Environment International 143 (2020) 105927

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Fine particulate matter constituents and cause-specific mortality in China: A nationwide modelling study

Jun Yang[a,b,c,1,*], Maigeng Zhou[d,1], Mengmeng Li[e,1], Peng Yin[d], Jianlin Hu[f], Chunlin Zhang[a,b,c], Hao Wang[a,b,c], Qiyong Liu[g,*], Boguang Wang[a,b,c,*]

[a] Institute for Environmental and Climate Research, Jinan University, Guangzhou 511443, China
[b] Guangdong-Hongkong-Macau Joint Laboratory of Collaborative Innovation for Environmental Quality, Guangzhou 511443, China
[c] JNU-QUT Joint Laboratory for Air Quality Science and Management, Jinan University, Guangzhou 511443, China
[d] National Center for Chronic and Noncommunicable Disease Control and Prevention, Beijing 100050, China
[e] International Agency for Research on Cancer, Lyon 69372, France
[f] Jiangsu Key Laboratory of Atmospheric Environment Monitoring and Pollution Control, Jiangsu Engineering Technology Research Center of Environmental Cleaning Materials, Collaborative Innovation Center of Atmospheric Environment and Equipment Technology, School of Environmental Science and Engineering, Nanjing University of Information Science and Technology, 219 Ningliu Road, Nanjing 210044, China
[g] State Key Laboratory of Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China

ARTICLE INFO

Handling Editor: Hanna Boogaard

Keywords:
$PM_{2.5}$ constituents
Cause-specific mortality
Vulnerable population
China

ABSTRACT

Background: Fine particulate matter (with aerodynamic diameter ≤2.5 μm, $PM_{2.5}$) causes huge disease burden worldwide. However, evidence is still inadequate and inconsistent on the relationships between $PM_{2.5}$ constituents and mortality, especially in low resource settings.
Objectives: To evaluate the impact of $PM_{2.5}$ constituents on cause-specific mortality in China.
Methods: We obtained daily mortality data for 161 communities in 2011–2013 from the Disease Surveillance Point system in China. Daily concentrations of major $PM_{2.5}$ constituents, including organic carbon (OC), elemental carbon (EC), sulphate (SO_4^{2-}), nitrate (NO_3^-) and ammonium (NH_4^+), were estimated by using the modified Community Multiscale Air Quality model. For each community, we applied quasi-Poisson regression and polynomial distributed lag models to estimate the effects of $PM_{2.5}$ constituents on cause-specific mortality. Then, the pooled effect estimates were calculated by a random-effect meta-analysis based on the restricted maximum likelihood estimation. Stratification analyses were performed by region, gender, age group and education level to identify the vulnerable populations.
Results: Each interquartile range change of EC, OC, SO_4^{2-}, NO_3^- and NH_4^+ at lag 0–3 day was associated with increments in non-accidental mortality of 0.45% (95%CI: 0.21, 0.69), 1.43% (0.97, 1.89), 0.71% (0.28, 1.15), 0.70% (0.10, 1.30) and 0.95% (0.39, 1.51), respectively. The associations were stronger for the deaths from cardiovascular disease and myocardial infarction, the elderly, illiterates, and people living in the South region.
Conclusions: Our findings suggest positive associations between $PM_{2.5}$ constituents and cause-specific mortality, particularly for myocardial infarction.

1. Introduction

Ambient particulate matter pollution is a high-ranking risk factor for mortality worldwide (Cohen et al., 2017), and the disease burden is extremely high in China – it has been estimated that around 1.2 million deaths in 2017 were attributable to particulate matter (Zhou et al., 2019). Among those particles, fine particulate matter (with aerodynamic diameter ≤2.5 μm, $PM_{2.5}$) is of greater concern with the capacity to deposit in the lung and smaller airways. $PM_{2.5}$ is a mixture of various organic and inorganic substances, and among the major constituents are organic carbon (OC), elemental carbon (EC), sulphate (SO_4^{2-}), nitrate (NO_3^-) and ammonium (NH_4^+) (Liang et al., 2016; Zhou et al., 2016). OC and EC are both carbonaceous aerosols. OC can be emitted primarily or produced secondarily by atmospheric

* Corresponding authors at: Institute for Environmental and Climate Research, Jinan University, Guangzhou 511443, China. (J. Yang and B. Wang). National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China. (Q. Liu).
E-mail addresses: yangjun_eci@jnu.edu.cn (J. Yang), liuqiyong@icdc.cn (Q. Liu), tbongue@jnu.edu.cn (B. Wang).
[1] Co-first authors.

https://doi.org/10.1016/j.envint.2020.105927
Received 21 March 2020; Received in revised form 6 June 2020; Accepted 22 June 2020
Available online 30 June 2020

photochemical reactions, and EC is primarily from vehicle emissions and combustion sources. Among the water-soluble inorganic ions, SO_4^{2-}, NO_3^- and NH_4^+ are the most abundant. SO_4^{2-} and NO_3^- are secondary ions formed from their precursors' sulfur dioxide and nitrogen oxides which are emitted during biomass and fossil combustion.

The short-term impact of $PM_{2.5}$ mass on mortality has been well documented (Cohen et al., 2017; Lu et al., 2015; Qi et al., 2020), but evidence on the relationships between particle constituents and mortality is inadequate and the results are mixed. Although positive associations between EC, as well as OC, and mortality have been found in several studies (Achilleos et al., 2017; Forouzanfar et al., 2015; Yang et al., 2019b), the magnitude of excess risk varies greatly – for instance, the excess non-accidental mortality per interquartile range (IQR) increase of EC ranged from 0.2% to 7.9% in previous findings (Cakmak et al., 2009; Krall et al., 2013). The relationships between other major constituents and mortality risk still remain controversial.

Most of the heterogeneity in the effect estimates can be explained by regional differences (Achilleos et al., 2017). Therefore, the results from previous studies, which were conducted mostly in Europe and North America (Achilleos et al., 2017; Forouzanfar et al., 2015), may not be applicable to China, where the levels and composition of $PM_{2.5}$ differ greatly from those countries in high resource settings (Snider et al., 2016). Although sporadic evidence has begun to emerge in some highly developed cities (Beijing, Shanghai, Guangzhou, and Xi'an) (Geng et al., 2013; Huang et al., 2012; Li et al., 2015; Lin et al., 2016), it remains unclear of the impact of each $PM_{2.5}$ constituent on the mortality risk among the general population in China.

Therefore, in order to address this knowledge gap and to identify priorities in reducing $PM_{2.5}$ related premature mortality, we conducted this modelling study to estimate the relationships between $PM_{2.5}$ constituents and cause-/gender-/age-/education-/region-specific mortality in 161 Chinese communities based on the national mortality database.

2. Methods

2.1. Study area

This population-based study was based on time-series data from the Disease Surveillance Points system (DSPs), a national registration network comprising 161 communities and covering 6% of the total Chinese population. These communities were selected through a multistage stratification, evaluation and adjustment process, with each community representing a county in rural areas or a city district in urban areas. DSPs has shown good representativeness both nationally and regionally (Zhou et al., 2010). The geographical locations of the communities are shown in Supplementary Material Figure S1. In the main analyses, we included all the 161 communities to obtain the national estimate, and then we divided these communities into the North and South regions according to the Qinling-Huaihe Line to get the regional results. In the sensitivity analysis, we further selected those communities with at least three deaths per day on average, by which criterion 133 communities were included.

2.2. Data sources

We derived daily mortality data for each community in 2011–2013, and then aggregated the cause-specific deaths based on the International Classification of Diseases, 10th version (ICD-10): non-accidental mortality (A00-R99), cardiovascular disease (I00-I99), stroke (I60-I69), ischemic heart disease (I20-I25), myocardial infarction (I21-I22), respiratory disease (J00-J99) and chronic obstructive pulmonary disease (J40-J47). The daily meteorological data for each community in the same period were obtained from the China Meteorological Data Service Centre (http://data.cma.cn/), which included temperatures (°C), air pressure (hPa) and relative humidity (%). These data were collected from the basic weather monitoring station in each community.

The daily concentrations of $PM_{2.5}$ and its constituents (EC, OC, SO_4^{2-}, NO_3^- and NH_4^+) at the horizontal resolution of 36 × 36 km during 2011–2013 were estimated by the modified Community Multiscale Air Quality (CMAQ) model. The details of the methodology were described elsewhere (Hu et al., 2016; Hu et al., 2017a). Briefly, the inputs of the model included: the meteorological parameters generated using the Weather Research and Forecasting mode (WRF); the anthropogenic emissions based on the Multi-resolution Emission Inventory (MEIC); the biogenic emissions generated using the Model for Emissions of Gases and Aerosols from Nature (MEGAN); and the open biomass burning emissions generated from the Fire Inventory, which was based on satellite observations. The capability of the model to predict $PM_{2.5}$ mass has been evaluated with monitoring data from 422 sites in 60 large cities across China (Hu et al., 2016); and $PM_{2.5}$ constituents have been evaluated against observational data from monitoring stations in multiple major Chinese cities, such as Beijing, Shanghai, Nanjing, Xi'an, Chongqing and Guangzhou (Hu et al., 2017b; Shi et al., 2017). The outputs of the CMAQ model, i.e., the gridded spatial data of $PM_{2.5}$ mass and its constituents, were then overlaid with the community shapefile of China to extract estimates of average concentrations in each community.

2.3. Data analysis

We applied a two-stage analytical strategy to assess the cause-specific mortality risk associated with $PM_{2.5}$ constituents. Firstly, we calculated the effect estimates of $PM_{2.5}$ constituents on cause-specific mortality for each community. In the second stage, we used the random-effect meta-analysis to pool the effect estimates from all communities to obtain the combined results.

2.3.1. First-stage analysis

We used generalized additive quasi-Poisson regression with polynomial distributed lag model (PDLM) to fit the relationship between $PM_{2.5}$ constituents and cause-specific mortality in each community. We incorporated the following confounding variables in the model: (1) a natural cubic spline function with 7 degrees of freedom (df) per year for the long-term trend and seasonality; (2) natural cubic spline functions with 3 df for 4-day moving average of relative humidity and 6 df for 4-day moving average of daily mean temperature; (3) categorical variables for public holidays and day of the week. These model specifications on adjusting for covariates were consistent with previous studies (Liu et al., 2019; Liu et al., 2018; Yang et al., 2016; Yang et al., 2020). In order to capture lag effect of $PM_{2.5}$ constituents on mortality, PDLM with a maximum lag of four days was used in the main analyses, because previous studies have consistently found that the short-term health risks of $PM_{2.5}$ constituents were limited to four days, such as in California, United States (Ostro et al., 2007), and Shanghai, China (Wang et al., 2019). Smoothing spline function was used to examine the concentration-response relationship between each $PM_{2.5}$ constituent and mortality; if a linear curve was observed, the linear functions would then be used instead. The lag effect was modelled using a prior third degree polynomial (Sun et al., 2019). The lag pattern of $PM_{2.5}$ constituent was examined at single-day lags (lag 0, 1, 2, 3 and 4 day) and cumulative lags (lag 0–1, 0–2, 0–3 and 0–4 day). The lags that yielded the minimal generalized cross validation (GCV) score, indicating the best model performance, were used in the main analyses (Liu et al., 2019). The mortality risk of each $PM_{2.5}$ constituent was first estimated using single-constituent model. Then, to assess the influence of other constituents and $PM_{2.5}$ mass, we further conducted the two-pollutant models by including a pair of pollutants that are not highly correlated to avoid the model collinearity (Pearson's correlation coefficient less than 0.7) (Mela and Kopalle, 2002).

2.3.2. Second-stage analysis

A random-effect meta-analysis based on restricted maximum likelihood estimation was conducted to pool the effect estimates of $PM_{2.5}$ constituents on cause-specific mortality across 161 communities. The impact of $PM_{2.5}$ constituents on mortality was represented as the percentage change in mortality rate per IQR change in $PM_{2.5}$ constituents. Cochran's Q test and the I^2 statistics were used to examine the between-community heterogeneity (Viechtbauer, 2010).

Furthermore, we estimated the concentration-response curves between $PM_{2.5}$ constituents and mortality at national level using the similar approach as previous studies (Gasparrini et al., 2012; Liu et al., 2019). The natural cubic spline function was firstly applied to examine community-specific concentration-response association between $PM_{2.5}$ constituents and mortality risk, with three knots at the 25th, the 50th and the 75th percentiles of $PM_{2.5}$ constituents in each community and minimum average concentration of $PM_{2.5}$ constituents as reference. Then, we obtained four regression coefficients and the 4 × 4 variance-covariance matrix in each community. Finally, we combined the community-specific components of the spline function using random-effect meta-analysis.

2.3.3. Stratification analyses

In order to identify the vulnerable subpopulations to the mortality risk of $PM_{2.5}$ constituents, we separately repeated the aforementioned two-stage analysis by region, gender, age group and education level. Difference test between mortality risks of $PM_{2.5}$ constituents across strata was performed through the following formula: $Z = \frac{E_1 - E_2}{\sqrt{SE(E_1)^2 + SE(E_2)^2}}$, where Z denotes the statistic for Z-test; E_1 and E_2 are the logarithm transformed values of relative risks (RRs), i.e., the β coefficients in the models for each stratum; and $SE(E_1)$ and $SE(E_2)$ are the corresponding standard errors (Altman and Bland, 2003; Yang et al., 2019a).

2.3.4. Sensitivity analyses

A series of sensitivity analyses were conducted in this study. To reduce the influence caused by small number of daily deaths in some communities and to test the robustness of our results, we excluded the communities where the average counts of daily deaths were less than three, after which 133 communities were left for this sensitivity analysis. Furthermore, we changed the dfs for the long-term and seasonal trend of mortality from 4 to 8 per year, and from 3 to 7 for relative humidity and mean temperature, separately.

All data preparations and analyses were performed using the R language (version 3.5.3, R Development Core Team 2018). The PDLM was fitted using "dlnm" package (Gasparrini, 2011) and the meta-analysis was conducted using "metafor" package (Viechtbauer, 2010). Two-tailed *P* values less than 0.05 were considered as statistically significant for all statistical analyses.

3. Results

Table 1 summarizes the statistics of environment and mortality data in 161 communities from 2011 to 2013. The average of annual mean EC, OC, SO_4^{2-}, NO_3^- and NH_4^+ was 3.3 μg/m^3 (range: 0.6–18.0 μg/m^3), 7.8 μg/m^3 (2.0–28.3 μg/m^3), 14.8 μg/m^3 (2.9–62.3 μg/m^3), 13.5 μg/m^3 (0.7–42.1 μg/m^3) and 8.9 μg/m^3 (1.2–29.4 μg/m^3), respectively. On average, there were eight non-accidental deaths per day, four deaths from cardiovascular disease and one from respiratory disease.

Fig. 1 shows the pooled percentage changes in non-accidental mortality associated with per IQR change in $PM_{2.5}$ constituents at different lags from the single-pollutant models. Generally, the associations between $PM_{2.5}$ constituents and mortality were statistically significant at lag 0 and lag 1. Models using lag 0–3 day produced the minimal GCV scores (Supplementary Material Table S1), therefore the cumulative effect estimates we present below are based on lag 0–3 day. The concentration-response curves between $PM_{2.5}$ constituents and mortality at lag 0–3 day were approximately linear, and the steepest slope was observed for OC (Supplementary Material Figure S2).

Table 1
Summary statistics of environment and mortality data in 161 Chinese communities, 2011–2013.

Variables	Mean	SD	Min	P25	P50	P75	Max
Weather conditions							
Mean temperature (°C)	13.7	9.6	−5.4	5.1	15.3	22.4	28.0
Relative humidity (%)	66.3	7.6	44.9	61.7	67.2	72.5	82.6
Concentration (μg/m^3)							
$PM_{2.5}$	60.6	32.5	11.4	36.9	50.7	78.3	177.1
EC	3.3	2.0	0.6	1.9	2.7	4.4	18.0
OC	7.8	4.5	2.0	4.6	6.3	9.7	28.3
SO_4^{2-}	14.8	8.8	2.9	8.8	12.5	17.7	62.3
NO_3^-	13.5	8.7	0.7	6.4	10.8	19.0	42.1
NH_4^+	8.9	5.3	1.2	4.9	7.5	11.7	29.4
Daily deaths							
Non-accidental	8	1	5	7	7	8	13
Cardiovascular	4	1	2	3	4	4	7
IHD	1	0	1	1	1	2	3
Stroke	2	0	1	2	2	2	4
MI	1	0	0	1	1	1	2
Respiratory	1	0	1	1	1	1	2
COPD	1	0	0	1	1	1	2
Gender							
Male	4	1	3	4	4	5	7
Female	3	1	2	3	3	4	5
Age (years)							
0–74	4	1	3	3	4	4	6
75+	4	1	2	3	4	4	7
Education							
Illiterate	3	1	2	2	3	3	6
Primary school and above	4	1	3	4	4	5	7

Note: P25, P50 and P75 denote the 25, 50 and 75 percentiles, respectively; SD, standard deviation; IHD, ischemic heart disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease.

Table 2 presents the pooled percentage changes in cause-specific mortality risk associated with per IQR change in $PM_{2.5}$ constituents at lag 0–3 day. The associations between $PM_{2.5}$ constituents and cause-specific mortality showed low to moderate between-community heterogeneity, with median I^2 of 29.61% (range: 0.01%, 45.24%). Per IQR change in EC, OC, SO_4^{2-}, NO_3^- and NH_4^+ was related to increments in non-accidental mortality of 0.45% (95%CI: 0.21, 0.69), 1.43% (0.97, 1.89), 0.71% (0.28, 1.15), 0.70% (0.10, 1.30) and 0.95% (0.39, 1.51), respectively. The effect estimates of $PM_{2.5}$ constituents were larger in deaths from cardiovascular diseases than the non-accidental mortality, particularly for myocardial infarction [0.86% (−0.03, 1.77), 1.94% (0.76, 3.14), 0.83% (−0.04, 1.71), 1.15% (−0.19, 2.5) and 1.33% (0.18, 2.49) correspondingly].

Table 3 shows the results of the stratified analyses by gender, age group and education level. Similar effect estimates of $PM_{2.5}$ constituents at lag 0–3 day were observed between males and females. The effect estimates were stronger in people aged 75 or older and illiterates than younger people and those with higher education level, although the between-subgroup differences were not statistically significant.

Fig. 2 presents the associations between $PM_{2.5}$ constituents and mortality across lag 0–3 day by region and urban–rural status. The percentage changes of mortality per IQR increases of $PM_{2.5}$ constituents were generally higher in the South than in the North, especially for NO_3^- [1.16% (0.24, 2.09) in the South and 0.32% (−0.46, 1.10) in the North] and NH_4^+ [1.35% (0.43, 2.28) and 0.68% (0.01, 1.35) correspondingly]. While an exception was found for EC, with estimates of 0.33% (0.07, 0.59) and 1.06% (0.45, 1.68) in the South and the North, respectively. Moreover, higher mortality risks of $PM_{2.5}$ constituents were consistently observed in the urban communities, although the

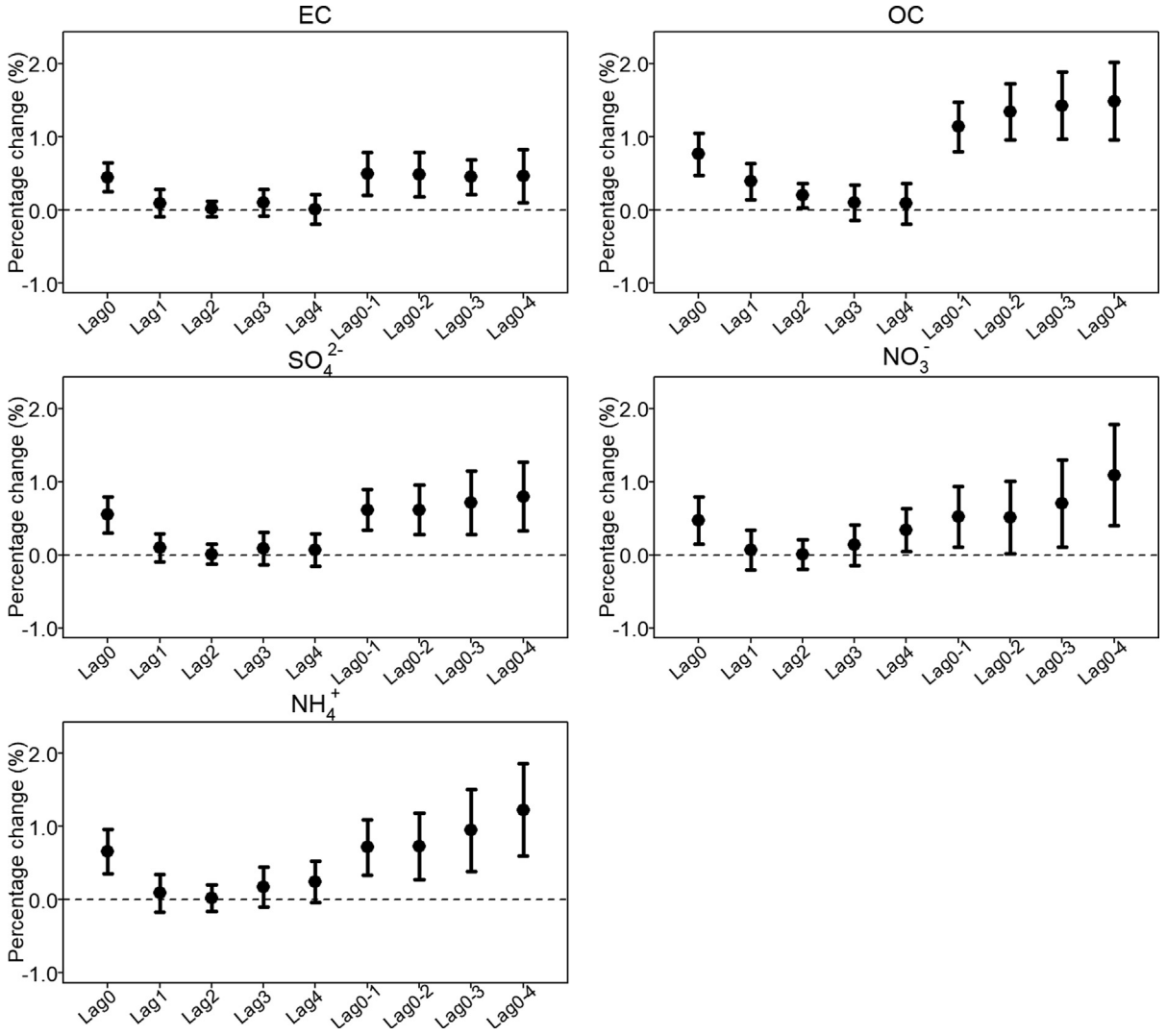

Fig. 1. The pooled percentage changes in daily non-accidental mortality per IQR change in $PM_{2.5}$ constituents during single-day lags (lag 0, 1, 2, 3 and 4 day) and cumulative lags (lag 0–1, 0–2, 0–3 and 0–4 day). A quasi-Poisson regression with polynomial distributed lag model was used to fit the lag effect of $PM_{2.5}$ constituent on non-accidental mortality in each community. A univariate random effect meta-analysis based on the restricted maximum likelihood estimation was conducted to pool the effect estimates.

Table 2
The pooled percentage change (% and 95%CI) in cause-specific mortality per IQR change in $PM_{2.5}$ constituents at lag 0–3 day.

Cause of deaths	EC	OC	SO_4^{2-}	NO_3^-	NH_4^+
Non-accidental	0.45(0.21,0.69)	1.43(0.97,1.89)	0.71(0.28,1.15)	0.70(0.10,1.30)	0.95(0.39,1.51)
Cardiovascular	0.68(0.18,1.18)	1.73(1.04,2.42)	0.80(0.20,1.41)	0.95(0.15,1.75)	1.15(0.40,1.89)
IHD	0.57(−0.13,1.29)	1.78(0.85,2.72)	0.82(0.10,1.54)	0.98(−0.09,2.05)	1.16(0.22,2.11)
Stroke	0.39(−0.17,0.96)	1.45(0.57,2.33)	0.93(0.18,1.69)	0.91(−0.11,1.95)	1.22(0.26,2.19)
MI	0.86(−0.03,1.77)	1.94(0.76,3.14)	0.83(−0.04,1.71)	1.15(−0.19,2.5)	1.33(0.18,2.49)
Respiratory	0.59(0.09,1.09)	1.30(0.33,2.28)	0.51(−0.48,1.51)	0.46(−0.84,1.77)	0.66(−0.61,1.94)
COPD	0.51(−0.24,1.27)	1.54(0.38,2.71)	0.78(−0.35,1.93)	0.44(−1.15,2.05)	0.94(−0.58,2.49)

Note: IHD, ischemic heart disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease. A quasi-Poisson regression with polynomial distributed lag model (PDLM) was used to fit the community-specific relationship between $PM_{2.5}$ constituents and cause-specific mortality. A univariate random effect meta-analysis based on the approach of restricted maximum likelihood estimation was conducted to pool the effect estimates.

differences were not statistically significant.

In the two-pollutant models, we only considered the pairs of EC–SO_4^{2-}, EC– NO_3^- and EC– NH_4^+, because the other pairs were highly correlated with each other (Pearson's correlation coefficient > 0.7) (Supplemental Material Table S2). Overall, effect estimates of EC were attenuated when separately introducing SO_4^{2-}, NO_3^- and NH_4^+ into the model. With the adjustment for EC, the impact of NO_3^-on mortality was not statistically significant, while the effect estimates of $SO_4^{2-}$and NH_4^+ were relatively stable (Supplemental Material Table S3).

In the sensitivity analyses, similar effect estimates of $PM_{2.5}$ constituents were observed when only including communities with at least three deaths per day on average (Supplemental Material Table S4). Additionally, effect estimates of $PM_{2.5}$ constituents were stable when we changed the dfs for potential confounders, i.e., 4–8 dfs per year for

Table 3
The pooled percentage change (% and 95%CI) in daily non-accidental mortality per IQR change in $PM_{2.5}$ constituents at lag 0–3 day, stratified by individual characteristics.

Variables	EC	OC	SO_4^{2-}	NO_3^-	NH_4^+
Gender					
Male	0.46(0.15,0.76)	1.42(0.89,1.95)	0.65(0.14,1.15)	0.72(0.01,1.44)	0.94(0.27,1.61)
Female	0.46(0.01,0.91)	1.43(0.76,2.10)	0.75(0.18,1.32)	0.68(−0.11,1.47)	0.92(0.20,1.64)
Age (years)					
0–74	0.33(−0.07,0.74)	1.08(0.48,1.69)	0.36(−0.17,0.89)	0.37(−0.40,1.14)	0.49(−0.21,1.19)
75+	0.59(0.18,1.01)	1.72(1.08,2.35)	0.94(0.35,1.54)	1.00(0.24,1.77)	1.30(0.56,2.06)
Education					
Illiterate	0.38(−0.12,0.88)	1.48(0.74,2.24)	0.77(0.13,1.42)	1.22(0.34,2.10)	1.26(0.44,2.09)
Primary school and higher	0.57(0.14,1.00)	1.46(0.89,2.03)	0.64(0.1,1.19)	0.40(−0.33,1.13)	0.71(0.01,1.41)

Note: A quasi-Poisson regression with polynomial distributed lag model (PDLM) was used to fit the community-specific relationship between $PM_{2.5}$ constituents and mortality. A univariate random effect meta-analysis based on the approach of restricted maximum likelihood estimation was conducted to pool the effect estimates. Stratification analysis was performed by individual characteristics.

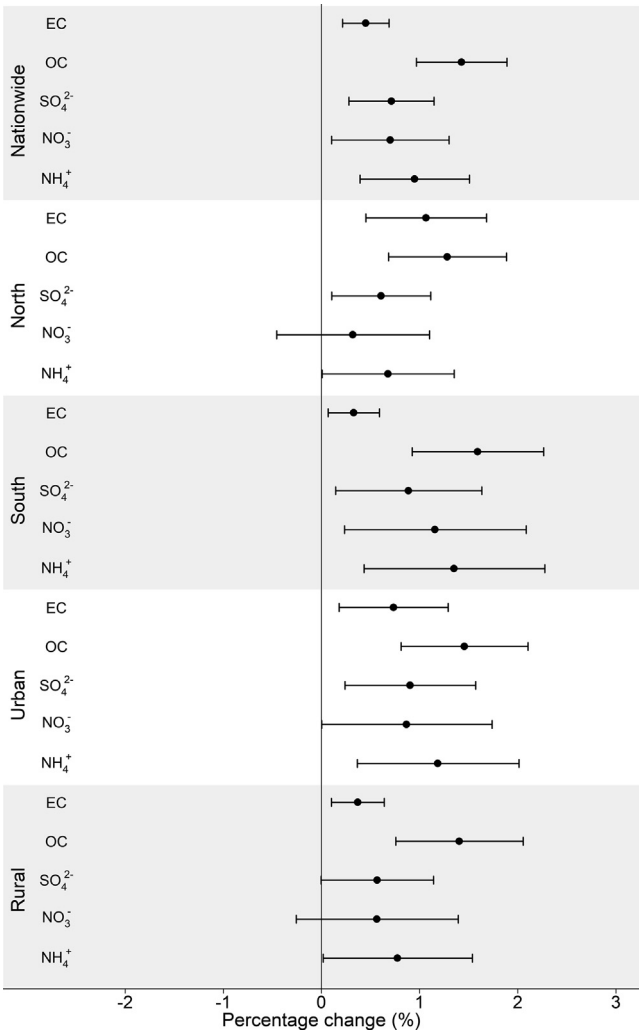

Fig. 2. Percentage change (% and 95%CI) in daily non-accidental mortality per IQR change in $PM_{2.5}$ constituents at lag 0–3 day, stratified by region and urban–rural status. A quasi-Poisson regression with polynomial distributed lag model (PDLM) was used to fit the community-specific relationship between $PM_{2.5}$ constituents and mortality. A univariate random effect meta-analysis based on the approach of restricted maximum likelihood estimation was conducted to pool the effect estimates.

time variable, 3–7 dfs for relative humidity and 3–7 dfs for mean temperature (Supplementary Material Figures S3-S5).

4. Discussions

To our knowledge, this is the first nationwide study to evaluate the impact of major $PM_{2.5}$ constituents on cause-specific mortality in China. These constituents were significantly associated with elevated risk of non-accidental mortality at lag 0–3 day, with the highest estimates observed for OC. Those with cardiovascular disease, the elderly and people with less educational attainment were at higher risks of $PM_{2.5}$ constituents. The harmful effects of NO_3^- and NH_4^+ were slightly higher in the South, while those of EC were higher in the North.

In our study, the highest short-term impact on mortality has been found for carbonaceous constituents, which is consistent with those reported by others (Forouzanfar et al., 2015), and the mortality risk of OC is higher than EC. Higher excess all-cause mortality caused by OC was also found in Seoul, Korea and Xi'an, China (Heo et al., 2014; Huang et al., 2012), but some other studies reported similar effects between these two constituents (Yang et al., 2019b) or lower effect for OC (Cakmak et al., 2009). Total OC concentrations are contributed by both primary and secondary constituents, the latter of which could be produced by the gas-to-particle conversion from volatile or semi-volatile organic compositions (Liang et al., 2016). The emission sources of primary OC and the properties of the secondary OC can greatly influence the toxicity of the mixture, and may partly explain the heterogeneity of the findings across study sites. We also found that the increments of OC and EC were associated with excess cardiorespiratory deaths, which are coherent with previous epidemiological findings (Achilleos et al., 2017; Yang et al., 2019b). EC has been found to be associated with ST-segment depressions in older adults with coronary heart disease (Lanki et al., 2006). Increase of cardiovascular morbidity were accompanied with the increase of EC on the same day and OC with one day lag, while only OC was found to be related to hospital admissions for respiratory diseases (Peng et al., 2009).

Furthermore, positive associations of SO_4^{2-}, NO_3^- and NH_4^+ with death risks were also observed. The harmful toxicological responses elicited by SO_4^{2-} in the cardiorespiratory systems may be related to its direct and indirect effects (Gwynn et al., 2000; Reiss et al., 2007). The acidic property could directly induce airway hyper-responsivity, clearance abnormalities and changes in lung function; or indirectly enhance the absorption, formation and bioavailability of more toxic compounds. Short term exposure to SO_4^{2-} has also been found to be positively correlated with biomarkers of oxidative stress, an important mechanism of acute cardiovascular adverse events (Li et al., 2016). The underlying biological mechanism for NH_4^+ is not well understood. NH_4^+ usually coexists with SO_4^{2-} and NO_3^- in the form of $(NH_4)^2SO_4$, NH_4NO_3, and NH_4HSO_4, and these constituents are highly correlated in our study.

Also, the impact of NO_3^-on mortality was not statistically significant after adjusting for EC. Our results were comparable with previous findings, which showed positive but nonsignificant effects of NO_3^-(Heo et al., 2014; Huang et al., 2012), especially on cardiovascular diseases (Yang et al., 2019b).

Our results on the cause-specific risk, as well as the individual-level effect modifiers, have important public health implications in identifying the susceptible diseases and vulnerable populations. Among the cardiorespiratory diseases studied, patients with myocardial infarction were affected most by several constituents. Of note, due to the consideration of the minimum sample size of daily deaths to ensure model robustness, we only focused on the common causes of death. From the perspective of prevention, the risk ratios we have estimated can help to assess the reducible death burden by lowering the exposure levels of the particle constituents studied. In addition, we found higher risk of mortality due to constituents in older citizens and people with lower educational attainment. The social inequality may be related to pre-existing conditions, poor living and working environment, and hence higher exposure to air pollutants, co-exposure to other risk factors such as smoking and limited access to health care. Therefore, it involves multi-sectoral efforts to reach out the disadvantaged population and break the link between socioeconomic disparity and health inequity. The effect modification by gender varied across previous studies. For instance, Chen and colleagues observed higher risk of total $PM_{2.5}$ in females in China (Chen et al., 2017), but the opposite trend was reported in the United States (Zeka et al., 2006). The reasons behind the inconsistency in the gender-specific vulnerability to air pollutants remain unclear and warrant further studies.

One interesting finding of the present study is the higher mortality risk for residents living in the South associated with NO_3^- and NH_4^+, but higher risk in the North associated with EC. North and South regions vary greatly in the source apportionment, concentration and proportion of various constituents and weather conditions (Zhang et al., 2017), which may influence the results on the health effects of the studied constituents. For instance, the source contribution of coal and biomass combustion is higher in the North, while the traffic emission contributes more in the South (Zhang et al., 2017). Previous study confirmed that the health effects of particulate matter constituents varied greatly by their sources (Krall et al., 2017). Moreover, the complex interactions of air pollutants, as well as their constituents, could possibly modify the effect of each of them, which was confirmed in our results from the two-pollutant models. As to the meteorological conditions, although we have statistically adjusted for the potential confounding effects of temperature and humidity, we couldn't rule out the possibility of residual confounding, or the impact of other unmeasured meteorological parameters.

Additionally, we observed consistently higher effect estimates of $PM_{2.5}$ constituents in urban areas than rural areas, although the differences were not statistically significant. Direct comparison with previous studies on the urban-rural difference is limited, as there is no quantitative evidence on assessing the health risks of $PM_{2.5}$ constituents by urban and rural status. This difference in susceptibility may be contributed by two major mechanisms (O'Neill et al., 2003) – differential exposures (such as variations in the source apportionment of $PM_{2.5}$ constituents and in the distribution of co-exposures) and differential vulnerability (for instance, higher number of the elderly and people with existing medical conditions in the urban areas may enlarge the impact of $PM_{2.5}$ constituents).

Our results add to those previously reported in several ways. To our knowledge, only limited number of studies had evaluated the short-term health impact of particle constituents in China (Huang et al., 2012; Lin et al., 2016; Sun et al., 2019; Yang et al., 2019b), but they only focused on highly developed cities. Our analyses addressed this gap by estimating the differential toxicity of major constituents at the national level, which can provide evidence for the national policy making, and inform the priority in the air pollution control strategy. Additionally, the associations with all-cause and broad categories of cardiorespiratory mortality have been examined in a number of studies, but few of them examined specific causes of death (Achilleos et al., 2017; Yang et al., 2019b), which could provide more insights into the possible biological mechanism of their health impact, and evidence on the targeted population protection.

Some limitations should be noted in the present study. First, our aim is not to conduct an exhaustive assessment of all air pollutants, and we didn't control for other air pollutants or constituents of $PM_{2.5}$ due to lack of data and the consideration of stability of the statistical models. Second, we didn't adjust for potential confounders such as smoking and indoor air pollutants, but these factors may have minimum influence on our results because they are unlikely to change on a day-to-day basis, which is the time unit of measurement in our methodology to measure the short-term effect. Third, due to lack of long-term time-series monitoring data on $PM_{2.5}$ constituents across mainland China, we used the concentrations of $PM_{2.5}$ constituents predicted by CMAQ approach. Although these predicted $PM_{2.5}$ constituent data have been validated by the observed data from monitoring stations (Hu et al., 2016; Hu et al., 2017b), uncertainties in the emission inventories and model specifications may cause potential bias in the exposure assessment. Fourth, similar to most previous time-series studies (Huang et al., 2012; Li et al., 2015; Liu et al., 2018; Sun et al., 2019), data on air pollutants and weather variables were from population level instead of individual level. Therefore, the exposure measurement may be subject to misclassification bias. However, this non-differential bias may lead to an underestimate of the health risk of air pollution (Zanobetti and Schwartz, 2009). Fifth, the ecological design of this study restrains us from making inference on the causal relationship.

5. Conclusions

Our study implies that the major constituents of $PM_{2.5}$ differ in the mortality risk in the Chinese population. Our results highlight the importance of controlling sources emitting carbonaceous constituents, especially OC related activities. Along with the measures to monitor and control air pollutants, the protection of vulnerable populations, particularly those with susceptible diseases, should be incorporated in the future strategic plans.

Ethical approval

Ethical approval was not required for secondary analysis of anonymous data in this study.

CRediT authorship contribution statement

Jun Yang: Conceptualization, Resources, Writing - original draft, Formal analysis, Funding acquisition, Supervision. **Maigeng Zhou:** Resources, Writing - review & editing. **Mengmeng Li:** Conceptualization, Writing - original draft, Formal analysis. **Peng Yin:** Resources, Writing - review & editing. **Jianlin Hu:** Resources, Writing - review & editing. **Chunlin Zhang:** Investigation, Writing - review & editing. **Hao Wang:** Investigation, Writing - review & editing. **Qiyong Liu:** Resources, Writing - review & editing, Supervision. **Boguang Wang:** Conceptualization, Writing - review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The study was supported by the National Key Research and Development Program of China (No. 2018YFC0213600), Guangdong Basic and Applied Basic Research Foundation (No. 2020A1515011161), the Natural Science Foundation of Guangdong Province (No. 2018A030310655), Guangdong Province Science and Technology Department (2019B121202002, 2019B121205004, 2019B110206002) and the Fundamental Research Funds for the Central Universities (No. 11618323). Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105927.

References

Achilleos, S., Kioumourtzoglou, M.A., Wu, C.D., Schwartz, J.D., Koutrakis, P., Papatheodorou, S.I., 2017. Acute effects of fine particulate matter constituents on mortality: A systematic review and meta-regression analysis. Environ. Int. 109, 89–100.

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. BMJ 326, 219.

Cakmak, S., Dales, R.E., Vida, C.B., 2009. Components of particulate air pollution and mortality in Chile. Int. J. Occup. Environ. Health 15, 152–158.

Chen, R., Yin, P., Meng, X., Liu, C., Wang, L., Xu, X., et al. Fine particulate air pollution and daily mortality. A nationwide analysis in 272 Chinese Cities. Am. J. Respir. Crit. Care Med. 2017; 196: 73–81.

Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., Estep, K., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. The Lancet 389, 1907–1918.

Forouzanfar, M.H., Alexander, L., Anderson, H.R., Bachman, V.F., Biryukov, S., Brauer, M., et al., 2015. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386, 2287–2323.

Gasparrini, A., 2011. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. J. Stat. Softw. 43, 1–20.

Gasparrini, A., Armstrong, B., Kenward, M.G., 2012. Multivariate meta-analysis for non-linear and other multi-parameter associations. Stat. Med. 31, 3821–3839.

Geng, F.H., Hua, J., Mu, Z., Peng, L., Xu, X.H., Chen, R.J., et al., 2013. Differentiating the associations of black carbon and fine particle with daily mortality in a Chinese city. Environ. Res. 120, 27–32.

Gwynn, R.C., Burnett, R.T., Thurston, G.D., 2000. A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ. Health Perspect. 108, 125–133.

Heo, J., Schauer, J.J., Yi, O., Paek, D., Kim, H., Yi, S.M., 2014. Fine particle air pollution and mortality: importance of specific sources and chemical species. Epidemiology 25, 379–388.

Hu, J., Chen, J., Ying, Q., Zhang, H., 2016. One-year simulation of ozone and particulate matter in China using WRF/CMAQ modeling system. Atmos. Chem. Phys. 16, 10333–10350.

Hu, J., Li, X., Huang, L., Ying, Q., Zhang, Q., Zhao, B., et al., 2017a. Ensemble prediction of air quality using the WRF/CMAQ model system for health effect studies in China. Atmos. Chem. Phys. 17, 13103–13118.

Hu, J., Wang, P., Ying, Q., Zhang, H., Chen, J., Ge, X., et al., 2017b. Modeling biogenic and anthropogenic secondary organic aerosol in China. Atmos. Chem. Phys. 17, 77–92.

Huang, W., Cao, J.J., Tao, Y.B., Dai, L.Z., Lu, S.E., Hou, B., et al., 2012. Seasonal Variation of Chemical Species Associated With Short-Term Mortality Effects of PM2.5 in Xi'an, a Central City in China. Am. J. Epidemiol. 175, 556–566.

Krall, J.R., Anderson, G.B., Dominici, F., Bell, M.L., Peng, R.D., 2013. Short-term exposure to particulate matter constituents and mortality in a national study of U.S. urban communities. Environ. Health Perspect. 121, 1148–1153.

Krall, J.R., Mulholland, J.A., Russell, A.G., Balachandran, S., Winquist, A., Tolbert, P.E., et al., 2017. Associations between source-specific fine particulate matter and emergency department visits for respiratory disease in Four U.S. Cities. Environ. Health Perspect. 125, 97–103.

Lanki, T., de Hartog, J.J., Heinrich, J., Hoek, G., Janssen, N.A., Peters, A., et al., 2006. Can we identify sources of fine particles responsible for exercise-induced ischemia on days with elevated air pollution? The ULTRA study. Environ. Health Perspect. 114, 655–660.

Li, P., Xin, J.Y., Wang, Y.S., Li, G.X., Pan, X.C., Wang, S.G., et al., 2015. Association between particulate matter and its chemical constituents of urban air pollution and daily mortality or morbidity in Beijing City. Environ. Sci. Pollut. Res. 22, 358–368.

Li, W., Wilker, E.H., Dorans, K.S., Rice, M.B., Schwartz, J., Coull, B.A., et al., 2016. Short-term exposure to air pollution and biomarkers of oxidative stress: the Framingham heart study. J. Am. Heart Assoc. 5.

Liang, C.-S., Duan, F.-K., He, K.-B., Ma, Y.-L., 2016. Review on recent progress in observations, source identifications and countermeasures of PM2.5. Environ. Int. 86, 150–170.

Lin, H., Tao, J., Du, Y., Liu, T., Qian, Z., Tian, L., et al., 2016. Particle size and chemical constituents of ambient particulate pollution associated with cardiovascular mortality in Guangzhou, China. Environ. Pollut. 208, 758–766.

Liu, C., Chen, R., Sera, F., Vicedo-Cabrera, A.M., Guo, Y., Tong, S., et al., 2019. Ambient particulate air pollution and daily mortality in 652 cities. N. Engl. J. Med. 381, 705–715.

Liu, C., Yin, P., Chen, R., Meng, X., Wang, L., Niu, Y., et al., 2018. Ambient carbon monoxide and cardiovascular mortality: a nationwide time-series analysis in 272 cities in China. The Lancet Planetary Health 2, e12–e18.

Lu, F., Xu, D., Cheng, Y., Dong, S., Guo, C., Jiang, X., et al., 2015. Systematic review and meta-analysis of the adverse health effects of ambient PM2.5 and PM10 pollution in the Chinese population. Environ. Res. 136, 196–204.

Mela, C.F., Kopalle, P.K., 2002. The impact of collinearity on regression analysis: the asymmetric effect of negative and positive correlations. Appl. Econ. 34, 667–677.

O'Neill, M.S., Jerrett, M., Kawachi, I., Levy, J.I., Cohen, A.J., Gouveia, N., et al., 2003. Health, wealth, and air pollution: advancing theory and methods. Environ. Health Perspect. 111, 1861–1870.

Ostro, B., Feng, W.-Y., Broadwin, R., Green, S., Lipsett, M., 2007. The effects of components of fine particulate air pollution on mortality in California: results from CALFINE. Environ. Health Perspect. 115, 13–19.

Peng, R.D., Bell, M.L., Geyh, A.S., McDermott, A., Zeger, S.L., Samet, J.M., et al., 2009. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. Environ. Health Perspect. 117, 957–963.

Qi, J., Ruan, Z., Qian, Z., Yin, P., Yang, Y., Acharya, B.K., et al., 2020. Potential gains in life expectancy by attaining daily ambient fine particulate matter pollution standards in mainland China: A modeling study based on nationwide data. PLoS Med. 17, e1003027.

Reiss, R., Anderson, E.L., Cross, C.E., Hidy, G., Hoel, D., McClellan, R., et al., 2007. Evidence of health impacts of sulfate-and nitrate-containing particles in ambient air. Inhal Toxicol 19, 419–449.

Shi, Z., Li, J., Huang, L., Wang, P., Wu, L., Ying, Q., et al., 2017. Source apportionment of fine particulate matter in China in 2013 using a source-oriented chemical transport model. Sci. Total Environ. 601–602, 1476–1487.

Snider, G., Weagle, C.L., Murdymootoo, K.K., Ring, A., Ritchie, Y., Stone, E., et al., 2016. Variation in global chemical composition of PM2. 5: emerging results from SPARTAN. Atmos. Chem. Phys. 16, 9629–9653.

Sun, S., Cao, W., Pun, V.C., Qiu, H., Ge, Y., Tian, L., 2019. Respirable particulate constituents and risk of cause-specific mortality in the Hong Kong population. Environ. Sci. Technol. 53, 9810–9817.

Viechtbauer, W., 2010. Conducting Meta-Analyses in R with the metafor Package. J. Stat. Softw. 36, 1–48.

Wang, Y., Shi, Z., Shen, F., Sun, J., Huang, L., Zhang, H., et al., 2019. Associations of daily mortality with short-term exposure to PM2. 5 and its constituents in Shanghai, China. Chemosphere 233, 879–887.

Yang, J., Ou, C.Q., Song, Y.F., Li, L., Chen, P.Y., Liu, Q.Y., 2016. Estimating years of life lost from cardiovascular mortality related to air pollution in Guangzhou, China. Sci. Total Environ. 573, 1566–1572.

Yang, J., Yin, P., Sun, J., Wang, B., Zhou, M., Li, M., et al., 2019a. Heatwave and mortality in 31 major Chinese cities: Definition, vulnerability and implications. Sci. Total Environ. 649, 695–702.

Yang, J., Zhou, M., Zhang, F., Yin, P., Wang, B., Guo, Y., et al., 2020. Diabetes mortality burden attributable to short-term effect of PM10 in China. Environ. Sci. Pollut. Res. 27, 18784–18792.

Yang, Y., Ruan, Z., Wang, X., Yang, Y., Mason, T.G., Lin, H., et al., 2019b. Short-term and long-term exposures to fine particulate matter constituents and health: A systematic review and meta-analysis. Environ. Pollut. 247, 874–882.

Zanobetti, A., Schwartz, J., 2009. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ. Health Perspect. 117, 898–903.

Zeka, A., Zanobetti, A., Schwartz, J., 2006. Individual-level modifiers of the effects of particulate matter on daily mortality. Am. J. Epidemiol. 163, 849–859.

Zhang, Y., Cai, J., Wang, S., He, K., Zheng, M., 2017. Review of receptor-based source apportionment research of fine particulate matter and its challenges in China. Sci. Total Environ. 586, 917–929.

Zhou, M., Wang, H., Zeng, X., Yin, P., Zhu, J., Chen, W., et al., 2019. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 394, 1145–1158.

Zhou, M.G., Jiang, Y., Huang, Z.J., Wu, F., 2010. Adjustment and representativeness evaluation of national disease surveillance points system. Disease Surveillance 13, 6295–6378.

Zhou, X., Cao, Z., Ma, Y., Wang, L., Wu, R., Wang, W., 2016. Concentrations, correlations and chemical species of PM2.5/PM10 based on published data in China: Potential implications for the revised particulate standard. Chemosphere 144, 518–526.