HHS Public Access

Author manuscript

Environ Sci Technol. Author manuscript; available in PMC 2019 June 05.

Published in final edited form as:

Environ Sci Technol. 2018 October 02; 52(19): 11378–11386. doi:10.1021/acs.est.8b00424.

Fine Particle Constituents and Mortality: A Time-Series Study in Beijing, China

Chen Chen[†], **Dandan Xu**[†], **Mike Z. He**[‡], **Yanwen Wang**[†], **Zonghao Du**[†], **Yanjun Du**[†], **Yan Qian**[§], **Dongsheng Ji**[‖], and **Tiantian Li**[*,†]

[†] Department of Environmental Health Risk Assessment, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing 100021, China

[‡] Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, New York 10032, United States

[§] State Key Laboratory of Environmental Criteria and Risk Assessment, Chinese Research Academy of Environmental Sciences, Beijing 100012, China

[‖] State Key Laboratory of Atmospheric Boundary Layer and Atmospheric Chemistry, Institute of Atmospheric Physics, Chinese Academy of Sciences, Beijing 100029, China

Abstract

There is a rising concern that fine particle ($PM_{2.5}$) compositions may play an important role in explaining $PM_{2.5}$-related mortality risks. However, $PM_{2.5}$ constituents responsible for these risks have not yet been determined. To date, there are few $PM_{2.5}$ constituent health studies in developing countries. We adopted a time-series approach, using generalized linear regression models to examine associations between short-term exposure to $PM_{2.5}$ constituents and mortality. We analyzed data stratified by sex and by age groups (<65, 65–74, and >74) from 2013 to 2015 in Beijing, China. We also investigated seasonal patterns of such associations. For a 0 day lag, interquartile range increases in potassium, calcium, magnesium, and organic carbon were associated with 0.51% (95% CI: 0.17–0.85), 2.07% (95% CI: 0.71–3.44), 0.26% (95% CI: 0.08–0.44), and 2.65% (95% CI: 0.18–5.18) increases in respiratory mortality, and sulfate with a 1.57% (95% CI: 0.04–3.12) increase in cardiovascular mortality. In the season-stratified analysis, the association of some constituents (potassium, calcium, magnesium, nitrate, sulfate, and organic carbon) with respiratory mortality appeared to be stronger in cold seasons than in warm seasons. Older adults (65–74) may be susceptible to certain compositions. Our findings provide evidence that link $PM_{2.5}$ constituents with mortality and suggest that adverse effects vary among constituents in different seasons.

[*]**Corresponding Author:** Telephone: 008613671359855. tiantianli@gmail.com. Mailing address: No. 7 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China.

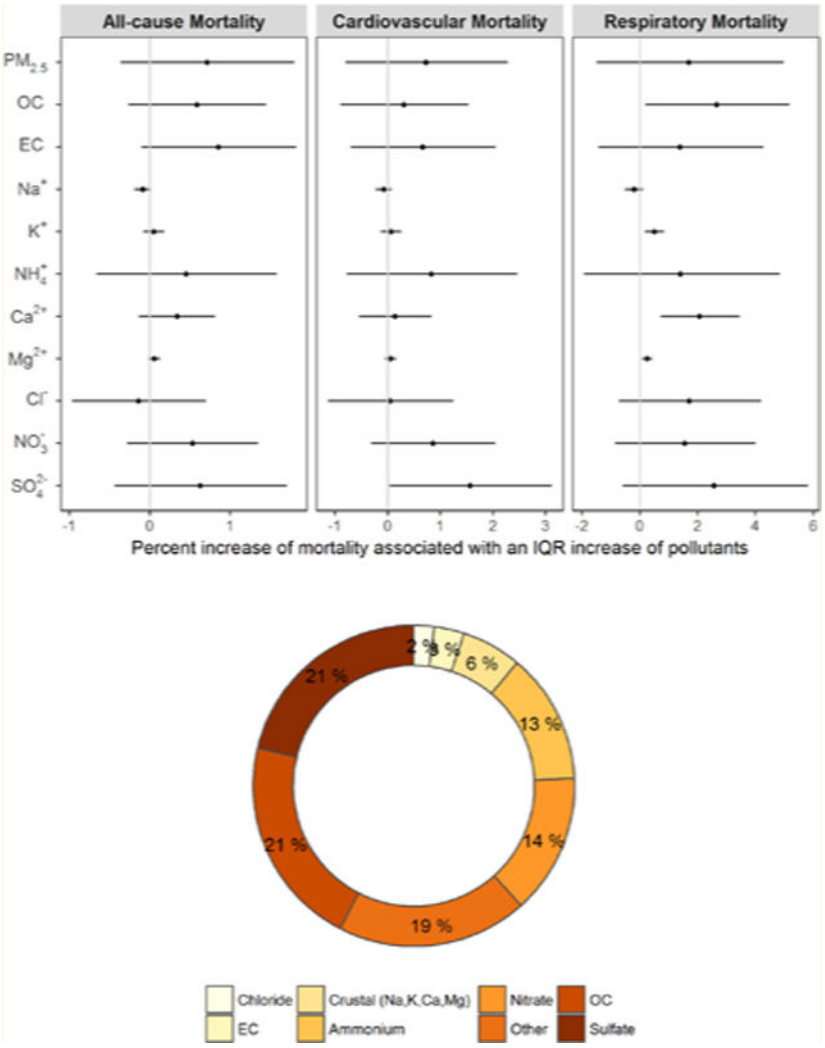
Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b00424.

Map of study area and fixed-site monitors (Figure S1), table of correlation coefficients between $PM_{2.5}$ and chemical constituents (Table S1), and results of the sensitivity analysis: using alternative values of the df for temporal trend and meteorological indicators, as well as including $PM_{2.5}$ mass in the statistical model as a potential confounder (Table S2), replacing the BDL values with half of the detection limit (Table S3), and conducting sensitivity analysis for extreme values of each constituent (Table S4) (PDF)

The authors declare no competing financial interest.

Graphical abstract



INTRODUCTION

Recent epidemiologic studies have confirmed that short-term exposure to fine particle (PM < 2.5 μm in aerodynamic diameter, or $PM_{2.5}$) increases the risk of human mortality.[1–4] Policy makers and regulators have sought to determine which components of the particulate mixture are most harmful to human health.[5] The evidence indicates that the mechanism of $PM_{2.5}$-related mortality may be related to oxidative stress and inflammatory response,[2,6,7] but it is uncertain if the specific chemical constituents of $PM_{2.5}$ play a role. Previous research studies conducted in the U.S. and Europe have tried to determine which constituents pose the highest risks to human health,[8–11] mostly through single-center studies.[10,11] The increasing availability of national-scale monitoring data of the composition of $PM_{2.5}$ has permitted some nationwide multicenter studies in recent years.[12–16] These studies have reported that sulfate, nitrate, elemental carbon, and organic carbon are positively related to the risks of mortality and hospitalization[12–16] and that transition metals including

zinc, nickel, chromium, and iron are also responsible for $PM_{2.5}$-related effects.[12,15,16] However, because of a lack of available data for chemical components and spatial–temporal variations in their distributions,[10,11] the evidence currently available does not allow us to directly link the epidemiological effects of specific constituents with mortality.

China now experiences nationwide air pollution, and $PM_{2.5}$ has become the main risk factor to population health. Numerous studies have confirmed the acute health effects of $PM_{2.5}$ in China and have found that the magnitude of the effect is much less than what has been reported in similar studies conducted in the U.S. and Europe.[17–19] The reason for this discrepancy can be explained by different characteristics of population exposure, the shape of the exposure-response function, and regional socioeconomic factors. Another probable reason is that excess risks vary among constituents, and different proportions of them in $PM_{2.5}$ may induce either greater or fewer $PM_{2.5}$-related effects. Information about how the constituents contribute to mortality in China can provide epidemiological evidence to safeguard human health and can also provide evidence for the differences in the health effects of $PM_{2.5}$ observed in developed countries and China. In most heavy-polluting countries, it is difficult to comprehensively reduce emissions and achieve air quality standards in a short period of time. If the $PM_{2.5}$-related effects can be linked directly to certain chemical compositions or the sources of its constituents, $PM_{2.5}$ pollution can be regulated more effectively by targeting these specific constituents. To date, there have been few studies of the links between constituents and mortality in China, and researchers have mainly examined individual cities such as Beijing,[20] Shanghai,[21] Guangzhou,[22] and Xi'an[23] using a single-center research design. Because monitoring for measuring composition in China is very limited and there is no nationwide network, no multicenter studies have yet been published. Existing studies[20–24] have mainly considered carbonaceous particles and water-soluble ions (WSI) and have consistently shown that the levels of combustion species which have been shown to be largely responsible for $PM_{2.5}$-related health impacts, such as elemental carbon and organic carbon, are higher in China[20–23] than in developed countries.

In light of the severe pollution and the knowledge gaps mentioned above, we utilized a time-series design to estimate how short-term exposure to different chemical constituents of $PM_{2.5}$ influence the risks of mortality in Beijing. We also investigated seasonal patterns of associations between each constituent and mortality. Furthermore, we used the grouping factors sex and age to divide the study population into several subgroups and explored which sector of the population was most vulnerable to short-term exposure to the chemical constituents.

MATERIALS AND METHODS

Study Sites.

Beijing is the largest city in China and experiences the worst air pollution in the country. The study population included individuals who lived continuously in Beijing for at least six months. Our study covered seven districts of Beijing, including Dongcheng, Fengtai, Tongzhou, Mentougou, Changping, Yanqing, and Miyun, which together had a combined population of 6.61 million. We chose these districts because data for daily mortality, $PM_{2.5}$ and its constituents, and meteorological factors were available for at least 1000 days

between 1 January 2013 and 31 December 2015. The locations of study sites are shown in Figure S1 in the Supporting Information.

Mortality Data.

Daily mortality counts were obtained from the Disease Surveillance Point System (DSPS) of the Chinese Center for Disease Control and Prevention (China CDC). We excluded external deaths and then classified the deaths by cause into three categories—all-cause (excluding external) mortality (ICD-10, A00–R99), cardiovascular diseases (ICD-10, I00–I99), and respiratory diseases (ICD-10, J00–J99)—in line with the International Statistical Classification of Disease, 10th Revision (ICD-10; World Health Organization 2007). We divided the data into subgroups and classified all-cause mortality by sex (male and female) and age (<65 years, 65–74 years, and >74 years).

Air Pollution Data.

We obtained $PM_{2.5}$ data from the Beijing Municipal Environmental Monitoring Center (http://zx.bjmemc.com.cn/). We calculated $PM_{2.5}$ mass concentrations by averaging the data from three fixed monitoring stations in Chaoyang District. We also obtained information about $PM_{2.5}$ constituents—including organic carbon (OC), elemental carbon (EC), sodium (Na^+), ammonium (NH_4^+), potassium (K^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), chloride (Cl^-), sulfate (SO_4^{2-}), and nitrate (NO_3^-)—from the particulate composition monitoring station in Chaoyang, which is measured as the average over a 24-h period. We measured the concentrations of ions in $PM_{2.5}$ with an online monitoring instrument (MARGA ADI 2080, Metrohm and Applikon), and we measured organic carbon (OC) and elemental carbon (EC) with a real-time ECOC analyzer (U.S. Sunset Lab RT-4). We chose these constituents because they make up the majority of $PM_{2.5}$ pollution in Beijing, and their concentration levels are mostly above the method detection limits. The detection limit for each constituent was 0.05 $\mu g/m^3$. In our analysis, we replaced hourly reported values that were below the detection limit (BDL) with the detection limit values.

Meteorological Data.

We obtained data for the 24-h average temperature and relative humidity for Beijing Station No. 54511 from the Chinese Meteorological Data Network of the Chinese Meteorological Bureau, and we adjusted for the potential confounding impacts of meteorology on daily mortality.

Analytical Strategy.

We summarized daily mortality, $PM_{2.5}$ mass and its chemical constituents, and meteorological data using the mean, standard deviation (SD), minimum value (min), maximum value (max), and interquartile range (IQR). In our time-series analysis, considering that the data over-dispersion (mean does not equal variance) assumption may be violated in a standard Poisson regression model, we applied a quasi-Poisson regression in a generalized linear model framework to estimate the association between daily mortality and $PM_{2.5}$ constituents for each cause of death and each subgroup for the entire study period. Regression models were also run for the seasonal subset as well. We stratified the three- year

time series data by warm (May–October) and cold (November–April) seasons to explore potential seasonal influences.

In the basic model, we controlled for seasonal and long-term trends with a natural cubic regression spline with five degrees of freedom (df) per year, and same-day daily temperature and relative humidity with a natural cubic regression spline with three df for each. We included indicator variables to allow baseline mortality rates to vary for each day of the week. In the seasonal stratified model, we chose three df per year for the temporal trend and two df for the meteorological parameters. The following model was fitted to obtain an estimate of each $PM_{2.5}$ constituent log-relative rate β

$$\log E\left(Y_t\right) = \text{intercept} + \text{ns(time, df)} + \text{ns(temperature, df)} + \text{ns(humidity, df)} + \text{dow} + \beta Z_t$$

where $E(Y_t)$ represents the expected number of deaths at day t, ns(time, df) is the natural-spline function of the temporal trend, ns(temperature, df) and ns(humidity, df) are the natural-spline functions of the meteorological parameters on day t, dow is a dummy variable for the day of the week, β represents the log-relative rate of mortality associated with a unit increase in a certain constituent of $PM_{2.5}$, and Z_t is the constituent of $PM_{2.5}$ at day t.

We included same day (lag = 0) $PM_{2.5}$ constituent exposure into the basic model to assess the mortality effect. Previous studies[8,9] have reported strong associations between mortality and $PM_{2.5}$ for lags of 1 or 2 days, so we also considered $PM_{2.5}$ constituents with lags of up to 3 days (lag1, lag2, and lag3).

We examined the sensitivity of our key findings in the all-cause mortality relative to the df specified in the smooth functions of time (df = 6, 7) and meteorological indicators (df = 5) to assess model stability. We included linearly controlled daily $PM_{2.5}$ mass in the statistical model as a potential confounder to adjust for potential influence of the daily variation of mass, and we replaced values that were below the detection level by half of the detection limit. In addition, to examine the role of outliers and extreme values, we subtracted the values above the 99th percentile from the three-year data and used this data set to perform regression analyses.

We used R version 3.4.2 for the data analysis. We expressed the effect estimates as a percent increase in mortality for each increase in the interquartile range (IQR) of the $PM_{2.5}$ constituents.

RESULTS

During the period from 2013 to 2015, there were 87 843 deaths from all natural causes, of which 42 491 and 9 043 were related to cardiovascular disease (CVD) and respiratory disease, respectively, in the seven districts of Beijing. Descriptive statistics and seasonal characteristics of the deaths from specific causes, the $PM_{2.5}$ mass and its chemical constituents, and meteorological data used in this present study are presented in Table 1. There were, on average, 81 nonaccidental deaths per day, comprising 42 men and 39 women. When divided into age groups, there were approximately 19, 14, and 48 deaths daily

for the <65, 65–74, and >74 age groups, respectively. On average, 39 people died from CVD and 8 people died from respiratory disease per day. The mean concentrations of $PM_{2.5}$ in Beijing generally exceeded 90 $\mu g/m^3$ (ranging from 5.5 to 512.2 $\mu g/m^3$) over the study period (from 2013 to 2015). More daily deaths occurred in the cold seasons than in the warm seasons. The overall mean concentrations of OC and EC were 15.52 and 2.28 $\mu g/m^3$, respectively. Of the ion chemical constituents, the concentrations of NH_4^+(11.97 $\mu g/m^3$), NO_3^-(14.23 $\mu g/m^3$), and SO_4^{2-}(18.52 $\mu g/m^3$) were the highest. The daily temperature and relative humidity averaged around 13.6 °C and 58%, respectively. A seasonal pattern was exhibited in the average concentrations of $PM_{2.5}$ and compositions, which was substantially higher in the cold seasons. Table S1 of the Supporting Information displays correlations among $PM_{2.5}$ mass and constituents. The Pearson's coefficients of $PM_{2.5}$ mass with OC, EC, NH_4^+, NO_3^-, and SO_4^{2-} were above 0.7 ($p < 0.05$). The major constituents (OC, NH_4^+, NO_3^-, and SO_4^{2-}) were highly correlated with each other (range: 0.62–0.82).

Year-round and season-specific estimates [percentage increase and 95% confidence interval (CI)] of $PM_{2.5}$ mass and the constituents from regression models are presented in Figure 1. In the year-round regression model, most point estimates of the constituents were positive except for Na^+ and Cl^-. Adjusted positive associations of the per IQR increase in OC, K^+, Ca^{2+}, and Mg^{2+} concentrations on current-day exposure with respiratory mortality and of SO_4^{2-} concentration with cardiovascular mortality were found at the $p < 0.05$ level: In terms of results in the season-stratified analysis, OC and EC were associated with all-cause mortality in the warm season at lag 0 day: 2.74% (95% CI, 0.60–4.91) and 2.02% (95% CI, 0.00–4.08), respectively. Stronger associations were observed in the cold season: an IQR increase in NO_3^- was associated with a 1.33% increase (95% CI, 0.38–2.29) in all-cause mortality, IQR increases in NO_3^- and SO_4^{2-} were associated with a 1.86% increase (95% CI, 0.51–3.23) and a 2.69% increase (95% CI, 0.90–4.51) in cardiovascular mortality, and IQR increases in OC, K^+, Ca^{2+}, Mg^{2+}, and NO^-_3 were associated with a 3.04% (95% CI, 0.36–5.79), 0.59% (95% CI, 0.24–0.94), 2.60% (95% CI, 1.05–4.17), 0.27% (95% CI, 0.08–0.46), and 2.87% (95% CI, 0.16–5.66) increase, respectively, in respiratory mortality.

The estimated risks of mortality per IQR increase in $PM_{2.5}$ and the constituents calculated by the lag structure models from 2013 to 2015 are presented in Figure 2. Compared to other lag days, the highest estimates were observed at lag 0 or 1 in the year-round regression model.

The associations between the $PM_{2.5}$ chemical constituents and all-cause mortality by age and sex subgroups are presented in Table 2. There were no statistical differences between the estimated risks of short-term exposure to the mass and the constituents between men and women. We also found that four constituents were responsible for greater risks in the 65–74 age group: mortality by all causes increased by 2.68% (95% CI, 0.44–4.96), 2.71% (95% CI, 0.08–5.4), 2.28% (95% CI, 0.38–4.22), and 2.51% (95% CI, 0.01–5.07) for the 65–74 age group with IQR increases in the concentrations of EC, NH_4^+, NO_3^-, and SO_4^{2-}.

We examined the effects of the $PM_{2.5}$ constituents using alternative values of df for the temporal trend and meteorological indicators in sensitivity analyses, and the results presented in Supporting Information Table S2 suggest that our results were relatively robust.

There were few changes in the estimated effects of the $PM_{2.5}$ constituents, apart from Ca^{2+}, NH_4^+, and NO_3^-, when the number of df per year changed between 5 and 7 in the temporal trend. Between 3 and 5 df, the estimated effects of the $PM_{2.5}$ constituents were almost identical when the number of df for temperature and relative humidity changed. When we compared the results from single- and two-pollutant models that included $PM_{2.5}$ mass, we found that there were large changes in the effects of OC, Cl^-, NO_3^-, and SO_4^{2-} on all-cause mortality at 0 lag. When the BDL values were replaced by half of the detection limit (Supporting Information Table S3), the effects of the $PM_{2.5}$ constituents produced little change in all-cause mortality at 0 lag. By comparing the model estimates between the full data set and subset which had values below the 99th percentile, we found that the point estimates of Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^- changed a lot, but their confidence intervals still overlapped each other (Table S4 of the Supporting Information).

DISCUSSION

This study is one of very few to date that has attempted to quantify the acute effects of chemical constituents of $PM_{2.5}$ in developing countries. We found that the pollution concentrations of carbonaceous particles, secondary aerosol anions, and some WSI were much higher than those reported in developed countries, and that short-term exposure to certain constituents was associated with increases in mortality risks. Our results also suggest that those constituents might increase the risks of $PM_{2.5}$-related mortality in different seasonal patterns. OC and EC were significantly associated with all- cause mortality in warm seasons, and strong associations of OC, K^+, Ca^{2+}, Mg^{2+}, NO_3^-, and SO_4^{2-} were observed in cold seasons. Most commonly, effect estimates were higher for lag 0 or 1 day exposure. Our findings supplement existing evidence that shows $PM_{2.5}$-related effects are modified by age, and that people between 65 and 74 years old are particularly susceptible to EC, SO_4^{2-}, and NH_4^+.

As in previous studies,[10–16] the estimates of acute effects were mostly related to the constituents that made the greatest contributions to the $PM_{2.5}$ mass. The constituents most frequently considered in studies carried out in the U.S. and Europe were SO_4^{2-}, carbonaceous particles (usually EC and OC), and some metals.[10–16] Sulfate and carbonaceous particles were positively associated with increases in all-cause, CVD, and respiratory mortalities.[10,11] However, the roles of other $PM_{2.5}$ constituents are still uncertain, as those constituents were present in quantities that were insufficient for pooling estimates.[11] Earlier Chinese studies have generally focused on the adverse effects of sulfate and WSI.[20–23] Our study and two other studies, Qiao et al. (2014)[21] and Lin et al. (2016),[22] included carbon-containing components to examine. It is, however, difficult to reach consistent conclusions mainly because of regional variations, such as the temporal–spatial distributions of $PM_{2.5}$ constituents, population adaptation, incomparable methodologies, and insufficient evidence.

Carbonaceous particles are considered the most important contributors to $PM_{2.5}$-related health impacts.[8–16] Most studies of mortality or hospital admissions and biomarkers have reported significant associations between CVD mortalities[8,9,11–13] and either EC, OC, or both. Positive excess risks have also been estimated for respiratory outcomes but less

consistently. In a systematic review of epidemiological evidence for the adverse effects of particle components worldwide, Atkinson et al. (2015)[11] conducted a meta-analysis of 19 different studies of OC/EC and mortality and found that an increase of 1 $\mu g/m^3$ in OC and EC was significantly associated with increases of 0.56% (0.01–1.10%) and 1.66% (0.52–2.81%) in CVD mortality but not respiratory mortality. In our study, OC was positively associated with the increase in respiratory mortality risk, and this result was consistent with findings from two single-city studies in Xi'an, China[25] and Madrid, Spain,[26] which support a link between exposure to OC and increased risks of respiratory mortality. Therefore, our findings suggest that OC is one of the major constituents which is responsible for the adverse respiratory effects of $PM_{2.5}$. In addition, short-term exposure to carbonaceous particles was reported to be associated with increased concentrations of exhaled nitric oxide,[27,28] an indicator of airway inflammation, which provides the biological plausibility that carbonaceous particles may contribute to respiratory mortality.

We found positive associations between EC and daily mortality in our main analysis, and this association became statistically significant in our age-stratified analyses. Bell et al. (2009)[12] examined people of 65 years or older in 106 U.S. counties and concluded that estimates of the short-term effects of EC were statistically and positively related to cardiovascular and respiratory hospitalizations. The magnitude of the EC effect on the older group had a greater number of mortalities in our study than in the study of the general population of the U.S., in which an IQR increase in EC was associated with a 0.22% (95% PI, 0.00–0.44) increase in mortality risk. These results suggest that EC has an important role in $PM_{2.5}$-related acute effects on mortality and that it may have been modified by age.

Our results also suggest that WSI may impact mortality and especially respiratory-related mortality. Penttinen et al.[29] examined a panel of adult asthmatics from urban Helsinki and found a soil factor containing Ca^{2+} and Mg^{2+} that was negatively associated with any changes in peak expiratory flow. Our estimate of the effects of Mg^{2+} on mortality was slightly lower than that of Son et al.[30] in Korea, which reported that all- cause mortality increased by 1.4% (95% CI, 0.2–2.6) per IQR increase in Mg^{2+}. SO^{2-}_4had the largest association of all measured WSI species. Its adverse effect on CVD has been presented in a recent meta-analysis.[31] One study in Guangzhou of China (2007–2010)[22] reported that the mortality of the general population from CVD increased by 2.21% (95% CI, 1.05–3.38) per IQR increase in sulfate at daily average concentrations of around 18.52 $\mu g/m^3$.

There is an increased recognition of seasonal variations in constituents contributing to the seasonal pattern in association with short-term exposure to $PM_{2.5}$ and mortality. As toxic constituents appear in certain time periods, the adverse effects of $PM_{2.5}$ would differ across different seasons. Our study showed a stronger association between six constituents (OC, K^+, Ca^{2+}, Mg^{2+}, NO_3^-, and SO_4^{2-}) and mortality in cold seasons, especially for respiratory-related mortality, when their concentrations were higher. In Beijing, Ca^{2+} was mainly derived from soil dust and construction materials in urban aerosol.[32] K^+ most likely comes from open stalk burning and household heating in cold seasons.[33] Poor weather conditions in cold seasons may lead to increased concentrations of certain constituents. SO_4^{2-} and NO_3^- represent secondary aerosols formed by the transformation of their precursors, SO_2 and nitrogen oxides, in the atmosphere.[32] The mass ratio of NO_3^-/SO_4^{2-} has been used as

an indicator to evaluate the relative importance between mobile and stationary sources of nitrate and sulfate in the atmosphere.[33] In our study, these ratios of cold seasons and warm seasons were below 1, which may point to the importance of mobile source emissions. The ratio would be greater than 1 when stationary emissions were more prevailing.[34] Both increasing the number of vehicles and emission reduction of atmospheric SO_2, e.g., a strict implementation of flue gas desulfurization in coal-fired power plants, would increase the ratio.

We found greater estimates of OC and EC occurring in warm seasons when their concentrations slightly declined. Recent evidence on source apportionment and seasonal variation of carbonaceous particles in Beijing showed that OC and EC in $PM_{2.5}$ across seasons were mainly generated from coal combustion, vehicle exhaust, and biomass burning, with vehicle exhaust contributing to 63% of emissions in the summer.[35] This means that OC not only includes primary OC but also secondary OC produced via photochemical reactions in the summer. EC has stable chemical properties and is mainly produced by direct emissions from incomplete combustion. EC in Beijing mainly comes from gasoline and diesel vehicle emissions.[35] Thus, these carbonaceous particles were not greatly different between warm and cold seasons. In addition, seasonal associations between components and mortality did not necessarily match the seasonal variations of concentrations from fixed monitors, possibly because of personal behavioral factors increasing personal exposure which would lead to a larger effect. Activities such as more open windows and ventilation in warm seasons and longer times for outdoor activities could contribute to higher air pollutant exposure.

Studies have frequently reported that people older than 65 years are more susceptible to $PM_{2.5}$ short-term exposure than younger people[1,8,19] because of degraded functioning of cardiopulmonary systems and increased prevalence of pre-existing chronic diseases (such as coronary heart disease, hypertension, and chronic obstructive pulmonary disease) in the elderly. However, studies of the vulnerability of subpopulations to $PM_{2.5}$ chemical constituents are still limited. We examined our data to ascertain whether there were any subpopulation patterns between health effects and the $PM_{2.5}$ constituents. We found that the 65–74 year old age group differed from the others and that the estimated effects for EC, SO_4^{2-}, and NH^+_4 were particularly different. The smaller magnitudes of estimated risks for the 74 years old and above age group, compared to the 65–74 years old age group, might be because of the lower intensity and shorter time spent on outdoor physical activities. Given the results of indoor/outdoor ratios of $PM_{2.5}$ that are less than 1 in Beijing,[36,37] the elderly population (>74 years old) is expected to be exposed to lower levels of $PM_{2.5}$ mass and constituents. Ostro and colleagues[8] also found that mortality was linked with certain $PM_{2.5}$ components among those over 65 years of age. There is increasing evidence of the acute effects associated with exposure to secondary aerosol anions, especially sulfate.[10,11] In a review of 12 single- and multicity studies, all-cause mortality was estimated to increase by 0.15% (0.06, 0.25) per 1 $\mu g/m^3$ increase in sulfate.[11] There was insufficient epidemiologic evidence for a meaningful meta-analysis, and while these summary estimates showed positive effects in the general population, they were imprecise at the subgroup level. Our findings could be improved to provide more evidence about whether subgroups are vulnerable to specific $PM_{2.5}$ components.

There are several limitations associated with this study, as follows. An observational study cannot identify the independent impacts of individual constituents. One common strategy to examine the association between constituents and health outcomes involves examining individual constituent concentration alone in modeling work.[8,9,12,21] With this strategy, it is easy to interpret the question of what the effect of a specific constituent is. However, since $PM_{2.5}$ is positively correlated with both constituent concentration and health outcomes, estimates of individual constituents on adverse effects would be confounded and biased upward.[38] Therefore, we included both the concentrations of individual constituent and $PM_{2.5}$ mass in a two-pollutant modeling work to explore the estimates of specific constituents after adjusting for total $PM_{2.5}$. The model parameter for individual constituent concentration represents the impact of the constituent (and its correlates), holding the other constituents constant.[38] The model parameter for $PM_{2.5}$ mass concentration represents the difference in mortality risk associated with the other constituents.[38] However, this association may be prone to overadjustment if constituents are strongly correlated with $PM_{2.5}$.[38] In our two-pollutant model, estimates of OC, Cl^-, NO_3^-, and SO_4^{2-} were much smaller after adjustment for $PM_{2.5}$, which indicate strong correlations with total $PM_{2.5}$. It is hard to say whether the smaller effect estimates represent an accurate portrayal of the impact of certain constituents independent of $PM_{2.5}$ or not. This raises an issue that the current statistical strategy of an observational study cannot completely interpret the roles of specific constituents in $PM_{2.5}$-related risks.

Our study was based on the assumption that constituent concentrations of a fixed-monitoring site located in the center of a city are representative of population exposure and did not account for exposure misclassification. In fact, there could be two types of exposure misclassification in this study. One is a classical type, caused by variations between the ambient level and personal exposure. The true personal exposure is varied by the outdoor level, individual time−activity patterns, residential characteristics, and indoor sources of pollutants. And this exposure misclassification tends to bias associations between pollutants and health outcomes toward the null.[39,40]

The other type occurs due to spatial heterogeneity of constituent levels. Evidence on community-level spatial heterogeneity of constituent levels showed that exposure misclassification differed by constituents.[39] Ambient secondary pollutants, such as OC, sulfate, nitrate, and ammonium, had less spatial variation than primary pollutants (e.g., EC) and were uniformly distributed within a spatial unit, which could have better representation and less exposure error.[39] Future work should focus on obtaining a more accurate picture of exposure or new methods for assessing exposure error induced by spatial variability.

In addition, when the daily concentrations of specific constituents are very low, the values of measurement may be below the detection level, resulting in an unstable evaluation of the constituents. Although we have performed a sensitivity analysis on values below the detection limits, there was still a limitation of detection limits which might result in inaccurate estimates. The degree of measurement error may differ between components. Some components with many BDL days (e.g., Ca^{2+}, Na^+, Mg^{2+}, and K^+) had a large proportion of inaccurate values in the entire time series. The uncertainty created from these measurement errors of constituents leads to large variances of the residuals from models,

which may negatively influence their estimates.[38] The coefficients for some models may be larger simply due to less measurement error.[38]

In our sensitivity analysis removing extreme values, regression estimates of these components were unstable and varied greatly. Further research is needed to develop statistical methods which could adjust estimate error obtained from detection limits and extreme values. Furthermore, the study design was ecological in nature, and it was difficult to identify the role of one specific $PM_{2.5}$ constituent as the estimates of the effects of single constituents might have been a collaborative proxy of many constituents. Finally, because of limited data availability, our study was only conducted in Beijing over a relatively short time period. To account for the differences in the temporal−spatial distribution of chemical constituents and reduction of measurement error, future epidemiological studies of large populations will be developed over longer time frames at the national scale.

In our study, we found evidence to support our hypothesis that specific chemical constituents of $PM_{2.5}$ play a role in $PM_{2.5}$-related mortality risks. Our findings suggest that adverse effects vary among constituents in different seasons, and certain constituents may be more harmful to the elderly. We believe that stricter regulations on $PM_{2.5}$ mass emissions in conjunction with targeting specific, more toxic components of $PM_{2.5}$ will be a more effective way of protecting the public's health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This research was funded by grants from National Natural Science Foundation of China (Grant: 91543111, 21277135), Natural Science Foundation of Beijing Municipality (Grant: 7172145), National High-Level Talents Special Support Plan of China for Young Talents, and National Institute of Environmental Health Sciences, National Institutes of Health (Award Number F31ES029372).

REFERENCES

(1). Atkinson RW; Kang S; Anderson HR; Mills IC; Walton HA Epidemiological Time Series Studies of PM2.5 and Daily Mortality and Hospital Admissions: A Systematic Review and Meta-Analysis. Thorax 2014, 69, 660–665. [PubMed: 24706041]

(2). Brook RD; Rajagopalan S; Pope CA; Brook JR; Bhatnagar A; Diez-Roux AV; Holguin F; Hong Y; Luepker RV; Mittleman MA Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement From the American Heart Association. Circulation 2010, 121 (21), 2331–2378. [PubMed: 20458016]

(3). Apte JS; Marshall JD; Cohen AJ; Brauer M Addressing Global Mortality from Ambient $PM_{2.5}$. Environ. Sci. Technol 2015, 49 (13), 8057–8066. [PubMed: 26077815]

(4). Vos T; Barber RM; Bell B; Bertozzi-Villa A; Biryukov S; Bolliger I; Charlson F; Davis A; Degenhardt L; Dicker D Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015, 386 (9995), 743–800. [PubMed: 26063472]

(5). WHO. Review of evidence on health aspects of air pollution—REVIHAAP project: Final technical report; The WHO European Centre for Environment and Health: Bonn, Switzerland, 2013.

(6). Xing Y-F; Xu Y-H; Shi M-H; Lian Y-X The Impact of PM2.5 on the Human Respiratory System. J. Thorac. Dis 2016, 8 (1), E69–E74. [PubMed: 26904255]

(7). Mills NL; Donaldson K; Hadoke PW; Boon NA; MacNee W; Cassee FR; Sandström T; Blomberg A; Newby DE Adverse cardiovascular effects of air pollution. Nat. Clin. Pract. Cardiovasc. Med 2009, 6 (1), 36–44. [PubMed: 19029991]

(8). Ostro B; Feng W-Y; Broadwin R; Green S; Lipsett M The Effects of Components of Fine Particulate Air Pollution on Mortality in California: Results from CALFINE. Environ. Health Perspect 2007, 115 (1), 13–19. [PubMed: 17366813]

(9). Ito K; Mathes R; Ross Z; Nádas A; Thurston G; Matte T Fine Particulate Matter Constituents Associated with Cardiovascular Hospitalizations and Mortality in New York City. Environ. Health Perspect 2011, 119 (4), 467–473. [PubMed: 21463978]

(10). Rohr AC; Wyzga RE Attributing health effects to individual particulate matter constituents. Atmos. Environ 2012, 62, 130–152.

(11). Atkinson RW; Mills IC; Walton HA; Anderson HR Fine particle components and health—a systematic review and meta- analysis of epidemiological time series studies of daily mortality and hospital admissions. J. Exposure Sci. Environ. Epidemiol 2015, 25 (2), 208–214.

(12). Bell ML; Ebisu K; Peng RD; Samet JM; Dominici F Hospital Admissions and Chemical Composition of Fine Particle Air Pollution. Am. J. Respir. Crit. Care Med 2009, 179 (12), 1115–1120. [PubMed: 19299499]

(13). Levy JI; Diez D; Dou Y; Barr CD; Dominici F A Meta-Analysis and Multisite Time-Series Analysis of the Differential Toxicity of Major Fine Particulate Matter Constituents. Am. J. Epidemiol 2012, 175 (11), 1091–1099. [PubMed: 22510275]

(14). Krall JR; Anderson GB; Dominici F; Bell ML; Peng RD Short-term exposure to particulate matter constituents and mortality in a national study of U.S. urban communities., Short-term Exposure to Particulate Matter Constituents and Mortality in a National Study of U.S. Urban Communities. Environ. Health Perspect 2013, 121 (10), 1148–1153. [PubMed: 23912641]

(15). Dai L; Zanobetti A; Koutrakis P; Schwartz JD Associations of Fine Particulate Matter Species with Mortality in the United States: A Multicity Time-Series Analysis. Environ. Health Perspect 2014, 122 (8), 837–842. [PubMed: 24800826]

(16). Basagaña X; Jacquemin B; Karanasiou A; Ostro B; Querol X; Agis D; Alessandrini E; Alguacil J; Artiñano B; Catrambone M Short-term effects of particulate matter constituents on daily hospitalizations and mortality in five South-European cities: Results from the MED-PARTICLES project. Environ. Int 2015, 75, 151–158. [PubMed: 25461424]

(17). Lu F; Xu D; Cheng Y; Dong S; Guo C; Jiang X; Zheng X Systematic review and meta-analysis of the adverse health effects of ambient $PM_{2.5}$ and PM_{10} pollution in the Chinese population. Environ. Res 2015, 136, 196–204. [PubMed: 25460637]

(18). Chen R; Yin P; Meng X; Liu C; Wang L; Xu X; Ross JA; Tse LA; Zhao Z; Kan H Fine Particulate Air Pollution and Daily Mortality. A Nationwide Analysis in 272 Chinese Cities. Am. J. Am. J. Respir. Crit. Care Med 2017, 196 (1), 73–81. [PubMed: 28248546]

(19). Chen C; Zhu P; Lan L; Zhou L; Liu R; Sun Q; Ban J; Wang W; Xu D; Li T Short-term exposures to $PM_{2.5}$ and cause-specific mortality of cardiovascular health in China. Environ. Res 2018, 161, 188–194. [PubMed: 29154226]

(20). Li P; Xin J; Wang Y; Li G; Pan X; Wang S; Cheng M; Wen T; Wang G; Liu Z Association between particulate matter and its chemical constituents of urban air pollution and daily mortality or morbidity in Beijing City. Environ. Sci. Pollut. Res 2015, 22 (1), 358–368.

(21). Qiao L; Cai J; Wang H; Wang W; Zhou M; Lou S; Chen R; Dai H; Chen C; Kan H $PM_{2.5}$ Constituents and Hospital Emergency-Room Visits in Shanghai, China. Environ. Environ. Sci. Technol 2014, 48 (17), 10406–10414. [PubMed: 25119795]

(22). Lin H; Tao J; Du Y; Liu T; Qian Z; Tian L; Di Q; Rutherford S; Guo L; Zeng W; Xiao J; Li X; He Z; Xu Y; Ma W Particle size and chemical constituents of ambient particulate pollution associated with cardiovascular mortality in Guangzhou, China. Environ. Pollut 2016, 208, 758–766. [PubMed: 26561449]

(23). Huang W; Cao J; Tao Y; Dai L; Lu S-E; Hou B; Wang Z; Zhu T Seasonal Variation of Chemical Species Associated With Short-Term Mortality Effects of $PM_{2.5}$ in Xi'an, a Central City in China. Am. J. Epidemiol 2012, 175 (6), 556–566. [PubMed: 22323403]

(24). Xu J; Martin RV; van Donkelaar A; Kim J; Choi M; Zhang Q; Geng G; Liu Y; Ma Z; Huang L; Wang Y; Chen H; Che H; Lin P; Lin N Estimating ground-level $PM_{2.5}$ in Eastern China using aerosol optical depth determined from the GOCI Satellite Instrument. Atmos. Chem. Phys. Discuss 2015, 15, 17251–17281.

(25). Cao J; Xu H; Xu Q; Chen B; Kan H Fine Particulate Matter Constituents and Cardiopulmonary Mortality in a Heavily Polluted Chinese City. Environ. Health Perspect 2012, 120 (3), 373–378. [PubMed: 22389181]

(26). Guaita R; Pichiule M; Maté T; Linares C; Díaz J Short-Term Impact of Particulate Matter (PM2.5) on Respiratory Mortality in Madrid. Int. J. Environ. Health Res 2011, 21 (4), 260–274. [PubMed: 21644129]

(27). Chen R; Qiao L; Li H; Zhao Y; Zhang Y; Xu W; Wang C; Wang H; Zhao Z; Xu X Fine Particulate Matter Constituents, Nitric Oxide Synthase DNA Methylation and Exhaled Nitric Oxide. Environ. Sci. Technol 2015, 49 (19), 11859–11865. [PubMed: 26372312]

(28). Shi J; Chen R; Yang C; Lin Z; Cai J; Xia Y; Wang C; Li H; Johnson N; Xu X Association between Fine Particulate Matter Chemical Constituents and Airway Inflammation: A Panel Study among Healthy Adults in China. Environ. Res 2016, 150, 264–268. [PubMed: 27340812]

(29). Penttinen P; Vallius M; Tiittanen P; Ruuskanen J; Pekkanen J Source-Specific Fine Particles in Urban Air and Respiratory Function Among Adult Asthmatics. Inhalation Toxicol. 2006, 18 (3), 191–198.

(30). Son J-Y; Lee J-T; Kim K-H; Jung K; Bell ML Characterization of Fine Particulate Matter and Associations between Particulate Chemical Constituents and Mortality in Seoul, Korea. Environ. Health Perspect 2012, 120 (6), 872–878. [PubMed: 22440884]

(31). Achilleos S; Kioumourtzoglou M-A; Wu C-D; Schwartz JD; Koutrakis P; Papatheodorou SI Acute Effects of Fine Particulate Matter Constituents on Mortality: A Systematic Review and Meta-Regression Analysis. Environ. Int 2017, 109, 89–100. [PubMed: 28988023]

(32). Wang Y; Zhuang G; Sun Y; An Z The Variation of Characteristics and Formation Mechanisms of Aerosols in Dust, Haze, and Clear Days in Beijing. Atmos. Environ 2006, 40 (34), 6579–6591.

(33). Gao J; Tian H; Cheng K; Lu L; Zheng M; Wang S; Hao J; Wang K; Hua S; Zhu C The Variation of Chemical Characteristics of $PM_{2.5}$ and PM_{10} and Formation Causes during Two Haze Pollution Events in Urban Beijing, China. Atmos. Environ 2015, 107, 1–8.

(34). Yang H; Chen J; Wen J; Tian H; Liu X Composition and Sources of $PM_{2.5}$ around the Heating Periods of 2013 and 2014 in Beijing: Implications for Efficient Mitigation Measures. Atmos. Environ 2016, 124, 378–386.

(35). Wang G; Cheng S; Li J; Lang J; Wen W; Yang X; Tian L Source Apportionment and Seasonal Variation of $PM_{2.5}$ Carbonaceous Aerosol in the Beijing-Tianjin-Hebei Region of China. Environ. Monit. Assess 2015, 187 (3), 143. [PubMed: 25716523]

(36). Han Y; Li X; Zhu T; Lv D; Chen Y; Hou L; Zhang Y; Ren M Characteristics and Relationships between Indoor and Outdoor PM2.5 in Beijing: A Residential Apartment Case Study. Aerosol Air Qual. Res 2016, 16 (10), 2386–2395.

(37). Zhao L; Chen C; Wang P; Chen Z; Cao S; Wang Q; Xie G; Wan Y; Wang Y; Lu B Influence of Atmospheric Fine Particulate Matter (PM 2.5) Pollution on Indoor Environment during Winter in Beijing. Building and Environment 2015, 87, 283–291.

(38). Mostofsky E; Schwartz J; Coull BA; Koutrakis P; Wellenius GA; Suh HH; Gold DR; Mittleman MA Modeling the Association Between Particle Constituents of Air Pollution and Health Outcomes. Am. J. Epidemiol 2012, 176 (4), 317–326. [PubMed: 22850792]

(39). Bell ML; Ebisu K; Peng RD Community-Level Spatial Heterogeneity of Chemical Constituent Levels of Fine Particulates and Implications for Epidemiological Research. J. Exposure Sci. Environ. Epidemiol 2011, 21 (4), 372–384.

(40). Zeger SL; Thomas D; Dominici F; Samet JM; Schwartz J; Dockery D; Cohen A Exposure Measurement Error in Time-Series Studies of Air Pollution: Concepts and Consequences. Environ. Health Perspect 2000, 108 (5), 419–426. [PubMed: 10811568]

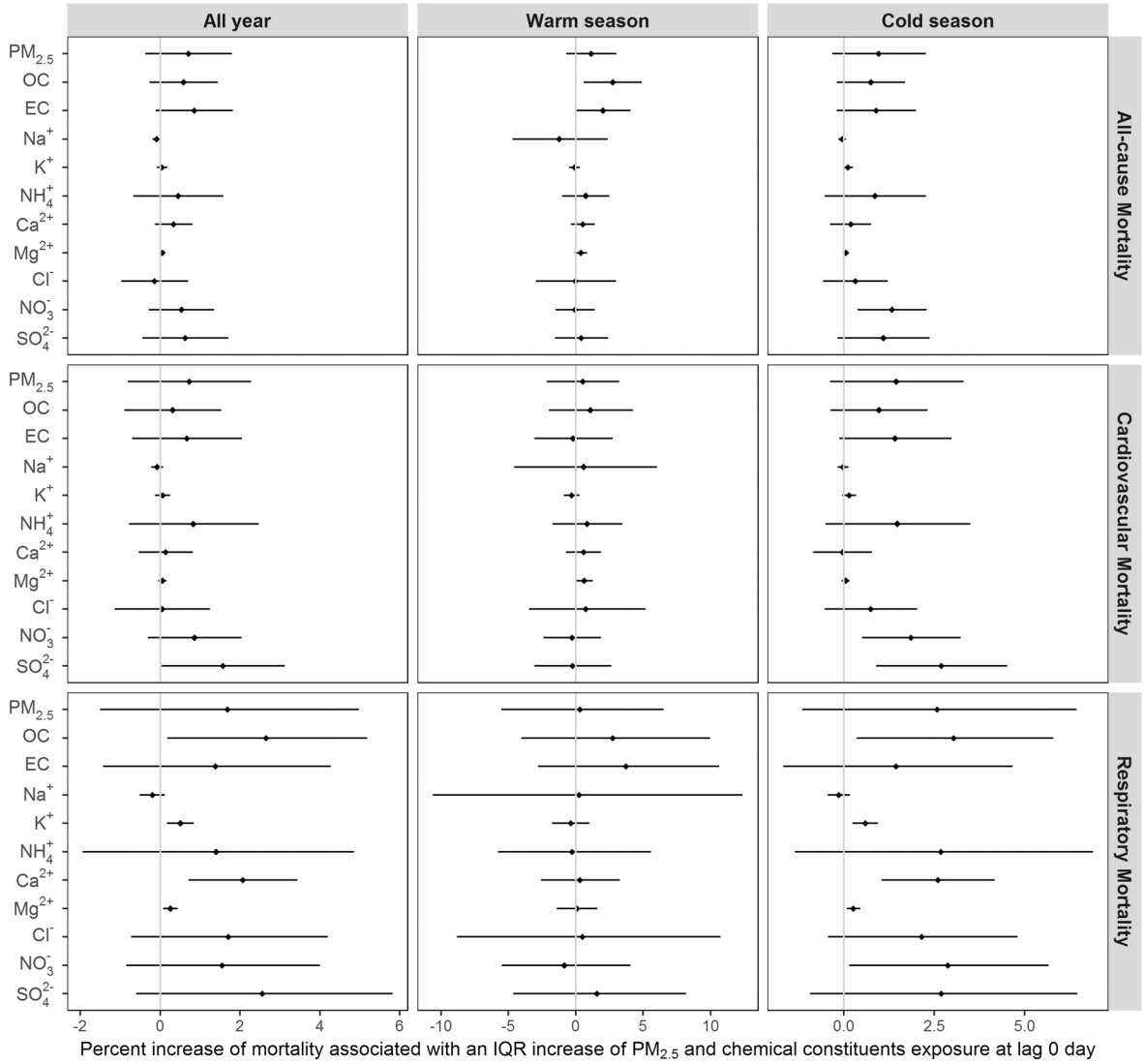


Figure 1.

Estimated risk for mortality of year-round and seasonal stratification per IQR increase in $PM_{2.5}$ mass and chemical constituents, adjusted for temporal trend, day-of-week, and same-day meteorological parameters (temperature and relative humidity).

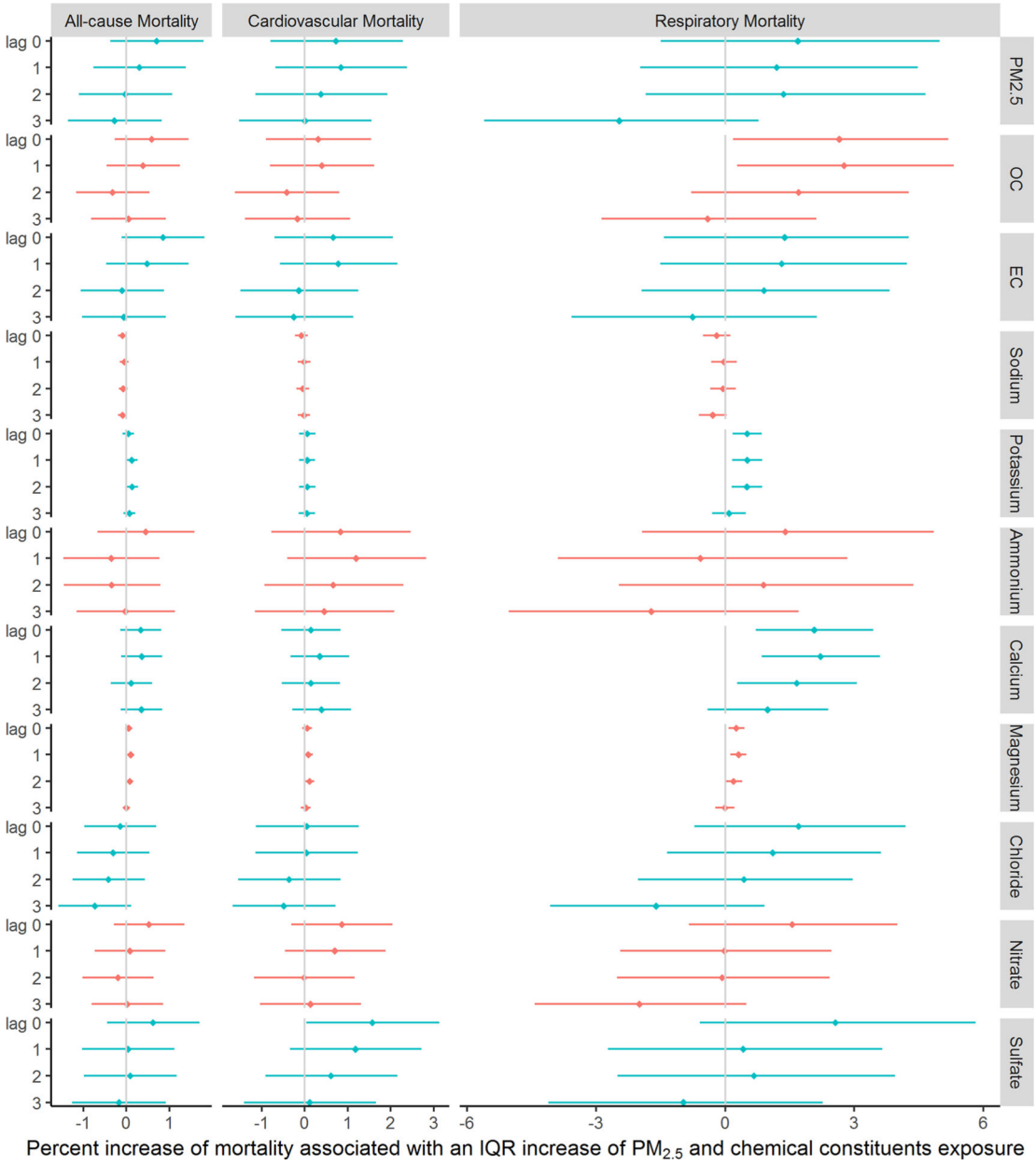


Figure 2.
Estimated effects of 0–3 day lags in $PM_{2.5}$ mass and chemical constituents.

Table 1.

Year-Round and Seasonal Stratified Summary Statistics for Daily Mortality, $PM_{2.5}$ Mass and Chemical Constituents, and Meteorological Factors in Beijing, China (from January 2013 to December 2015)

		year-round				warm seasons		cold seasons	
	days of data available	**mean**	**SD**	**IQR**	**min, max**	**mean**	**SD**	**mean**	**SD**
cause of mortality									
all cause (excluded external deaths)	1083	81	13	19	46, 126	74	10	88	12
male	1083	42	9	13	20, 74	38	8	46	9
female	1083	39	9	12	19, 70	36	8	43	9
0–64 years old	1083	19	5	6	6, 39	18	4	21	5
65–74 years old	1083	14	4	6	4, 27	13	3	15	4
>74 years old	1083	48	9	12	20, 81	43	7	53	9
cardiovascular diseases	1083	39	9	12	15, 70	35	7	44	8
respiratory diseases	1083	8	4	4	1, 24	7	3	10	4
air pollution (24-h average, $\mu g/m^3$)									
$PM_{2.5}$	1095	92.6	77.4	83.0	5.5, 512.2	78.1	60.7	107.4	89.0
organic carbon	1078	15.52	11.49	10.11	0.05, 84.77	11.41	6.31	19.62	13.79
elemental carbon	1078	2.28	1.95	2.03	0.05, 17.59	1.73	1.34	2.83	2.28
Na^+	1079	1.46	6.72	0.89	0.05, 128.63	0.41	0.36	2.54	9.42
K^+	1049	1.58	5.62	1.01	0.05, 91.65	0.63	2.61	2.61	7.50
NH_4^+	1080	11.97	11.65	12.44	0.05, 73.88	10.38	10.02	13.58	12.90
Ca^{2+}	1080	0.40	0.61	0.37	0.05, 6.38	0.32	0.50	0.49	0.69
Mg^{2+}	1077	0.15	0.44	0.05	0.05, 8.55	0.09	0.12	0.21	0.60
Cl^-	1082	2.34	3.28	2.86	0.05, 27.61	0.87	1.33	3.84	3.93
NO_3^-	1082	14.23	16.72	14.50	0.05, 126.13	11.76	13.62	16.74	19.05
SO_4^{2-}	1083	18.52	18.19	20.10	0.05, 120.00	14.88	13.90	21.99	21.10
meteorological parameters									
temperature (°C)	1094	13.7	11.0	20.6	−9.7, 32.6	22.6	5.3	4.5	7.0
humidity (%)	1095	54	20	31	8, 99	61	17	47	20

Table 2.

Percent Increase (95% Confidence Interval) in All-Causes Mortality by Sex and Age Group Associated with an IQR Increase at Lag 0 in Beijing, China from 2013 to 2015

	sex		age		
$PM_{2.5}$ components	**male**	**female**	**<65**	**65–74**	**>74**
$PM_{2.5}$	0.86 (−0.63, 2.36)	0.53 (−0.97, 2.05)	−0.22 (−2.36, 1.97)	2.24 (−0.27, 4.81)	0.59 (−0.76, 1.96)
organic carbon	0.71 (−0.4S, 1.89)	0.53 (−0.67, 1.74)	0.49 (−1.22, 2.23)	1.51 (−0.48, 3.54)	0.40 (−0.67, 1.48)
elemental carbon	1.06 (−0.23, 2.38)	0.64 (−0.71, 2.01)	0.32 (−1.59, 2.26)	**2.68 (0.44, 4.96)**	0.53 (−0.67, 1.74)
Na^+	−0.2 (−0.34, −0.05)	0.03 (−0.11, 0.18)	−0.02 (−0.22, 0.19)	−0.16 (−0.41, 0.10)	−0.1 (−0.24, 0.03)
K^+	0.01 (−0.17, 0.19)	0.10 (−0.10, 0.29)	0.05 (−0.22, 0.32)	0.20 (−0.11, 0.50)	0.01 (−0.16, 0.17)
NH_4^+	0.69 (−0.84, 2.24)	0.20 (−1.37, 1.79)	−0.92 (−3.12, 1.32)	**2.71 (0.08, 5.40)**	0.34 (−1.07, 1.76)
Ca^{2+}	0.41 (−0.23, 1.06)	0.19 (−0.48, 0.86)	0.36 (−0.58, 1.31)	−0.21 (−1.31, 0.91)	0.43 (−0.17, 1.02)
Mg^{2+}	0.02 (−0.08, 0.12)	0.09 (−0.01, 0.20)	0.03 (−0.12, 0.19)	0.14 (−0.03, 0.31)	0.03 (−0.06, 0.13)
Cl^-	−0.16 (−1.30, 1.00)	−0.10 (−1.26, 1.08)	−0.42 (−2.08, 1.27)	1.28 (−0.66, 3.26)	−0.44 (−1.48, 0.61)
NO_3^-	0.55 (−0.57, 1.67)	0.52 (−0.62, 1.68)	−0.44 (−2.05, 1.20)	**2.28 (0.38, 4.22)**	0.40 (−0.62, 1.43)
SO_4^{2-}	0.24 (−1.20, 1.70)	1.04 (−0.48, 2.58)	−0.83 (−2.93, 1.32)	**2.51 (0.01, 5.07)**	0.64 (−0.70, 2.00)