HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Environ Int. 2017 December ; 109: 89–100. doi:10.1016/j.envint.2017.09.010.

Acute effects of fine particulate matter constituents on mortality: a systematic review and meta-regression analysis

Souzana Achilleos[a,*], **Marianthi-Anna Kioumourtzoglou**[b], **Chih-Da Wu**[c], **Joel D. Schwartz**[a,d], **Petros Koutrakis**[a], and **Stefania I. Papatheodorou**[e]

[a]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

[b]Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY, USA

[c]Department of Forestry and Natural Resources, National Chiayi University, Chiayi, Taiwan

[d]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

[e]Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus

Abstract

Background—The link between $PM_{2.5}$ exposure and adverse health outcomes is well documented from studies across the world. However, the reported effect estimates vary across studies, locations and constituents. We aimed to conduct a meta-analysis on associations between short-term exposure to $PM_{2.5}$ constituents and mortality using city-specific estimates, and explore factors that may explain some of the observed heterogeneity.

Methods—We systematically reviewed epidemiological studies on particle constituents and mortality using PubMed and Web of Science databases up to July 2015. We included studies that examined the association between short-term exposure to $PM_{2.5}$ constituents and all-cause, cardiovascular, and respiratory mortality, in the general adult population. Each study was summarized based on pre-specified study key parameters (e.g., location, time period, population, diagnostic classification standard), and we evaluated the risk of bias using the Office of Health Assessment and Translation (OHAT) Method for each included study. We extracted city-specific mortality risk estimates for each constituent and cause of mortality. For multi-city studies, we requested the city-specific risk estimates from the authors unless reported in the article. We performed random effects meta-analyses using city-specific estimates, and examined whether the effects vary across regions and city characteristics ($PM_{2.5}$ concentration levels, air temperature,

*Corresponding author: Souzana Achilleos, Harvard T.H. Chan School of Public Health, Department of Environmental Health, Landmark Center 4th Floor West, Room 422, 401 Park Drive, Boston, MA 02215, USA; tel.: +1 617 384 8848; soa080@mail.harvard.edu.

elevation, vegetation, size of elderly population, population density, and baseline mortality) can explain the observed heterogeneity.

Results—We found a 0.89% (95% CI: 0.68, 1.10%) increase in all-cause, a 0.80% (95% CI: 0.41, 1.20%) increase in cardiovascular, and a 1.10% (95% CI: 0.59, 1.62%) increase in respiratory mortality per 10 μg/m^3 increase in $PM_{2.5}$. Accounting for the downward bias induced by studies of single days, the all-cause mortality estimate increased to 1.01% (95% CI: 0.81, 1.20%). We found significant associations between mortality and several $PM_{2.5}$ constituents. The most consistent and stronger associations were observed for elemental carbon (EC) and potassium (K). For most of the constituents, we observed high variability of effect estimates across cities.

Conclusions—Our meta-analysis suggests that (a) combustion elements such as EC and K have a stronger association with mortality, (b) single lag studies underestimate effects, and (c) estimates of $PM_{2.5}$ and constituents differ across regions. Accounting for PM mass in constituent's health models may lead to more stable and comparable effect estimates across different studies.

Systematic review registration—PROSPERO: CRD42017055765

Keywords

Particulate matter constituents; fine particulate matter ($PM_{2.5}$); mortality; time series; acute effects; meta-analysis

1 Introduction

Ambient air pollution, one of the leading causes of mortality and disability worldwide, was associated with approximately 3.7 million premature deaths (6.7% of all deaths) in 2012 (Lim et al., 2012, WHO, 2014). Air pollution is usually described in terms of the criteria air pollutants: particulate matter (PM), ozone (O_3), sulfur dioxide (SO_2), nitrogen oxides (NO_x), carbon monoxide (CO), benzene, and lead (Pb). Of these, PM affects more people than any other pollutant (Brook et al., 2010).

Air quality standards and regulatory guidelines for inhalable PM (PM_{10}, PM with aerodynamic diameter ≤ 10 μm) and fine PM ($PM_{2.5}$, PM with aerodynamic diameter ≤ 2.5 μm) have been established by health and regulatory authorities across the world. Air quality standards are usually set mostly based on epidemiological studies, and to a lesser extent on toxicological studies, examining the effects of PM mass on human health (McClellan, 2002). $PM_{2.5}$ can reach deep into the lungs, and the associations between $PM_{2.5}$ and cardiovascular and respiratory mortality and morbidity are well documented (WHO, 2013).

However, $PM_{2.5}$ is a complex mixture of several constituents with different physicochemical properties and toxicity, the proportion of which over the total particle mass varies by source and season (Son et al. 2012; Valdés et al., 2012; Dai et al., 2014; Basagaña et al., 2015). For example, Elemental (or Black) and Organic Carbon (EC/BC, OC), are emitted from traffic (EC) and combustion sources (EC,OC), vegetation (OC), and atmospheric photochemical reactions (OC); and have been previously associated with short-term cardiovascular (CVD) and respiratory diseases (Delfino et al., 2010; Janssen et al., 2012; Kim et al., 2012). Other combustion sources such as biomass burning (potassium, K, as the main trace element) have

been associated with CVD and respiratory admissions, as well as CVD mortality (Mar et al., 2006; Andersen et al., 2007; Sarnat et al., 2008). Oil combustion particles, particularly vanadium (V) and nickel (Ni), have been associated with CVD and respiratory hospital admissions (Andersen et al., 2007; Zanobetti et al., 2009; Kioumourtzoglou et al., 2014a). Nitrate (NO_3^-) and sulfate (SO_4^{2-}) are secondary ions formed from the oxidation of nitrogen oxides and sulfur gases emitted during fossil and coal combustion and biogenic activities. Epidemiological evidence has also implicated exposure to NO_3^- and SO_4^{2-} in increased CVD (Zanobetti et al., 2009; Ito et al., 2011; Kioumourtzoglou et al., 2014a) and respiratory (Atkinson et al., 2010; Kim et al., 2012; Son et al., 2012) hospital admissions.

The underlying biological mechanism by which $PM_{2.5}$ constituents and sources are associated with cardiorespiratory health effects has been proposed by several studies. For example, transition metals (e.g., V) enhance inflammation and oxidative stress (Brook et al. 2010) and can be mobilized by SO_4^{2-} (Ghio et al., 1999); BC and SO_4^{2-} have been associated with changes in vascular (O' Neill et al., 2005) and lung function (Lepeule et al., 2014); BC has also been associated with decreased DNA methylation which leads to oxidative stress and CVD (Baccarelli et al., 2009); and wood smoke with systemic oxidative stress, coagulation, inflammation and lipid peroxidation (Barregard et al., 2006).

Identifying the $PM_{2.5}$ constituents that are the most harmful to human health can help regulatory authorities, researchers, and physicians to reduce or prevent exposure to those constituents and sources. Yet, there is substantial inconsistency in the observed health effect estimates between epidemiological studies, and it is still not clear which constituent(s) are associated with the highest risks to human health (Cassee et al., 2013; Wyzga and Rohr, 2015). Atkinson et al. (2015) performed a meta-analysis on the adverse health effects of $PM_{2.5}$ constituents based on epidemiological time-series studies conducted up to 2013. The strongest association was found for EC but the number of existing studies was insufficient to perform a meta-analysis for metals.

Between 2013 and 2015, a large number of studies on the health effects of short-term exposure to $PM_{2.5}$ constituents, covering a broad spectrum of elements and geographic locations, have been published. We performed an extended meta-analysis of studies on short-term exposure to $PM_{2.5}$ constituents and mortality using city-specific estimates, and explored factors that may explain some of the potentially observed heterogeneity. We systemically reviewed observational epidemiological studies regarding PM composition and mortality, and used the city-specific effect estimates to explore the variability of the effect estimates across locations.

2 Methods

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017055765. A complete PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Moher et al., 2009) can be found in the supplementary material.

2.1 Studies selection

We conducted a systematic search for studies on particle constituents and mortality using PubMed and Web of Science databases up to July 31, 2015. We also searched for additional studies using the 'similar articles' tool in PubMed, and the reference lists of the eligible studies. Since BC has been described by several terms in past studies, we conducted a separate search for BC to include all possible terms. For this reason, we used two separate keyword sets: ("particulate" OR "particles" OR "PM") AND ("metals" OR "sulfates" OR "sulfate" OR "nitrate" OR "nitrates" OR "ammonium" OR "carbon" OR "elements" OR "constituents" OR "species") AND "mortality"; and ("black carbon" OR "black smoke" OR "light reflectance" OR "blackness" OR "light absorption" OR "soot") AND "mortality." Synonyms of PM, constituents, and mortality were included using Medical Subject Headings (MeSH) terms. Following the PRISMA guidelines, article titles and abstracts were first reviewed independently by two of the authors (SA, SIP) to include epidemiological studies on particle constituents and mortality. The final inclusion of studies was based on full text evaluation. In case of disagreement, a third researcher (JS) resolved any discrepancies. Studies were considered eligible, if: i) they examined and reported a risk estimate for the association between exposure to $PM_{2.5}$ constituent and mortality in the general adult population, and ii) they were published in a peer-reviewed journal.

2.2 Data extraction

For each study, the two independent reviewers (SA, SIP) extracted information on location, time period, sample size, population, diagnosis standard (mortality International Classification of Diseases, ICD, code), study design (e.g., time-series), study characteristics, particle constituents examined, lag pattern used, and health model covariates into Microsoft Word. We then entered into a Microsoft Excel sheet the city-specific regression coefficients and their standard errors (reported in the study, or calculated from reported relative risk or percent change in mortality and their 95% confidence intervals) for each constituent and cause of mortality for the meta-analysis. For multi-city studies, we requested the city-specific regression coefficients and standard errors from the authors unless they were reported in the article. The extracted data was independently reviewed by a third investigator (MAK) for quality assurance/quality control.

Based on previous studies, we used the lag with the strongest association for each mortality cause: the previous day (lag 1) for all-cause and respiratory mortality and same day (lag 0) for cardiovascular mortality (Peng et al., 2005; Son et al., 2012; Krall et al., 2013). While higher associations of air pollution and respiratory mortality had been found for longer exposure windows than one day before death (Zanobetti et al., 2003; Grass and Cane, 2008), most of the studies examined lag 1 day. Therefore, in the meta-analysis, we included the studies with lag 1 or 0–1 average for all-cause and respiratory mortality, and lag 0 or 0–1 average for cardiovascular mortality. Studies with distributed lag models 0–3, 0–5, and 0–6 were also included.

2.3 Risk of bias assessment

To our knowledge, there is no established tool for risk of bias assessment for time series and case-crossover studies. Therefore, we assessed the risk of bias within each study based on

the Office of Health Assessment and Translation (OHAT) tool by the National Institutes of Environmental Health Sciences-National Toxicology Program (NIEHS-NTP), and the Navigation Guide by the University of California, San Francisco (OHAT, 2015; Lam et al., 2016). Both of these tools assess the risk of bias of individual studies based on several risk of bias domains (e.g., selection bias, confounding, measurement, missing data, reporting) in a similar way. Each domain is evaluated as "low", "probably low", "probably high", "high", or "not applicable" risk according to specific criteria. We assessed our studies for selection bias, confounding, exposure assessment, outcome assessment, incomplete outcome data, selective reporting, and conflict of interest based on pre-specified criteria (Table A.1).

Based on OHAT guidelines, it is recommended to remove studies for which the key elements (for observational human studies: exposure assessment, outcome assessment, and confounding) and most of the other criteria are characterized as 'high' or 'probably high' risk.

2.4 Data analysis

Our analysis focused on $PM_{2.5}$ mass and its constituents: SO_4^{2-}, NO_3^-, ammonium (NH_4^+), EC, black smoke (BS), OC, sodium (Na), magnesium (Mg), aluminum (Al), silicon (Si), chlorine (Cl), K, calcium (Ca), titanium (Ti), V, manganese (Mn), iron (Fe), Ni, Cu, and Zn, and their association with all-cause non-accidental, cardiovascular, and respiratory mortality for the entire population (all ages). For black carbon, we used all three measurement methods, referred to as EC (thermal optical transmittance, and reflectance) and BS (optical method). We did not convert BS to EC because their relation depends on geographic location and season (Janssen et al., 2011). In addition, we used both $PM_{2.5}$ and PM_{10} SO_4^{2-} since most SO_4^{2-} is present mostly in the fine fraction (Masri et al., 2015). Also, since most sulfur (S) is in the SO_4^{2-} form in fine particles (Masri et al., 2015; Achilleos et al., 2016), we converted S effect estimates to SO_4^{2-} estimates by dividing the regression coefficients and SEs by their molar mass ratio (SO_4^{2-}/S). Similarly, organic carbon matter (OCM) coefficients were converted to OC coefficients (OC = OCM/1.4) for comparability with the rest of the studies (Krall et al., 2013).

We first estimated the pooled effect estimates for total $PM_{2.5}$ mass. We applied a random-effects meta-analysis, using the inverse of the effect estimates variance (within plus the between-studies/cities variance) as weights, to estimate the association between $PM_{2.5}$ and cause-specific mortality (Berkey et al., 1998). The same approach was used for constituents of $PM_{2.5}$, for which we had at least three coefficient estimates. We performed a separate analysis for the population ≥65 years of age. It should be noted that the $PM_{2.5}$ meta-analysis includes only studies that also reported constituent-specific effect estimates and we did not conduct an exhaustive literature review on papers only assessing the association between PM and mortality.

One of the main objectives of the study was to estimate pooled constituent-specific effect estimates from city-specific estimates. Most studies we included did not account for potential confounding by the total PM mass in any way. However, since recent studies have shown that the association between a $PM_{2.5}$ constituent and a health outcome could indeed be confounded by total mass, some more recent studies accounted for this in the health

models (Mostofsky et al., 2012). The studies we included in the meta-analyses did so by including an interaction term between the proportion of the constituent concentration to total $PM_{2.5}$ mass and $PM_{2.5}$ mass in the health model. In doing so, they estimated whether the increased contribution of that specific constituent to the total mass modified the association between the average PM and mortality. Since these are two separate ways to assess constituent-specific associations, we ran separate meta-analyses for these two types of effect estimates. For studies that did not account for total $PM_{2.5}$ mass, we simply pooled the constituent specific effect estimates. For the studies that used an interaction between the proportion of the component to total $PM_{2.5}$ mass concentrations and $PM_{2.5}$ mass, we pooled the interaction coefficients. These correspond to the additive effect estimate to the average $PM_{2.5}$ effect estimate (i.e. the main effect of $PM_{2.5}$ in the model) if all of the $PM_{2.5}$ mass were the studied constituent.

We also tested for inter-city heterogeneity in the reported effect estimates, and we provided the p-values of the I^2-based Cochran Q test and the I^2 metric of inconsistency (Der Simonian and Laird, 2015). We considered I^2 >50% to represent substantial heterogeneity (Higgins et al., 2003). We screened for publication bias using funnel plot analysis with standard error as the measure of study size and Egger's regression test of asymmetry (Egger et al., 1997; Sterne and Egger, 2001), and adjusted for publication bias following the "trim and fill" method if needed (Duval and Tweedie, 2000). These statistical methods were applied for the PM constituents with more than 10 estimates as suggested by Sterne et al. (2011).

To explore factors that explain the potentially observed heterogeneity across the city-specific estimates, and whether they modify the association between constituents and mortality, we ran meta-regression models including (a) an indicator variable for lag pattern to examine the difference between single and average lag days, and (b) an indicator variable for region to examine regional differences, including only the regions with data from more than one city. US cities were further classified according to NOAA US climate regions (http://www.ncdc.noaa.gov/monitoring-references/maps/us-climate-regions.php): Northwest, West, Southwest, West North Central, East North Central, Central, South, Northeast, and Southeast. We combined West North Central and East North Central US regions because data were available for only one city in the West North Central region (Omaha, NE); we referred to the two combined regions as the North Central US.

We also examined city characteristics ($PM_{2.5}$ concentration levels, air temperature, elevation, vegetation, the size of the elderly population, population density, and baseline mortality) that were found to influence mortality in previous epidemiological studies (Zanobetti et al., 2012; Burtscher, 2014; Shi et al., 2015), to explain some of the observed heterogeneity by including each city-specific variable separately in the meta-regression model (Table B.1). Since some of these variables are correlated, we also conducted a factor analysis using a non-orthogonal rotation method and regressed the city-specific effect estimates on the identified factors in the meta-regression.

Meta-regression analyses were performed only when a significant association and substantial heterogeneity (I^2>50%) were found and when more than five city effect estimates were available.

Statistical significance was assessed at the $\alpha = 0.05$ level, unless otherwise reported. For our statistical analyses, we used the “meta”, “rmeta” and “mvmeta” packages in R Statistical Software, version 3.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Studies and cities included

A total of 3,850 peer-reviewed articles were identified from our search, and one additional study through references screening. Of the 3,851 articles, 837 studies were identified from BC/BS search. The number of included studies was reduced to 148 after title and abstract screening (Fig. 1). The association between chronic exposure to PM constituents and mortality is not extensively studied, and therefore we did not identify many original cohort studies since most of them were reanalyzing previous published data. Hence, we combined the time-series and case-crossover design studies to examine the association between short-term exposure to $PM_{2.5}$ constituent and all-cause, cardiovascular, and respiratory mortality. Studies were screened for overlapping population and final inclusion was based on the most recent publication date and largest number of deaths; 37 studies were excluded for overlapping population. We identified 41 studies (142 cities) that met inclusion criteria and were included in the meta-analysis; 37 studies were used for all-ages analysis and nine for the subgroup analysis of the population ≥65 years of age (Table 1, Table C.1).

Eighteen studies were conducted in Europe, ten in the USA, five in West Pacific, six in Canada, and two in South America. However, we had more cities from USA than any other region. From the 41 selected studies (14 multi-city and 27 single-city studies), we were able to obtain the city-specific estimates from 11 multi-city studies. Therefore, the main analysis included 129 city-specific estimates from 38 studies. We repeated the analysis using study-specific estimates (single city estimates and the pooled estimate from multicity studies) in order to include the remaining three multicity studies. These three studies examined the association between $PM_{2.5}$ constituents and all-cause mortality and they refer to the same population.

Two of our all-ages studies (76 cities) examined the association between $PM_{2.5}$ constituents and mortality by including an interaction between the proportion of constituent to $PM_{2.5}$ mass concentrations and total $PM_{2.5}$ mass (Valdés et al., 2012; Dai et al., 2014). One study (4 cities) reported the association of non-adjusted and PM-adjusted effect estimates using the constituent residual method (Basagaña et al., 2015). For the latter, we used only the un-adjusted estimates because it was the only study applying the residual method.

3.2 Risk of bias assessment

The risk of bias ratings for the individual studies are shown in Table 2 and more analytically in Appendix D. Most of the studies were rated with ‘low risk’ in most domains, except for exposure assessment which was rated mostly as ‘probably low’ risk and in some cases it reached to ‘high’ risk. In these types of studies design, we always have some risk of exposure misclassification because it is very difficult to assess the true average population exposure that gives attenuated effect estimates (Dominici et al., 2000; Zeger et al., 2000).

The risk is higher for more spatially heterogeneous pollutants, e.g. BC which is a traffic tracer with local sources, *versus* SO_4^{2-} that is more homogeneous in space (Sarnat et al., 2010).

None of our studies had a 'high' or 'probably high' risk rating in all of the key elements (exposure assessment, outcome assessment, and confounding) and therefore no studies were excluded from the analyses.

3.3 Pooled effect estimates

For the meta-analysis, we used mortality city-specific effect estimates for $PM_{2.5}$ mass and constituents, derived from time-series and case-crossover studies.

3.3.1 All-cause mortality—We found a 0.89% (95% CI: 0.68, 1.10%; number of cities, n_{cities}=114) increase in all-cause mortality per 10 μg/m^3 increase in $PM_{2.5}$, and a significant heterogeneity in the $PM_{2.5}$ effect estimates across the cities (Table E.1).

The pooled mortality effect estimates of each constituent, expressed as percent change per inter-quantile range (IQR; the average of IQRs across studies) of each constituent, are presented in Figure 2.

We observed significantly positive associations between all-cause mortality and BS (pooled effect estimate, β_{pooled} : 6.00×10^{-4}; 95% CI: 4.04×10^{-4}, 7.96×10^{-4}), EC (β_{pooled} : 6.00×10^{-3}; 95% CI: 2.28 $\times10^{-3}$, 9.72×10^{-3}), OC (β_{pooled} : 2.10×10^{-3}; 95% CI: 0.73×10^{-3}, 3.47×10^{-3}), SO_4^{2-} (β_{pooled} : 8.00×10^{-4}; 95% CI: 4.08×10^{-4}, 1.19×10^{-3}), Na (β_{pooled} : 1.36×10^{-2}; 95% CI: 0.28×10^{-2}, 2.44×10^{-2}), and Si (β_{pooled} : 1.42×10^{-2}; 95% CI: 0.32×10^{-2}, 2.52×10^{-2}). The results also suggested an association between all-cause mortality and NO_3^- (β_{pooled} : 7.00×10^{-4}; 95% CI: -8.40×10^{-5}, 1.48×10^{-3}), K (β_{pooled} : 1.31×10^{-2}; 95% CI: -2.19×10^{-3}, 2.84×10^{-2}), and Mn (β_{pooled} : 1.70; 95% CI: −0.21, 3.62). We observed significant heterogeneity (I^2 >50%) for BS (I^2=60%), OC (I^2=60%), Ca (I^2=86%), Mn (I^2=91%), Fe (I^2=90%), Cu (I^2=90%), and Zn (I^2=93%) effect estimates across cities. In addition, we observed positive associations with EC (β_{pooled} : 1.03×10^{-2}; 95% CI: 1.08×10^{-4}, 2.05×10^{-2}), K (β_{pooled} : 7.22×10^{-2}; 95% CI: 2.07×10^{-2}, 1.24×10^{-1}), and Cu (β_{pooled} : 0.77; 95% CI: 0.19, 1.35) in the meta-analysis from the adjusted models (number of studies, $n_{studies}$=1, n_{cities}=75).

In addition, we performed the meta-analysis for EC, BS, and SO_4^{2-} mortality effect estimates among the elderly population (≥65 years of age). EC (2.35%; 95% CI: 1.05, 3.66 % increase per 2.6 μg/m^3; $n_{studies}$ =3, n_{cities}=4) and BS (0.74%; 95% CI: 0.46, 1.02% increase per 10 μg/m^3; $n_{studies}$=2, n_{cities}=15) were statistically significantly associated with all-cause mortality. None of the studies examining associations among the elderly adjusted for $PM_{2.5}$ mass.

3.3.2 Cardiovascular mortality—We found a 0.80% (95% CI: 0.41, 1.20%; n_{cities}=89) increase in cardiovascular mortality per 10 μg/m^3 increase in $PM_{2.5}$, and a significant heterogeneity in the $PM_{2.5}$ effect estimates across the cities (Table E.2).

The observed pooled associations between PM constituents and cardiovascular mortality were not as consistent as all-cause mortality. Positive associations were observed with BS (β_{pooled} : 7.00×10^{-4}; 95% CI: 5.04×10^{-4}, 8.96×10^{-4}), EC (β_{pooled} : 5.70×10^{-3}; 95% CI: 1.19×10^{-3}, 1.02×10^{-2}), NH_4^+ (β_{pooled} : 4.40×10^{-3}; 95% CI: 1.26×10^{-3}, 7.54×10^{-3}), NO_3^- (β_{pooled} : 1.50×10^{-3}; 95% CI: 0.32×10^{-3}, 2.68×10^{-3}), Cl (β_{pooled} : 2.64×10^{-2}; 95% CI: 0.48×10^{-3}, 4.80×10^{-2}), and Ca (β_{pooled} : 4.77×10^{-2}; 95% CI: 1.48×10^{-2}, 8.06×10^{-2}); with some evidence for SO_4^{2-} (β_{pooled} : 9.00×10^{-4}; 95% CI: -8.00×10^{-5}, 1.88×10^{-3}), Fe (β_{pooled} : 5.17×10^{-2}; 95% CI: -8.47×10^{-3}, 1.12×10^{-1}), K (β_{pooled} : 2.77×10^{-2}; 95% CI: -3.07×10^{-3}, 5.85×10^{-2}), and Mg (β_{pooled} : 0.19; 95% CI: −0.02, 0.40) (Fig. 3). We did not observe any significant heterogeneity of the estimates across cities (Table D.2). No significant associations were found for the $PM_{2.5}$ adjusted effect estimates, except for V (β_{pooled}: 2.60; 95% CI: 0.27, 4.93; $n_{studies}$=1, n_{cities}=75).

3.3.3 Respiratory mortality—We found a 1.10% (95% CI: 0.59, 1.62%; n_{cities}=86) increase in respiratory mortality per 10 μg/m^3 increase in $PM_{2.5}$, and no significant heterogeneity in the $PM_{2.5}$ effect estimates across the cities (Table E.3). Among PM components, we found positive associations between respiratory mortality and BS only (β_{pooled} : 1.10×10^{-3}; 95% CI: 0.60×10^{-3}, 1.50×10^{-3}) (Fig. 4). High heterogeneity was detected for EC, OC, and Cl across cities (I^2 >50%). We observed positive associations with the $PM_{2.5}$-adjusted V (β_{pooled} : 5.15; 95% CI: 0.42, 9.89; $n_{studies}$=1, n_{cities}=75) and Zn (β_{pooled} : 1.00×10^{-3}; 95% CI: 2.00×10^{-5}, 1.98×10^{-3}; $n_{studies}$=2, n_{cities}=76), with some evidence for SO_4^{2-} (β_{pooled} : 6.10×10^{-3}; 95% CI: -4.48×10^{-3}, 1.67×10^{-2}; $n_{studies}$=2, n_{cities}=76), as well.

3.3.4 Additional analyses—The meta-analysis was repeated using study-specific estimates to include the three multi-city studies for which we did not obtain the city-specific estimates, and results are included in the supplementary material (Tables E.1–E.3, Fig. F.1–F.4). We were able to assess for publication bias for $PM_{2.5}$ (all-cause, cardiovascular, respiratory) and SO_4^{2-} (all-cause, cardiovascular) effect estimates. Even if there was some asymmetry in the funnel plots (e.g., $PM_{2.5}$ and all-cause), Egger's test showed no statistically significant asymmetry in the plots and therefore no further adjustments for publication bias were made (Fig. G.1–G.5).

The results of the study-specific analysis were in good agreement with the city-specific analysis.

3.4 Meta-regression analyses

We found significant heterogeneity in $PM_{2.5}$ effect estimates and in many unadjusted constituent estimates. In contrast, the heterogeneity among the adjusted effect estimates was low (I^2<25%) for all constituents and mortality causes (see Tables E.1–E.3). Meta-regression analyses were performed only when a significant association and substantial heterogeneity (I^2>50%) were found and when more than five city effect estimates were available.

3.4.1 Exposure window—First, we explored whether the effect estimates for the all-age population varied by the exposure window examined, namely, a single-day exposure *versus*

a two-day average exposure. However, we were not able to assess the impact of exposure duration in the associations between constituents and mortality, since most studies used a single day exposure window and thus, no constituent satisfied our criteria for meta-regression except $PM_{2.5}$ mass. The all-cause mortality effect estimate of $PM_{2.5}$ for a single day exposure (0.50%; 95% CI: 0.06, 0.94%; n_{cities}=29; lag1) was statistically significantly lower than the two-day average exposure (1.01%; 95% CI: 0.77, 1.26%; n_c =85; lag0–1). Similar effects, but not statistically significant, were observed for cardiovascular and respiratory mortality.

3.4.2 Regional differences—We also explored whether the associations between short-term exposure to $PM_{2.5}$ and EC, and all-cause mortality vary across the regions (Fig. 5). Among the constituents, only EC satisfied the criteria for inclusion in the meta-regression. Our analysis included $PM_{2.5}$ and PM-unadjusted EC city-specific effect estimates from the US (n_{cities}-$PM_{2.5}$=101, n_{cities}-EC=72), Europe (n_{cities}-$PM_{2.5}$=6, n_{cities}-EC=4), and West Pacific (n_{cities}-$PM_{2.5}$=5, n_{cities}-EC=4). Table H.1 presents the cities we included in each region. The highest effect estimates on all-cause mortality were observed in North Central US ($PM_{2.5}$: 1.74%; 95% CI: 0.97, 2.50% per 10 μg/m^3), and Europe (EC: 4.45%; 95% CI: −0.44, 9.42% per 2.6 μg/m^3). Regional differences explained most of the variability in the $PM_{2.5}$ (difference in the I^2 before and after adding the regions, ΔI^2=28%), and EC (ΔI^2=84%) effect estimates. The remaining heterogeneity in $PM_{2.5}$ (I^2=23%) was still statistically significant (Q=130.7, p=0.03) after inclusion of the regions.

3.4.3 City characteristics—We also observed modification of the association between $PM_{2.5}$ mass, and its constituents, and mortality by several variables. In the case of $PM_{2.5}$ and all-cause mortality, we controlled for the exposure window (single day *versus* two-day average exposure) in the meta-regression models to avoid bias caused by the lag pattern. We found higher $PM_{2.5}$ effect estimates in cities with lower summer temperatures (ΔI^2=16%), and with some evidence for higher elevation (ΔI^2=1%, p-value of elevation = 0.065). No effect modification was observed for cardiovascular mortality. BS showed stronger association with all-cause mortality in cities with lower elevation (ΔI^2=9%), vegetation (ΔI^2=3%), and temperature difference (ΔI^2=9%). Stronger associations were also found in cities with low vegetation (ΔI^2=70%) for EC, and higher altitudes (ΔI^2=91%) for EC and OC (ΔI^2=60%).

We identified five factors that explained 82% of the variance of the city-specific variables: $PM_{2.5}$ concentration, winter temperature, temperature difference, vegetation (annual and summer), elevation, size of elderly population, population density and baseline mortality. Factor 1 was described by high vegetation and low elevation; factor 2 by high elevation and temperature difference, and low winter temperature; factor 3 by high mortality rate and elderly population; factor 4 by population density; and factor 5 by high vegetation and low $PM_{2.5}$ levels. However, these factors did not explain the observed variability across the cities.

We repeated the meta-regression analyses using only the US cities effect estimates on all-cause mortality. The city-specific variables and their factors did not explain the observed variability.

4 Discussion

Our systematic review identified studies that examined the association between short term exposure to $PM_{2.5}$ constituents and mortality in the Americas, Europe, and Western Pacific. SO_4^{2-} has been the most studied PM constituent, followed by EC/BC. BS has been studied only in Europe since 1990s.

In this meta-analysis, we derived the pooled effect estimates for $PM_{2.5}$ and for each of the constituents on mortality using city specific effect estimates. $PM_{2.5}$ had a stronger association with respiratory mortality, than with all-cause and cardiovascular mortality. We also found that studies using a single day of $PM_{2.5}$ as the exposure variable under-estimated the effect of PM mass on mortality compared to studies using a two-day average, which could be useful for future studies and risk assessments.

We found significantly positive associations for several $PM_{2.5}$ constituents: EC, BS, OC, SO_4^{2-}, Na, and Si with all-cause mortality with some evidence for NO_3^-, Mn, and K; BS, EC, NH_4^+, NO_3^-, Cl, and Ca, with cardiovascular mortality, with some evidence for K; and BS with respiratory mortality. The association between mortality and EC and BS was stronger among the elderly. Restricting to studies that controlled for PM mass, we found associations with EC, K, and Cu (for all-cause deaths); V (for cardiovascular and respiratory deaths); and Zn (for respiratory deaths).

Our analysis based on $PM_{2.5}$ unadjusted estimates suggests that Na and Si have the highest effect (coefficient) on all-cause mortality, and Cl on cardiovascular mortality. However, we are not convinced that these elements have the highest toxicity among all $PM_{2.5}$ constituents for several reasons. First, we found high heterogeneity in the effect sizes in the unadjusted meta-analyses, but much less heterogeneity in the meta-analysis of the $PM_{2.5}$ adjusted city coefficients. This indicates that failure to control for $PM_{2.5}$ mass is contributing to substantial variability in the estimates, which may obscure detecting which components truly have the highest toxicity. Moreover, the effects from the $PM_{2.5}$-unadjusted models may be confounded by total $PM_{2.5}$ and other constituents that co-vary, since some constituents are present in high proportion or highly correlated with the total mass. In this case, the health effects of the constituent(s) may be due to the total $PM_{2.5}$ mass or other constituents that are emitted from the same sources (Mostofsky et al., 2012). Controlling for $PM_{2.5}$ mass, EC, K, and Cu were associated with all-cause mortality, and V with cardiovascular and respiratory mortality. The consistency of the EC and K associations in the two analyses are more convincing of a true effect.

Second, the exposure measurement error of each constituent is different and potentially larger than that of the total $PM_{2.5}$. In time-series studies, larger exposure measurement error is expected to result in attenuated effect estimates (Zeger et al., 2000). Measurement error can be caused by measurement/analytical errors, indoor-outdoor relationships which are affected by weather, and source spatial heterogeneity (Koutrakis et al., 2005; Sarnat et al., 2010; Bell et al., 2011). For example, traffic emissions exhibit large spatial variability, whereas this is not the case for regional pollutants like SO_4^{2-} (Sarnat et al., 2010). Moreover, larger contribution of locally-generated particles has been shown to result in

significantly increased measurement error due to spatial heterogeneity in the $PM_{2.5}$ mass concentrations (Kioumourtzoglou et al., 2014b). BC, even though it is a heterogeneous pollutant, it appears to be an important predictor of health effects suggesting that it is either directly toxic or acts as a surrogate of harmful traffic emissions.

The included studies varied in several study design characteristics, which could bias and modify the estimates, such as: i) method of chemical analysis (e.g., some constituents can be measured with ion chromatography, inductively coupled plasma mass spectrometry, or X-ray fluorescence; EC with reflectance or thermal optical method) since the form of the constituent studied (elemental or ion) can give different results (Cao et al., 2012), ii) number and type of constituents examined, iii) sampling frequency; most of the studies used daily $PM_{2.5}$ mass data but $PM_{2.5}$ constituent's measurements were available in a more reduced frequency (e.g., every third or sixth day) which could introduce error in the estimated effects (Klemm et al., 2011), iv) number and type (e.g., background, urban) of sites per city, v) specifications of the health regression model (e.g., degrees of freedom (df) used per year for time variable, adjusting or not for influenza and holidays, lag and df used to control for weather variables), and vi) mortality cause; most of the studies examined the association with all-cause mortality but very few studies examined other causes of death (e.g., Chronic Obstructive Pulmonary Disease, ischemic heart disease).

We observed large variability among mortality effect estimates across cities and studies. The coefficients of $PM_{2.5}$ constituents were too few to explore the impact of study-specific characteristics and whether these modify the association between constituent and mortality, except in the case of the exposure window (single *versus* average lag exposure). Regional differences explained most of the observed variability. The regional differences in the effect estimates are probably due to spatial variation in $PM_{2.5}$ composition and sources, and individual or community characteristics such as income, education, smoking, prevalence of air conditioning use, and other potential effect modifiers that vary across locations (Bell et al., 2011; Dai et al., 2014; Kioumourtzoglou et al., 2016). However, we were not able to explain much of the variability in the effect estimates with city-specific variables ($PM_{2.5}$ concentration, temperature, elevation, vegetation, population density, baseline mortality, elderly population size). Even though some city characteristics explained some of the observed variability, their effect did not remain statistically significant when non-US cities were removed from the analysis. These include summer temperature that showed a negative effect, elevation a positive effect, and vegetation that resulted in a negative and positive effect. Among these, elevation had the most consistent positive effect and agrees with Burtscher (2014) findings.

To our knowledge, this is the first meta-analysis on $PM_{2.5}$ constituents (ions, metals, elements) and mortality. One other strength of this analysis is the use of city-specific estimates that gave the ability to: i) exclude duplicate populations without excluding studies, since some multi-city studies were overlapping; and ii) explore whether city characteristics can modify the effect estimates. Our studies were selected based on a priori protocol and the analysis included studies that examined the same lag exposure to ensure comparability. However, the exposure window was selected based on the strongest association between

mortality and $PM_{2.5}$, but not with $PM_{2.5}$ constituents since there is no sufficient evidence per constituent about this.

5 Conclusions

In our meta-analysis, we found high variability among the individual time-series studies and their conclusions on which constituent(s) has (have) the highest association with mortality. This makes it difficult to conclude which component per se has the highest toxicity, but from both estimates ($PM_{2.5}$ - adjusted and unadjusted), EC and K, traffic and wood combustion elements, had a stronger association with mortality than other constituents.

The observed variability across constituent's effect estimates remains a key question. For this reason, further research is needed to improve air pollution health models. For example, accounting for PM mass in constituent's health models may lead to more stable and comparable effect estimates across different studies. Future studies can also examine the effect of other PM constituents and properties (e.g., oxidative stress) and whether these may explain some of the observed variability across the effect estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the Harvard Cyprus Program and the Cyprus International Initiative for Environmental and Public Health in association with Harvard T.H. Chan School of Public Health. In addition, this publication was made possible by U.S. EPA grant numbers RD83479801 and RD83587201, and NIH T32 grant ES007069. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the U.S. EPA. Further, U.S. EPA does not endorse the purchase of any commercial products or services mentioned in the publication. The authors will also like to thank Dr. X. Basagaña, Dr. J.R. Krall, Ms. L. Dai, Prof. K. Katsouyanni, Dr. E. Samoli, Dr. F. Ballester, Prof. R. Agius, Dr. M. Carder, Dr. H. Kan, Dr. A. Zanobetti, and Dr. A. Valdes for providing us the city-specific mortality effect estimates of their studies.

References

Achilleos S, Wolfson JM, Ferguson ST, Kang CM, Hadjimitsis DG, Hadjicharalambous M, et al. Spatial variability of fine and coarse particle composition and sources in Cyprus. Atmos Res. 2016; 169:255–270.

Aga E, Samoli E, Touloumi G, Anderson HR, Cadum E, Forsberg B, et al. Short-term effects of ambient particles on mortality in the elderly: results from 28 cities in the APHEA2 project. Eur Respir J Suppl. 2003; 40:28s–33s. [PubMed: 12762571]

Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, et al. Short-term effects of ambient particles on cardiovascular and respiratory mortality. Epidemiology. 2006; 17:230–233. [PubMed: 16477266]

Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Scheike T, Lof S. Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. J Expo Sci Environ Epidemiol. 2007; 17:625–636. [PubMed: 17495872]

Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Strachan DP. Air pollution and daily mortality in London: 1987–92. BMJ. 1996; 312:665–669. [PubMed: 8597732]

Anderson HR, Bremner SA, Atkinson RW, Harrison RM, Walters S. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom:

associations with fine and coarse particles, black smoke and sulphate. Occup Environ Med. 2001; 58:504–510. [PubMed: 11452044]

Atkinson RW, Fuller GW, Anderson HR, Harrison RM, Armstrong B. Urban ambient particle metrics and health: a time-series analysis. Epidemiology. 2010; 21:501–511. [PubMed: 20502338]

Atkinson RW, Mills IC, Walton HA. Fine particle constituents and health - A systematic review and meta-analysis of epidemiological time series studies of daily mortality and hospital admissions. J Expos Sci Environ Epidemiol. 2015; 25:208–214.

Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, Suh HH, et al. Rapid DNA methylation changes after exposure to traffic particles. Am J Respir Crit Care Med. 2009; 179:572–578. [PubMed: 19136372]

Ballester F, Corella D, Pérez-Hoyos S, Hervás A. Air pollution and mortality in Valencia, Spain: a study using the APHEA methodology. J Epidemiol Community Health. 1996; 50:527–533. [PubMed: 8944859]

Ballester F, Sáez M, Pérez-Hoyos S, Iñíguez C, Gandarillas A, Tobías A, et al. The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. Occup Environ Med. 2002; 59:300–308. [PubMed: 11983845]

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3.Rating the quality of evidence. J Clin Epidemiol. 2011; 64(4):401–406. [PubMed: 21208779]

Barregard L, Sällsten G, Gustafson P, Andersson L, Johansson L, Basu S, et al. Experimental exposure to wood-smoke particles in healthy humans: effects on markers of inflammation, coagulation, and lipid peroxidation. Inhal Toxicol. 2006; 18:845–853. [PubMed: 16864402]

Basagaña X, Jacquemin B, Karanasiou A, Ostro B, Querol X, Agis D, et al. MED-PARTICLES Study group. Short-term effects of particulate matter constituents on daily hospitalizations and mortality in five South-European cities: results from the MED-PARTICLES project. Environ Int. 2015; 75:151–158. [PubMed: 25461424]

Bell ML, Ebisu K, Peng RD. Community-level spatial heterogeneity of chemical constituent levels of fine particulates and implications for epidemiological research. J Expo Sci Environ Epidemiol. 2011; 21:372–384. [PubMed: 20664652]

Berkey CS, Hoaglin DC, Antczak-Bouckoms A, Mosteller F, Colditz GA. Meta-analysis of multiple outcomes by regression with random effects. Stat Med. 1998; 17:2537–2550. [PubMed: 9839346]

Bilotta GS, Milner AM, Boyd IL. Quality assessment tools for evidence from environmental science. Environmental Evidence. 2014; 3(14):1–14.

Brook JR, Burnett RT, Dann TF, Cakmak S, Goldberg MS, Fan X, Wheeler AJ. Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. J Expo Sci Environ Epidemiol. 2007; 17(Suppl 2):S36–44. [PubMed: 18079763]

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010; 121:2331–2378. [PubMed: 20458016]

Burnett RT, Brook J, Dann T, Delocla C, Philips O, Cakmak S, et al. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol. 2000; 12(Suppl 4):15–39.

Burnett RT, Stieb D, Brook JR, Cakmak S, Dales R, Raizenne M, et al. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Health. 2004; 59(5):228–36. [PubMed: 16201668]

Burtscher M. Effects of Living at Higher Altitudes on Mortality: A Narrative Review. Aging Dis. 2014; 54:274–280.

Cakemak S, Dales RE, Vida CB. Components of particulate air pollution an mortality in Chile. Int J Occup Environ Health. 2009; 15:152–158. [PubMed: 19496481]

Cao J, Xu H, Xu Q, Chen B, Kan H. Fine particulate matter constituents and cardiopulmonary mortality in a heavily polluted Chinese city. Environ Health Perspect. 2012; 120:373–378. [PubMed: 22389181]

Carder M, McNamee R, Beverland I, Elton R, Van Tongeren M, Cohen GR, et al. Interacting effects of particulate pollution and cold temperature on cardiorespiratory mortality in Scotland. Occup Environ Med. 2008; 65:197–204. [PubMed: 17928391]

Carroll, ML., DiMiceli, CM., Sohlberg, RA., Townshend, JRG. 250m MODIS Normalized Difference Vegetation Index. Collection. Vol. 4. University of Maryland; College Park, Maryland: 2004.

Cassee FR, Héroux ME, Gerlofs-Nijland ME, Kelly FJ. Particulate matter beyond mass: recent health evidence on the role of fractions, chemical constituents and sources of emission. Inhalation Toxicology. 2013; 25:802–812. [PubMed: 24304307]

Delfino RJ, Tjoa T, Gillen DL, Staimer N, Polidori A, Arhami M, et al. Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. Epidemiology. 2010; 21:396–404. [PubMed: 20335815]

Dai L, Zanobetti A, Koutrakis P, Schwartz JD. Associations of fine particulate matter species with mortality in the United States: a multicity time-series analysis. Environ Health Perspect. 2014; 122:837–842. [PubMed: 24800826]

Der Simonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015; 45:139–145. [PubMed: 26343745]

Dominici F, Zeger SL, Samet JM. A measurement error model for time-series studies of air pollution and mortality. Biostatistics. 2000; 1:157–175. [PubMed: 12933517]

Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56(2):455–463. [PubMed: 10877304]

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–634. [PubMed: 9310563]

Fairley D. Mortality and Air Pollution for Santa Clara County, California, 1989–1996. Revised Analyses of Time-Series Studies of Air Pollution and Health. Health Effects Institute. Special Report. 2003:97–106.

Filleul L, Le Tertre A, Baldi I, Tessier JF. Difference in the relation between daily mortality and air pollution among elderly and all-ages populations in southwestern France. Environ Res. 2004; 94:249–253. [PubMed: 15016591]

Fischer P, Ameling C, Marra M, Cassee FR. Absence of trends in relative risk estimates for the association between Black Smoke and daily mortality over a 34 years period in The Netherlands. Atmos Environ. 2009; 43:481–485.

Fischer PH, Marra M, Ameling CB, Janssen N, Cassee FR. Trends in relative risk estimates for the association between air pollution and mortality in The Netherlands, 1992–2006. Environ Res. 2011; 111:94–100. [PubMed: 20970785]

Geng F, Hua J, Mu Z, Peng L, Xu X, Chen R, et al. Differentiating the associations of black carbon and fine particle with daily mortality in a Chinese city. Environ Res. 2013; 120:27–32. [PubMed: 22981950]

Gent JF, Koutrakis P, Belanger K, Triche E, Holford TR, Bracken MB, et al. Symptoms and medication use in children with asthma and traffic related sources of fine particle pollution. Environ Health Perspect. 2009; 117:1168–1174. [PubMed: 19654929]

Ghio AJ, Stoneheurner J, McGee JK, Kinsey JS. Sulfate content correlates with iron concentrations in ambient air pollution particles. Inhal Toxicol. 1999; 11:293–307. [PubMed: 10380171]

Goldberg MS, Burnett RT, Bailar JC 3rd, Brook J, Bonvalot Y, Tamblyn R, et al. The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 1. Nonaccidental mortality. Environ Res. 2001a; 86:12–25. [PubMed: 11386737]

Goldberg MS, Burnett RT, Bailar JC 3rd, Brook J, Bonvalot Y, Tamblyn R, et al. The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 2. Cause-specific mortality. Environ Res. 2001b; 86:26–36. [PubMed: 11386738]

Goldman GT, Mulholland JA, Russell AG, Strickland MJ, Klein M, Waller LA, Tolbert PE. Impact of exposure measurement error in air pollution epidemiology: effect of error type in time-series studies. Environ Health. 2011; 10:61. [PubMed: 21696612]

Grass D, Cane M. The effects of weather and air pollution on cardiovascular and respiratory mortality in Santiago, Chile during the winters of 1988–1996. Int J Climatol. 2008; 28:1113–1126.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J. 2008; 336:924–926. [PubMed: 18436948]

Gwynn RC, Burnett RT, Thurston GD. A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ Health Perspect. 2000; 108:125–133. [PubMed: 10656852]

Heo J, Schauer JJ, Yi O, Paek D, Kim H, Yi SM. Fine particle air pollution and mortality: importance of specific sources and chemical species. Epidemiology. 2014; 25:379–388. [PubMed: 24718091]

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–560. [PubMed: 12958120]

Hoek G, Brunekreef B, Verhoeff A, van Wijnen J, Fischer P. Daily mortality and air pollution in The Netherlands. J Air Waste Manag Assoc. 2000; 50:1380–1389.

Huang W, Cao J, Tao Y, Dai L, Lu SE, Hou B, Wang Z, Zhu T. Seasonal variation of chemical species associated with short-term mortality effects of $PM_{2.5}$ in Xi'an, a Central City in China. Am J Epidemiol. 2012; 175(6):556–566. [PubMed: 22323403]

Ito K, Mathes R, Ross Z, Nádas A, Thurston G, Matte T. Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. Environ Health Perspect. 2011; 119:467–473. [PubMed: 21463978]

Janssen NAH, Hoek G, Simic-Lawson M, Fischer P, van Bree L, ten Brink H, et al. Black carbon as an additional Indicator of the adverse health effects of airborne particle compared with PM_{10} and $PM_{2.5}$. Environ Health Perspect. 2011; 119:1691–1699. [PubMed: 21810552]

Janssen, NAH., Gerlofs-Nijland, ME., Lanki, T., Salonen, RO., Cassee, F., Hoek, G., et al. Health Effects of Black Carbon. WHO Regional Office for Europe; Copenhagen: 2012.

Katsouyanni K, Schwartz J, Spix C, Touloumi G, Zmirou D, Zanobetti A, et al. Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. J Epidemiol Community Health. 1996; 50:S12–S18. [PubMed: 8758218]

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology. 2001; 12:521–531. [PubMed: 11505171]

Kim SY, Peel JL, Hannigan MP, Dutton SJ, Sheppard L, Clark ML, et al. The temporal lag structure of short-term associations of fine particulate matter chemical constituents and cardiovascular and respiratory hospitalizations. Environ Health Perspect. 2012; 120:1094–1099. [PubMed: 22609899]

Kim SY, Dutton SJ, Sheppard L, Hannigan MP, Miller SL, Milford JB, et al. The short-term association of selected components of fine particulate matter and mortality in the Denver Aerosol Sources and Health (DASH) study. Environ Health. 2015; 14:49. [PubMed: 26047618]

Kioumourtzoglou MA, Coull BA, Dominici F, Koutrakis P, Schwartz J, Suh H. The impact of source contribution uncertainty on the effects of source-specific PM2.5 on hospital admissions: a case study in Boston, MA. J Expo Sci Environ Epidemiol. 2014a; 24:365–371. [PubMed: 24496220]

Kioumourtzoglou MA, Spiegelman D, Szpiro AA, Sheppard L, Kaufman JD, Yanosky JD, et al. Exposure measurement error in $PM_{2.5}$ health effects studies: a pooled analysis of eight personal exposure validation studies. Environmental Health. 2014b; 13(1):2. [PubMed: 24410940]

Kioumourtzoglou MA, Schwartz J, James P, Dominici F, Zanobetti A. $PM_{2.5}$ and mortality in 207 US cities: Modification by temperature and city characteristics. Epidemiology. 2016; 27:221–227. [PubMed: 26600257]

Klemm RJ, Mason RM Jr, Heilig CM, Neas LM, Dockery DW. Is Daily Mortality Associated Specifically with Fine Particles? Data Reconstruction and Replication of Analyses. J Air Waste Manag Assoc. 2000; 50:1215–1222. [PubMed: 10939214]

Klemm RJ, Thomas EL, Wyzga RE. The impact of frequency and duration of air quality monitoring: Atlanta, GA, data modeling of air pollution and mortality. J Air Waste Manag Assoc. 2011; 61:1281–1291. [PubMed: 22168111]

Koutrakis P, Suh HH, Sarnat JA, Brown KW, Coull BA, Schwartz J. Characterization of particulate and gas exposures of sensitive subpopulations living in Baltimore and Boston. Res Rep Health Eff Inst. 2005; 131:1–65.

Krall JR, Anderson GB, Dominici F, Bell ML, Peng RD. Short-term exposure to particulate matter constituents and mortality in a national study of U.S. urban communities. Environ Health Perspect. 2013; 121:1148–1153. [PubMed: 23912641]

Lall R, Ito K, Thurston GD. Distributed lag analyses of daily hospital admissions and source-apportioned fine particle air pollution. Environ Health Perspect. 2011; 119:455–460. [PubMed: 21172759]

Lam J, Sutton P, Kalkbrenner A, Windham G, Halladay A, Koustas E, et al. A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder. PLoS ONE. 2016; 11:e0161851. [PubMed: 27653281]

Lepeule J, Litonjua AA, Coull B, Koutrakis P, Sparrow D, Vokonas PS, et al. Long-term effects of traffic particles on lung function decline in the elderly. Am J Respir Crit Care Med. 2014; 190:542–548. [PubMed: 25028775]

Le Tertre A, Quénel P, Eilstein D, Medina S, Prouvost H, Pascal L, et al. Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. Arch Environ Health. 2002; 57:311–319. [PubMed: 12530597]

Li P, Xin J, Wang Y, Li G, Pan X, Wang S, et al. Association between particulate matter and its chemical constituents of urban air pollution and daily mortality or morbidity in Beijing City. Environ Sci Pollut Res Int. 2015; 22:358–368. [PubMed: 25074829]

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012; 380:2224–2260.

Lippmann M, Ito K, Nádas A, Burnett RT. Association of particulate matter components with daily mortality and morbidity in urban populations. Res Rep Health Eff Inst. 2000; 95:5–72.

Mar TF, Ito K, Koenig JQ, Larson TV, Eatough DJ, Henry RC, et al. PM source apportionment and health effects. 3. Investigation of inter-method variations in associations between estimated source contributions of PM2.5 and daily mortality in Phoenix, AZ. J Expo Sci Environ Epidemiol. 2006; 16:311–320. [PubMed: 16288316]

Masri S, Kang CM, Koutrakis P. Composition and sources of fine and coarse particles collected during 2002–2010 in Boston, MA. J. Air Waste Manage Assoc. 2015; 65:287–297.

McClellan RO. Setting ambient air quality standards for particulate matter. Toxicology. 2002; 181–182:329–347.

Mittleman MA. Optimal referent selection strategies in case-crossover studies: a settled issue. Epidemiology. 2005; 16:715–716. 1. [PubMed: 16222159]

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PloS Med. 2009; 6(6):e1000097. Available: www.prisma-statement.org. [PubMed: 19621072]

Mostofsky E, Schwartz J, Coull BA, Koutrakis P, Wellenius GA, Suh HH, et al. Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol. 2012; 176:317–326. [PubMed: 22850792]

OHAT (Office of Health Assessment and Translation). Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. Division of the National Toxicology Program. National Institute of Environmental Health Sciences. 2015. Available: https://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html#Ongoing-Methods-Development-Activities

O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation. 2005; 111:2913–2920. [PubMed: 15927967]

Ostro B, Rauch S, Green S. Quantifying the health impacts of future changes in temperature in California. Environ Res. 2011; 111:1258–1264. [PubMed: 21975126]

Ostro B, Tobias A, Karanasiou A, Samoli E, Querol X, Rodopoulou S, et al. MEDPARTICLES Study Group. The risks of acute exposure to black carbon in Southern Europe: results from the MED-PARTICLES project. Occup Environ Med. 2015; 72:123–129. [PubMed: 25385880]

Peng RD, Dominici F, Pastor-Barriuso R, Zeger SL, Samet JM. Seasonal analyses of air pollution and mortality in 100 US cities. Am J Epidemiol. 2005; 161:585–594. [PubMed: 15746475]

Peng RD, Dominici F, Louis TA. Model choice in time series studies of air pollution and mortality. J R Statistic Soc A. 2006; 169:179–203.

Sacks JD, Ito K, Wilson WE, Neas LM. Impact of covariate models on the assessment of the air pollution-mortality association in a single- and multipollutant context. Am J Epidemiol. 2012; 176:622–634. [PubMed: 22984096]

Samoli E, Schwartz J, Wojtyniak B, Touloumi G, Spix C, Balducci F, et al. Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. Environ Health Perspect. 2001; 109:349–353. [PubMed: 11335182]

Samet, JM., Zeger, SL., Dominici, F., Curriero, F., Coursac, I., Dockery, DM., et al. Research Report. Vol. 94. Health Effects Institute; Cambridge MA: 2000. The National Morbidity, Mortality and Air Pollution Study, Part, II: Morbidity and Mortality from Air Pollution in the United States.

Sarnat JA, Marmur A, Klein M, Kim E, Russell AG, Sarnat SE, et al. Fine particle sources and cardiorespiratory morbidity: an application of chemical mass balance and factor analytical source-apportionment methods. Environ Health Perspect. 2008; 116:459–466. [PubMed: 18414627]

Sarnat SE, Klein M, Sarnat JA, Flanders WD, Waller LA, Mulholland JA, et al. An examination of exposure measurement error from air pollutant spatial variability in time-series studies. J Expo Sci Environ Epidemiol. 2010; 20:135–146. [PubMed: 19277071]

Shi L, Kloog I, Zanobetti A, Liu P, Schwartz JD. Impacts of temperature and its variability on mortality in New England. Nat Clim Chang. 2015; 5:988–991. [PubMed: 26640524]

Son JY, Lee JT, Kim H, Yi O, Bell ML. Susceptibility to air pollution effects on mortality in Seoul, Korea: a case-crossover analysis of individual-level effect modifiers. J Expo Sci Environ Epidemiol. 2012; 22:227–234. [PubMed: 22395258]

Stanković A, Nikić D, Nikolić M, Bogdanović D. Short-term effects of air pollution on cardiovascular mortality in elderly in Nis, Serbia. Cent Eur J Public Health. 2007; 15:95–98. [PubMed: 17958199]

Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001; 54(10):1046–1055. [PubMed: 11576817]

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011; 343:d4002. [PubMed: 21784880]

Valdés A, Zanobetti A, Halonen JI, Cifuentes L, Morata D, Schwartz J. Elemental concentrations of ambient particles and cause specific mortality in Santiago, Chile: a time series study. Environ Health. 2012; 11:82. [PubMed: 23116481]

Villeneuve PJ, Burnett RT, Shi Y, Krewski D, Goldberg MS, Hertzman C, et al. A time-series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. J Expo Anal Environ Epidemiol. 2003; 13:427–435. [PubMed: 14603343]

Wells G, Shea B, O'Connell D, Robertson J, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2011

WHO (World Health Organization) Europe. Copenhagen, Denmark: World Health Organization Regional Office for Europe; 2013. Review of evidence on health aspects of air pollution—REVIHAAP project. Available: http://www.euro.who.int/

WHO (World Health Organization). Geneva, Switzerland: Public Health, Social and Environmental Determinants of Health Department, World Health Organization; 2014. Burden of disease from Ambient Air Pollution for 2012. Available: http://www.who.int/phe/

Wilson EW. The relationship between daily cardiovascular mortality and daily ambient concentrations of particulate pollutants (sulfur, arsenic, selenium, and mercury) and daily source contributions from coal power plants and smelters (individually, combined, and with interaction) in Phoenix, AZ, 1995–1998: A multipollutant approach to acute, time-series air pollution epidemiology: I. J Air Waste Manag Assoc. 2015; 65:599–610. [PubMed: 25947318]

Wyzga RE, Rohr AC. Long-term particulate matter exposure: Attributing health effects to individual PM components. J Air Waste Manag Assoc. 2015; 65:523–543. [PubMed: 25947312]

Zanobetti A, Franklin M, Koutrakis P, Schwartz J. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environ Health. 2009; 8:1–12. [PubMed: 19138417]

Zanobetti A, O'Neill MS, Gronlund CJ, Schwartz JD. Summer temperature variability and long-term survival among elderly people with chronic disease. Proc Natl Acad Sci. 2012; 109:6608–6613. [PubMed: 22493259]

Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Peacock J, et al. The temporal pattern of respiratory and heart disease mortality in response to air pollution. Environ Health Perspect. 2003; 111:1188–1193. [PubMed: 12842772]

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect. 2000; 108:419–426. [PubMed: 10811568]

Highlights

- A meta-analysis of acute effects of $PM_{2.5}$ constituents on mortality was conducted.
- EC and K had the strongest and most consistent association with mortality.
- Single lag studies underestimate effects.
- Mortality effects of $PM_{2.5}$ and constituents differ across regions.

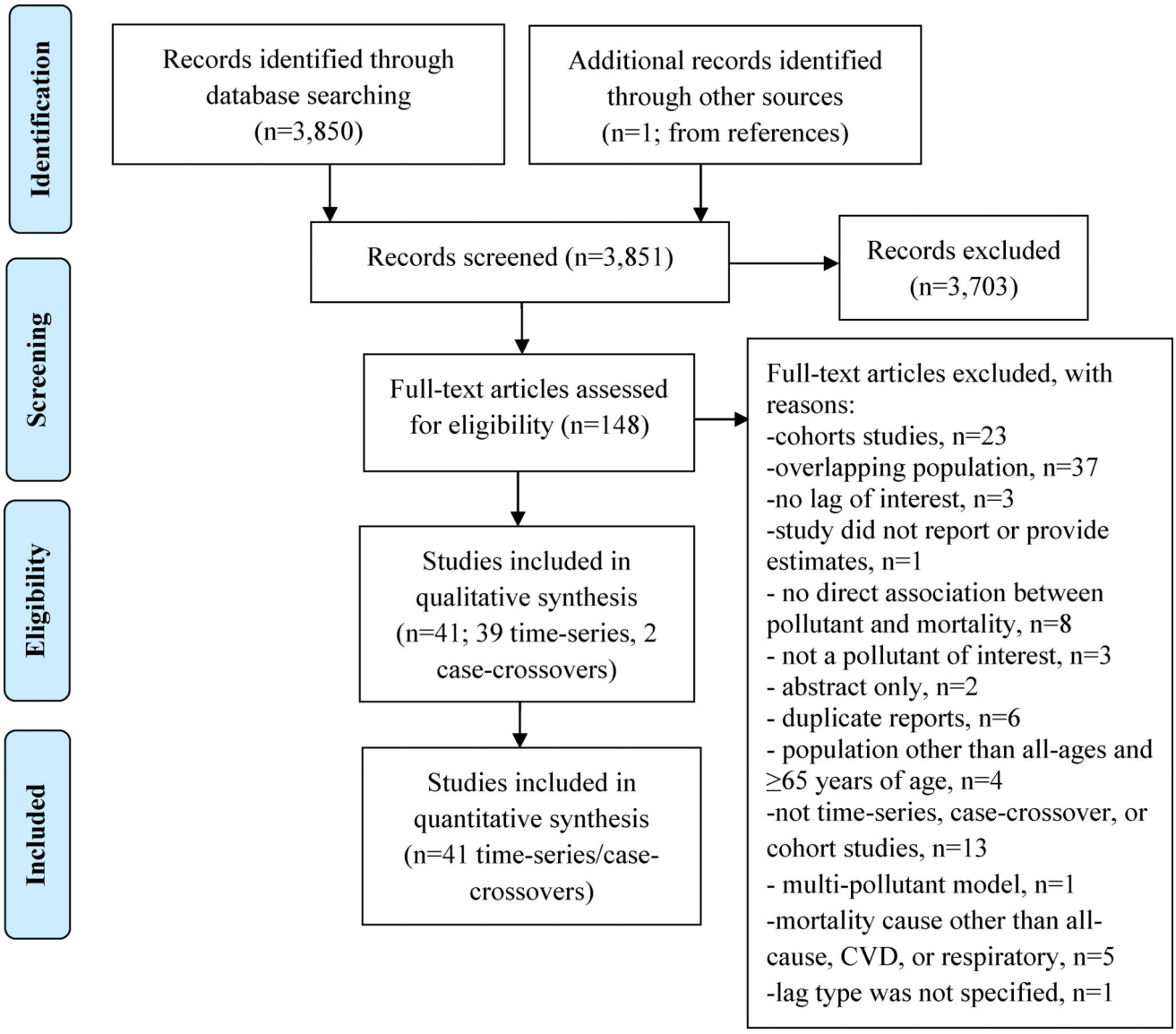

Figure 1.
PRISMA flow diagram (modified from Moher et al. 2009).

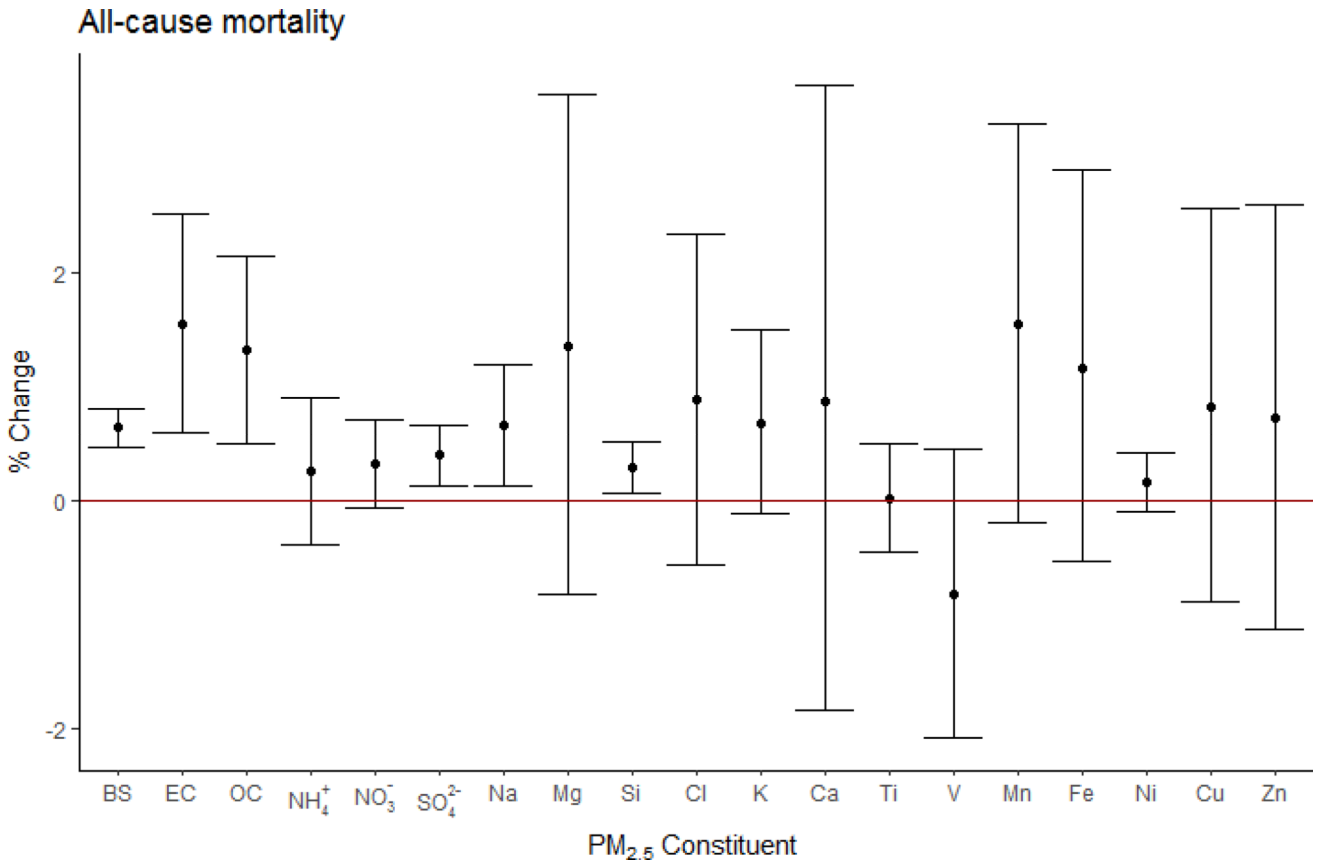

Figure 2.

All-cause mortality pooled effect estimates using city-specific estimates, expressed in percent change in mortality per IQR* increase in $PM_{2.5}$ constituent with 95 % confidence intervals. (*BS:10, EC:2.6, OC:6.1, NH_4^+:4.7, NO_3^-:5.0, SO_4^{2-}:5.1, Na:0.48, Mg:0.17, Si: 0.21, Cl: 1.1, K:0.53, Ca:0.17, Ti:0.017, V:0.007, Mn:0.009, Fe:0.15, Ni:0.005, Cu:0.014, Zn:0.054) μg/m^3).

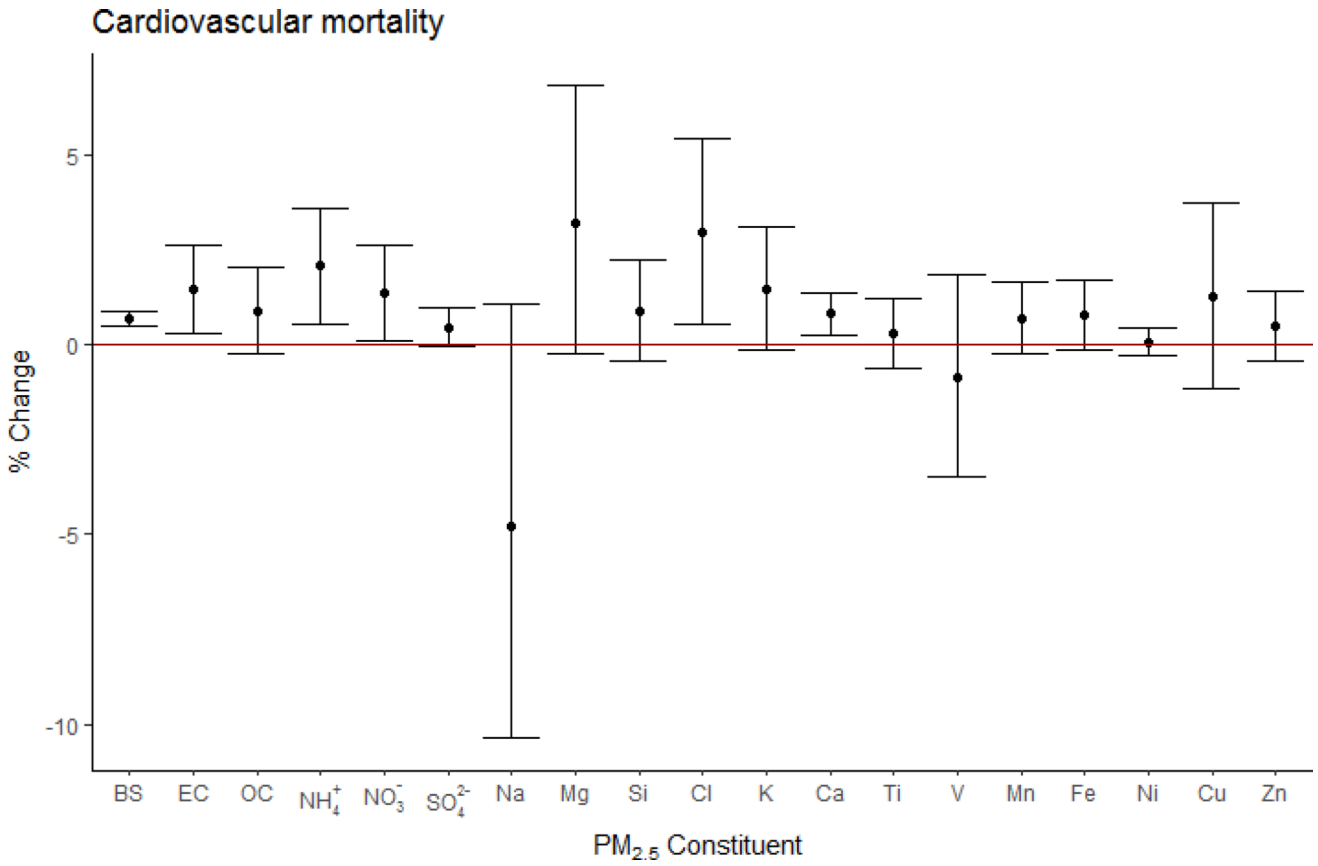

Figure 3.

Cardiovascular mortality pooled effect estimates using city-specific estimates, expressed in percent change in mortality per IQR* increase in $PM_{2.5}$ constituent with 95 % confidence intervals. (*BS:10, EC:2.6, OC:6.1, NH_4^+:4.7, NO_3^-:5.0, SO_4^{2-}:5.1, Na:0.48, Mg:0.17, Si: 0.21, Cl: 1.1, K:0.53, Ca:0.17, Ti:0.017, V:0.007, Mn:0.009, Fe:0.15, Ni:0.005, Cu:0.014, Zn:0.054) μg/m^3).

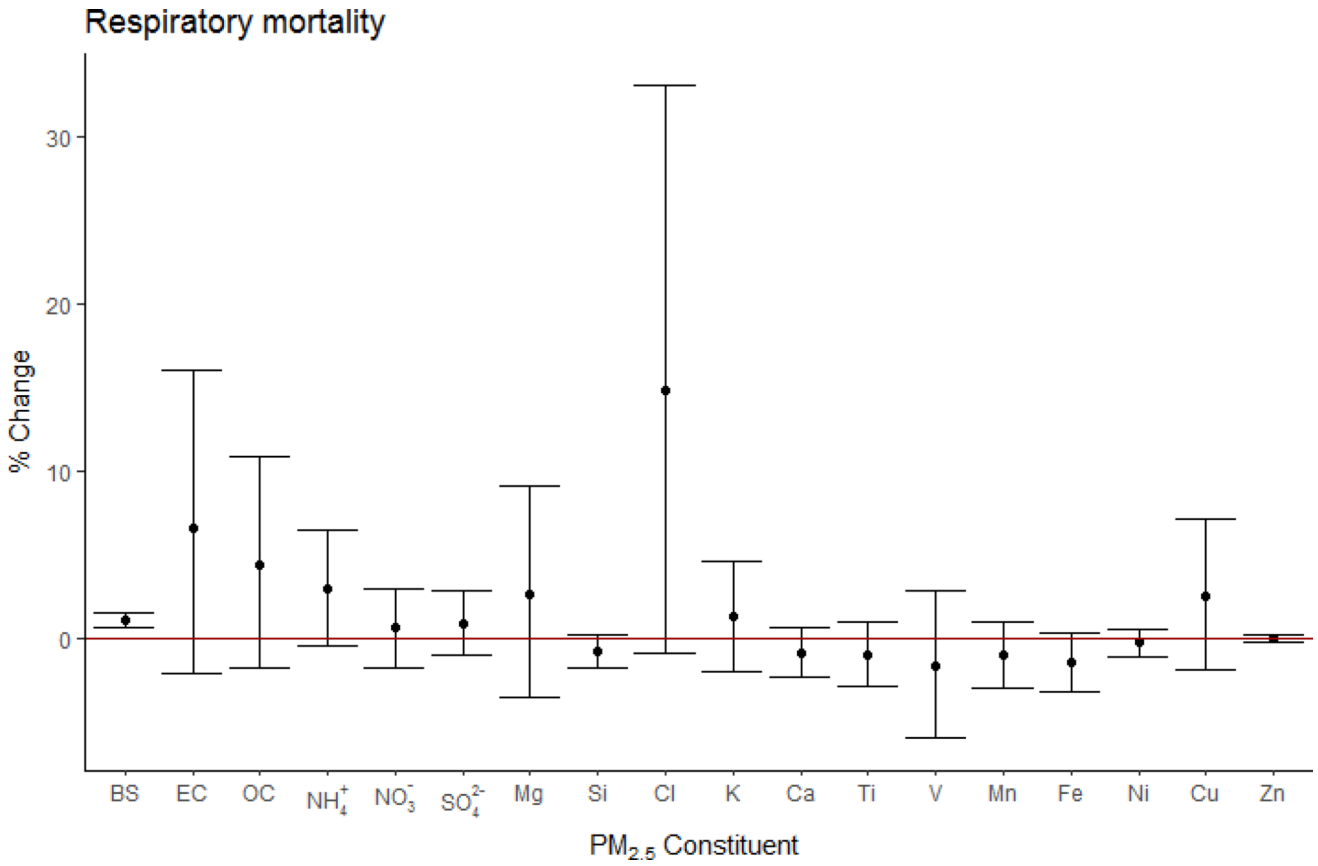

Figure 4.

Respiratory mortality pooled effect estimates using city-specific estimates, expressed in percent change in mortality per IQR* increase in $PM_{2.5}$ constituent with 95 % confidence intervals. (* BS: 10, EC: 2.6, OC: 6.1, NH_4^+: 4.7, NO_3^-: 5.0, SO_4^{2-}: 5.1, Na: 0.48, Mg: 0.17, Si: 0.21, Cl: 1.1, K: 0.53, Ca: 0.17, Ti: 0.017, V: 0.007, Mn: 0.009, Fe: 0.15, Ni: 0.005, Cu: 0.014, Zn: 0.054 μg/m^3).

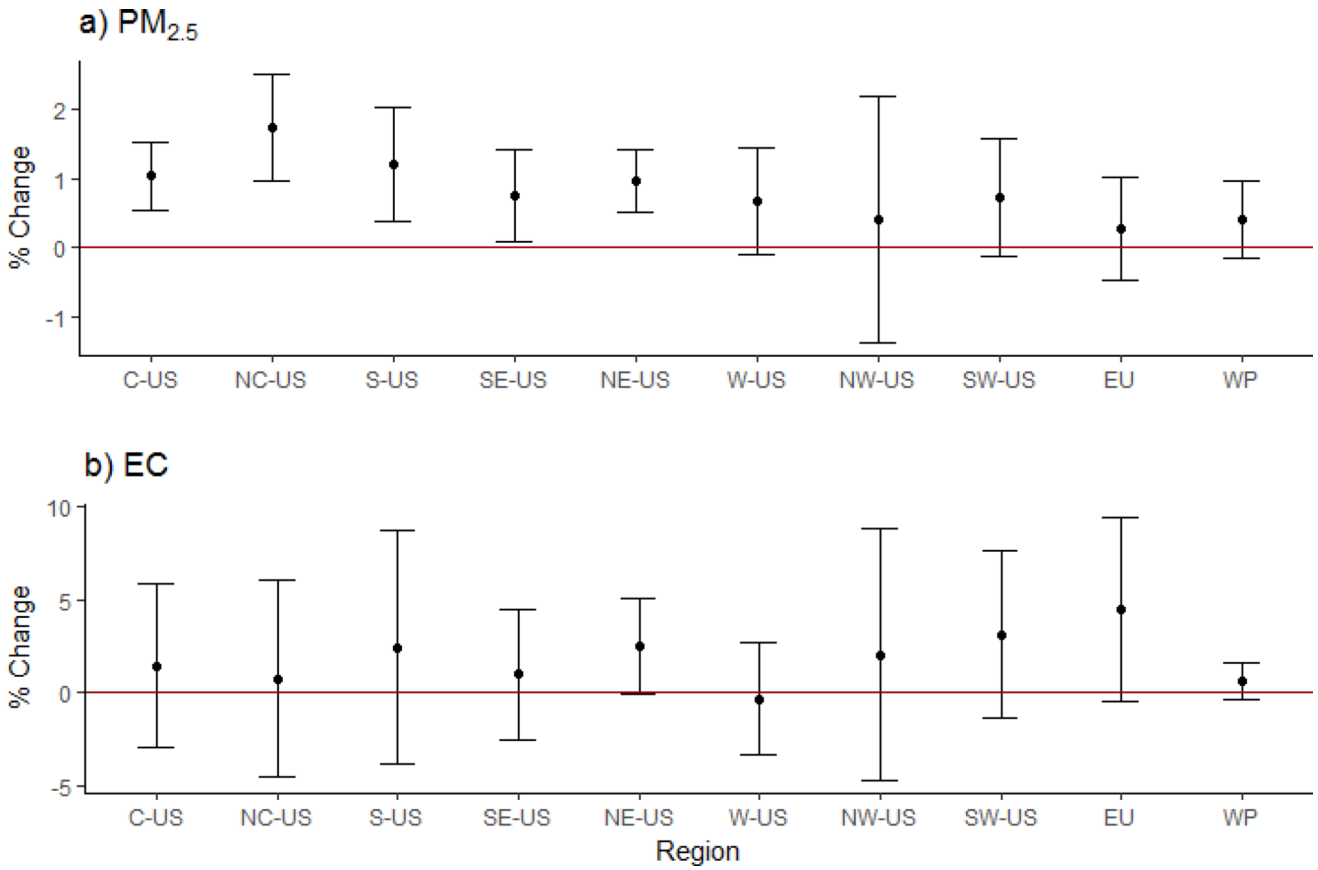

Figure 5.

All-cause mortality combined effect estimates, expressed in percent change in mortality per 10 μg/m^3 increase in $PM_{2.5}$ (a), and 2.6 μg/m^3 increase in EC (b). C-US indicates Central US; NC-US, North Central US; S-US, Southern US; SE-US, Southeastern US; NE-US, Northeastern US; W-US, Western US; NW-US, Northwestern US; SW-US, Southwestern US; EU, Europe; WP, West Pacific.

Table 1

Studies included in the meta-analysis.

#	Study	Cities		Additional comments
		All ages	≥65 years old	
1	Basagaña et al. 2015	4EU		
2	Kim et al. 2015	1 USA		
3	Li et al. 2015	1 WP		
4	Ostro et al. 2015	2 EU	2 EU	
5	Wilson et al. 2015		1 USA	
6	Dai et al. 2014	75 USA		
7	Heo et al. 2014	1 WP		
8	Geng et al. 2013	1 WP	1 WP	
9	Krall et al. 2013	72 USA		
10	Huang et al. 2012	1 WP		
11	Sacks et al. 2012	1 USA		
12	Son et al. 2012	1 WP		
13	Valdés et al. 2012	1 SA		
14	Fischer et al. 2011	1 EU		Country of Netherlands
15	Klemm et al. 2011		1 USA	
16	Atkinson et al. 2010	1 EU		
17	Cakmak et al. 2009	1 SA		
18	Fischer et al. 2009	1 EU		Country of Netherlands
19	Carder et al. 2008	3 EU		
20	Brook et al. 2007	10 CA		City-specific estimates were not provided
21	Stankovic et al. 2007	1 EU	1 EU	
22	Analitis et al. 2006	11 EU		
23	Burnett et al. 2004	12 CA		City-specific estimates were not provided
24	Filleul et al. 2004	1 EU	1 EU	
25	Aga et al. 2003		14 EU	
26	Fairley et al. 2003	1 USA		
27	Villeneuve et al. 2003		1 CA	
28	Ballester et al. 2002	6 EU		
29	Le Tertre et al. 2002	3 EU		
30	Anderson et al. 2001	1 EU		
31	Goldberg et al. 2001a	1 CA		Not included in the meta-analysis with the studies specific estimates because of duplicate population with Burnett et al. 2004
32	Goldberg et al. 2001b	1 CA	1 CA	
33	Katsouyanni et al. 2001	11 EU		
34	Samoli et al. 2001	2 EU		
35	Burnett et al. 2000	8 CA		City-specific estimates were not provided
36	Gwynn et al. 2000	1USA		
37	Hoek et al. 2000	1 EU		Country of Netherlands
38	Klemm et al. 2000	6 USA		

#	Study	Cities		Additional comments
		All ages	≥65 years old	
39	Lippmann et al. 2000	1 USA		
40	Anderson et al. 1996	1 EU		
41	Ballester et al. 1996	1 EU		

EU, European Union region; CA, Canada; SA, South America; USA, United States of America; WP, West Pacific

Table 2

Risk of bias rating for each study.