 4 car (with a diesel particle filter). Significant pulmonary inflammation (i.e., BALF polymorphonuclear leukocytes (PMN) number) and injury (i.e., BALF protein concentration) occurred 24 hours after treatment. The strongest associations with these effects were observed for the PM components, P, Mn, Fe, Pb, reactive oxygen species (ROS), benz(*a*)anthracene, chrysene, and medium and heavy PAHs. A strong association was also observed between pulmonary injury and S.

A number of studies evaluated the impact of inhaled diesel exhaust on the cardiovascular system with and without filtration (Gordon et al., 2012; Lamb et al., 2012; Seilkop et al., 2012; Campen et al., 2010). Different cardiovascular effects were reported after filtration of diesel exhaust by Gordon et al. (2012) and Lamb et al. (2012). Campen et al. (2010) found that filtration of PM from diesel exhaust did not alter the vascular responses observed. Seilkop et al. (2012) ranked components of diesel or gasoline exhaust, wood smoke, or simulated "downwind" coal emissions by their ability to induce pro-atherosclerotic responses in the aorta of mice that inhaled these pollutant mixtures 6 hours/day for 50 days. Filtration of PM did not have a large effect on the responses measured. Gases (i.e., SO_2, ammonia (NH_3), NO_2, CO)) were found to be most highly predictive of the response indicators. These studies using filtration of PM from whole mixtures did not consistently identify whether PM or gases from whole air pollution mixtures led to the cardiovascular, respiratory, or reproductive effects observed.

Summary

The few epidemiologic studies that have been conducted since the completion of the 2009 PM ISA continue to report health effects with a number of sources and components. Toxicological studies have attempted to identify whether particular sources or components are responsible for the health effects observed by comparing the health effects, primarily cardiopulmonary effects, observed in response to exposures to ambient fine PM sources and components and source-derived PM and components. However, the toxicology studies did not find consistent evidence that one source or component is most closely related to a specific health effect. Collectively these studies continue to report that a variety of sources and components are linked with cardiopulmonary effects and mortality; however, there is still insufficient evidence to determine which sources or components are most closely related to the observed effects.

3. SUMMARY AND CONCLUSIONS

The new studies published since the completion of the 2009 PM ISA provide additional evidence indicating a relationship between exposure to ambient PM and health effects. The new studies provide important insights on the health effects of PM exposure, with the results continuing to support a relationship between PM exposure and health effects at ambient concentrations similar or lower than those observed in previous studies. Overall: (a) the new studies generally strengthen the evidence that acute and chronic exposures to fine PM; (b) although limited in number, coarse PM studies provide evidence of an association with short-exposures and pediatric asthma ED visits, but no association between long-term exposure and mortality; (c) some of the new epidemiologic studies report effects in areas with long-term mean or mean 24-h avg $PM_{2.5}$ concentrations lower than that reported in the 2009 PM ISA; and (d) new toxicology and epidemiologic studies continue to link various health outcomes with a range of fine PM sources and components. In conclusion, the results of the new studies identified and described in this provisional assessment does not materially change any of the broad scientific conclusions regarding the health effects of PM exposure made in the 2009 PM ISA.

In summary, this provisional assessment found:

Long-term PM Exposure

- Mortality: Generally, the results of recent studies are consistent with the evidence for an association between long-term exposure to $PM_{2.5}$ and mortality (i.e., all-cause and cardiovascular) within the range of long-term mean $PM_{2.5}$ concentrations characterized in the 2009 PM ISA (i.e., 13.2 – 32.0 $\mu g/m^3$), with one new Canadian multi-city study showing associations at concentrations below 10 $\mu g/m^3$. New studies provide additional evidence for respiratory mortality, including lung cancer. Two recent studies that examined associations between long-term $PM_{10-2.5}$ exposure and mortality do not observe an association in either men or women.

- Cardiovascular morbidity: Recent studies continue to demonstrate the strongest cardiovascular effects in women, specifically for stroke, incident MI, and incident hypertension at long-term mean $PM_{2.5}$ concentrations ranging from 9.7 – 21.5 $\mu g/m^3$.

- Respiratory morbidity: Recent studies provide additional evidence for respiratory symptoms and incident asthma, as well as respiratory hospitalizations at long-term mean $PM_{2.5}$ concentrations ranging from 9.7 – 27.0 $\mu g/m^{3,}$ which is consistent with the conclusions of the 2009 PM ISA.

- Reproductive and Developmental Outcomes: Recent studies continue to provide evidence for developmental outcomes, specifically reductions in birth weight, at long-term mean $PM_{2.5}$

concentrations ranging from 11.0 – 19.8 μg/m^3, which further support the conclusions of the 2009 PM ISA.

Short-Term PM Exposure

- Mortality: The limited number of mortality studies conducted in the U.S. and Canada further support the conclusions of the 2009 PM ISA and continue to demonstrate associations between short-term $PM_{2.5}$ exposure and mortality at mean 24-h average concentrations greater than 12.8 μg/m^3. Since the completion of the 2009 PM ISA no new studies have been conducted that examined associations between short-term exposure to $PM_{10-2.5}$ and mortality.

- Respiratory hospital admissions/ED visits: New multi-city and single-city studies demonstrate consistent positive associations for all respiratory-related hospital admissions/ED visits, and provide additional evidence for increases in asthma hospital admissions/ED visits in areas with mean 24-h average $PM_{2.5}$ concentrations ranging from 6.7 – 22.0 μg/m^3, which further supports the conclusions of the 2009 PM ISA. One new study was identified that examined the association between short-term $PM_{10-2.5}$ exposure and respiratory-related ED visits, and provided evidence of increases in pediatric asthma ED visits.

- Cardiovascular hospital admissions/ED visits: New studies focusing primarily on all cardiovascular hospital admissions/ED visits continue to demonstrate consistent positive associations in areas with mean 24-h average $PM_{2.5}$ concentrations ranging from 6.7 – 15.3 μg/m^3. Additionally, there is new evidence for potential associations with hypertension ED visits, and a new study demonstrating an association with stroke onset.

Health Effects Related to Sources or Components of PM

- Consistent with those studies evaluated in the 2009 PM ISA, new studies continue to demonstrate cardiovascular and mortality effects with sources and components related to a number of combustion activities (e.g., motor vehicle emissions, coal combustion, oil burning, power plants, and wood smoke/vegetative burning), crustal sources, and secondary sulfate. Additional new studies also add to the limited number of studies that have examined associations between sources and components and respiratory and birth outcome effects, as well as, long-term exposure and mortality. Overall, new studies support the conclusions of the 2009 PM ISA that many PM components 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.

Appendix A Studies Included in the PM Provisional Science Assessment

Table A- 1 Characterization of studies of Long-term Exposure to $PM_{2.5}$ and Mortality

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Crouse et al. (2012)	1991-2001	Canada (nation-wide)	All-Cause, CVD, IHD Mortality	Non-immigrant Canadian adults	$PM_{2.5}$	8.7	Max: 19.2
Gan et al. (2011)	AQ: 1994-1998; Deaths: 1999-2002	Vancouver, BC Canada	CHD Mortality	Adults (45-85) without known CHD at baseline	$PM_{2.5}$	4.08	Max: 10.24
Greven et al. (2011)	2000-2006	U.S. (nation-wide)	All-Cause	Medicare recipients (65+ yrs)	$PM_{2.5}$	13.0	75th: 14.7
Hart et al. (2010)	AQ: 2000 Deaths: 1985-2000	U.S. (nation-wide)	All-Cause, Lung Cancer, CVD Disease, IHD, Respiratory Disease, COPD Mortality	Adult males from 4 U.S. trucking companies	$PM_{2.5}$	14.1	NR
Jerrett et al. (2009b)	1992-2002	Toronto, Canada	All-Cause, Circulatory Mortality	Adults from respiratory clinic	$PM_{2.5}$	8.71	75th: 8.83
Jerrett et al. (2009a)	AQ: 1999-2000 Deaths: 1982-2000	U.S. (nation-wide; 86 MSAs)	All-Cause, Cardio-pulmonary, CVD, IHD, Respiratory	Adults	$PM_{2.5}$	14.3	NR
Lepeule et al. (2012)	1974-2009	U.S (6 cities in East and Midwest)	All Cause, CVD and Lung Cancer Mortality	Adults	$PM_{2.5}$	15.9 (six cities combined); means for individual cities ranged from 11.4-23.6	NR

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Lipsett et al. (2011)	AQ: 1999-2005; Deaths: 1995-2005	California	All-Cause, CVD, Respiratory, Lung Cancer, IHD, CBD	Adults (Female teachers)	$PM_{2.5}$	15.64	Max: 28.35
McKean-Cowden et al. (2009)	AQ: 1979-1983; 1999-2000; Deaths: 1982-2000	U.S. (nation-wide)	Brain Cancer Mortality	Adults	$PM_{2.5}$	1979-1983: 21.1 1999-2000: 14.0 Avg: 17.7	Max: 1979-1983: 30.0 1999-2000: 22.2 Avg: 23.6
Ostro et al. (2010)	AQ: 2002-2007	California	All-Cause, CPD, IHD Mortality	Adults (Female teachers)	$PM_{2.5}$ and components (EC, OC, SO_4, NO_3, Fe, K, Si, Zn)	17.0	Max: 34.7
Puett et al. (2009)	1992-2002	U.S. (East and Midwest)	All Cause and CHD Mortality	Adults (Female Nurses)	$PM_{2.5}$	13.9	75th: 15.6 Max: 27.6
Puett et al. (2011)	1986-2002	U.S. (East and Midwest)	All Cause and CHD Mortality	Adults (Male Health Professionals)	$PM_{2.5}$	17.8 (at baseline)	NR

CVD: Cardiovascular Disease, CHD: Coronary Heart Disease; IHD: Ischemic Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; CBD: Cerebrovascular Disease; NR: Not reported

Table A- 2 Characterization of Studies of Long-term Exposure to $PM_{10-2.5}$ and Mortality

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Puett et al. (2009)	1992-2002	U.S. (East and Midwest)	All-Cause and CHD Mortality	Adults (Female Nurses)	$PM_{10-2.5}$	7.7	75th: 9.2 Max: 26.9
Puett et al. (2011)	1986-2002	U.S. (East and Midwest)	All-Cause and CHD Mortality	Adults (Male Health Professionals)	$PM_{10-2.5}$	10.1 (at baseline)	NR

CHD: Coronary Heart Disease; NR: Not reported

Table A- 3 Characterization of Studies of Long-term Exposure to $PM_{2.5}$ and Cardiovascular Effects

Author	Study Years	Location	Outcome	Population	Size Fraction	Long-term Mean Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Puett et al. (2011)	1989 - 2003	North-east and Midwest, U.S.*	All-cause Mortality, Nonfatal MI, Fatal CHD, and Hemorrhagic and Ischemic Stroke	Health Professionals Follow-Up Study Men, 40-75 yrs of age	$PM_{2.5}$, $PM_{10-2.5}$	Predicted $PM_{2.5}$ = 17.8 ± 3.4 Predicted $PM_{10-2.5}$ = 10.1 ± 3.3	Inter-quartile range (IQR): $PM_{2.5}$: 4.3 $PM_{10-2.5}$: 4.3
Lipsett et al. (2011)	1995-2000	California	All Cause Mortality, CVD Mortality, IHD Mortality, Cerebro-vascular Disease Mortality, MI Incidence, Stroke Incidence	California Teachers Study N=124,614 Women, 20- >80 yrs		15.64	Max: 28.35
Coogan et al. (2012)	1995-2005	Los Angeles, CA	Hypertension and Diabetes Mellitus (incidence)	Black Women's Health Study N=4204 (Hyper-tension) N-3236 (Diabetes) Disease free at baseline	$PM_{2.5}$	20.7	75th: 21.6

Author	Study Years	Location	Outcome	Population	Size Fraction	Long-term Mean Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Beckerman et al. (2012)	1992-1999	Toronto, Ontario	IHD (prevalence)	N=2360 Pulmonary Clinic patients	$PM_{2.5}$	50th percentile: 8.71	75th: 8.83
Adar et al. (2010)	2002-2003	6 US Cities**	Retinal Micro-vasculature	MESA, N=4,607 46-87 years, No clinical cardio-vascular disease at baseline	$PM_{2.5}$	16 (± 3)	75th: 17.2 Personal PM prediction: 17.2; Nearest monitor PM: 17.3 Max: Personal PM prediction: 26.3; Nearest monitor PM: 25.4
O'Neill et al. (2011)	2000-2002	6 US Cites**	Arterial Stiffness	MESA N=3,996 Men and Women, 44-84 yrs	$PM_{2.5}$	Imputed 20 yr avg: 21.47 ± 5.00 16.80 ± 3.90 (2005)	
Van Hee et al. (2011)	July 2000-Aug 2002	6 US Cites**	Ventricular Conduction and Repolarization Abnormalities	MESA N=4,783 45 to 84 yrs	$PM_{2.5}$		
Kloog et al. (2012a)	2000-2006	New England	Hospital Admissions	≥65 years	$PM_{2.5}$ (pre-dicted)	9.65	17.79

Table A- 4 Characterization of Studies of Long-term Exposure to $PM_{2.5}$ and Respiratory Effects

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Noonan et al. (2012)	2003-2009	Libby, MT	Respiratory infections (including bronchitis)		$PM_{2.5}$	19.0-27.0	NR
Bhattacharyya (2009)	1997-2006	US (Nationwide)	Hay Fever and Sinusitis	National Health Interview Survey respondents	$PM_{2.5}$	13.4-11.6	NR
Bhattacharyya and Shapiro (2010)	1997-2006	US (Nationwide)	Ear Infections	National Health Interview Survey respondents	$PM_{2.5}$	13.4-11.6	NR
Patel et al. (2009)	1998-2006	NYC, NY	Wheeze and Cough	Participants in Columbia Center for Children's Environmental Health birth cohort	$PM_{2.5}$	13.0	Max: 38.4
Parker et al. (2009)	1999-2005	US (Nationwide)	Respiratory Allergies	Children (ages 3-17) in National Health Interview Survey	$PM_{2.5}$	13.1	75^{th}: 15.2
Nachman and Parker (2012)	2002-2005	US (Nationwide)	Asthma, sinusitis, chronic bronchitis	National Health Interview Survey respondents	$PM_{2.5}$	12.1	75^{th}: 14.4 Max: 27.5
Karr et al. (2009a)	1997-2003	Puget Sound Region, WA	Bronchiolitis hospital admission	Washington State Birth Events Registry Database	$PM_{2.5}$	12.0	75th: 14.0 Max: 36.9
Karr et al. (2009b)	1999-2003	Georgia Air Basin of BC, Canada	Inpatient or outpatient bronchiolitis	Infants born between 1999-2002	$PM_{2.5}$	5.8	Max: 12.0
Kloog et al. (2012a)	2000-2006	New England	Respiratory hospital admission	Residents ≥65 years	$PM_{2.5}$	9.7	75th: 10.1 Max: 17.8

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Neupane et al. (2010)	2003-2005	Hamilton, ON, Canada	Pneumonia hospital admissions	Residents ≥65 years	$PM_{2.5}$	10.7	75th: 113 95th: 12.4 Max: 13.0
Meng et al. (2010)	2000-2001	San Joaquin Valley, CA	Asthma Symptoms; Asthma ED visits or Hospitalizations	San Joaquin Valley residents participating in 2001 California Health Interview Survey)	$PM_{2.5}$	21.4	75th: 23.5
Akinbami et al. (2010)	2001-2004	US (Nationwide)	Asthma prevalence	Children (ages 3-17) in National Health Interview Survey	$PM_{2.5}$	13.3	75th: 15.7
Carlsten et al. (2011)	1995-2003	Vancouver, BC, Canada	Incident Asthma	Birth cohort born in 1995	$PM_{2.5}$	5.6	NR
Clark et al. (2010)	1999-2004	Southwestern BC, Canada	Incident Asthma	Children born in 1999 and 2000 and followed up to 3-4 yrs	$PM_{2.5}$	5.6	75th: 6.1
McConnell et al. (2010)	2002-2006	Southern California	Incident Asthma	Kindergarten and First grade children in Southern California Children's Health Study	$PM_{2.5}$	13.9	Max: 17.4

Table A- 5 Characterization of Studies of Long-term Exposure to $PM_{2.5}$ and Reproductive and Developmental Effects

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Lee et al. (2011)	1997-2001	PA	C-reactive protein	Healthy women	$PM_{2.5}$	16.4	75th: 18.7 95th: 26.2 100th: 40.8
Legro et al. (2010)	2000-2007	North-eastern U.S.	In Vitro Fertilization (IVF) success	Women undergoing IVF	$PM_{2.5}$	14.0-14.5	NR
Vinikoor-Imler et al. (2012)	2000-2003	NC	Gestational Hyper-tension	All births in NC	$PM_{2.5}$	14.5	75th: 15.7
Rich et al. (2009)	1999-2003	NJ	Fetal Growth	All births in NJ	$PM_{2.5}$	13.8	NR
Chang et al. (2012b)	2001-2005	NC	Pre-term birth (PTB)	All births in NC	$PM_{2.5}$	13.0-15.3	NR
Darrow et al. (2009)	1994-2004	Atlanta, GA	PTB	All births in Atlanta (5 counties)	$PM_{2.5}$	16.5	Max: 34.1
Rudra et al. (2011)	1996-2006	Western WA	PTB	Healthy Women	$PM_{2.5}$	10.0	75th: 12.7 100th: 17.2
Wilhelm et al. (2011)	2004-2006	Los Angeles, CA	PTB	All births in LA county	$PM_{2.5}$	18.0	NR
Marshall et al. (2010)	1998-2003	NJ	Birth Defects (Oral Clefts)	All births in NJ	$PM_{2.5}$	13.4	NR
Bell et al. (2012)	2000-2004	CT and MA	Birth weight (BW)	All births from 5 counties	$PM_{2.5}$	14.0	75th: 16.0
Bell et al. (2010)	2000-2004	CT and MA	BW	All births from 5 counties	$PM_{2.5}$	14.0	NR
Darrow et al. (2011b)	1994-2004	Atlanta, GA	BW	All births in Atlanta (5 counties)	$PM_{2.5}$	16.5	NR

Author	Years of Study	Location	Outcome	Population	Size Fraction	Long-term Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Ghosh et al. (2012)	1995-2006	Los Angeles, CA	BW	All births in LA county	$PM_{2.5}$	19.8	NR
Kloog et al. (2012b)	2000-2008	MA	BW, PTB	All births in MA	$PM_{2.5}$	9.6	75th: 11.6
Kumar (2012)	2000-2004	Chicago, IL	BW	All births from Chicago MSA	$PM_{2.5}$	18.0	NR
Morello-Frosch et al. (2010)	1996-2006	CA	BW	All births in CA	$PM_{2.5}$	16.7	75th: 21.0
Salihu et al. (In Press)	2000-2007	Tampa, FL	BW, PTB	Women participating in Health Start Project	$PM_{2.5}$	11.0	Max: 23.2
Wilhelm et al. (2012)	2004-2006	Los Angeles, CA	BW	All births in LA county	$PM_{2.5}$	17.9	NR
Faiz et al. (2012)	1998-2004	NJ	Stillbirth	All births in NJ	$PM_{2.5}$	14.0	NR

Table A- 6 Characterization of U.S. and Canadian Studies of Short-term Exposure to $PM_{2.5}$ and Mortality

Author	Years	Location	Mortality	Population	Size Fraction	Mean 24-h avg Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Ito et al. (2011a)	2000-2006	New York, NY	Cardio-vascular	≥ 40	$PM_{2.5}$, PM components (EC, OC, SO_4, Ni, V, Zn, Si, Se, Na, Br, NO_3)	$PM_{2.5}$ All-Year: 14.4 Warm (April - Sept): 14.8 Cold (Oct-Mar): 14.1	NR
Zhou et al. (2011)	2000-2004	Detroit, MI Seattle, WA	Non-accidental, Cardio-vascular, Respirator y	All	$PM_{2.5}$, PM components (Al, Fe, K, Na, Ni, S, Si, V, Zn, EC)	Detroit All-Year (Median): 13.2 Warm (April-September) (Mean): 15.3 Cold (October-March) (Mean): 14.9	Detroit Max: 65.8
						Seattle All-Year (Median): 7.9 Warm (April-September) (Mean): 8.0 Cold (October-March) (Mean): 11.4	Seattle Max: 41.3

Author	Years	Location	Mortality	Population	Size Fraction	Mean 24-h avg Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Chang et al. (2012a)	2001-2005	New York, NY	Cardio-vascular, Respiratory	≥ 65	$PM_{2.5}$	Spring (March-May): 14.3 Summer (June-Aug): 17.5 Fall (Sept-Nov): 13.3 Winter (Dec-Feb): 15.4	NR
Klemm et al. (2011)	1998-2007	Atlanta, GA (4 counties)	Non-accidental, Cardio-vascular, Respiratory	≥ 65	$PM_{2.5}$, PM components (EC, OC, NO_3, SO_4)	17.0	75th: 21.6 Max: 72.9

Table A- 7 Characterization of U.S. and Canadian Studies of Short-term Exposure to $PM_{2.5}$ and Respiratory Hospital Admissions and Emergency Department Visits

Author	Years	Location	Hospital Admission /ED Visit	Popul-ation	Size Fraction	Mean 24-h avg Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Bell et al. (2012)	2000-2005	187 U.S. counties	Hospital admissions: All respiratory	≥ 65	$PM_{2.5}$, PM components	All-Year: 14.0 Summer: 16.2 Winter: 13.9	Max: All Year: 26.0 Summer: 28.5 Winter: 32.8
Zanobetti et al. (2009)	2000-2003	26 U.S. communities	ED Visits: All respiratory	≥ 65	$PM_{2.5}$, PM components (As, Al, Br, Cr, Fe, Pb, Mn, Ni, K, Si, V, Zn, NO3, SO4, NH4, Na^+, EC, OC)	15.3	$PM_{2.5}$ Max Spring: 24 (Riverside, CA) $PM_{2.5}$ Max Winter: 29.9 (Fresno, CA)

Author	Years	Location	Hospital Admission /ED Visit	Popul-ation	Size Fraction	Mean 24-h avg Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Stieb et al. (2009)	1992-2003	7 Canadian cities	ED Visits: Asthma COPD Respiratory Infection	All	$PM_{2.5}$	Montreal (1/97-12/02): 8.6 Ottawa (4/92-12/00): 6.7 Edmonton (4/92-3/02): 8.5 Halifax (1/99-12/02): 9.8 Toronto (4/99-6/03): 9.1 Vancouver (1/99-2/03): 6.8	75th: Montreal: 10.9 Ottawa: 8.7 Edmonton: 10.9 Halifax: 11.3 Toronto: 11.9 Vancouver: 8.5
Levy et al. (2012)	2000-2008	119 U.S. counties	Hospital Admissions: All respiratory	≥ 65	PM components (EC, OC, SO4, NO3)	---	---
Darrow et al. (2011a)	1993-2004 ($PM_{2.5}$ collected from 8/1/98-12/31/04)	Atlanta, GA	ED Visits: All respiratory	All	$PM_{2.5}$	1-h max: 29 24-h avg: 16 Commute: 17 Day-time: 15 Night-time: 17	1-h max: 75th: 36 Max: 188 24-h avg: 75th: 21 Max: 72 Commute: 75th: 21 Max: 76 Day-time: 75th: 19 Max: 71 Night-time: 75th: 14 Max: 88

Author	Years	Location	Hospital Admission /ED Visit	Popul-ation	Size Fraction	Mean 24-h avg Concen-tration ($\mu g/m^3$)	Upper Percentile Concen-trations ($\mu g/m^3$)
Strickland et al. (2010)	1993-2004 ($PM_{2.5}$ collected from 8/1/98-12/31/04)	Atlanta, GA	ED Visits: Asthma	5-17	$PM_{2.5}$, PM components (SO_4, EC, OC, water-soluble metals)	$PM_{2.5}$ All-Year: 16.4 Warm (May-Oct): 18.4 Cold (Nov-Apr): 14.3 $PM_{10-2.5}$ All-Year: 9.0 Warm: 9.7 Cold: 8.3	NR
Kim et al. (2011)	2003-2007	Denver, CO	Hospital Admissions: All respiratory COPD Asthma Pneumonia	All	$PM_{2.5}$, PM components (EC, OC, SO_4, NO_3)	8.0	59.4
Mar et al. (2010)	1998-2002	Tacoma, WA	ED Visits: Asthma	All	$PM_{2.5}$	12.3	NR
Kloog et al. (2012a)	2000-2006	New England	Hospital Admissions: All respiratory	≥ 65	$PM_{2.5}$	9.6	Max: 72.6
Li et al. (2011)	2004-2006	Detroit, MI	ED Visits: Asthma	2-18	$PM_{2.5}$	15.0	75th: 18.5 Max: 69.0
Glad et al. (2012)	2002-2005	Pittsburgh, PA	ED Visits: Asthma	All	$PM_{2.5}$	13.3	Max: 55.0
Grineski et al. (2011)	2000-2003	El Paso, TX	Hospital Admissions: Asthma Acute bronchitis	≥ 1	$PM_{2.5}$	12.8	75th: 15.6 95th: 26.6 Max: 119.1

Table A- 8 Characterization of U.S. and Canadian Studies of Short-term Exposure to PM10-2.5 and Respiratory Hospital Admissions and Emergency Department Visits

Author	Years	Location	Hospital Admissions /ED Visits	Population	Size Fraction	Mean 24-h avg Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Strickland et al. (2010)	1993-2004 ($PM_{2.5}$ collected from 8/1/98-12/31/04)	Atlanta, GA	ED Visits: Asthma	5-17	$PM_{10-2.5}$	$PM_{10-2.5}$ All-Year: 9.0 Warm: 9.7 Cold: 8.3	NR

Table A- 9 Characterization of U.S. and Canadian Studies of Short-term Exposure to $PM_{2.5}$ and Cardiovascular Hospital Admissions and Emergency Department Visits

Author	Study Years	Location	Outcome	Population	Size Fraction	Mean 24-h avg Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Zanobetti et al. (2009)	2000-2003	U.S. (26 communities)	ED Visits: MI, CHF	Older adults ≥ 65 yrs	$PM_{2.5}$ $PM_{2.5}$ components: As, Al, Br, Cr, Fe, Pb, Mn, Ni, K, Si, V, Zn, NO_3, SO_4, NH4, Na^+, EC, OC	15.3	$PM_{2.5}$ Max Spring: 24 (Riverside, CA) $PM_{2.5}$Max Winter: 29.9 (Fresno, CA)
Stieb et al. (2009)	1990's-early 2000s (depending on city)	Canada (7 Cities)	ED Visits: Angina/MI, Heart Failure, Dysrhythmia		$PM_{2.5}$	City-specific means (range): 6.7-9.8	City Specific 75th Percentiles: 8.5-11.9

Author	Study Years	Location	Outcome	Population	Size Fraction	Mean 24-h avg Concentration (µg/m^3)	Upper Percentile Concentrations (µg/m^3)
Ito et al. (2011a)	2000-2006	New York, NY	ED Visits: CVD	≥40 yrs	$PM_{2.5}$ $PM_{2.5}$ components: EC, OC, SO_4, NO_3, Na+, Ni, V, Zn, Si, Se, Br	All year / Warm / Cold: 14.44 / 14.79 / 14.09 1.13 / 1.03 / 1.24 4.3 / 4.51 / 4.08 4.14 / 4.81 / 3.42 2.12 / 1.52 / 2.78 0.14 / 0.14 / 0.15 0.0171 / 0.0111 / 0.0236 0.0066 / 0.0054 / 0.0080 0.0300 / 0.0216 / 0.0389 0.0769 / 0.0886 / 0.0643 0.0013 / 0.0011 / 0.0015 0.0036 / 0.0031 / 0.0040	Not presented (Note: SD provided so we could compute)
Mathes et al. (2011)	2000-2002	New York, NY	ED Visits: CVD	≥40 yrs	$PM_{2.5}$	---	---
Szyszkowicz et al. (2012)	Apr 1992-Mar 2002	Canada (Edmonton)	ED Visits: Hypertension	N=5,365	$PM_{2.5}$	8.5	75th percentile: 10.9 Max: 1.3.1
Haley et al. (2009)	2001-2005	New York State	ED Visits	Discharges from all NYS hospitals	$PM_{2.5}$	NR	NR
Bunch et al. (2011)	1993-1998	Wasatch Front, Utah	Hospital Admissions	All	$PM_{2.5}$	City specific means (range): 9.3-11.1	City specific Max: 9.3-11.1
Kloog et al. (2012a)		New England	Hospital Admissions	≥65	$PM_{2.5}$ (predicted)	9.6	72.59

Author	Study Years	Location	Outcome	Population	Size Fraction	Mean 24-h avg Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
Kim et al. (2011)	2003-2007	Denver	Hospital Admissions	All	$PM_{2.5}$	7.98	59.41
					EC	0.47	3.02
					OC	3.09	10.28
					Sulfate	1.08	14.32
					Nitrate	1.03	19.72

Table A- 10 Characterization of U.S. and Canadian Studies of Short-term Exposure to $PM_{2.5}$ and Out of Hospital Cardiac Arrests

Author	Study Years	Location	Outcome	Population	Size Fraction	Mean 24-h avg Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Silverman et al. (2010)	2002-2006	USA (New York City)	Out-of-hospital cardiac arrests	N=8,216 <40 to ≥ 70 yrs	$PM_{2.5}$	Median: All year = 12 Apr-Sept = 12 Oct-Mar = 12	Upper (95%): All year = 30 Apr-Sept = 31 Oct-Mar = 28

Table A- 11 Characterization of U.S. and Canadian Studies of Short-term Exposure to $PM_{2.5}$ and Time of Stroke Symptom Onset

Author	Study Years	Location	Outcome	Population	Size Fraction	Mean 24-h avg Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Wellenius et al. (2012)	1999-2008	Boston, MA	Time of Symptom Onset (Ischemic Stroke)	Patients admitted to BIDMC	$PM_{2.5}$	NR	NR

BIDMC= Beth Israel Deaconess Medical Center

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