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ORIGINAL ARTICLE

Fine particle components and health—a systematic review and meta-analysis of epidemiological time series studies of daily mortality and hospital admissions

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Short-term exposure to fine particle mass (PM) has been associated with adverse health effects, but little is known about the relative toxicity of particle components. We conducted a systematic review to quantify the associations between particle components and daily mortality and hospital admissions. Medline, Embase and Web of Knowledge were searched for time series studies of sulphate (SO_4^{2-}), nitrate (NO_3^-), elemental and organic carbon (EC and OC), particle number concentrations (PNC) and metals indexed to October 2013. A multi-stage sifting process identified eligible studies and effect estimates for meta-analysis. SO_4^{2-}, NO_3^-, EC and OC were positively associated with increased all-cause, cardiovascular and respiratory mortality, with the strongest associations observed for carbon: 1.30% (95% CI: 0.17%, 2.43%) increase in all-cause mortality per 1 μg/m^3. For PNC, the majority of associations were positive with confidence intervals that overlapped 0%. For metals, there were insufficient estimates for meta-analysis. There are important gaps in our knowledge of the health effects associated with short-term exposure to particle components, and the literature also lacks sufficient geographical coverage and analyses of cause-specific outcomes. The available evidence suggests, however, that both EC and secondary inorganic aerosols are associated with adverse health effects.

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INTRODUCTION

Exposure to outdoor particulate matter with a median aerodynamic diameter < 2.5 microns ($PM_{2.5}$) has been associated with a range of adverse health outcomes.[1–3] Epidemiological evidence comes from cohort studies linking long-term exposure to $PM_{2.5}$ to adverse health effects and from time series studies that have reported associations between daily concentrations of $PM_{2.5}$ and increases, within a period of days, in daily numbers of deaths and emergency hospital admissions.

$PM_{2.5}$ mass is regulated in the United States, Europe and elsewhere but no consideration is given to particle size, source or chemical composition. Policy makers and regulatory authorities have sought to establish which, if any, component of the particle mixture is most dangerous to human health.[2] To date, literature reviews have focused on specific components, such as black carbon;[4,5] or specific sources such as traffic;[6] have been limited by the relatively sparse literature available for review;[7–9] or have been restricted to specific geographical regions.[10,11] Other reviews have not provided a systematic, quantitative assessment of the evidence but relied instead upon a qualitative review of a range of study designs and health outcomes.[2,12–14] We conducted a systematic review of the epidemiological time series literature for adverse effects of particle components on mortality and hospital admissions using original research indexed in online databases to October 2013 and without limitation by geographical region, particle component or source or language. We included studies of secondary inorganic aerosols, elemental and organic carbon and size-fractionated particle number concentrations. Our focus was the selection of effects estimates for meta-analysis to provide concentration-response functions for comparative purposes and for health impact assessment. We also provide a qualitative overview of the growing time series literature reporting results for the elemental content of particles.

MATERIALS AND METHODS

The Air Pollution Epidemiology Database (APED)[15] was used to identify ecological time series studies of the health effects associated with short-term exposure to a range of particle metrics: nitrate (NO_3^-); sulphate (SO_4^{2-}); elemental (EC) and organic (OC) carbon; and size-fractionated particle number concentrations (PNC), including nucleation mode (particles with a diameter generally < 0.05 μm), Aitken mode (generally 0.05–0.1 μm) and accumulation mode (generally 0.1–0.5 μm)[6,16,17] and metals. APED and our systematic review protocol have been described previously.[3,15,18] In brief, APED contains details of time series studies (including case crossover designs) published in peer reviewed journals and indexed in PubMed, EMBASE or Web of Science (which includes the Science Citation Index). Studies are identified through periodic searches using the following search criteria: "(particle* or particulate* or aerosol or sulphate or nitrate or carbon or metal) and (timeseries or time-series or time series) and (mortality or death* or dying or hospital admission* or admission* or emergency)". For this review, studies of particle components indexed up to October 2013

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were included. We also cross-checked studies identified in APED against publications selected for other reviews[2,9] and publications from the Health Effects Institute.[6,13,19] APED includes only studies that meet specific criteria, including: (1) at least 1 year of daily data relating to a general population; (2) a reasonable attempt to control for important confounding factors, such as long-term temporal trends, season and meteorological conditions; and (3) sufficient information for the calculation of a regression estimate and standard error (SE) for inclusion in the quantitative analysis.

Study details were entered into a Microsoft Access database and included publication details, and all data required to characterize the health outcomes, pollutants and effect estimates. From these data, we calculated standardized effect estimates expressed as the percentage change (and 95% confidence interval) in the mean number of daily events associated with a 1-μg/m^3 increase in particle concentrations.

A multi-stage process to select estimates for meta-analysis avoided duplication by selecting the most recently published evidence. Meta-analysis was performed only when ≥4 estimates for an outcome/disease/age group were available. Summary estimates were derived using a random-effects model, which calculates a weighted summary estimate using weights determined from the precision of individual study effect estimates.[20] The random-effects model assumes that the associations observed in individual studies can vary because of real differences between the associations in each study as well as simple sampling variability (chance) between studies and adjusts the pooled estimates and their 95% confidence intervals accordingly. Where sufficient estimates were available, we carried out stratified analyses by WHO region (details of countries included in each region are available at http://www.who.int/choice/demography/regions/en/) to assess geographical variation. Heterogeneity between study estimates was assessed using the I^2 statistic,[21] which describes the proportion of the variation in effect estimates attributable to heterogeneity rather than chance.

All analyses were conducted in STATA (STATA/SE 10. StataCorp, Texas, USA).

RESULTS

Literature Search

Our review identified 63 studies indexed in medical databases to October 2013. Two studies were excluded from our review: a reanalysis of the existing data sets[22] and one that was unavailable online[23]. Of the 61 studies, 40 investigated daily mortality and 27 hospital admissions. Secondary inorganic aerosols were investigated in 35 studies (SO_4^{2-}), 11 of which also considered NO_3^-; elemental and organic carbon was investigated in 19 studies; particle number concentrations in 12 studies; and particle elemental composition in 19 studies. Table 1 gives the numbers of studies by outcome, disease category and particle metric investigated stratified by WHO Region. The majority of studies were from North America and Europe although we note the very recent growth in studies from China (published in 2011–12). A number of cities were the subject of investigation on multiple occasions, both in single- and multi-city studies. A bibliography for the 63 studies included in our review is given in the Supplementary Data.

Secondary Inorganic Aerosols and Elemental and Organic Carbon

Mortality. Summary estimates (95% confidence intervals) per 1 μg/m^3 increment in SO_4^{2-}, NO_3^-, EC and OC for all-age, all-cause and cause-specific mortality are presented in Table 2. Individual study results are presented in a series of forest plots in the (Supplementary Figures S1–S12). The number of all-cause mortality estimates selected for meta-analysis was largest for SO_4^{2-} (12) compared with 6, 6 and 4 for NO_3^-, EC and OC, respectively. All four metrics were positively associated with increased all-cause mortality; the largest association per unit mass for elemental carbon, 1.30% (95% CI: 0.17%, 2.43%) and the lowest for SO_4^{2-}, 0.15% (0.06%, 0.25%). All pollutants were positively associated with cardiovascular mortality, between 1.66% (0.52%, 2.81%) for EC and 0.11% (−0.12%, 0.35%) for NO_3^-. Associations with respiratory mortality were broadly comparable to those for cardiovascular disease although in all cases confidence intervals straddled 0%. For all but one outcome, there was a strong evidence of between-study heterogeneity.

For SO_4^{2-}, sufficient estimates were available for a subgroup analysis by WHO region (Figure 1). There was evidence of heterogeneity between WHO regions for all-cause mortality ($\chi^2=15.0$; $P=0.001$), cardiovascular ($\chi^2=5.2$; $P=0.08$) and respiratory mortality ($\chi^2=4.7$; P = 0.10). For each disease group, associations in North America were larger than in European and Western Pacific regions. Mortality associations for secondary inorganic aerosols and carbon were reported for a range of other disease/age group combinations but with too few estimates for meta-analysis.

Hospital admissions. Both cardiovascular (including cardiac) and respiratory hospital admissions in all-ages/65+ years were associated with increases in SO_4^{2-}: 0.12% (−0.04%, 0.29%) (5 estimates, $I^2=61\%$) and 0.14% (−0.07%, 0.35%) (6 estimates, $I^2=57\%$) per 1 μg/m^3, respectively. Individual study results are presented in Supplementary Figures S13 and S14. For NO_3^-, EC and OC, there were insufficient numbers of estimates to carry out a meaningful meta-analysis. We note, however, the findings from a large, multi-city study of 119 US counties reporting positive associations for EC and mixed evidence for NO_3^- and OC and both cardiovascular and respiratory admissions.[9]

Particle Number Concentrations

Studies of PNC concentrations assessed a range of size-fractionated number concentrations in relation to daily mortality. After application of our estimate selection protocol, there were too few estimates within each disease/mode grouping to carry out separate meta-analyses. Figure 2 summarizes the results for mortality for nucleation, Aitkin/accumulation mode particles and for total number concentrations where reported in the selected studies. The figure shows results scaled by interquartile range for individual metrics to facilitate within-, rather than between-, study comparison. Although the majority of associations were positive, most had confidence intervals that overlapped 0 (%), and little pattern in the associations could be discerned between the different modes. For PNC and hospital admissions, there were insufficient numbers of estimates to carry out a meaningful meta-analysis (data not shown).

Table 1. Numbers of time series studies stratified by outcome, disease, particle metric and continent.

Continent (WHO region codes)	*Outcome*		*Disease*			*Particle metric*				
	Mortality	*Admissions*	*All cause*	*Cardiovascular*	*Respiratory*	SO_4^{2-}	NO_3^-	*EC/OC*	*PNC*	*Metals*
North America (AMR A & B)	21	20	16	21	20	29	6	13	—	12
South America (AMR C)	2	1	1	2	3	—	—	2	—	2
Europe (EUR A, B & C)	10	7	7	11	8	3	2	—	10	1
Western Pacific (WPR B)	7	—	5	6	5	3	3	4	2	4
Total	40	28	29	40	36	35	11	19	12	19

Table 2. Random effects summary estimates for particle metrics and all-cause and cause-specific mortality.

Pollutant	*Disease*	*All SC/MC[a]*	*Selected SC/MC[b]*	*RE (95% CI)[c]*	*I^2 (%)[d]*
SO_4^{2-}	All-cause	14/4	9/3	0.15 (0.06, 0.25)	71
	Cardiovascular	9/1	8/1	0.21 (−0.01, 0.44)	42
	Respiratory	8/1	7/1	0.23 (−0.07, 0.52)	38
NO_3^-	All-cause	6/1	5/1	0.17 (0.12, 0.23)	0
	Cardiovascular	6/1	5/1	0.11 (−0.12, 0.35)	70
	Respiratory	4/1	3/1	0.15 (−0.29, 0.59)	68
EC	All-cause	6/1	5/1	1.30 (0.17, 2.43)	92
	Cardiovascular	5/1	4/1	1.66 (0.52, 2.81)	97
	Respiratory	4/1	3/1	1.09 (−1.59, 3.85)	99
OC	All-cause	4/1	3/1	0.37 (−0.19, 0.94)	99
	Cardiovascular	5/1	4/1	0.56 (0.01, 1.10)	97
	Respiratory	4/1	3/1	0.57 (−1.11, 2.28)	98

[a]Number of estimates available from all single/multi-city studies. [b]Number of estimates from single/multi-city studies selected for meta-analysis (see Methods for details of estimate selection protocol). [c]Random effects summary estimate expressed as percentage of change in the number of deaths per 1 μg/m^3 (95% confidence interval). [d]I^2 percentage of between-city variability attributed to heterogeneity.

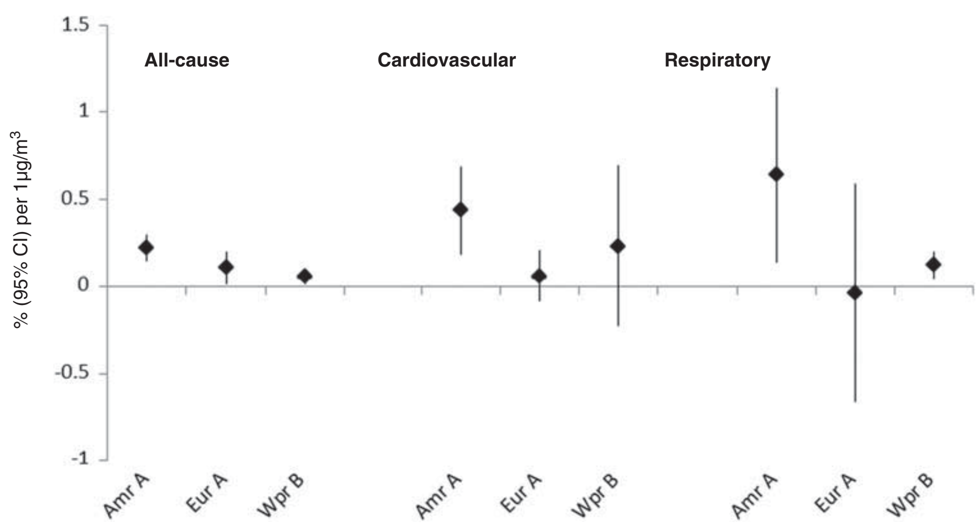

Figure 1. Region-specific summary estimates for the associations between sulphate and all-cause and cause-specific mortality.

Metals

Table 3 summarizes the scope and main findings of the 19 studies reporting results for the elemental content of particles. Studies from North America dominate the available literature (11 from the USA and 2 from Canada). Daily mortality and hospital admissions were investigated in 14 and 5 studies, respectively, and a range of the metals studied (between 3 and 57 elements). Fourteen studies reported regression coefficients for individual elemental concentrations, and five studies reported coefficients for $PM_{2.5}$ mass in proportion to elemental composition. For mortality, zinc was positively associated with daily mortality in 8/11 studies, nickel in 5/9 studies and vanadium in 3/5 studies.

DISCUSSION

Our review identified a growing literature regarding the health effects associated with short-term exposure to particle components, including secondary aerosols, carbon, particle number concentrations and metals. In the 3 years since the last review of the literature on secondary aerosols and carbon and mortality and hospital admissions,[9] the number of published studies has increased by 50% (14–21). Furthermore, the broad search strategy used for our review identified an additional 26 population-based time series studies of mortality and hospital admissions, with additional studies including PNC and metals. Although the majority of the studies in our review were still from North America, we note the very recent growth in the number of studies conducted in Asia (six studies in 2012) covering a range of health outcomes and particle metrics. The larger number and scope of studies included in our review has therefore enabled: (1) the quantification of associations between secondary aerosols and carbon and cause-specific mortality; (2) quantification for sulphate and respiratory and cardiovascular admissions; and (3) a comprehensive, descriptive assessment of the evidence for PNC and metals.

In our review, meta-analytical summary estimates were positive but lacked precision for most cause-specific mortality groups. The largest association observed was for elemental carbon, 1.3% increase in all-cause mortality per 1 μg/m^3 increase in EC based upon only six studies from the United States, Chile, China and South Korea. Previous reviews of EC have incorporated results for Black Smoke (a light reflectance measurement method calibrated to mass concentration) in their analyses due to the sparseness of direct estimates for EC and have tended to report smaller effect estimates.[5,9] We also note the strong heterogeneity between these six estimates and the lack of adjustment for co-pollutants,

RMID	Author	City	Year	Age	Mode	Size	Range
All Cause							
517	Atkinson	London	2010	All	PNC	-	10,166
2051	Branis	Prague	2010	All	Accumulation	0.21-0.49	1,000
2051	Branis	Prague	2010	All	Aitken	0.05-0.21	1,000
2051	Branis	Prague	2010	All	Nucleation	0.015-0.05	1,000
2051	Branis	Prague	2010	All	PNC	0.015-0.49	1,000
1954	Breitner	Erfut	2009	>1 yr.	Aitken	0.03-0.05	1,483
1954	Breitner	Erfut	2009	>1 yr.	Aitken	0.05-0.1	805
1954	Breitner	Erfut	2009	>1 yr.	Nucleation	0.003-0.03	5,336
Cardiovascular							
517	Atkinson	London	2010	All	PNC	-	10,166
2051	Branis	Prague	2010	All	Accumulation	0.21-0.49	1,000
2051	Branis	Prague	2010	All	Aitken	0.05-0.21	1,000
2051	Branis	Prague	2010	All	Nucleation	0.015-0.05	1,000
2051	Branis	Prague	2010	All	PNC	0.015-0.49	1,000
205	Breitner	Beijing	2011	>15yr.	Aitken	0.03-0.1	6,250
205	Breitner	Beijing	2011	>15yr.	Nucleation	0.003-0.03	10,203
205	Breitner	Beijing	2011	>15yr.	PNC	<0.8	13,790
238	Halonen	Helsinki	2009	65+ yr.	Accumulation	0.1-0.29	287
238	Halonen	Helsinki	2009	65+ yr.	Aitken	0.03-0.1	2,467
238	Halonen	Helsinki	2009	65+ yr.	Nucleation	<0.03	3,583
Respiratory							
517	Atkinson	London	2010	All	PNC	-	10,166
2051	Branis	Prague	2010	All	Accumulation	0.21-0.49	1,000
2051	Branis	Prague	2010	All	Aitken	0.05-0.21	1,000
2051	Branis	Prague	2010	All	Nucleation	0.015-0.05	1,000
2051	Branis	Prague	2010	All	PNC	0.015-0.49	1,000
238	Halonen	Helsinki	2009	65+ yr.	Accumulation	0.1-0.29	287
238	Halonen	Helsinki	2009	65+ yr.	Aitken	0.03-0.1	2,467
238	Halonen	Helsinki	2009	65+ yr.	Nucleation	<0.03	3,583

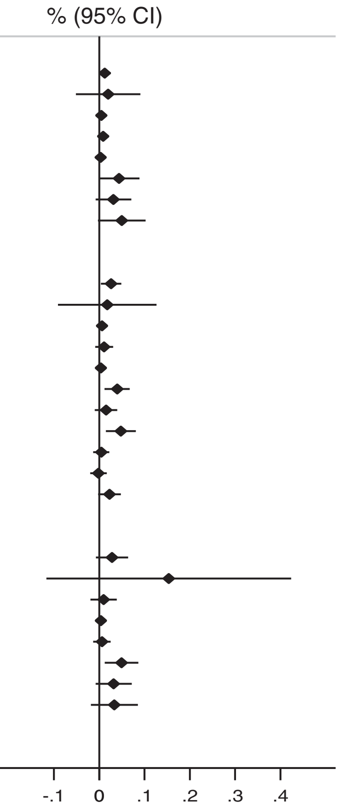

Figure 2. Individual study results for particle number concentrations and mortality.

both of which require careful investigation before assigning prominence to these findings.

Our findings for SO_4^{2-} and NO_3^- and mortality were consistent with the findings of Levy *et al.*[9] but are based upon a broader geographical literature incorporating evidence from Asia and without duplication of study locations. To our knowledge, our summary estimates for SO_4^{2-} and NO_3^- and hospital admissions for cardiovascular and respiratory disease are new. However, they are dominated by the 119 US counties study,[9] with little evidence available from other parts of the world. The literature is also sparse for studies of specific disease sub-groups and tends to be limited to North America, Europe and Western Pacific region.

Ultrafine particles (UFP) are characterized by size (<100 nm), high numbers and relatively large surface area. Our review found little consistent evidence of an association between UFP and daily mortality—a conclusion also reached in recent reviews.[1,2,19] UFPs are also characterized in terms of the particle size; nucleation mode particles (<50 nm in diameter) result from gas-to-particle conversion of different chemical compounds and Aitken mode particles (50–100 nm) by direct emission from combustion processes, for example, soot particles from cars.[6] In our review, neither modes were differentiated in terms of their effects on mortality although the evidence base was too limited to draw firm conclusions. Of the 15 studies of UFP identified for review, 10 were conducted in just four locations: Erfurt (4), Helsinki (2), Copenhagen (2) and Beijing (2). A broader geographical study base would therefore be advantageous in building a more complete picture of the evidence for the adverse health effects of UFP.

Our qualitative review of the literature reporting results for the elemental content of particles suggests that in the majority of studies Zn, Ni and vanadium were associated with increased mortality. Zn may be indicative of a road dust and possibly a tyre wear source, Fe and Zn are linked to steel production and Ni linked to oil combustion[24] or, in a specific case, to a Nickel smelter.[25] Our qualitative review highlighted some of the difficulties in assessing the relative effects of particle elemental composition: (1) studies varied in the range of metals investigated making synthesis difficult; (2) in a number of studies measurements were frequently below detection limits[13] or not measured daily,[26] reducing statistical power; (3) measurements were poorly correlated across monitor locations or measured at one location only with the potential for exposure measurement error;[27–29] and (4) statistical methods varied with some studies considering mass concentrations of individual elements and others reporting coefficients for $PM_{2.5}$ apportioned by elemental composition. The need to properly account for potential confounding by $PM_{2.5}$ in the analyses of particle constituents has been suggested by Mostofsky *et al*[30] adding to the difficulty in synthesizing the evidence. A significant strength of these studies, however, is their ability to characterize fully the particle mixture. Some studies that have characterized particles fully have utilized source apportionment techniques.[31–32] However, they have not been included in our review as they do not report numerical coefficients suitable for inclusion in a quantitative review and meta-analysis for health impact assessment, but we recognize the policy relevance of identifying PM source components most associated with adverse health outcomes. Finally, as for particle numbers, a broader geographical study base would be helpful in identifying the toxic components of particles and deriving concentration-response functions.

Our study had a number of strengths, including a very recent literature search (to October 2013); an *a priori* protocol for the identification of relevant studies and selection of effect estimates for meta-analysis to minimize selection bias; and no limitations on language (although all of the studies were written in English). Our study protocol ensured that multiple results from a single location did not have a disproportionate influence upon summary estimates. However, this approach reduced the number of meta-analyses possible when the evidence was limited to a small

Table 3. Summary of main findings from studies of elemental content of particles.

First Author	*Year*	*City/country*	*Diseases*	*Study period*	*Pollutants*	*Statistical approach*	*Findings*
Hoek	1997	Rotterdam, Netherlands	All-cause mortality	1983–1991	Fe	Poisson regression, single pollutant	No statistically significant associations with mortality
Burnett	2000	8 cities in Canada	All-cause mortality	1986–1996	47 elements	Poisson regression, single pollutant	Fe, Ni, and Zn were most strongly associated with increased mortality. Fine-fraction of Ca, Cu, Sc, Co, Zr, P, La and Mg were also found to have some association with mortality
Mar	2000	Phoenix, USA	All-cause and cardiovascular mortality	1995–1997	S, Zn, Pb	Poisson regression, single pollutant	S and Pb negatively associated with total mortality. No other statistically significant associations. Metals represent between 0.3 and 0.5% of total $PM_{2.5}$ mass
Cancado	2006	Piracicaba, Brazil	Respiratory hospital admissions	1997–1998	Al, Si, S, K and Mn	Poisson regression, single pollutant	Al, Si, S, K and Mn significantly associated with child respiratory admissions. K associated with elderly respiratory hospital admissions. Biomass burning predominant source of particles
Lippmann	2006	60 MSAs in USA	Mortality	2000–2003	Al, As, Cr, Cu, Fe, Mn, Ni, Pb, Se, Si, V, Zn	Meta-regression of PM_{10} risk on components	PM_{10} risk coefficients were high in MSAs where Ni and V were significantly high (95th percentile) compared with the MSAs where Ni was low (5th percentile)
Brook	2007	10 cities in Canada	All-cause mortality	1980–2000	Fe, Zn, Ni, Mn, As, Al, Cu, Pb, Si, Se	Poisson regression, single pollutant	Zn and Pb significantly associated with increased mortality; Ni borderline significance. All others (except Al) positive but not statistically significant
Ostro	2007	6 California counties, USA	All-cause, cardiovascular and respiratory mortality	2000–2003	Al, Br, Ca, Cl, Cu, Fe, K, Mn, Ni, Pb, S, Si, Ti, V, Zn	Poisson regression, single pollutant	Strongest associations were observed for Cu, K, Ti and Zn. All except Al, Br, Cu and Ni positively and significantly associated with all-cause mortality in cooler months
Franklin	2008	25 US communities	All-cause, cardiovascular and respiratory mortality	2000–2005	Al, As, Br, Cr, Fe, K, Mn, Ni, Pb, Si, V, Zn	Meta-regression of $PM_{2.5}$ risk on components	$PM_{2.5}$ association higher when $PM_{2.5}$ mass contained a higher proportion of Al, Arsenic, Si and Ni
Ostro	2009	6 California counties, USA	Respiratory hospital admissions	2000–2003	Cu, Fe, K, Si, Zn	Poisson regression, single pollutant	Cu, Fe and Si significantly associated with increased respiratory admissions and Cu, Fe and Si with asthma admissions in subjects aged <19 years
Ito	2010	New York, USA	Cardiovascular mortality and hospital admissions	2000–2006	Ni, V, Zn, Si, Se, Br	Poisson regression, single pollutant	Se showed a strong association with CVD mortality as did Br (warm season only). Ni, V and Zn associated with CVD mortality (stronger in cold season). Ni, Zn, Si, Se and Br associated with CVD hospitalizations (strongest in the cold season
Suh	2011	Atlanta, USA	Cardiovascular and respiratory hospital admissions	1998–2006	Transition metal oxides of Cu, Mn, Zn, Ti, Fe	Two stage: Logistic regression and meta-regression to categories	Consistent and significant associations between transition metals and increased hospital admissions for CVD, CHF and IHD in both first-stage and second-stage analyses
Zhou	2011	Detroit and Seattle, USA	All-cause, cardiovascular and respiratory mortality	2002–2004	Al, Fe, K, Na, Ni, S, Si, V, Zn	Poisson regression, single pollutant	Detroit: Warm season, S positively associated with AC and CV mortality. Seattle: cold season, Al, K, Si and Zn positively associated with AC and CV mortality
Valdes	2012	Santiago, Chile	All-cause, cardiovascular and respiratory mortality	1998–2007	Al, Na, Si, S, Cl, Ca, Cr, Mn, Ni, K, Fe, Cu, Zn, Se, Br, Pb	Poisson regression using mean monthly ratio of each individual element to $PM_{2.5}$ mass	Zn associated with higher cardiovascular mortality. Particles with high content of Cr, Cu and S showed stronger associations with respiratory and COPD mortality. Zn and Na content of $PM_{2.5}$ amplified the association with cerebrovascular disease

Table 3. (Continued).

First Author	*Year*	*City/country*	*Diseases*	*Study period*	*Pollutants*	*Statistical approach*	*Findings*
Cao	2012	Xi'an, China	Cardiovascular and respiratory mortality	2004–2008	S, Cl, K, Ca, Ti, Cr, Mn, Fe, Ni, Zn, As, Br, Mo, Cd, Pb	Poisson regression, singly and adjusted for $PM_{2.5}$	Cl and Ni showed the strongest associations followed by S, K and As. No positive associations observed for Ca, Ti, Cr, Mn, Fe, Zn, Br, Mo, Cd and Pb
Huang	2012	Xi'an, China	All-cause, cardiovascular and respiratory mortality	2004–2008	S, K, Ca, Fe, Zn, Cl, Pb, Mn, Br, Cd, Ni, Cr	Poisson regression, single pollutant	S, Cl, Cr, Pb, Ni andZn appeared most responsible for increased risk of death, particularly in the cold months
Son	2012	Seoul, South Korea	All-cause, cardiovascular and respiratory mortality	2008–2009	Cl, Ca, Mg, K and Na	Poisson regression, single pollutant	Mg associated with increased total mortality. Mg and Cl exhibited moderate associations with respiratory mortality
Sacks	2012	Philadelphia, USA	Cardiovascular mortality	1992–1995	Cu, Zn, Br, Pb, Fe, Si, Ca, Mn, Ni, V, Se, S and K	Poisson regression, single pollutant	Consistent positive associations were observed for all pollutants, except Ni
Bell	2012	187 US counties, USA	Cardiovascular and respiratory hospital admissions	2000–2005	52 chemical components of $PM_{2.5}$	Component fraction of $PM_{2.5}$ total mass	Higher $PM_{2.5}$ effect estimates for cardiovascular or respiratory hospitalizations were observed in seasons and counties with a higher $PM_{2.5}$ content of Ni and V
Wong	2012	Hong Kong, China	All-cause, cardiovascular and respiratory mortality	1990–1995	Al, Fe, Mn, Ni, V, Pb, Zn	Poisson regression, single pollutant	Ni and V significantly associated with all-cause and respiratory mortality

number of locations that were repeatedly studied. Other limitations of our review included potential bias arising from reliance upon authors' selection of results to submit for publication and limited ability to investigate reasons for the heterogeneity observed between studies. New studies are required to assess fully the impact of these factors upon the size and precision of the concentration-response functions derived in our meta-analysis. Our review focused upon the evidence from single pollutant models as our primary aim was quantification of effect estimates using meta-analysis. However, a single pollutant approach provides only limited insight into the differential toxicity of particle constituents, a point noted by Levy *et al.*[9] The literature for multi-constituent models remains limited with heterogeneity in the analytical methods used and the reporting of results.

The current literature is dominated by studies of mortality from broad disease categories. Few studies have reported effect estimates for specific causes of death, for example, from ischaemic heart disease, stroke or COPD or for age- and disease-specific hospital admissions. Furthermore, only a handful of studies have considered a range of health end points, diseases and particle components in the same population and hence facilitating meaningful within-study comparison. The literature is also dominated by studies from North America although we note the recent increase in studies from Asia. Further studies from other developed, and developing, countries, are needed to confirm the observed associations. Also, additional studies including specific, rather than broad, categories of diseases would provide additional understanding of the populations at risk and may also add to our understanding of mechanism of effect.

Fine particle mass ($PM_{2.5}$) has been studied and reviewed extensively, and little doubt remains regarding the adverse health effects of both long- and short-term exposure.[2,8,11,24,33,34] However, the uncertainty regarding the components of PM responsible for the adverse health effects remains despite efforts to evaluate the relative toxicity of the various chemical and physical properties of PM.[2,9,13,14] Our review of the time series literature provides support for these conclusions although we note, albeit with some caution as our analyses were based upon single-pollutant models only, the larger relative risks for mortality per unit mass of EC compared with other metrics. It should be noted that the interquartile range for EC is much smaller than for sulphate and nitrate aerosol and that both potency and total impact are relevant for policy decisions. A recent review of the toxicological literature[35] concluded that the limited new evidence did not change the view from an earlier review[36] that secondary inorganic aerosols "have little biological potency in normal human beings". They do, however, offer a word of caution noting that "it cannot be excluded that these secondary inorganic components produce an interactive biological effect with constituents of the overall pollutant mix by, for example, influencing the bioavailability of other components, such as metals". The authors of the 2013 review also note a word of caution regarding elemental carbon suggesting "(EC) may not be a major directly toxic component of fine PM" and suggesting, as for secondary inorganic aerosols, that it may act as a "a universal carrier of a wide variety of combustion derived chemical constituents of varying toxicity to sensitive targets in the human body".

The NPACT investigators recommended that further studies should improve individual and population exposure estimates before "it can be concluded that regulations targeting specific sources or components of $PM_{2.5}$ will protect public health more effectively than continuing to follow the current practice of targeting $PM_{2.5}$ mass as a whole".[13,14] Systematic review and quantitative meta-analysis will continue to have an important role in collating and combining the growing body of evidence. Further characterization of air pollution environments and sources will also enable the between-study heterogeneity and any potential confounding to be investigated further improving our understanding of the role of specific particle components. In the mean time, we recommend that the potential health benefits of air pollution mitigation policies are evaluated for a range of particle metrics, particularly elemental carbon, in addition to a single mass metric.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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