

RESEARCH ARTICLE

Fine Particulate Air Pollution and Hospital Emergency Room Visits for Respiratory Disease in Urban Areas in Beijing, China, in 2013

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Abstract

Background

Heavy fine particulate matter (PM_{2.5}) air pollution occurs frequently in China. However, epidemiological research on the association between short-term exposure to PM_{2.5} pollution and respiratory disease morbidity is still limited. This study aimed to explore the association between PM_{2.5} pollution and hospital emergency room visits (ERV) for total and cause-specific respiratory diseases in urban areas in Beijing.

Methods

Daily counts of respiratory ERV from Jan 1 to Dec 31, 2013, were obtained from ten general hospitals located in urban areas in Beijing. Concurrently, data on PM_{2.5} were collected from the Beijing Environmental Protection Bureau, including 17 ambient air quality monitoring stations. A generalized-additive model was used to explore the respiratory effects of PM_{2.5}, after controlling for confounding variables. Subgroup analyses were also conducted by age and gender.

Results

A total of 92,464 respiratory emergency visits were recorded during the study period. The mean daily PM_{2.5} concentration was 102.1±73.6 µg/m³. Every 10 µg/m³ increase in PM_{2.5} concentration at lag₀ was associated with an increase in ERV, as follows: 0.23% for total respiratory disease (95% confidence interval [CI]: 0.11%-0.34%), 0.19% for upper respiratory tract infection (URTI) (95%CI: 0.04%-0.35%), 0.34% for lower respiratory tract infection (LRTI) (95%CI: 0.14%-0.53%) and 1.46% for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (95%CI: 0.13%-2.79%). The strongest association was

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identified between AECOPD and PM_{2.5} concentration at lag₀₋₃ (3.15%, 95%CI: 1.39%-4.91%). The estimated effects were robust after adjusting for SO₂, O₃, CO and NO₂. Females and people 60 years of age and older demonstrated a higher risk of respiratory disease after PM_{2.5} exposure.

Conclusion

PM_{2.5} was significantly associated with respiratory ERV, particularly for URTI, LRTI and AECOPD in Beijing. The susceptibility to PM_{2.5} pollution varied by gender and age.

Introduction

Because of the rapid industrialization and economic growth experienced over the past ten years, air pollution has become a serious issue in China. Heavy haze-fog episodes have frequently occurred in recent years [1, 2]. From 2013 to 2014, the annual mean fine particulate matter (PM_{2.5}, particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$) concentration for most of the 31 provincial capital cities in China exceeded the Chinese Ambient Air Quality Standards Grade II standard (35 $\mu\text{g}/\text{m}^3$) [3]. In particular, as the capital of China, Beijing has experienced a more serious challenge in terms of deteriorating air quality because of the coal burning and wind-blown dust from the surrounding industrial cities as well as the vehicle exhaust from the rapidly growing number of automobiles [4]. For example, starting in early January 2013, Beijing experienced multiple prolonged periods of severe smog; the peak hourly concentration of ambient PM_{2.5} soared to 800 $\mu\text{g}/\text{m}^3$, and the annual ambient PM_{2.5} concentration in 2013 reached 89.5 $\mu\text{g}/\text{m}^3$ [5]. The extremely high ambient PM_{2.5} concentration has attracted extensive public attention because of the adverse health effects.

Toxicological evidence suggests that the exposure of PM_{2.5} can cause lung inflammation and affect pulmonary immune function [6]. During the past two decades, several studies have demonstrated the effects of PM_{2.5} on the mortality for total respiratory disease [5, 7] or on the number of hospital admissions due to cause-specific respiratory diseases, such as pneumonia, chronic obstructive pulmonary disease and asthma [8–11]. However, few reports have directly evaluated the effects of PM_{2.5} on total and cause-specific respiratory diseases using hospital emergency room visits (ERV) as a morbidity indicator. In addition, most of these studies were conducted in Western developed countries; however, because of the different level of effects, such as ambient PM_{2.5} levels, characteristics of ambient PM_{2.5}, population susceptibility, and weather patterns, there is still a need to assess the health effects of PM_{2.5} exposure in developing countries such as China.

It was not until March 1, 2012, that the PM_{2.5} level was required to be included in the air quality standards in China [1]. Previous studies evaluating the short-term adverse effects of ambient particles pollution in China have primarily focused on the effects of PM₁₀ (particles with an aerodynamic diameter $\leq 10 \mu\text{m}$) [12, 13]. Researchers have suggested that PM_{2.5} is more harmful to health than PM₁₀ is, because smaller particles are more readily able to deposit deeper into the lungs and can carry larger concentrations of adsorbed or condensed toxic air pollutants per unit mass. Although numerous studies have reported the effects of PM_{2.5} on mortality [14, 15], a recent meta-analysis has noted that the observed association between ambient PM_{2.5} and morbidity in China has not been validated [16]. Although one study reported the association between PM_{2.5} and hospital admissions for respiratory diseases in Beijing, the correlation was explored from the perspective of geography and spatial analysis using

grey correlation analysis, and it considered particles measuring less than 1.0 μm [17]. Another study employed hospital admissions data from one hospital in the Haidian district in Beijing, but it did not detect the effects of PM_{2.5} on cause-specific respiratory diseases [18].

The availability of the thorough monitoring network for PM_{2.5} from Beijing Environmental Protection Bureau since October 2012 provided us with an opportunity to assess the adverse effects of PM_{2.5} pollution. This study aimed to explore association between PM_{2.5} concentration and ERV for total and cause-specific respiratory diseases using a time-series design by controlling for long-term trends and seasonality in daily ERV, day of the week, and weather variables in Beijing. Subgroup analyses were also performed using different age groups and gender to identify the most susceptible subpopulations.

Materials and Methods

Ethics statement

The study protocol was approved by the Institutional Review Board at the School of Public Health, Capital Medical University. Written informed consent was not required because we used aggregated data and no individualized data. The patient information was anonymized and de-identified prior to analysis.

Study site

Beijing is located in the north of China (latitude 39°54'N and longitude 116°25'E). As the capital, Beijing is the political, economical and cultural center of China, with six urban districts (Dongcheng, Xicheng, Chaoyang, Haidian, Fengtai, Shijingshan) and ten suburban districts (Changping, Mentougou, Daxing, Fangshan, Tongzhou, Shunyi, Huairou, Pinggu, Minyun and Yanqing). According to the Chinese Health Statistical Yearbook, in 2012, Beijing had a population of 20,690,000, with 10,685,164 males (51.64%) and 10,004,836 females (48.36%). Approximately 75% of Beijing's total population live in six urban districts, which cover all high population density areas in Beijing ($> 5,000$ people/km²) [19].

Data collection

Daily data on emergency room visits from Jan 1 to Dec 31, 2013, were collected from ten general hospitals located in urban areas in Beijing. To obtain a representative sample of the urban population, one to three publicly funded hospitals in each urban district were selected (Fig 1). Patient data were derived from the computerized medical record system including age, gender, visit date and diagnosis at discharge. ERV for respiratory diseases were extracted according to the principal diagnosis, using the International Classification of Diseases-(ICD) 10th Revision Code of J00-J99. Specifically, we focused on total respiratory disease (ICD-10: J00-J99), upper respiratory tract infection (URTI) (ICD-10: J00, J02-J06), lower respiratory tract infection (LRTI) (ICD-10: J12-J22, J44 [except J44.103 and J44.901]), acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (ICD-10: J44.103, J44.901) and asthma (ICD-10: J45-46).

Since October 2012, daily average and hourly real-time air pollution data were released to the public through a web platform (<http://zx.bjmec.com.cn/>) by Beijing Environmental Protection Bureau, which established 35 ambient air quality monitoring stations in the 16 districts of Beijing city. Daily 24-hour average concentration data for PM_{2.5} (unit, $\mu\text{g}/\text{m}^3$), sulfur dioxide (SO₂) (unit, $\mu\text{g}/\text{m}^3$), ozone (O₃) (unit, $\mu\text{g}/\text{m}^3$), nitrogen dioxide (NO₂) (unit, $\mu\text{g}/\text{m}^3$) and carbon monoxide (CO) (unit, mg/m^3) levels during the study period were collected, including data from 17 ambient air quality monitoring stations located in urban areas in Beijing city.

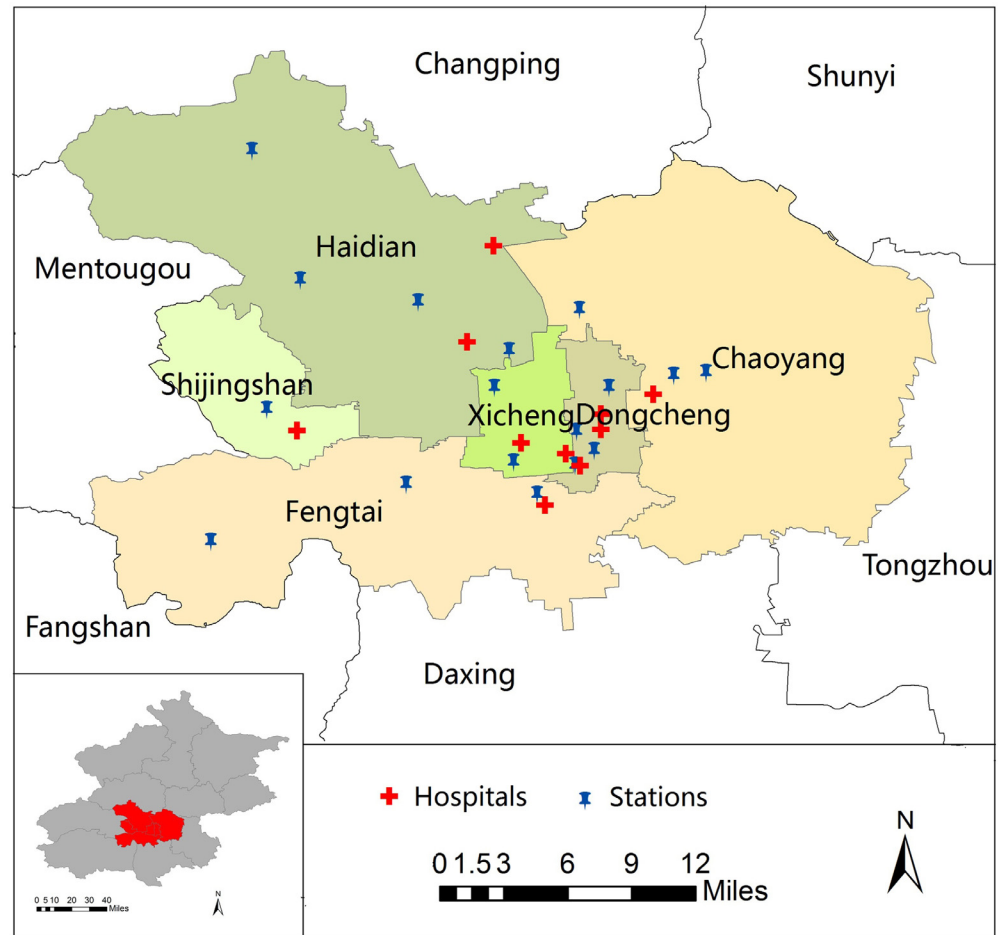


Fig 1. The distribution of 17 monitoring stations for air pollutants and 10 hospitals located in urban areas in Beijing, China. Note: ArcGIS (ArcMap, version 10.0, ESRI Inc. Redlands, CA, USA) was used to create the map.

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(Fig 1). The rates of the missing values from the 17 monitoring stations ranged from 9.0% to 15.6%. Some daily data were missing for all districts, primarily due to technical problems (i.e., website maintenance) during the study period. Imputation will produce errors, therefore, we did not fill in the missing values. We used the mean PM_{2.5} concentrations from the 17 monitoring stations to represent the daily exposure of the urban population. In addition, to allow for the effects of weather conditions, during the same period, we obtained daily meteorological data from the Chinese Meteorological Bureau, including the mean temperature and relative humidity.

Data analysis

A generalized-additive model (GAM) with the Poisson link function was used to explore the association between the daily PM_{2.5} concentration and outcomes, after adjusting for temperature, relative humidity, day of the week (*DOW*), public holidays and influenza outbreaks. First, the basic model was set up, excluding air pollutant variables. The natural cubic smoothing spline (*ns*) functions of calendar time, daily mean temperature and relative humidity were incorporated in the model, allowing for nonlinear relationships with the outcomes. The partial

autocorrelation function was used to guide the selection of the best degrees of freedom (*df*) for the spline function of calendar time. Note that the absolute values of the partial autocorrelation function for the model residuals had to be < 0.1 for the first 2 lag days [20], and then the Akaike Information Criterion (AIC) was used to determine the best *df* for calendar time. Thus, a natural cubic smoothing spline for calendar time (*df* = 11) was used to control for the seasonal and long-term trends. Natural cubic smoothing spline for temperature and relative humidity (*df* = 3) on current day of ERV occurred was incorporated into the model, based on previous studies [21, 22]. The day of the week (*DOW*), public holidays and influenza outbreaks were all categorical variables. After the basic model was established, the air pollutant variables were then added. The final model is described below:

$$\begin{aligned} \text{Log}[E(Y_t)] = & \alpha + \beta_1 PM_{2.5,t-i} + ns(Temp_0, df = 3) + ns(RH_0, df = 3) \\ & + ns(Time, df = 11) + \beta_2 DOW + \beta_3 Holiday + \beta_4 Influenza \end{aligned}$$

$E(Y_t)$ is the expected count for respiratory ERV on day t ; $PM_{2.5,t-i}$ is the mean $PM_{2.5}$ concentration from 17 monitoring stations on day t , and i is the day lag; ns is the natural cubic splines; $Temp_0$ and RH_0 are the daily mean temperature (°C) and relative humidity (%) of the current day, respectively; $Time$ denotes long-term trends and seasonality using the calendar time days; DOW is the day of the week; $holiday$ indicates a public holiday on day t (0 indicates no holiday, and 1 indicates a holiday); $influenza$ is a dummy variable for the weeks, with a number of influenza ERV exceeding the 75 percentile in a year [23].

Smoothing function in GAM was used to graphically analyze the exposure-response relationship to verify the assumption of linearity between the predicted log-relative risk of respiratory ERV and $PM_{2.5}$ concentration. The linear effects of $PM_{2.5}$ were then estimated for the current day and up to 5 day before the outcome (lag₀ to lag₅). Considering that a single-day lag model might underestimate the association [19], the overall cumulative effects were estimated using 2-day, 4-day and 6-day moving averages of $PM_{2.5}$ concentrations (lag₀₋₁, lag₀₋₃ and lag₀₋₅). We also investigated whether the associations were still sensitive after adjusting for the other gaseous pollutants (SO₂, O₃, CO or NO₂) in two-pollutant models [24]. In the single-pollutant models, $PM_{2.5}$ was placed in the model alone; in the two-pollutant models, SO₂, O₃, CO or NO₂ was jointly included with $PM_{2.5}$. Effects across age groups (0–14 years, 15–34 years, 35–59 years, and ≥ 60 years) and genders were examined using the respiratory ERV subgroups for the health outcomes to identify the most susceptible subpopulation [25]. A Z-test was then used to test the statistical significance of differences by gender or age by calculating $(\beta_1 - \beta_2) / \sqrt{SE_1^2 + SE_2^2}$, where β_1 and β_2 are the estimates coefficient for the two categories (i.e., male and female patients), and SE_1 and SE_2 are the respective standard errors [26].

Sensitivity analyses were conducted to examine the impact of $PM_{2.5}$ on total respiratory ERV using different *df*: time trend (6–12), temperature (2–6) and relative humidity (2–6). Studies have shown that temperature effects on health would lag for more than 10 days [27]; therefore, the effects of $PM_{2.5}$ were also checked in our model using the 14-day moving average temperature [28]. All sensitivity analyses were performed only for total respiratory ERV in the whole population.

All analyses were performed using the “mgcv” and “nlme” packages in the statistical environment R 3.2.2 (Development Core Team, 2015). The results are presented as the percentage change (PC) and 95% confidence interval (CI) in the daily respiratory ERV per 10 μg/m³ increase in $PM_{2.5}$ concentration.

Results

Descriptive statistics

A total of 92,464 emergency visits for total respiratory diseases were recorded from the ten hospitals in 2013, with URTI accounting for the largest proportion (55.3%). The mean daily count for total respiratory disease was 253 (range, 129 to 556), and 45.5% were male patients. The mean patient age was 44.1 years for male patients and 43.0 years for female patients. There were 19 patients (0.021%) with missing gender information and 6 patients (0.006%) with missing age information, which had little effect on the subgroup analyses. The mean daily visits for cause-specific respiratory diseases were URTI (113 visits), LRTI (122 visits), AECOPD (2 visits) and asthma (6 visits) (Table 1).

During the study period, the overall mean daily PM_{2.5} concentration was 102.1 µg/m³ (range, 6.7 µg/m³ to 508.5 µg/m³). In terms of the Chinese Ambient Air Quality Standards Grade II standards for 24-hour average PM_{2.5} concentration (≤ 75 µg/m³), 45.7% (155 days) of the daily PM_{2.5} concentrations were below this standard during the study period. However, in terms of the WHO Air Quality Standards (24-hour average PM_{2.5} concentration ≤ 25 µg/m³), only 8.8% (30 days) days met the standard. The mean daily concentrations of SO₂, O₃, CO and NO₂ were 31.2 µg/m³, 104.3 µg/m³, 2.2 mg/m³ and 66.7 µg/m³, respectively (Table 2). All Spearman correlations among the pollutants and weather variables were statistically significant at 0.05 level (2-tailed). Generally, PM_{2.5} was strongly correlated with SO₂, CO and NO₂ (*r_s* = 0.56, 0.80 and 0.72, respectively) and negatively correlated with O₃ (*r_s* = -0.15). The time series graph showed the daily variations of ERV for respiratory diseases and PM_{2.5} concentrations during study period (Fig 2).

Associations between PM_{2.5} and ERV for respiratory disease

There were clear exposure-response relationships between PM_{2.5} concentration and total respiratory ERV (Fig 3). The exposure-response relationships were approximately linear, with a tiny fluctuation when the PM_{2.5} concentrations were below 200 µg/m³ and a sharper response at higher PM_{2.5} concentrations.

Table 1. Characteristics and distribution of the main health outcomes and sub-categories of the different gender and age groups.

	Total respiratory disease		URTI		LRTI		AECOPD		Asthma	
	N	Daily Median (P ₂₅ -P ₇₅)	N	Daily Median (P ₂₅ -P ₇₅)	N	Daily Median (P ₂₅ -P ₇₅)	N	Daily Median (P ₂₅ -P ₇₅)	N	Daily Median (P ₂₅ -P ₇₅)
Total	92464	241 (207-275)	51134	126 (108-155)	34904	93 (76-109)	712	2 (1-3)	2052	5 (4-7)
Gender										
Male	42095	110 (96-127)	22119	55 (47-68)	16877	45 (37-54)	425	1 (0-2)	867	2 (1-3)
Female	50350	130 (109-151)	29003	71 (60-89)	18021	47 (38-57)	287	1 (0-1)	1185	3 (2-4)
Age group										
0-14	5159	13 (9-18)	3002	8 (5-11)	2030	5 (3-7)	0	0 (0-0)	53	0 (0-0)
15-34	38228	99 (83-117)	28304	72 (59-87)	7973	20 (15-28)	1	0 (0-0)	431	1 (0-2)
35-59	24792	63 (54-76)	14111	35 (28-44)	8471	22 (17-28)	79	0 (0-0)	868	2 (1-3)
60-	24279	65 (54-74)	5713	14 (10-19)	16428	44 (37-51)	632	2 (1-3)	700	2 (1-3)

Note: URTI-upper respiratory tract infection, LRTI-lower respiratory tract infection, AECOPD-acute exacerbation of chronic obstructive pulmonary disease, N-counts of event, daily median (P₂₅-P₇₅)-median (25th percentile and 75th percentile) of daily event counts.

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Table 2. Summary of the environmental and meteorological variables in urban areas in Beijing during the study period.

Variables	Percentiles						
	Mean	SD	Min	25 th	Median	75 th	Max
PM _{2.5} (µg/m ³)	102.1	73.6	6.7	53.1	82.4	129.5	508.5
SO ₂ (µg/m ³)	31.2	25.7	3.6	11.0	23.3	43.7	133.8
O ₃ (µg/m ³)	104.3	68.3	4.4	53.0	89.4	146.5	305.4
CO (mg/m ³)	2.2	1.5	0.3	1.2	1.9	2.6	17.7
NO ₂ (µg/m ³)	66.7	25.0	12.4	50.1	62.3	78.3	171.5
Temperature (°C)	11.3	11.6	-12.6	1.2	11.0	22.2	29.0
Relative humidity (%)	58.7	17.3	18.9	46.7	59.0	73.3	93.3

Abbreviations: PM_{2.5}-particles with an aerodynamic diameter ≤ 2.5 µm, SO₂-sulfur dioxide, O₃-ozone, CO-carbon monoxide, NO₂-nitrogen dioxide, SD-standard deviation, Max-maximum, and Min-minimum.

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[Fig 4](#) shows the associations between the PM_{2.5} concentration and total respiratory ERV. We observed statistically significant associations between the total respiratory ERV and PM_{2.5} concentration on the current day (lag₀), the previous day (lag₁), the previous three day (lag₃), the 2-day moving average (lag₀₋₁) and the 4-day moving average (lag₀₋₃). We estimated increases of 0.23% (95%CI: 0.11%-0.34%), 0.12% (95%CI: 0.01%-0.22%), 0.17% (95%CI: 0.07%-0.27%), 0.22% (95%CI: 0.09%-0.35%) and 0.21% (95%CI: 0.05%-0.37%) in total respiratory ERV associated with every 10 µg/m³ increase in PM_{2.5} at lag₀, lag₁, lag₃, lag₀₋₁ and lag₀₋₃, respectively. The largest estimated effect was observed on the current day (lag₀). The estimated effects of PM_{2.5} on total respiratory ERV changed little after adjusting for O₃, but fluctuated with attenuating tendencies after adjusting for SO₂ or CO and increasing tendencies after adjusting for NO₂. Significant results were observed at different lag days in the two-pollutant models ([Fig 4](#)).

[Table 3](#) lists the effects of PM_{2.5} on cause-specific respiratory ERV. Every 10 µg/m³ increase of PM_{2.5} on the current day (lag₀) was associated with an increase in ERV: 0.19% for URTI (95%CI: 0.04%-0.35%), 0.34% for LRTI (95%CI: 0.34%-0.53%), and 1.46% for AECOPD (95%CI: 0.13%-2.79%), respectively. Single-day delayed effects of PM_{2.5} were significant with URTI on lag₁ and lag₃, with LRTI on lag₂ and lag₃, and with AECOPD on lag₁ and lag₂. For the cumulative effects, the 2-day moving average PM_{2.5} concentration (lag₀₋₁) was significantly associated with ERV for URTI, LRTI and AECOPD. The estimated effect of PM_{2.5} on AECOPD at lag₀₋₃ (3.15%, 95%CI: 1.39%-4.91%) was the largest. No significant association was found between PM_{2.5} and asthma ERV at any lag patterns (P>0.05). The estimated effects of PM_{2.5} on cause-specific respiratory ERV in two-pollutant models are shown in the supporting information, [S1 Table](#).

The association between PM_{2.5} and total respiratory ERV differed by gender and age group ([Fig 5](#)). PM_{2.5} exposure resulted in slightly larger effects in females than in males at all lag patterns. Meanwhile, the gender differences were statistically significant at lag₂, lag₀₋₃ and lag₀₋₅ (P<0.05). We observed that the estimated effects of PM_{2.5} on total respiratory ERV among people 60 years of age and older were significant at all lag patterns and higher when compared with other age groups. In terms of the estimated effects, the differences between age groups were statistically significant in the following categories: between people 60 years of age and older and the age group younger than 15 years at lag₀₋₁, lag₀₋₃ and lag₀₋₅; between people 60 years of age and older and the age group 15 years of age and older and younger than 35 years at

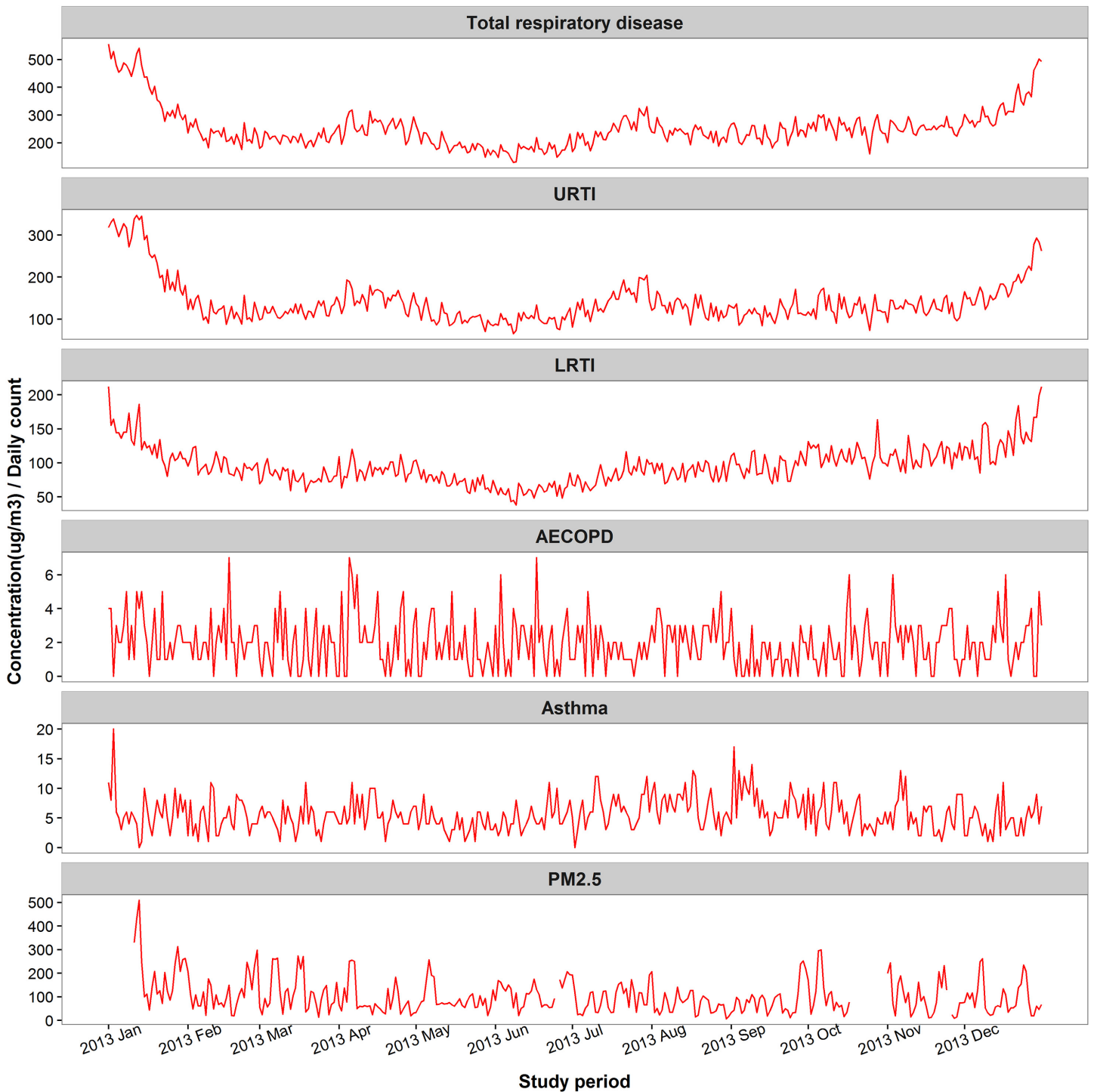


Fig 2. Time series plot of emergency room visits for respiratory diseases (number of daily cases) and PM_{2.5} concentrations in Beijing, China during study period. Abbreviations: URTI-upper respiratory tract infection, LRTI-lower respiratory tract infection, AECOPD-acute exacerbation of chronic obstructive pulmonary disease, PM_{2.5}- particles with an aerodynamic diameter ≤ 2.5 μm.

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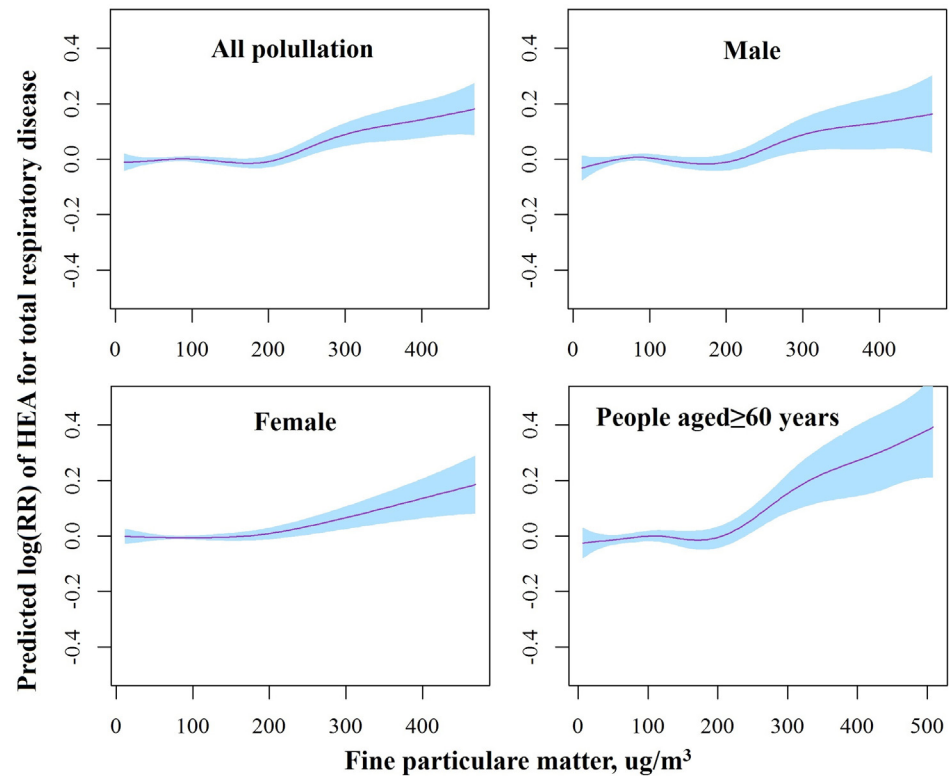


Fig 3. The smoothed exposure-response curves of daily average PM_{2.5} concentrations at lag₀₋₁ against the risk of total respiratory ERV in different subgroups. Note: The X-axis shows the moving averages of PM_{2.5} concentrations at lag₀₋₁ ($\mu\text{g}/\text{m}^3$). The Y-axis is the predicted log relative risk (RR). The pink line represents central estimates, and the blue shaded area represents the 95% CI.

doi:10.1371/journal.pone.0153099.g003

lag₀, lag₀₋₁ and lag₀₋₅; and between people 60 years of age and older and the age group 35 years of age and older and younger than 60 years at lag₀, lag₃, lag₀₋₃ and lag₀₋₅ ($P < 0.05$) (Fig 5).

Sensitivity analysis results

S2 Table shows the percentage change in total respiratory ERV associated with a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} on the current day (lag₀), under different *df* for calendar time, temperature and relative humidity. The AIC of the basic model was lowest, and the estimated effect became stable when *df* of spline for calendar time was 11; different *df* of spline for temperature and relative humidity had little effect on the estimated effect, suggesting that the findings on the associations of PM_{2.5} concentration with respiratory ERV were robust in our study. The estimated effects changed little when the 14-day moving average temperature was controlled for in our model. As shown in S3 Table, similar results have been found.

Discussion

This study provided strong evidence of the associations between PM_{2.5} and respiratory disease morbidity in Beijing. PM_{2.5} was significantly associated with ERV for total respiratory disease and cause-specific respiratory diseases, including URTI, LRTI, and AECOPD. Females and people 60 years of age and older suffered a higher risk from PM_{2.5} exposure. To our knowledge, this study is one of the few that have thoroughly investigated the short-term effects of PM_{2.5} air pollution on total and cause-specific respiratory diseases.

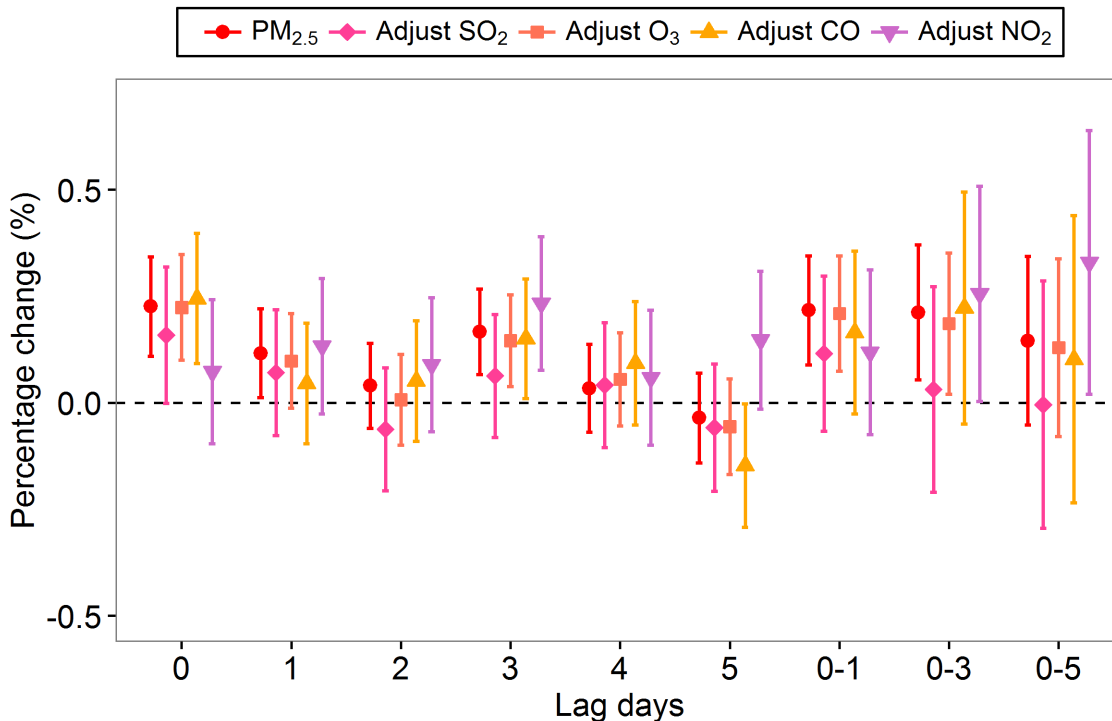


Fig 4. Percentage increase of total respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations using the single- and two-pollutant models.

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Previous studies have identified significant positive associations between PM_{2.5} and respiratory morbidity in Beijing, but they were restricted to one or two districts [17, 18]. To obtain more representative results for the population in the entire city, we correlated the daily ERV for respiratory diseases from ten hospitals located in the six urban districts in Beijing with the citywide daily mean PM_{2.5} concentration from 17 monitoring stations. We were not able to

Table 3. Percentage changes with 95% CI in cause-specific respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations for different lag structures.*

Lag Days	URTI		LRTI		AECOPD		Asthma	
	PC	95% CI	PC	95% CI	PC	95% CI	PC	95% CI
lag ₀	0.19	(0.04, 0.35)	0.34	(0.14, 0.53)	1.46	(0.13, 2.79)	-0.62	(-1.46, 0.22)
lag ₁	0.14	(0.00, 0.27)	0.08	(-0.09, 0.25)	2.40	(1.26, 3.53)	0.19	(-0.54, 0.93)
lag ₂	-0.09	(-0.22, 0.05)	0.19	(0.03, 0.36)	1.22	(0.11, 2.34)	0.07	(-0.63, 0.77)
lag ₃	0.14	(0.00, 0.27)	0.19	(0.02, 0.35)	0.92	(-0.22, 2.07)	0.01	(-0.68, 0.70)
lag ₄	0.02	(-0.12, 0.16)	0.09	(-0.08, 0.26)	-0.81	(-2.04, 0.42)	-0.42	(-1.13, 0.29)
lag ₅	0.02	(-0.12, 0.16)	-0.10	(-0.27, 0.08)	-1.48	(-2.75, -0.22)	-0.33	(-1.05, 0.39)
lag ₀₋₁	0.20	(0.03, 0.37)	0.27	(0.06, 0.48)	2.70	(1.25, 4.14)	-0.21	(-1.13, 0.70)
lag ₀₋₃	0.18	(-0.03, 0.39)	0.24	(-0.02, 0.50)	3.15	(1.39, 4.91)	0.09	(-1.00, 1.19)
lag ₀₋₅	0.10	(-0.17, 0.37)	0.21	(-0.11, 0.53)	1.81	(-0.43, 4.06)	-0.36	(-1.70, 0.99)

*statistically significant results at the 5% level are indicated in bold.

Abbreviations: URTI-upper respiratory tract infection, LRTI-lower respiratory tract infection, AECOPD-acute exacerbation of chronic obstructive pulmonary disease, PC- percentage change.

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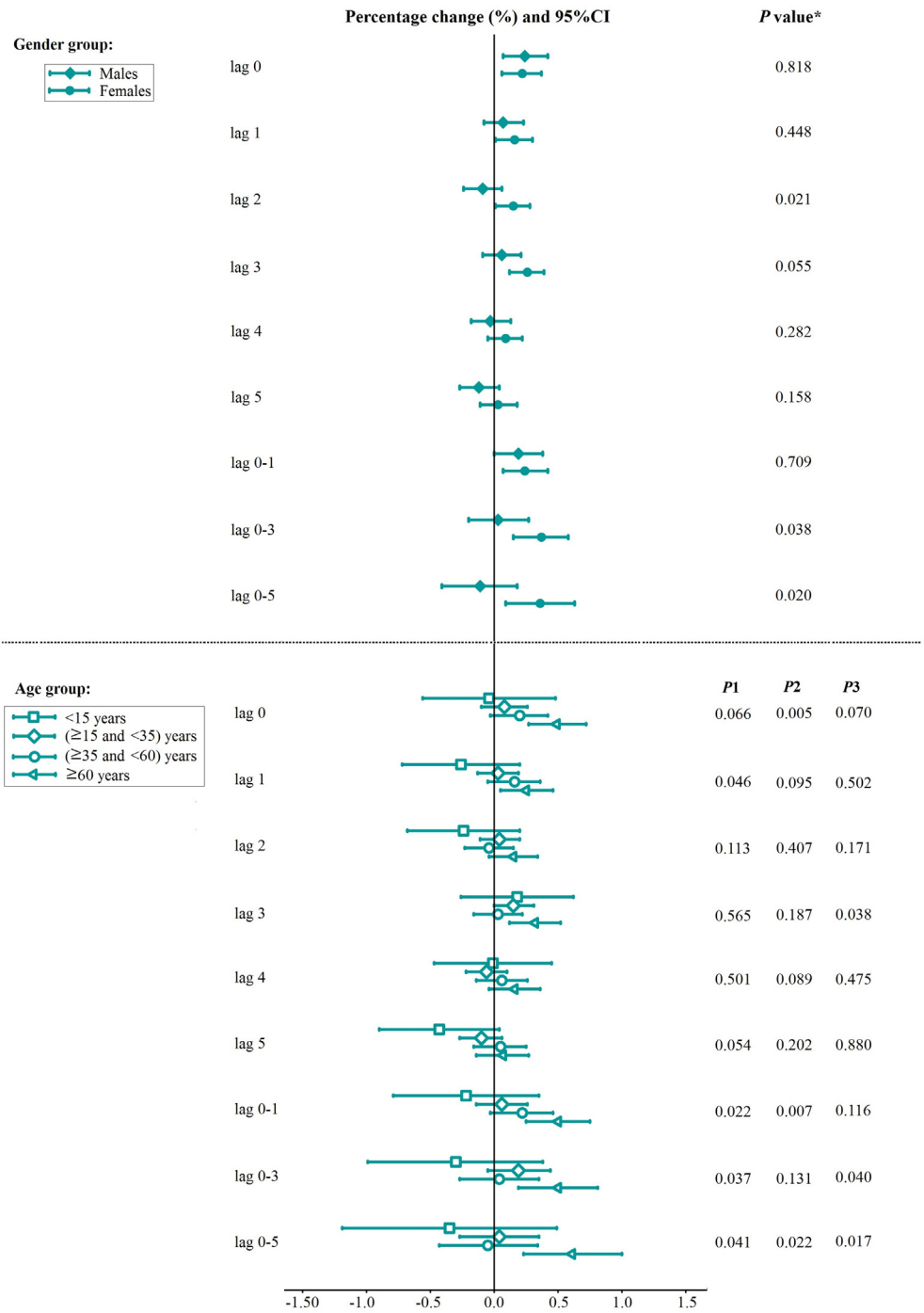


Fig 5. Percentage change with 95%CI in total respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations by gender and age. Note: The P Value obtained from the Z-test for the difference between the two relative risks derived from the subgroup analysis. P₁: 60 years of age and older vs the age group younger than 15 years; P₂: 60 years of age and older vs the age group 15 years of age and older and younger than 35 years; P₃: age 60 years of age and older vs the age group 35 years of age and older and younger than 60 years.

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allot each patient a unique PM_{2.5} concentration because we did not have individual information on his or her residential address. We assumed that residents would be more likely to go to the nearest hospital in Beijing, therefore, we assigned the monitored concentrations to patients based on their proximity to the hospitals, and then we used generalized additive mixed model (GAMM) to examine the impacts of the spatially assigned PM_{2.5} concentration on health outcomes. However, the estimated effects using spatially assigned PM_{2.5} concentrations in the GAMM were slightly smaller, and the confidence intervals were larger than those using mean PM_{2.5} in the GAM (supporting information, [S1 Fig](#) and [S4 Table](#)), which was not consistent with the results reported by Xu M, et al [21], likely due to the larger standard error generated by more missing values of air pollutants in the GAMM in our study or because of the smaller spatial variation of PM_{2.5} concentrations in urban areas compared to that in the entire city.

Toxicological studies have proposed that acute impairment of the lung cellular defense and immune system might be causative mechanisms for the short-term effects of PM_{2.5} on respiratory disease [29]. Our current findings on the short-term associations between PM_{2.5} and respiratory ERV are consistent with other toxicological and epidemiological findings. To date, many epidemiological studies have examined and reported the adverse health effects of PM_{2.5} on hospital admissions for LRTI, COPD and asthma [8–11]; however, few reports have directly addressed total respiratory disease using ERV as a morbidity indicator. Our study found statistically significant associations between PM_{2.5} and ERV for total respiratory disease and cause-specific diseases, including URTI, LRTI and AECOPD. Likely due to the higher PM_{2.5} concentration in Beijing in 2013, a longer lag association was observed in our study compared to previous reports of a 0–2 day lag [22, 30]. We found that the effects of PM_{2.5} on LRTI were higher overall compared to the effects on URTI in our study. LRTI, including pneumonia and acute bronchitis, is more severe and can cause a higher disease burden during an individual's life span than URTI; therefore, most previous studies likely focused on the effect of PM_{2.5} on LRTI rather than URTI [31, 32]. A study conducted in Rome showed a significant association between PM_{2.5} and LRTI at lag₂, with a higher effect (2.82%, 95%CI: 0.52%–5.19%) than the estimated effect in our study (0.19%, 95%CI: 0.09%–0.36%) [30]. Studies of the effects of PM_{2.5} on COPD admissions are rare and inconsistent [9, 31, 32]. We found that the effects of PM_{2.5} on AECOPD are the largest compared with other respiratory diseases groups. Due to the slow progression and chronic nature of the disease, COPD can also result in a massive and growing disease burden that affects a patient's health quality. Thus, COPD patients should stay at home as long as possible during a PM_{2.5} pollution outbreak to avoid possible acute exacerbation. We did not find any statistically significant associations between PM_{2.5} and asthma ERV, likely due to the small daily number of asthma patients. A simulation study suggested that the power of a time-series study of the acute health effects of air pollution can be increased by increasing either the mean daily count of the outcome or the time-series length [33]. In our study, the total cases of AECOPD and asthma were small, which limited our calculation power. In addition, air pollution health effects over a short time interval (e.g., 1-year time series study) are often small; and lower estimated effects also decrease power [33]. The lack of power may inhibit the identification of an association with specific causes of respiratory diseases that have low counts, as is the case with asthma, especially when the estimated effect is low [34].

When examining the associations between PM_{2.5} and total respiratory ERV, we considered the confounding factors of the other gaseous pollutants. The estimated effects of PM_{2.5} on total respiratory disease were affected by the inclusion of SO₂, CO or NO₂, but not O₃ in the two-pollutant models, possibly caused by the strong correlations between PM_{2.5} and SO₂ ($r_s = 0.56$), PM_{2.5} and CO ($r_s = 0.80$) or PM_{2.5} and NO₂ ($r_s = 0.72$). In studies that have estimated the adverse effects of PM_{2.5} in multi-pollutant models, positive associations between PM_{2.5} and

respiratory causes persisted after adjusting for other gaseous pollutants [8, 24, 35]. In Taiwan, the PM_{2.5} concentration on the current day (lag₀) increased hospital admissions for COPD on cool days (<25°C), and the risk estimates reduced after adjustment for O₃, CO or NO₂, and increased after adjustment for SO₂ in the model [8]. In a time-series study conducted in New York City, PM_{2.5} was shown to increase emergency department visits for asthma during warm season in single pollutant models, but the risk estimate was attenuated once SO₂, O₃, CO or NO₂ was included in the model [35]. In another time-series study conducted in Hong Kong, the risk estimate of PM_{2.5} on COPD emergency hospital admissions also became unstable after adjusting for CO and NO₂ [24]. These results may reflect the actual difference in the toxicity of the corresponding air pollutants themselves, but it is unlikely to differentiate the independent effects of each air pollutant in multi-pollutant models [21]. In the present study, PM_{2.5} was positively associated with respiratory causes ERV in both single-pollutant and multi-pollutant models at different lags, reflecting the actual adverse effects of PM_{2.5} on human respiratory system.

The shape of the exposure—response relationship between PM_{2.5} concentration and respiratory disease risk is crucial to determine the pattern of the adverse response. Most studies have assumed linear associations between particulate matter air pollution and health outcomes in epidemiological studies [7, 12, 18, 19, 24]. Schwartz et al explored the exposure—response association between PM_{2.5} and daily deaths by using a hierarchical model in the United States, and found a linear relationship without threshold [36]. This result is support by a cohort study conducted in Europe, which indicated PM_{2.5} was associated with natural-cause mortality, even within concentration ranges well below the present European annual mean limit value (<25 ug/m³) [37]. Tian L et al found that in Hong Kong, the exposure-response curve between PM_{2.5} and COPD was almost identical to that noted by Schwartz et al [24]. However, using regression splines to model the exposure-response relationship between PM_{2.5} and ischemic heart disease morbidity in Beijing, Xie W et al showed that the curve was non-linear, with predicted effect values less than zero at lower concentrations (0–90 ug/m³), a stable response at intermediate concentrations (90–180 ug/m³) and then a relatively shallower response at higher PM_{2.5} concentrations, which is partly consistent with our results [19]. Samoli et al provided evidence for deviation from linearity at lower level of particulate distribution in a multicity study, which estimated the exposure—response relationships between PM₁₀ and mortality [38]. They also proposed that the different city-specific relations can be explained partly by factors characterizing the air pollution mix and climate [38]. For example, Wong CM et al found no clear exposure—response relationships in warm seasons between respiratory mortality and PM₁₀, but observed a positive exposure—response relationship when PM₁₀ concentrations up to 80 ug/m³ in the cool seasons [39].

We found that the effects of PM_{2.5} pollution on total respiratory ERV were significantly greater in females than in males. In previous studies, the gender-specific short-term effects of air pollution were inconsistent [25, 40, 41]. Kan H, et al suggested that nonsmokers may be more sensitive to PM_{2.5} exposure [25], whereas the prevalence of smoking in females is lower than that in males in the Chinese population [42]. Moreover, Sunyer, et al suggested that different particles deposition patterns between males and females may partly explain these differences [43]. The age subgroup analysis results suggested that elderly people might be more susceptible to PM_{2.5} exposure. Elderly people may have a weaker immune system and a higher prevalence of chronic respiratory diseases, thus, they are more vulnerable to PM_{2.5} pollution. Generally, in accordance with previous studies [17, 25, 44], our study suggested that special attention should be paid to elderly people, in terms of their PM_{2.5} exposure.

Compared with previous studies focusing on the associations between PM_{2.5} pollution and respiratory diseases in relatively lower polluted areas in developed countries, our study

investigated the association between PM_{2.5} pollution and respiratory ERV in a heavy polluted city (i.e., Beijing, China). Given the high level of PM_{2.5} pollution in Beijing, we were able to explore the exposure-response relationship in a wide range of PM_{2.5} concentrations. We used respiratory ERV as the health outcomes, and these unscheduled respiratory diseases therapy were more likely to be community-acquired and might reflect the acute effects of PM_{2.5} pollution. Compared to the other study in Beijing [18], our air pollution data were entirely derived from the 17 monitoring stations in urban areas in Beijing, which were more representative of the general population exposure than data from a single monitoring station.

Several limitations of our study should be mentioned. First, exposure measurement error was inevitable in this time-series study, which has been shown to bias estimates downward [45]. Second, we could not identify the re-admissions for patients with the same respiratory disease from the available data. However, it was possible that some patients, particularly children and elderly people, were admitted to hospitals multiple times in a short time period. Such repeated admissions could lead to temporal dependence among the outcomes, which may lead to an underestimation of the variance of PM_{2.5} pollution risk estimates [46]. Third, we only collected 1 year of emergency data from ten general hospitals in the current study due to the constraints of emergency data availability in multiple hospitals, which might have led to bias in the results and also limit our research power. Therefore, further studies are warranted.

Conclusions

In conclusion, our study provides evidence that PM_{2.5} pollution can increase the risk of respiratory ERV, particularly for URTI, LRTI and AECOPD in urban areas in Beijing. The strongest association was between AECOPD and the 4-day moving average PM_{2.5} concentration. Different ages and genders varied in their susceptibility to PM_{2.5} pollution. The government should pay more attention to the health effects of PM_{2.5} pollution and provide appropriate solutions to control PM_{2.5} pollution to improve air quality.

Supporting Information

S1 Database. Air pollution data, meteorological data and emergency data.
(XLS)

S1 Fig. Percentage increase of total respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations in GAM and GAMM.
(TIF)

S1 Table. Percentage changes with 95% CI in cause-specific respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations for the different lag structures in two-pollutant models. *
(DOC)

S2 Table. Percentage changes with 95% CI in total respiratory ERV associated with a 10 µg/m³ increase in the PM_{2.5} concentrations at lag₀ by different degrees of freedom (*df*) for time, temperature, and relative humidity.
(DOC)

S3 Table. Percentage changes with 95% CI in total respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations when the current day's temperature and 14-day moving average temperature were controlled.
(DOC)

S4 Table. Percentage changes with 95% CI in cause-specific respiratory ERV associated with a 10 µg/m³ increase in PM_{2.5} concentrations for different lag structures in single-pollutant GAMM. *

(DOC)

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Author Contributions

Conceived and designed the experiments: XG WW. Performed the experiments: QX XL WW XG. Analyzed the data: QX XL. Contributed reagents/materials/analysis tools: QX XL SW CW FH QG LW LT JG. Wrote the paper: QX XL SW CW FH QG LW LT JG WW XG.

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