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Qin Xu

Shuo Wang

Yuming Guo

Chao Wang

Fangfang Huang

See next page for additional authors

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Authors

Qin Xu, Shuo Wang, Yuming Guo, Chao Wang, Fangfang Huang, Xian Li, Qi Gao, Lijuan Wu, Lixin Tao, Jin Guo, Wei Wang, and Xiuhua Guo

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Acute exposure to fine particulate matter and cardiovascular hospital emergency room visits in Beijing, China☆

Qin Xu [a, b, 1], Shuo Wang [c, 1], Yuming Guo [d], Chao Wang [a, b], Fangfang Huang [a, b], Xia Li [a, e], Qi Gao [a, b], Lijuan Wu [a, b], Lixin Tao [a, b], Jin Guo [a, b], Wei Wang [a, b, f], Xiuhua Guo [a, b, *]

[a] School of Public Health, Capital Medical University, Beijing, China
[b] Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China
[c] Beijing Chao-yang Hospital, Capital Medical University, Beijing, China
[d] Division of Epidemiology and Biostatistics, School of Public Health, University of Queensland, Brisbane, Australia
[e] Graduate Entry Medical School, University of Limerick, Limerick, Ireland
[f] School of Medical Sciences, Edith Cowan University, Perth, Australia

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ABSTRACT

Fine particulate matter ($PM_{2.5}$) air pollution outbreaks have recently occurred frequently in China. However, evidence of the associations between short-term exposure to $PM_{2.5}$ and cardiovascular morbidity is still limited in China. This study aimed to evaluate the associations between $PM_{2.5}$ and hospital emergency room visits (ERVs) for cardiovascular diseases in urban areas in Beijing. Daily counts of cardiovascular ERVs were collected from ten large general hospitals from Jan 1 to Dec 31, 2013. Air pollution data were obtained from the Beijing Environmental Protection Bureau including 17 monitoring stations. A generalized additive Poisson model was used to examine the associations between $PM_{2.5}$ and cardiovascular ERVs after controlling for seasonality, day of the week, public holidays, influenza outbreaks, and weather conditions. In total, there were 56,221 cardiovascular ERVs during the study period. The daily mean $PM_{2.5}$ concentration was 102.1 μg/m^3, ranging from 6.7 μg/m^3 to 508.5 μg/m^3. Per 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.14% (95% confidence interval [*CI*]: 0.01%–0.27%) increase in cardiovascular ERVs at lag_3. Cumulative delayed estimates were greatest at lag_{0-5} (0.30%, 95% *CI*: 0.09%–0.52%). The estimates of percentage change in daily ERVs per 10 μg/m^3 increase in $PM_{2.5}$ were 0.56% (*95%CI*: 0.16%–0.95%) for ischemic heart disease (IHD) at lag_{0-1}, 0.81% (*95%CI*: 0.05%–1.57%) for heart rhythm disturbances (HRD) at lag_{0-1} and 1.21% (*95%CI*: 0.27%–2.15%) for heart failure (HF) at lag_0, respectively. The effects of $PM_{2.5}$ on IHD ERVs during high temperature days (>11.01 °C) were significantly higher than that on low temperature days (≤11.01 °C) at lag_0, lag_{0-1}, lag_{0-3} and lag_{0-5} ($P < 0.05$). The study suggests that $PM_{2.5}$ has acute impacts on cardiovascular ERVs in Beijing, especially on IHD, HRD and HF. The effects of $PM_{2.5}$ on IHD ERVs vary by temperature.

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1. Introduction

Cardiovascular diseases have become the leading cause of death throughout the world (Lozano et al., 2012; World Health Organization [WHO], 2014). Risk factors for cardiovascular diseases mainly include family history, advanced age, and lifestyle-dependent factors such as smoking, abdominal obesity, and physical inactivity. In recent years, there has been growing evidence that exposure to particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}) and ≤2.5 μm ($PM_{2.5}$, fine particulate matter) is associated with increased risks of cardiovascular diseases (Dominici et al., 2006; Pope et al., 2006; Thurston et al., 2016), even though the effects appear smaller when compared with those of other major risk factors. However, with more and more populations exposed to particulate matter air pollution, this form of pollution has become a great public health burden around the world (Lim et al., 2012). Due to its small size, $PM_{2.5}$ is (compared to PM_{10}) more likely to cross the lung-blood barrier and translocate into the

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* Corresponding author. School of Public Health, Capital Medical University, No. 10 Xitoutiao, You Anmen, Fengtai District, Beijing 100069, China.
E-mail address: statguo@ccmu.edu.cn (X. Guo).

[1] Qin Xu and Shuo Wang contributed equally to this study.

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circulatory system, where it causes additional systemic cardiovascular effects.

Previously, the short-term effects of $PM_{2.5}$ on cardiovascular diseases, measured as deaths and/or morbidity indicators such as hospital admissions and hospital emergency room visits (ERVs), have been extensively reported in the U.S. and Europe (Belleudi et al., 2010; Stafoggia et al., 2013; Rodopoulou et al., 2014; Samoli et al., 2014). Evidence of the associations between short-term $PM_{2.5}$ exposure and cardiovascular morbidity is more limited in China than in other developed countries because Chinese Air Quality Standards were based on PM_{10} until $PM_{2.5}$ was added as a criterion in 2012 (Lu et al., 2015). Moreover, only a few studies have been performed in other large Asian countries (Kim et al., 2012; Lee et al., 2015; Michikawa et al., 2015). It is clear that epidemiological evidence reported in Western countries cannot be directly generalized to Asian populations (Lee et al., 2015). Therefore, the cardiovascular effects of $PM_{2.5}$ exposure require further study in Asia.

With rapid urbanization and industrialization during the past three decades, $PM_{2.5}$ air pollution in China, especially in the Capital city—Beijing, has become a serious public health problem (Dominici and Mittleman, 2012; Zhou et al., 2015). There are a few studies that have examined the associations between $PM_{2.5}$ and cardiovascular morbidity in Beijing (Guo et al., 2009, 2010; Su et al., 2015). However, these studies only used ERVs data from one hospital and $PM_{2.5}$ data from a fixed monitoring station, which might make the results insufficiently representative due to Beijing's large population size and wide residential distribution. Another study conducted in Beijing only evaluated the effects of $PM_{2.5}$ on ischemic heart disease and did not include other cardiovascular diseases, such as cerebrovascular disease (Xie et al., 2015). Moreover, the $PM_{2.5}$ monitoring data have been released by the Beijing Environmental Protection Bureau (BEPB) since October 2012 and can be accessed by the general population (Huang et al., 2015). The availability of data from this monitoring network provided us with an opportunity to assess the short-term effects of $PM_{2.5}$ on cardiovascular morbidity.

This study aimed to evaluate the associations between $PM_{2.5}$ and cardiovascular ERVs in urban areas in Beijing from Jan 1 to Dec 31, 2013, and to examine whether the associations differed across temperature, gender and age, after controlling for seasonality, day of the week, public holidays, influenza outbreaks, and weather variables.

2. Methods

2.1. Study area

Beijing is the capital of China, located in the north of the country at latitude 39°54′N and longitude 116°25′E. The city has a total area of approximately 16,410 square kilometers (km^2), including six urban districts (Dongcheng, Xicheng, Chaoyang, Haidian, Fengtai, Shijingshan) and ten suburban districts (Changping, Mentougou, Daxing, Fangshan, Tongzhou, Shunyi, Huairou, Pinggu, Minyun and Yanqing County). It had a population of more than 21.14 million people (51.6% male) in 2013 (Beijing Municipal Bureau of Statistics, 2014a). Our study area was limited to the urban districts of Beijing (1381 km^2) where nearly 60% of the city's residents live and where the majority of large general hospitals are located. We excluded the suburban districts due to ERVs data not being available in those areas.

The major sources of air pollution in Beijing are coal burning, wind-blown dust from the surrounding industrial cities, and vehicle exhaust. The total number of automobiles has reached 5.43 million in 2013 (Beijing Municipal Bureau of Statistics, 2014b), increasing considerably the emissions of air pollutants in Beijing.

2.2. Data collection

Daily data of ERVs from Jan 1 to Dec 31, 2013 were provided by ten large general hospitals in urban areas in Beijing. Patient data were derived from the computerized medical record system of each hospital, including age, gender, visit date and diagnosis. ERVs for cardiovascular diseases were extracted according to the principal diagnosis using the International Classification of Diseases 10th version (ICD-10) Code of I00-I99. We considered cardiovascular diseases (ICD-10 codes I00-I99) and cause-specific diseases including cerebrovascular disease (CD, ICD-10 codes I60-I69), ischemic heart disease (IHD, ICD-10 codes I20–I25), heart rhythm disturbances (HRD, ICD-10 codes I44-I49), and heart failure (HF, ICD-10 code I50). Daily counts for influenza (ICD-10 codes J09-11) were used to identify influenza epidemics, which were adjusted in the data analysis (Qiu et al., 2013a).

Air pollutants including $PM_{2.5}$, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3) were obtained from the network (http://zx.bjmemc.com.cn/) of BEPB from Jan 1 to Dec 31, 2013, in Beijing. The average concentration of each pollutant across the 17 monitoring stations in urban areas were calculated to represent the daily exposure of the urban population (Qiu et al., 2013a). On a particular day, there might have been a lack of data from any of the stations due to the technical problem of website maintenance during our study period. We only used measured values without imputation in data analysis. The location of the 17 monitoring stations for air pollutants and the 10 hospitals has been published elsewhere (Xu et al., 2016). Daily mean temperature and relative humidity were obtained from the Chinese Meteorological Bureau over the same period.

The protocol of this study was approved by the Institutional Review Board at the School of Public Health, Capital Medical University. Written informed consent was not required because all health data were analyzed at the aggregate level, private information about patients was not involved, and no patients were contacted.

2.3. Statistical methods

A time-series design with generalized additive model (GAM) was employed to explore the associations between $PM_{2.5}$ concentrations and cardiovascular ERVs (Hastie and Tibshirani, 1990). Because it is generally assumed that daily ERVs followed an over-dispersed Poisson distribution, we used the quasi-Poisson link in the GAM. A penalized cubic spline function was used to adjust for seasonality in daily ERVs and potential non-linear effects of temperature and relative humidity. The degrees of freedom (*df*) for splines were selected based on previous studies (Dominici et al., 2006; Qiu et al., 2014); then, we used sensitivity analyses to test the robustness of our results. Specifically, we used 7 *df* per year for calendar time and 3 *df* for mean temperature and relative humidity. Studies suggested the effects of temperature on health would be lagged for more than 10 days (Guo et al., 2011; Ma et al., 2014), so the 14-day moving average temperature was controlled in our model. The relative humidity on the day ERVs occurred was incorporated into the models because no evidence of lagged confounding by relative humidity has been shown in air pollution epidemiology (Chen et al., 2014). In addition, all models were adjusted for day of the week (DOW), public holidays and influenza outbreaks (Schwartz et al., 1996; Qiu et al., 2013a). The core model can be specified as:

$$Log[E(Y_t|X)] = \alpha + S(Temp, 3) + S(Humid, 3) + S(Time, 7) + factor(DOW_t) + Holiday_t + Infulenza_t \quad (1)$$

Here t refers to the day of the observation; $E(Y_t|X)$ denotes expected daily case counts on day t; α is the intercept term; $S()$ denotes the smoother based on the penalized cubic spline. The variables *Temp* and *Humid* refer to 14-day moving average temperature and the current day's relative humidity, respectively; *Time* represents calendar time; DOW_t is the day of the week on day t as a categorical variable; $Holiday_t$ is categorized as a dummy variable (0 indicates no holiday, and 1 indicates a holiday); $Influenza_t$ is a dummy variable for the weeks with a number of influenza ERVs exceeding the 75th percentile in a year (Qiu et al., 2013a).

We examined the residuals of the core model to check whether there was autocorrelation by partial autocorrelation function (PACF) plot. The absolute values of the PACF plot for the model residuals had to be <0.1 for the first 2 lag days. Our initial analyses show that no autocorrelation was found in this study. The linear effects of $PM_{2.5}$ were then estimated for the same day and up to 4 days before the outcome (lag_0, lag_1, lag_2, lag_3 and lag_4) and moving averages of 2-day, 4-day and 6-day (lag_{0-1}, lag_{0-3} and lag_{0-5}). Subgroup analyses were conducted according to gender group (men and women) and age group (≥65 years and <65 years). A Z test was used to compare the two relative risks derived from each subgroup (Kan et al., 2008). In addition, we tested whether the associations were still sensitive after adjusting for other gaseous pollutants (NO_2, SO_2, O_3 and CO) in two-pollutant models. The exposure–response relationships between $PM_{2.5}$ concentrations and the log-relative risk of each cause-specific cardiovascular ERVs were investigated by replacing the linear term of $PM_{2.5}$ concentrations with the smoothing function (4 df).

Additionally, we applied a temperature-stratified parametric model to examine whether the effects of $PM_{2.5}$ on cardiovascular ERVs were heterogeneous across different levels of temperature. In this model, we categorized 14-day moving average temperature into two levels (low and high) using the median of 14-day moving average temperature (11.01 °C) as the cut-off value. The model was modified as follows:

$$Log[E(Y_t|X)] = \alpha + \beta_1 PM_t + \beta_2 temp_k + \beta_3 (PM_t : temp_k) + S(Humid, 3) + S(Time, 7) + factor(DOW_t) + Holiday_t + Influenza_t \quad (2)$$

Where $temp_k$ denotes levels of 14-day moving average temperature, β_1 signifies the main effects of $PM_{2.5}$, β_2 reflects the main effects of temperature, and β_3 represents the interactive effect of $PM_{2.5}$ and temperature. We adjusted for the same covariates as in model 1. The estimated effects of $PM_{2.5}$ on low temperature days were obtained from the main effects of $PM_{2.5}$ (β_1); the estimated effects of $PM_{2.5}$ on high temperature days were obtained from $\beta_1 + \beta_3$ (Li et al., 2011). A Z test was used to compare the two relative risks obtained from low/high temperature days (Kan et al., 2008).

To evaluate the robustness of our results, we estimated the effects of $PM_{2.5}$ on cardiovascular ERVs by using temperature on the day the ERVs occurred and by changing the degrees of freedom that were used in the smooth function of calendar time (6–13 *df*), temperature (2–6 *df*) and relative humidity (2–6 *df*) in sensitivity analysis. To check the potential exposure misclassification resulting from using average $PM_{2.5}$ concentrations across 17 monitoring stations, we checked the effects by using spatially assigned $PM_{2.5}$ concentrations and $PM_{2.5}$ concentrations from a single station. For spatially assigned $PM_{2.5}$ concentrations, we assumed that residents would be more likely to go to the nearest hospital in Beijing, so we assigned the monitored concentrations to patients based on their proximity to the hospitals and then did a similar analysis by using a generalized additive mixed model (GAMM), which adds random effects to the additive predictor accounting for over-dispersion and correlation (Coull et al., 2001). We also reanalyzed the time-series models after imputing the missing $PM_{2.5}$ concentrations for the days without values (26 days) by multiple imputation using the mice function in the R mice package.

All analyses were performed using R, version 3.2.2, with the "mgcv" package. The estimated effects were expressed as the percentage change (PC) and 95% confidence interval (*CI*) in daily cardiovascular ERVs with 10 μg/m^3 increases in the daily $PM_{2.5}$ concentration. All statistical tests were two-sided, and values of $P < 0.05$ were considered statistically significant.

3. Results

Of the 56,221 cardiovascular emergency cases that occurred during the study period, 50.1% of the data were men and 46.9% were under 65 years of age. On average, there were approximately 75 cases per day for CD, 24 IHDs, 7 HRDs, and 3 HFs (Table 1).

During the study period, the daily mean $PM_{2.5}$ concentration was 102.1 μg/m^3, with 8.8% (30 days) achieved the target of WHO Air Quality Guidelines (24-h average concentration ≤25 μg/m^3) (Table 1). The daily mean concentrations of NO_2, SO_2, O_3 and CO were 66.7 μg/m^3, 31.1 μg/m^3, 104.3 μg/m^3 and 2.2 mg/m^3,

Table 1
Distribution of cardiovascular ERVs, air pollutants and meteorological conditions in urban areas in Beijing, China.

Variables	No. of days	Mean ± SD	Percentile				
			Minimum	25th	Median	75th	Maximum
ERVs							
Cardiovascular diseases	365	154.0 ± 29.8	80.0	134.5	155.0	176.0	222.0
CD	365	75.2 ± 19.7	18.0	63.0	76.0	88.5	125.0
IHD	365	24.0 ± 7.4	9.0	19.0	23.0	28.0	47.0
HRD	365	6.5 ± 3.0	0.0	4.0	6.0	8.0	17.0
HF	365	3.4 ± 2.0	0.0	2.0	3.0	5.0	10.0
Air pollution							
$PM_{2.5}$ (μg/m^3)	339	102.1 ± 73.6	6.7	53.1	82.4	129.5	508.5
NO_2 (μg/m^3)	325	66.7 ± 25.0	12.4	50.1	62.3	78.3	171.5
SO_2 (μg/m^3)	325	31.1 ± 25.7	3.6	11.0	23.3	43.7	133.8
O_3(μg/m^3)	302	104.3 ± 68.3	4.4	53.0	89.4	146.5	305.4
CO(mg/m^3)	325	2.2 ± 1.5	0.3	1.2	1.9	2.6	17.7
Meteorological variables							
Temperature (°C)	365	11.3 ± 11.6	−12.6	1.2	11.0	22.2	29.0
Humidity (%)	365	58.7 ± 17.3	18.9	46.7	59.0	73.3	93.3

ERVs indicates emergency room visits; CD: cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure; $PM_{2.5}$: particles with an aerodynamic diameter ≤2.5 μm; NO_2: nitrogen dioxide; SO_2: sulfur dioxide; O_3: ozone; CO: carbon monoxide; SD: standard deviation.

respectively. The results showed considerable variation in temperature and relative humidity: −12.6~29.0 °C for daily mean temperature and 18.9~93.3% for relative humidity. The time series plot showed the daily variations of $PM_{2.5}$ concentrations and ERVs for cardiovascular diseases during the study period (Fig. 1).

Table 2 shows the correlations between air pollutants, temperature, and relative humidity. $PM_{2.5}$ was strongly correlated with other pollutants (correlation coefficients, $r_s > 0.56$) except for O_3 ($r_s = -0.15$). $PM_{2.5}$ was negatively correlated with temperature ($r_s = -0.07$) and positively correlated with relative humidity ($r_s = 0.33$).

The range of $PM_{2.5}$ exposures was wide and the concentrations were considerably high in the study. This pollution feature provides an opportunity to evaluate the shape of the exposure-response relationship across the full range of $PM_{2.5}$ exposures. Different curves were observed for the four specific cardiovascular ERVs (Fig. 2). For CD ERVs, there appeared to be little increase in risk until $PM_{2.5}$ concentrations exceeded approximately 190 μg/m^3. For IHD ERVs, the smoothed curve was non-linear with a steeper response at lower concentrations and a shallower response at higher concentrations. For HRD ERVs, the curve tended to be plateau at higher $PM_{2.5}$ concentrations (190 μg/m^3). For HF ERVs, there appeared to be an approximately flat response.

Table 2
Spearman correlation coefficients between air pollutants and weather variables.[a]

Variables	$PM_{2.5}$	NO_2	SO_2	O_3	CO	Temperature
NO_2	0.72					
SO_2	0.56	0.68				
O_3	−0.15	0.74	0.70			
CO	0.80	−0.23	−0.46	−0.44		
Temperature	−0.07	−0.22	−0.62	0.79	−0.41	
Relative humidity	0.33	0.12	−0.25	0.12	0.23	0.39

[a] All correlation coefficients were statistically significant ($P < 0.05$), except that between $PM_{2.5}$ and temperature.

As shown in Fig. 3, after adjusting for seasonality, day of the week, public holidays, influenza outbreaks, and weather variables, each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.14% (95% *CI*: 0.01%–0.27%) increase in cardiovascular ERVs at lag_3 in single-pollutant model. Cumulative delayed effects of $PM_{2.5}$ on

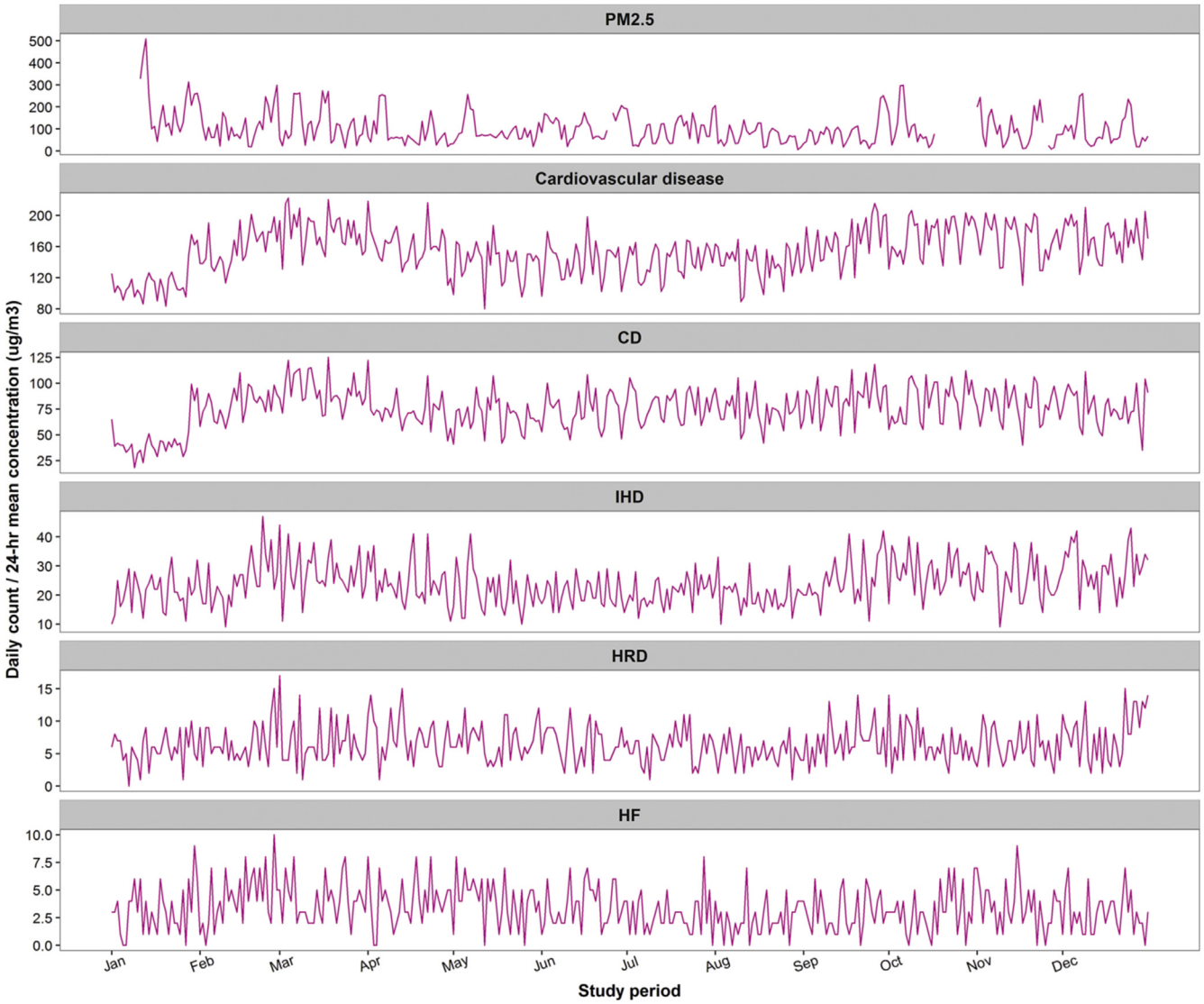


Fig. 1. Time series plot of $PM_{2.5}$ concentrations and emergency room visits for cardiovascular diseases (number of daily cases) in Beijing, China during the study period. CD indicates cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure.

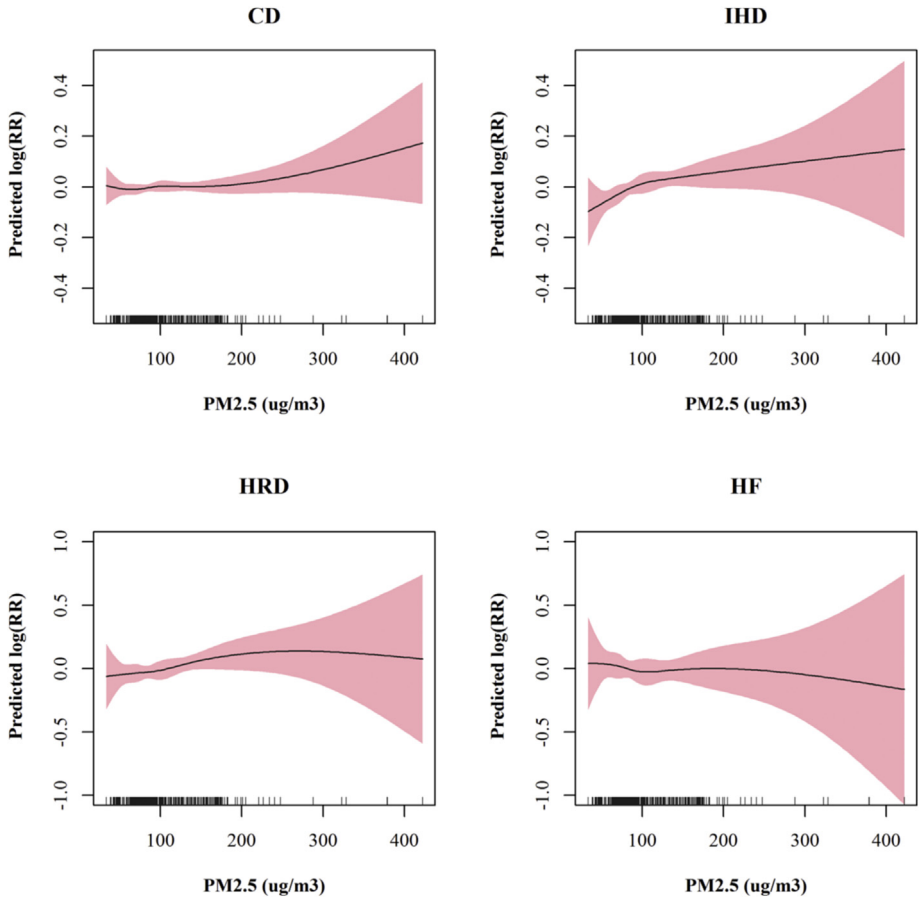


Fig. 2. The smoothing plot of daily average $PM_{2.5}$ concentrations at lag_{0-5} against the risk of each cause-specific cardiovascular ERVs.
The X-axis shows the 6-day moving averages of $PM_{2.5}$ concentrations ($\mu g/m^3$). The Y-axis is the predicted log relative risk (*RR*). The black line represents central estimates and the pink shaded area represents the 95% CI. CD indicates cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

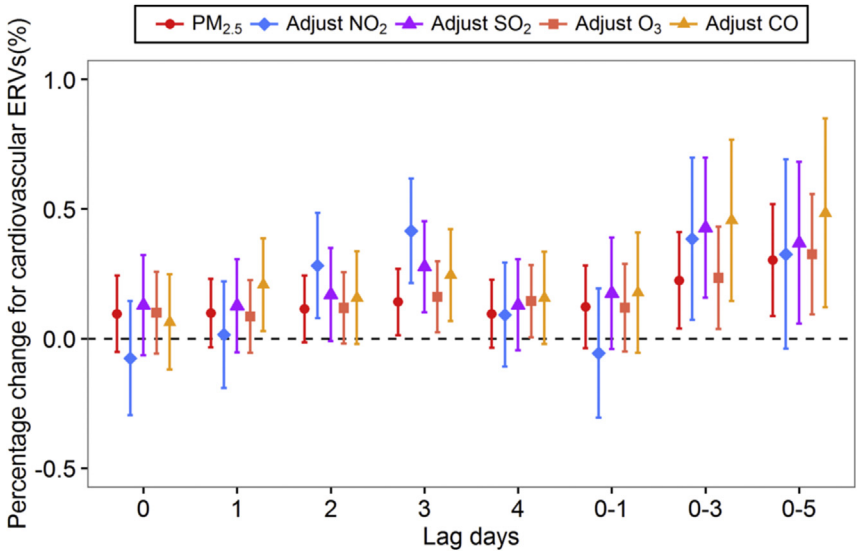


Fig. 3. Percentage changes (95% CI) in cardiovascular ERVs associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in single-pollutant and two-pollutant models.
In the single-pollutant model, $PM_{2.5}$ was used alone in the model. In the two-pollutant model, NO_2, SO_2, O_3 or CO was jointly included with $PM_{2.5}$.

cardiovascular ERVs were also significant at lag_{0-3} and lag_{0-5}; the greatest estimates occurred at lag_{0-5} (0.30%, 95% *CI*: 0.09%–0.52%). When adjusting for other pollutants (NO_2, SO_2, O_3 or CO) in the two-pollutant models, the estimated effects of $PM_{2.5}$ on cardiovascular ERVs fluctuated but remained statistically significant as in single-pollutant models.

Table 3
Percentage changes (95% CI) in cause-specific cardiovascular ERVs associated with a 10 μg/m^3 increase in $PM_{2.5}$.[a]

Lag days	CD		IHD		HRD		HF	
	PC	95% CI	PC	95% CI	PC	95% CI	PC	95% CI
lag_0	0.05	(−0.16, 0.27)	0.32	(−0.05, 0.68)	0.39	(−0.31, 1.09)	**1.21**	**(0.27, 2.15)**
lag_1	0.11	(−0.08, 0.30)	**0.50**	**(0.17, 0.82)**	**0.88**	**(0.26, 1.50)**	0.09	(−0.80, 0.97)
lag_2	0.08	(−0.10, 0.27)	**0.45**	**(0.14, 0.76)**	0.59	(−0.01, 1.19)	−0.17	(−1.04, 0.70)
lag_3	0.14	(−0.05,0.32)	0.08	(−0.25, 0.40)	0.30	(−0.32, 0.91)	−0.11	(−0.99, 0.77)
lag_4	0.06	(−0.12, 0.25)	0.12	(−0.21, 0.45)	−0.03	(−0.66, 0.61)	−1.58	(−2.51, −0.65)
lag_{0-1}	0.10	(−0.13, 0.34)	**0.56**	**(0.16, 0.95)**	**0.81**	**(0.05, 1.57)**	0.92	(−0.12, 1.96)
lag_{0-3}	0.17	(0.10, 0.44)	**0.67**	**(0.21, 1.13)**	**1.05**	**(0.18, 1.93)**	0.58	(−0.65, 1.81)
lag_{0-5}	0.19	(−0.13, 0.51)	**0.76**	**(0.23, 1.29)**	0.94	(−0.08, 1.96)	−0.33	(−1.77, 1.10)

[a] $PM_{2.5}$ was put alone in the model after controlling for seasonality, *DOW*, public holidays, influenza outbreaks, 14-day moving average temperature and relative humidity. Statistically positive significant results at the 5% level ($P < 0.05$) are indicated in bold. CD indicates cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure.

Table 3 shows the estimated effects of $PM_{2.5}$ on cause-specific cardiovascular ERVs in single-pollutant models. The association between $PM_{2.5}$ and HF ERVs was significant at lag_0 (1.21%, 95% *CI*: 0.27%–2.15%). $PM_{2.5}$ was significantly associated with IHD and HRD ERVs at different lag days. For example, the estimates of percentage change in daily ERVs per 10 μg/m^3 increase in $PM_{2.5}$ at lag_{0-1} were 0.56% (95% *CI*: 0.16%–0.95%) for IHD and 0.81% (95% *CI*: 0.05%–1.57%) for HRD. Interestingly, positive but non-significant associations were found between $PM_{2.5}$ and CD ERVs at all lag structures ($P > 0.05$).

There was no significant difference between the effects of $PM_{2.5}$ on cardiovascular ERVs during low temperature days (≤11.01 °C) and that on high temperature days (>11.01 °C) ($P > 0.05$), even though significant associations were only observed at some lags on high temperature days (Table 4). However, higher estimated effects of $PM_{2.5}$ on IHD ERVs were observed on high temperature days and the between-temperature differences were statistically significant at lag_0, lag_{0-1}, lag_{0-3} and lag_{0-5}. (Fig. 4).

Among men, the associations between $PM_{2.5}$ and cardiovascular ERVs were significant at lag_0, lag_3, lag_4 and all the cumulative lag patterns (Table 5). Meanwhile, the between-gender differences were statistically significant at lag_4 and lag_{0-5} ($P < 0.05$). The associations of $PM_{2.5}$ with IHD ERVs were significant both among men and women at different lag days. (Fig. 5). $PM_{2.5}$ was significantly associated with CD ERVs among men at lag_{0-5}, with HRD ERVs among men at lag_1 and with HF ERVs among women at lag_0 and lag_{0-1}.

We observed that the estimated effects of $PM_{2.5}$ on cardiovascular ERVs among people aged <65 years were significant at lag_3, lag_4, lag_{0-3} and lag_{0-5} (Table 5). The differences between age groups were significant for CD ERVs at lag_3 and lag_4, and for IHD ERVs at lag_3, lag_{0-3} and lag_{0-5}, with higher estimated effects among people aged <65 years ($P < 0.05$) (Fig. 6). Among people aged ≥65 years, positive significant associations were only observed between $PM_{2.5}$ and HRD ERVs at lag_1, as well as between $PM_{2.5}$ and HF ERVs at lag_0.

The estimated effects changed little when the temperature on the day the ERVs occurred was controlled in our models or under varying degrees of freedom for the smooth functions of time and weather variables (see Supplementary Tables S1 and S2). Fig. S1 shows the result using average $PM_{2.5}$ data across 17 monitoring stations, spatially assigned $PM_{2.5}$ concentrations and $PM_{2.5}$ concentrations from a single station. Table S3 shows that the differences between the estimated effects from the imputation dataset created by multiple imputation and that from the original dataset were not statistically significant ($P > 0.05$). All the sensitivity results suggested that our findings were robust.

Table 4
Percentage changes (95% CI) in cardiovascular ERVs per 10 μg/m^3 increase in $PM_{2.5}$ across temperature levels.[a]

Lag days	Temperature		*P* value[b]
	Low	High	
lag_0	0.09(−0.09, 0.26)	0.13(−0.10, 0.36)	0.785
lag_1	0.12(−0.04, 0.28)	0.07(−0.15, 0.30)	0.738
lag_2	0.09(−0.07, 0.24)	0.18(−0.03, 0.40)	0.774
lag_3	0.06(−0.09, 0.22)	**0.30(0.08, 0.51)**	0.081
lag_4	0.01(−0.15, 0.17)	**0.25(0.03, 0.46)**	0.079
lag_{0-1}	0.13(−0.06, 0.32)	0.13(−0.13, 0.38)	0.976
lag_{0-3}	0.18(−0.04, 0.40)	**0.34(0.03, 0.65)**	0.407
lag_{0-5}	0.25(−0.01, 0.51)	**0.40(0.04, 0.77)**	0.499

[a] All models were controlled for seasonality, *DOW*, public holidays, influenza outbreaks, and relative humidity. Temperature was categorized as a binary variable for low or high temperature, using the median of 14-day moving average temperature (11.01 °C) as the cut-off value, and was added to the models together with the product term of $PM_{2.5}$ and binary temperature. Statistically positive significant results at the 5% level ($P < 0.05$) are indicated in bold.

[b] The *P* value was obtained from the *Z* test for the difference between the two relative risks of high/low temperature level.

4. Discussion

In the study, we found that $PM_{2.5}$ was positively associated with cardiovascular ERVs as well as cause-specific diseases, including IHD, HRD and HF, even adjusting for other pollutants. The effects of $PM_{2.5}$ on IHD ERVs during high temperature days (>11.01 °C) were higher than that on low temperature days (≤11.01 °C). To our knowledge, this is one of a few to investigate the associations between $PM_{2.5}$ air pollution and cardiovascular morbidity under the high pollution level that have developed in China in recent years.

Although previous studies have found positive associations between short-term exposure to $PM_{2.5}$ pollution and cardiovascular hospitalizations or emergency admissions (Bell et al., 2008a; Qiu et al., 2013b; Stafoggia et al., 2013), few have revealed no significant associations (Brook et al., 2010; Milojevic et al., 2014; Nakhle et al., 2015). We conducted a time-series study in urban areas in Beijing and found that $PM_{2.5}$ was significantly associated with an increased risk of cardiovascular ERVs at lag_3. This was a shorter lag effect than another similar time-series study in Beijing, which found a significant association at lag_7 (1.20%, 95% *CI:* 0.20%–2.20%) (Su et al., 2015). However, that study used cardiovascular emergency data from one hospital located in the Haidian district and $PM_{2.5}$ data from a fixed monitoring station near the hospital, which might cause selection bias due to population mobility and the spatial variability of $PM_{2.5}$ (Altman and Bland, 2003). The same problem also exists in another case-crossover study in Beijing (Guo et al., 2009), which found a positive association at lag_0 (0.50%, 95% *CI:* 0.10%–0.90%).

Associations between $PM_{2.5}$ and cardiovascular ERVs in our

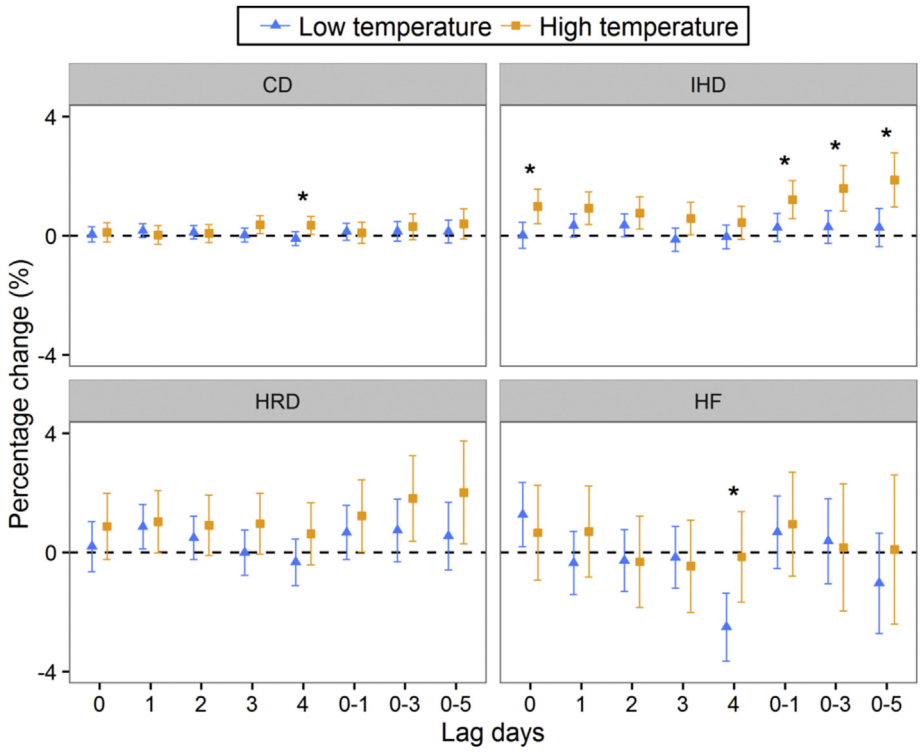


Fig. 4. Percentage changes (95% CI) in cause-specific cardiovascular ERVs per 10 μg/m^3 increase in $PM_{2.5}$ across temperature levels.
All models were controlled for seasonality, DOW, public holidays, influenza outbreaks, and relative humidity. Temperature was categorized as a binary variable for low or high temperature, using the median of 14-day moving average temperature (11.01 °C) as the cut-off value, and was added to the model together with the product term of $PM_{2.5}$ and binary temperature. The "*" in the figure indicated a *P* value less than 0.05 for the difference between the two relative risks of high/low temperature level. CD indicates cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure.

Table 5
Percentage changes (95% CI) in cardiovascular ERVs per 10 μg/m^3 increase in $PM_{2.5}$ by gender and age groups.[a]

Lag days	Gender group			Age group		
	Men	Women	*P* value[b]	Age < 65 years	Age ≥ 65years	*P* value[b]
lag_0	**0.21(0.00, 0.41)**	−0.02(−0.23, 0.18)	0.126	0.08(−0.14, 0.29)	0.10(−0.10, 0.30)	0.872
lag_1	0.16(−0.02, 0.35)	0.03(−0.16, 0.22)	0.326	0.08(−0.12, 0.27)	0.14(−0.04, 0.32)	0.642
lag_2	0.11(−0.07, 0.29)	0.12(−0.07, 0.30)	0.957	0.14(−0.05, 0.33)	0.12(−0.06, 0.30)	0.901
lag_3	**0.18(0.00, 0.36)**	0.10(−0.08, 0.28)	0.571	**0.28(0.10, 0.47)**	0.07(−0.10, 0.25)	0.110
lag_4	**0.24(0.05, 0.42)**	−0.05(−0.24, 0.13)	0.030	**0.21(0.02, 0.40)**	0.04(−0.13, 0.22)	0.228
lag_{0-1}	**0.24(0.02, 0.47)**	−0.01(−0.24, 0.22)	0.121	0.09(−0.15, 0.32)	0.16(−0.06, 0.38)	0.662
lag_{0-3}	**0.32(0.05, 0.58)**	0.12(−0.14, 0.39)	0.211	**0.28(0.01, 0.55)**	0.23(−0.05, 0.51)	0.736
lag_{0-5}	**0.56(0.25, 0.86)**	0.04(−0.26, 0.35)	0.019	**0.43(0.12, 0.75)**	0.05(−0.25, 0.35)	0.412

[a] Statistically positive significant results at the 5% level ($P < 0.05$) are indicated in bold.
[b] The *P* value was obtained from the *Z* test for the difference between the two relative risks of subgroup analysis.

study were minimally affected by NO_2, SO_2, O_3 or CO when evaluated in two-pollutant models. In most studies, positive associations between $PM_{2.5}$ and cardiovascular causes persisted after other gaseous pollutants were included in the model (Guo et al., 2010; Samoli et al., 2014; Lee et al., 2015; Michikawa et al., 2015). Some studies also reported no statistically significant association in multi-pollutant models (Stafoggia et al., 2013; Guo et al., 2009). In the study, the estimated effects of $PM_{2.5}$ on cardiovascular ERVs remained statistically significant in two-pollutant models, suggesting the independent adverse effects of $PM_{2.5}$ on human circulatory system.

In the present study, we found that $PM_{2.5}$ was associated with subcategories of cardiovascular ERVs, including IHD, HRD and HF. Other studies have also found statistically significant associations between $PM_{2.5}$ and hospital admissions due to IHD (Pope et al., 2006; Qiu et al., 2013b; Xie et al., 2015), HRD (Chiu et al., 2013; Su et al., 2015) and HF (Dominici et al., 2006; Pope et al., 2008). However, we did not detect a significant association between $PM_{2.5}$ and CD ERVs. The biologic mechanisms for the association between short-term exposures to $PM_{2.5}$ and CD have not been fully or well established. Although few previous studies have found $PM_{2.5}$ to be associated with hospital admissions due to CD (Leiva et al., 2013; Su et al., 2015), others reported results similar to ours (Bell et al., 2008b; Qiu et al., 2013b).

To our knowledge, this is one of the few studies to investigate the exposure–response functions of $PM_{2.5}$ with cause-specific cardiovascular morbidity. Previous studies conducted in the U.S. and Europe have indicated no apparent departures from linearity between particulate matter and cardiovascular mortality/morbidity (Daniels et al., 2004; Schwartz et al., 2008; Thurston et al., 2016). The present study suggests some approximately non-linear effects of $PM_{2.5}$ on the four specific cardiovascular ERVs. Curves for IHD

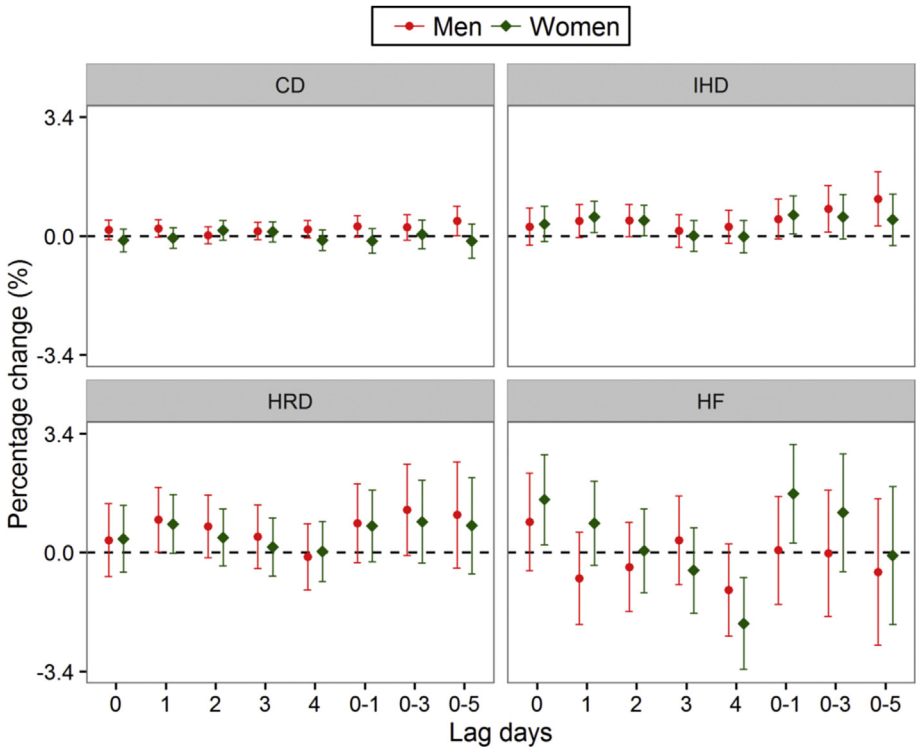


Fig. 5. Percentage Changes (95% CI) in cause-specific cardiovascular ERVs associated with a 10 μg/m^3 increase in $PM_{2.5}$ by gender group.
CD indicates cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure.

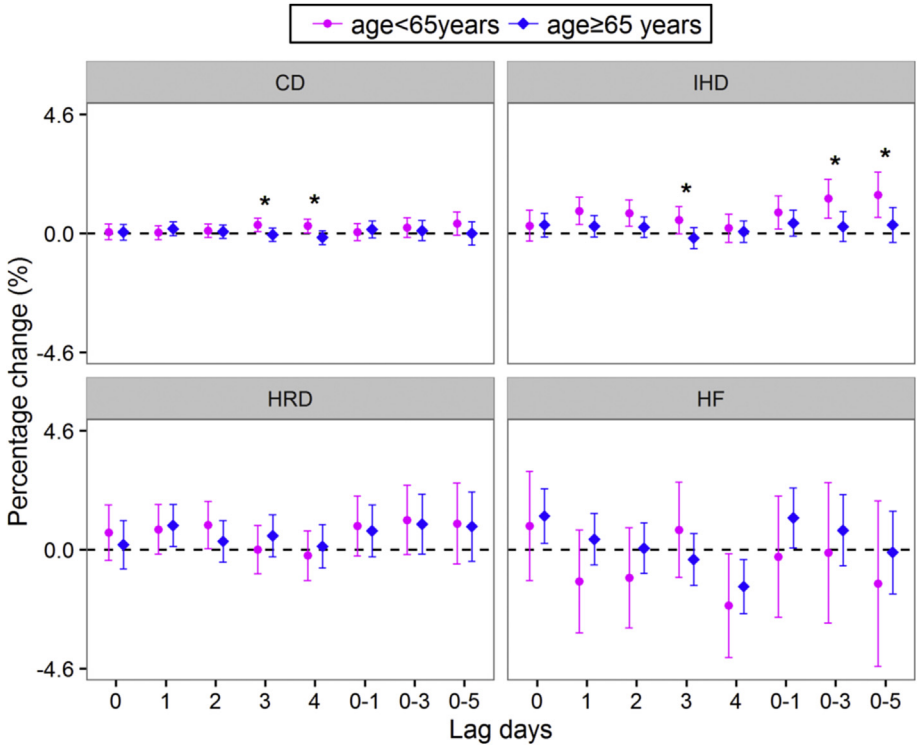


Fig. 6. Percentage Changes (95% CI) in cause-specific cardiovascular ERVs associated with a 10 μg/m^3 increase in $PM_{2.5}$ by age group.
The "*" in the figure indicated a *P* value less than 0.05 for the difference between the two relative risks of each age group. CD indicates cerebrovascular disease; IHD: ischemic heart disease; HRD: heart rhythm disturbances; HF: heart failure.

and HRD ERVs in association with $PM_{2.5}$ were steeper at lower levels of exposure than at higher levels, consistent with the exposure-response curve previously reported by a large cohort study, which estimated the long-term effects of $PM_{2.5}$ on cardiovascular mortality (Pope et al., 2009). This result is also supported by other studies conducted in China (Kan et al., 2007; Cao et al., 2012; Xie et al., 2015) and a multicity study conducted in Europe (Stafoggia et al., 2013). The curves illustrate that short-term increase in $PM_{2.5}$ could correspondingly increase the risks of the exacerbation of IHD and HRD and that further control of $PM_{2.5}$ concentration could bring appreciable benefits in IHD and HRD morbidity. Approximately flat responses were observed for CD ERVs when $PM_{2.5}$ concentrations were below 190 $\mu g/m^3$ and for HF ERVs at the full range of $PM_{2.5}$ exposures, supporting their insignificant associations with $PM_{2.5}$ at lag_{0-5}. Lin et al. (2016) suggested an approximately linear relationship between $PM_{2.5}$ and stroke, with no clear evidence of obvious threshold concentrations, which is not consistent with our results. The result from the ESCAPE Project suggested an association between $PM_{2.5}$ and incidence of CD in Europe, even in concentration ranges well below the current European air quality limit value (<25 $\mu g/m^3$) (Stafoggia et al., 2014). This difference may be explained by the different characteristics of the study background, such as $PM_{2.5}$ levels, population sensitivity, age structure, and particle composition (Kan et al., 2007). These results require further investigation in other cities and using other analytical approaches.

The small quantity of previous relevant studies reported conflicting results on the interactions between particulate matter air pollution and temperature (Samet et al., 1998; Qian et al., 2008; Stafoggia et al., 2008; Li et al., 2011; Chang et al., 2015). Li et al. (2011), for example, found a significant effect of the interaction between PM_{10} and high temperature on cardiovascular and IHD mortality in Tianjin, China. However, Samet et al. (1998) found no significant evidence that temperature modified the particulate pollution–mortality relationship. We found that the $PM_{2.5}$–IHD ERVs associations during high temperature days (>11.01 °C) were stronger than that on low temperature days (≤11.01 °C). This result indicates specific interventions for specific days should be developed (e.g., heatwave days with serious $PM_{2.5}$ air pollution).

We found that men had a higher risk of cardiovascular diseases than women, but there were no differences between men and women in cause-specific analysis. Previous studies on gender-specific effects of air pollution were inconsistent (Kan et al., 2008; Xie et al., 2014, 2015; Su et al., 2015; Zhou et al., 2015). The gender difference was not easy to explain because men may have an increased risk of cardiovascular events (Xie et al., 2014), but increased depositions of particles in the lung and higher airway responsiveness could make women more vulnerable to $PM_{2.5}$ pollution (Kan et al., 2008). In our study, we detected positive associations between $PM_{2.5}$ and cardiovascular ERVs in people aged <65 years, but no significant associations in the elderly. This contrasts with the common belief that the elderly should be more susceptible to air pollution due to their weaker immune systems and possible preexisting cardiovascular diseases (Kan et al., 2008; Xie et al., 2014, 2015; Su et al., 2015). A previous multicity time-series study by Lee et al. (2015) also found significant association between $PM_{2.5}$ and cardiovascular mortality among people aged <65 years. Considering the serious air pollution problem in Beijing, more and more people have realized the adverse effects of $PM_{2.5}$. Therefore, the elderly might reduce their time spent outdoors and make use of indoor air purifiers to lower their exposure when $PM_{2.5}$ pollution outbreaks occur. This result indicates that younger people should also become more conscious of protecting themselves by remaining indoors or using an efficient face mask as much as possible when the $PM_{2.5}$ concentration is extremely high.

$PM_{2.5}$ concentrations were averaged across 17 monitoring stations in the study. There are several reasons why we chose average $PM_{2.5}$ concentrations for our data analysis. There is a small spatial variation in $PM_{2.5}$ concentrations among the urban districts of Beijing (Huang et al., 2015); the hospitals selected for our study are located in the urban district, at the same time, they are almost surrounded by the 17 monitoring stations. Therefore, the average $PM_{2.5}$ concentrations are representative when analyzing their influence on cardiovascular ERVs. However, they may be less representative than the nearest monitoring stations located around the hospitals. When conducting sensitivity analysis, the $PM_{2.5}$ concentrations of the nearest monitoring station were assigned to patients in the hospital. Possibly due to the larger standard error generated by more missing $PM_{2.5}$ values in the GAMM, the confidence intervals of the estimated effects using spatially assigned $PM_{2.5}$ concentrations were larger than those using averaged $PM_{2.5}$ concentrations. In addition, if we assigned the monitored concentrations of the nearest station to patients based on their proximity to the hospitals and then performed pooled analysis, the count of each cause-specific cardiovascular disease in each hospital would be very small, which would limit our calculation power. This lack of power could inhibit the identification of an association, especially when the estimated effect is low.

This study has several strengths. First, a large sample size of 56,221 cardiovascular ERVs allows for sufficient statistical power to examine a significant association. Second, we used ERVs for cardiovascular diseases; these unscheduled cardiovascular emergency admissions were more likely to be community-acquired and might be more sensitive to reflect the acute effects of $PM_{2.5}$ pollution than hospitalization data or mortality data. Third, the averaged air pollutants across 17 monitoring stations were used in the study, which can reduce measurement error than use of data from one single monitoring station.

Our study also has some limitations. First, we relied on monitor-based pollution data as the proxy for the population's exposure level, which may result in inevitable measurement error. This measurement error has been shown to bias estimates downward (Goldman et al., 2011). Second, the unknown sensitivity and specificity of emergency data to determine the occurrence of cardiovascular diseases can result in a bias toward the null and minimize the potential impact of $PM_{2.5}$ on cardiovascular diseases morbidity. Third, we could not identify re-admissions for patients with cardiovascular diseases according to the available data. Some patients may be admitted to the hospital more than once during a short time period. Such repeated admissions may lead to underestimation of the variance of $PM_{2.5}$ risk estimates (Schwartz et al., 2007). Finally, the diagnosis of ERVs for cardiovascular diseases could not be 100% correct, it may cause information bias. Although we did our best to identify the different cause-specific cardiovascular diseases, potential misclassification might still exist, especially when patients suffer from several subtypes of cardiovascular diseases concurrently.

5. Conclusions

Our results have demonstrated that acute exposure to $PM_{2.5}$ air pollution could increase the risks of cardiovascular ERVs as well as cause-specific diseases, including IHD, HRD and HF in Beijing, China. The effects of $PM_{2.5}$ on IHD ERVs during high temperature days were higher than that on low temperature days. Our findings might be useful for the primary prevention of cardiovascular diseases exacerbated by $PM_{2.5}$ pollution and may have implications for local policy makers working to address poor air quality.

Author contributions

Q.X., S.W. and X.G. conceived and designed the project. Q.X.,

S.W., C.W., F.H., Q.G., L.W., L.T., J. G. collected data. Q.X. and S.W. analyzed data. Q.X. S.W., Y. G., C.W., F.H., L.X. W.W. and X.G. wrote the main manuscript text. All authors reviewed and approved the manuscript.

Conflicts of interest

The authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2016.09.065.

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