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Review article

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

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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, 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 $\mu g/m^3$ 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.

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).

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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_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