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RESEARCH ARTICLE

Investigating the impact of air pollution on AMI and COPD hospital admissions in the coastal city of Qingdao, China

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HIGHLIGHTS

- The impact of air pollution on AMI/COPD hospital admissions were examined.
- Significant connection was found between air pollutants and AMI/COPD in Qingdao.
- Nonlinearity exists between air pollution and AMI/COPD hospital admissions.

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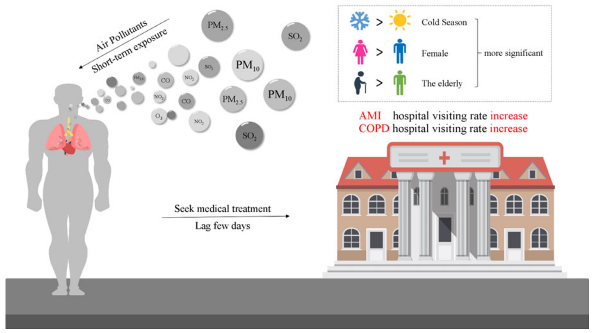

ABSTRACT

Air pollution has been widely associated with adverse effects on the respiratory and cardiovascular systems. We investigated the relationship between acute myocardial infarction (AMI), chronic obstructive pulmonary disease (COPD) and air pollution exposure in the coastal city of Qingdao, China. Air pollution in this region is characterized by inland and oceanic transportation sources in addition to local emission. We examined the influence of $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3 concentrations on hospital admissions for AMI and COPD from October 1, 2014, to September 30, 2018, in Qingdao using a Poisson generalized additive model (GAM). We found that $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO exhibited a significant short-term (lag 1 day) association with AMI in the single-pollutant model among older adults (>65 years old) and females, especially during the cold season (October to March). In contrast, only NO_2 and SO_2 had clear cumulative lag associations with COPD admission for females and those over 65 years old at lag 01 and lag 03, respectively. In the two-pollutant model, the exposure-response relationship fitted by the two-pollutant model did not change significantly. Our findings indicated that there is an inflection point between the concentration of certain air pollutants and the hospital admissions of AMI and COPD even under the linear assumption, indicative of the benefits of reducing air pollution vary with pollution levels. This study has important implications for the development of policy for air pollution control in Qingdao and the public health benefits of reducing air pollution levels.

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1 Introduction

Air pollution has become recognized as an important factor that threatens public health and safety (Bell et al., 2005; Landrigan et al., 2018; Zhang et al., 2020). A systematic analysis for the Global Burden of Disease Study 2019 showed that air pollution has become the fourth leading risk for global death for both males and females. Ambient particulate matter as the disability-adjusted life-years (DALYs) risk ranked from 13th to 7th during 1990–2019 (Murray et al., 2020). A joint policy statement from the European Respiratory Society and American Thoracic Society (ERS/ATS) indicated that air pollution has a substantial impact on the respiratory and cardiovascular systems (Thurston et al., 2017). As a result, many studies have investigated the effect of air pollutants on cardiopulmonary diseases using epidemiological statistical models. The emphasis of the impact of air pollution on public health is a reference for formulating air pollution control and governance policies on a local and even global scale.

For instance, a study of pulmonary diseases in developed countries, Islam et al. (2007) found that exposure to high levels of $PM_{2.5}$ reduced lung function through an eight-year follow-up test among adolescents in 12 communities in southern California (USA) from 1994 to 2003. Using a similar approach and with the consideration traffic exposure, Schikowski et al. (2005) found that long-term exposure to PM_{10} and NO_2 was associated with poorer lung function for women living near busy roads in the Rhine-Ruhr Basin of Germany from 1985 to 1994. By recruiting three groups of people (with heart disease, with COPD or healthy) older than 60 years, Sinharay et al. (2018) found that a two hour walk in a clean park may improve lung function, while this effect is attenuated for walking in a more polluted area with commercial streets. Using case-crossover analysis for the period 1999–2009, Wang et al. (2015) found that exposure to NO_2 was an important risk factor for acute myocardial infarction (AMI) in Alberta, Canada, especially for people with hypertension. A Belgian study observed the estimated effect of NO_2 and PM_{10} on AMI was particularly pronounced during warm seasons (Collart et al., 2015).

With the rapid economic development of China in recent years, air pollution has become severe (Chan and Yao, 2008), which may have significant effects on human health (Kan et al., 2008; Huang et al., 2018). Two main methods have been applied to investigate the short-term exposure of air pollution on cardiopulmonary diseases, case crossover (Collart et al., 2015) and time series (Cai et al., 2015). Time series studies based on the Poisson generalized additive model (GAM) are more widely used because they yield better estimate with lower autocorrelation of residuals than case crossover analysis (Guo et al., 2010a; Ren et al., 2017). For instance, studies that investigate the effect of different pollutants on hospital admission rates for cardiopulmonary diseases using GAM-based time series have been reported in several major cities in China. Goggins et al. (2013) found a more significant estimated impact of NO_2 on AMI in the cold season than in the warm season in Hong Kong (China) and Taiwan (China). This temperature-dependent relationship was also revealed in Xu et al. (2017), who found that under colder conditions, $PM_{2.5}$ tended to play a more significant role in the risk of cardiovascular diseases, including ischemic heart disease (IHD), heart rhythm disturbances (HRD) and heart failure (HF), in Beijing (China). In addition to the temperature dependent relationship, the effect of air pollution on cardiorespiratory diseases may also vary by sex and age differences in population. Wang et al. (2018b) found that $PM_{2.5}$ exerted a more significant estimated effect on females or people aged 15–60 years in Shanghai (China) for respiratory diseases, including acute upper respiratory tract infection, asthma, COPD, etc. Similar results were found by Zhang et al. (2014), indicating that NO_2 played a vital role in increasing the morbidity of COPD among women and people aged 19–64 years in Guangzhou (China). While most of the research in China has focused on northern inland cities such as Chengdu (Chen et al., 2021), Wuhan (Ren et al., 2017) and Lanzhou (Zhai et al., 2021) as well as southern coastal cities such as Guangzhou (Zhang et al., 2014) and Shanghai (Wang et al., 2018b), coastal cities in northern China such as Qingdao have not been well investigated.

Qingdao has seven districts (Laoshan, Shinan, Shibei, Licang, West Coast New Area, Chengyang and Jimo), with a total population of 9.39 million and a high urbanization rate of 70%, which is one of the developed cities worldwide (Wang and Fang, 2016). Since it is a coastal city located on the Shandong Peninsula downwind of the North China Plain, severe air pollution events frequently occur (Ma et al., 2019; Zhang et al., 2019). In contrast to northern inland cities, the air pollution in Qingdao enhance heterogeneous reactions due to the increase in sea salt (Athanasopoulou et al., 2008; Neumann et al., 2016) and the concentration of V and Ni is high due to ship emissions, which is an important contributor of $PM_{2.5}$ with an annual contribution of 25% (Bie et al., 2021). Compared to northern coastal cities such as Yantai, Rizhao and Tianjin (China), Qingdao experiences more severe air pollution (Xu et al., 2015). Similarly, in comparison to southern coastal cities, Qingdao has higher organic carbon and elemental carbon in winter due to a heating effect (Li et al., 2017a). Meanwhile, Qingdao has been frequently invaded by strong haze pollution, particularly during the winter (Li et al., 2017a; Gao et al., 2020). Together with the perception of air quality and the associated health risks of the population in different regions are closely related to the social and demographic attributes of the individual and the physical, environmental and social conditions of the community in which the individual lives (Goggins et al., 2013; Reames and Bravo, 2019), it is urgent to explore the impact of air pollution on public health in Qingdao.

In this paper, we used GAM-based time series methods to analyze the impact of air pollution in Qingdao on short-term hospital admissions of AMI and COPD, which are important factors in the global burden of disease (Lozano et al., 2012). We also aim to provide a reference value for the development of air pollution prevention and control policies.

2 Data and methods

2.1 Data

Daily hospital admissions for AMI and COPD were obtained from the Affiliated Hospital of Qingdao University from October 1, 2014, to September 30, 2018. Three branches, located in different districts (Laoshan, Shinan and West Coast New Area), accept patients from densely populated urban areas with respiratory and cardiovascular diseases. AMI (I21) and COPD (J44) were classified according to the International Classification of Diseases 10th version (ICD-10) code. Patient information included age, sex, and date of visit. Considering the characteristics of chronic illness and to avoid double-counting, the recurrent visits of COPD within the same month was excluded.

Hourly concentrations of six pollutants (particulate matter with aerodynamic diameter of $\leqslant 2.5$ μm ($PM_{2.5}$), particulate matter with aerodynamic diameter of $\leqslant 10$ μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3)) at nine national monitoring stations located in seven administrative areas of Qingdao were collected from the China National Environmental Monitoring Centre and can represent the overall pollution characteristics and levels of Qingdao. The daily mean concentrations of air pollutants over the nine monitoring sites were used. Pollution data on January 1, 2015, are missing. In addition, we ignored the abnormal observation results of CO from November 7, 2014, to November 10, 2014. Daily meteorological data were collected from the China Meteorological Data Service Center. The locations of the meteorological data monitoring station, air pollutant monitoring stations and hospital branches are shown in Table 1.

2.2 Methods

First, the GAM model was used to quantify the relationship between daily pollutant concentrations and the number of cause-specific hospital admissions (Dominici et al., 2002). The log-linear GAM was fitted as follows:

$$\begin{aligned}\mathrm{Log(Y)} &= \alpha + \beta X + \mathrm{ns}\ (\mathrm{Temperature},\ \mathrm{df}=3)\\ &\quad + \mathrm{ns}\ (\mathrm{Humidity},\ \mathrm{df}=4)\\ &\quad + \mathrm{ns}\ (\mathrm{Time},\ \mathrm{df}=7{*}4)\\ &\quad + \mathrm{DOW} + \mathrm{Holiday},\end{aligned} \tag{1}$$

where Y indicates the observed number of daily hospital admissions for a particular disease, α is the intercept, β indicates the log-relative hospital admission rate relative to the concentration of a certain air pollutant X (e.g., $PM_{2.5}$, O_3); ns is the nonparametric spline function of temperature, relative humidity and time; and DOW and holiday are categorical variables for day of the week and public holidays, respectively. We used quasi-Poisson likelihood to account for possible overdispersion in the case count. For the selection of degrees of freedom, we initially used a

Table 1 The locations of the hospital branches and air pollutant monitoring stations

Site	Longitude	Latitude	Administrative district
Meteorological data monitoring station	120.3333°E	36.0666°N	Qingdao Shibei District
Air pollution data monitoring stations	120.6659°E	36.2403°N	Qingdao Laoshan District
	120.4587°E	36.0852°N	Qingdao Laoshan District
	120.4001°E	36.2403°N	Qingdao Chengyang District
	120.3905°E	36.1851°N	Qingdao Licang District
	120.3471°E	36.0699°N	Qingdao Shibei District
	120.3664°E	36.1032°N	Qingdao Shibei District
	120.4134°E	36.0654°N	Qingdao Shinan District
	120.2992°E	36.0544°N	Qingdao Shinan District
	120.1926°E	35.9586°N	Qingdao West Coast New Area
Hospital branches	120.4536°E	36.1019°N	Qingdao Laoshan District
	120.3277°E	36.0670°N	Qingdao Shinan District
	120.1563°E	35.9871°N	Qingdao West Coast New Area

range of 3 to 5 degrees of freedom for temperature, relative humidity and 5–7 degrees of freedom for time based on previous studies (Bell et al., 2004; Guo et al., 2009; Cai et al., 2014; Zhang et al., 2014) and then applied Akaike information criteria (AIC) to identify the most suitable degrees of freedom for each specific variable, with selection of the degrees of freedom achieving the minimum AIC (Li et al., 2017b) (Table S1). We used the likelihood ratio test to evaluate the difference between linear and nonlinear simulations (Table S2).

When establishing the basic model, we considered the single-day lag effect (lag 0 to lag 7, where lag 1 represents bringing in the air pollutant and meteorological data of the previous day into the model, etc.) and cumulative lag (lag 01 to lag 06, where lag 01 represents bringing in the average air pollutant and the previous day, etc.). The analyses took into consideration age, sex, and season as factors that contribute to a potential modify the effect from air pollution (Touloumi et al., 2006; Kan et al., 2008). In this study, age was classified into two groups (0–64 years and over 65 years old), and season was divided into the warm season (April to September) and cold season (October to March). To evaluate the exposure effect of multiple pollutants, we also selected the day with the largest effect of the single pollution model to make the two-pollutant models.

After the GAM model was fitted, the regression coefficient β and standard error were used to calculate the relative risk (RR), and the upper and lower limits at the 95% confidence interval (95% CI) were used for an interquartile range (IQR) increase in pollutant concentrations. To facilitate comparison with other research, we also present the estimated changes in the risk of hospitalizations for air pollutant concentration increments of 10 μg/m^3. All statistical tests were two-sided, with statistical significance set at $P < 0.05$. For the subgroup analysis, the P value used for the statistical significance was adjusted based on Bonferroni correction (Table S3). The GAM model was analyzed using the mgcv package in R 3.3.1.

3 Results

The distributions of hospital admissions for AMI and COPD, air pollutants and meteorological data in Qingdao from October 1, 2014, to September 30, 2018, are shown in Table 2. The numbers of patients with AMI and COPD during this period were 25299 and 255597, respectively. The number of male hospitalizations for AMI (17100) and COPD (173953) were 68% of the cause-specific hospitalizations. Regardless of sex, the majority of the patients were older than 65 years, constituting 61% (15345 patients) and 76% (194766 patients) of the AMI and COPD patients, respectively.

Figure 1 shows the time series of air pollutant concentrations over the study period. With the exception of a clear decreasing trend of SO_2, the other air pollutants fluctuated over different years. For example, the mean

Table 2 Distribution of daily hospital admissions of AMI and COPD, air pollutant data and meteorological data in Qingdao, China (from October 1, 2014, to September 30, 2018)

Type	Variable	Mean±SD	Min	25th	50th	75th	Max	IQR
Hospital admissions	AMI (Total)	14±8	0	7	14	20	51	13
	AMI (Age < 65 years)	6±4	0	3	5	8	33	5
	AMI (Age⩾65 years)	9±5	0	4	8	12	32	8
	AMI (Male)	10±6	0	5	9	14	36	9
	AMI (Female)	5±3	0	2	4	7	20	5
	COPD (Total)	121±72	6	54	115	166	367	112
	COPD (Age < 65 years)	31±15	3	19	29	41	107	22
	COPD (Age⩾65 years)	90±59	3	34	85	127	307	93
	COPD (Male)	81±49	6	35	77	113	252	78
	COPD (Female)	40±24	0	18	38	55	121	37
Air pollutants	$PM_{2.5}$ (μg/m^3)	43.3±33.6	5.8	21.2	33.5	54.0	311.7	32.8
	PM_{10} (μg/m^3)	86.4±51.3	16.5	51.2	73.4	106.7	454.7	55.5
	NO_2 (μg/m^3)	34.6±16.2	2.5	23.2	32.1	43.1	107.6	19.9
	SO_2 (μg/m^3)	20.4±14.7	3.2	10.4	17.0	24.9	113.0	14.5
	CO (mg/m^3)	0.8±0.01	0.3	0.5	0.7	0.9	3.2	0.4
	O_3 (μg/m^3)	71.9±29.3	12.5	48.7	69.6	90.8	188.1	42.1
Meteorological data	Temperature (°C)	13.9±9.4	– 11.5	5.5	14.7	22.0	31.0	16.5
	Humidity (%)	68.8±16.7	16	56	71	83	100	27

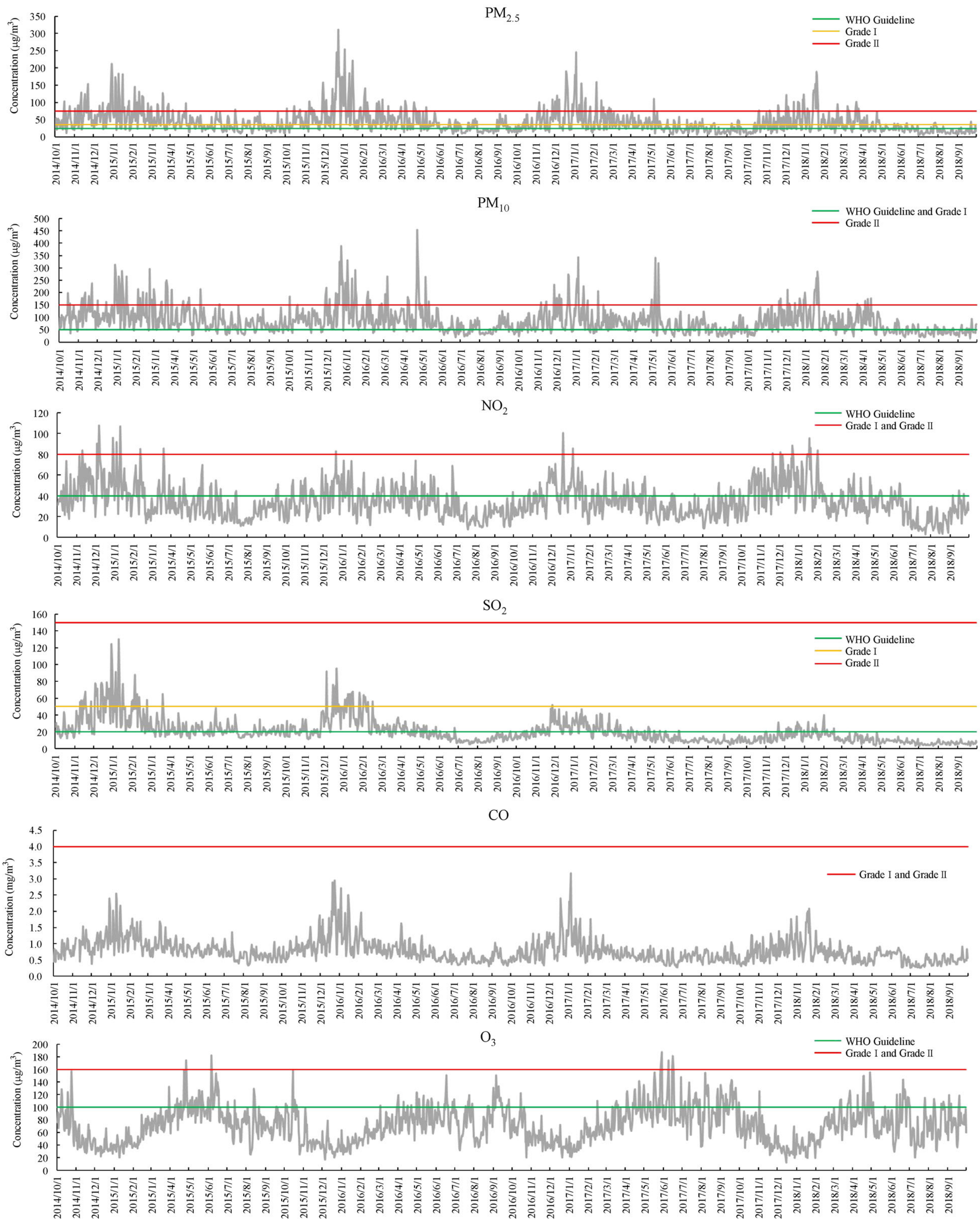

Fig. 1 Time series of daily levels of pollutant concentrations during the study period.

seasonal $PM_{2.5}$ concentration was highest in the winter of 2015, during which transport from the north and west of Qingdao played a major role (Gao et al., 2020) and severe pollution over the upwind areas (i.e., North China Plain) was attributable to the modulation of El Niño (Zhang et al., 2019). The majority of the air pollutants levels exceeded World Health Organization (WHO) guidelines (Interim Target-2). When lower standards such as Grade II of the ambient air quality standards (GB 3095-2012) of China were implemented, most of the air pollutants satisfied the criteria except $PM_{2.5}$ and PM_{10}. The number of days exceeding or satisfying the standard is summarized in Table S4 in the supporting materials.

The single-day lag model results are shown in Table S5 for AMI and COPD, indicating that AMI was significantly associated at a lag of one day (lag 1). The risk of hospitalizations was estimated to increase by 0.73% (95% CI: 0.12%, 1.37%), 0.39% (95% CI: 0.01%, 0.79%), 1.60% (95% CI: 0.22%, 3.01%), 2.50% (95% CI: 0.43%, 4.63%) and 0.1% (95% CI: 0.03%, 16.29%) for pollutant increases of 10 μg/m^3 for $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO, respectively. For COPD hospital admission, associations were statistically significant for NO_2, SO_2 and CO, with increases of 1.36% (95% CI: 0.31%, 2.43%), 1.60% (: 0.17%, 3.05%) and 0.05% (95% CI: 0.00%, 0.10%) in hospitalizations per 10 μg/m^3 increase at lag 0, respectively. The association for SO_2 was slightly higher if a lag of 1 day was considered.

To investigate the potential nonlinearity of the influence of air pollutants on AMI and COPD, we estimated the exposure response curves for $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO with the risk of AMI (lag 1) and NO_2, SO_2 and CO with the risk of COPD (lag 0) hospitalizations, as shown in Fig. 2. The selection of lags was based on the statistical significance displayed in Table S5. Statistical significance tests were applied to the results based on the linear assumption model and the nonlinear hypothesis model with likelihood ratios (Table S2), yielding in general non-significant difference except the relationship between CO and COPD. Under the linear assumption, most of the exposure response curves behave in a linear manner, despite the occasional inflection points. For example, the $PM_{2.5}$ concentration seemed to exert the largest relative risk to AMI when pollution levels exceeded approximately 100 μg/m^3, indicating that AMI patients were more sensitive to high levels of $PM_{2.5}$. The effect of SO_2 on COPD tends to be flat after 60 μg/m^3. The impact of CO on COPD visits has an inflection point around 1.5 mg/m^3, after which the risk increases significantly.

Figure 3 shows the estimated risk exerted by air pollutants on AMI by sex, season, and age. If the entire period was considered (black lines in Fig. 3), it showed the correlation of estimated AMI risk with the male sex cohort was not significant but the correlation with female sex cohort was significant, such as for $PM_{2.5}$, NO_2 and SO_2. Age was not significant in the warm season but showed some significance, i.e., PM_{10} for people younger than 65 years old and SO_2 for elderly people older than 65 years old. When season was taken into consideration, more significant results emerged. The effect of the cold season seemed to strengthen the sex and age characteristics of the AMI onset of pollutants, showing a particularly significant impact on females or people older than 65 years old. For female patients, the changes in percentage of visiting during the cold season were 1.34% (95% CI: 0.64%, 2.97%) for $PM_{2.5}$, 1.16% (95% CI: 0.38%, 1.98%) for PM_{10}, 4.16% (95% CI: 1.32%, 7.18%) for NO_2, and 5.61% (95% CI: 1.86%, 9.60%) for SO_2 at lag 1 day and for the elderly were 0.96% (95% CI: 0.40%, 2.16%), 0.90% (95% CI: 0.31%, 1.51%), 2.89% (95% CI: 0.75%, 5.14%) and

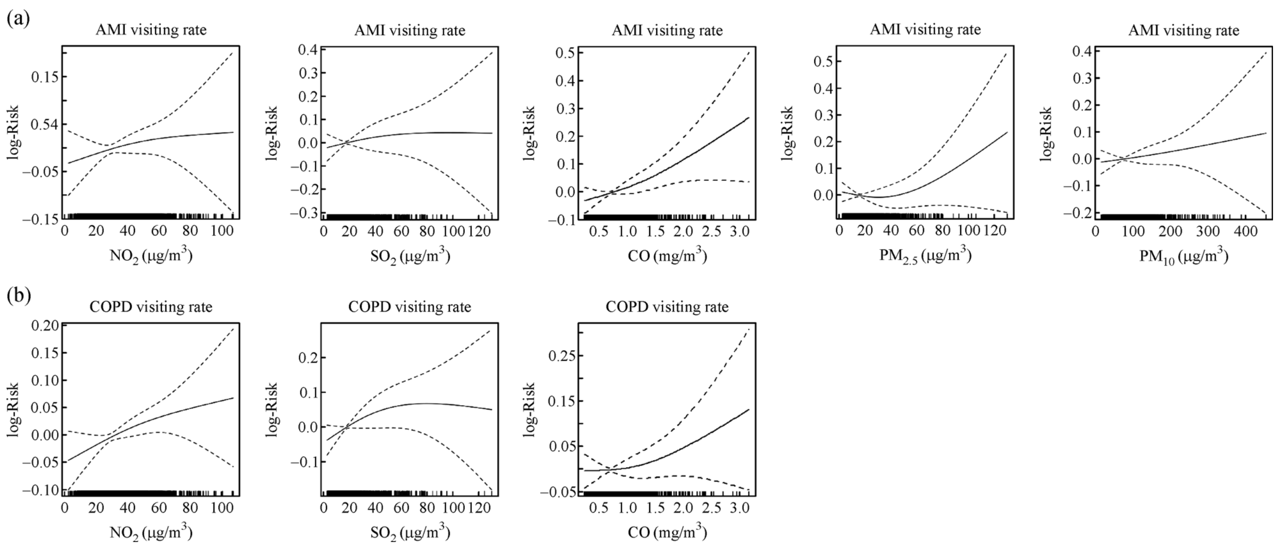

Fig. 2 Estimated exposure-response curve: relative risk of AMI (a) hospital admissions for lag 1 pollution for daily average NO_2, SO_2, CO, $PM_{2.5}$ and PM_{10} concentrations and COPD (b) for lag 0 pollution for daily average NO_2, SO_2 and CO concentrations.

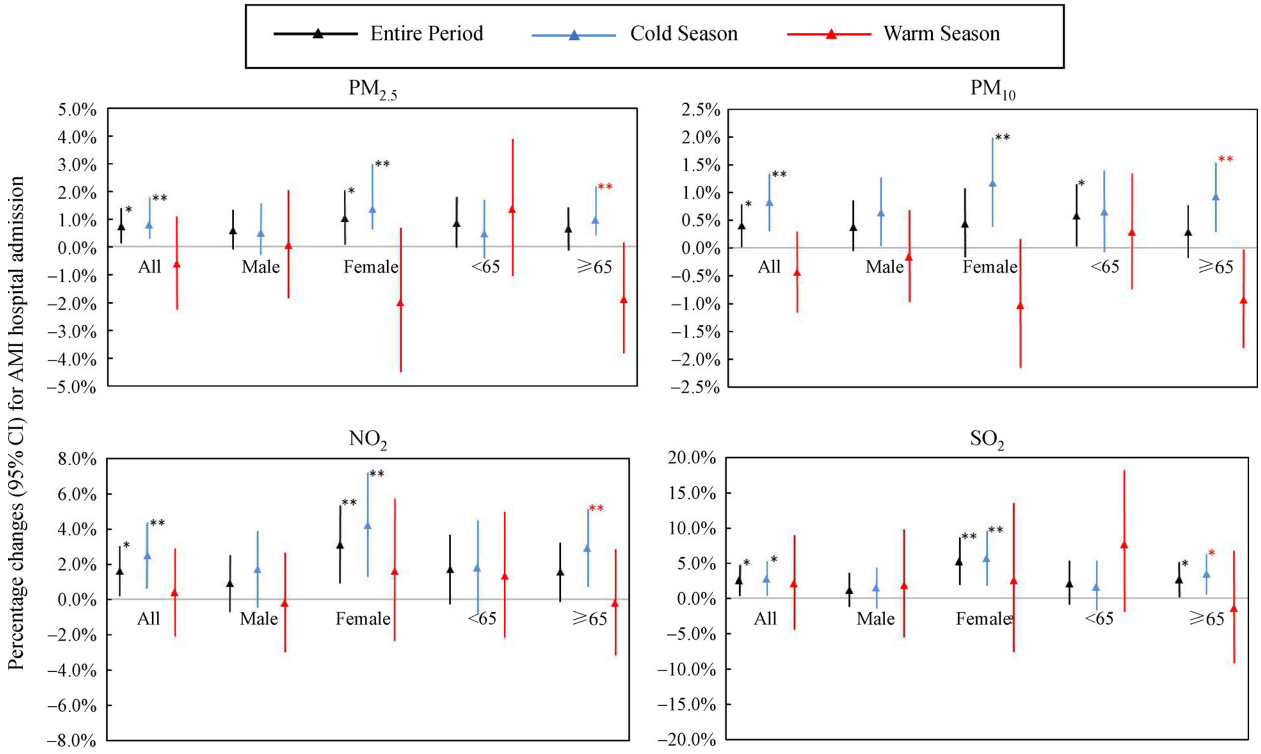

Fig. 3 Percentage changes (95% CI) in AMI all and subgroups for hospital admissions reported in different study periods (entire period, cold period and warm period) with pollutant concentration increases of 10 μg/m^3 at Lag 1. "*" represents $P < 0.05$; "**" represents $P < 0.01$. Adjust P value after Bonferroni correction: season_age: 2.90×10^{-4}, season_gender: 0.58.

3.34% (95% CI: 0.63%, 6.36%) at lag 1 day, respectively. However, after adjusting the P value with Bonferroni correction (Fig. 3), we found that in the multiple subgroup analysis, the results of the age group were not statistically significant.

For COPD, only NO_2 and SO_2 exerted significant impacts; thus, their impact by sex and age was further investigated. The effect of NO_2 (Fig. 4) on sex and age was not significantly different. While SO_2 was quite different (Fig. 5), it showed a particularly significant impact on females and the elderly. The percentage changes in the visit rate were 2.60% (95% CI: 0.93%, 4.32%) and 1.86% (95% CI: 0.29%, 3.48%) at lag 1, respectively. The effect of pollutants on the visit rate of COPD did not seem to be affected by seasonality in our study.

In addition to the single-day lag effect, the cumulative lag may also play a role. Through the examination of the influence of air pollutants on AMI and COPD based on a number of cumulative lag days, the effect of air pollutants on AMI was not significant, while NO_2 and SO_2 exerted a significant influence on COPD. For instance, both NO_2 and SO_2 share similarity in affecting COPD significantly for the subgroups, primarily for females and the elderly (⩾65 years old) (Fig. 4); however, the cumulative days differ. A significant effect occurred mainly at lag 01 days from NO_2, whereas a significant influence was achieved for SO_2 over lag 01 to lag 06 days, especially at lag 03 days (Table S6 and Fig. 5).

In the AMI two-pollution model at lag 1 day, CO was still significant in the cold season after adjusting for other pollutants, and the estimate was higher (Table 3). For example, after adjustment for CO and $PM_{2.5}$, the RR value rose from 1.051 (95% CI: 1.021–1.082) to 1.078 (95% CI: 1.006–1.155). Several pollutants were still significant even after adjusting for O_3 and had a slightly stronger impact on AMI hospital admission (Table S7). However, the impact of other pollutants on hospital admission was weakened or insignificant after adjustment. In the COPD two-pollutant model, the confounding effect of pollutants is almost insignificant.

To make a comprehensive comparison with other studies, a number of references were compiled and are shown in Tables S8 and S9 for respiratory and cardiovascular diseases and are discussed later.

4 Discussion

For AMI, we found that $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO had a significant effect (Table S5), which is consistent with previous studies focusing on Europe and other cities of China (Samoli et al., 2006; Guo et al., 2009; Lin and Kuo, 2013; Lin et al., 2013; Lee et al., 2015; Xu et al., 2017). A review paper by Brook et al. (2010) illustrated that both short-term and long-term exposure to particulate matter played important roles in affecting cardiovascular disease

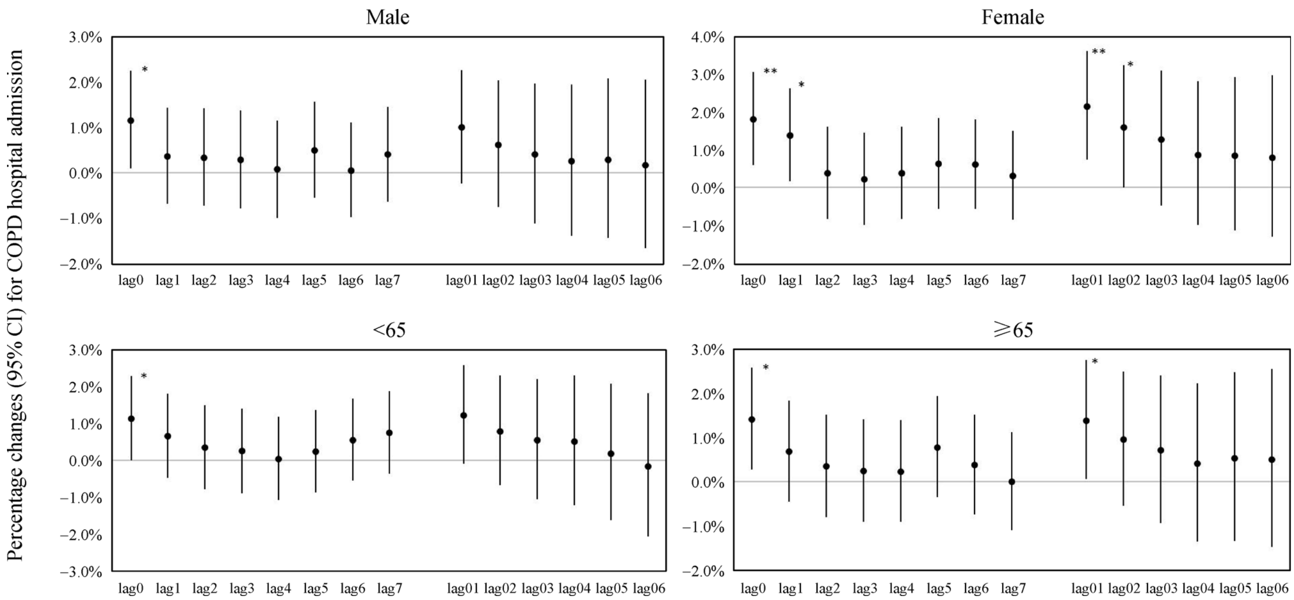

Fig. 4 Percentage change (95% CI) in COPD subgroups for hospital admissions and a NO_2 concentration increase of 10 μg/m^3 during the entire study period single-day lag and multiday lag. "*" represent $P < 0.05$; "**" represent $P < 0.01$.

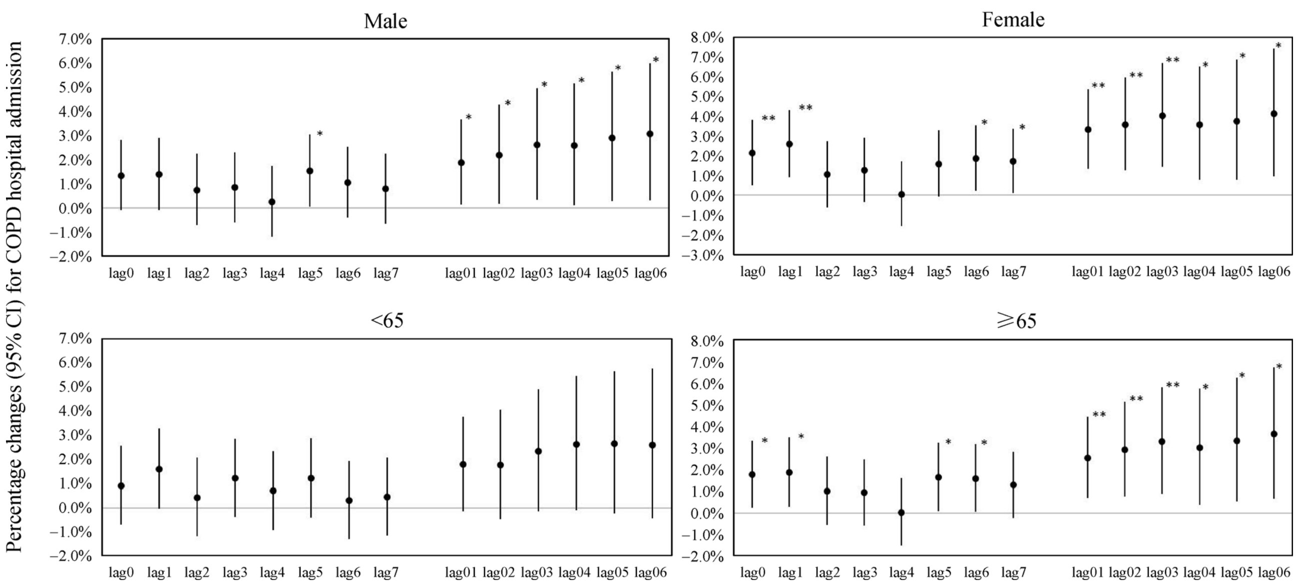

Fig. 5 Percentage change (95% CI) in COPD subgroups for hospital admissions with a SO_2 concentration increase of 10 μg/m^3 during the entire study period single-day lag and multiday lag. "*" represent $P < 0.05$; "**" represent $P < 0.01$.

Table 3 Relative risk (95% CI) at lag 1 day of AMI hospital admissions in two-pollutant models, CO as the main pollutant

Model	Whole period	Cold season	Warm season
CO	1.038(1.013–1.063)*	1.051(1.021–1.082)*	0.976(0.921–1.035)
+ $PM_{2.5}$	1.039(0.989–1.091)	1.078(1.006–1.155)*	0.994(0.906–1.089)
+ PM_{10}	1.037(1.001–1.075)*	1.040(0.982–1.101)	0.990(0.923–1.062)
+ NO_2	1.031(0.995–1.068)	1.053(1.005–1.103)*	0.959(0.890–1.032)
+ SO_2	1.029(0.996–1.064)	1.059(1.016–1.103)*	0.947(0.879–1.021)
+ O_3	1.037(1.012–1.062)*	1.050(1.019–1.083)*	0.980(0.921–1.042)

Notes: "*" represent $P < 0.05$.

incidence. According to the results of our study, $PM_{2.5}$ had a greater impact on the rate of AMI hospital admissions than PM_{10}, and a similar conclusion was drawn in the study on daily CVD mortality rate in Shanghai by Kan et al. (2007), who found a more detrimental effect from $PM_{2.5}$ in comparison to the coarse particulate matter ($PM_{10-2.5}$) on cardiovascular patients. Another mechanism pointed out by Stone et al. (2000) was that particulate matter might increase calcium influx and cause oxidative stress responses after exposure to macrophages. In contrast, the influencing mechanism of NO_2 was through the enhancement of fibrinogen, a risk factor for cardiovascular disease (Pekkanen et al., 2000). The effect of SO_2 was mainly through the production of degraded hemoglobin, which subsequently reduced the permeability of red blood cells and resulted in the lack of oxygen in organs (Baskurt et al., 1990). In results, the estimation of SO_2 was the most significant. At a 1-day lag, the hospital admission for AMI increased by 2.50% (95% CI: 0.43%, 4.63%) for every 10 μg/m^3 increase. CO is a recognized cardiovascular toxin, and exposure to high environmental levels can cause myocardial infarction (Marius-Nunez, 1990). However, even at low levels of exposure, carboxyhemoglobin can aggravate myocardial ischemia in patients with coronary artery disease (Allred et al., 1989), which supports the conclusion that although the CO concentration in Qingdao has always been below Grade II (Table S4), it still has a significant impact on AMI hospital admissions. There were no significant relationships between O_3 and the incidence of AMI in our study which is consistent with prior literature (Kan et al., 2008; Lin et al., 2013; Wang et al., 2015). However, a study conducted by Chang et al. (2005) using a case-crossover analysis method found that O_3 in Taiwan (China) had positive associations with cardiovascular admissions, especially in the warm season during 1997–2001, which may be related to the subtropical climate in Taipei (China) and the high concentration during the warm season, may explained by the variable reduce of heart rate due to a decrease in vagal tone (Gold et al., 2000).

Regarding the lag effect for AMI (Table S5), the short-term response of one day lag was found by other studies in southern Europe (Stafoggia et al., 2013) and Canada (Stieb et al., 2009). However, the number of lag days showed a statistically significant impact of air pollutants on AMI might not be the same in different studies, i.e., lag 0 days (Middleton et al., 2008; Kim et al., 2012) and lag 2 days (Xu et al., 2017). Nevertheless, a study of particulate matter and the number of daily cardiovascular emergencies in Beijing (China) showed that the impact of $PM_{2.5}$ on cardiovascular emergencies was most significant at a lag of 7 days, exhibiting an RR of 1.012 (95% CI: 1.002–1.022) (Su et al., 2016). Based on a large number of references shown in Table S8, it can be seen that most studies indicate that a statistically significant impact of air pollutant on AMI may be obtained when a lag day of 0 to 2 is applied; these results are consistent with the findings in our study.

Regarding whether seasonal temperature changes might affect the change in estimated values, our results showed that during the cold season, the impact of air pollutants on the incidence of AMI was more dramatic (Fig. 3). This finding is supported by the study of Goggins et al. (2013), showing that the hospitalization rate of AMI in Hong Kong (China) and Taipei (China) may increase by 3.7% and 2.6% for each degree reduction starting from 24°C, respectively. A similar finding was also drawn for most studies in Asia (Chang et al., 2005; Lee et al., 2015; Su et al., 2016). Another study in Charleroi, Belgium, by Collart et al. (2015) found that the risk of AMI admission was significantly enhanced by PM_{10} and NO_2 during the warm season, attributable to longer exposure times during the warm season. A comparably stronger relationship of $PM_{2.5}$-IHD (ischemic heart disease) ERVs was also found during high temperature days (>11.01°C) in Beijing (China) (Xu et al., 2017).

In terms of sex, we found that females were more susceptible to air pollution than males, consistent with other studies (Kan et al., 2008; Zhang et al., 2011; Chen et al., 2012; Lin et al., 2013; Su et al., 2016). This was primarily connected to the stronger responsiveness to airways and enhanced particle deposition in the lungs of females (Kim and Hu, 1998; Kohlhäufl et al., 1999). In contrast, the studies by Xu et al. (2016) and Chen et al. (2018) showed a statistically significant influence of air pollution on CVD for males but not for females, likely caused by compounding factors such as smoking (Cohen et al., 2017). This contributes to our findings the number of male patients with AMI was more than twice that of female patients (Table 2). Although after adjusting the *P* value with Bonferroni correction, the sex subgroup analysis in the cold season did not show significant differences.

In regard to age, the elderly was more likely to be affected by air pollution and subsequently have a higher risks of suffering AMI, supported by a number of studies in China and abroad (Kan et al., 2008; Chen et al., 2012; Goggins et al., 2013; Lin and Kuo, 2013; Wang et al., 2015; Chen et al., 2018). It might be the result of the decline of body functions and a fragile cardiovascular system and organs (Fischer et al., 2003).

In the multi-pollutant model, prior research indicates that the confounder between pollutants would increase the incidence of cardiopulmonary diseases more than single pollutants (Guo et al., 2010b; Lee et al., 2015). However, our results showed that after adjusting for co-pollutants, the estimates were reduced or insignificant, except when adjusting for O_3, and in the cold season when CO is the main pollutant, the estimates were still significant, but the changes were almost negligible (Tables 3 and S7). A study by Guo et al. (2009) in Beijing (China) on the relationship between particulate matter and cardiovascular emergency departments also concluded that in the multipollutant model, no significant statistical association between air pollutants and CVD was found. Similar conclusions are also reflected in many studies (Stafoggia et al., 2013; Newell et al., 2017). Wang et al. (2018b) indicated that although pollutants are highly correlated, they do not have confounder effects. Some scholars contend that pollutants have relatively independent effects (Xu et al., 2017).

Compared to cardiovascular diseases, the pathogenesis of respiratory diseases such as COPD is different (Fischer et al., 2003; Chang et al., 2005; Chen et al., 2012; Phung et al., 2016), which may lead to different responses of COPD to air pollution. We found a statistically significant relationship between gas pollutants, including NO_2, SO_2, and COPD, while no significant correlation was observed between particulate matter (i.e., $PM_{2.5}$ and PM_{10}) and COPD (Table S5), inconsistent with a few previous studies (Dominici et al., 2006; Samoli et al., 2006; Cai et al., 2014). For instance, Wang et al. (2018a) conducted lung function tests based on a large population sample and found that relatively high $PM_{2.5}$ concentrations, such as annual mean concentrations greater than 50 μg/m^{3,} tend to be a risk factor for COPD. However, the mean annual $PM_{2.5}$ concentration in Qingdao is 43.3 μg/m^3 (Table 2), possibly not high enough to significantly affect COPD. Meanwhile, Wang et al. (2018a) demonstrated that other factors, such as family history of diseases and education level, might also play vital roles in modulating COPD, and these confounding factors could yield an insignificant relationship between $PM_{2.5}$ and COPD. Consistently, the pulmonary function test conducted in Europe indicated that $PM_{2.5}$ was not necessarily related to COPD (Götschi et al., 2008).

Regarding the lag effect of air pollution on COPD (Fig. 5), our results showed a significant cumulative lag effect of NO_2 and SO_2 on COPD, consistent with a few studies focusing on Shanghai, China (Kan et al., 2008) and the Netherlands (Fischer et al., 2003) (Table S9). The exact mechanism modulating the lag is unclear so far, requiring future efforts to delve into the mechanism.

The seasonal influence of air pollutants on COPD was not significant in our study, which is supported by Liu et al. (2017), who investigated pediatric outpatient visits for respiratory diseases in Yichang, Hubei, China. However, seasonal differences were revealed by other studies, with some showing significance in the cold season (Kan et al., 2008; Cai et al., 2014; Lee et al., 2015; Wang et al., 2018b) and others in the warm season (Middleton et al., 2008; Stieb et al., 2009; Zhang et al., 2014). In revealing the differences in sex and age subgroups in responding to the influence of air pollutants on COPD (Figs. 4 and 5), our study's finding that women and the elderly were more vulnerable to air pollution is generally consistent with prior research (Kan et al., 2008; Tao et al., 2014; Xu et al., 2016).

The exposure response curve had an inflection point under the assumption of linearity, indicating that the public health benefits of air pollution concentration control may vary depending on the slope. Similar results have also appeared in other literature. For instance, Xu et al. (2017) found a consistent exposure response curve like this study, which is steeper at high concentrations between $PM_{2.5}$ and cerebrovascular diseases in Beijing, while Liu et al. (2017) illustrated comparable variation pattern between SO_2 and COPD (Fig. 2 in this study vs. Fig. 4 in Liu et al., 2017) which tends to become flat when the concentration of SO_2 exceeds a certain value. This striking feature implies the necessity and importance of emission reduction and a subsequent decrease in air pollutant concentration, as well as the dependence of hospital admission risk reduction on the slope. Specifically, the reduction in high concentrations of $PM_{2.5}$ is likely to be most effective in reducing the risk of AMI hospital admission considering the strong correlation, the same can be said for the relationship between CO and COPD. However, the effectiveness is relatively low for COPD if only high SO_2 concentration is reduced due to the nearly flat or even negative slope (Fig. 2).

There are a couple of limitations in our study. First, only one hospital is selected in Qingdao due to data availability, and if possible, more hospitals might be included in the examination of the relationship between air pollutants and human health in the future. Second, the distributions of air pollutant observations are limited, which will cause exposure measurement errors to a certain extent. Therefore, a more intensive observation network could be enhanced, or experimental methods of portable air quality measuring instruments could be tested in the future. Nevertheless, please note that a sensitivity test was conducted by selecting four closest stations to the three branches of the hospital, yielding comparable exposure-response results to that based on nine stations. Third, the high correlation between pollutants will cause estimation bias due to the collinearity of the model (Table S10). Last, compounding factors such as smoking and individual lifestyle were not taken into consideration and deserve further investigation in the future.

5 Conclusions and summary

Overall, our study revealed significant effects of air pollutants on cardiorespiratory diseases, we found that $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO exhibited a significant short-term association with AMI in the single-pollutant model, especially for the elderly and females during the cold season. In contrast, for COPD, only NO_2 and SO_2 displayed clear cumulative lag associations with COPD admission for females and the elderly. The exposure response curve may provide useful guidance in the enforcement of air quality control aiming to achieve the maximal benefit in both protecting human health and maintaining the progress of the economy. Given the close relationship exhibited in the exposure response curve, we suggest that the timely notification of near-term forecasts of health impacts due to air pollution may be a good alternative to emission control.

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References

Allred E N, Bleecker E R, Chaitman B R, Dahms T E, Gottlieb S O, Hackney J D, Pagano M, Selvester R H, Walden S M, Warren J (1989). Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. New England Journal of Medicine, 321(21): 1426–1432

Athanasopoulou E, Tombrou M, Pandis S N, Russell A G (2008). The role of sea-salt emissions and heterogeneous chemistry in the air quality of polluted coastal areas. Atmospheric Chemistry and Physics, 8(19): 5755–5769

Baskurt O K, Levi E, Caglayan S, Dikmenoglu N, Kutman M N (1990). Hematological and hemorheological effects of air pollution. Archives of Environmental Health, 45(4): 224–228

Bell M L, Dominici F, Samet J M (2005). A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology (Cambridge, Mass.), 16(4): 436–445

Bell M L, McDermott A, Zeger S L, Samet J M, Dominici F (2004). Ozone and short-term mortality in 95 US urban communities, 1987–2000. Journal of the American Medical Association, 292(19): 2372–2378

Bie S, Yang L, Zhang Y, Huang Q, Li J, Zhao T, Zhang X, Wang P, Wang W (2021). Source appointment of $PM_{2.5}$ in Qingdao Port, East of China. Science of the Total Environment, 755(Pt 1): 142456

Brook R D, Rajagopalan S, Pope C A 3rd, Brook J R, Bhatnagar A, Diez-Roux A V, Holguin F, Hong Y, Luepker R V, Mittleman M A, Peters A, Siscovick D, Smith S C Jr, Whitsel L, Kaufman J D, the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, Council on Nutrition, Physical Activity and Metabolism (2010). Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation, 121(21): 2331–2378

Cai J, Chen R, Wang W, Xu X, Ha S, Kan H (2015). Does ambient CO have protective effect for COPD patient? Environmental Research, 136: 21–26

Cai J, Zhao A, Zhao J, Chen R, Wang W, Ha S, Xu X, Kan H (2014). Acute effects of air pollution on asthma hospitalization in Shanghai, China. Environment and Pollution, 191: 139–144

Chan C K, Yao X (2008). Air pollution in mega cities in China. Atmospheric Environment, 42(1): 1–42

Chang C C, Tsai S S, Ho S C, Yang C Y (2005). Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan, China. Environmental Research, 98(1): 114–119

Chen C, Zhu P, Lan L, Zhou L, Liu R, Sun Q, Ban J, Wang W, Xu D, Li T (2018). Short-term exposures to $PM_{2.5}$ and cause-specific mortality of cardiovascular health in China. Environmental Research, 161: 188–194

Chen J Y, Shi C L, Li Y, Ni H Z, Zeng J, Lu R, Zhang L (2021). Effects of short-term exposure to ambient airborne pollutants on COPD-related mortality among the elderly residents of Chengdu city in Southwest China. Environmental Health and Preventive Medicine, 26, 7

Chen R, Kan H, Chen B, Huang W, Bai Z, Song G, Pan G, the CAPES Collaborative Group (2012). Association of particulate air pollution with daily mortality: the China air pollution and health effects study. American Journal of Epidemiology, 175(11): 1173–1181

Cohen A J, Brauer M, Burnett R, Anderson H R, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, et al. (2017). Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. Lancet, 389(10082): 1907–1918

Collart P, Coppieters Y, Mercier G, Massamba Kubuta V, Leveque A (2015). Comparison of four case-crossover study designs to analyze the association between air pollution exposure and acute myocardial infarction. International Journal of Environmental Health Research, 25(6): 601–613

Dominici F, McDermott A, Zeger S L, Samet J M (2002). On the use of generalized additive models in time-series studies of air pollution and health. American Journal of Epidemiology, 156(3): 193–203

Dominici F, Peng R D, Bell M L, Pham L, McDermott A, Zeger S L, Samet J M (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. Journal of the American Medical Association, 295(10): 1127–1134 PMCID: PMC3543154

Fischer P, Hoek G, Brunekreef B, Verhoeff A, van Wijnen J (2003). Air pollution and mortality in The Netherlands: are the elderly more at risk? European Respiratory Journal. Supplement, 21(Supplement 40): 34S–38S

Gao Y, Shan H, Zhang S, Sheng L, Li J, Zhang J, Ma M, Meng H, Luo K, Gao H, Yao X (2020). Characteristics and sources of $PM_{2.5}$ with focus on two severe pollution events in a coastal city of Qingdao, China. Chemosphere, 247: 125861

Goggins W B, Chan E Y, Yang C Y (2013). Weather, pollution, and acute myocardial infarction in Hong Kong (China) and Taiwan (China). International Journal of Cardiology, 168(1): 243–249

Gold D R, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R (2000). Ambient pollution and heart rate variability. Circulation, 101(11): 1267–1273

Götschi T, Sunyer J, Chinn S, de Marco R, Forsberg B, Gauderman J W, Garcia-Esteban R, Heinrich J, Jacquemin B, Jarvis D, Ponzio M, Villani S, Künzli N (2008). Air pollution and lung function in the European Community Respiratory Health Survey. International Journal of Epidemiology, 37(6): 1349–1358

Guo Y, Barnett A G, Zhang Y, Tong S, Yu W, Pan X (2010a). The short-term effect of air pollution on cardiovascular mortality in Tianjin, China: Comparison of time series and case-crossover analyses.

Science of the Total Environment, 409(2): 300–306

Guo Y, Jia Y, Pan X, Liu L, Wichmann H E (2009). The association between fine particulate air pollution and hospital emergency room visits for cardiovascular diseases in Beijing, China. Science of the Total Environment, 407(17): 4826–4830

Guo Y, Tong S, Zhang Y, Barnett A G, Jia Y, Pan X (2010b). The relationship between particulate air pollution and emergency hospital visits for hypertension in Beijing, China. Science of the Total Environment, 408(20): 4446–4450

Huang J, Pan X, Guo X, Li G (2018). Health impact of China's Air Pollution Prevention and Control Action Plan: An analysis of national air quality monitoring and mortality data. Lancet. Planetary Health, 2(7): e313–e323

Islam T, Gauderman W J, Berhane K, McConnell R, Avol E, Peters J M, Gilliland F D (2007). Relationship between air pollution, lung function and asthma in adolescents. Thorax, 62(11): 957–963

Kan H, London S J, Chen G, Zhang Y, Song G, Zhao N, Jiang L, Chen B (2007). Differentiating the effects of fine and coarse particles on daily mortality in Shanghai, China. Environment International, 33(3): 376–384

Kan H, London S J, Chen G, Zhang Y, Song G, Zhao N, Jiang L, Chen B (2008). 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. Environmental Health Perspectives, 116(9): 1183–1188

Kim C S, Hu S C (1998). Regional deposition of inhaled particles in human lungs: comparison between men and women. Journal of Applied Physiology, 84(6): 1834–1844

Kim S Y, Peel J L, Hannigan M P, Dutton S J, Sheppard L, Clark M L, Vedal S (2012). The temporal lag structure of short-term associations of fine particulate matter chemical constituents and cardiovascular and respiratory hospitalizations. Environmental Health Perspectives, 120(8): 1094–1099

Kohlhäufl M, Brand P, Scheuch G, Meyer T S, Schulz H, Häussinger K, Heyder J (1999). Increased fine particle deposition in women with asymptomatic nonspecific airway hyperresponsiveness. American Journal of Respiratory and Critical Care Medicine, 159(3): 902–906

Landrigan P J, Fuller R, Acosta N J R, Adeyi O, Arnold R, Basu N, Baldé A B, Bertollini R, Bose-O'reilly S, Boufford J I, et al. (2018). The Lancet Commission on pollution and health. Lancet, 391 (10119): 462–512

Lee H, Honda Y, Hashizume M, Guo Y L, Wu C F, Kan H, Jung K, Lim Y H, Yi S, Kim H (2015). Short-term exposure to fine and coarse particles and mortality: A multicity time-series study in East Asia. Environment and Pollution, 207: 43–51

Li L, Yan D, Xu S, Huang M, Wang X, Xie S (2017a). Characteristics and source distribution of air pollution in winter in Qingdao, eastern China. Environment and Pollution, 224: 44–53

Li Y, Shi X, Yang M, Liang L (2017b). Variable selection in data envelopment analysis via Akaike's information criteria. Annals of Operations Research, 253(1): 453–476

Lin C M, Kuo H W (2013). Sex-age differences in association with particulate matter and emergency admissions for cardiovascular diseases: a hospital-based study in Taiwan, China. Public Health, 127 (9): 828–833

Lin H, An Q, Luo C, Pun V C, Chan C S, Tian L (2013). Gaseous air pollution and acute myocardial infarction mortality in Hong Kong, China: A time-stratified case-crossover study. Atmospheric Environment, 76: 68–73

Liu Y, Xie S, Yu Q, Huo X, Ming X, Wang J, Zhou Y, Peng Z, Zhang H, Cui X, Xiang H, Huang X, Zhou T, Chen W, Shi T (2017). Short-term effects of ambient air pollution on pediatric outpatient visits for respiratory diseases in Yichang city, China. Environment and Pollution, 227: 116–124

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn S Y, et al. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet, 380(9859): 2095–2128

Ma M, Gao Y, Wang Y, Zhang S, Leung L R, Liu C, Wang S, Zhao B, Chang X, Su H, Zhang T, Sheng L, Yao X, Gao H (2019). Substantial ozone enhancement over the North China Plain from increased biogenic emissions due to heat waves and land cover in summer 2017. Atmospheric Chemistry and Physics, 19(19): 12195–12207

Marius-Nunez A L (1990). Myocardial infarction with normal coronary arteries after acute exposure to carbon monoxide. Chest, 97(2): 491–494

Middleton N, Yiallouros P, Kleanthous S, Kolokotroni O, Schwartz J, Dockery D W, Demokritou P, Koutrakis P (2008). A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. Environmental Health, 7: 39

Murray C J L, Aravkin A Y, Zheng P, Abbafati C, Abbas K M, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, Abdollahpour I, et al. (2020). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet, 396(10258): 1223–1249

Neumann D, Matthias V, Bieser J, Aulinger A, Quante M (2016). Sensitivity of modeled atmospheric nitrogen species and nitrogen deposition to variations in sea salt emissions in the North Sea and Baltic Sea regions. Atmospheric Chemistry and Physics, 16(5): 2921–2942

Newell K, Kartsonaki C, Lam K B H, Kurmi O P (2017). Cardiorespiratory health effects of particulate ambient air pollution exposure in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet. Planetary health, 1(9): e368–e380

Pekkanen J, Brunner E J, Anderson H R, Tiittanen P, Atkinson R W (2000). Daily concentrations of air pollution and plasma fibrinogen in London. Occupational and Environmental Medicine, 57(12): 818–822

Phung D, Hien T T, Linh H N, Luong L M, Morawska L, Chu C, Binh N D, Thai P K (2016). Air pollution and risk of respiratory and cardiovascular hospitalizations in the most populous city in Vietnam. Science of the Total Environment, 557– 558: 322–330

Reames T G, Bravo M A (2019). People, place and pollution: Investigating relationships between air quality perceptions, health concerns, exposure, and individual- and area-level characteristics. Environment International, 122: 244–255

Ren M, Li N, Wang Z, Liu Y, Chen X, Chu Y, Li X, Zhu Z, Tian L, Xiang H (2017). The short-term effects of air pollutants on respiratory disease mortality in Wuhan, China: Comparison of time-series and case-crossover analyses. Scientific Reports, 7(1): 40482

Samoli E, Aga E, Touloumi G, Nisiotis K, Forsberg B, Lefranc A, Pekkanen J, Wojtyniak B, Schindler C, Niciu E, Brunstein R, Dodic Fikfak M, Schwartz J, Katsouyanni K (2006). Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. European Respiratory Journal, 27(6): 1129–1138

Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann H E, Krämer U (2005). Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Respiratory Research, 6(1): 152

Sinharay R, Gong J, Barratt B, Ohman-Strickland P, Ernst S, Kelly F J, Zhang J J, Collins P, Cullinan P, Chung K F (2018). Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. Lancet, 391(10118): 339–349

Stafoggia M, Samoli E, Alessandrini E, Cadum E, Ostro B, Berti G, Faustini A, Jacquemin B, Linares C, Pascal M, Randi G, Ranzi A, Stivanello E, Forastiere F, MED-PARTICLES Study Group (2013). Short-term associations between fine and coarse particulate matter and hospitalizations in Southern Europe: results from the MED-PARTICLES project. Environmental Health Perspectives, 121(9): 1026–1033

Stieb D M, Szyszkowicz M, Rowe B H, Leech J A (2009). Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. Environmental Health, 8(1): 25

Stone V, Brown D M, Watt N, Wilson M, Donaldson K, Ritchie H, MacNee W (2000). Ultrafine particle-mediated activation of macrophages: intracellular calcium signaling and oxidative stress. Inhalation Toxicology, 12(Suppl 3): 345–351

Su C, Breitner S, Schneider A, Liu L, Franck U, Peters A, Pan X (2016). Short-term effects of fine particulate air pollution on cardiovascular hospital emergency room visits: a time-series study in Beijing, China. International Archives of Occupational and Environmental Health, 89(4): 641–657

Tao Y, Mi S, Zhou S, Wang S, Xie X (2014). Air pollution and hospital admissions for respiratory diseases in Lanzhou, China. Environment and Pollution, 185: 196–201

Thurston G D, Kipen H, Annesi-Maesano I, Balmes J, Brook R D, Cromar K, De Matteis S, Forastiere F, Forsberg B, Frampton M W, et al. (2017). A joint ERS/ATS policy statement: What constitutes an adverse health effect of air pollution? An analytical framework. European Respiratory Journal, 49(1): 1600419

Touloumi G, Samoli E, Pipikou M, Le Tertre A, Atkinson R, Katsouyanni K, APHEA-2 Project Group (2006). Seasonal confounding in air pollution and health time-series studies: Effect on air pollution effect estimates. Statistics in Medicine, 25(24): 4164–4178

Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, et al. (2018a). Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): A national cross-sectional study. Lancet, 391(10131): 1706–1717

Wang X, Kindzierski W, Kaul P (2015). Air pollution and acute myocardial infarction hospital admission in Alberta, Canada: A three-step procedure case-crossover study. PLoS One, 10(7): e0132769

Wang Y, Zu Y, Huang L, Zhang H, Wang C, Hu J (2018b). Associations between daily outpatient visits for respiratory diseases and ambient fine particulate matter and ozone levels in Shanghai, China. Environment and Pollution, 240: 754–763

Wang Z B, Fang C L (2016). Spatial-temporal characteristics and determinants of $PM_{2.5}$ in the Bohai Rim Urban Agglomeration. Chemosphere, 148: 148–162

Xu H, Bi X H, Zheng W W, Wu J H, Feng Y C (2015). Particulate matter mass and chemical component concentrations over four Chinese cities along the western Pacific coast. Environmental Science and Pollution Research International, 22(3): 1940–1953

Xu Q, Li X, Wang S, Wang C, Huang F, Gao Q, Wu L, Tao L, Guo J, Wang W, Guo X (2016). Fine particulate air pollution and hospital emergency room visits for respiratory disease in urban areas in Beijing, China, in 2013. PLoS One, 11(4): e0153099

Xu Q, Wang S, Guo Y, Wang C, Huang F, Li X, Gao Q, Wu L, Tao L, Guo J, et al. (2017). Acute exposure to fine particulate matter and cardiovascular hospital emergency room visits in Beijing, China. Environment and Pollution, 220(Pt A): 317–327

Zhai G, Zhang K, Chai G (2021). Lag effects of size-fractionated particulate matter pollution on outpatient visits for respiratory diseases in Lanzhou, China. Annals of Agricultural and Environmental Medicine, 28(1): 131–141

Zhang G, Gao Y, Cai W, Leung L R, Wang S, Zhao B, Wang M, Shan H, Yao X, Gao H (2019). Seesaw haze pollution in North China modulated by the sub-seasonal variability of atmospheric circulation. Atmospheric Chemistry and Physics, 19(1): 565–576

Zhang L, Gao Y, Wu S, Zhang S, Smith K R, Yao X, Gao H (2020). Global impact of atmospheric arsenic on health risk: 2005 to 2015. Proceedings of the National Academy of Sciences of the United States of America, 117(25): 13975–13982

Zhang P, Dong G, Sun B, Zhang L, Chen X, Ma N, Yu F, Guo H, Huang H, Lee Y L, Tang N, Chen J (2011). Long-term exposure to ambient air pollution and mortality due to cardiovascular disease and cerebrovascular disease in Shenyang, China. PLoS One, 6(6): e20827

Zhang Z, Wang J, Chen L, Chen X, Sun G, Zhong N, Kan H, Lu W (2014). Impact of haze and air pollution-related hazards on hospital admissions in Guangzhou, China. Environmental Science and Pollution Research International, 21(6): 4236–4244