Environmental Pollution 231 (2017) 761–767

Contents lists available at ScienceDirect

Environmental Pollution

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

# Nonmalignant respiratory mortality and long-term exposure to $PM_{10}$ and $SO_2$: A 12-year cohort study in northern China☆

Xi Chen [a], Xue Wang [a], Jia-ju Huang [a], Li-wen Zhang [a], Feng-ju Song [b, c], Hong-jun Mao [d], Ke-xin Chen [b, c], Jie Chen [e], Ya-min Liu [f], Guo-hong Jiang [g], Guang-hui Dong [h], Zhi-peng Bai [i, **], Nai-jun Tang [a, *]

[a] *Department of Occupational and Environmental Health, School of Public Health, Tianjin Medical University, Tianjin, 300070, China*
[b] *Department of Epidemiology, Key Laboratory of Cancer Prevention and Therapy, Tianjin, National Clinical Research Center of Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China*
[c] *Department of Biostatistics, Key Laboratory of Cancer Prevention and Therapy, Tianjin, National Clinical Research Center of Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China*
[d] *College of Environmental Science and Engineering, Nankai University, No. 94 Weijin Road, Nankai District, Tianjin, 300071, China*
[e] *Department of Occupational and Environmental Health, School of Public Health, China Medical University, No. 77 Puhe Road, Shenbei New District, 110122, Shenyang, Liaoning, China*
[f] *Institute of Medicine and Health Information, Shandong Academy of Medical Sciences, Jinan, Shandong, China*
[g] *Tianjin Center for Disease Control and Prevention, No. 6 Huayue Road, Hedong District, Tianjin, 300011, China*
[h] *Department of Preventive Medicine, School of Public Health, Sun Yat-sen University, Guangzhou 510080, China*
[i] *State Key Laboratory of Environmental Criteria and Risk Assessment, Chinese Research Academy of Environmental Sciences, No. 8 Dayangfang, Chaoyang District, Beijing, China*

ARTICLE INFO

*Article history:*
Received 28 November 2016
Received in revised form
14 June 2017
Accepted 23 August 2017

## 1. Introduction

Numerous epidemiologic studies suggest that ambient air pollution is associated with increased mortality from chronic diseases. However, most of these studies are from North America (Lepeule et al., 2012; Dockery et al., 1993; Gan et al., 2013; Hart et al., 2011; Kloog et al., 2013; Laden et al., 2006; Lipsett et al., 2011; Pope et al., 2002, 2004) and Europe (Beelen et al., 2008, 2014; Carey et al., 2013; Cesaroni et al., 2013; Filleul et al., 2005; Hales et al., 2012; Heinrich et al., 2013; Janssen et al., 2013; Naess et al., 2007; Schikowski et al., 2007; Yap et al., 2012), where the concentration of air pollutants is relatively low. Furthermore, most studies have focused on the outcomes of all-cause cardiovascular diseases or lung cancer, but not on nonmalignant respiratory diseases, due to lack of statistical power or small number of respiratory deaths.

As the largest developing country in the world, China has achieved rapid development over the past three decades accompanied by high levels of ambient air pollution. Several studies from Chinese cities have been conducted to explore the association between cause-specific mortality and ambient air pollution, although the majority of these are time-series studies or applied case-crossover approaches (Gao et al., 2014; Yang et al., 2013). Studies on long-term air pollution-related health effects in China are limited. Besides our cohort, only two cohort studies (Cao et al., 2011; Zhou et al., 2014) related to long-term exposure to ambient air pollution have been reported in the medical literature and neither of these was originally designed to examine the association between mortality and long-term exposure to ambient air pollution.

In the present study, we reported a large population-based cohort study of 39,054 subjects from four cities in northern China and examined the association between high air pollution levels measured by a range of ambient air pollutants and nonmalignant respiratory mortality. We also explored how other personal and

☆ This paper has been recommended for acceptance by David Carpenter.

* Corresponding author. Department of Occupational and Environmental Health, School of Public Health, Tianjin Medical University, No. 22 Qixiangtai Road, Heping District, Tianjin, 300070, China.
** Corresponding author.
*E-mail addresses:* baizp@craes.org.cn (Z.-p. Bai), tangnaijun@tmu.edu.cn (N.-j. Tang).

http://dx.doi.org/10.1016/j.envpol.2017.08.085

socio-demographic factors may modify the health effects of these pollutants in the study population.

## 2. Material and methods

### 2.1. Study area and population

Our cohort study was conducted in four selected cities from northern China: Tianjin, Shenyang, Taiyuan, and Rizhao. These cities cover the full range of particulate air pollution levels in northern China (Chen et al., 2016; Zhang et al., 2014).

Briefly, Tianjin (longitude: 116°43′ to 118°04′; latitude: 38°34′ to 40°15′), comprising an area of 11917.3 $km^2$, lies southeast of Beijing with a population of 12.3 million in 2009. As one of the first heavy industrial cities in China, Tianjin consumes a major proportion of energy derived from the combustion of coal. Shenyang (longitude: 122°25′ to 123°48′; latitude: 41°11′ to 43°2′) has a total area of 13,308 $km^2$ and a population of 7.9 million as of 2009. The major industries in Shenyang are steel manufacturing, nonferrous metals, machinery, chemical- and coke-related industries, and electric power generation. Taiyuan (longitude: 110°30′ to 113°09′; latitude: 37°27′ to 38°25′) is the capital of Shanxi province, which is the largest coal-producing area in China. It is located on the eastern edge of the Loess Plateau, and the altitude of the residential area is 800 m above the mean sea level. The population was 3.5 million in 2009. Rizhao (longitude: 118°25′ to 119°39′; latitude: 35°04′ to 36°04′), located on the west coast of the Yellow China Sea, is an emerging coastal city. Its population was 2.7 million in 2009.

According to our design, our cohort included 10,000 participants from each study site. They were selected from the communities located around the fixed environmental monitoring stations in the four study sites. Specifically, within the defined area around each environmental monitoring station, small neighborhoods were first numbered to form a sampling frame, from which random samples were drawn until a desired sample size was met. Each neighborhood included approximately 500–700 households. Study eligibility criteria were birth before January 1st, 1975, and living in the defined area for at least 10 years since January 1, 1998. The ethical committee of the coordinating center of Tianjin Medical University approved the study. Informed consent was obtained from all participants. There was a total cohort of 48,114 individuals at the beginning of the study.

In the retrospective follow-up, the interviewers contacted all selected participants inviting them to complete a standardized survey questionnaire, containing questions regarding socio-demographic information, lifestyle, and diet. A total of 39,054 participants completed the study as shown in Table 1; the attrition rate was 20.80%.

### 2.2. Outcomes

All mortality information was checked according to death certificates from the databases of Centers for Disease Control and Prevention (CDCs). The cause of death was classified according to the International Classification of Disease-10 coding system (ICD-10). Cause of death attributed to respiratory diseases (J00-J99) and chronic obstructive pulmonary disease (COPD; J40-J44) were confirmed. COPD is a subset of respiratory diseases. Survival time was calculated from the enrollment date to the date of death. The data for participants who were still alive at the end of follow-up were censored in the analyses.

### 2.3. Assessment of air pollutant concentration

Air pollutant data were acquired from the local governmental Environmental Monitoring Centers. Methods based on tapered element oscillating microbalance and ultraviolet fluorescence were used for the measurement of $PM_{10}$ and $SO_2$, respectively. We selected seven monitoring stations in Tianjin, five monitoring stations in Shenyang, three monitoring stations in Taiyuan, and one monitoring stations in Rizhao, using both residential and commercial areas. Twenty-four-hour average concentrations were calculated, from which annual average concentrations were subsequently computed (Fig. 1).

Previously, we estimated exposure for the study participants by taking the mean concentration of $PM_{10}$ pollution over their surviving years during the cohort study. This resulted in highly biased effect estimates due to decreased pollution levels over time (due to the substantial downward trend in pollution levels) and survivors were, therefore, assigned a lower exposure value, as opposed to participants who died during the study. In this study, we analyzed the HR estimates of nonmalignant respiratory mortality and air pollution based on the time-varying Cox model for the assessment of exposure.

### 2.4. Statistical analyses

We performed a descriptive analysis to explore the distribution of the selected characteristics of the cohort.

We used Cox proportional hazards models (SPSS Statistics, Version 16.0, IBM) to investigate associations between $PM_{10}$ concentrations and nonmalignant respiratory mortality and COPD mortality between 1999 and 2009 without any adjustment. Then, we expanded the model by introducing other hypothesis covariates. The following covariates were used: age at baseline (entered as a continuous variable) (Hoek et al., 2002), education (high school education or above versus below high school education), personal income (<500 Yuan and ≥500 Yuan), marital status (two variables, separated/divorced/widowed or single versus married), BMI (BMI<20, 20–25, 25–30, and 30+ $kg/m^2$), smoking status (two variables, former and current smokers versus never smoked), alcohol consumption, occupational exposure (self-reported exposure in the workplace versus non-exposure), and dietary habits (frequency of consumption of vegetables, fruits, meat, and seafood, according to three categories: less than once per week, two or three times per week, and over four times per week), physical activities per week ('yes' and 'no').

Third, we applied stratified Cox proportional hazards models to assess the effect of age, sex, education level, individual income, smoking status, alcohol consumption, and occupational exposure.

Inhabitants of the same neighborhoods usually share similar characteristics (socioeconomic status and access to services) and environmental exposure, which means that confounding and clustering of neighborhoods in the association between air pollution and mortality should be investigated. A shared frailty model (16, 19) was performed to investigate the role of the district in the sensitivity analysis. Statistical analyses were calculated using the survival package of the STATA version 12.0 (StataCorp, College Station, TX, USA).

## 3. Results

### 3.1. Characteristics of the study population

Baseline characteristics are shown in Table 1. The entire study population consisted of 39,054 participants contributing 462,177 person-years at risk (average time of follow-up was 11.83 years) with 67 deaths due to nonmalignant respiratory diseases and 46 deaths due to COPD during the follow-up period. Overall, average age of participants was 44.29 years at the start of follow-up

**Table 1**
Baseline characteristics of the cohort participants from the four selected cities.

| Characteristic | Tianjin | Shenyang | Taiyuan | Rizhao | Total |
|---|---|---|---|---|---|
| Total case | 9663 | 9921 | 10,090 | 9380 | 39,054 |
| Attrition rate | 20.80% | 17.50% | 17.69% | 20.39% | 18.83% |
| Sex (%) | | | | | |
| male | 4661(48.2) | 4811(48.5) | 5051(50.1) | 4937(52.6) | 19,460(49.8) |
| female | 5002(51.8) | 5110(51.5) | 5039(49.9) | 4443(47.4) | 19,594(50.2) |
| Age | 46.29 ± 13.00 | 47.30 ± 14.41 | 44.78 ± 14.00 | 38.53 ± 12.56 | 44.29 ± 13.95 |
| BMI ($kg/m^2$) | 22.93 ± 3.19 | 22.38 ± 3.36 | 22.87 ± 2.66 | 22.35 ± 2.52 | 22.63 ± 2.97 |
| Income (%) | | | | | |
| <500 | 5325(55.1) | 5959(60.1) | 4894(48.5) | 5555(59.2) | 21,733(55.6) |
| >=500 | 4338(44.9) | 3962(39.9) | 5196(51.5) | 3825(40.8) | 17,321(44.4) |
| Education (%) | | | | | |
| <high school | 4642(48.0) | 5966(60.1) | 4926(48.8) | 6631(70.1) | 22,165(56.8) |
| >=high school | 4959(51.3) | 3955(39.9) | 5164(51.2) | 2535(27.0) | 16,613(42.5) |
| Smoking status (%) | | | | | |
| never | 6521(67.5) | 6833(68.9) | 7276(72.1) | 7474(79.7) | 28,104(72.0) |
| former | 271(2.8) | 228(2.3) | 218(2.2) | 354(3.8) | 1071(2.7) |
| current | 2853(29.5) | 2852(28.7) | 2539(25.7) | 1552(16.5) | 9850(25.2) |
| Alcohol intake (%) | 2064(21.4) | 2027(20.4) | 1827(18.1) | 2021(21.5) | 7939(20.3) |
| Exercise (%) | 5423(56.1) | 4229(42.6) | 4990(49.5) | 4882(52.0) | 19,524(50.0) |
| Occupational exposure (%) | 712(7.4) | 476(4.8) | 1256(12.4) | 381(4.1) | 2825(7.2) |
| Meat consumption (%) | | | | | |
| low | 3923(40.6) | 3855(38.8) | 3303(32.7) | 4129(44.0) | 15,210(38.9) |
| middle | 3373(34.9) | 3871(39.0) | 4723(46.8) | 3644(38.8) | 15,611(40.0) |
| high | 2367(24.5) | 2195(22.1) | 2064(20.5) | 1607(17.1) | 8233(21.1) |
| Vegetable consumption (%) | | | | | |
| low | 451(4.8) | 65(0.7) | 70(0.7) | 335(3.6) | 921(2.4) |
| middle | 573(5.9) | 93(0.9) | 301(3.0) | 1004(10.7) | 1971(5.0) |
| high | 8639(89.4) | 9763(98.4) | 9719(96.3) | 8041(85.7) | 36,162(92.6) |
| Fruit consumption (%) | | | | | |
| low | 1404(14.5) | 1981(20.0) | 1807(17.9) | 3554(37.9) | 8746(22.4) |
| middle | 1397(14.5) | 2182(22.0) | 3166(31.4) | 2249(24.0) | 8994(23.0) |
| high | 6780(70.2) | 5741(57.9) | 5113(50.7) | 3468(37.0) | 21,102(54.0) |
| Total mortality (%) | 234(2.4) | 501(5.0) | 386(3.8) | 314(3.3) | 1435(3.7) |
| Respiratory disease (%) | 6(0.1) | 18(0.2) | 29(0.3) | 14(0.1) | 67(0.2) |
| COPD (%) | 4(0.04) | 13(0.1) | 21(0.2) | 8(0.1) | 46(0.1) |

The values are presented as percentages (%) or means ± SD.
Some columns do not add up to 100% because of missing data.

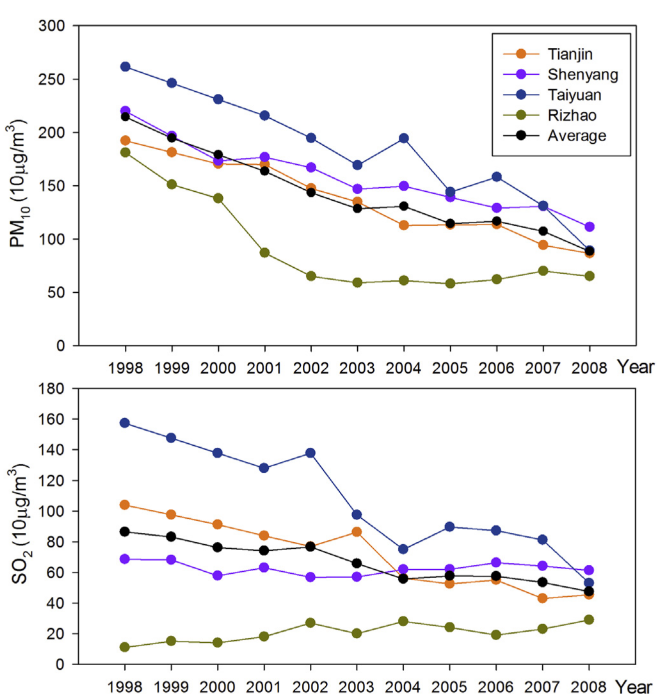


**Fig. 1.** $PM_{10}$ ($\mu g/m^3$) and $SO_2$ ($\mu g/m^3$) annual average density trended between 1998 and 2009 in four cities of northern China.

(SD = 13.95; range, 23–98). The mean BMI was 22.63 $kg/m^2$. Over a quarter of participants (male 53.3%, female 7.4%) were current smokers and one-fifth (male 41.0%, female 3.0%) were drinkers. As shown in Table 1, the four study sites were comparable with respect to age, sex, smoking status, and alcohol consumption; differences for other characteristics (e.g., dietary habits) were observed.

### 3.2. *Assessment of ambient air pollution*

The 12-year average concentrations (1998–2009) of $PM_{10}$ and $SO_2$ across the four study areas were 91.0–185.9 $\mu g/m^3$ and 20.7–109.1 $\mu g/m^3$, respectively. Detailed information is provided in Fig. 1. For both $PM_{10}$ and $SO_2$, the highest levels of ambient air pollution were measured in Taiyuan city, while Rizhao city levels were the lowest. Declining trends in pollutant annual concentration in the four study areas were clearly evident. The overall mean $PM_{10}$ and $SO_2$ concentration for the entire cohort was 144.3 $\mu g/m^3$ (SD, 36.3; range 90.6–274.0) and 66.9 $\mu g/m^3$ (SD, 34.0; range 11.0–224.4). Within our cohort, annual concentrations of $SO_2$ were strongly correlated with $PM_{10}$ ($r = 0.87$).

### 3.3. *Related factors of mortality*

The associations between ambient air pollution concentrations and nonmalignant respiratory mortality between 1998 and 2009 are shown in Table 2. Positive associations were statistically significant for both $PM_{10}$ and $SO_2$. After adjusting for sex, age at baseline, BMI, educational level, smoking status, alcohol consumption, occupational exposure, and personal income, $PM_{10}$ and

**Table 2**
Adjusted HRs (95% CIs) for the association between cause-specific mortality in full cohort (1998–2009) with a 10 μg/m$^3$ increase in $PM_{10}$ and $SO_2$, respectively.

| Cause of death and baseline variable adjusted for | | $PM_{10}$ | $SO_2$ |
|---|---|---|---|
| | | HR(95% CIs) | HR(95% CIs) |
| Respiratory diseases | 67 | | |
| None | | 1.461(1.296,1.648) | 1.101(1.028,1.179) |
| +age, gender | | 1.480(1.322,1.658) | 1.093(1.010,1.183) |
| +age, gender, personal characteristic[a] | | 1.432(1.280,1.603) | 1.085(1.003,1.175) |
| +age, gender, personal characteristic[a], dietary habits[b] | | 1.461(1.301,1.641) | 1.105(1.022,1.195) |
| COPD | 46 | | |
| None | | 1.721(1.446,2.048) | 1.158(1.067,1.257) |
| +age, gender | | 1.631(1.422,1.871) | 1.160(1.061,1.270) |
| +age, gender, personal characteristic[a] | | 1.582(1.375,1.821) | 1.140(1.041,1.249) |
| +age, gender, personal characteristic[a], dietary habits[b] | | 1.563(1.356,1.801) | 1.146(1.047,1.254) |

[a] Personal characteristics included smoking status (never/former versus current), education level (below high school or high school and above), personal income (coded as <500 and ≥500), BMI (coded as <20, 20–25, 25–30 and >30 kg/m$^2$), alcohol consumption(yes/no), occupational exposure(yes/no), marital status(married/single, divorced, widowed).

[b] Dietary habits included fruit consumption, vegetable consumption, seafood consumption, and meat consumption. All the covariates are classified into high, medium, and low.

$SO_2$ were significantly associated with both nonmalignant respiratory and COPD mortality: HRs associated with 10 μg/m$^3$ increases in pollutants were 1.432 (1.280, 1.603) and 1.085 (1.003, 1.175) for nonmalignant respiratory diseases; and 1.582 (1.375, 1.821) and 1.140 (1.041, 1.249) for COPD, respectively. There was some attenuation of effects in the adjusted model, but the estimates remained significant.

Stratified analyses of the association with the two outcomes of mortality by selected covariates for both $PM_{10}$ and $SO_2$ are shown in Table 3a and Table 3b, respectively. A strong association was found between $PM_{10}$ and nonmalignant respiratory and COPD mortality in the following groups: male participants, high education level group, high personal income group, and smokers. For example, a 10-μg/m$^3$ increase in $PM_{10}$ produced a HR of 1.324 (95% CI, 1.165–1.505) for participants classified as nonsmokers at baseline, whereas the corresponding number was 1.839 (95% CI, 1.463–2.311) among those who were classified as former or current smokers. There was a significant positive association between $SO_2$ levels and nonmalignant respiratory and COPD disease among participants with a low education level and high personal income. In low education level group, the HR is 1.088 (1.002, 1.182) for nonmalignant respiratory mortality and is 1.187 (1.030, 1.368) for COPD mortality; in high personal income group, the HR is 1.149 (1.044, 1.265) for nonmalignant respiratory mortality and is 1.242 (1.034, 1.492) for COPD mortality.

In two-pollutant models, including $PM_{10}$ and $SO_2$ (Table 4), the associations were attenuated between $PM_{10}$ and nonmalignant respiratory mortality. Similar trends were also detected in COPD mortality. For $SO_2$, the associations with respiratory mortality negative were borderline statistically significant (HR: 0.846, 95% CI: 0.717–0.998), whereas negative but not statistically significant with COPD mortality (HR: 0.962, 95% CI: 0.818–1.131). Attenuated effects were obvious after adjusting for personal characteristics and dietary habits.

Sensitivity analyses to adjust for within-neighborhood clustering using shared frailty models showed that the association between the pollutants and nonmalignant respiratory or COPD mortality remained robust.

**Table 3a**
Stratified analysis of the association between mortality of respiratory diseases and increases by 10 μg/m$^3$ in $PM_{10}$ and $SO_2$ according to selected characteristics.

| Characteristic | No. | $PM_{10}$ | $SO_2$ |
|---|---|---|---|
| | | HR(95%CI) | HR(95%CI) |
| Sex | | | |
| Male | 40 | 1.502(1.289,1.750) | 1.102(0.996,1.220) |
| Female | 27 | 1.353(1.141,1.605) | 1.062(0.936,1.204) |
| Education level | | | |
| Low | 61 | 1.421(1.264,1.598) | 1.088(1.002,1.182) |
| High | 6 | 1.578(1.047,2.378) | 0.995(0.737,1.345) |
| Personal income | | | |
| Low | 47 | 1.262(1.128,1.412) | 1.037(0.942,1.141) |
| High | 20 | 3.322(2.297,4,805) | 1.187(1.030,1.368) |
| Smoking status | | | |
| Never | 43 | 1.324(1.165,1.505) | 1.090(0.989,1.201) |
| Former and current | 24 | 1.839(1.463,2.311) | 1.084(0.944,1.245) |
| Occupational exposure | | | |
| No | 58 | 1.352(1.209,1.512) | 1.061(0.972,1.157) |
| Yes | 9 | 4.995(2.317,10.767) | 1.205(0.962,1.509) |

Covariates included age, sex, smoking status (never/former and current), education level (below high school or high school and higher), personal income (<500 Yuan and ≥500 Yuan), BMI (coded as <20, 20–25, 25–30, and >30 kg/m$^2$), alcohol consumption(yes/no), occupational exposure (yes/no), and marital status (married/single, divorced, widowed).

**Table 3b**
Stratified analysis of the association between COPD mortality and increases by 10 μg/m$^3$ in $PM_{10}$ and $SO_2$ according to selected characteristics.

| Characteristic | No. | $PM_{10}$ | $SO_2$ |
|---|---|---|---|
| | | HR(95%CI) | HR(95%CI) |
| Sex | | | |
| Male | 27 | 1.551(1.295,1.857) | 1.131(1.002,1.276) |
| Female | 19 | 1.681(1.330,2.124) | 1.161(1.008,1.338) |
| Education level | | | |
| Low | 41 | 1.555(1.339,1.807) | 1.149(1.044,1.265) |
| High | 5 | 1.890(1.215,2.940) | 0.994(0.720,1.373) |
| Personal income | | | |
| Low | 34 | 1.429(1.234,1.655) | 1.101(0.989,1.226) |
| High | 12 | 3.277(2.074,5.178) | 1.242(1.034,1.492) |
| Smoking status | | | |
| Never | 28 | 1.527(1.288,1.810) | 1.163(1.038.1.303) |
| Former and current | 18 | 1.741(1.355,2.235) | 1.104(0,944,1.290) |
| Occupational exposure | | | |
| No | 37 | 1.460(1.264,1.686) | 1.118(1.008,1.240) |
| Yes | 9 | 4.995(2.317,10.767) | 1.205(0.962,1.509) |

Covariates included age, sex, smoking status (never/former and current), education level (below high school or high school versus higher), personal income (<500 Yuan and ≥500 Yuan), BMI (<20, 20–25, 25–30, and >30 kg/m$^2$), alcohol consumption (yes/no), occupational exposure (yes/no), and marital status (married/single, divorced, widowed).

## 4. Discussion

From this large-scaled retrospective cohort study, we found

**Table 4**
Adjusted HRs and 95% confidence intervals of cause-specific mortality associated with a 10 μg/m$^3$ increase of average ambient air pollution in the two-pollutant model 1998–2009 (N = 39,054).

| Cause of death | No. | Two-pollutant model | |
|---|---|---|---|
| | | $PM_{10}$ (10 μg/m$^3$) | $SO_2$ (10 μg/m$^3$) |
| Respiratory diseases | 67 | | |
| None | | 2.067(1.750,2.441) | 0.658(0.565,0.767) |
| +age, sex, personal characteristics[a] | | 1.753(1.518,2.025) | 0.828(0.700,0.979) |
| +age, sex, personal characteristics[a], dietary habits | | 1.819(1.565,2.115) | 0.846(0.717,0.998) |
| COPD | 46 | | |
| None | | 2.198(1.829,2.641) | 0.729(0.622,0.855) |
| +age, sex, personal characteristics[a] | | 1.807(1.538,2.124) | 0.954(0.812,1.120) |
| +age, sex, personal characteristics[a], dietary habits | | 1.896(1.584,2.269) | 0.962(0.818,1.131) |

[a] Personal characteristic included smoking status (coded as never/former/current), education level (coded as below high school or high school and higher), personal income (coded as <500 Yuan and ≥500 Yuan), BMI (coded as <20, 20–25, 25–30, and >30 kg/m$^2$), alcohol consumption (yes/no), occupational exposure (yes/no), and marital status (married/single, divorced, widowed).

statistically significant associations between the elevated risk of nonmalignant respiratory mortality and long-term exposure to $PM_{10}$ and $SO_2$ in the adult population of north China. Similar trends were also observed in COPD mortality.

Cohort evidence of chronic exposure to air pollution and mortality is predominately based on studies from Europe and North America, where the annual concentrations of ambient air pollution are relatively lower than in developing countries, such as China. The most recent reports of the Environmental Protection Agency presented the annual average concentrations of $PM_{2.5}$, $PM_{10}$, and $SO_2$ were 12 μg/m$^3$, 25 μg/m$^3$, and 4 ppb, respectively, and the ESCAPE project reported that the mean concentrations of $PM_{10}$ ranged from 13.5 to 48.1 μg/m$^3$ in Europe (Raaschou-Nielsen et al., 2013). The mean annual concentrations of ambient air pollutant in our studies (144.34 μg/m$^3$ for $PM_{10}$ and 66.90 μg/m$^3$ for $SO_2$) were clearly higher. Most studies focused on the associations with cardiovascular disease, partly due to limited death from nonmalignant respiratory diseases. Therefore, most of the studies used cardiopulmonary mortality as the outcome to explore the associations between ambient air pollution and respiratory mortality (Filleul et al., 2005; Pope et al., 2002). Because ambient particular matter is the most common indicator of air pollution, numerous earlier cohort studies have used $PM_{2.5}$ or $PM_{10}$ as an exposure metric to investigate the long-term effects of ambient PM on respiratory mortality.

Data on the associations between ambient particulate matter and nonmalignant respiratory mortality are limited and inconsistent. A 2014 meta-analysis from the ESCAPE project calculated a pooled hazard ratio of 0.86 (95% CI, 0.67–1.04) for $PM_{10}$ and nonmalignant respiratory mortality (Dimakopoulou et al., 2014). The Harvard Six Cities Study (Dockery et al., 1993; Laden et al., 2006; Lepeule et al., 2012), the reanalysis of the ACS cohort (Pope et al., 2004), several European studies (Cesaroni et al., 2013; Filleul et al., 2005; Janssen et al., 2013), and Asian studies (Cao et al., 2011; Zhang et al., 2014) reported positive associations for $PM_{2.5}$ or $PM_{10}$, although only a few of these were statistically significant. Our estimate when scaled to a 10 μg/m$^3$ increment, and adjusted for age, sex, and personal characteristics, produced an HR of 1.432 (95% CI, 1.280–1.603). Further details are summarized in Table 2. Compared with our recent study on cardiovascular mortality and $PM_{10}$ (Zhang et al., 2014), reporting a HR of 1.24 (95% CI, 1.22–1.27), stronger associations can be found with respiratory mortality. This result was consistent with a recently published English national cohort study (Carey et al., 2013).

Similar trends were found with the subcategorized outcome, COPD. This result may be partly due to the fact that the majority of deaths from respiratory diseases were from COPD (69%). The identification of subcategories of respiratory disease was similar to a study from Japan (Katanoda et al., 2011).

Covariates' modified effects were also considered in our study. Education level and personal income were selected as the indicators to estimate the modified effect of social economic status on the association between the ambient air pollution and respiratory mortality. We found that people in high socioeconomic status (SES) were much more susceptible to particulate matter and died from respiratory diseases. However, inverse but not statistically significant trends were observed in other studies (Filleul et al., 2005). Our results were reasonable because people in high SES were more likely to gather in metropolitan areas, where educational and occupational resources are sufficient and the ambient air pollution is more severe.

Smoking status is another effect modifier that cannot be overlooked. We were not surprised to find that ambient air pollutants were more harmful to smokers, which is consistent with the ACS studies (Pope et al., 2002, 2004) and the FAARC study (Filleul et al., 2005). However, other studies (Andersen et al., 2011; Mehta et al., 2012), found that non-smokers may be more susceptible to the adverse health effects of air pollution. We performed further studies to explore the effect of passive smoking in nonsmokers and found that exposure to second-hand smoke increased the risk of dying from respiratory diseases due to air pollutants (Fig. 2). All particle exposures produce an oxidative stress (Wang et al., 2012). Although the mechanism of PM-mediated pathophysiology remains unknown, the $PM_{10}$ has its effect mainly by a mechanism involving oxidative stress (Sethi and MacNee, 2011; Wang et al., 2012). Our findings suggest that, for respiratory disease, the primary role of air pollution may not be merely the exacerbation of existing diseases but also contribution to the long-term progression of nonmalignant respiratory diseases.

Compared with $PM_{10}$, the association between $SO_2$ and respiratory mortality were weaker, and some stratified results were combined into one. Our findings were generally comparable with most previous studies. Three Asian studies (Cao et al., 2011; Dimakopoulou et al., 2014) also reported similar positive results that were statistically significant. However, some European and North American studies did not report a significant association between $SO_2$ and mortality (Beelen et al., 2008; Hart et al., 2011); this may be due to the relatively low levels of $SO_2$. Our two-pollutant results found a negative association between $SO_2$ and respiratory mortality, suggesting that the causal nature of the association between mortality and $SO_2$ is disputable, partly due to the correlation between $SO_2$ and particulate matter. The mechanism of the interaction between $SO_2$ and $PM_{10}$ should be explored in future studies.

Our study has several strengths. It was based on a retrospective cohort, the largest original cohort existing in China, to explore the

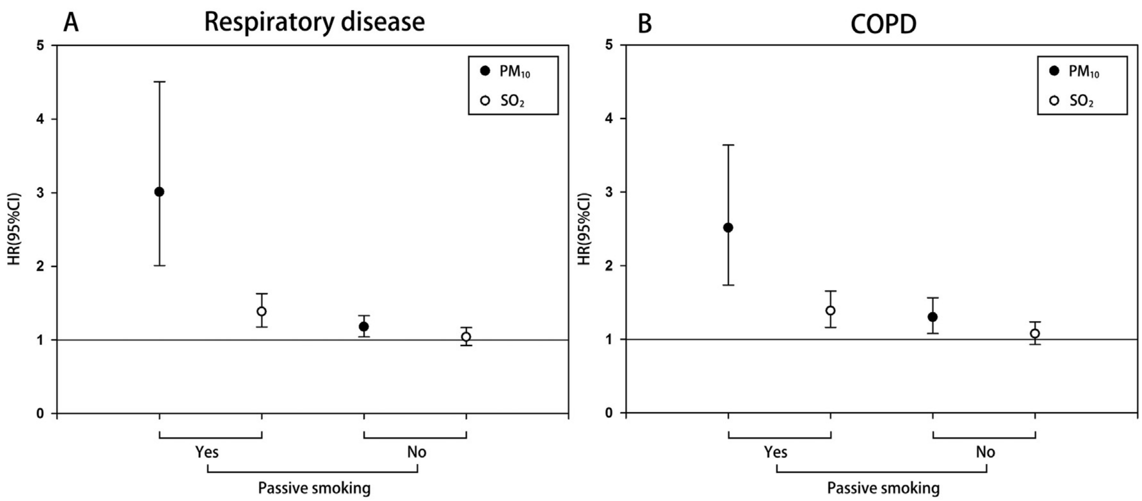


**Fig. 2. A**: Among nonsmokers, after stratification by population characteristics of passive smoking, adjusted HRs (95% CIs) for nonmalignant respiratory mortality per 10 μg/m$^3$ increase in $PM_{10}$ and $SO_2$ concentrations. **B**: Among nonsmokers, after stratification by population characteristics of passive smoking, adjusted HRs (95% CIs) for COPD mortality per 10 μg/m$^3$ increase in $PM_{10}$ and $SO_2$ concentrations.

association between mortality and ambient air pollution. To our knowledge, there are only two published air pollution cohort studies (Cao et al., 2011; Zhou et al., 2014) and these were not originally designed to examine the adverse effects of ambient air pollution. Moreover, the concentration of ambient air pollutants in our study area was relatively higher than that in similar cohort studies. However, there are limitations to our study that cannot be overlooked. Individual exposure assessment may be the main limitation, because it was estimated on the basis of residential postal codes. This method can only approximately reflect individual exposure because it lacks environmental determinants (wind direction and housing characteristics) which may affect individual exposure assessment. Future studies require a more detailed exposure assessment, such as a land-use regression model or geocoded air pollution data.

## 5. Conclusion

In conclusion, the present study provided strong evidence that in northeast China nonmalignant respiratory disease mortality was significantly associated with with every 10-μg/m3 increase in $PM_{10}$ (HR 1.461, 95% CI 1.296–1.648), and borderline significantly associated with every 10-μg/m3 increase in $SO_2$ (HR 1.105, 95% CI, 1.022–1.195). Sex, smoking status, educational level, personal income, and occupational exposure modified the association between the ambient air pollution and respiratory mortality. These findings have implications for local and central governments to regulate and formulate environmental protection measures to reduce ambient air pollution. It is necessary to be aware of the dangers of air pollution and to inform the public on how to minimize their risks from serious air pollution.

## Acknowledgements

This work was supported by the Special Environmental Research Fund for Public Welfare (No. 200709048) from Ministry of Environmental Protection of the People's Republic of China.

## References

Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Loft, S., Sorensen, M., Tjonneland, A., Overvad, K., Raaschou-Nielsen, O., 2011. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Am. J. Respir. Crit. Care Med. 183, 455–461.

Beelen, R., Hoek, G., van den Brandt, P.A., Goldbohm, R.A., Fischer, P., Schouten, L.J., Jerrett, M., Hughes, E., Armstrong, B., Brunekreef, B., 2008. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ. Health Perspect. 116, 196–202.

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., Wolf, K., Samoli, E., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Oudin, A., Forsberg, B., Modig, L., Havulinna, A.S., Lanki, T., Turunen, A., Oftedal, B., Nystad, W., Nafstad, P., De Faire, U., Pedersen, N.L., Ostenson, C.G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Overvad, K., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Sugiri, D., Kramer, U., Heinrich, J., de Hoogh, K., Key, T., Peters, A., Hampel, R., Concin, H., Nagel, G., Ineichen, A., Schaffner, E., Probst-Hensch, N., Kunzli, N., Schindler, C., Schikowski, T., Adam, M., Phuleria, H., Vilier, A., Clavel-Chapelon, F., Declercq, C., Grioni, S., Krogh, V., Tsai, M.Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Katsoulis, M., Trichopoulou, A., Brunekreef, B., Hoek, G., 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383, 785–795.

Cao, J., Yang, C., Li, J., Chen, R., Chen, B., Gu, D., Kan, H., 2011. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. J. Hazard Mater 186, 1594–1600.

Carey, I.M., Atkinson, R.W., Kent, A.J., van Staa, T., Cook, D.G., Anderson, H.R., 2013. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am. J. Respir. Crit. Care Med. 187, 1226–1233.

Cesaroni, G., Badaloni, C., Gariazzo, C., Stafoggia, M., Sozzi, R., Davoli, M., Forastiere, F., 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ. Health Perspect. 121, 324–331.

Chen, X., Zhang, L.W., Huang, J.J., Song, F.J., Zhang, L.P., Qian, Z.M., Trevathan, E., Mao, H.J., Han, B., Vaughn, M., Chen, K.X., Liu, Y.M., Chen, J., Zhao, B.X., Jiang, G.H., Gu, Q., Bai, Z.P., Dong, G.H., Tang, N.J., 2016. Long-term exposure to urban air pollution and lung cancer mortality: a 12-year cohort study in Northern China. Sci. Total Environ. 571, 855–861.

Dimakopoulou, K., Samoli, E., Beelen, R., Stafoggia, M., Andersen, Z.J., Hoffmann, B., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W., Hoek, G., Raaschou-Nielsen, O., Oudin, A., Forsberg, B., Modig, L., Jousilahti, P., Lanki, T., Turunen, A., Oftedal, B., Nafstad, P., Schwarze, P.E., Penell, J., Fratiglioni, L., Andersson, N., Pedersen, N., Korek, M., De Faire, U., Eriksen, K.T., Tjonneland, A., Becker, T., Wang, M., Bueno-de-Mesquita, B., Tsai, M.Y., Eeftens, M., Peeters, P.H., Meliefste, K., Marcon, A., Kramer, U., Kuhlbusch, T.A., Vossoughi, M., Key, T., de Hoogh, K., Hampel, R., Peters, A., Heinrich, J., Weinmayr, G., Concin, H., Nagel, G., Ineichen, A., Jacquemin, B., Stempfelet, M., Vilier, A., Ricceri, F., Sacerdote, C., Pedeli, X., Katsoulis, M., Trichopoulou, A., Brunekreef, B., Katsouyanni, K., 2014. Air pollution and nonmalignant respiratory mortality in 16 cohorts within the ESCAPE project. Am. J. Respir. Crit. Care Med. 189, 684–696.

Dockery, D.W., Pope 3rd, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris Jr., B.G., Speizer, F.E., 1993. An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329, 1753–1759.

Filleul, L., Rondeau, V., Vandentorren, S., Le Moual, N., Cantagrel, A., Annesi-Maesano, I., Charpin, D., Declercq, C., Neukirch, F., Paris, C., Vervloet, D., Brochard, P., Tessier, J.F., Kauffmann, F., Baldi, I., 2005. Twenty five year mortality and air pollution: results from the French PAARC survey. Occup. Environ. Med. 62, 453–460.

Gan, W.Q., FitzGerald, J.M., Carlsten, C., Sadatsafavi, M., Brauer, M., 2013. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am. J. Respir. Crit. Care Med. 187, 721–727.

Gao, Y., Chan, E.Y., Li, L., Lau, P.W., Wong, T.W., 2014. Chronic effects of ambient air pollution on respiratory morbidities among Chinese children: a cross-sectional study in Hong Kong. BMC Public Health 14, 105.

Hales, S., Blakely, T., Woodward, A., 2012. Air pollution and mortality in New Zealand: cohort study. J. Epidemiol. Community Health 66, 468–473.

Hart, J.E., Garshick, E., Dockery, D.W., Smith, T.J., Ryan, L., Laden, F., 2011. Long-term ambient multipollutant exposures and mortality. Am. J. Respir. Crit. Care Med. 183, 73–78.

Heinrich, J., Thiering, E., Rzehak, P., Kramer, U., Hochadel, M., Rauchfuss, K.M., Gehring, U., Wichmann, H.E., 2013. Long-term exposure to $NO_2$ and $PM_{10}$ and all-cause and cause-specific mortality in a prospective cohort of women. Occup. Environ. Med. 70, 179–186.

Hoek, G., Brunekreef, B., Goldbohm, S., Fischer, P., van den Brandt, P.A., 2002. Association between mortality and indicators of traffic-related air pollution in The Netherlands: a cohort study. Lancet 360, 1203–1209.

Janssen, N.A., Fischer, P., Marra, M., Ameling, C., Cassee, F.R., 2013. Short-term effects of $PM_{2.5}$, $PM_{10}$ and $PM_{2.5-10}$ on daily mortality in The Netherlands. Sci. Total. Environ. 463–464, 20–26.

Katanoda, K., Sobue, T., Satoh, H., Tajima, K., Suzuki, T., Nakatsuka, H., Takezaki, T., Nakayama, T., Nitta, H., Tanabe, K., Tominaga, S., 2011. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J. Epidemiol. 21, 132–143.

Kloog, I., Ridgway, B., Koutrakis, P., Coull, B.A., Schwartz, J.D., 2013. Long- and short-term exposure to PM2.5 and mortality: using novel exposure models. Epidemiology 24, 555–561.

Laden, F., Schwartz, J., Speizer, F.E., Dockery, D.W., 2006. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am. J. Respir. Crit. Care Med. 173, 667–672.

Lepeule, J., Laden, F., Dockery, D., Schwartz, J., 2012. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ. Health Perspect. 120, 965–970.

Lipsett, M.J., Ostro, B.D., Reynolds, P., Goldberg, D., Hertz, A., Jerrett, M., Smith, D.F., Garcia, C., Chang, E.T., Bernstein, L., 2011. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am. J. Respir. Crit. Care. Med. 184, 828–835.

Mehta, A.J., Miedinger, D., Keidel, D., Bettschart, R., Bircher, A., Bridevaux, P.O., Curjuric, I., Kromhout, H., Rochat, T., Rothe, T., Russi, E.W., Schikowski, T., Schindler, C., Schwartz, J., Turk, A., Vermeulen, R., Probst-Hensch, N., Kunzli, N., Team, S., 2012. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss cohort study on air pollution and lung and heart diseases in adults. Am. J. Respir. Crit. Care. Med. 185, 1292–1300.

Naess, O., Nafstad, P., Aamodt, G., Claussen, B., Rosland, P., 2007. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo. Nor. Am. J. Epidemiol. 165, 435–443.

Pope 3rd, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., Thurston, G.D., 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287, 1132–1141.

Pope 3rd, C.A., Burnett, R.T., Thurston, G.D., Thun, M.J., Calle, E.E., Krewski, D., Godleski, J.J., 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109, 71–77.

Raaschou-Nielsen, O., Andersen, Z.J., Beelen, R., Samoli, E., Stafoggia, M., Weinmayr, G., Hoffmann, B., Fischer, P., Nieuwenhuijsen, M.J., Brunekreef, B., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Sommar, J., Forsberg, B., Modig, L., Oudin, A., Oftedal, B., Schwarze, P.E., Nafstad, P., De Faire, U., Pedersen, N.L., Ostenson, C.G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Sorensen, M., Tjonneland, A., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Key, T.J., de Hoogh, K., Concin, H., Nagel, G., Vilier, A., Grioni, S., Krogh, V., Tsai, M.Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Trichopoulou, A., Bamia, C., Vineis, P., Hoek, G., 2013. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European study of cohorts for air pollution effects (ESCAPE). Lancet Oncol. 14, 813–822.

Schikowski, T., Sugiri, D., Ranft, U., Gehring, U., Heinrich, J., Wichmann, H.E., Kramer, U., 2007. Does respiratory health contribute to the effects of long-term air pollution exposure on cardiovascular mortality? Respir. Res. 8, 20.

Sethi, S., MacNee, W., 2011. Human models of exacerbations of COPD: no extrapolation needed. Am. J. Respir. Crit. Care. Med. 183, 691–692.

Wang, T., Wang, L., Moreno-Vinasco, L., Lang, G.D., Siegler, J.H., Mathew, B., Usatyuk, P.V., Samet, J.M., Geyh, A.S., Breysse, P.N., Natarajan, V., Garcia, J.G., 2012. Particulate matter air pollution disrupts endothelial cell barrier via calpain-mediated tight junction protein degradation. Part. Fibre Toxicol. 9, 35.

Yang, Y., Li, R., Li, W., Wang, M., Cao, Y., Wu, Z., Xu, Q., 2013. The association between ambient air pollution and daily mortality in Beijing after the 2008 olympics: a time series study. PLoS One 8, e76759.

Yap, C., Beverland, I.J., Heal, M.R., Cohen, G.R., Robertson, C., Henderson, D.E., Ferguson, N.S., Hart, C.L., Morris, G., Agius, R.M., 2012. Association between long-term exposure to air pollution and specific causes of mortality in Scotland. Occup. Environ. Med. 69, 916–924.

Zhang, L.W., Chen, X., Xue, X.D., Sun, M., Han, B., Li, C.P., Ma, J., Yu, H., Sun, Z.R., Zhao, L.J., Zhao, B.X., Liu, Y.M., Chen, J., Wang, P.P., Bai, Z.P., Tang, N.J., 2014. Long-term exposure to high particulate matter pollution and cardiovascular mortality: a 12-year cohort study in four cities in northern China. Environ. Int. 62, 41–47.

Zhou, M., Liu, Y., Wang, L., Kuang, X., Xu, X., Kan, H., 2014. Particulate air pollution and mortality in a cohort of Chinese men. Environ. Pollut. 186, 1–6.