Review article

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

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ARTICLE INFO

Keywords:
Particulate matter constituents
Fine particulate matter (PM\textsubscript{2.5})
Mortality
Time series
Acute effects
Meta-analysis

ABSTRACT

Background: The link between PM\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2.5} concentration levels, air temperature, elevation, vegetation, size of elderly population, population density, and baseline mortality).

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 \textmu g/m\textsuperscript{3} increase in PM\textsubscript{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\textsubscript{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\textsubscript{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.

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\textsubscript{3}), sulfur dioxide (SO\textsubscript{2}), nitrogen oxides (NO\textsubscript{x}), carbon monoxide (CO), benzene, and lead (Pb). Of these, PM affects more people than any other pollutant (Brook et al., 2010).

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http://dx.doi.org/10.1016/j.envint.2017.09.010
Received 22 December 2016; Received in revised form 1 September 2017; Accepted 9 September 2017
Available online 05 October 2017
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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$_2^-$ 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$_4^{2-}$ (Ghiob 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 systematically 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 distributed lag models 0–5, and 0–1 studies with lag 1 or 0 examined lag 1 day. Therefore, in the meta-analysis, we included the previous day (lag 1) for all-cause and respiratory mortality and same day (lag 0) for cardiovascular mortality and respiratory 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 (NIH-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 SO_{2}^{2−} is present mostly in the fine fraction (Marsi et al., 2015). Also, since most sulfur (S) is in the SO_{2}^{2−} form in fine particles (Marsi 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 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 > 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 α = 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 3850 peer-reviewed articles were identified from our search, and one additional study through references screening. Of the 3851 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 multi-city 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, $n_{\text{cities}} = 114$) 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 Fig. 2.

We observed significantly positive associations between all-cause mortality and BS (pooled effect estimate, $\beta_{\text{pooled}}: 6.00 \times 10^{-4}$; 95% CI:...
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0.73 × 10^−2; 95% CI = 0.19, 1.35) in the meta-analysis from the adjusted models (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: 2.60 × 10^−2; 95% CI: 0.27, 4.93; n cities = 75). 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).

3.3.2. 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 results also suggested an association between all-cause mortality and NO_{3}^− (β pooled: 2.64 × 10^−3; 95% CI: 0.32, 4.80 × 10^−3), and Si (β pooled: 1.26 × 10^−3; 95% CI: 2.44 × 10^−4). The observed pooled associations between PM constituents and mortality estimates were not provided (Table E.2).

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).

In the meta-analysis, we performed the pooled analysis for EC, BS, and SO_{4}^− mortality effect estimates among the elderly population (≥ 65 years of age). EC (2.35%; 95% CI: 1.95, 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.
Table 2
Risk of bias rating for each study.

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Risk of bias rating: Low, Probably low, Probably high, High.
Fig. 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$^3$).

Fig. 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$^3$).
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/m³ increase in PM2.5, and no significant heterogeneity in the PM2.5 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 (I² > 50%). We observed positive associations with the PM2.5-adjusted V (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 SO₄²⁻ (β_pooled: 6.10 × 10⁻³; 95% CI: -4.48 × 10⁻³, 1.67 × 10⁻²; n_studies = 2, n_cities = 76), as well.

3.4. 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, Figs. F.1–F.4). We were able to assess for publication bias for PM2.5 (all-cause, cardiovascular, respiratory) and SO₄²⁻ (all-cause, cardiovascular) effect estimates. Even if there was some asymmetry in the funnel plots (e.g., PM2.5 and all-cause), Egger’s test showed no statistically significant asymmetry in the plots and therefore no further adjustments for publication bias were made (Figs. G.1–G.5).

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

3.5. Meta-regression analyses

We found significant heterogeneity in PM2.5 effect estimates and in many unadjusted constituent estimates. In contrast, the heterogeneity among the adjusted effect estimates was low (I² < 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 (I² > 50%) were found and when more than five city effect estimates were available.

3.5.1. 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 PM2.5 mass. The all-cause mortality effect estimate of PM2.5 for a single day exposure (0.50%; 95% CI: 0.06, 0.94%.
ncities = 29; lag1) was statistically significantly lower than the two-day average exposure (1.01%; 95% CI: 0.77, 1.26%; nc = 85; lag0–1). Similar effects, but not statistically significant, were observed for cardiovascular and respiratory mortality.

3.5.2. 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, $\Delta I^2 = 28\%$), and EC ($\Delta I^2 = 84\%$) 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.

3.5.3. 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 ($\Delta I^2 = 16\%$), and with some evidence for higher elevation ($\Delta I^2 = 1\%$, 

Fig. 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.
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.

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.

Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2017.09.010.

References


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