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Long-Term Exposure to Ambient Air Pollution and Respiratory Disease Mortality in Shenyang, China: A 12-Year Population-Based Retrospective Cohort Study

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Key Words
Air pollution · Mortality · Long-term effect · Retrospective cohort study

Abstract
Background: In China, both the levels and patterns of outdoor air pollution have altered dramatically with the rapid economic development and urbanization over the past two decades. However, few studies have investigated the association of outdoor air pollution with respiratory mortality, especially in the high pollution range. ***Objective:*** We conducted a retrospective cohort study of 9,941 residents aged ≥35 years old in Shenyang, China, to examine the association between outdoor air pollutants [particulate matter <10 μm in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2)] and mortality using 12 years of data. ***Methods:*** We applied extended Cox proportional hazards modeling with time-dependent covariates to respiratory mortality. Analyses were also stratified by age, sex, educational level, smoking status, personal income, occupational exposure and body mass index (BMI) to examine the association of air pollution with mortality. ***Results:*** We found significant associations between PM_{10} and NO_2 levels and respiratory disease mortality. Our analysis found a relative risk of 1.67 [95% confidence interval (CI) 1.60–1.74] and 2.97 (95% CI 2.69–3.27) for respiratory mortality per 10 μg/m^3 increase in PM_{10} and NO_2, respectively. The effects of air pollution were more apparent in women than in men. Age, sex, educational level, smoking status, personal income, occupational exposure, BMI and exercise frequency influenced the relationship between outdoor PM_{10} and NO_2 and mortality. For SO_2, only smoking, little regular exercise and BMI above 18.5 influenced the relationship with mortality. ***Conclusion:*** These data contribute to the scientific literature on the long-term effects of air pollution for the high-exposure settings typical in developing countries.

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Introduction

China has been undergoing urbanization and westernization at an unprecedented rate over the past several decades, and the levels and patterns of outdoor and indoor air pollutants have altered dramatically. Despite significant improvements in ambient air quality over the past 10 years due to environmental protection requirements in China, the levels of thoracic particles [less than 10 μm in diameter (PM_{10})] and sulfur dioxide (SO_2) are still higher than the national standard and criterion concentration of the World Health Organization in many cities in China. At the same time, the rapid increase in motor vehicle ownership and use has been accompanied by traffic-related air pollution, which poses an increasingly serious problem in urban areas of China. Consequently, urban outdoor air pollution in China has changed from the coal combustion type to a compound air pollution type due to the coexistence of coal smoke and motor vehicle emissions. However, few studies have evaluated the health effects of the changing and mixing air pollution in the past decades.

Numerous epidemiological studies have demonstrated associations between outdoor and indoor air pollution and health outcomes, including morbidity and mortality, in the general population [1–6]. The development of respiratory diseases resulting from direct contact of the respiratory system with air pollutants has been widely acknowledged as a major component of the adverse health effects of air pollution [3, 7]. However, the inconsistent results obtained to date do not provide a clear overall picture of health damage. Even more importantly, most of the previous studies were conducted in developed countries, and only a small number of studies have been conducted in Asia [8–10]. Therefore, the currently available data might not apply to developing countries, especially China, where both the levels and constituents of air pollutants may differ from those in North America, Europe and Japan, and, in addition, meteorological conditions and sociodemographic patterns also differ greatly from those in the aforementioned places. For example, the annual average ambient concentration of PM_{10} in Rome during 1998–2004 was about 47.3 $\mu g/m^3$ [11], while the level in Shenyang was about 176.6 $\mu g/m^3$, approximately 4 times greater. For SO_2, the annual average ambient concentration in Tokyo during 2000–2005 was below 10 $\mu g/m^3$ [12]; in the same period, the value in Shenyang was 59.8 $\mu g/m^3$. These values suggest that the magnitude of the association between pollution and mortality in the Chinese population may differ from that in the developed countries.

The present study was a population-based, retrospective cohort study. Its aim was to estimate the long-term effects of air pollutants [PM_{10}, SO_2 and nitrogen dioxide (NO_2)] on mortality from respiratory diseases in northern China, with a specific interest in factors that may modify these effects, including sex, age, education and socioeconomic status (SES). The results of this study will provide a scientific basis for making public policies, controlling air pollution, setting air quality standards and risk assessment.

Methods

Sample Design

Between July and December 2009, a population-based, retrospective cohort study was conducted in Shenyang, in northeast China (longitude: 122° 25′ to 123° 48′; latitude: 41° 12′ to 42° 17′). The altitude of the residential area is 50 m above the mean sea level, and the mean annual air temperature is 6.5°C (range –37.4 to 38.0°C). Shenyang is comprised of both urban and suburban districts and counties, with a total area of 13,308 km^2 and a population of 10 million in 2007. The major industries include steel manufacturing, nonferrous metals, machinery, chemical- and coke-related industries and electric power generation. Our study area was limited to the traditional 5 urban districts of Shenyang (230 km^2). The target population included all permanent residents living in the area, approximately 5.1 million individuals in 2007.

There are 5 air monitoring sites located in the 5 urban districts of Shenyang. In March 2009, two communities within 1,000 m of each monitoring site were randomly selected from each district, and 500–700 families were then randomly selected from each of these communities. The entry criterion was that families needed to have resided at the present location for at least 10 years (since 1 January 1998). Families who strictly met this criterion were included in the study. The participants were limited to members of the selected families who were at least 25 years of age in 1998 (or were born before 1 January 1973). The resulting 10 communities and a cohort of approximately 13,000 subjects were followed for 12 years, from 1998 through 2009. Trained interviewers administered a standardized questionnaire to all cohort subjects. They interviewed subjects directly, when feasible, or surrogate respondents for subjects who were deceased or not present. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of the China Medical University. The ethics committee and other relevant regulatory bodies in Liaoning province approved the study. Written informed consent was obtained from each participant before data collection. The questionnaire elicited information on demographics (age, sex and residential area), residential history, lifetime use of household stove and fuel types, SES (education level, marital status and annual household income), cigarette smoking, alcohol consumption, diet, occupational history, exercise frequency and medical history for 1998 and for 2009. The questionnaire interview typically took about 30 min.

The cohort was followed until 1 January 2009. Deaths among the cohort during the study period were identified using death

certifications, local public security bureaus and local public health bureaus. In the event of a death in Shenyang, the decedent's family needed to obtain a death certificate from the hospital or local community clinic and submit it to the police station to cancel the decedent's household registration. In addition, the decedent's family needed to submit the death certificate to the local public health station, which in turn 'sterilizes' the decedent's home. Therefore, the decedent's family obtains two certificates (i.e. one from the police station and the other from the local public health station), both of which were required for cremation. Information abstracted from the death records included name, sex, date of birth, residence and date and cause of death. The name, sex, date of birth and residence information was used to create a unique identifier for members of the cohort. Through this personal identifier and a link with the National Cause of Death Register, it was possible to identify subjects who had died from respiratory disease. The International Classification of Diseases, 9th revision categories 460–519 and 10th revision categories J00–J99 were used for the diagnosis of respiratory disease.

Air Pollution Data

Since 1981, there has been a network of ambient air monitoring stations in Shenyang operated by the World Health Organization/United Nations Environment Program Global Environmental Monitoring System and local governments. Total suspended particles and SO_2 were monitored at that time. Beginning 1 January 1995, outdoor PM_{10}, SO_2 and NO_2 concentrations were also measured by the Shenyang Environmental Monitoring Center (the governmental agency in charge of collecting air pollution data in Shenyang) at Global Environmental Monitoring System sites in 5 representative urban areas, as follows: (1) Tiexi district (industrial), (2) Dadong district (residential), (3) Heping district (commercial), (4) Shenhe district (cultural) and (5) Huanggu district (clean). The daily levels for each pollutant were averaged from the available monitoring results of 5 fixed-site stations in the representative urban districts and covered by China National Quality Control. These stations are mandated to be located away from major roads, industrial sources, buildings or residential sources of emissions from the burning of coal, waste or oil; thus, our monitoring results reflect the background urban air pollution level in Shenyang rather than that from local sources, such as traffic or industrial combustion. Levels of each pollutant were measured continuously and reported hourly, PM_{10} by beta attenuation, SO_2 by ultraviolet fluorescence and NO_2 by chemiluminescence. Exposure parameters in the present study were the 1-year average, and the yearly deviations at each station were calculated from the 24-hour NO_2, SO_2 and PM_{10}.

Statistical Analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the time to mortality from respiratory diseases and mortality associated with an increase of 10 $\mu g/m^3$ in the levels of long-term exposure to PM_{10}, SO_2 and NO_2. In all models, factors that were hypothesized a priori to potentially confound the relationship between air pollution and respiratory diseases were included. These factors included age, body mass index (BMI), smoking status, the number of cigarettes smoked per day, the number of years of smoking, educational level, household income and race or ethnic group. The 'time-dependent covariate effect' was analyzed using a Cox regression model for counting processes. In this current study, yearly means of air pollutants in different districts and at different time points were included in the model as time-dependent covariates. This model can handle time-dependent covariates as well as left truncation and right censoring while controlling for risk factors. All tests of significance were two-sided, and a 5% significance level was used throughout. Data management was carried out using Epidata 3.01 (Epidata Association), and statistical analyses were conducted using SAS software 9.13 (SAS Institute Inc., Cary, N.C., USA).

Results

Description of the Study Subjects

Table 1 shows the detailed distribution of the demographic characteristics of the subjects included in this study. In total, 12,584 residents were selected for the study, and 9,941 subjects completed the medical questionnaire (79%). The average age of the participants was 58.09 years (range 35–103 years).

There were a total of 505 deaths, 72 due to respiratory diseases, including 42 deaths due to lung cancer, 12 deaths due to pulmonary emphysema and 6 deaths due to respiratory failure. The mortality rates for respiratory diseases and lung cancer were 0.72% (95% CI 0.55–0.89) and 0.42% (95% CI 0.29–0.55), respectively, among subjects 39–90 years old at study entry; 50% of the deaths occurred among those who were 64–78 years old.

Characteristics of Air Pollution

The mean annual levels of PM_{10}, SO_2 and NO_2 in each of the representative districts were measured. During the study period, the mean annual level of PM_{10} was 154 $\mu g/m^3$ (SD 41; range 78–274). For SO_2, the mean level was 63 $\mu g/m^3$ (SD 15; range 26–106). Finally, for NO_2, the mean level was 46 $\mu g/m^3$ (SD 13; range 18–78).

Figure 1 shows the annual trends for the 3 air pollutants. At the beginning of the study, the concentrations of PM_{10} and NO_2 were highest in the Tiexi district, and during the 12-year study period, they were lowest in the Huanggu district. For SO_2, the concentration was also highest in the Tiexi district but was lowest in the Dadong district. Annual mean PM_{10} and NO_2 levels decreased during the study period in all areas, but this decrease was most dramatic in the Tiexi district, where the average decline in PM_{10} was 16 $\mu g/m^3$ per year. For SO_2, the concentration decreased markedly in the Tiexi district but increased in the Dadong and Huanggu districts, while it remained stable throughout the study period in the Shenhe district.

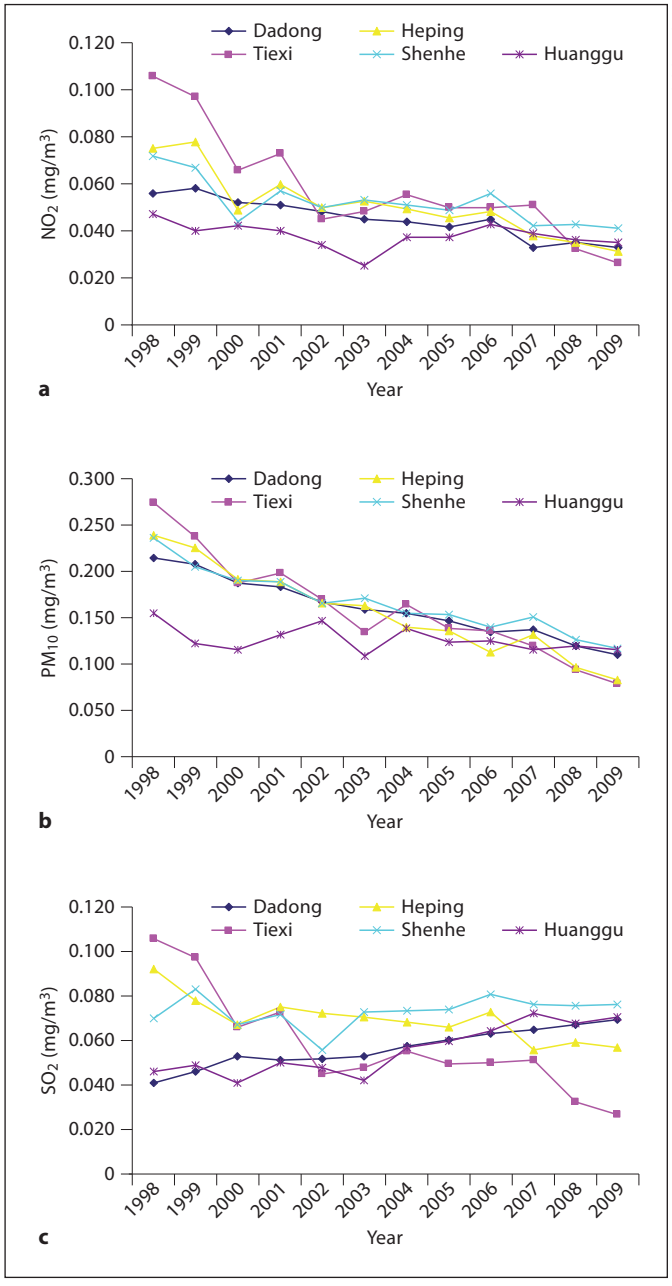

Fig. 1. Annual trends in air pollutant levels from 1998 through 2009 in the 5 study areas. Mean annual concentrations of NO_2 (**a**), PM_{10} (**b**) and SO_2 (**c**) during the study period.

Color version available online

Table 1. Characteristics of the study population in the 5 districts of Shenyang city, 1998–2009

Characteristic	Death due to respiratory disease (n = 72)	All subjects (n = 9,941)
Age[a], years	70.36 ± 10.83*	58.09 ± 14.22
Gender		
Male	54 (75.00%)*	4,824 (48.53%)
Female	18 (25.00%)	5,117 (51.47%)
Nation		
Han	70 (97.22%)	9,449 (95.05%)
Other	2 (2.78%)	492 (4.95%)
Marital status		
Married	63 (87.50%)	8,921 (89.74%)
Unmarried[b]	9 (12.50%)	1,020 (10.26%)
Educational level[c]		
Low	47 (65.28%)	5,970 (60.05%)
High	25 (34.72%)	3,971 (39.95%)
Personal income[d]		
RMB <200/month	14 (20.00%)	1,817 (18.35%)
RMB 200–500/month	24 (34.29%)	3,081 (31.11%)
RMB 500–800/month	12 (17.14%)	2,386 (24.10%)
RMB ≥800/month	20 (28.57%)	2,618 (26.44%)
Smoking		
No	35 (48.61%)*	7,091 (71.33%)*
Yes	37 (51.39%)	2,850 (28.67%)
Occupational exposure		
Yes	5 (6.94%)	820 (8.25%)
No	67 (93.06%)	9,121 (91.75%)
BMI		
<18.5	12 (16.67%)	1,010 (10.16%)
≥18.5 to <25	50 (69.44%)	6,981 (70.22%)
≥25	10 (13.89%)	1,950 (19.62%)
Exercise		
Yes	33 (45.83%)	4,146 (41.71%)
No	39 (54.17%)	5,795 (58.29%)

* $p < 0.05$: significantly different from controls.
[a] Mean ± SD.
[b] Includes separated, divorced, single or widowed.
[c] Low: illiterate, primary and junior high school; high: high school or above.
[d] A total of 39 subjects did not report their personal income.

Overall, PM_{10}, SO_2 and NO_2 levels were relatively highly correlated with each other. The Pearson's correlation coefficient for the mean annual PM_{10} and SO_2 levels was 0.49 ($p < 0.01$); for PM_{10} and NO_2 levels, it was 0.88 ($p < 0.01$), and for SO_2 and NO_2 levels, it was 0.65 ($p < 0.01$).

Factors Associated with Mortality

Based on univariate analysis, a significant association was seen between mortality from respiratory disease and age, sex, educational level, BMI and smoking. There were no statistically significant differences between mortality and nationality, marital status, personal income, exercise frequency and occupational exposure (data not shown).

Table 2. Factors associated with respiratory mortality from the Cox proportional hazards model (n = 9,941)

Factor	Respiratory death	
	HR	95% CI
Age (years)[a]	1.08	1.08–1.09
Gender (reference: male)[a]	0.46	0.37–0.57
Educational level (reference: low)[a]	1.37	1.12–1.68
Personal income (reference: <RMB 200/month)[a]		
RMB 200–500/month	0.89	0.69–1.13
RMB 500–800/month	0.58	0.43–0.78
RMB ≥800/month	0.82	0.63–1.08
Smoking (reference: no)[a]	2.30	1.91–2.78
Occupational exposure (reference: no)[a]	1.03	0.74–1.43
BMI (reference: <18.5)[a]		
≥18.5 to <25	0.53	0.42–0.67
≥25	0.35	0.26–0.48
Exercise (reference: no)[a]	0.65	0.54–0.78
PM_{10} ($\mu g/m^{3)b}$	1.67	1.60–1.74
SO^2 ($\mu g/m^3$)[b]	1.04	0.97–1.12
NO^2 ($\mu g/m^3$)[b]	2.97	2.69–3.27

[a] Obtained in the model without air pollutants.
[b] HRs and 95% CIs associated with 10 $\mu g/m^3$ changes in each pollutant, respectively, and adjusted for age, gender, educational level, smoking status, personal income, occupational exposure, BMI and exercise.

Table 2 shows the results of the Cox regression analysis for the impact of air pollution exposure on respiratory disease mortality adjusted for confounders. Multivariate analysis was conducted for each pollutant using the annual mean levels every year for the period from 1998 to 2009. After adjusting for age, sex, BMI, educational level, smoking status, personal income, occupational exposure and exercise frequency, PM_{10} and NO_2 were significantly associated with mortality from respiratory disease, but there was no significant association with SO_2. After excluding air pollutants from the model, significant associations were observed between respiratory disease mortality and age, sex, BMI, educational level, smoking status and exercise frequency. The HRs with 95% CIs are shown in table 2.

The modifying effects of age, sex, personal income, occupational exposure, BMI and exercise frequency on the association between both PM_{10} and NO_2 and mortality were statistically significant. For SO_2, the modifying effects of smoking, little regular exercise and BMI above 18.5 were statistically significant, while the remaining factors were not statistically significant. The detailed HRs with 95% CIs are shown in table 3.

Discussion

The present study demonstrated the associations between long-term exposure to ambient air pollution and an elevated risk of respiratory disease mortality, after controlling for potential confounding factors. The major strengths of the present study were as follows. Firstly, it was a retrospective cohort study that included information about relevant confounders such as smoking, BMI, history of occupational exposure and exercise frequency. All information on subjects was collected by face-to-face interviews, ensuring no self-reporting bias. Secondly, deaths among the cohort during the study period were identified using death certifications of local public security bureaus, local public health bureaus and information from the bereaved, which ensured that we obtained accurate data. Thirdly, only a few previous studies have reported an association between high long-term exposure to air pollution and respiratory disease mortality evaluated by a Cox proportional hazards regression model. Finally, all participants lived in one city and within 1,000 m of an air pollution measurement point, thus avoiding the possibility of between-city heterogeneity.

This study gives strong support to the link between ambient air pollution exposure and the risk of mortality from respiratory disease for PM_{10} and NO_2, and these findings are completely consistent with previously published findings [2, 12–17]. Quantitatively, the observed increase in risk ranged from 27 to 286% for a 10-unit increase in air pollution levels; these values were higher than those reported in previous studies conducted in the USA, European countries and Japan. For example, as reported from Norway in 2004, Nafstad et al. [13] investigated the associations between mortality and long-term air pollution in a cohort of Norwegian men and found an HR for respiratory deaths in men of 1.16 (95% CI 1.06–1.26) for every 10 $\mu g/m^3$ increase in NO_2; the value of NO_2 varied from 11.5 to 21.7 $\mu g/m^3$. The overall HR for respiratory deaths was 0.55 (95% CI 0.47–0.62) [13]. However, in our study, the HR for respiratory disease mortality was 2.97 (95% CI 2.69–3.27) for every 10 $\mu g/m^3$ increase in NO_2. In contrast to the above, Zhang et al. [17] reported that the concentration of NO_2 was not significantly associated with daily respiratory mortality in Tianjin city after adjusting for the effects of long-term and seasonal trends. In light of these differing results, it is likely that any discrepancies in the effects of air pollutants could be related to differences in the pollutant composition between regions. At the same time, these findings also suggest that the concentration-response gradi-

Table 3. Estimated HRs and 95% CIs for respiratory mortality associated with an increase of 10 μg/m^3 in the level of PM_{10}, SO^2 and NO^2

Factor	PM^{10}		SO^2		NO_2	
	HR	95% CI	HR	95% CI	HR	95% CI
Age						
≤60 years	1.68	1.52–1.86	1.13	0.94–1.36	3.82*	2.93–4.99
>60 years	1.66	1.59–1.74	1.04	0.97–1.13	2.88	2.60–3.20
Gender						
Male	1.62*	1.55–1.70	1.04	0.96–1.13	2.86*	2.56–3.20
Female	1.81	1.66–1.99	1.05	0.91–1.20	3.30	2.71–4.03
Educational level						
Low	1.61	1.54–1.70	1.05	0.96–1.14	2.92	2.59–3.30
High	1.78	1.66–1.92	1.02	0.90–1.16	3.03	2.57–3.58
Smoking						
Yes	1.73	1.63–1.84	1.12*	1.01–1.24	3.10	2.70–3.56
No	1.61	1.52–1.70	0.98	0.88–1.08	2.86	2.49–3.28
Personal income						
RMB <200	1.77	1.59–1.96	0.87	0.72–1.04	2.76*	2.20–3.48
RMB 200–500	1.55	1.46–1.65	1.11	0.98–1.25	3.00	2.54–3.54
RMB 500–800	1.79	1.61–2.00	1.18	0.99–1.41	3.86	2.98–5.01
RMB ≥800	1.73	1.60–1.87	0.96	0.84–1.10	2.72	2.29–3.24
Occupational exposure						
Yes	1.27*	1.14–1.42	0.92	0.74–1.15	2.41*	1.72–3.37
No	1.73	1.65–1.80	1.06	0.98–1.14	3.02	2.73–3.35
BMI						
<18.5	1.53	1.40–1.67	0.77*	0.66–0.90	2.43*	1.94–3.06
≥18.5 to <25	1.74	1.65–1.83	1.10	1.01–1.20	3.10	2.75–3.49
≥25	1.55	1.40–1.71	1.26	1.03–1.55	3.14	2.42–4.08
Exercise						
Yes	1.62	1.53–1.72	0.90*	0.81–1.00	2.57*	2.23–2.95
No	1.72	1.62–1.82	1.17	1.06–1.30	3.38	2.94–3.88

All estimates were adjusted for age, gender, educational level, smoking status, personal income, occupational exposure, BMI and exercise. * $p < 0.05$: interaction between the modifier variables and air pollutants.

ent for air pollutants from the studies conducted in US, European and Japanese populations may not be applicable to China.

In this study, we found no significant associations between respiratory disease mortality and SO_2; the reasons for this are not clear, but we hypothesize that the effects of SO_2 might have been masked by those of NO_2 and PM_{10}, as the levels of both of these pollutants were fairly high in comparison. In a Dutch cohort study which evaluated the effects of long-term air pollution on mortality, Beelen et al. [18] reported significant associations between respiratory mortality and NO_2 and $PM_{2.5}$, but no association was found for SO_2. Results from the French PAARC survey also indicated that SO_2 assessed in the 1970s was not associated with an increase in any-cause mortality, including respiratory mortality, over a period of 25 years [2]. In contrast to the long-term effects of air pollution on mortality, significant associations between SO_2 and mortality were often found with short-term effects of air pollution. A previous study of the short-term effects of air pollution in London from 1992 to 1994 found significant associations between SO_2 and respiratory mortality [19]. As a part of the Public Health and Air Pollution in Asia study, Kan et al. [10] conducted a time-series analysis to examine the association between outdoor air pollutants and daily mortality in Shanghai, China, using 4 years of daily data (2001–2004), and the results showed that an increase of 10 μg/m^3 in a 2-day average concentration of SO_2 corresponded to an increase in respiratory mortality of 2.47% (95%

CI 1.41–3.54); even after adjustment for PM_{10} and other air pollutants, the effect of SO_2 remained significant [20]. Also, some studies indicated that SO_2 is more closely associated with respiratory mortality than other air pollutants [9], the explanation being that SO_2 is very soluble in the upper respiratory tract and thus may produce an immediate irritant effect on the respiratory mucosa [21], which would account for the fact that the effect of SO_2 on respiratory mortality manifests mainly as acute attacks rather than chronic harm.

We found a great disparity in the effect of ambient air pollution on respiratory mortality in women and men. Previous studies are not consistent regarding the sex-specific effects of air pollution on respiratory mortality [12, 14, 22]. For example, in a Dutch cohort, the results showed that there were no significant differences in effect estimates between men and women [18]. However, Katanoda et al. [12] found the highest risk of mortality related to air pollution exposure among men. Miller et al. [23] and Kan et al. [10] suggested that the adverse health effects of ambient air pollution may be intensified in women. Our study results were identical with the latter conclusion, possibly because there are differences between the male and female airways from early fetal lung development throughout life [24, 25]. In addition, women have slightly greater airway reactivity than men, as well as smaller airways [26]; therefore, a dose-response relationship might be detected more easily in women than in men. Moreover, deposition of particles in the lung varies according to sex, with a greater percentage of lung deposition of 1-μM particles in all lung regions for women [27, 28].

In the present analysis, BMI values were included in the proportional hazards models. Consistent with previous American Cancer Society analysis, BMI was significantly associated with respiratory mortality [29]. However, in another study, the mortality risk associated with fine-particulate air pollution at levels found in more-polluted US metropolitan areas was lower than that associated with the high-BMI group but comparable with the estimated effect in the low-BMI group [14]. In contrast, we observed a stronger association between PM_{10} and respiratory disease mortality among the individuals with a normal BMI than for those with a BMI of less than 18.5 or of 25 or greater. The reasons for our BMI-specific observations are unclear and deserve further investigation. They could have been due to the low frequency of low or high BMI, which would make the results for BMI less precise. Our study results also indicated that the effect estimates of PM_{10}, SO_2 and NO_2 on mortality in smokers were higher than in nonsmokers. However, one study suggested that the effects of air pollution may be stronger in nonsmokers than in smokers [30]. Oxidative and inflammatory effects of smoking may dominate to such an extent that the additional exposure to air pollutants may not further enhance the effects in airways in smokers.

The important role of SES has been noted in numerous epidemiological studies. In the present study, we found educational level to modify the effects of air pollution on respiratory mortality but did not find any effect of household income. Kan et al. [10] also found that residents with low educational attainment were more sensitive to air pollution exposure than those with high educational attainment. In contrast, in the Women's Health Initiative observational study [23], the results showed that neither educational level nor household income significantly affected the relationship between air pollution and respiratory disease, although there was a trend toward greater effects among subjects with less education. A variety of explanations for the relationship between SES and the effects of air pollution on respiratory mortality have been discussed in many papers. Most of the studies suggest that persons with lower SES have a higher prevalence of preexisting diseases that confer a greater risk of mortality due to air pollution exposure, and also that they may receive inferior medical treatment for preexisting diseases. Furthermore, these persons may not be able to obtain foods with enough antioxidants, such as fish, fresh fruits and vegetables, resulting in reduced intake of antioxidants, polyunsaturated fatty acids and vitamins that may protect against the adverse consequences of particle exposure [31]. These individuals are more likely to live near busy roadways and have coexposures due to either poor housing or occupation [32].

Finally, the limitations of the present study should be noted. Firstly, as a retrospective cohort study, it is inevitable that there are some recall biases in our study, because the events of interest may have already occurred. Secondly, in the analytic process, we used mean ambient concentrations in or near each study area, instead of individual exposure levels, which may have led to bias because of differing levels of individual exposure to air pollutants. Thirdly, we were unable to control for weather factors (e.g. temperature or humidity) in this analysis. Finally, air pollutant concentrations were highly correlated with each other. Hence, we could not assess the independent effect for each pollutant. It is necessary to understand the biological mechanisms underlying the in-

creased risk of respiratory disease, but these are unknown at present. In addition, in contrast to other studies in Europe and North America, our data were limited to only one city, and the number of deaths (only 72) was quite small, which may have led to a very high HR.

In conclusion, the present study provides strong evidence that respiratory disease mortality is significantly associated with PM_{10} (HR 1.67, 95% CI 1.60–1.74) and NO_2 (HR 2.97, 95% CI 2.69–3.27) in northeast China. Sex, smoking, BMI and exercise frequency modified the relationship between outdoor PM_{10} and NO_2 and mortality. These findings have implications for regulatory and environmental policies, including implementation of measures to reduce ambient air pollution.

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Financial Disclosure and Conflicts of Interest

The authors declare no competing interests.

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