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Abbreviations:

$\mu g/m^3$	micrograms per cubic meter
95% CI	95 percent confidence interval
df	degree of freedom
DOW	day of the week
EC	elemental carbon
GLM	generalized linear model
ICD-10	the 10^{th} revision of International Classification of Diseases
IQR	interquartile range
km^2	square kilometers
NO_2	nitrogen dioxide
ns	natural splines
O_3	ozone
OC	organic carbon
PACF	partial autocorrelation function
$PM_{2.5}$	particulate matter less than 2.5 microns in diameter
SO_2	sulfur dioxide
SPCDCP	Shanxi Provincial Center for Disease Control and Prevention

Abstract:

Background: Although ambient $PM_{2.5}$ has been linked to adverse human health effects, the chemical constituents that cause harm are unknown. To our knowledge, the health impacts of $PM_{2.5}$ constituents have not been reported for a developing country.

Objectives: To examine the short-term association between $PM_{2.5}$ constituents and daily mortality in Xi'an, a heavily polluted Chinese city.

Methods: We obtained daily mortality data and daily concentrations of $PM_{2.5}$, organic carbon (OC), elemental carbon (EC), and ten water-soluble ions between January 1, 2004 and December 31, 2008. We also measured concentrations of fifteen elements between January 1, 2006 and December 31, 2008. We analyzed the data using over-dispersed generalized linear Poisson models.

Results: During our study period, the mean daily average concentration of $PM_{2.5}$ in Xi'an was 182.2 $\mu g/m^3$. Major contributors to $PM_{2.5}$ mass included OC, EC, sulfate, nitrate, and ammonium. After adjustment for $PM_{2.5}$ mass, we found significant positive associations of total, cardiovascular, or respiratory mortality with OC, EC, ammonium, nitrate, chlorine ion, chlorine, and nickel for at least one lag. Nitrate demonstrated stronger associations with total and cardiovascular mortality than $PM_{2.5}$ mass. For a 1-day lag, inter-quartile range increases in $PM_{2.5}$ mass and nitrate (114.9 and 15.4 $\mu g/m^3$, respectively) were associated with 1.8% (95% CI: 0.8%, 2.8%) and 3.8% (95% CI: 1.7%, 5.9%) increases in total mortality.

Conclusions: Our findings suggest that $PM_{2.5}$ constituents from the combustion of fossil fuel may have an appreciable influence on the health impact attributable to $PM_{2.5}$ in Xi'an.

Introduction

Numerous epidemiological studies during the past 20 years have confirmed that short-term and long-term exposure to outdoor air pollution contributes to increased cardiopulmonary mortality and morbidity (Brunekreef and Holgate 2002; Pope and Dockery 2006). Among various pollutants in the ambient mixture, fine particulate matter ($PM_{2.5}$, defined as particle less than 2.5 microns in aerodynamic diameter) shows the most consistent association with adverse health outcomes and therefore is of great public health concern (Ito et al. 2011; Ostro et al. 2007; Peng et al. 2009; Thurston et al. 2005; Zhou et al. 2011). However, the chemical components of $PM_{2.5}$ responsible for these effects are still unknown. As the U.S. National Academy of Science pointed out, it is important to understand the contributions of specific components of ambient particulate matter (PM) to cardiopulmonary and other health effects (National Research Council 1998).

China is one of the countries with the highest $PM_{2.5}$ level in the world (van Donkelaar et al. 2010). However, $PM_{2.5}$ is still not a criteria pollutant in China, and few studies in the country have investigated the adverse health impact of $PM_{2.5}$ due to lack of monitoring data. Currently, the Chinese government is reviewing the Air Quality Standards (AQS) and proposing to set the $PM_{2.5}$ standard as 35 $\mu g/m^3$ for annual average and 75 $\mu g/m^3$ for daily average (Chinese Ministry of Environmental Protection 2010). To our knowledge, only three published studies in China estimated the effects of $PM_{2.5}$ on daily mortality (Kan et al. 2007; Ma et al. 2011; Venners et al. 2003). Kan et al. (2007) and Ma et al. (2011) found significant associations between $PM_{2.5}$ and daily mortality in Shanghai and Shenyang, while Venners et al. (2003) observed negative and statistically insignificant associations between $PM_{2.5}$ and daily mortality in Chongqing. Obviously, more studies are needed to investigate the health

impacts of $PM_{2.5}$ and its chemical constituents in China.

In the current study, we examined short-term associations between $PM_{2.5}$ constituents and cardiopulmonary mortality in Xi'an, a heavily polluted Chinese city.

Materials and Methods

Data

Xi'an, with an area of 9,983 square kilometers (km^2) and a resident population over 8.1 millions by 2005, is the capital of Shanxi Province of China. As the largest city in northwestern China, Xi'an experiences some of the worst air pollution among China's cities (Cao et al. 2005). Our study area was limited to the urban area of Xi'an, with an area of 1,166 km^2 and a resident population of over 2.7 millions.

Mortality data

We obtained numbers of deaths among urban residents in Xi'an for each day between January 1, 2004 and December 31, 2008 from the Shanxi Provincial Center for Disease Control and Prevention (SPCDCP). In Xi'an, all deaths, regardless of whether they occur in a hospital or at home, must be reported to appropriate authorities before cremation. Hospital or community doctors indicate the cause of death on a Death Certificate Card that is sent to SPCDCP. SPCDCP staff classify the causes of death according to the International Classification of Diseases, Revision 10 (ICD-10) as deaths due to total non-accidental causes (A00-R99), cardiovascular diseases (I00-I99), respiratory diseases (J00-J98), or injury (S00-T98). The Chinese government has mandated detailed quality assurance (QA) and quality control (QC) programs for the Death Registry at SPCDCP.

Pollutant and meteorological data

For this study, we measured daily concentrations of $PM_{2.5}$, organic carbon (OC),

elemental carbon (EC), and ten water-soluble ions (Na^+, NH_4^+, K^+, Mg^{2+} Ca^{2+}, F^-, Cl^-, NO_2^-, SO_4^{2-} and NO_3^-) between January 1, 2004 and December 31, 2008 (1,827 days). We also measured concentrations of fifteen elements (S, Cl, K, Ca, Ti, Cr, Mn, Fe, Ni, Zn, As, Br, Mo, Cd and Pb) between January 1, 2006 and December 31, 2008 (1,096 days).

The $PM_{2.5}$ monitoring site was located on the rooftop of the Chinese Academy of Sciences' Institute of Earth Environment building in an urban-scale zone of representation (Chow et al. 2002). The site was surrounded by a residential area where there were no major industrial activities, nor local fugitive dust sources (see Supplemental Material, Figure 1). $PM_{2.5}$ samples were obtained 10 m above ground. Our previous studies suggest that the measured $PM_{2.5}$ concentrations at this monitoring station are representative of the general status of $PM_{2.5}$ pollution in Xi'an (Cao et al. 2005; Cao et al. 2007; Cao et al. 2009).

Daily $PM_{2.5}$ samples were collected using two battery-powered mini-volume samplers (Airmetrics, Oregon, USA) operating at a flow rate of 5 liters per minute (Cao et al. 2003). We used a relatively low flow rate due to high PM loading in Xi'an. $PM_{2.5}$ samples were collected on 47mm Whatman quartz microfiber filters that were pre-heated at 900 ℃ for three hours before sampling. Quartz-fiber filters were analyzed gravimetrically for mass concentrations.

A 0.5 cm^2 punch from each samples was analyzed for OC and EC with a Desert Research Institute (DRI) Model 2001 Thermal/Optical Carbon Analyzer (Atmoslytic Inc., Calabasas, CA, USA) for eight carbon fractions following the IMPROVE (Interagency Monitoring of Protected Visual Environments) thermal/optical reflectance (TOR) protocol (Chow et al. 2004). Five water-soluble anions (F^-, Cl^-, NO_2^-, SO_4^{2-} and NO_3^-) and five water-soluble cations (Na^+, NH_4^+, K^+, Mg^{2+} and Ca^{2+}) in

aqueous extracts of the sample filters were determined by an ion chromatograph (Dionex 600, Dionex). Cation concentrations were determined with the use of a CS12A column (Dionex) and anions were separated by an AS11-HC column (Dionex). The elemental concentrations of these samples were determined by Energy Dispersive X-Ray Fluorescence (ED-XRF) spectrometry (the PANalytical Epsilon 5 XRF analyzer). Detailed descriptions of the sample pretreatment, specific methods, detection limits, and QA/QC have been published (Cao et al. 2003; Cao et al. 2005; Shen et al. 2009a; Shen et al. 2009b).

To allow adjustment for the effect of gaseous pollutants and weather on mortality, we obtained daily concentrations of sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) from the Xi'an Environmental Monitoring Center, and daily mean temperature and humidity from Xi'an Meteorological Bureau. The SO_2 and NO_2 concentrations were averaged from the available monitoring results across seven stations in our study area. As per the rules of the Chinese government, the monitoring data from these stations generally reflected the background urban air pollution of Xi'an rather than the pollution from local sources.

Statistical methods

Due to different time periods for the measurement of $PM_{2.5}$ constituents, we constructed two datasets to analyze the data: the first includes daily measurement of $PM_{2.5}$, OC, EC, and ions between January 1, 2004 and December 31, 2008; the second includes daily concentrations of $PM_{2.5}$ and elements between January 1, 2006 and December 31, 2008.

Daily counts of deaths and air pollution levels were linked by date and were therefore analyzed with time-series analyses (Bell et al. 2004). Because daily counts of deaths approximately follow a Poisson distribution and the relationship between

mortality and explanatory variables is mostly nonlinear, we used over-dispersed generalized linear Poisson models (quasi-likelihood) with natural spline (*ns*) smoothers to analyze mortality, $PM_{2.5}$ constituents, and covariate data.

In the basic model, we incorporated smoothed spline functions of time, which accommodate both nonlinear and non-monotonic relations between mortality and time and thus provide a flexible model to control for long-term and seasonal trends (Hastie and Tibshirani 1990). Day of the week (*DOW*) was included as a dummy variable (a variable that takes on the values 1 and 0; also called an indicator variable) in the basic models. Partial autocorrelation function (*PACF*) was used to guide the selection of degrees of freedom (*df*) for the time trend until the absolute values of the sum of *PACF* of the residuals for lags up to 30 reached a minimal value (Peng et al. 2006; Touloumi et al. 2004; Touloumi et al. 2006). We used residual plots and *PACF* plots to examine residuals of the basic model for discernable patterns and autocorrelation.

After establishing the basic model, we introduced the $PM_{2.5}$ constituents and covariates (including temperature, humidity, SO_2 and NO_2 concentrations) in the model. Based on the previous literature (Dominici et al. 2006) we used smoothed spline functions with 3 *df* (for the whole period of the study) to control for temperature and relative humidity. To examine the temporal relationship of $PM_{2.5}$ constituents with mortality, we fitted the models with different lag structures from lag 0 to lag 3, because our previous work on $PM_{2.5}$ and daily mortality in China showed little evidence of a significant association with a lag beyond 3 days (Kan et al. 2007; Ma et al. 2011). A lag of day 0 (lag 0) corresponds to the current-day $PM_{2.5}$, and a lag of day 1 (lag 1) refers to the previous-day $PM_{2.5}$. We used the smoothing spline, with 3 *df* for the $PM_{2.5}$, to graphically describe its relationships with mortality. We compared the linear

and spline models by computing the difference between the deviances of the fitted two models (Dominici et al. 2002; Samoli et al. 2005). We estimated associations of $PM_{2.5}$ constituents with mortality before and after adjustment for $PM_{2.5}$ mass. Finally, to examine the robustness of our choice on the optimal values of *df* for time trend, we performed a sensitivity analysis to test the impact of *df* selection on the regression results.

All analyses were conducted in R 2.10.1 using the MGCV package. The results are presented as the percent change in daily mortality per inter-quartile range (IQR) increase of pollutant concentrations unless specified otherwise. Statistical significance was defined as $p < 0.05$.

Results

From January 1, 2004 to December 31, 2008, a total of 47,838 deaths were identified in our study population. On average, there were 26.2 non-accidental deaths per day, including 12.1 from cardiovascular diseases and 7.2 from respiratory diseases (Table 1). The mean daily average temperature and humidity in Xi'an were 13.4 ℃ and 66.5 %, respectively.

During 2004-2008, the mean daily average concentration of $PM_{2.5}$ was 182.2 $\mu g/m^3$ in Xi'an (Table 2), which was much higher than the Global Guidelines set by the World Health Organization (WHO) (annual average: 10 $\mu g/m^3$) and reported levels of $PM_{2.5}$ in other Chinese cities such as Beijing (annual average: 122 $\mu g/m^3$) (Guo et al. 2009), Shanghai (annual average: 55 $\mu g/m^3$) (Kan et al. 2007), and Shenyang (annual average: 75 $\mu g/m^3$) (Ma et al. 2011). Meanwhile, the mean daily average concentrations of SO_2 and NO_2 were 48.4 and 38.2 $\mu g/m^3$.

During the five years (1,827 days), there were 1,749 observations of OC and EC;

the averaged concentrations were 28.3 μg/m^3 for OC and 12.0 μg/m^3 for EC, accounting for 15.5% and 6.6% of the total $PM_{2.5}$ mass, respectively (Table 2). In additional to OC and EC, the other largest contributors to $PM_{2.5}$ were SO_4^{2-} (17.4 %), NO_3^- (8.4 %), NH_4^+ (4.8 %), and S (2.8%).

Generally, moderate to high correlations (r = 0.5 - 0.8) were observed for $PM_{2.5}$ with OC, EC, S, Cl, K, Mg^{2+}, Cl^-, K^+, SO_4^{2-}, NO_3^-, and NH_4^+ (see Supplemental Material, Table 1). $PM_{2.5}$ was modestly correlated with Na^+ (r = 0.33). Consistent with previous studies (Ostro et al. 2007), Ni was weakly correlated with $PM_{2.5}$ (r = 0.13) and other constituents.

Figure 1 summarizes the quantitative regression results for single-day lags 0-3 of $PM_{2.5}$ mass and various constituents (before adjustment for $PM_{2.5}$). We found significant associations of $PM_{2.5}$ mass with daily mortality; an IQR increment in the 1-day lagged concentrations of $PM_{2.5}$ (182.2 μg/m^3) corresponded to 1.8% [95% confidence interval (CI): 0.8%, 2.8%], 3.1% (95%CI: 1.6%, 4.6%), and 4.5% (95%CI: 2.5%, 6.4%) increase of total, cardiovascular, and respiratory mortality, respectively. Consistent with previous studies (Ito et al. 2011; Ostro et al. 2007; Peng et al. 2009), the effect estimates of $PM_{2.5}$ constituents varied by lag structures and mortality outcomes. OC, EC, NH_4^+, Cl^-, NO_3^-, Cl, and Ni showed the strongest associations in that more than half of the associations assessed were positive and statistically significant. At least one positive significant association was found for Na^+, K^+, Mg^{2+}, SO_4^{2-}, S, K, and As. We did not observe positive significant associations for F^-, Ca, Ti, Cr, Mn, Fe, Zn, Br, Mo, Cd, or Pb (see Supplemental Material, Figure 2).

Figure 2 shows the effect estimates of $PM_{2.5}$ constituents (OC, EC, NH_4^+, NO_3^-, Cl^-, Cl, and Ni) that were significantly associated with at least one outcome and lag period after further adjustment for $PM_{2.5}$ mass. OC and EC were positively associated

with cardiovascular and respiratory mortality (for lags 1-3 and lag 3, respectively), but were not clearly associated with total mortality. NH_4^+ and NO_3^- were significantly associated with total and cardiovascular mortality, but not with respiratory mortality. Cl^-, Cl, and Ni were significantly associated with all three mortality outcomes for at least one lagged exposure. It should be noted that NH_4^+ (lag 3) and Cl^- (lag 1) were negatively and statistically significantly associated with cardiovascular or respiratory mortality. Na^+, K^+, Mg^{2+}, SO_4^{2-}, S, K, and As, after adjustment for $PM_{2.5}$, were no longer positively and statistically significantly associated with any of the outcomes, and some of the adjusted associations even became negative and statistically significant (see Supplemental Material, Figure 3). Interestingly, associations with an IQR increase in NO_3^- (after adjustment for $PM_{2.5}$) were stronger than associations with an IQR increase in $PM_{2.5}$ mass for total and cardiovascular mortality. For instance, for lag 1, an IQR increase in NO_3^- (15.2 μg/m^3) was associated with 3.8% (95% CI: 1.7%, 5.9%) increase in total mortality, compared with 1.8% (95% CI: 0.8%, 2.8%) for an IQR increase (182.2 μg/m^3) in $PM_{2.5}$ mass.

Figure 3 graphically shows the exposure-response relationships for $PM_{2.5}$ mass (single day lag 1) with total, cardiovascular and respiratory mortality between 2004 and 2008 in Xi'an. For all three mortality outcomes, we observed almost linear relationships, without evidence of obvious threshold concentrations below which $PM_{2.5}$ had no effect on mortality outcomes. The differences in the deviance between the linear and spline models did not indicate a statistically significant improvement in the fit of the spline versus linear models. In the linear models, a 10 μg/m^3 increment in the 1-day lagged $PM_{2.5}$ was associated with 0.2% (95%CI: 0.1%, 0.3%), 0.3% (95%CI: 0.1%, 0.4%), and 0.4% (95%CI: 0.2%, 0.6%) increases in total mortality, cardiovascular mortality, and respiratory mortality, respectively.

Consistent with expectations, deaths due to injury were not associated with $PM_{2.5}$ constituents (only 1 significant association out of 92 comparisons when adjusted for $PM_{2.5}$, see Supplemental Material, Table 3). Altering the *df* per year for time trend (within a range of 3-10 *df*) did not substantially change the regression results (data not shown).

Discussion

Evidence obtained in this time-series analysis showed that $PM_{2.5}$ mass and several constituents were associated with mortality from all causes and from cardiopulmonary diseases in Xi'an. The observed levels of $PM_{2.5}$ and its constituents in our study were much higher than prior health studies of $PM_{2.5}$ constituents in developed countries. Several constituents that were associated with mortality (NH_4^+, NO_3^-, Cl^-, OC, EC, Cl) are associated with the combustion of fossil fuel (e.g. coal and heavy oil) in Xi'an (Cao et al. 2005; Cao et al. 2009). Nitrate demonstrated stronger associations with total and cardiovascular mortality than $PM_{2.5}$ mass. We did not observe evidence of threshold concentrations below which $PM_{2.5}$ was not associated with mortality in Xi'an. To our knowledge, this is the first study of its kind in a developing country to investigate the health impact of $PM_{2.5}$ constituents.

Our study in Xi'an indicates considerable risk heterogeneity among various $PM_{2.5}$ constituents. Consistent with previous epidemiological studies on PM constituents (Ostro et al. 2007; Ostro et al. 2008; Peng et al. 2009; Ito et al. 2011; Zhou et al. 2011; Laden et al. 2000), we found that $PM_{2.5}$ constituents from the combustion of fossil fuel (e.g. NH_4^+, NO_3^-, Cl^-, OC, EC, Cl and Ni) still had significant positive associations with mortality outcomes after adjustment for $PM_{2.5}$. In contrast, we did not estimate significant associations between mortality and common crustal elements (e.g. Ca and

K) in Xi'an, which was consistent with one previou study in six U.S. cities showing that $PM_{2.5}$ crustal particles were not associated with daily mortality (Laden et al. 2000). It should be noted that we observed statistically significant associations for some, but not all, lag structures of $PM_{2.5}$ constituents. Further research is needed to clarify relationships between the timing of exposures and their potential health effects.

Our analysis indicates positive associations of cardiopulmonary mortality with IQR increases in OC/EC during the previous 1-3 days even after adjustment for $PM_{2.5}$ mass. This is consistent with a meta-analysis of short-term exposure time-series studies of EC and daily mortality that reported positive associations with cardiopulmonary mortality (Smith et al. 2009). A recent cohort study in California suggests that long-term exposure to OC also increase cardiopulmonary mortality (Ostro et al. 2010). Several previous studies support the biological plausibility of a link between exposure to OC/EC and exacerbations of cardiopulmonary diseases (Gold et al. 2005; Lewne et al. 2007; Shih et al. 2008; von Klot et al. 2009; Lanki et al. 2006; Henneberger et al. 2005; Jansen et al. 2005; Mar et al. 2005). For example, one study in Germany examined weekly electrocardiograms of 56 men with a history of heart disease, and found significant associations of OC/EC with changes in myocardial repolarization, which could increase the risk of sudden cardiac death (Henneberger et al. 2005). Gold et al. found associations of EC with ST-segment depression among a panel of 24 elderly Boston residents (Gold et al. 2005). Similarly, Lanki et al. (2006) examined the health effects of five $PM_{2.5}$ components (Si, S, Ni, Cl and EC), and found only EC had significant association with ST-segment depression in multipolluant models. Exposure to OC/EC was also associated with increased nitric oxide in exhaled breath, a marker of airway inflammation (Mar et al. 2005). Thus, exposures to both OC and EC are associated with a number of indicators that could

contribute to cardiopulmonary mortality.

NO_3^- was positively associated with mortality in our study. To date, only a few epidemiological studies have examined the relationships of NO_3^- with mortality, and the findings are inconclusive. For example, one study in Atlanta, US found positive but insignificant association between NO_3^- and mortality (Klemm et al. 2004), while Ostro et al. (2007) found significant association between NO_3^- and mortality in six California counties (Ostro et al. 2007). More studies are needed to understand the health impact of NO_3^-. SO_4^{2-} in our study (mean level: 31.6 μg/m^3) was not associated with mortality which is consistent with toxicological studies showing little toxic evidence of SO_4^{2-} effects on the cardiopulmonary system at typical environmental concentrations (Reiss et al. 2007). As Schlesinger and Cassee pointed out, minimally effective concentration of SO_4^{2-} to alter pulmonary mechanical function in normal humans following acute exposure is > 1000 μg/m^3 (Schlesinger and Cassee, 2003).

In our analysis, an IQR increase (0.01 μg/m^3) in 1-day lagged Ni was associated with 0.4% (95% CI: 0.0%, 0.8%), 0.6% (95% CI: -0.1%, 1.2%) and 0.9% (95% CI: 0.2%, 1.7%) increases in total, cardiovascular and respiratory mortality. As a transition metal, Ni may affect health by producing reactive oxygen species and increasing oxidative stress (Schlesinger et al. 2006; Lippmann et al. 2006). Existing epidemiological studies provide evidence of adverse effects for several transition metals (Ostro et al. 2007; Ostro et al. 2008; Lippmann et al. 2006; Dominici et al. 2007; Huang et al. 2003). For example, Huang et al found that exposure to a factor including V, Zn and Cu from concentrated ambient particles was associated with an increase in blood fibrinogen (Huang et al. 2003). Using the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) database, Lippmann et al. (2006) found that daily mortality rates in the 60 U.S. cities with speciation data were significantly

associated with average Ni and V, but not with other measured species (Lippmann et al. 2006). In Xi'an, the major source of Ni in $PM_{2.5}$ is from fossil fuel combustion, especially from heavy oil (Shen et al. 2009b). The role of Ni in $PM_{2.5}$ health hazards should be investigated further.

In our analysis, a 10 $\mu g/m^3$ increment in the 1-day lagged concentrations of $PM_{2.5}$ was associated with 0.2% (95%CI: 0.1%, 0.3%), 0.3% (95%CI: 0.1%, 0.4%), and 0.4% (95%CI: 0.2%, 0.6%) increases in total, cardiovascular, and respiratory mortality, respectively. Compared with studies of $PM_{2.5}$ and daily mortality in developed countries (Franklin et al. 2007; Ostro et al. 2006; Ueda et al. 2009; Zanobetti and Schwartz 2009), our estimated effects per unit increase in $PM_{2.5}$ were relatively low. For example, a multi-city analysis in 112 U.S. cities reported that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.0 % increase in total mortality, a 0.9 % increase in cardiovascular mortality, and a 1.7 % increase in respiratory mortality (Zanobetti and Schwartz 2009). Our findings add to previous evidence suggesting weaker associations between health outcomes and unit increases in air pollution exposures in China than in developed countries (Aunan and Pan 2004). This may be explained by differences in the composition and toxicity of PM, as well as difference in local PM concentrations, population sensitivity to PM, age structure, and other population characteristics. Lower risks of death per unit increases in pollutants when concentrations are high may reflect the selective attrition of vulnerable members of the population that die before concentrations reach the maximum level (Wong et al. 2008). Also, associations between mortality and PM exposures ranging from low (ambient air pollution) to high (cigarette smoking) concentrations suggest that the exposure-response curve of PM often tends to become flat at higher concentrations (Pope et al. 2009).

Accurate information on the shape of exposure-response relationships is crucial for public health assessment and there has been growing demand for providing the relevant curves (Dominici et al. 2002). Dose-response relationships may vary by location, depending on factors such as the air pollution mixture, climate and the health of the studied population (Samoli et al. 2005). We did not observe evidence for a threshold concentration below which $PM_{2.5}$ was not associated with mortality in our study population, suggesting that linear models without a threshold are appropriate for assessing the effect of $PM_{2.5}$ on daily mortality for high exposure settings typical in developing countries.

Our study has limitations. First, we evaluated associations of multiple constituents and lags with three different mortality outcomes, and some significant associations therefore may have occurred by chance. Second, due to moderate to high collinearity among $PM_{2.5}$ constituents, we could not adjust for multiple exposures, and some associations may reflect effects of other correlated components. We did not measure several elements such as selenium (Se), vanadium (V), and silicon (Si), though previous studies have reported significant associations between these elements and adverse health outcomes (Ostro et al. 2007; Laden et al. 2000), and we could not evaluate ozone (O_3) due to a lack of monitoring data in Xi'an. As in many previous time-series studies, we used $PM_{2.5}$ monitoring results from a fixed station as a proxy measure for population exposures to air pollution. A number of issues may arise given that ambient monitoring results differ from personal exposure level to air pollutants (Sarnat et al. 2005; Sarnat et al. 2001). In addition, variation in the extent of exposure misclassification among individual constituents may influence associations. Finally, we did not conduct formal source apportionment of $PM_{2.5}$ constituents, and therefore cannot identify the source components that contributed most to the

associations between $PM_{2.5}$ and mortality.

In summary, our findings suggest that $PM_{2.5}$ constituents from fossil fuel combustion may have an appreciable influence on the health impact attributable to $PM_{2.5}$. Associations of $PM_{2.5}$ with mortality in Xi'an are somewhat lower in magnitude, per amount of $PM_{2.5}$ mass, than associations reported for populations in developed countries. Our findings add support to previously reported evidence of $PM_{2.5}$-related health effects in China, and suggest that combustion-associated pollutants are particularly important.

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Table 1. Distribution of daily data on mortality and weather conditions in Xi'an, China (2004-2008)

	Mean ± SD	Min	P(25)	P(50)	P(75)	Max
Daily death counts						
Total (non-accident)	26.2 ± 9.7	4.0	20.0	25.0	31.0	128.0
Cardiovascular	12.1 ± 5.7	0.0	8.0	11.0	15.0	39.0
Respiratory	7.2 ± 3.8	0.0	4.0	7.0	9.0	29.0
Injury	1.8 ± 1.7	0.0	1.0	1.0	3.0	19.0
Weather conditions						
Temperature (℃)	13.4 ± 9.8	-8.0	5.0	14.0	22.0	32.0
Relative humidity (%)	66.5 ± 16.7	15.0	55.0	68.0	79.0	100.0

Table 2. Descriptive statistics for air pollutants in Xi'an, China

Observation period	Pollutants	Observation number	Mean ± SD ($\mu g/m^3$)	Min	Max	IQR ($\mu g/m^3$)	Percent $PM_{2.5}$ mass (%)
January 1, 2004 -December 31, 2008	$PM_{2.5}$	1,756	182.2 ± 110.1	16.4	768.6	114.9	-
	SO_2	1,827	48.4 ± 28.9	8.0	260.0	30.0	-
	NO_2	1,827	38.2 ± 15.0	6.4	110.0	21.0	-
	OC	1,749	28.3 ± 18.3	5.1	142.3	19.3	15.5
	EC	1,749	12.0 ± 8.3	0.2	84.2	8.8	6.6
	Na^+	1,649	2.9 ± 1.4	0.0	12.7	1.9	1.6
	NH_4^+	1,538	8.8 ± 8.5	0.0	61.1	10.7	4.8
	K^+	1,616	2.2 ± 2.3	0.0	35.3	1.9	1.2
	Mg^{2+}	1,666	0.5 ± 0.3	0.0	3.7	0.3	0.3
	Ca^{2+}	730	2.0 ± 2.4	0.0	22.4	1.9	1.1
	F^-	1,429	0.6 ± 0.3	0.0	3.4	0.5	0.3
	Cl^-	1,670	5.1 ± 3.5	0.3	32.6	3.6	2.8
	NO_2^-	563	0.7 ± 0.4	0.0	3.0	0.4	0.4
	SO_4^{2-}	1,666	31.6 ± 24.4	0.8	198.2	27.8	17.4
	NO_3^-	1,644	15.2 ± 12.7	0.0	85.5	15.4	8.4

Table 2 (continued)

Observation period	Pollutants	Observation number	Mean ± SD ($\mu g/m^3$)	Min	Max	IQR ($\mu g/m^3$)	Percent $PM_{2.5}$ mass (%)
January 1, 2006 - December 31, 2008	S	1,028	5.1 ± 3.5	0.1	24.8	4.3	2.8
	Cl	1,027	1.3 ± 1.6	0.0	11.8	1.5	0.7
	K	1,007	1.8 ± 1.7	0.0	22.5	1.6	1.0
	Ca	904	2.5 ± 3.3	0.0	30.6	2.3	1.4
	Ti	1026	0.14 ± 0.15	0.00	1.63	0.10	0.08
	Cr	952	0.01 ± 0.01	0.00	0.10	0.01	0.01
	Mn	1,026	0.11 ± 0.08	0.00	0.56	0.09	0.06
	Fe	1,013	1.6 ± 1.7	0.0	20.0	1.3	0.87
	Ni	836	0.01 ± 0.03	0.00	0.55	0.01	0.01
	Zn	1028	1.4 ± 1.1	0.0	8.6	1.2	0.79
	As	676	0.04 ± 0.03	0.00	0.24	0.03	0.02
	Br	962	0.04 ± 0.05	0.00	0.56	0.04	0.02
	Mo	1,009	0.06 ± 0.05	0.00	0.37	0.03	0.03
	Cd	990	0.03 ± 0.02	0.00	0.13	0.03	0.02
	Pb	1,025	0.50 ± 0.38	0.00	3.13	0.41	0.27

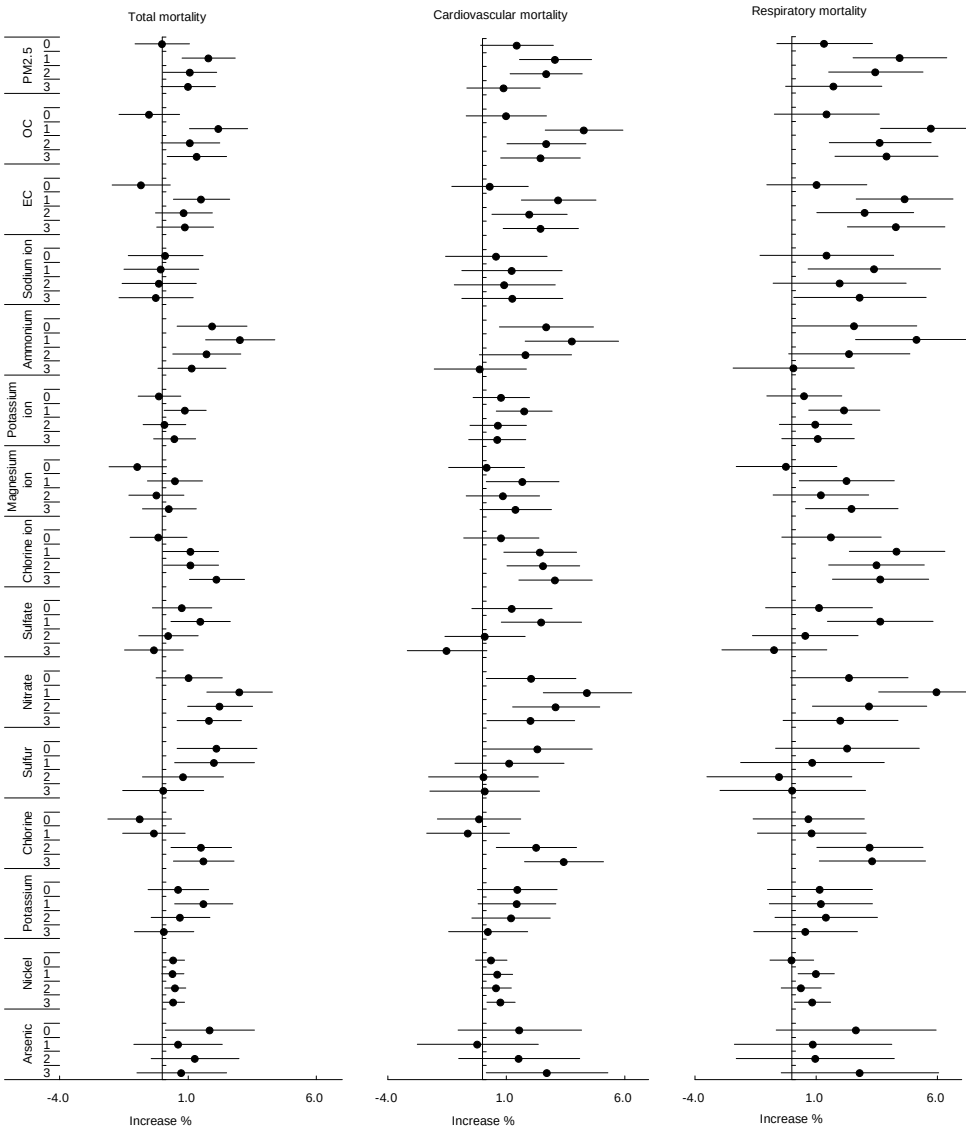
IQR: interquartile range.

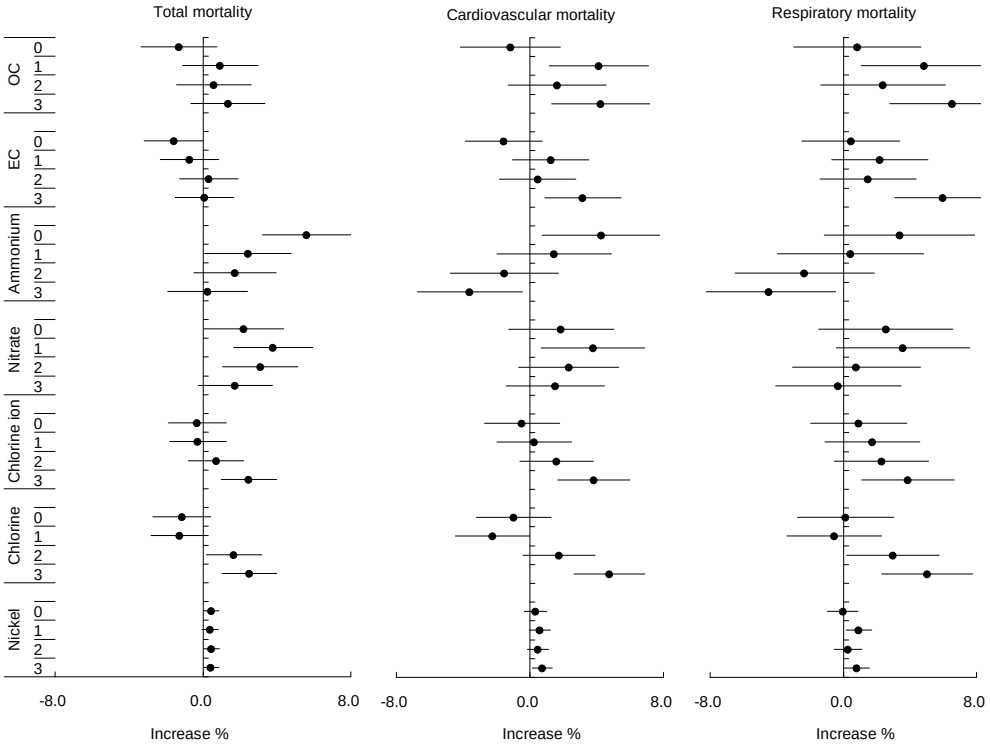
Figure legends

Figure 1. Estimated percent increase [mean (95% CI)] in mortality per IQR increase in pollutant concentrations on the current day (lag 0) or the previous 1-3 days (lags 1, 2 and 3), adjusted for temporal trend, day of the week, temperature, relative humidity, and SO_2 and NO_2 concentrations.

Figure 2. Estimated percent increase [mean (95% CI)] in mortality per IQR increase in pollutant concentrations on the current day (lag 0) or the previous 1-3 days (lags 1, 2 and 3), adjusted for $PM_{2.5}$ mass, temporal trend, day of the week, temperature, relative humidity, and SO_2 and NO_2 concentrations.

Figure 3. Smoothing plots of $PM_{2.5}$ against total (a), cardiovascular (b) and respiratory (c) mortality (*df* = 3), adjusted for temporal trend, day of the week, temperature, relative humidity, and SO_2 and NO_2 concentrations. X-axis is the $PM_{2.5}$ concentrations ($\mu g/m^3$) (singe day lag, L1). Y-axis is the estimated percent change in deaths (%). The solid lines indicate the estimated mean percent change (%) in daily death numbers using the lowest $PM_{2.5}$ concentration as the reference level, and the dotted lines represent the 95% CI.


Total mortality
Cardiovascular mortality
Respiratory mortality
PM2.5
OC
EC
Sodium ion
Ammonium
Potassium ion
Magnesium ion
Chlorine ion
Sulfate
Nitrate
Sulfur
Chlorine
Potassium
Nickel
Arsenic
0
1
2
3
-4.0
1.0
6.0
Increase %


Total mortality
Cardiovascular mortality
Respiratory mortality
OC
EC
Ammonium
Nitrate
Chlorine ion
Chlorine
Nickel
0
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0.0
8.0
Increase %

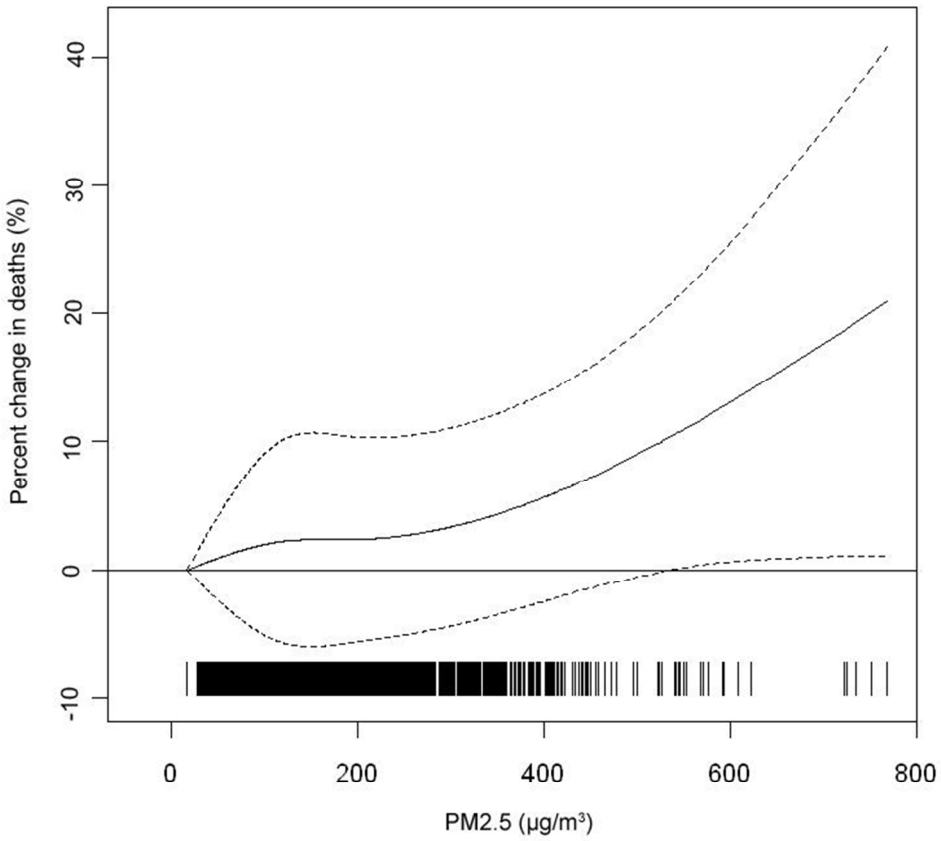

Figure 3. Smoothing plots of PM2.5 against total (a), cardiovascular (b) and respiratory (c) mortality (df = 3), adjusted for temporal trend, day of the week, temperature, relative humidity, and SO2 and NO2 concentrations. X-axis is the PM2.5 concentrations (μg/m3) (singe day lag, L1). Y-axis is the estimated percent change in deaths (%). The solid lines indicate the estimated mean percent change (%) in daily death numbers using the lowest PM2.5 concentration as the reference level, and the dotted lines represent the 95% CI.
273x272mm (72 x 72 DPI)

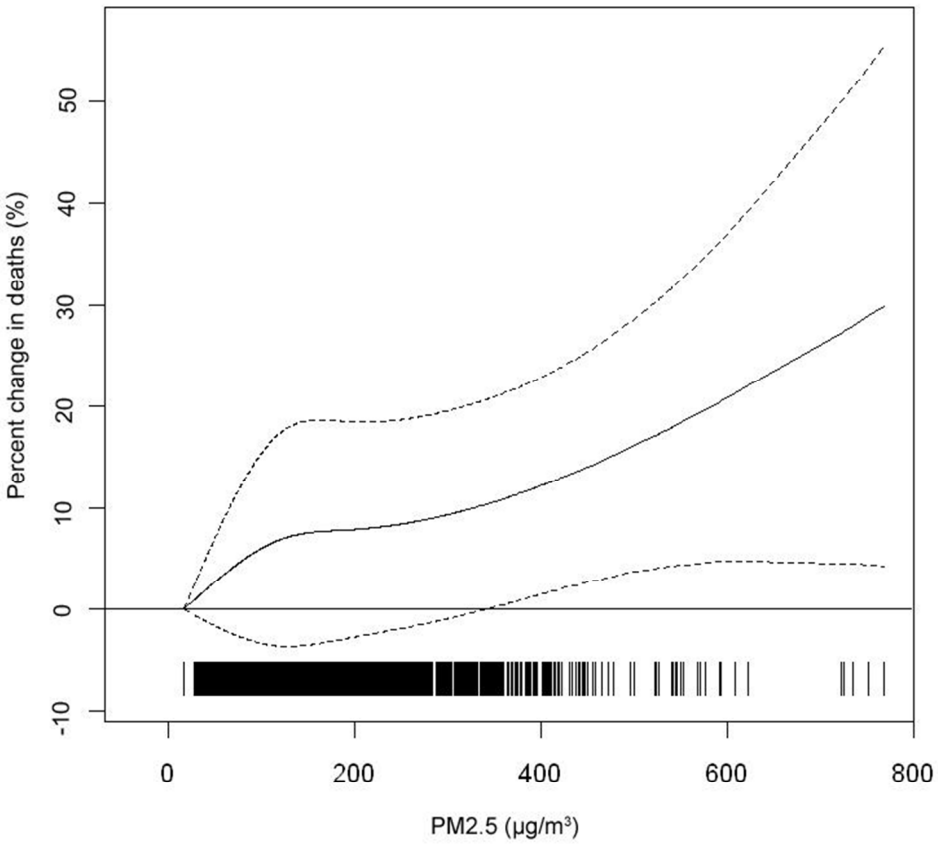

Figure 3b
273x272mm (72 x 72 DPI)

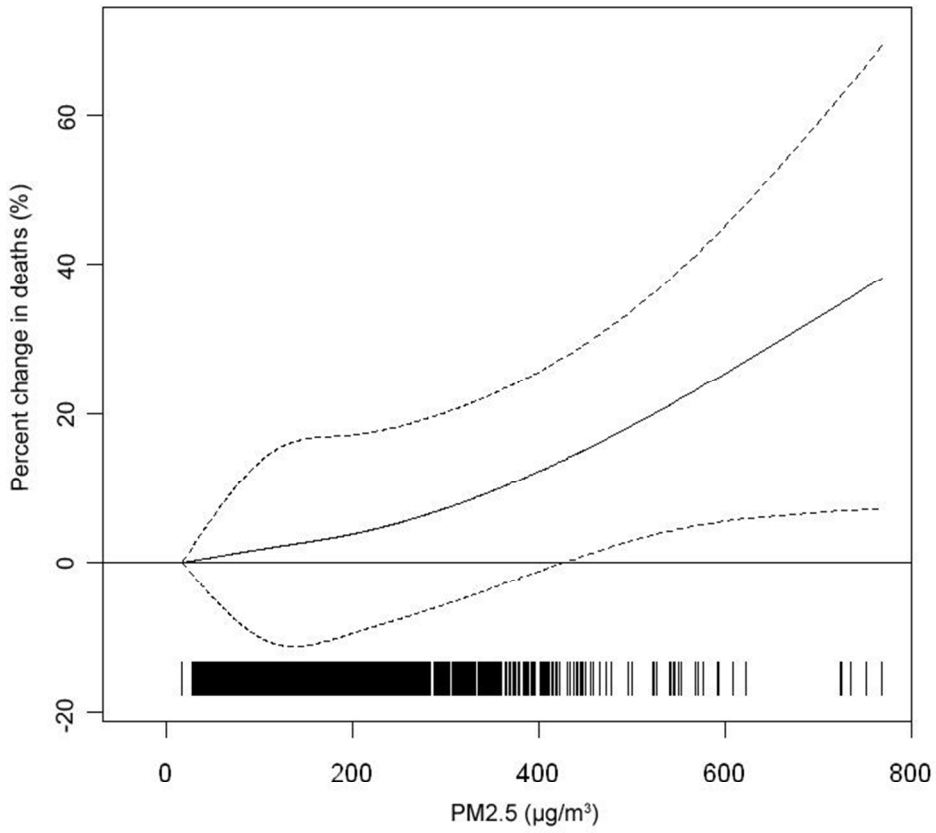

Figure 3c
273x272mm (72 x 72 DPI)