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Long-term exposure to urban air pollution and lung cancer mortality: A 12-year cohort study in Northern China

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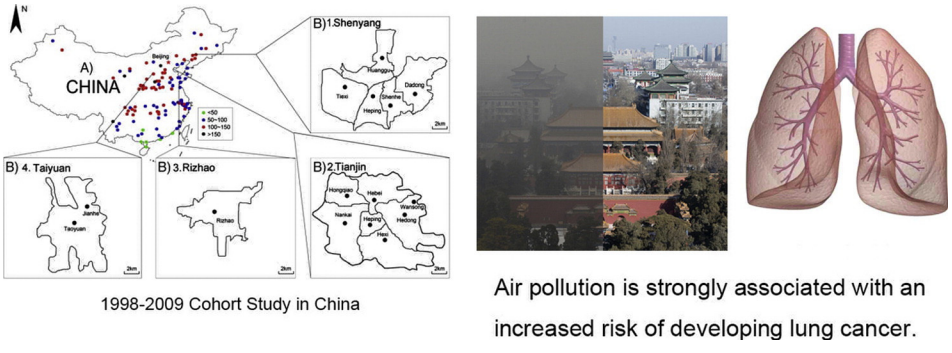
HIGHLIGHTS

- The relationship between exposure to air pollution and lung cancer is proposed.
- Levels of PM_{10} and SO_2 were associated with lung cancer mortality independently.
- The association was different in men and women, and varied across smoking status.

GRAPHICAL ABSTRACT



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ABSTRACT

Cohort evidence that links long-term exposures to air pollution and mortality comes largely from the United States and European countries. We investigated the relationship between long-term exposures to particulate matter <10 μm in diameter (PM_{10}), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) and mortality of lung cancer in Northern China. A cohort of 39,054 participants were followed during 1998–2009. Annual average concentrations for PM_{10}, NO_2, and SO_2 were determined based on data collected from central monitoring stations. Lung cancer deaths (n = 140) were obtained from death certificates, and hazard ratios (HRs) were estimated using Cox proportional hazards models, adjusting for age, gender, BMI, education, marital status, smoking status,

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passive smoking, occupation, alcohol consumption, etc. Each 10 mg/m^3 increase in PM_{10} concentrations was associated with a 3.4%–6.0% increase in lung cancer mortality in the time-varying exposure model and a 4.0%–13.6% increase in the baseline exposure model. In multi-pollutant models, the magnitude of associations was attenuated, most strongly for PM_{10}. The association was different in men and women, also varying across age categories and different smoking status. Substantial differences exist in the risk estimates for participants based on assignment method for air pollution exposure.

1. Introduction

The complex mixture of outdoor air pollutants contains a number of known carcinogens that have been found to be associated with increased risk of lung cancer in numerous studies over the past 50 years (Hamra et al., 2014). The International Agency for Research on Cancer (IARC) recently concluded that "*exposure to outdoor air pollution and particulate matter (PM) in outdoor air is carcinogenic to humans (IARC Group 1) and causes lung cancer*" (Hamra et al., 2014). Despite drawing on many of the latest studies conducted around the globe to reach this conclusion, few studies were conducted in China and other developing countries to demonstrate the association between outdoor air pollution and lung cancer deaths (Cao et al., 2011; Loomis et al., 2014).

China did not officially monitor national-wide $PM_{2.5}$ levels until Jan. of 2013. According to the Chinese Ministry of Environmental Protection, the annual average PM_{10} concentration in major Chinese cities increased from 87 μg/m^3 in 2009 to 118 μg/m^3 in 2012 (Report on the State of the Environment in China, 2009, 2012). This level of air pollution is much higher compared to levels in European and American countries. In the past three decades, China's extensive industrial development, coal-dependent energy consumption, and increasing number of vehicles have led to a dramatic rise in air pollutant emissions. The country is now experiencing two important challenges: 1) China produces a large number of major pollutants, which causes high levels of air pollution and substantially reduced visibility (Ouyang, 2013), and 2) air pollution over time has changed from the traditional coal combustion form to the mixed coal combustion/motor vehicle emission type (Kan et al., 2009).

Lung cancer is now one of the major health threats experienced in China, and the burden is getting increasingly serious. In the annual report of cancer in China, lung cancer was listed as the number one cause of cancer incidence in males and the leading cause of cancer mortality for both males and females (National Office for Cancer Prevention and Control et al., 2014). In 2004–2005, the death rate from lung cancer was 30.84 per 100,000, representing a 464.8% increase over rates in 1973–1975 in China (Loomis et al., 2014). Positive exposure-response associations were reported in studies that collected quantitative pollutant exposure data (Krewski et al., 2009; Raaschou-Nielsen et al., 2013).

In the previous analysis of this cohort, we evaluated the PM_{10} exposure–response relationship for cardiovascular mortality. We reported that long-term exposure to PM_{10} was independently associated with the mortality of cardiovascular disease after controlling for other risk factors (Zhang et al., 2014). In the present study, we explore the association of ambient exposures to PM_{10}, sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) and lung cancer mortality.

2. Methods

2.1. Study area and population

As with the previous study, this cohort study was conducted from January 1998 to December 2009 in four Northern Chinese cities: Tianjin, Shenyang, Taiyuan, and Rizhao. These cities present a wide range of particle air pollution levels in northern China. The locations of the four cities and monitoring stations have been described in detail elsewhere (Zhang et al., 2014). Briefly, Tianjin comprises an area of 11,917.3 km^2 with a population of 12.3 million in 2009. Shenyang has an area of a total 13,308 km^2 and had a population of 7.9 million as of 2009. In the city of Shenyang, the main industries include nonferrous metals, steel manufacturing, electric power generation machinery, and chemical- and coke-related industries. Taiyuan is the capital of Shanxi province and is the largest coal-producing area in China. The city is 800 m above sea level, and is located on the eastern side of the Loess Plateau. The population was 3.5 million in 2009. Rizhao, a merging coastal city, is located on the west coast of the Yellow China Sea and possessed a population of 2.7 million as of 2009. The number of environmental monitor stations in each city varied from one (Rizhao, the smallest city) to seven (Tianjin, the largest city). Small neighborhoods (street blocks or apartment buildings) within a 1 km radius from the monitoring stations were selected and numbered to form a sampling frame. Random samples were then drawn until the desired sample size was achieved. Each neighborhood unit contains households ranging from 500 to 700 persons. Eligible participants must have been born prior to January 1, 1975, and had to be a resident in the defined area since January 1, 1998.

Among 48,114 participants, a total of 188 individuals (0.6%) were not linked to provincial administrative data maintained by the Institute for Clinical Evaluative Sciences (ICES) in Toronto. In addition, 2743 (0.6%) with missing residence location detail and 52 (0.2%) with incomplete data on covariates were excluded, yielding 39,054 participants (81.17%) in the study population. Participants completed a questionnaire during the visit, including demographic characteristics, smoking status, alcohol consumption, occupational exposures, and leisure exercise. The majority of the cohort (81.17%) did not change residences from January 1998 to the end of follow-up, whereas a move within the city was registered for the other 7353 residents.

Written informed consent was obtained from all participants. Use of data on human subjects was approved by the California Health and Human Services Agency's Committee for the Protection of Human Subjects and the institutional review boards for each participating organization.

2.2. Outcome assessment

Family members completed the questionnaire for deceased participants. They were asked to provide information surrounding the death of the study participants including place, time, and cause of death. These data were crosschecked against death certificates obtained from the local Center for Disease Control and Prevention (CDC). More than 98% of all known causes of death were recorded in this survey. We classified deaths according to the cause of death using the International Classification of Disease-10 (ICD-10) (C33, C34 for lung cancer) coding system.

2.3. Estimation of exposure

Air pollutant data were acquired from the local Environmental Monitoring Centers, the government agencies in charge of the collection of data on air pollution. Measurement methods included tapered element oscillating microbalance, ultraviolet fluorescence, and chemiluminescence for PM_{10} (μg/m^3), SO_2 (μg/m^3), and NO_2 (μg/m^3), respectively. We selected seven monitoring stations in Tianjin, five in

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Shenyang, two in Taiyuan, and one in Rizhao. The locations of these stations were sufficiently far from any source of emissions. The exposure levels of air pollution for the participants were estimated according to the data of the nearest monitoring stations. There was no professional ambient PM_{10} monitoring until 2000 in the city of Rizhao. Thus, the missing PM_{10} data for the first two years was converted from the concentrations of total suspended particles (TSP, the commonly used ratio is closer to 55 μg/m^3 PM_{10} per 100 TSP (Ho and Nielsen, 2013)). Annual average concentrations were computed based on calculated 24-hour average concentrations.

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 (Zhang et al., 2014). This resulted in effect estimates that were biased high because pollution levels have decreased over time (as shown Fig. 1) and survivors were therefore assigned a lower exposure value, as opposed to participants who died during the study. This is not appropriate as had been observed previously in the California teacher study. For the purposes of this study, the baseline exposure model is most appropriate for evaluating lung cancer (Ostro et al., 2010; Ostro et al., 2011). Two methods were used to assign exposure to study subjects in the present analysis: 1) assigning the 1998 air pollution exposure for all and 2) time-varying exposures for both deaths and survivors. (How the time-varying exposure is defined should be described in detail.) We also added the HR estimates of lung cancer mortality and air pollution based on the average pollution for the surviving period for comparison.

2.4. Covariates

Covariates we considered were: age (continuous variable), gender (male or female), marital status (single/separated/divorced/widowed or married), education (high school or more, less than high school), body mass index (BMI) (<20, 20–25, 25–30, >30 kg/m^2), smoking status (with cigarette amounts per day, 0, 1–10, 11–20, >20), alcohol consumption (yes or no), occupational exposures (self-reported exposure to dust and fumes in the workplace, yes or no) and leisure exercise (active or non-active).

2.5. Statistical analysis

We used Cox proportional hazards models (PASW Statistics, Version 18.0, IBM) to analyze the associations between pollution concentrations and subsequent mortality in 1999–2009 (Beelen et al., 2008). We adjusted the analyses using age at baseline, gender, BMI, education, marital status, smoking status, passive smoking, alcohol consumption, occupation, diet, and leisure exercise. (not consistent with the variables listed in "Covariates") To estimate the effects of NO_2, SO_2 and PM_{10}, we used single-pollutant and bi-pollutant models. Because the average pollution of PM_{10} was highly correlated with SO_2 ($r = 0.947$) from Pearson correlation analysis, the bi-pollutant models were used as PM_{10}-and-NO_2 model, SO_2-and-NO_2 model.

We performed stratified analyses to assess effect modification by the covariates. We modeled the Cox proportional hazards estimates described above separately for males and females to evaluate potential effect modification by sex. In addition, the model was stratified by age (<60 and ≥60). Furthermore, we conducted analyses that stratified cigarettes-per-day by cigarette amount to account for the impact of smoking on effect estimates and the shape of the exposure–response relationship.

Because neighborhoods are usually inhabited by residents with similar characteristics (socioeconomic, health, diets) and similar environmental exposures, we also assessed confounding and clustering of the association between exposure and mortality by sensitivity analysis. We performed a shared frailty model to investigate the role of city as an additional sensitivity analysis. These models were calculated with the survival package of the Stata version 12.0 (StataCorp LP, College Station, TX) (Carey et al., 2013; Cesaroni et al., 2013).

3. Results

3.1. Description of the study subjects

Table 1 shows the characteristics of the study participants from the four cities. The 39,054 members of the cohort were on average 44.29 years of age at the start of follow-up (SD = 13.95; range, 23–89). The average BMI was 22.63. More than 25% (male 45.77%, female

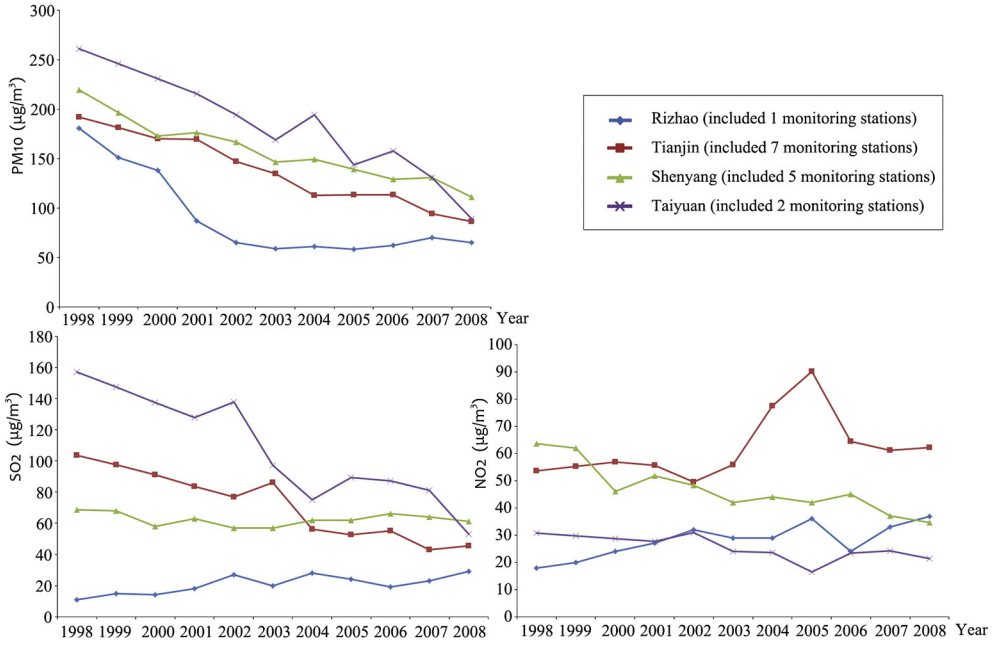

Fig. 1. Average annual PM_{10}, NO_2 and SO_2 concentrations (μg/m^3) during the period of 1998 to 2008 in four cities in China. Seven monitoring stations in Tianjin, five in Shenyang, two in Taiyuan, and one in Rizhao were selected in the present study. Measurement methods included tapered element oscillating microbalance, ultraviolet fluorescence, and chemiluminescence for PM_{10}, SO_2, and NO_2, respectively.

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Table 1
Baseline characteristics of the cohort participants from four 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 (%)					
Males	4661 (48.2)	4811 (48.5)	5051 (50.1)	4937 (52.6)	19,460 (49.8)
Females	5002 (51.8)	5110 (51.5)	5039 (49.9)	4443 (47.4)	19,594 (50.2)
Age (mean (SD))	46.29 (13.00)	47.30 (14.41)	44.78 (14.00)	38.53 (12.56)	44.29 (13.95)
BMI (mean (SD))	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 Amount (%)					
None	6565 (67.9)	6963 (70.2)	7386 (73.2)	7483 (79.8)	28,397 (72.7)
1–10	1290 (13.3)	1390 (14.0)	1418 (14.1)	1165 (12.4)	5263 (13.5)
11–20	1394 (14.4)	1230 (12.4)	1111 (11.0)	597 (6.4)	4332 (11.1)
>20	219 (2.3)	225 (2.3)	142 (1.4)	57 (0.6)	643 (1.6)
Alcohol intake (%)	2064 (21.4)	2027 (20.4)	1827 (18.1)	2021 (21.5)	7939 (20.3)
Exercise (%)	2584 (27.5)	4642 (48.0)	4153 (41.2)	2584 (27.5)	14,946 (38.3)
Occupational exposure (%)	712 (7.4)	476 (4.8)	1256 (12.4)	381 (4.1)	2825 (7.2)
Marital status(%)					
Married	9001 (93.1)	8913 (89.8)	9265 (91.8)	8757 (93.4)	35,936 (92.0)
Single/separated/divorced	632 (6.5)	1008 (10.2)	825 (8.2)	623 (6.6)	3088 (7.9)
Total mortality (%)	177 (1.8)	489 (4.9)	375 (3.7)	312 (3.3)	1353 (3.5)
Lung cancer (%)	18 (0.2)	42 (0.4)	62 (0.6)	18 (0.2)	140 (0.4)

The values are presented as percentages (%) or mean (SD).
Some columns do not add up to 100% because of missing data.
Attrition includes "moved out", "nobody at home" and "refused to participate in the study" or "refused to complete the questionnaire".

4.84%) were current smokers, and 20% (male 38.20%, female 4.60%) were drinkers. A total of 1353 (3.46%) participants died during the 12 years of follow-up (from 1998 to 2009, average length of follow-up: 11.83 years); of these, 140 (0.36%) died from lung cancer. As shown in Table 1, the four study sites were similar with respect to age, sex, smoking and drinking behavior. However, differences were evident for other characteristics (e.g. diet habits). The crude mortality rate (CMR) in the present study was 35 per 10,000 person-years. Lung cancer was responsible for 10.35% of all deaths (CMR = 4 per 10,000 person-years).

3.2. Pollution exposure

We calculated annual average concentrations from the 24-hour average concentrations of PM_{10}, SO_2 and NO_2 of all monitoring stations in each city (Fig. 1). The baseline average pollution levels [mean (SD, range, 25th percentile, 50th percentile, 75th percentile)] were 144.34 μg/m^3 (3.63, 90.64–274.00, 125.50, 146.95, 183.88) for PM_{10}, 40.66 μg/m^3 (1.57, 18.00–78.59, 27.13, 38.18, 53.09) for NO_2, and 66.90 μg/m^3 (3.40, 11.00–224.40, 54.66, 70.64, 89.83) for SO_2. The 1998 to 2009 average pollution of PM_{10} was highly correlated with SO_2 (Correlation coefficient: 0.947, P = 0.000).

3.3. Association of air pollution and mortality

Adjusted HRs (95% CIs) for lung cancer mortality in relation to air pollution (PM_{10}, SO_2 and NO_2 concentrations) are presented in Tables 2 and 3. Two methods were used to assign exposure to study subjects: 1) assigning the 1998 air pollution exposure value for all and 2) time-varying exposures for both deaths and survivors. Additionally, average pollution for the surviving period was also used to assign exposure to subjects in Tables 2 and 3 to compare results with other two pollution-assign methods. There are overlapping CIs, the magnitudes are about the same, and there is the expected lessened precision in the time-varying model. These associations were greatly attenuated and very small after mutual adjustment.

In the fully adjusted single-pollutant models (PM_{10}, SO_2, and NO_2 were modeled independently), each 10 μg/m^3 increase in PM_{10} was associated with a 3.4%–6.0% increase in the risk of lung cancer death (HR per each 10 μg/m^3 = 1.047; 95% CI: 1.034, 1.060) in time-varying exposure model, and with a 4.0%–13.6% increase in the risk of lung cancer death (HR per each 10 μg/m^3 = 1.087; 95% CI: 1.040, 1.136) in 1998-exposure model.

A significant positive association was also observed for SO_2, with a 1.0%–2.5% increase in time-varying exposure model and a 0.8%–6.7% increase in 1998-exposure model. No association was observed between NO_2 and mortality from all-cause disease and lung cancer in the fully adjusted single-pollutant model. The HRs (95% CI) of selected risk factors in the PM_{10} single-pollutant model were shown in Table S1 in the online data supplement.

As the average pollution of PM_{10} was highly correlated with SO_2, the concentrations of PM_{10} and SO_2 were not included simultaneously in the bi-pollutant model. As shown in Table 3, PM_{10} and SO_2 were statistically significant predictors of all-cause mortality and lung cancer in the bi-pollutant models.

3.4. Stratified analysis for PM_{10} and lung cancer mortality

We evaluated the potential modification effects on the independent effect of PM_{10} with stratified analyses. Fig. 2 presents adjusted HRs (95% CIs) for lung cancer mortality in relation to mean PM_{10} concentrations stratified according to the selected characteristics at the baseline (gender, age, and daily cigarette amounts). There were some suggestions of modification effects by age (with <60-year-old at higher risk than ≥60-year-old) and by gender (with men at higher risk than women) for lung cancer mortality.

As reported in Fig. 2, the adjusted HRs were at higher levels in the population that smoked >20 cigarettes/day. Among never-smokers, the adjusted HR of PM_{10} was higher in those exposed to second-hand smoke for lung cancer mortality than that in those not exposed to second hand smoke.

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3.5. Sensitivity analysis

Confounding and clustering by city in the association between exposure and mortality was investigated in the sensitivity analysis, and the effect estimates in the shared frailty model were comparable to those obtained from the standard Cox model.

4. Discussion

Using data from the four cities cohort in northern China, we found an association between increased lung cancer mortality and long-term exposure to urban air pollution. Each 10 μg/m^3 increase in PM_{10} was associated with a significant 3.4%–6.0% increase in the risk of lung cancer death in time-varying exposure model. In addition, the average exposure of the cohort for 12 years (144.34 μg/m^3 for PM_{10}, 40.66 μg/m^3 for NO_2 and 66.90 μg/m^3 for SO_2) was higher than that in other study populations from Europe or North America. The mean concentrations of $PM_{2.5}$ ranged from 9 to 21 μg/m^3 in America during 1999–2009, and from 13.6 to 48.1 μg/m^3 in Europe from 2008 to 2011 (Lepeule et al., 2012; Raaschou-Nielsen et al., 2013). In England in 2002, the mean concentrations of NO_2 and SO_2 were 22.5 and 3.9 μg/m^3, respectively (Carey et al., 2013). The mean concentration of NO_2 from 1988 to 2002 was 12.27 ppb (25.19 μg/m^3) in North America (Jerrett et al., 2013).

The atmosphere contains many compounds with known carcinogenic potential, such as polycyclic aromatic hydrocarbons and heavy metals. In such a complex mixture, it is difficult to ascribe the responsibility of causing lung cancer to a single component. Until a clear pathogenetic mechanism is defined, it would be prudent to consider the pollutants mentioned above as possible substitute markers of sources of air pollution, such as traffic or industrial pollution. PM can induce oxidative stress mediated by a particle-induced inflammation causing macrophages to release reactive oxygen species (ROS), transition metals on the particle surface capable of generating ROS through the Fenton reaction, or quinones in the particles that produce ROS through redox cycling. The variable concentrations of transition metals and organic compounds detected in the collected PM samples might be the active agents leading to a cumulative DNA damage, critical for carcinogenesis. NO_2 has been shown to be a good indicator of traffic-related pollution, and SO_2 can be used to estimate diesel and industrial emissions. It is important to note that large cohort studies on lung cancer and air pollution rely on measures of specific pollutants (Cui et al., 2015; Fajersztajn et al., 2013; Tseng et al., 2012).

Previous cohort studies found associations that were statistically significant or of borderline significance (Beeson et al., 1998; Cao et al., 2011; Cesaroni et al., 2013; Cesaroni et al., 2012; Hales et al., 2012; Heinrich et al., 2013; Katanoda et al., 2011; Pope et al., 2002; Turner et al., 2011). Our study provides additional evidence to the current body of knowledge regarding the PM effects on lung cancer mortality. The present study, with 140 lung cancer cases, estimated an HR of 1.087 (95% CI: 1.040, 1.136) per 10 μg/m^3 of PM_{10} in the single-pollutant model and 1.090 (95% CI: 1.044, 1.138) per 10 μg/m^3 of PM_{10} in the bi-pollutant model with NO_2 using 1998 exposure for all. This finding is slightly lower than the estimate of an extended follow-up of the Harvard Six Cities study in a US cohort (351 cases) of 1.37 HR (95% CI: 1.07, 1.75) per 10 μg/m^3, and the original and extended study of ACS CPS-II cohort (with a 15–27% increase in lung cancer mortality per 10 μg/m^3 $PM_{2.5}$) (Lepeule et al., 2012; Turner et al., 2011). The result was also higher than the meta-analysis of 17 cohorts in nine European countries from the European Study of Cohorts for Air Pollution Effects (ESCAPE) (HR = 1.22 (95% CI: 1.03, 1.45) for PM_{10}, HR = 1.18 (95% CI: 0.96, 1.46) for $PM_{2.5}$, and HR = 1.09 (95% CI: 0.88, 1.33) for PMcoarse), from studies in Japan (HR = 1.24, 95% CI: 1.12, 1.37 with a 10-unit increase in $PM_{2.5}$) and China (Cao et al., 2011; Katanoda et al., 2011; Raaschou-Nielsen et al., 2013). The HRs for lung cancer were lower in the present cohort, indicating that the dose-response curves were not linear, especially at higher concentrations than existing European Union and American air quality values for PM.

The associations of lung cancer mortality with NO_2 and SO_2 were also estimated in this cohort. In the single-pollutant models, the effects of PM_{10} and SO_2 exposure on lung cancer mortality were both statistically significant. In the bi-pollutant models, the effects of PM_{10} and SO_2 were also significant on lung cancer mortality with the combined effect of NO_2, with HRs of 1.051 (95% CI: 1.032, 1.069) for PM_{10} and 1.013 (95% CI: 1.006, 1.021) for SO_2. Results from recent studies conducted in Rome and the Netherlands observed that the spatial distribution of air pollution is stable across the 10-year study periods (Cesaroni et al., 2012; Rosenlund et al., 2008). Since the latency period for lung cancer can be several decades and long-term exposure to air pollution is important in the development of lung cancer, high exposure levels of heating-related SO_2 in the early years of the study period are especially important (Gulliver et al., 2011; Nicolich and Gamble, 2001). Our results reveal associations between air pollution and lung cancer in participants who did not move during the follow-up. Although the increasing number of vehicles has led to a rise in emissions of air pollutants, the effects of PM_{10}, NO_2 and SO_2 in the present study suggest that China's substantial coal-dependent energy consumption still played an important role in health problems, since heating-related SO_2, rather than traffic-related NO_2, was consistently the stronger risk indicator.

Identifying population subgroups susceptible to air pollution is an additional focus of this study. Some research has suggested that socioeconomic status, sex, and health characteristics, which are usually treated as confounders, could modify the association. In the present analysis, we identified the characteristics of participants who are most susceptible to the effects of air pollution by stratifying analyses (Cesaroni et al., 2013; Puett et al., 2009; Puett et al., 2008). Because active smoking and tobacco smoke are well-known risk factors for lung cancer, we also evaluated effect modification by daily amount of cigarette smoking and passive smoking. Among never-smokers, the adjusted relative risk (RR) for lung cancer mortality due to PM_{10} was higher in individuals exposed to second-hand smoke than in those who did not. Also, cigarette quantity caused risk ratios to fluctuate indicating that the quantity of cigarettes is

Table 2
Adjusted[a] HR (95%CI) for lung cancer mortality in relation to each 10 μg/m^3 increase in air pollution according to selected risk factors, multiplicative scale, follow-up 1998–2009, China (single-pollutant models).

Methods	Cause of death	No. of death	PM_{10} (10 μg/m^3)		SO_2(10 μg/m^3)		NO_2(10 μg/m^3)	
			HR	95% CI	HR	95% CI	HR	95% CI
TVE	All-cause	1353	1.010	1.008, 1.012	0.997	0.995, 0.999	0.977	0.972, 0.982
	Lung cancer	140	1.047	1.034, 1.060	1.018	1.010, 1.025	0.969	0.953, 0.984
1998 E	All-cause	1353	1.013	0.999, 1.027	0.971	0.961, 0.981	0.925	0.899, 0.952
	Lung cancer	140	1.087	1.040, 1.136	1.037	1.008, 1.067	0.898	0.821, 0.982
APSP	All-cause	1353	1.233	1.208, 1.260	1.028	1.009, 1.047	0.889	0.857, 0.922
	Lung cancer	140	1.653	1.527, 1.791	1.224	1.164, 1.286	0. 837	0.746, 0.938

TVE, time-varying exposures for both deaths and controls; 1998E, assigning the 1998 air pollution exposure value for all; APSP, average pollution for the surviving period was used to assign exposure to subjects. CI, confidence interval. HR, hazard ratio. PM10, particulate matter <10 μm in diameter; NO2, nitrogen dioxide; SO2, sulfur dioxide.

[a] Adjusted for age at baseline, gender, BMI, education, marital status, smoking status, passive smoking, household income, alcohol consumption, occupation, diet, and leisure exercise.

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Table 3
Adjusted[a] HR (95%CI) for lung cancer mortality in relation to each 10 μg/m^3 increase in air pollution according to selected risk factors, multiplicative scale, follow-up 1998–2009, China (bi-pollutant models).

Methods	Cause of death	No. of death	Bi-pollutant model 1				Bi-pollutant model 2			
			PM_{10} (10 μg/m^3)		NO_2(10 μg/m^3)		SO_2(10 μg/m^3)		NO_2(10 μg/m^3)	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
TVE	All-cause	1353	1.007	1.005, 1.009	0.980	0.976, 0.985	0.997	0.994, 0.999	0.976	0.971, 0.981
	Lung cancer	140	1.051	1.032, 1.069	1.007	0.985, 1.028	1.013	1.006, 1.021	0.977	0.961, 0.992
1998 E	All-cause	1353	1.017	1.003, 1.031	0.922	0.896, 0.948	0.975	0.965, 0.985	0.933	0.907, 0.960
	Lung cancer	140	1.090	1.044, 1.138	0.888	0.812, 0.972	1.033	1.005, 1.061	0.902	0.823, 0.989
APSP	All-cause	1353	1.234	1.205, 1.264	1.003	0.963, 1.044	1.021	1.003, 1.038	0.893	0.861, 0.926
	Lung cancer	140	1.813	1.657, 1.984	1.304	1.148, 1.481	1.210	1.145, 1.278	0.947	0.842, 1.067

TVE, time-varying exposures for both deaths and controls; 1998E, assigning the 1998 air pollution exposure value for all; APSP, average pollution for the surviving period was used to assign exposure to subjects. CI, confidence interval. HR, hazard ratio. PM10, particulate matter < 10 μm in diameter; NO2, nitrogen dioxide; SO2, sulfur dioxide. Bi-pollutant model 1 and 2: because the average pollution of PM10 was highly correlated with SO2, the bi-pollutant models were used as PM10-and-NO2 model (bi-pollutant model 1), SO2-and-NO2 model (bi-pollutant model 2), in turn.

[a] Adjusted for age at baseline, gender, BMI, education, marital status, smoking status, passive smoking, household income, alcohol consumption, occupation, diet, and leisure exercise.

a modifying influence of the relationship between exposure to PM_{10} and lung cancer mortality (Beelen et al., 2008; Gallus et al., 2008; Pope et al., 2011).

Our study has several limitations. First, individual-level exposures were estimated from participants' residence and nearest monitor data, which assumed that PM_{10} levels were relatively uniform in the surrounding areas. This limitation warrants the need for a more detailed exposure assessment (the land-use regression model) and the consideration of sources of exposure assessment (e.g. influence of indoor sources of air pollution). Second, owing to the nature of this retrospective cohort study, recall bias may be introduced for certain covariates, such as diet habits and physical activities. Additionally, data for histological subtypes of lung cancer was not obtained, which is a potential limitation of the study because the associations of air pollution and lung cancer were stronger for adenocarcinomas of the lung in some studies. For this reason the ICD-10 was used for classification instead of International Classification of Diseases for Oncology, 3rd edition [ICDO3].

5. Conclusion

The association between lung cancer mortality and PM_{10} was pronounced in this extended follow-up study. Long-term exposure to SO_2 was also associated with increased risk of lung cancer mortality in single-pollution models. The combined effect of NO_2 and PM_{10} resulted in a significant increase in mortality risk for lung cancer. Significant differences exist in the risk estimates for participants based on assignment method for air pollution exposure. The present study results add to the limited literature of the long-term effects of high levels of air pollution on lung cancer in developing countries.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.07.064.

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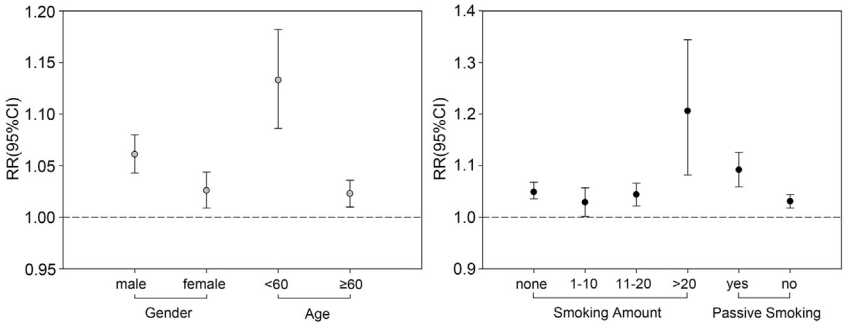

Fig. 2. Adjusted hazard ratio (95% CIs) for lung cancer mortality per 10 μg/m^3 elevation in PM_{10} concentrations, stratified by population characteristics of gender, age, quantity of cigarettes, and passive smoking in never smokers. The passive smoking population (Yes + No) was equal to the nonsmoking population.

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