

## ORIGINAL RESEARCH

# The Gender-Based Differences in Vulnerability to Ambient Air Pollution and Cerebrovascular Disease Mortality: Evidences Based on 26781 Deaths

Guangcong Liu<sup>1,2</sup>, Baijun Sun<sup>3</sup>, Lianzheng Yu<sup>4</sup>, Jianping Chen<sup>3</sup>, Bing Han<sup>1</sup>, Yizhuo Li<sup>2</sup> and Jie Chen<sup>1</sup>

<sup>1</sup> Department of Occupational and Environmental Health, School of Public Health, China Medical University, Shenyang, CN

<sup>2</sup> Liaoning Key Laboratory of Urban Ecology, Shenyang Academy of Environmental Sciences, Shenyang, CN

<sup>3</sup> Shenyang Center for Disease Control and Prevention, Shenyang, CN

<sup>4</sup> Department of Noncommunicable Chronic Disease Prevention, Liaoning Center for Disease Control and Prevention, Shenyang, CN

Corresponding author: Jie Chen ([jchen@cmu.edu.cn](mailto:jchen@cmu.edu.cn))

The gender-based differences in the vulnerability to ambient air pollution have not been widely explored. This study aimed to investigate vulnerability differences to the short-term effects of PM<sub>2.5</sub>, PM<sub>10</sub> and O<sub>3</sub> between cerebrovascular diseases (CEVD) deaths of men and women. The general additive models (GAMs) and distributed lag non-linear models (DLNMs) were adopted, and both single-pollutant and two-pollutant models were performed to analyze the associations between ambient air pollution and daily CEVD deaths. Both models indicated that O<sub>3</sub> was the most suspicious pollutant that could induce excess CEVD deaths, and women tended to be more vulnerable to O<sub>3</sub>. These results were confirmed by seasonal analysis, in which we also found both genders were more vulnerable to O<sub>3</sub> in winter. The exposure-response relationships revealed that women were usually more vulnerable to ambient air pollution than men, and the exposure-response curves differed significantly between genders. Our findings suggested that more attention should be paid on the adverse effects of ambient O<sub>3</sub>, and the protection of women CEVD population against air pollution should be emphasized.

**Keywords:** ozone; CEVD; vulnerability; gender differences

## 1 Introduction

The Deaths caused by cerebrovascular diseases (CEVD) account for a large proportion of the population mortality [1]. Recently, the associations between ambient air pollution exposure and CEVD mortality have gained more attention. Some current evidences suggest that short-term exposure to ambient air pollution can increase daily CEVD mortality on the same day or several days after the exposure [2–4]. But some studies also indicated no associations between air pollution and CEVD mortality [5, 6]. These divergences have not been adequately reviewed, but spatial variations were reported to be a key factor [7]. Spatial variations may include environmental factors, social-economic factors and other domestic characteristics of the study population. During the past few years, the gender-based differences in the vulnerability to ambient air pollution have been given more importance. There are already some evidences implying that the vulnerability to ambient air pollution between the two genders might be considerable different, and women could be more susceptible under most circumstances [8, 9]. So far, the age-based differences in susceptibility to air pollution have been frequently reported [10–12]. However, few studies about the gender-based differences on deaths caused by CEVD have been published. Moreover, the current environment protection and health-care policies also pay more attention on the infants, the elderly or people with specific diseases, but seldom take the gender-based vulnerability into consideration. To provide more evidences for sifting susceptible population, further exploration of gender-based vulnerability to ambient air pollution are urgently needed.

On the other hand, low social-economic status are reported to aggravate the vulnerability to air pollution [13]. Therefore, although some relevant studies have been published, those who were carried out under worse air quality and among lower social-economic status population (for example, in developing countries) could yield different results. Therefore, to further explore the effects of short-term ambient air pollution exposure on CEVD mortality, the relevant studies in developing countries with worse air quality are still necessary.

In this study, a time-series analysis was performed. We aimed to: a. explore the associations between short-term ambient  $PM_{2.5}$ ,  $PM_{10}$  and  $O_3$  and daily CEVD mortality; b. detect the potential differences of the gender-based vulnerability to ambient air pollution.

## 2 Materials and Methods

### 2.1 Study area and population

The population of Shenyang, which is the largest city in Northeastern China, were selected. According to the yearbook of Liaoning Province of 2017, the number of Shenyang's residents was 7.3 million. As a city dedicating to heavy industry, Shenyang was once named as the top 10 heavy polluted cities around the world by the World Bank in 2001. Although the environment has been significantly improved in the past decades, the levels of some air pollutants still kept above the national ambient air quality standard of China (NAAQS). According to the Shenyang Environmental Bulletin, for example, there are 174, 158 and 117 polluted days in Shenyang during 2014, 2015 and 2016, respectively [14].

### 2.2 Data Sources

The daily CEVD (ICD-10, code: I60-I69.9) mortality data during 2014–2017 were obtained from Center of Disease Control (CDC) of Shenyang. The access to the ambient air pollution monitoring data and the meteorological data of Shenyang were presented in detail in a previous study [15]. In brief, daily mean concentration of Particulate matter with diameter  $<2.5\mu m$  ( $PM_{2.5}$ ), Particulate matter with diameter  $<10\mu m$  ( $PM_{10}$ ), Ozone ( $O_3$ ) were retrieved from 11 state-controlled environmental air quality automatic monitoring stations through the website of Shenyang Bureau of Ecology and Environment. The overall mean concentration of the 11 stations for each type of pollutant were calculated and used as the general exposure level of the Shenyang population [16–19]. During 2015 April 4th to 9th, the air quality monitoring data were missing. Therefore, a total of 1455 days' air quality data (four years total days of 1461 minus 6 days) were available. The source of the meteorological information was from National Oceanic and Atmospheric Administration (NOAA), and was retrieved via the R package 'worldmet'. Factors such as daily average temperature and daily average relative humidity were extracted.

### 2.3 Statistical Methods

Similar statistical approaches in our previous study were adopted [15]. Briefly, we used a generalized additive model (GAM) with a time series approach, in which daily CEVD deaths were reckoned following a quasi-Poisson distribution. The relationships between daily CEVD deaths and air pollution were considered linear, and both single-pollutant and two-pollutant models were calculated [20–21]. Meteorological factors including relative humidity and daily average temperature were also included.

The models were listed as below (Model 1):

$$M_i \sim \text{quasiPoisson}(\mu_i)$$

$$\text{Log}[\mu_i] = \alpha + \beta_1 P_i + \text{ns}(\text{RH}, \text{df}_1) + \text{ns}(\text{T}, \text{df}_2) + \text{ns}(\text{days}_i, \text{df}_3) + \text{Factor}(\text{DOW}_i) \quad (1)$$

Where  $M_i$  denotes the expected daily CEVD death (including total, men or women) counts of the day  $i$ ;  $\alpha$  is the intercept;  $\beta_j$  refers to the corresponding coefficient of ambient air pollutants listed in the models; meteorological factors including daily average temperature (T) and average relative humidity (RH);  $\text{ns}(X, x)$  is the natural spline function; Factor is a categorical datum;  $\text{DOW}_i$  is the day of the week on day  $i$ ;  $\text{df}_s$  is the degree of freedom of the natural spline function, which is selected from the model with the smallest unbiased risk estimator score; and  $\text{day}_i$  is the consecutively numbered day of the study, in which January 1, 2014 is  $\text{day}_1$  and January 1, 2015 is  $\text{day}_{366}$ .

Excess Relative Risk ( $\text{ERR}_{10}$ ), which means the excess risks caused by a 10 unit elevation of pollutants, as well as Relative Risk (RR) was used to represent the risks of the ambient air pollutants on the CEVD population. The lag effects during lag0-2, lag0-3, lag0-5, and lag0-7 were explored. To further detect the gender-based differences in the vulnerability to air pollution, we used the Distributed lag nonlinear models

(DLNMs) to explore the seasonal exposure-response relationships (during lag0-7) [22]. Considering the exposure-response relationships were not always linear or monotonic, we selected a natural spline function whose dfs were chosen according to the minimum unbiased risk estimator (UBRE) value [23–25].

Cross-validations were performed with a leave-1-year-out cross-validation strategy to check the stability of the findings. All statistical processes were performed with the help of the R statistic (version 3.5.1, the comprehensive R Archive Network, <http://cran.r-project.org/>).

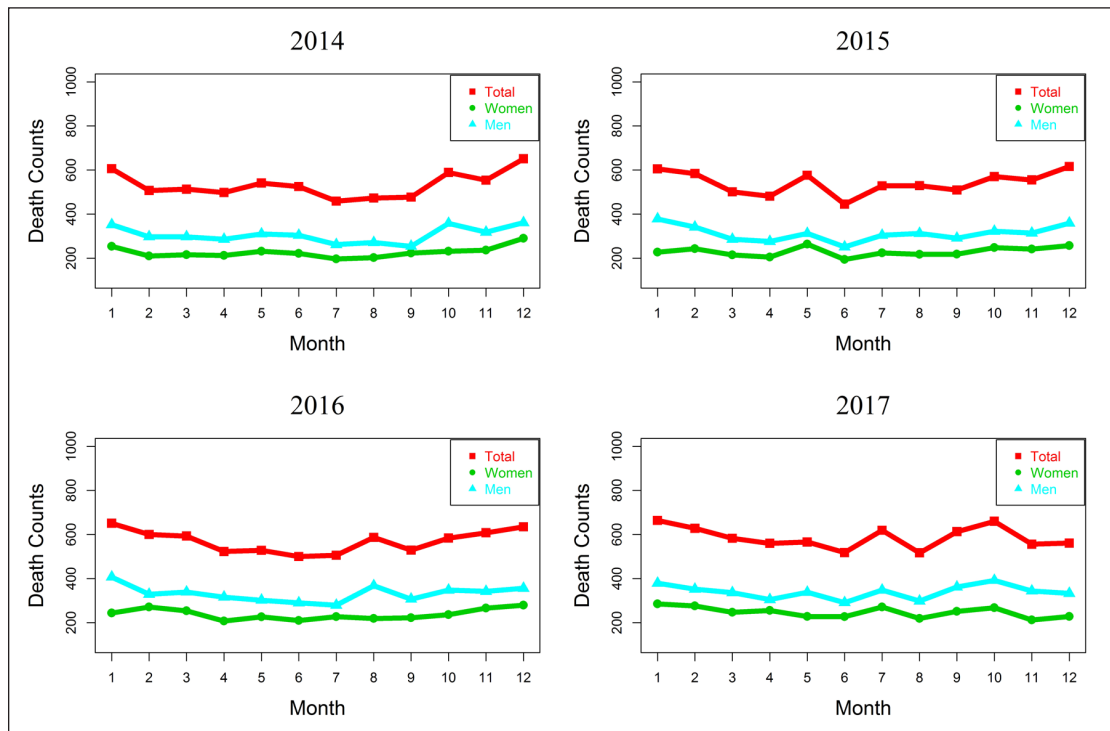
### 3 Results

#### 3.1 CEVD Mortality

There were 26,781 CEVD deaths in Shenyang City during 2014–2017, in which the daily deaths of men (57.79%) were significantly more than women (42.21%,  $P < 0.01$ ). More deaths occurred in cold period (November to February) than in other periods. As to the deaths in each month, CEVD deaths were at peak in January with a 4 year average monthly CEVD deaths of 664, and declined to the minimum of 517 deaths in August. Details about the CEVD deaths in Shenyang during 2014-2017 were presented in **Figure 1** and **Table 1**.

#### 3.2 Associations between pollutants and CEVD deaths

In the two-pollutant models, we found short-term  $O_3$  exposure, instead of  $PM_{2.5}$  or  $PM_{10}$ , was positively associated with daily CEVD deaths, implying  $O_3$  might be the most suspicious air pollutant that lead to the excess CEVD mortality. For example, with the  $ERR_{10}$  of total CEVD deaths during lag0-1, lag0-2 and lag0-3



**Figure 1:** Monthly CEVD deaths during 2014–2017. Generally CEVD deaths of women were more than those of men, and CEVD deaths were more in cold season than in warm season in both men and women.

**Table 1:** Descriptives of daily CEVD deaths during 2014–2017.

Year	Total			Men			Women		
	Counts	Daily Mean	SD	Counts	Daily Mean	SD	Counts	Daily Mean	SD
2014	6393	17.52	4.62	3670	10.05	3.42	2723	7.46	2.80
2015	6499	18.10	4.65	3746	10.43	3.26	2753	7.67	2.89
2016	6844	18.70	4.67	3983	10.88	3.36	2861	7.82	3.00
2017	7045	19.30	5.41	4078	11.17	4.00	2967	8.13	2.99
All Time	26781	18.41	4.89	15477	10.64	3.55	11304	7.77	2.93

were 1.02% (95%CI 0.63%–1.4%), 0.95% (95%CI 0.62%–1.27%) and 0.74% (95%CI 0.46%–1.03%), respectively. Women tended to be more vulnerable to O<sub>3</sub> that the ERRs of women were generally larger than those of men. In addition, the ERRs of women decreased with the extension of the lag period, while the ERRs of men increased at lag0-3 and then decreased with time. No positive associations were found between PM<sub>2.5</sub> or PM<sub>10</sub> and CEVD deaths. The results of the single-pollutant models varied slightly from those in the two-pollutant models. The association between short-term ambient air pollution exposure and CEVD mortality were shown in **Table 2** and **Figure 2** (from the two-pollutant model) and Figure S1 (from the single-pollutant model) of supplementary files.

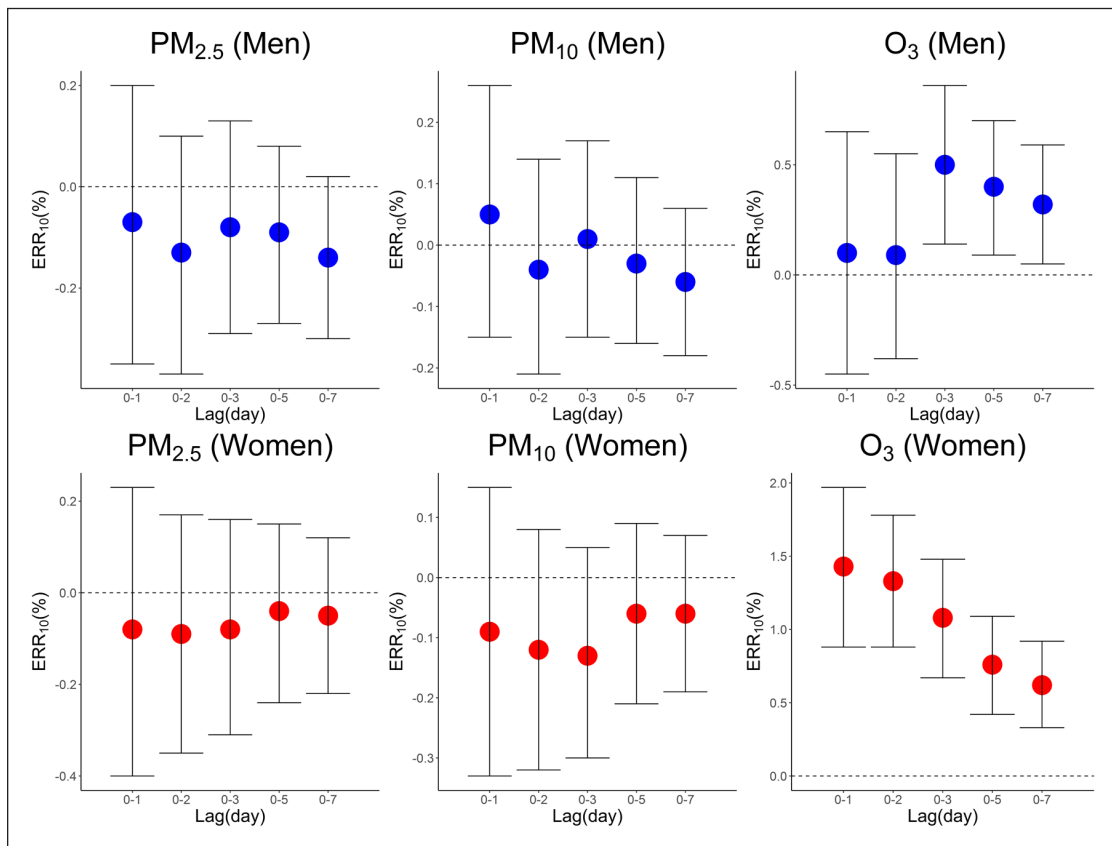
### 3.3 Seasonal analyses

The Seasonal analyses by two-pollutant model indicated that the CEVD population were more vulnerable to air pollution in cold seasons (winter and spring). In cold seasons, for example, the ERRs of O<sub>3</sub> among both men and women were mostly significantly above 0. However, we can hardly find significant positive associations in summer or autumn. Some negative associations were found between PMs and CEVD deaths. They might suggest non-linear relationships between short-term PMs exposure and CEVD deaths, since air pollution exposure cannot be a protective factor. Even in the seasonal analyses, the ERRs of women were generally larger than those of men, and this was more obvious in ERRs of O<sub>3</sub> during winter. The details of seasonal analyses are shown in **Table 3**.

The seasonal exposure-response relationships of PM<sub>2.5</sub>, PM<sub>10</sub> and O<sub>3</sub> by two-pollutant were shown in **Figures 3, 4** and **5**, respectively. Among these curves, some unignorable non-linear curves confirmed our hypothesis that the exposure-response relationships were not always linear. For example, the curves of O<sub>3</sub> in autumn (**Figure 5**) of both genders are obviously not linear, which usually increased first and then decreased. Some curves also increased and then decreased, but they showed a generally decreasing trend, such as the PM<sub>10</sub> curve of men in spring and winter. This can possibly explain some of the negative associations between PMs and CEVD mortality in the linear models. Another notable result is that the trends of curves sometimes differed significantly between men and women. For example, the O<sub>3</sub> exposure-response curve of men in autumn was obviously bell-shaped, but the curve of women in autumn showed a slightly bell-shaped trend. And the PM<sub>2.5</sub> or PM<sub>10</sub> curves of men in winter generally increased, while those curves of women were generally decreased.

**Table 2:** Cumulative ERR<sub>10</sub> of each pollutant at different lags (Unit: %).

Lags	Pollutants	Single-pollutant model						Two-pollutant model					
		Men		Women		All		Men		Women		All	
		ERR	Sig	ERR	Sig	ERR	Sig	ERR	Sig	ERR	Sig	ERR	Sig
<b>lag0-1</b>	PM <sub>2.5</sub>	-0.07		-0.03		-0.01		-0.07		-0.08		-0.04	
	PM <sub>10</sub>	0.05		-0.06		0.03		0.05		-0.09		0.01	
	O <sub>3</sub>	0.09		1.42	*	1.01	*	0.1		1.43	*	1.02	*
<b>lag0-2</b>	PM <sub>2.5</sub>	-0.13		-0.04		-0.06		-0.13		-0.09		-0.1	
	PM <sub>10</sub>	-0.04		-0.1		-0.05		-0.04		-0.12		-0.07	
	O <sub>3</sub>	0.08		1.32	*	0.94	*	0.09		1.33	*	0.95	*
<b>lag0-3</b>	PM <sub>2.5</sub>	-0.07		-0.05		-0.06		-0.08		-0.08		-0.09	
	PM <sub>10</sub>	0.02		-0.12		-0.05		0.01		-0.13		-0.06	
	O <sub>3</sub>	0.49	*	1.07	*	0.74	*	0.5	*	1.08	*	0.74	*
<b>lag0-5</b>	PM <sub>2.5</sub>	-0.08		-0.02		-0.06		-0.09		-0.04		-0.08	
	PM <sub>10</sub>	-0.02		-0.05		-0.04		-0.03		-0.06		-0.05	
	O <sub>3</sub>	0.39	*	0.75	*	0.54	*	0.4	*	0.76	*	0.55	*
<b>lag0-7</b>	PM <sub>2.5</sub>	-0.13		-0.03		-0.09		-0.14		-0.05		-0.1	
	PM <sub>10</sub>	-0.05		-0.05		-0.05		-0.06		-0.06		-0.06	
	O <sub>3</sub>	0.31	*	0.62	*	0.43	*	0.32	*	0.62	*	0.44	*



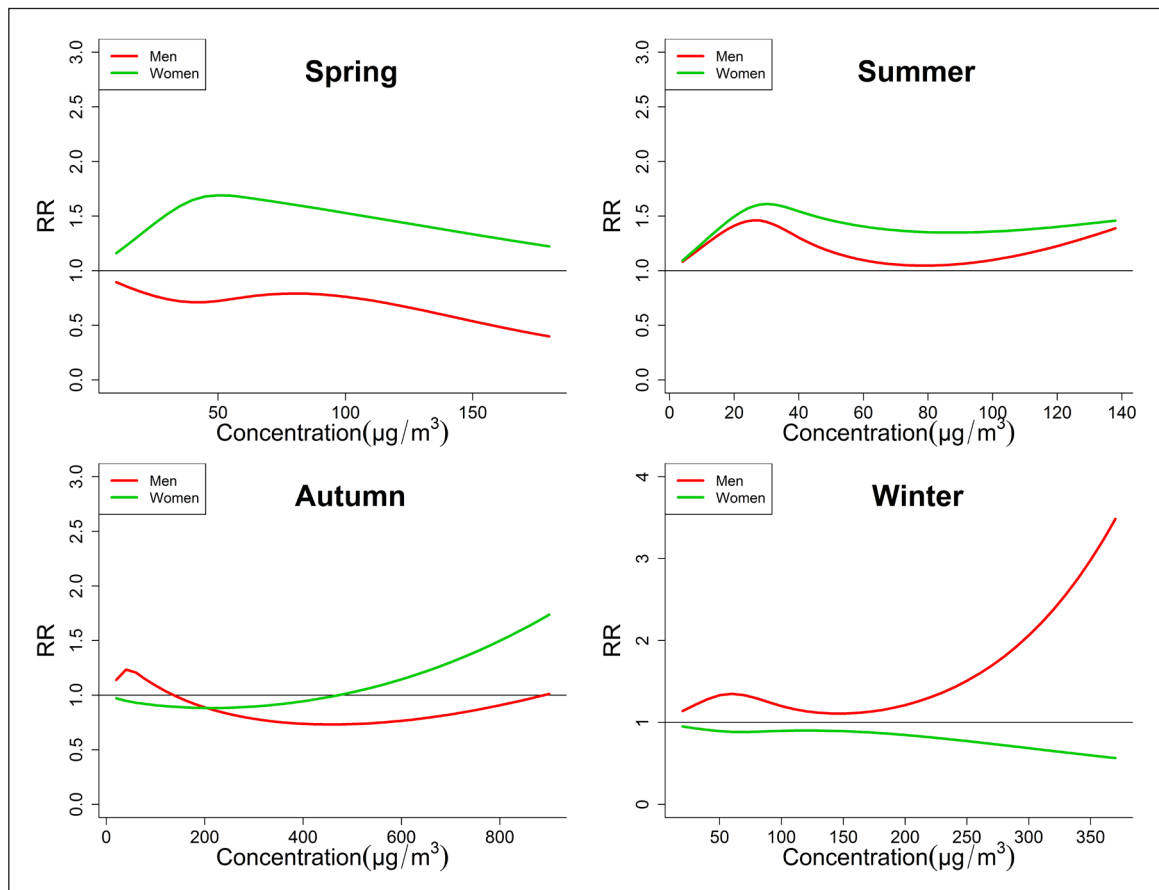
**Figure 2:** The associations between ambient air pollution and daily CEVD mortality. O<sub>3</sub> seems to be the most suspicious pollutant that leads to excess CEVD mortality. Generally women with CEVD were more vulnerable to ambient air pollutants.

**Table 3:** Seasonal analyses of the associations between short-term ambient air pollution exposure and CEVD death.

Group	Lags	Pollutant	Spring		Summer		Autumn		Winter	
			ERR	Sig	ERR	Sig	ERR	Sig	ERR	Sig
Women	lag0-1	PM <sub>2.5</sub>	-0.1		-0.07		0.05		0.18	
		PM <sub>10</sub>	-0.28		-0.35		0.06		0.2	
		O <sub>3</sub>	1.39	*	0.07		1.51	*	4.12	*
	lag0-2	PM <sub>2.5</sub>	0.19		-0.11		0.03		-0.24	
		PM <sub>10</sub>	-0.16		-0.39		0.04		-0.09	
		O <sub>3</sub>	1.65	*	0.32		0.9		3.2	*
	lag0-3	PM <sub>2.5</sub>	0.06		-0.54		0.05		-0.26	
		PM <sub>10</sub>	-0.18		-0.8		0.05		-0.15	
		O <sub>3</sub>	1.25	*	0.34		0.45		2.78	*
	lag0-5	PM <sub>2.5</sub>	0.2		-0.66		0.13		-0.41	*
		PM <sub>10</sub>	0.11		-0.75		0.13		-0.18	
		O <sub>3</sub>	1.36	*	0.29		-0.2		2.23	*
lag0-7	PM <sub>2.5</sub>	0.13		-0.72		0.08		-0.25		
	PM <sub>10</sub>	0.02		-0.9	*	0.09		-0.04		
	O <sub>3</sub>	1.37	*	0.33		-0.31		2.44	*	

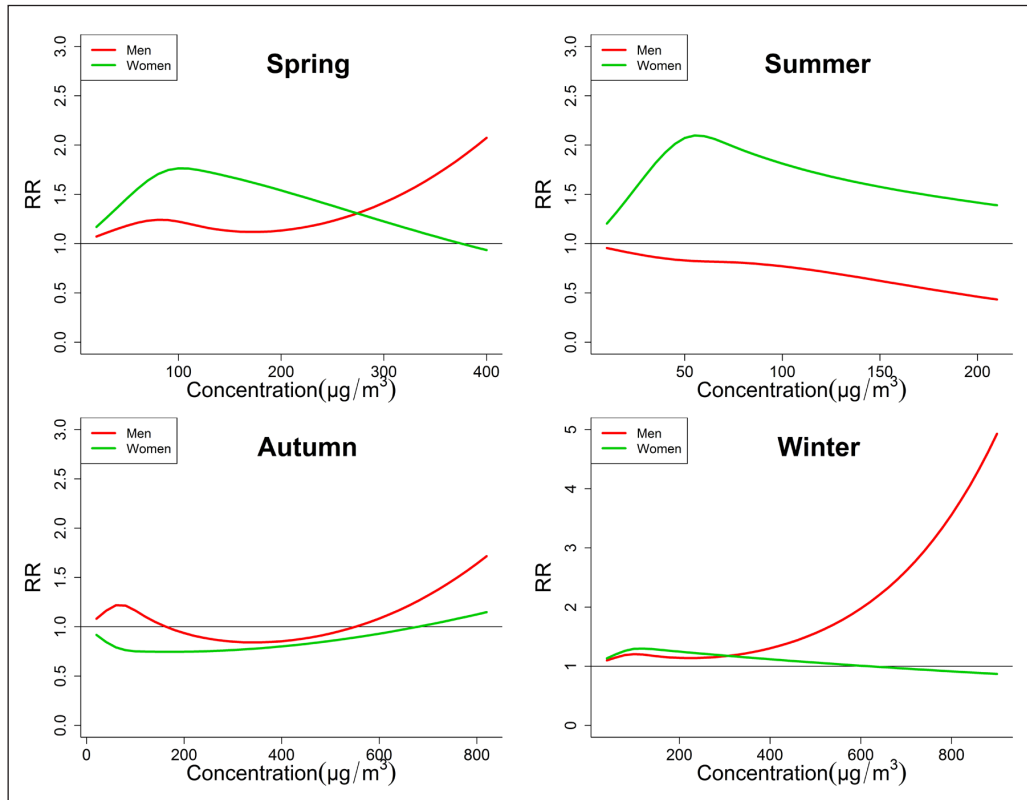
(Contd.)

Group	Lags	Pollutant	Spring		Summer		Autumn		Winter	
			ERR	Sig	ERR	Sig	ERR	Sig	ERR	Sig
Men	lag0-1	PM <sub>2.5</sub>	-0.29		-1.68		0.04		-0.12	
		PM <sub>10</sub>	0.67	*	-0.89		-0.02		0.22	
		O <sub>3</sub>	1.29	*	-0.13		-0.99		1.57	
	lag0-2	PM <sub>2.5</sub>	-0.29		-1.48		-0.06		-0.27	
		PM <sub>10</sub>	0.25		-0.9		-0.1		0.08	
		O <sub>3</sub>	1.24	*	-0.11		-1.04		1.41	
	lag0-3	PM <sub>2.5</sub>	-0.69		-1.41	*	-0.1		-0.12	
		PM <sub>10</sub>	-0.03		-0.93	*	-0.11		0.17	
		O <sub>3</sub>	1.47	*	-0.05		-1.14	*	1.04	
	lag0-5	PM <sub>2.5</sub>	-0.61		-2.01	*	-0.17		0.03	
		PM <sub>10</sub>	-0.02		-1.47	*	-0.17		0.18	
		O <sub>3</sub>	0.99	*	-0.03		-0.8		1.34	*
	lag0-7	PM <sub>2.5</sub>	-0.6		-1.16	*	-0.28	*	0.12	
		PM <sub>10</sub>	-0.02		-1.33	*	-0.27	*	0.23	*
		O <sub>3</sub>	0.54		-0.14		-0.63		1.57	*

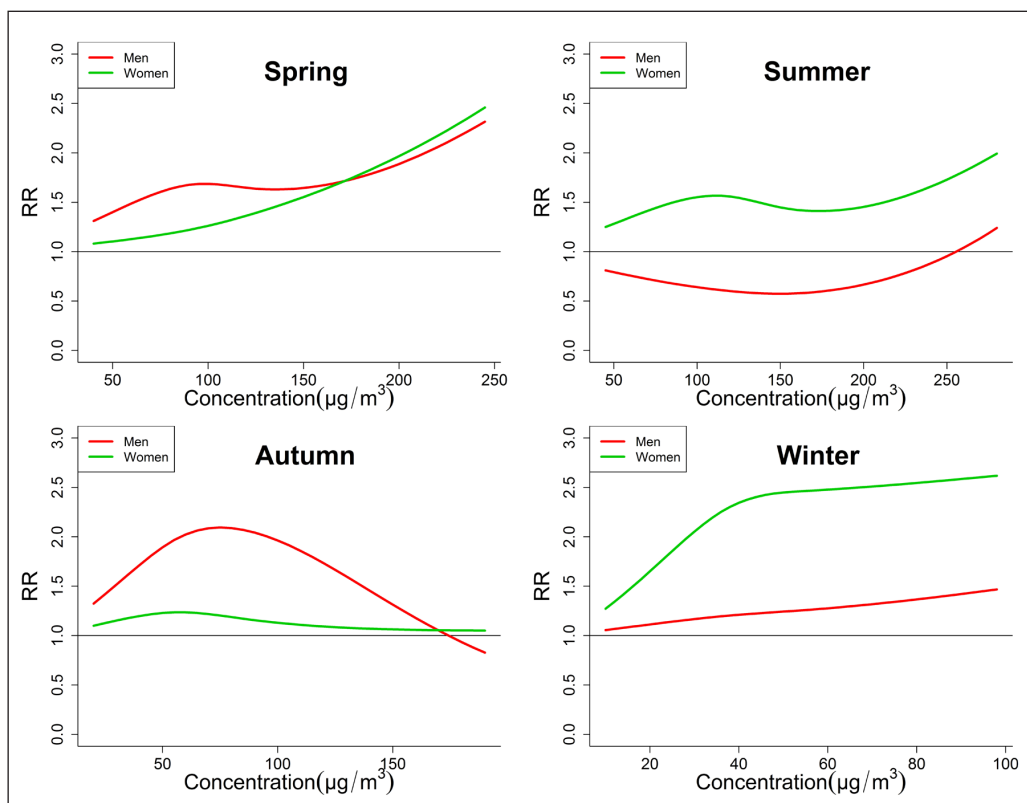


**Figure 3:** Comparison of Seasonal exposure-response curves of PM<sub>2.5</sub>-CEVD mortality between men and women. Most curves of both men and women tended to be non-linear, and the RRs of women were generally larger than those of men. However, men CEVD mortality were shown to be more vulnerable to PM<sub>2.5</sub> in winter.

No significant variations were found when using the eliminated data of one-year each time, suggesting good robustness of the results.



**Figure 4:** Comparison of Seasonal exposure-response curves of  $PM_{10}$ -CEVD mortality between men and women. Some curves showed both non-linear and generally increasing or decreasing trend, which may provide a possible explanation for the insignificant associations between PMs and daily CEVD deaths. Generally women were more vulnerable to  $PM_{10}$  in spring and summer, but men were more vulnerable in autumn and winter.



**Figure 5:** Comparison of Seasonal exposure-response curves of  $O_3$ -CEVD mortality between men and women. Significant differences of gender-based vulnerability were observed. In spring and autumn, men were more vulnerable, but in the other seasons women were more vulnerable.

## 4 Discussion

In this study, we found limited evidences that PMs could induce increased CEVD mortality when adopting linear relationships. However, O<sub>3</sub> was shown to associate with increased daily CEVD mortality in both men and women, and women tended to be more vulnerable. These findings implied that O<sub>3</sub> could be the primary risk pollutant of the excess CEVD deaths, and women were more vulnerable to ambient air pollutants than men.

We found the ERRs of women were larger than those of men in general. This accorded with the previous outcomes among Shanghai, Hong Kong and Japanese population [26–29]. They are also supported by the mechanism studies indicating that women were more susceptible to oxidative stress (OS) [30]. Bell et al. suggested geographical variation in the magnitude of gender difference, which were larger in the Northeast than in other regions of the US [26]. This is also similar to our study that was performed in the North, since some studies that were performed in middle or southern China indicated no gender differences or men were more vulnerable. However, a recent comprehensive assessment by EPA noted there were not enough evidences to draw a conclusion on this issue [31]. Therefore more relevant studies are still in need.

In addition, we found men might be more vulnerable to PM<sub>2.5</sub> in winter. Although more papers reported women as the susceptible gender to ambient air pollution, there are also studies indicated that the mortality of men was more sensitive to PM<sub>2.5</sub> [9, 32, 33]. These variations of the gender-based vulnerability to PM<sub>2.5</sub> across the studies may be due to different components of PMs as well as their proportions, since the components vary significantly across regions [34, 35]. The haze is also a key risk for circulatory mortality, and most of the haze days in Shenyang occurred in winter [36]. This may also aggravate the adverse effects of short-term air pollution on the CEVD population. As to short-term O<sub>3</sub> exposure, it has been frequently reported to associate with elevated risk of the increased circulatory mortality. In this study, we further confirmed ambient O<sub>3</sub> as a fatal risk for CEVD population, as well as the gender-based vulnerability differences. The mechanisms that O<sub>3</sub> induces excess CEVD mortality are not yet clear, but the influences of O<sub>3</sub> on circulatory system have been validated by previous studies. One possible path is by inducing hypertension, when ET-1 were generated after short term exposure to O<sub>3</sub> and then further elevated the blood pressure [37]. And vasoconstriction caused by O<sub>3</sub> exposure not only induces hypertension, but can also slow the vascular flow, which was also fatal for the CEVD population [38].

Seasonal analyses suggested that both men and women CEVD were more vulnerable to air pollution in cold seasons (winter and spring), and It was more evident in the ERRs of O<sub>3</sub>. Some previous papers reported that O<sub>3</sub> could elevate the cardiovascular mortality only in warm seasons, but more recent studies (especially those carried out in east Asia) reported more robust associations in cold seasons [29, 39–41]. In this study, the seasonal variations could largely attribute to the cold climate in Shenyang City. The mean of the daily lowest temperature was –13.5°C in Shenyang' winter during 2014 to 2017. As the triggers of CEVD deaths, the increased blood pressure and blood viscosity can be induced by the exposure to low ambient temperatures [42]. Several studies also indicated that low ambient temperature can exacerbate the fatal effects of air pollution [36]. Therefore, even if average daily O<sub>3</sub> concentration were significantly lower than in cold seasons than in warm seasons, the CEVD population of Shenyang could also be more sensitive.

It is interesting that the result of CEVD differed from those of CHD in Liu et al., that CHD mortality was associated with PM<sub>2.5</sub> while CEVD mortality was associated with O<sub>3</sub>. This may be attributed to the negative correlation between O<sub>3</sub> and PM<sub>2.5</sub>, and the different triggers of acute onset between CHD and CEVD. First, in this study the ERRs of O<sub>3</sub> is higher than PMs, indicating that O<sub>3</sub> induces more risks in the CEVD population of Shenyang. Second, the paths of air pollution-induced acute CHD and acute CEVD may be different. Many studies proved that short-term exposure to either PM<sub>2.5</sub> or O<sub>3</sub> would result in acute increase of blood pressure, which is possibly how short-term air pollution exposure increased CEVD mortality [43–45]. However, the role of acute increasing blood pressure in inducing the onset of acute CHD was not as strong as in inducing acute CEVD (such as hemorrhagic stroke). Third, the concentration of PM<sub>2.5</sub> and O<sub>3</sub> were negatively correlated in Shenyang (shown in supplementary files). In summary, it is possible that in the linear models O<sub>3</sub> associated with CEVD mortality while PM<sub>2.5</sub> not.

It is not rare that no associations between PMs and daily CEVD deaths were found in men or women. Several studies failed to prove the short-term PMs exposure as a risk factor that could elevate daily cardiovascular hospital admissions or mortality [46, 47]. One main reason for these inconsistencies is that the exposure-response relationships can be non-linear [23–25]. Moreover our previous study also indicated



that this relationship between ASHD mortality and air pollution seemed to be non-linear [15]. Just as shown in **Figures 3, 4 and 5**, some exposure-response curves of PMs were bell-shaped, so if they were treated as linear the generally tendency can be decreasing. On the other hand, the inconsistencies may also be attributed to spatial variation; however the potential influences of detailed individual factors remained to be explored.

This study provided the further evidence that women CEVD population were more vulnerable to ambient air pollution, especially more vulnerable to O<sub>3</sub>. It also offered evidence for policy making. The public attention should not only focus on the total air quality, but also on each type of pollutants as well as their susceptible population. In addition, the concentrations of O<sub>3</sub> are usually higher on sunny days with lower PMs concentrations, so people are more likely to misjudge the air quality and ignore its potential risks. And currently the most efforts to improve air quality focus on controlling the concentrations of PMs. Therefore the ambient O<sub>3</sub> also deserved great attention in both environment protection and in public education.

There are also some deficiencies in this study. First, although over 26,000 CEVD death cases were included, the outcomes of the multi-center studies can be more convincible. Second, the findings in the exposure-response curves cannot be completely explained by the current evidences. Therefore, more studies on the gender-based differences in the vulnerability to ambient air pollution are needed.

## 5 Conclusions

Women were generally more vulnerable to short-term air pollution exposure than men in Shenyang. Ozone can induce excess daily CEVD mortality, which deserves more attention in public health education.

## Additional File

The additional file for this article can be found as follows:

- **Supplementary file.** Figure S1. DOI: <https://doi.org/10.5334/gh.849.s1>

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## Competing Interests

The authors have no competing interests to declare.

## Author Contributions

GC Liu, LZ Yu and J Chen contributed to the conception or design of the work. GC Liu, BJ Sun and JP Chen contributed to the acquisition, analysis, or interpretation of data for the work. GC Liu and LZ Yu drafted the manuscript. All listed authors had critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

## References

1. **Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E.** Deaths: Final data for 2016. 2018.
2. **Chien T, Ting H, Chan C, Yang N, Pan R, Lai KR,** et al. Does the Short-Term Effect of Air Pollution Influence the Incidence of Spontaneous Intracerebral Hemorrhage in Different Patient Groups? Big Data Analysis in Taiwan. *International Journal of Environmental Research and Public Health*. 2017; 14: 1547. DOI: <https://doi.org/10.3390/ijerph14121547>
3. **Qian Y, Yu H, Cai B, Fang B, Wang C.** Association between incidence of fatal intracerebral hemorrhagic stroke and fine particulate air pollution. *Environmental Health and Preventive Medicine*. 2019; 24: 38. DOI: <https://doi.org/10.1186/s12199-019-0793-9>
4. **Zhang R, Liu G, Jiang Y, Li G, Pan Y, Wang Y,** et al. Acute Effects of Particulate Air Pollution on Ischemic Stroke and Hemorrhagic Stroke Mortality. *Frontiers in Neurology*. 2018; 9. DOI: <https://doi.org/10.3389/fneur.2018.00827>
5. **Ljungman PL, Mittleman MA.** Ambient air pollution and stroke. *Stroke; A Journal of Cerebral Circulation*. 2014; 45: 3734–41. DOI: <https://doi.org/10.1161/STROKEAHA.114.003130>
6. **Susanne B, Kathrin W, Annette P, Alexandra S.** Short-term effects of air temperature on cause-specific cardiovascular mortality in Bavaria, Germany. *Heart*. 2014; 100: 1272–80. DOI: <https://doi.org/10.1136/heartjnl-2014-305578>

7. **Xu M, Guo Y, Zhang Y, Westerdahl D, Mo Y, Liang F**, et al. Spatiotemporal analysis of particulate air pollution and ischemic heart disease mortality in Beijing, China. *Environ Health*. 2014; 13: 109. DOI: <https://doi.org/10.1186/1476-069X-13-109>
8. **Clougherty JE**. A growing role for gender analysis in air pollution epidemiology. *Ciência & Saúde Coletiva*. 2010; 118: 167–176. DOI: <https://doi.org/10.1289/ehp.0900994>
9. **Kan H, London SJ, Chen G, Zhang Y, Song G, Zhao N**, et al. 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*. 2008; 116: 1183–1188. DOI: <https://doi.org/10.1289/ehp.10851>
10. **Alessandrini ER, Stafoggia M, Faustini A, Berti G, Canova C, De Togni A**, et al. Association Between Short-Term Exposure to PM<sub>2.5</sub> and PM<sub>10</sub> and Mortality in Susceptible Subgroups: A Multisite Case-Crossover Analysis of Individual Effect Modifiers. *Am J Epidemiol*. 2016; 184: 744–754. DOI: <https://doi.org/10.1093/aje/kww078>
11. **Simoni M, Baldacci S, Maio S, Cerrai S, Sarno G, Viegi G**. Adverse effects of outdoor pollution in the elderly. *J Thorac Dis*. 2015; 7: 34–45.
12. **Xue X, Chen J, Sun B, Zhou B, Li X**. Temporal trends in respiratory mortality and short-term effects of air pollutants in Shenyang, China. *Environ Sci Pollut Res Int*. 2018; 25: 11468–11479. DOI: <https://doi.org/10.1007/s11356-018-1270-5>
13. **Basu R**. High ambient temperature and mortality: A review of epidemiologic studies from 2001 to 2008. *Environ Health*. 2009; 8: 40. DOI: <https://doi.org/10.1186/1476-069X-8-40>
14. **Shenyang**. Shenyang Environmental Quality Bulletin. 2019. *Shenyang Bureau of Ecology and Environment*. 2017.
15. **Liu G, Sun B, Yu L, Chen J, Han B, Liu B**, et al. Short-term exposure to ambient air pollution and daily atherosclerotic heart disease mortality in a cool climate. *Environmental Science and Pollution Research*. 2019: 1–12. DOI: <https://doi.org/10.1007/s11356-019-05565-5>
16. **Kim SE, Lim YH, Kim H**. Temperature modifies the association between particulate air pollution and mortality: A multi-city study in South Korea. *Science of the Total Environment*. 524–525: 376–383. DOI: <https://doi.org/10.1016/j.scitotenv.2015.03.137>
17. **Lin GZ, Li L, Song Y-F, Zhou Y-X, Shen S-Q, Ou C-Q**. The impact of ambient air pollution on suicide mortality: A case-crossover study in Guangzhou, China. *Environmental Health*. 15: 90. DOI: <https://doi.org/10.1186/s12940-016-0177-1>
18. **Lin H, Liu T, Xiao J, Zeng W, Ma W**. Mortality burden of ambient fine particulate air pollution in six Chinese cities: Results from the Pearl River Delta study. *Environment International*. 2016; 96: 91–97. DOI: <https://doi.org/10.1016/j.envint.2016.09.007>
19. **Qiu H, Tian L, Ho K-f, Yu ITS, Thach T-Q, Wong C-M**. Who is more vulnerable to death from extremely cold temperatures? A case-only approach in Hong Kong with a temperate climate. *International Journal of Biometeorology*. 60: 711–717. DOI: <https://doi.org/10.1007/s00484-015-1065-z>
20. **Atkinson RW, Analitis A, Samoli E, Fuller GW, Green DC, Mudway IS**, et al. Short-term exposure to traffic-related air pollution and daily mortality in London, UK. *J Expo Sci Environ Epidemiol*. 2016; 26: 125–32. DOI: <https://doi.org/10.1038/jes.2015.65>
21. **Gouveia N, Junger WL, investigators E**. Effects of air pollution on infant and children respiratory mortality in four large Latin-American cities. *Environ Pollut*. 2018; 232: 385–391. DOI: <https://doi.org/10.1016/j.envpol.2017.08.125>
22. **Gasparrini A**. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. *Journal of Statistical Software*. 2011; 43: 1–20. DOI: <https://doi.org/10.18637/jss.v043.i08>
23. **Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z**. The 2016 global and national burden of diabetes mellitus attributable to PM<sub>2.5</sub> air pollution. *The Lancet Planetary Health*. 2018; 2: e301–e312. DOI: [https://doi.org/10.1016/S2542-5196\(18\)30140-2](https://doi.org/10.1016/S2542-5196(18)30140-2)
24. **Collart P, Dramaix M, Levêque A, Mercier G, Coppieters Y**. Concentration–response curve and cumulative effects between ozone and daily mortality: an analysis in Wallonia, Belgium. *International Journal of Environmental Health Research*. 2018; 28: 1–12. DOI: <https://doi.org/10.1080/09603123.2018.1453050>
25. **Giannakis E, Kushta J, Giannadaki D, Georgiou GK, Bruggeman A, Lelieveld J**. Exploring the economy-wide effects of agriculture on air quality and health: Evidence from Europe. *Sci Total Environ*. 2019; 663: 889–900. DOI: <https://doi.org/10.1016/j.scitotenv.2019.01.410>

26. **Bell ML, Son J-Y, Peng RD, Wang Y, Dominici F.** Brief Report: Ambient PM<sub>2.5</sub> and Risk of Hospital Admissions: Do Risks Differ for Men and Women? *Epidemiology*. 2015; 26: 575–9. DOI: <https://doi.org/10.1097/EDE.0000000000000310>
27. **Ng CF, Ueda K, Nitta H, Takeuchi A.** Seasonal variation in the acute effects of ozone on premature mortality among elderly Japanese. *Environ Monit Assess*. 2013; 185: 8767–76. DOI: <https://doi.org/10.1007/s10661-013-3211-6>
28. **Qin L, Gu J, Liang S, Fang F, Bai W, Liu X,** et al. Seasonal association between ambient ozone and mortality in Zhengzhou, China. *Int J Biometeorol*. 2017; 61: 1003–1010. DOI: <https://doi.org/10.1007/s00484-016-1279-8>
29. **Wong CM, Ma S, Hedley AJ, Lam TH.** Effect of air pollution on daily mortality in Hong Kong. *Environmental Health Perspectives*. 2001; 109: 335–340. DOI: <https://doi.org/10.1289/ehp.01109335>
30. **Guo H, Huang K, Zhang X, Zhang W, Guan L, Kuang D,** et al. Women are more susceptible than men to oxidative stress and chromosome damage caused by polycyclic aromatic hydrocarbons exposure. *Environ Mol Mutagen*. 2014; 55: 472–81. DOI: <https://doi.org/10.1002/em.21866>
31. **United States Environmental Protection Agency (USEPA).** Integrated Science Assessment (ISA) for Particulate Matter. 2019.
32. **Clougherty JE.** A growing role for gender analysis in air pollution epidemiology. *Ciência & Saúde Coletiva*. 2011; 16: 2221–38. DOI: <https://doi.org/10.1590/S1413-81232011000400021>
33. **Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C,** et al. Air Pollution and Mortality in the Medicare Population. *N Engl J Med*. 2017; 376: 2513–2522. DOI: <https://doi.org/10.1056/NEJMoa1702747>
34. **Kayo U, Makiko Y, Fumikazu I, Kunihiro H, Hiroshi N.** Associations Between Fine Particulate Matter Components and Daily Mortality in Nagoya, Japan. *Journal of Epidemiology*. 2016; 26: 249–257. DOI: <https://doi.org/10.2188/jea.JE20150039>
35. **Mukherjee A, Agrawal M.** A Global Perspective of Fine Particulate Matter Pollution and Its Health Effects. *Reviews of Environmental Contamination & Toxicology*. 2017. DOI: [https://doi.org/10.1007/398\\_2017\\_3](https://doi.org/10.1007/398_2017_3)
36. **Ho HC, Wong MS, Yang L, Shi W, Yang J, Bilal M,** et al. Spatiotemporal influence of temperature, air quality, and urban environment on cause-specific mortality during hazy days. *Environ Int*. 2018; 112: 10–22. DOI: <https://doi.org/10.1016/j.envint.2017.12.001>
37. **Xia Y, Niu Y, Cai J, Lin Z, Liu C, Li H,** et al. The effects of personal short-term exposure to ambient ozone on blood pressure and vascular endothelial function: A mechanistic study based on DNA methylation and metabolomics. *Environ Sci Technol*. 2018. DOI: <https://doi.org/10.1021/acs.est.8b03044>
38. **Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M,** et al. Air pollution and cardiovascular disease: A statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*. 2004; 109: 2655–71. DOI: <https://doi.org/10.1161/01.CIR.0000128587.30041.C8>
39. **Cox B, Gasparrini A, Catry B, Fierens F, Vangronsveld J, Nawrot TS.** Ambient Air Pollution-related Mortality in Dairy Cattle: Does It Corroborate Human Findings? *Epidemiology*. 2016; 27: 779–86. DOI: <https://doi.org/10.1097/EDE.0000000000000545>
40. **Turner MC, Jerrett M, Pope CA, 3rd, Krewski D, Gapstur SM, Diver WR,** et al. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. *Am J Respir Crit Care Med*. 2016; 193: 1134–42. DOI: <https://doi.org/10.1164/rccm.201508-1633OC>
41. **Ng CFS, Kayo U, Hiroshi N, Ayano T.** Seasonal variation in the acute effects of ozone on premature mortality among elderly Japanese. *Environmental Monitoring & Assessment*. 2013; 185: 8767–76. DOI: <https://doi.org/10.1007/s10661-013-3211-6>
42. **Eldwood PC, Beswick A, O'Brien JR, Renaud S, Fifield R, Limb ES,** et al. Temperature and risk factors for ischaemic heart disease in the Caerphilly prospective study. *British Heart Journal*. 1993; 70: 520. DOI: <https://doi.org/10.1136/hrt.70.6.520>
43. **Dai L, Koutrakis P, Coull BA, Sparrow D, Vokonas PS, Schwartz JD.** Use of the Adaptive LASSO Method to Identify PM<sub>2.5</sub> Components Associated with Blood Pressure in Elderly Men: The Veterans Affairs Normative Aging Study. *Environmental Health Perspectives*. 124. DOI: <https://doi.org/10.1289/ehp.1409021>

44. **Wang C, Chen R, Cai J, Shi J, Yang C, Tse LA**, et al. Personal exposure to fine particulate matter and blood pressure: A role of angiotensin converting enzyme and its DNA methylation. *Environment International*. S0160412016302598.
45. **Zeng XW, Qian Z, Vaughn MG, Nelson EJ, Dharmage SC, Bowatte G**, et al. Positive association between short-term ambient air pollution exposure and children blood pressure in China—Result from the Seven Northeast Cities (SNEC) study. *Environmental Pollution*. 224: 698–705. DOI: <https://doi.org/10.1016/j.envpol.2017.02.054>
46. **Bedada GB, Smith CJ, Tyrrell PJ, Hirst AA, Agius R**. Short-term effects of ambient particulates and gaseous pollutants on the incidence of transient ischaemic attack and minor stroke: A case-crossover study. *Environ Health*. 2012; 11: 77. DOI: <https://doi.org/10.1186/1476-069X-11-77>
47. **Young SS, Smith RL, Lopiano KK**. Air quality and acute deaths in California, 2000–2012. *Regul Toxicol Pharmacol*. 2017; 88: 173–184. DOI: <https://doi.org/10.1016/j.yrtph.2017.06.003>

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