



Short-term and long-term exposures to fine particulate matter constituents and health: A systematic review and meta-analysis[☆]



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ARTICLE INFO

Article history:

Received 22 June 2018

Received in revised form

17 December 2018

Accepted 18 December 2018

Available online 21 December 2018

Keywords:

Air pollution

Constituents of fine particulate matter

PM_{2.5}

Mortality

Morbidity

ABSTRACT

Background: Fine particulate matter (Particulate matter with diameter $\leq 2.5 \mu\text{m}$) is associated with multiple health outcomes, with varying effects across seasons and locations. It remains largely unknown that which components of PM_{2.5} are most harmful to human health.

Methods: We systematically searched all the relevant studies published before August 1, 2018, on the associations of fine particulate matter constituents with mortality and morbidity, using Web of Science, MEDLINE, PubMed and EMBASE. Studies were included if they explored the associations between short term or long term exposure of fine particulate matter constituents and natural, cardiovascular or respiratory health endpoints. The criteria for the risk of bias was adapted from OHAT and New Castle Ottawa. We applied a random-effects model to derive the risk estimates for each constituent. We performed main analyses restricted to studies which adjusted the PM_{2.5} mass in their models.

Results: Significant associations were observed between several PM_{2.5} constituents and different health endpoints. Among them, black carbon and organic carbon were most robustly and consistently associated with all natural, cardiovascular mortality and morbidity. Other potential toxic constituents including nitrate, sulfate, Zinc, silicon, iron, nickel, vanadium, and potassium were associated with adverse cardiovascular health, while nitrate, sulfate and vanadium were relevant for adverse respiratory health outcomes.

Conclusions: Our analysis suggests that black carbon and organic carbon are important detrimental components of PM_{2.5}, while other constituents are probably hazardous to human health. However, more studies are needed to further confirm our results.

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1. Introduction

A great number of epidemiology studies have revealed a significant association between fine particulate matter (PM_{2.5}, Particulate matter with diameter $\leq 2.5 \mu\text{m}$) and human health, particularly the cardiovascular and respiratory diseases (Ai et al., 2018; Dominici et al., 2006; Lin et al., 2017; Lin et al., 2016a). However, the magnitudes of such associations largely varies by

season and location (Beelen et al., 2015; Lin et al., 2016a; Qiao et al., 2014). One underlying explanation is the differences in the embedded chemical components of PM_{2.5} across times and regions (Ming et al., 2017; Sun et al., 2016; Tao et al., 2017). It is therefore crucial to identify the toxic components of PM_{2.5} in order to establish air pollution control standards and formulate specific measures, as well as to improve our understanding on the biological mechanism of their health effects. However, it remains largely uncertain that which specific components are most harmful to human health.

The associations between various PM_{2.5} constituents and a range of health endpoints have been reported in a few studies. For instance, elemental carbon (EC) or black carbon (BC), which mainly comes from the combustion sources, have been reported to be associated with hospital admissions and mortality for cardiovascular and respiratory diseases (Basagaña et al., 2015; Ostro et al.,

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2015b). For example, potassium (K), an indicator of biomass burning, was associated with the risk of cardiovascular and respiratory diseases (Ferreira et al., 2016; Krall et al., 2017); vanadium (V), nickel (Ni) and oil combustion particles were associated with natural cause and cardiovascular mortality (Beelen et al., 2015; Lin et al., 2018; Wang et al., 2014). Secondary pollutants, such as nitrate (NO_3^-) and sulfate (SO_4^{2-}), have also been found to associate with cardiovascular and respiratory health (Chung et al., 2015; Crouse et al., 2016; Ostro et al., 2009; Peng et al., 2009).

In the last decades, there have been accumulating studies regarding the health effects of constituents of fine particulate matter worldwide. However, those results were inconsistent across different studies. Therefore, we conducted a systematic review and meta-analysis to summarize the associations between different $\text{PM}_{2.5}$ constituents and different health endpoints (mortality and morbidity) in both short-term and long-term exposure time frames.

2. Methods

2.1. Search strategy and criteria for studies selection

We systematically searched Web of Science, MEDLINE, PubMed and EMBASE databases for all studies on health effects of constituents of fine particular matter as of August 1, 2018. The search strategy included the following combinations of keywords: (“fine particulate matter” OR “ $\text{PM}_{2.5}$ ”) AND (“constituents” OR “components” OR “species” OR “black carbon” OR “BC” OR “elemental carbon” OR “EC” OR “nitrate” OR “nitrates” OR “sulfate” OR “sulfates” OR “metals”) AND (“nonaccidental” OR “all” OR “cardiovascular” OR “respiratory”) AND (“mortality” OR “hospitalization” OR “hospital admissions” OR “emergency department visits”). In addition, we searched the additional studies from the reference list of the qualified studies.

Studies were included if they met the flowing criteria: 1) published on a peer-reviewed journal in English. 2) Studies types were restricted to time series studies, case crossover studies or cohort studies, 3) reported the association between fine particulate matter constituents and health outcomes (mortality or morbidity), and 4) the study was conducted for a general population.

We excluded studies of char or soot or black smoke, since the definition of such components usually lacked of precision (Luben et al., 2017). Two of the authors (YY and XW) reviewed the titles and abstracts separately and selected the relevant studies. The final included studies were based on the full text evaluation. Due to the limited study numbers for hospital admissions and emergency department visits, we combine the studies on them into one category of morbidity in our main analysis.

2.2. Data extraction

Two authors (YY and XW) extracted the data independently and discrepancies were settled by a group discussion. If the estimates of a study was presented in figures with specific description in text, we sent emails to ask for the relevant estimates and their 95% confidence intervals. No feedback after three emails deemed exclusion of these studies from quantitative synthesis, however, we still reviewed them in qualitative synthesis. For each study, we extracted the information including the study design, location, period, population size, fine particulate matter species, whether they adjusted $\text{PM}_{2.5}$ mass or not, and heath endpoints. In addition, we extracted the lag patterns for short-term studies and exposure assessment methods for cohort studies, respectively. Excess risks/relative risks and 95% confidence interval were extracted and transformed into regression coefficient (β) and standard error (SE) in each study.

For time series and case crossover studies, we extracted the effect on the lag day which the authors reported in their main analyses. If findings were reported from different lag days, we chose the lag days with the strongest estimates in accordance with previous studies (Krall et al., 2017; Son et al., 2012).

2.3. Risk of bias

2.3.1. Time series/case crossover study

We assessed the risk of bias for time series/case crossover studies across 3 components: outcome assessment, exposure assessment and confounding adjustment. The criteria for the risk of bias was adapted from OHAT (Achilleos et al., 2017; Program, 2015) and New Castle Ottawa as follows: 1) For, outcome assessment, mortality or morbidity data were considered to be at low risk of bias if the classification was based on International Classification of Diseases (ICD); 2) For, exposure assessment, studies were considered to be at low risk of bias if they met two out of the following three considerations: measurements were performed daily, less than 25% missing data, two or more air monitoring stations within a large geographical area; 3) For confounding adjustment, studies were considered at low risk of bias if long-term trends, seasonality and temperature were adjusted and two out of the following four covariates (humidity/day of week/holiday/influenza) were adjusted. If all these three criteria were at low risk, then the study was considered to be at low risk of bias.

2.3.2. Cohort study

We conducted quality assessment based on the Newcastle-Ottawa quality assessment scale for cohort studies (Wells et al., 2014). The system allowed for a maximum of nine points which representing the highest quality. The scale evaluated eight aspects for each study, which are in three areas (Selection, Comparability and Outcome).

2.4. Data synthesis

Some constituents of fine particulate matter were considered in this study, including BC, EC, OC, NO_3^- , SO_4^{2-} , ammonium (NH_4^+), calcium (Ca), copper (Cu), iron (Fe), K, sodium ion (Na^+), Ni, silicon (Si), V, zinc (Zn); and the health endpoints included mortality and morbidity for natural, cardiovascular and respiratory diseases. We combined the estimates from black carbon and elemental carbon, because both of them are important indicators for carbon-rich combustion sources, and considered almost the same components in $\text{PM}_{2.5}$ (Arnott et al., 2005). In addition, we converted S into SO_4^{2-} by dividing the regression coefficient by the ratio of molar mass ($\text{SO}_4^{2-}/\text{S}$), since the majority of S in $\text{PM}_{2.5}$ was in the presence of SO_4^{2-} (Achilleos et al., 2016; Masri et al., 2015).

Random-effects meta-analysis was applied to estimate the overall association between various constituents of $\text{PM}_{2.5}$ and cause-specific health outcomes. Excess Risks (ER) were pooled for an IQR (interquartile range) increase in the concentrations of each constituent. The IQR for each constituent in our analysis were the median among different studies: $0.605 \mu\text{g}/\text{m}^3$ for BC, $2.83 \mu\text{g}/\text{m}^3$ for OC, $2.3 \mu\text{g}/\text{m}^3$ for NO_3^- and SO_4^{2-} , $0.11 \mu\text{g}/\text{m}^3$ for Na, $0.14 \mu\text{g}/\text{m}^3$ for Ca, $0.017 \mu\text{g}/\text{m}^3$ for Cu, $0.13 \mu\text{g}/\text{m}^3$ for Fe, $0.15 \mu\text{g}/\text{m}^3$ for K, $0.004 \mu\text{g}/\text{m}^3$ for Ni and V, $0.1 \mu\text{g}/\text{m}^3$ for Si, $0.025 \mu\text{g}/\text{m}^3$ for Zn, $1.35 \mu\text{g}/\text{m}^3$ for NH_4^+ . In the main analysis, we only included studies which adjusted $\text{PM}_{2.5}$ mass in their model, since $\text{PM}_{2.5}$ mass is a potential confounder in the association between fine particular constituents and health (Mostofsky et al., 2012).

Two cohort studies (Beelen et al., 2015; Wang et al., 2014) and 23 short-term effect studies were conducted on a multi-city scale, we only used the combined effect estimates from these studies, since the city-specific estimates were not available.

Heterogeneity and between-study variance were examined using the I^2 -based Cochran Q test and Tau^2 , respectively. We did not evaluate the publication bias due to the relatively small number of studies in each category.

For sensitivity analysis, we estimated the excess risks for hospital admission and emergency department visits separately. In addition, we pooled the effects for studies which did not adjust PM_{2.5} mass in their model. We also excluded the studies with the largest and the smallest effect estimates from the meta-analyses to check their influence on the overall estimates.

Statistical analyses were performed using the “metaphor” and “forestplot” packages in R statistical software, version 3.4.2 (R Development Core Team, 2017).

3. Results

Our literature search initially identified 5316 records and 164 of them were included in full-text review after screening their titles and abstracts (Fig. 1). Finally, 42 studies were included in the final analysis, including 31 short-term effect studies (30 time-series studies and 1 case crossover study, Table S1 and Tables S2) and 11 cohort studies (Table S3). Seven studies were conducted in Europe, twenty-four in USA, one in Canada, eight in East Asia, and two in South America. Of these 42 studies, 19 are multi cities

studies, 23 are single cities studies. Thirty-five studies were analyzed for all ages; five studies with the population ≥ 65 years of age, one study with 50–79 years old and one with participants ≥ 40 years old were used for the age specific analyses.

3.1. Risk of bias assessment

The assessments for risk of bias were presented in Table 2 for time series/case crossover studies and Table 3 for cohort studies. Most time series and case crossover studies were at a low risk of bias. Studies at a high risk of bias are more likely to have some deficiency in exposure assessment or covariates selection. For cohort studies, most of them were at low risk of bias.

Table 1

Fine particulate matter constituents that are most likely or probably to cause adverse health effects.

	Constituents that are most likely to cause adverse health effects	Constituents that are probably to cause adverse health effects
All natural cause	BC, OC	K, Nitrate, Sulfate, NH ₄ ⁺ , Zn, Si
Cardiovascular	BC, OC	Nitrate, Sulfate, NH ₄ ⁺ , Ni, V, Na, Fe, Zn, Si
Respiratory	NA	OC, Nitrate, Sulfate, V

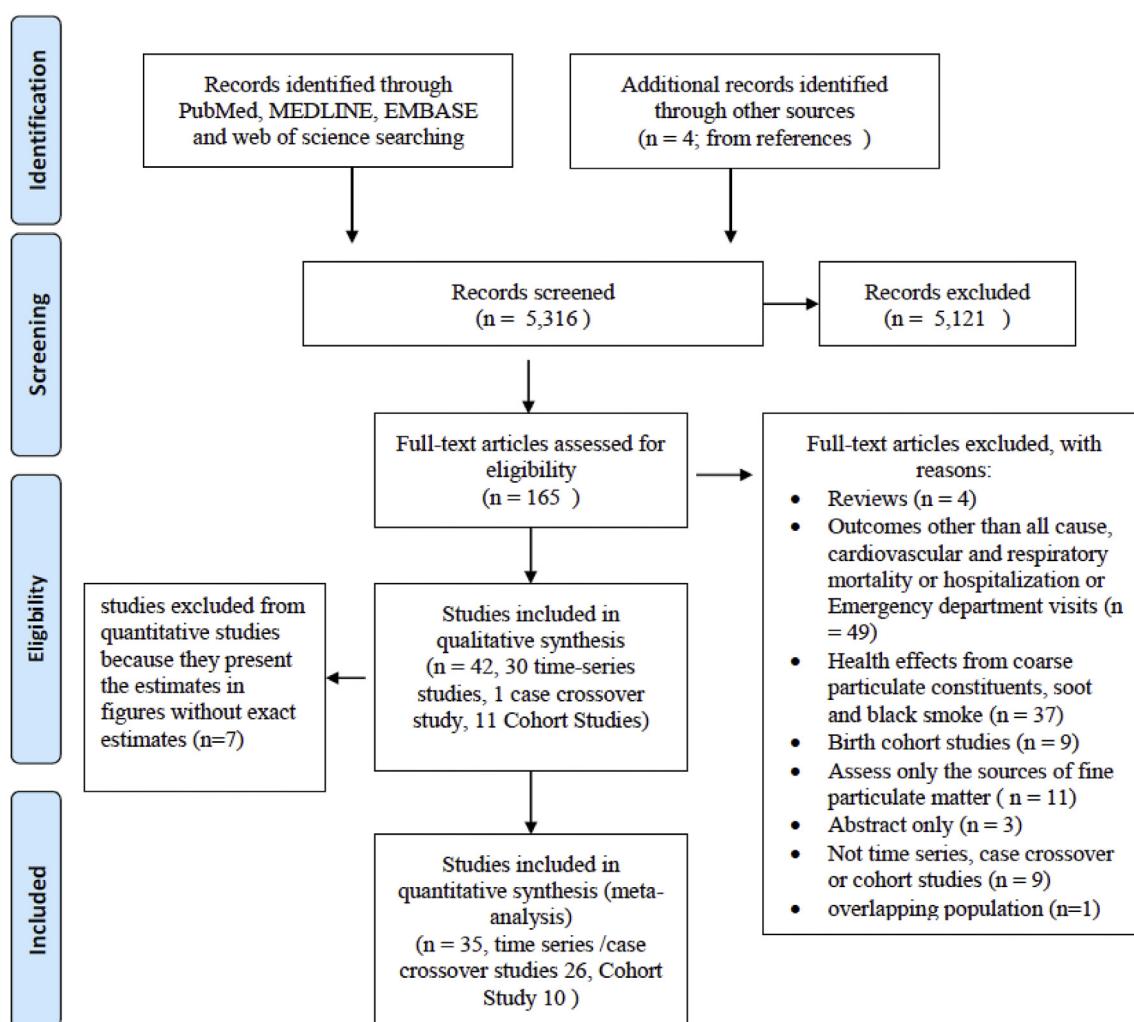


Fig. 1. PRISMA flow diagram summarizing the systematic literature search and inclusion and exclusion criteria for epidemiologic studies.

Table 2

Risk of bias assessment for included time-series and case-crossover analysis studies.

Reference	ICD	Data source	Single/multiplicities	Daily pollutant measurement	<25% missing data	Single/multi monitoring stations	Adjusted Long-term trends/seasonality/temperature	humidity	Day of the week	influenza	holiday	Low risk of bias
Krall et al. (2017)	9	Hospital records	M	Y	Y	S	Y	Y	Y	N	Y	Y
Liu et al. (2016b)	9	Regional Database	S	N	NA	S	Y	Y	Y	N	N	Y
Liu et al. (2016a)	9	Regional Database	S	N	NA	S	Y	Y	Y	N	N	Y
Ferreira et al. (2016)	10	National Database	S	NA	NA	NA	Y	Y	Y	N	Y	N
Liu and Zhang (2015)	10	Regional Database	S	N	NA	S	Y	Y	Y	N	N	Y
Lin et al. (2016b)	10	Regional Database	S	Y	Y	M	Y	Y	Y	Y	N	Y
Sarnat et al. (2015)	9	Hospital records	M	Y	Y	S	Y	Y	Y	N	Y	Y
Basagaña et al. (2015)	9/10	Death registries	M	Y/N	Y	S	NA	N	NA	Y	Y	N
Kim et al. (2015)	10	Regional Database	S	Y	Y	S	Y	Y	Y	N	N	Y
Wilson (2015)	9	Regional Database	S	Y	Y	S	Y	Y	Y	N	N	Y
Kim et al. (2012)	9	Hospital admission records	S	Y	Y	S	Y	Y	Y	N	N	Y
Qiao et al. (2014)	NA	Regional database	S	Y	Y	S	Y	Y	Y	N	N	Y
Bell et al. (2013)	9	Medicare Database	M	N	NA	M	Y	N	Y	N	N	N
Dai et al. (2014)	10	National Database	M	N	N	S	Y	N	Y	N	N	N
Ostro et al. (2015b)	9/10	NA	M	Y	NA	S	Y	N	Y	Y	Y	Y
Li et al. (2015)	10	National Database	S	Y	YS	S	Y	Y	Y	N	Y	Y
Heo et al. (2014)	10	National Database	S	N	Y	S	Y	Y	Y	Y	Y	Y
Geng et al. (2013)	10	Regional Database	S	Y	NA	S	Y	Y	Y	N	N	Y
Krall et al. (2013)	9	National Database	M	N	N	S/M	Y	N	N	N	N	N
Son et al. (2012)	10	National Database	S	Y	Y	S	Y	Y	Y	N	N	Y
Cao et al. (2012)	10	Regional Database	S	Y	NA	S	Y	Y	Y	N	N	Y
Sacks et al. (2012)	9	National Database	S	Y	Y	S	Y	Y	Y	N	N	Y
Huang et al. (2012)	10	Regional Database	S	Y	NA	S	Y	Y	Y	N	N	N
Valdés et al. (2012)	9	National Database	S	N	Y	S	Y	Y	Y	N	N	Y
Klemm et al. (2011)	10	Regional database	S	Y	Y	NA	Y	N	Y	N	N	Y
Ito et al. (2010)	9/10	Regional database	S	N	NA	M	Y	N	Y	N	N	N
Zhou et al. (2011)	10	National database	M	Y	NA	M	Y	Y	Y	N	N	Y
Suh et al. (2011)	9	Medicare database	M	Y	Y	S	Y	Y	Y	N	N	Y
Peng et al. (2009)	9	Medicare Hospital admission record	M	N	NA	M	Y	Y	Y	N	N	Y

Table 3 Newcastle-Ottawa Scale for assessing the quality of cohort studies in meta analysis.

Study	Selection			Comparability			Outcome	Adequacy of follow up of cohorts to occur	Quality score
	Represent activeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Assessment of outcome on the basis of the design or analysis				
Badaloni et al. (2017)	*	*	*	*	*	*	*	*	7
Crouse et al. (2016)	*	*	*	*	*	*	*	*	6
Chung et al. (2015)	*	*	*	*	*	*	*	*	8
Beelen et al. (2015)	*	*	*	*	*	*	*	*	7
Wang et al. (2014)	*	*	*	*	*	*	*	*	8
Ostro et al. (2010)	*	*	*	*	*	*	*	*	5
Ostro et al. (2015a)	*	*	*	*	*	*	*	*	6
Vedal et al. (2013)	*	*	*	*	*	*	*	*	6
Lippmann et al. (2013)	*	*	*	*	*	*	*	*	8
Beelen et al. (2014)	*	*	*	*	*	*	*	*	7
Lipfert et al. (2009)	*	*	*	*	*	*	*	*	5

3.2. Short-term health effects

Fig. 2 shows the pooled excess risks per IQR increase in each PM_{2.5} constituent. We only illustrated constituents which have sufficient number of studies. For short-term effects on non-accidental mortality, significant associations were observed for BC (ER = 0.33%, 95% CI: 0.12%, 0.55%), OC (ER = 0.35%, 95% CI: 0.09%, 0.61%), K (ER = 0.37%, 95% CI: 0.26%, 0.48%). For cardiovascular mortality, significant associations were observed for BC, OC, nitrate, sulfate, Zn, Si and K. We found that the effect estimates on cardiovascular mortality were larger than non-accidental mortality. However, we found that OC was only associated with respiratory mortality in short-term association studies. No significant heterogeneity ($I^2 \geq 50\%$) was observed across these studies.

For non-accidental morbidity, we found a 0.46% (95%CI: 0.11%, 0.80%) elevation for BC per IQR increase and 0.51% (95%CI: 0.03%, 0.98%) for OC. The effect estimates for cardiovascular morbidity are generally higher compared to non-accidental visits, we found 1.34% (95%CI: 0.65%, 2.04%) for BC and 1.53% (95%CI: 0.19%, 2.89%) for OC. Substantial heterogeneity was observed in Fe ($I^2 = 52.06\%$), K ($I^2 = 90.59\%$), V ($I^2 = 69.95\%$) and Zn ($I^2 = 62\%$). In respiratory morbidity, significant associations were found in nitrate (ER = 0.68%, 95%CI: 0.02%, 1.34). We found substantial heterogeneity in BC ($I^2 = 73.9\%$), NH₄⁺ ($I^2 = 89.87\%$), K ($I^2 = 53.68\%$), Ni ($I^2 = 58.01\%$), Zn ($I^2 = 65.85\%$) and Ca ($I^2 = 96.27\%$).

3.3. Long term health effects

Significant associations with non-accidental mortality were found in per IQR increase of BC (ER = 1.78%, 95% CI: 0.36%, 3.22%), nitrate (ER = 2.6%, 95% CI: 0.88%, 4.34%), Zn (ER = 9.4%, 95% CI: 6.33%, 12.56%) and Si (ER = 5.90%, 95%CI: 3.25, 8.61). We observed substantial heterogeneity among the studies with Cu ($I^2 = 89.6\%$) and Fe ($I^2 = 95.04\%$). In addition, we found that there were significant associations between Fe, nitrate, Zn, Si and cardiovascular mortality, and significant heterogeneity was found in Cu ($I^2 = 77.62\%$). For respiratory mortality, there were no sufficient studies for us to perform the meta-analysis (**Fig. 2**).

3.4. Sensitivity analyses

We synthesized the effect estimates for studies which did not adjust the PM_{2.5} mass in their model (**Table S5**). We found BC and OC were still significant for both cardiovascular mortality and morbidity. Sulfate stands out for non-accidental mortality and morbidity, CVD mortality and respiratory morbidity, while it remains insignificant in PM_{2.5} adjusted model. Nitrate was found to be associated with non-accidental and cardiovascular mortality. In addition, K was found in association with non-accidental and respiratory hospital admission. After excluding the studies with the largest and the smallest effect estimates from the meta-analysis, we found there is no difference on the overall effect estimates.

We synthesized the effect estimates of hospitalization and emergency department visits, respectively (**Fig. S1**). Since the studies which reported the association between emergency department visits and hospital admissions are quite limited, our combined morbidity effect estimates are more similar with hospital admissions effect estimates.

We classified the components of PM_{2.5} into two categories: constituents that are most likely to pose adverse health effects and constituents that has the potential to cause adverse health effects based on the statistical significance of the overall associations (We considered both PM_{2.5} adjusted and PM_{2.5} unadjusted studies) (**Fig. 2**, **Fig. S1**, **Fig. S2** and **Table S5**) and number of studies (**Table 1**).

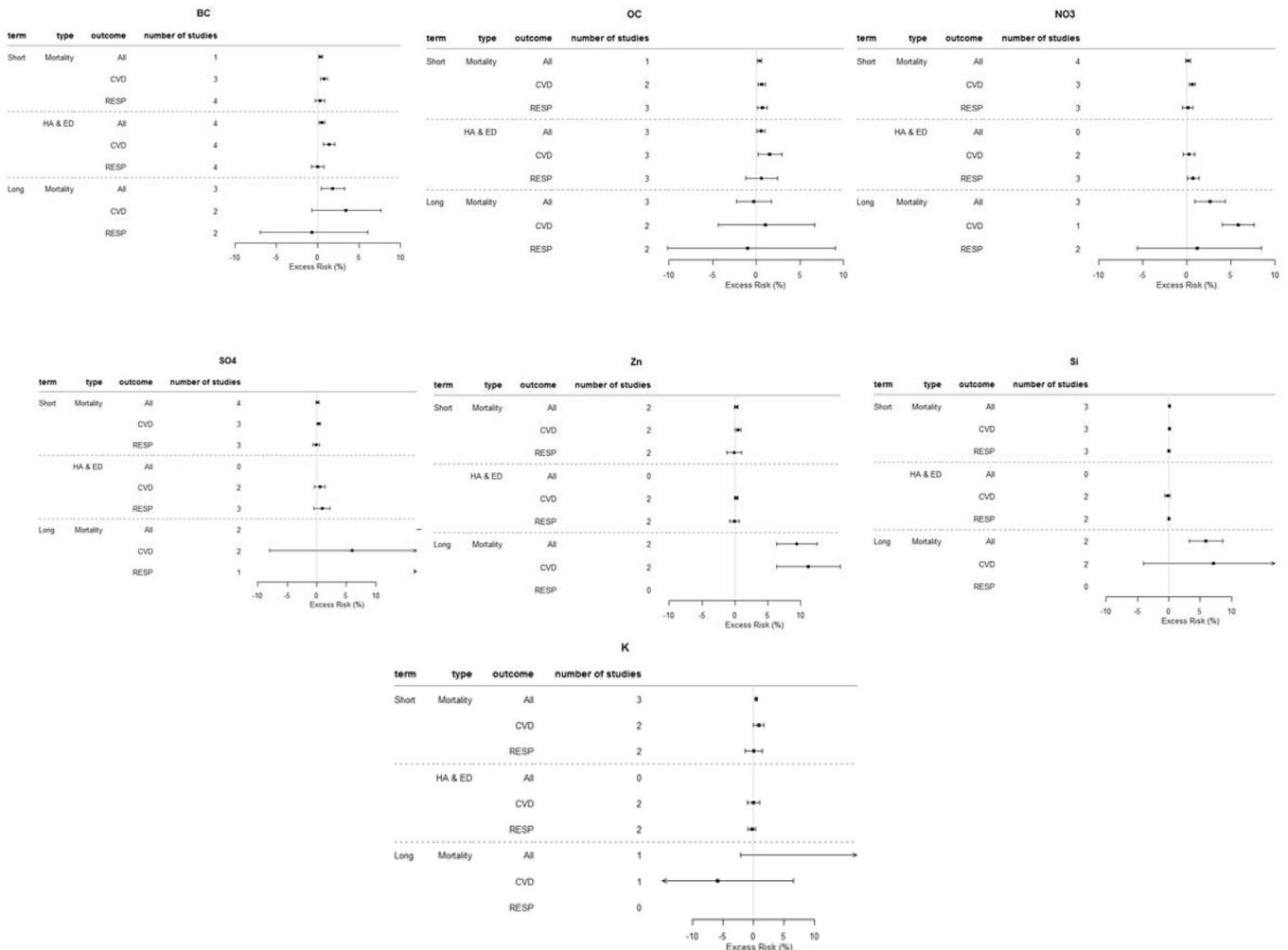


Fig. 2. Association between fine particulate matter constituents and mortality or hospital admission (HA) & emergency department visits (ED) for both short-term or long term exposure time frame (Combine HA and ED visits), adjusting PM_{2.5} in the model.

4. Discussion

We systematically reviewed studies on the associations of short-term and long-term exposures to various PM_{2.5} components with morbidity and mortality. Our meta-analysis suggested that the fine particulate matter constituents, which are most likely to cause adverse health effects, are BC, OC and K for all natural cause; BC, OC and nitrate for CVD cause. Constituents that are probably to cause adverse health effects are Sulfate, NH₄⁺, Zn and Si for all natural cause; sulfate, NH₄⁺, Ni, V, Na, Fe, Zn and Si for CVD diseases; OC, nitrate, sulfate and V for respiratory cause.

Our study suggested that the adverse health effects of BC were most convincing, especially on cardiovascular diseases. BC emissions mainly came from incomplete combustion of biomass or fossil fuel (Cheng et al., 2017; Schauer, 2003). Animal (Yamawaki and Iwai, 2006) and in vitro (Niwa et al., 2007) studies supported that exposure to black carbon could lead to damages in vascular function, as well as activation of ischemic and thrombotic mechanisms. In addition, animal studies also showed that BC could impact the cardiovascular system through promoting the formation of atherosclerotic plaque (Niwa et al., 2007). While the concentration of OC was mainly associated with mobile and biomass burning, we did not find significant association in the cohort studies. One of the important reasons is that there are too few cohort studies to

allow any reasonable combination of OC estimates.

Our study also found that the secondary aerosol constituents, such as nitrate, sulfate and ammonium, were also able to cause adverse health effects. There were relatively more studies focusing on the short-term exposure to nitrate, sulfate and ammonium comparing to other constituents. Our current findings were consistent with a recent meta-analysis which regarding to the short-term exposure to PM_{2.5} constituents and mortality (Achilleos et al., 2017). However, after adjusting for PM_{2.5} mass, only CVD mortality was still significantly associated with nitrate and sulfate, and only respiratory morbidity was significantly associated with nitrate. Furthermore, there is a lack of long-term exposure studies to support the hypothesis of the association between these three secondary aerosol constituents and adverse health effects. These results suggested that more future studies are needed to confirm the possible adverse health effects of nitrate, sulfate and ammonium.

Moreover, adverse health effects may also be caused by several metal components of PM_{2.5}. In accordance with our current results, a recent systematic review indicated that K and Si were the most frequent metal elements linked to adverse health effects, along with Zn, V and Ni (Rohr and Wyzga, 2012). A number of toxicological studies have revealed that Ni will induce the alterations in heart rate variability; delayed arrhythmogenesis, bradycardia and

hypothermia (Zhang et al., 2009). Zn is negatively associated with vasodilatation and vasoconstriction (Lippmann et al., 2013). V will lead to adverse response in human airway epithelial cells (Zhang et al., 2009). However, the number of studies regarding to metals is quite limited, and most of them were conducted in Europe and North American, studies in other regions are still needed.

We also reviewed the source information. Road dust, biomass burning, sea salt were likely to be associated with adverse cardiovascular and respiratory health effects. In cold seasons, coal combustion is the primary source responsible for adverse health effects, while in warm seasons, traffic and crustal source are the primary source. However, the specific sources which are associated with adverse health effects varied across different studies. This could be related to the differences in study design and population. The inconsistent findings across different studies may also be relate to the heterogeneity of particle mixture. In addition, the limited number of studies about sources could also affect us to draw conclusions.

There have been concerns over the discrepancies of the effect magnitudes for different exposure time frames. In the current meta-analysis, we found that the short-term exposure-mortality association for BC, Cu, Fe, Nitrate, Si and Zn were substantially lower than the corresponding long-term association. One possible reason could be due to cumulative effects of the air pollution exposure, which may increase the sensitivity of the highly exposed subgroups (Beverland et al., 2012). Another possible reason was that short-term health effect studies could only capture part of the long-term exposure effects (Li et al., 2017; Liang et al., 2018). Nevertheless, similar magnitudes were also observed in the effect estimates of short-term and long-term exposure to Na and OC. The possible reason could be the variability across different fine particulate matter constituents, exposure assessment methods, lag patterns, as well as different susceptibility in different populations (Nwanaji-Enwerem et al., 2017; Salinas-Rodríguez et al., 2018).

There were several issues regarding the variabilities across constituents and studies. First, the limited quantity of studies in each subcategory, especially the studies on short-term exposure associated hospital admission and emergency department visits, and long-term exposure associated mortality. This is one of the reasons why we combined the effect estimates of hospital admissions and emergency department visits together. Second, measurement error could be another concern. The measurement error of PM_{2.5} constituents is much greater than PM_{2.5} mass (Mostofsky et al., 2012) and measurement error can be different across different constituents. A stronger effect estimate for a certain constituent might have been due to its smaller measurement error comparing to other constituents. The third issue is that one source may be related to several constituents and a single constituent may be from multiple sources, which means that the effect of a certain constituent may be regarded as a mixture of its own effect and its interaction effect with other constituents. Fourth, the exposure measurement methods were different across different correlated studies. For time series studies, the concentrations from general monitoring station were represented the exposure level of an area. For cohort studies, several exposure assessment methods have been applied to estimate the individual level exposure, such as land use regression model (Dehbi et al., 2017; Pedersen et al., 2017; Wang et al., 2014), satellite model (Philip et al., 2014) etc. Hence, when it comes to pooled effect estimates, we have to take the exposure assessment methods into account. Fifth, geographical differences account for much variability across studies, since sources of fine particulate matter varied across different regions as well as community and individual characteristics. For instances, social economic status, education level, smoking status, air conditioning usage or other effect modifiers (Bell et al., 2011; Dai et al.,

2014; Lin et al., 2017). Sixth, our meta-analysis covered studies which conducted in the general population or elderly population. Elderly may be more susceptible to the effects of air pollution than younger population (Qiu et al., 2018).

To our knowledge, this is the first study to synthesize the health effects of both short-term and long-term exposures to fine particulate matter constituents, the results provided important insights on the harmful effects of specific chemical constituents of PM_{2.5}, as well as the future formulation of air pollution control measures. In addition, our sensitivity analyses suggested a robust effect of the chemical components when we restricted to studies which adjusted PM_{2.5} mass.

Our study also had limitations. The number of studies on fine particulate matter components and health effects was limited, especially for long-term health effects, which may lead to a low statistical power when we estimated the pooled effect estimates.

5. Conclusion

Our current meta-analysis suggests that BC and OC were most likely to cause adverse health effects, indicating that specific control standards should be formulated; other potential harmful constituents of PM_{2.5} include nitrate, sulfate, ammonium, Fe, Si, V, Zn. However, more studies are warranted to further investigate the health effects of these constituents.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2018.12.060>.

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