Journal of Hazardous Materials 186 (2011) 1594–1600

Contents lists available at ScienceDirect

Journal of Hazardous Materials

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

Association between long-term exposure to outdoor air pollution and mortality in China: A cohort study

Jie Cao[a,1], Chunxue Yang[b,c,1], Jianxin Li[a], Renjie Chen[b,c], Bingheng Chen[b], Dongfeng Gu[a,**], Haidong Kan[b,c,*]

[a] Cardiovascular Institute and Fu Wai Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College, and Chinese National Center for Cardiovascular Disease Control and Research, Beijing, China
[b] School of Public Health, Key Lab of Public Health Safety of the Ministry of Education, Fudan University, Shanghai, China
[c] Institute of Global Environmental Change Research, Fudan University, Shanghai, China

ARTICLE INFO

Article history:
Received 1 July 2010
Received in revised form
30 November 2010
Accepted 9 December 2010
Available online 15 December 2010

Keywords:
Air pollution
Cohort study
Lung cancer
Mortality

ABSTRACT

No prior cohort studies exist in China examining the association of outdoor air pollution with mortality. We studied 70,947 middle-aged men and women in the China National Hypertension Survey and its follow-up study. Baseline data were obtained in 1991 using a standard protocol. The follow-up evaluation was conducted in 1999 and 2000. Annual average air pollution exposure between 1991 and 2000, including total suspended particle (TSP), sulfur dioxide (SO_2) and nitrogen oxides (NO_x), were estimated by linking fixed-site monitoring data with resident zip code. We examined the association of air pollution with mortality using proportional hazards regression model. We found significant associations between air pollution levels and mortality from cardiopulmonary diseases and from lung cancer. Each 10 $\mu g/m^3$ elevation of TSP, SO_2 and NO_x was associated with a 0.9% (95%CI: 0.3%, 1.5%), 3.2% (95%CI: 2.3%, 4.0%), and 2.3% (95%CI: 0.6%, 4.1%) increased risk of cardiovascular mortality, respectively. We found significant effects of SO_2 on mortality after adjustment for TSP. Conclusively, ambient air pollution was associated with increased cardiopulmonary and lung cancer mortality in China. These data contribute to the scientific literature on long-term effects of air pollution for high exposure settings typical in developing countries.

1. Introduction

Outdoor air pollution has been found to be associated with a wide range of effects on human health, including increased mortality, increased rates of hospital admissions and emergency department visits, exacerbation of chronic respiratory conditions (e.g., asthma), and decreased lung function [1]. In contrast to daily time-series studies of acute exposure to air pollution, cohort studies provide information about the degree of life shortening, pollution effects on long-term mortality or morbidity, and role of pollution in inducing or accelerating the progress of chronic disease [2]. Several prospective cohort studies in North America and Europe have evaluated the effects of long-term exposure to outdoor air pollution [3–10], but there exist no prospective evidence in developing countries. There remains a need for cohort-based mortality studies in developing countries, where characteristics of outdoor air pollution (e.g., air pollution level and mixture, transport of pollutants), and socio-demographic status of local residents (e.g., disease pattern, age structure, and socioeconomic characteristics), may be different from developed countries.

As the largest developing country in the world, China has achieved rapid development in the recent two decades. However, levels of outdoor air pollution in China are among the highest in the world [11]. The relationship between outdoor air pollution and daily mortality/morbidity has been examined in several large Chinese cities, including Beijing [12], Chongqing [13], Shanghai [14], Wuhan [15], and Shenyang [16]. These studies basically followed the commonly used time-series and case-crossover approaches, and their results were in accordance with those reported from developed countries. Recent multi-city analyses in the Public Health and Air Pollution in Asia (PAPA) program provide further evidence supporting coherence and plausibility of the acute effect of ambient pollutants on cardiopulmonary health in China [17]. Compared with short-term effect studies of outdoor air pollution, there are even fewer studies in China examining the long-term effects of

* Corresponding author at: School of Public Health, Key Lab of Public Health Safety of the Ministry of Education, Fudan University, Box 249, 130 Dong-An Road, Shanghai 200032, China.
** Corresponding author at: Division of Population Genetics and Prevention, Cardiovascular Institute and Fu Wai Hospital, 167 Beilishi Rd., Beijing 100037, China.
E-mail addresses: haidongkan@gmail.com (H. Kan), gudongfeng@vip.sina.com (D. Gu).
[1] These authors contributed equally to this work.

0304-3894/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jhazmat.2010.12.036

air pollution. Some limited cross-sectional data exist from which we can draw some preliminary conclusions about long-term air pollution-related health effects in China [18,19]. However, the estimates of these cross-sectional analyses are difficult to interpret, due to the lack of information on potential confounders (such as sex, smoking, obesity, and socioeconomic status). The ecological nature also limited the power for causal inference. Prospective data are necessary to directly address the hypothesis that long-term air pollution exposure influences the development of mortality in Chinese residents.

In this study, we examined the association between long-term exposure to outdoor air pollution and mortality in a nationally representative cohort in China.

2. Methods

2.1. Participants

Our analysis is based on data collected by the China National Hypertension Follow-up Survey, a prospective study of 158,666 adults [20–22]. Briefly, in 1991, a multistage, random cluster-sampling design was used to identify a representative sample of the general Chinese population 15 years of age and older from all 30 provinces for the China National Hypertension Survey. In 1999, investigators from each province were invited to participate in the China National Hypertension Survey Epidemiology Follow-up Study. Of the 30 provinces included in the initial study, 13 were not included in the follow-up study because contact information for the study participants in those provinces was not available. However, sampling was conducted independently within each province for the 1991 China National Hypertension Survey, and study participants in the 17 provinces that were included in the follow-up study were evenly distributed among the different geographic regions of the entire country representing various stages of economic development. Overall, 83,533 men and 86,338 women who were 40 years of age or older at the time of their baseline examinations were eligible for participation in the follow-up study.

There were no adequate ambient monitoring stations in the rural areas of China; hence we limited our analysis to participants living in the urban area only. This left 70,947 subjects (44.7%) residing in 31 cities of 16 provinces (Fig. 1).

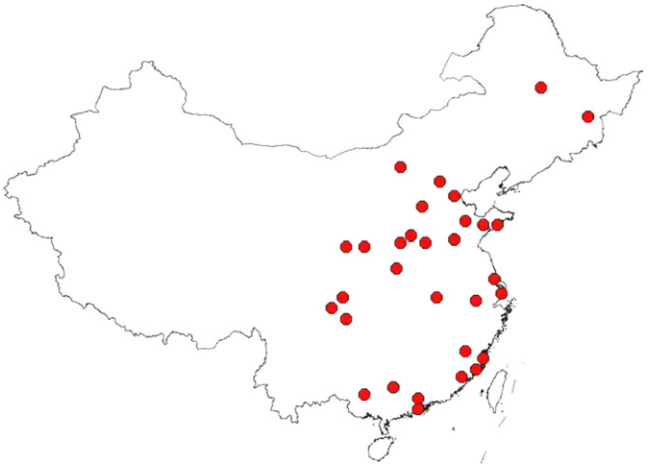

Fig. 1. Locations of selected cities in the China National Hypertension Follow-up Survey.

2.2. Baseline examination

Baseline data were collected during a single clinic visit by physicians and nurses trained in the use of standard methods and with stringent quality control [20–22]. Data on demographic characteristics, medical history, and lifestyle-related risk factors were obtained. Work-related physical activity was assessed. Data were collected on the amount and type of alcohol consumed during the previous year. Smoking variables included smoking status (never, former and current smokers), age at starting to smoke, years smoked, and cigarettes per day.

Three blood-pressure readings, measured with the use of a mercury sphygmomanometer according to a standard protocol, were obtained after the participant had been sitting quietly for five minutes. The first and fifth Korotkoff sounds were recorded as systolic and diastolic blood pressure, respectively. Hypertension was defined as one or more of the following: a mean systolic blood pressure greater than or equal to 140 mm Hg, a mean diastolic blood pressure greater than or equal to 90 mm Hg, or the use of antihypertensive medication. Body weight and height were measured when the participant was wearing light indoor clothing but not shoes, with the use of a standard protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters.

2.3. Follow-up data collection

Follow-up examinations, which were conducted between 1999 and 2000, included tracking participants or their proxies to a current address; conducting in-depth interviews to obtain information on the history of disease, hospitalizations, and death; and obtaining hospital records and death certificates [20–22]. All deaths identified in interviews with participants' proxies were verified by death certificates obtained from the local departments of public health or police. If death occurred while a participant was hospitalized, the participant's hospital records, including medical history, findings on physical examination, laboratory findings, autopsy findings, and discharge diagnosis, were abstracted by trained staff using a standard form. In addition, photocopies of selected sections of the participant's inpatient record, discharge summary, electrocardiogram, and pathology reports were obtained. An end-point assessment committee in each province reviewed and confirmed (or rejected) the hospital's discharge diagnosis and the cause of death on the basis of the abstracted information, using prespecified criteria. A study-wide end-point assessment committee at the Chinese Academy of Medical Sciences in Beijing reviewed all death records and determined the final underlying cause of death. Two committee members independently of each other verified the cause of death, and discrepancies were adjudicated by discussion involving other members of the committee. All members of the local and study-wide end-point assessment committees were unaware of information about the baseline risk factors of the study participants. The causes of death were coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9).

2.4. Air pollution exposure

Each participant was assigned a metropolitan area of residence based on address at time of baseline examination and 6-digit ZIP area code. Annual average air pollution exposure between 1991 and 2000 were estimated by linking fixed-site monitoring data with resident zip code. Between 1991 and 2000, total suspended particle (TSP), sulfur dioxide (SO_2) and nitrogen oxides (NO_x) were regularly monitored air pollutants in China. There existed no data on PM_{10}, $PM_{2.5}$, NO_2, or ozone (O_3) during the period.

The air monitoring data at each city were collected from the China National Environmental Monitoring Center (CNEMC).

CNEMC is part of the State Environmental Protection Ministry, China, and has authority over the entire environmental monitoring network at all levels – provincial, city – throughout China. According to relevant rules of Chinese government, the location of the monitoring stations should not be in the direct vicinity of traffic or of industrial sources. Moreover, the locations should not be influenced by local pollution sources and should also avoid buildings, or housing large emitters such as coal-, waste-, or oil-burning boilers, furnaces, and incinerators [23]. Thus the monitoring results of CNEMC reflect the general background urban air pollution level in Chinese cities rather than local sources such as traffic or industrial combustion. Totally, there were 103 monitoring stations in the 31 cities. The ZIP centers of all participants were within 15 km distance of a monitoring station.

The measurement methods used for air quality assessment comply with those recommended in China National Ambient Air Quality Standard [23]. Specifically, the methods based on gravimetric sampler, ultraviolet fluorescence and chemiluminescence were used for the measurement of TSP, SO_2, and NO_x, respectively. For the calculation of annual average concentrations of TSP, at least 60 daily values must be available on that particular year. At least 144 daily concentrations of SO_2 and NO_x must be available to calculate their annual average concentrations. The quality assurance (QA) and quality control (QC) procedures are implemented at CNEMC according to relevant Chinese rules and regulations. At each monitoring station, the monitoring program is supervised by an internal QA/QC team.

2.5. Statistical analysis

Statistical analyses were conducted using the statistical software package SAS, version 9.1 (SAS Institute Inc, Cary, NC). Follow-up time was calculated as the time from baseline to death, or the last follow-up contact, or through December 1999, whichever occurred first. Consistent with previous studies of air pollution in relation to mortality in which exposure was assessed at the beginning of follow-up [3–10], the air pollution exposure at the first 3-yr (1991–1993) was the primary exposure measure in our analysis.

The association of air pollution with mortality was examined using proportional hazards regression models, with adjustment for a wide range of individual risk factors. Both total and cause-specific mortality were assessed. Our basic models included age and sex only. In the adjusted models, we added factors that we identified a priori as potential confounders, including BMI, physical activity (low, moderate, and high), education (illiterate, elementary school, middle school, high school, and college or above), occupation (unemployed participants, farmer, worker or service staff, retiree, clerk, professional, and manager), smoking status (current, former, and never smoker), age at starting to smoke, years smoked, cigarettes per day, alcohol intake (never, former and current drinker), and hypertension (yes/no). BMI was treated as quintiles given its potential non-linear relationship with mortality [20]. We fitted both single-pollutant and multi-pollutant models to assess the stability of pollutants' effects.

We also conducted stratified analyses by sex, smoking status, obesity, and education to examine potential modifiers of the association between air pollution and mortality. We categorized BMI in two categories according to the standard definition [24]: normal/under weight (BMI less than 25) and overweight/obese (BMI equal to 25 or greater). We classified education into low (below high school) and middle (high school or above). To examine the potential non-linearity of the relationship between air pollution and mortality risk, we did a sensitivity analysis to estimate the relative risk (RR) of mortality for the highest relative to the lowest quartile of air pollutants concentrations.

Table 1
Baseline characteristics of participants in the China National Hypertension Follow-up Survey.[a]

	Total (n = 70,947)	Death (n = 8319)	Non-death (n = 62,628)
Age (yr)	55.8 (10.5)	67.1 (10.6)	54.3 (9.6)
BMI (kg/m^2)	23.6 (3.7)	23.0 (4.3)	23.7 (3.6)
Sex (%)			
Male	51.5	56.5	50.9
Female	48.5	43.5	49.1
Physical activity (%)			
Low	53.2	63.5	52.0
Medial	26.2	27.7	25.9
High	20.6	8.8	22.1
Smoking status (%)			
Never	63.1	58.2	63.7
Past	2.7	4.8	2.5
Current	34.2	37.1	33.9
Alcohol intake (%)	19.3	18.7	19.4
Hypertension (%)	18.8	32.2	17.1
Education level[b] (%)			
Low	62.0	76.4	60.2
High	38.0	23.6	39.8

[a] All values are mean (SD) unless specified as percentage.
[b] Low: (illiterate, elemental school or junior school); high: high school or college.

3. Results

Table 1 presents selected characteristics of participants at baseline, according to whether or not they died during follow-up. A total of 8319 subjects died during the follow up, among which 3013 died from cardiovascular disease, 921 from respiratory disease and 624 from lung cancer. As expected, the deceased subjects were older, more likely to be male or current smokers, and had less physical activity, and higher prevalence of hypertension.

During 1991–2000, the averaged concentrations of TSP, and SO_2 and NO_x in the 31 Chinese cities were 289, 73 and 50 $\mu g/m^3$, respectively (Table 2). From 1991 to 2000, the annual concentrations declined 5% for TSP and 35% for SO_2, but increased 28% for NO_x, suggesting that air pollution pattern in Chinese cities had gradually changed from the conventional coal combustion type to the mixed coal combustion/motor vehicle emission type in the 1990s. The correlation coefficients between the 1991 and 2000 concentrations were 0.83 for TSP, 0.81 for SO_2, and 0.87 for NO_x, suggesting that air pollution changes occurred generally uniformly across the 31 cities see (Fig. 2).

In both basic and adjusted models, air pollution was found to be associated with increased risk of cardiopulmonary mortality and lung cancer mortality (Table 3). In the adjusted model, an increase of 10 $\mu g/m^3$ of TSP, SO_2, and NO_x corresponded to 0.3% (95%CI: −0.1%, 0.6%), 1.8% (95%CI: 1.3%, 2.3%), and 1.5% (95%CI: 0.4%, 2.5%) increase of total mortality; .0.9% (95%CI: 0.3%, 1.5%), 3.2% (95%CI: 2.3%, 4.0%), and 2.3% (95%CI: 0.6%, 4.1%) increase of cardiovascular mortality; 0.3% (95%CI: −0.6%, 1.3%), 3.2% (95%CI: 1.8%, 4.7%) and 2.6% (95%CI: −0.2%, 5.6%) respiratory mortality; and 1.1% (95%CI: −0.1%, 2.3%), 4.2% (95%CI: 2.3%, 6.2%), and 2.7% (95%CI: −0.9%, 6.5%) increase of lung cancer mortality. We did not find significant association of any pollutant with other causes of cancer, a control cause of death in our analysis.

Table 4 compares the results of the single-pollutant and multiple-pollutant models. The association of TSP with cardiovascular mortality was almost not affected after adjustment for SO_2 or NO_x. The associations of SO_2 with total, cardiovascular, respiratory and lung cancer mortality did not change much after adding TSP or NO_x into the models. The associations of NO_x with total and cardiovascular mortality decreased after adjustment for SO_2 or TSP.

Since cardiovascular mortality showed the strongest association with air pollution, we further examined whether sex,

Table 2
Air pollution levels in the CNHS cities in 1991–2000 (μg/m³).

	TSP	SO_2	NO_x
Baoji	433	41	46
Beijing	356	112	120
Chendu	300	65	61
Daqing	143	11	27
Fuzhou	180	43	36
Guangzhou	255	60	122
Huhehaote	429	68	39
Huzhou	261	68	42
Jiaozuo	499	53	51
Jinin	378	130	56
Kaifeng	375	40	44
Luoyang	388	128	51
Luzhou	194	62	32
Mianyang	286	128	41
Mudanjiang	414	62	43
Nannin	184	53	19
Nantong	221	41	30
Qingdao	196	174	57
Quanzhou	188	15	25
Sanming	292	33	37
Shanghai	256	70	84
Shijizhuang	337	134	55
Shiyan	256	11	43
Tianjin	318	110	55
Weifang	265	136	47
Wuhan	238	40	70
Wuzhou	174	119	34
Xi'an	410	63	51
Zhangzhou	201	28	22
Zhuhai	113	18	60
Zibo	418	154	43
Average	289	73	50

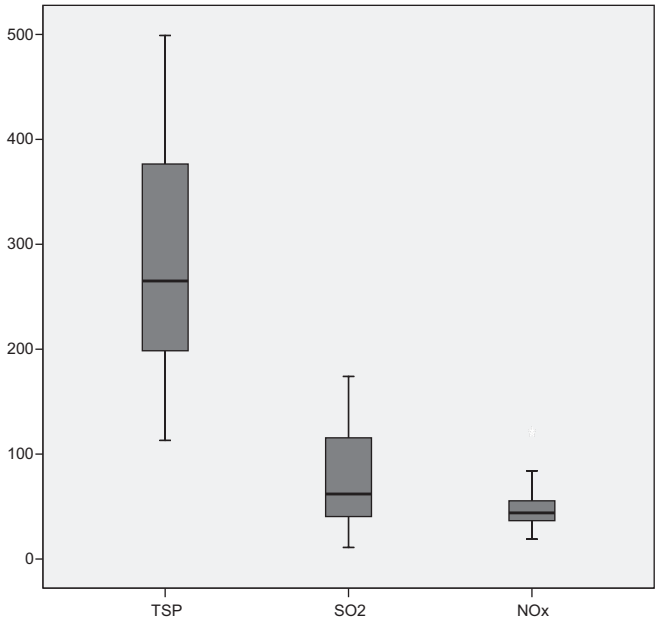

Fig. 2. Air pollution levels (in μg/m³) in 31 Chinese cities (1991–1999).

smoking status, obesity and education modified the association between air pollution and cardiovascular mortality (Table 5). Although results did not always achieve statistical significance with the reduced sample sizes in sub-group analyses, there were positive associations in most strata and little evidence of effect modification. The sensitivity analysis using quartiles of air pollutants concentrations showed that exposure–response relationships between TSP/NO_x and cardiovascular mortality tended to become flat at high concentrations, while SO_2 had an almost monotonic relationship with cardiovascular mortality (Fig. 3).

4. Discussion

Among adults from 31 Chinese cities followed prospectively, higher residential exposure to ambient air pollution was associated with an increased risk of cardiopulmonary and lung cancer mortality. To our knowledge, this study generates the first prospective evidence of the association between long-term exposure to air pollution and mortality in China or even developing countries. Our findings may have implications for environmental and social policies in China, and for the Chinese government to take steps to protect human health.

China is one of the few countries with the worst air pollution levels in the world. In setting air pollution control policy from a public health viewpoint, it is important to identify the health effects of air pollutants from local data. Since there existed no prospective evidence in China before, foreign data, most from developed countries, may be helpful for China's policy makers, but they may not be applicable due to different levels of air pollution, local population sensitivity, age distribution and especially different air pollutant components. Although dozens of prospective cohort studies in North America and Europe have evaluated the effects of long-term exposure to outdoor air pollution on cardiopulmonary mortality [25,26], it is unknown whether the findings from low air pollution exposure settings in developed countries apply to China. Our prospective evidence supports previous findings from cross-sectional studies examining the association between long-term air pollution exposure and cardiopulmonary mortality in China. For example, Wang et al. examined the chronic effects of air pollution on mortality in Shenyang using ecologically cross-sectional analysis, and observed significant differences in total and cardiopulmonary mortality among the high-, medium-, and relatively low-pollution areas [18]. Also, Zhang and colleagues used ecological analysis to assess the relationship between long-term exposure to SO_4^{2-}, an indication of air pollution, and mortality in Beijing, and found significant correlations between SO_4^{2-} concentration and cardiopulmonary mortality [19].

Table 3
Percent increase (and 95%CIs) of mortality associated with 10μg/m³ increase in air pollutants' concentrations.

Cause of mortality	TSP		SO_2		NO_x	
	Basic model[a]	Adjusted model[b]	Basic model[a]	Adjusted model[b]	Basic model[a]	Adjusted model[b]
All-cause	0.2 (−0.1, 0.5)	0.3 (−0.1, 0.6)	1.8 (1.4, 2.2)*	1.8 (1.3, 2.3)*	1.2 (0.2, 2.2)*	1.5 (0.4, 2.5)*
Cardiovascular	1.3 (0.7, 0.8)*	0.9 (0.3, 1.5)*	4.8 (4.0, 5.6)*	3.2 (2.3, 4.0)*	2.7 (1.0, 4.3)*	2.3 (0.6, 4.1)*
Respiratory	−0.1 (−1.1, 0.9)	0.3 (−0.6, 1.3)	1.5 (0.3, 2.8)*	3.2 (1.8, 4.7)*	1.7 (−1.3, 4.8)	2.6 (−0.2, 5.6)
Lung cancer	0.6 (−0.6, 1.7)	1.1 (−0.1, 2.3)	4.0 (2.4, 5.6)*	4.2 (2.3, 6.2)*	1.6 (−2.0, 5.3)	2.7 (−0.9, 6.5)

[a] Covariates included age and sex.
[b] Covariates included age, sex, BMI, physical activity, education, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension.
* $p < 0.05$.

Table 4
Percent increase (and 95%CIs) of mortality associated with 10 μg/m^3 increase in air pollutants' concentrations under single and multiple pollutant models [a]

	Model	Total mortality	Cardiovascular mortality	Respiratory mortality	Lung cancer mortality
TSP	Single-pollutant	0.3 (−0.1, 0.6)	0.9 (0.3, 1.5)	0.3 (−0.6, 1.3)	1.1 (−0.1, 2.3)
	Adjusted for SO_2	0.1 (−0.3, 0.4)	0.9 (0.2, 1.5)*	0.6 (−0.5, 1.6)	1.0 (−0.4, 2.4)
	Adjusted for NO_x	0.0 (−0.3, 0.4)	0.9 (0.2, 1.5)*	0.5 (−0.6, 1.6)	1.0 (−0.4, 2.4)
SO_2	Single-pollutant	1.8 (1.3, 2.3)	3.2 (2.3, 4.0)	3.2 (1.8, 4.7)	4.2 (2.3, 6.2)
	Adjusted for TSP	1.8 (1.3, 2.3)*	3.1 (2.2, 4.0)*	3.2 (1.7, 4.7)*	4.1 (2.1, 6.1)*
	Adjusted for NO_x	1.8 (1.3, 2.3)*	3.1 (2.2, 4.0)*	3.1 (1.6, 4.6)*	4.1 (2.1, 6.1)*
NO_x	Single-pollutant	1.5 (0.4, 2.5)	2.3 (0.6, 4.1)	2.6 (−0.2, 5.6)	2.7 (−0.9, 6.5)
	Adjusted for TSP	1.4 (0.3, 2.5)*	1.5 (−0.4, 3.3)	2.1 (−1.0, 5.3)	1.7 (−2.1, 5.7)
	Adjusted for SO_2	0.7 (−0.4, 1.8)	1.2 (−0.6, 3.0)	1.5 (−1.5, 4.6)	1.3 (−2.6, 5.3)

[a] Covariates included age, sex, BMI, physical activity, education, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension.
* $p < 0.05$.

Table 5
Percent increase (and 95%CIs) of cardiovascular mortality associated with 10 μg/m^3 increase in air pollutants' concentrations, stratified by sex, smoking status, BMI, and education.[a]

		TSP			SO_2			NO_x		
		Effect size	*p*	*p* for interaction	Effect size	*p*	*p* for interaction	Effect size	*p*	*p* for interaction
Sex	Male	1.2 (0.5, 2.0)	0.001	0.173	3.9 (2.7, 5.1)	<0.001	0.125	1.7 (−0.6, 4.0)	0.143	0.569
	Female	0.6 (−0.3, 1.5)	0.191		2.7 (1.4, 4.1)	<0.001		3.1 (0.6, 5.8)	0.017	
Smoking	Never	0.9 (0.2, 1.6)	0.017	0.853	3.5 (2.5, 4.6)	<0.001	0.411	3.1 (0.9, 5.4)	0.007	0.469
	Current or past	0.1 (0.0, 1.9)	0.040		2.2 (0.8, 3.7)	0.002		1.3 (−1.3, 4.0)	0.335	
Obesity	BMI <25	0.9 (0.2, 1.5)	0.012	0.621	2.6 (1.6, 3.6)	<0.001	0.056	1.9 (−0.2, 4.0)	0.070	0.377
	BMI ≥25	1.0 (−0.1, 2.0)	0.067		4.5 (2.8, 6.2)	<0.001		3.3 (0.1, 6.5)	0.040	
Education	Low	0.9 (0.3, 1.5)	0.005	0.870	2.9 (1.9, 3.8)	<0.001	0.074	3.4 (1.5, 5.3)	0.001	0.065
	High	1.0 (−0.4, 2.4)	0.158		4.1 (2.1, 6.1)	<0.001		−1.4 (−5.4, 2.7)	0.494	

[a] Covariates included age, sex, BMI, physical activity, education, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension.

In our study, an increase of 10 μg/m^3 of TSP, SO_2, and NO_x corresponded to 0.3% (95%CI: −0.1%, 0.6%), 1.8% (95%CI: 1.3%, 2.3%), and 1.5% (95%CI: 0.4%, 2.5%) increase of total mortality. Compared with air pollution long-term effects studies in developed countries (Table 6), our analysis reported relatively lower effect estimates per unit increase of pollutant concentrations. This strengthened the assumption that lower exposure–response functions may exist in Chinese air pollution studies compared with those conducted in North American and Europe. This may be explained by the different characteristics of the study contexts, such as local air pollution level, population sensitivity to air pollution, age structure, especially components and toxicity of pollution mixture. Compared with developed countries, the air pollution level in China is much higher. At higher concentrations, the risk of death per unit increase of pollutant concentrations often tended to be reduced, possibly because vulnerable subjects may have died before the concentration had reached the maximum level. Also, the exposure–response curve of air pollution often tends to become flat at higher concentrations. In addition, the composition of the motor vehicle fleet in Europe and North America may differ from that in China. This, together with other differences as the widespread use of coal in China, implies that the air pollution mixture may differ between China and the areas where most air pollution health studies were conducted.

We used air pollution exposure at the first 3 years (1991–1999). We found similar associations of air pollution with mortality when we used the first-year (1991) exposure data or averaged exposure data throughout the follow-up period (1991–2000). Although air pollution levels may vary over time due to changes in emission or economic activity, substantial changes are usually slow and affect the region in the same way.

Although the strongest evidence between outdoor air pollutants and adverse health effects is for thoracic and fine particles [26], many researchers have reported associations for gaseous

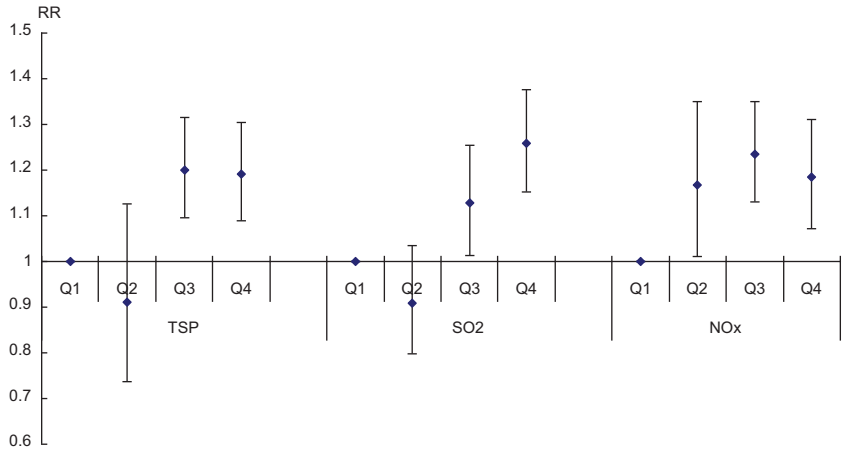

Fig. 3. Adjusted relative risk (RR) of cardiovascular mortality associated with increased quartiles (Q) of air pollutants concentrations.

Table 6
Percent increase (mean and 95%CI) of mortality associated with 10 μg/m³ increment of air pollutants concentrations in our study and studies in developed countries.

	Study site	Total mortality	Cardiovascular mortality	Respiratory mortality	Lung cancer mortality
TSP	Our study	0.3 (−0.1, 0.6)	0.9 (0.3, 1.5)	0.3 (−0.6, 1.3)	1.1 (−0.1, 2.3)
	French PAARC Survey [36]	5 (2, 8)	6 (1, 12)[a]	0 (−8, 10)	
$PM_{2.5}$	Our study[b]	0.9 (−0.3, 1.8)	2.8 (0.9, 4.6)	0.9 (−1.8, 4.0)	3.4 (−0.3, 7.1)
	ACS [10]	4 (1, 8)	6 (2, 10)[a]	8 (1, 16)	
	Harvard six cities [5]	13 (4, 23)	18 (6, 32)[a]	18 (−11, 57)	
	Women's health initiative [9]	–	76 (25, 147)	–	–
	Netherlands [6]	17 (−24, 78)	34 (−32, 164)[a]	–	
SO_2	Our study	1.8 (1.3, 2.3)	3.2 (2.3, 4.0)	3.2 (1.8, 4.7)	4.2 (2.3, 6.2)
	Hong Kong intervention study [27]	1.1 (0.5, 1.7)	1.0 (0.2, 1.9)	2.0 (0.8, 3.2)	0.6 (−0.4, 1.5)
NO_x	Our study	1.5 (0.4, 2.5)	2.3 (0.6, 4.1)	2.6 (−0.2, 5.6)	2.7 (−0.9, 6.5)
	Norwegian men cohort [37]	8 (6, 11)	8 (3, 12)	16 (6, 26)	11 (3, 19)

[a] Only cardiorespiratory mortality was reported.
[b] Conversion as $PM_{10}/TSP \approx 0.5$ and $PM_{2.5}/PM_{10} \approx 0.65$.

pollutants [25]. In our study, we found health effects of SO_2 independent of TSP (Table 4), suggesting that factors other than particle indicators are important for the air pollution mixture in China. Although it is well-known that SO_2 contribute to particle formation, the current analysis suggests that SO_2 is also a separately regulated pollutant independently related with adverse health effects, and the Chinese government should maintain "controlling/reducing total SO_2 emissions" as an index for reflecting the efficacy of air pollution control strategy. Previously, the independent health effect of SO_2 was extensively reported in China. For example, Xu and co-workers found that it was SO_2, not TSP, that was associated with daily mortality in Beijing [12]. Similarly, in Chongqing, Venners et al. found that SO_2 had significant effects on daily mortality even after adjustment for $PM_{2.5}$, while the effect of $PM_{2.5}$ diminished after adjustment for SO_2 [13]. Zhang et al. found that concentration of SO_4^{2-} in the air was closely associated with chronic disease mortality in Beijing [19]. The most convincing evidence of the independent health effects of SO_2 thus far is from an intervention study in Hong Kong which showed SO_2 resulting from sulfur-rich fuels had an direct impact on cardiorespiratory deaths [27]. In our analysis, an increase of 10 μg/m³ of SO_2 corresponded to 1.8% increase of total mortality, 3.2% increase of cardiovascular mortality, and 3.2% increase of respiratory mortality. In the Hong Kong intervention study, a decrease of 10 μg/m³ of SO_2 was associated with 1.1% decrease of total mortality, 1.0% decrease of cardiovascular mortality, and 2.0% decrease of respiratory mortality [26]. Generally, the magnitudes of our cohort-based estimates for SO_2 in Mainland China are comparable with those from the Hong Kong intervention study. Of course, most air pollution epidemiologic studies, including ours, use ambient pollutant concentrations as surrogates of personal exposure, which might induce unavoidable measurement error [28,29]. However, a consistent, significant health effect of SO_2 observed in China suggests that the role of outdoor exposure to SO_2 should be investigated further.

Among various health outcomes we examined, only cardiovascular mortality was significantly associated with any pollutant we examined. There is increasing evidence that exposure to higher levels of air pollution is associated with adverse cardiovascular consequences. A recent scientific statement from the American Heart Association concluded that short-term or long-term exposure to air pollution is associated with increased risk of cardiovascular disease and death [30]. Air pollutants may adversely affect the cardiovascular system directly and indirectly [30]. Direct effects may occur via agents that readily cross the pulmonary epithelium into the circulation, such as gaseous pollutants (e.g., nitrogen oxides) and possibly ultra-fine particles (UFPs), along with soluble constituents of particles (e.g., transition metals); indirect effects may occur via induction of pulmonary oxidative stress and inflammation, leading to endothelial dysfunction and systemic inflammation. All these direct and indirect effects may in turn activate haemostatic pathways and impair vascular function.

In China, lung cancer mortality has increased significantly during the last two decades [21,22]. However, data on association between lung cancer and air pollution are rather limited. Several cross-sectional analyses were conducted in Guangzhou [31] and Shenyang [32] from which we can draw some preliminary conclusions about potential association with lung cancer. Our analysis provides the first prospective evidence in China that air pollution (e.g., SO_2) may contribute to the increased risk of lung cancer mortality. Inhalation exposure to air pollutants, e.g., SO_2, has been associated with the DNA damage of multiple organs including the lung [33], providing a possible biological pathway through which air pollution may affect lung cancer incidence.

Various factors may modify the health effects of air pollution. As pointed by the US National Academy of Science [34], it is important to understand the characteristics of individuals who are at increased risk of adverse events due to outdoor air pollution. We did not find significant evidence for effect modification by sex, smoking, obesity and education. The information on modification of air pollution health effects is inconsistent [10,35]. Additional examination of modifying factors in future investigations will help in public policy making, risk assessment and standard setting.

Some limitations of our analysis should be noted. The primary limitation of our study is that it did not include planned prospective collection of study-specific air pollution monitoring data, but used routine government monitoring data. The air pollutants considered were limited to TSP, SO_2, and NO_x only, due to the limitation of monitoring data in the research period, although previous studies in Europe found significant effects of long-term exposure to TSP [36] and NO_x [37] on morality. As in most previous studies in this field, we used the fixed monitoring results as the proxy for population exposure level to air pollution. Although we believe it is reasonable to consider these measurements as good proxies for the population exposures, the differences between these proxy values and the true exposures are an inherent and unavoidable type of measurement error. The resulting measurement error may have substantial implication for interpreting air pollution health studies [28]. For example, TSP is not a specific PM indicator, and the observed health effects of SO_2 and NO_2 in our study might actually be a result of exposures to fine particles or traffic-related emissions [28,29]. However, due to lack of available information on personal exposure in China, we could not quantify such a bias. Also, we do not have measures of indoor air pollution; however, our study participants were limited to those living in urban areas only, and few of them used biomass or coal fuels that could produce substantial indoor pollution. As in any epidemiologic study, residual confounding is possible; however, we carefully adjusted for known and potential confounders, including demographic characteristics, medical history, lifestyle-related risk factors, blood pressure, and

body weight. Our study was semi-ecological in nature, because it includes risk factors measured both at the individual level, such as smoking, and at the spatial level, such as air pollution. We did not use the hierarchical model because previous analyses in the US [10] and Europe [36] showed that effect estimates of air pollution were not highly sensitive to the incorporation of spatial smoothing to account for regional clustering or other spatial patterns in the data. Finally, our results of multi-pollutant models should be interpreted with caution, because both SO_2 and NO_2 are precursors of secondary particles. Coal combustion was the major source of both particulate and gaseous pollutants in China in 1990s, thus limiting our ability to separate the independent effect for individual pollutant.

In summary, long-term exposure to outdoor air pollution was associated with increased risk of cardiopulmonary and lung cancer mortality in China. The results from this study contribute to very limited data in the scientific literature on long-term effects of air pollution for high exposure settings typical in developing countries.

Acknowledgements

The study was supported by the National Basic Research Program (973 program) of China (2011CB503802), a grant (2006BAI01A01) from the Ministry of Science and Technology, China, and the US National Institutes of Health grant 5R01TW008301-02. The authors declare they have no competing financial interests.

References

[1] J. Samet, D. Krewski, Health effects associated with exposure to ambient air pollution, J. Toxicol. Environ. Health A 70 (2007) 227–242.
[2] N. Kunzli, S. Medina, R. Kaiser, P. Quenel, F. Horak Jr., M. Studnicka, Assessment of deaths attributable to air pollution: should we use risk estimates based on time series or on cohort studies? Am. J. Epidemiol. 153 (2001) 1050–1055.
[3] D.E. Abbey, N. Nishino, W.F. McDonnell, R.J. Burchette, S.F. Knutsen, W. Lawrence Beeson, J.X. Yang, Long-term inhalable particles and other air pollutants related to mortality in nonsmokers, Am. J. Respir. Crit. Care Med. 159 (1999) 373–382.
[4] L.H. Chen, S.F. Knutsen, D. Shavlik, W.L. Beeson, F. Petersen, M. Ghamsary, D. Abbey, The association between fatal coronary heart disease and ambient particulate air pollution: are females at greater risk? Environ. Health Perspect. 113 (2005) 1723–1729.
[5] D.W. Dockery, C.A. Pope 3rd, X. Xu, J.D. Spengler, J.H. Ware, M.E. Fay, B.G. Ferris Jr., F.E. Speizer, An association between air pollution and mortality in six US cities, N. Engl. J. Med. 329 (1993) 1753–1759.
[6] G. Hoek, B. Brunekreef, S. Goldbohm, P. Fischer, P.A. van den Brandt, Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study, Lancet 360 (2002) 1203–1209.
[7] M. Jerrett, R.T. Burnett, C.A. Pope 3rd, K. Ito, G. Thurston, D. Krewski, Y. Shi, E. Calle, M. Thun, Long-term ozone exposure and mortality, N. Engl. J. Med. 360 (2009) 1085–1095.
[8] H. Kan, G. Heiss, K.M. Rose, E.A. Whitsel, F. Lurmann, S.J. London, Prospective analysis of traffic exposure as a risk factor for incident coronary heart disease: the atherosclerosis risk in communities (ARIC) study, Environ. Health Perspect. 116 (2008) 1463–1468.
[9] K.A. Miller, D.S. Siscovick, L. Sheppard, K. Shepherd, J.H. Sullivan, G.L. Anderson, J.D. Kaufman, Long-term exposure to air pollution and incidence of cardiovascular events in women, N. Engl. J. Med. 356 (2007) 447–458.
[10] C.A. Pope 3rd, R.T. Burnett, M.J. Thun, E.E. Calle, D. Krewski, K. Ito, G.D. Thurston, Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution, JAMA 287 (2002) 1132–1141.
[11] H. Kan, B. Chen, C. Hong, Health impact of outdoor air pollution in China: current knowledge and future research needs, Environ. Health Perspect. 117 (2009) A187.
[12] X. Xu, J. Gao, D.W. Dockery, Y. Chen, Air pollution and daily mortality in residential areas of Beijing, China, Arch Environ. Health 49 (1994) 216–222.
[13] S.A. Venners, B. Wang, Z. Xu, Y. Schlatter, L. Wang, X. Xu, Particulate matter, sulfur dioxide, and daily mortality in Chongqing, China, Environ. Health Perspect. 111 (2003) 562–567.
[14] H. Kan, S.J. London, G. Chen, Y. Zhang, G. Song, N. Zhao, L. Jiang, B. Chen, Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: The Public Health and Air Pollution in Asia (PAPA) study, Environ. Health Perspect. 116 (2008) 1183–1188.
[15] Z. Qian, Q. He, H.M. Lin, L. Kong, D. Liao, J. Dan, C.M. Bentley, B. Wang, Association of daily cause-specific mortality with ambient particle air pollution in Wuhan, China, Environ. Res. 105 (2007) 380–389.
[16] Z. Xu, D. Yu, L. Jing, X. Xu, Air pollution and daily mortality in Shenyang, China, Arch. Environ. Health 55 (2000) 115–120.
[17] C.M. Wong, N. Vichit-Vadakan, H. Kan, Z. Qian, Public Health, Air Pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality, Environ. Health Perspect. 116 (2008) 1195–1202.
[18] H. Wang, G. Lin, X. Pan, Association between total suspended particles (TSP) and cardiovascular mortality in Shenyang, J. Environ. Health 20 (2003) 13–15 (in Chinese).
[19] J. Zhang, H. Song, S. Tong, L. Li, B. Liu, L. Wan, Ambient sulfate concentration and chronic disease mortality in Beijing, Sci. Total Environ. 262 (2000) 63–71.
[20] D. Gu, J. He, X. Duan, K. Reynolds, X. Wu, J. Chen, G. Huang, C.S. Chen, P.K. Whelton, Body weight and mortality among men and women in China, JAMA 295 (2006) 776–783.
[21] D. Gu, T.N. Kelly, X. Wu, J. Chen, J.M. Samet, J.F. Huang, M. Zhu, J.C. Chen, C.S. Chen, X. Duan, M.J. Klag, J. He, Mortality attributable to smoking in China, N. Engl. J. Med. 360 (2009) 150–159.
[22] J. He, D. Gu, X. Wu, K. Reynolds, X. Duan, C. Yao, J. Wang, C.S. Chen, J. Chen, R.P. Wildman, M.J. Klag, P.K. Whelton, Major causes of death among men and women in China, N. Engl. J. Med. 353 (2005) 1124–1134.
[23] Ministry of Environmental Protection of China, Ambient Air Quality Standard. http://kjs.mep.gov.cn/hjbhbz/bzwb/dqhjbh/dqhjzlbz/199612/t19961206_67502.htm, 2010 (accessed 08.11.2010).
[24] Centers for Disease Control and Prevention, Overweight and Obesity: Defining Overweight and Obesity, 2006.
[25] B. Brunekreef, Health effects of air pollution observed in cohort studies in Europe, J. Expo. Sci. Environ. Epidemiol. 17 (Suppl. 2) (2007) S61–65.
[26] C.A. Pope 3rd, D.W. Dockery, Health effects of fine particulate air pollution: lines that connect, J. Air Waste Manage. Assoc. 56 (2006) 709–742.
[27] A.J. Hedley, C.M. Wong, T.Q. Thach, S. Ma, T.H. Lam, H.R. Anderson, Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study, Lancet 360 (2002) 1646–1652.
[28] J.A. Sarnat, K.W. Brown, J. Schwartz, B.A. Coull, P. Koutrakis, Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles, Epidemiology 16 (2005) 385–395.
[29] J.A. Sarnat, J. Schwartz, P.J. Catalano, H.H. Suh, Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? Environ. Health Perspect. 109 (2001) 1053–1061.
[30] R.D. Brook, S. Rajagopalan, C.A. Pope 3rd, J.R. Brook, A. Bhatnagar, A.V. Diez-Roux, F. Holguin, Y. Hong, R.V. Luepker, M.A. Mittleman, A. Peters, D. Siscovick, S.C. Smith Jr., L. Whitsel, J.D. Kaufman, Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association, Circulation 121 (2010) 2331–2378.
[31] X.X. Tie, D. Wu, G. Brasseur, Lung cancer mortality and exposure to atmospheric aerosol particles in Guangzhou, China, Atmos. Environ. 43 (2009) 2375–2377.
[32] Z.Y. Xu, W.J. Blot, H.P. Xiao, A. Wu, Y.P. Feng, B.J. Stone, J. Sun, A.G. Ershow, B.E. Henderson, J.F. Fraumeni Jr., Smoking, air pollution, and the high rates of lung cancer in Shenyang, China, J. Natl. Cancer Inst. 81 (1989) 1800–1806.
[33] Z. Meng, G. Qin, B. Zhang, DNA damage in mice treated with sulfur dioxide by inhalation, Environ. Mol. Mutagen 46 (2005) 150–155.
[34] National Research Council, Research Priorities for Airborne Particulate Matter, National Academy Press, Washington, DC, 1998.
[35] J.E. Clougherty, A growing role for gender analysis in air pollution epidemiology, Environ. Health Perspect. 118 (2010) 167–176.
[36] L. Filleul, V. Rondeau, S. Vandentorren, N. Le Moual, A. Cantagrel, I. Annesi-Maesano, D. Charpin, C. Declercq, F. Neukirch, C. Paris, D. Vervloet, P. Brochard, J.F. Tessier, F. Kauffmann, I. Baldi, Twenty five year mortality and air pollution: results from the French PAARC survey, Occup. Environ. Med. 62 (2005) 453–460.
[37] P. Nafstad, L.L. Haheim, T. Wisloff, F. Gram, B. Oftedal, I. Holme, I. Hjermann, P. Leren, Urban air pollution and mortality in a cohort of Norwegian men, Environ. Health Perspect. 112 (2004) 610–615.