Letter

Seasonal Effects of Air Pollutants on Stroke Deaths in Qingdao from 2014 to 2019

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Stroke is the third-leading cause of disability-adjusted life years (DALYs) and poses a significant public health challenge worldwide[1]. Developing countries, including China, continue to face a substantial burden from stroke. Since 1990, China has reported the highest global stroke burden, with 2.19 million deaths and 45.9 million DALYs recorded in 2019[2].

Air pollution remains a critical contributor to stroke-related mortality. Over the past few decades, global air pollution levels have steadily risen, with stroke mortality attributable to air pollution now estimated to account for approximately 14% of total deaths[3]. Numerous studies have demonstrated that short-term exposure to particulate matter with an aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$)[4] and ≤ 10 μm (PM_{10})[5], as well as carbon monoxide (CO)[6], sulfur dioxide (SO_2)[7], nitrogen dioxide (NO_2)[8], and ozone (8-hour average concentration) (O_3)[9], is associated with an increased risk of stroke mortality.

Qingdao, located on the east coast of China, features a unique geographical position and climate. This prominent city has experienced rapid development and has transformed into a major urban center with a population exceeding 9 million, largely owing to accelerated urbanization and national policy initiatives. However, this growth has also resulted in greater environmental pollution, driven by urban land expansion, as well as an increase in buildings and vehicles. Several studies have identified traffic exhaust, industrial emissions, and construction dust as the primary sources of pollution in Qingdao[10]. The city exhibits distinctive features, including a pronounced temperate monsoon climate, with dry, cool winters and wet, warm summers. It is essential to recognize that the rising levels of air pollution across different seasons cannot be overlooked. Therefore, incorporating climate characteristics into the analysis of air pollution is crucial.

Data on stroke mortality in Qingdao from 2014 to 2019 were obtained from the Chronic Disease Surveillance Monitoring System, with approval from the Ethics Committee of the Qingdao Municipal Center for Disease Control and Prevention. The committee determined that informed consent was not required for this study. The collected data included variables such as gender, age, date of death, International Classification of Diseases, 10th Revision (ICD-10) codes, cause of death, and cause-of-death diagnosis. Stroke-related mortality was classified based on ICD-10 codes for cerebrovascular diseases: hemorrhagic stroke (I60-I61), ischemic stroke (I63), and unclassified stroke (I64), accompanied by corresponding case summaries. To ensure study accuracy, residents of Qingdao were included, while patients whose cerebrovascular disease resulted from accidents or other unrelated causes were excluded from the analysis.

Daily average concentration data for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3, as well as daily mean pressure (hPa), temperature (°C), relative humidity (%), and wind speed (m/s), were collected from 10 districts in Qingdao from January 1, 2014, to December 31, 2019. The atmospheric pollutant data were provided by the Qingdao Eco-Environmental Monitoring Center of Shandong Province, while the meteorological data were sourced from the Qingdao

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In this study, a distributed lag nonlinear model (DLNM) was developed to estimate the delayed and nonlinear effects of atmospheric pollutants on stroke mortality risk. The findings aim to inform local initiatives for the effective prevention and control of stroke-related health issues. The model was formulated as follows:

$$Log(E(Yt)) = \alpha + cb(pollutants) + ns(temp, df = 3) + ns(rh, df = 3) + ns(pr, df = 3) + ns(wind, df = 3) + stratum + holidays$$

where *Yt* denotes the daily cases of stroke mortality at time *t*; *α* is the intercept; *cb (pollutants)* is a cross-basis function that fits the lagged effects of daily mean concentrations of $PM_{2.5}$, PM_{10}, CO, O_3, SO_2, and NO_2 in the single-pollutant model. Natural cubic splines (*ns*) with 3 degrees of freedom (*df*) were used to control for daily mean temperature (*temp*), relative humidity (*rh*), atmospheric pressure(*pr*), and wind speed(*wind*) based on previous literature[5]. Additionally, a *stratum* was employed to elucidate long-term and seasonal trends. We also adjusted the data to account for the effects of public *holidays*. The hysteresis effects of the average daily concentrations of $PM_{2.5}$, PM_{10}, CO, O_3, SO_2, and NO_2 were integrated into the model.

In our study, we utilized single-day lag exposures (ranging from lag 0 to lag 7 days) and moving average lag exposures (spanning from lag 1 to lag 7 days) to examine the acute effects of ambient air pollution on the percentage change in stroke mortality. We identified potentially susceptible subgroups and investigated differences among these groups by incorporating interaction terms and stratifying the data based on various factors. Specifically, we stratified the seasons into warm seasons (May to October) and cold seasons (November to April of the following year) and categorized strokes into hemorrhagic and ischemic types. We then conducted a comprehensive analysis of both ischemic and hemorrhagic strokes to further elucidate variations in risk within these stroke types. We also took into account gender (males and females) and age (N-aging: individuals younger than 75, and aging: individuals aged 75 or older). These subgroup analyses provided insights into specific population segments that may be more susceptible to the effects of air pollutants.

Subsequently, we conducted a sensitivity analysis by adjusting the degrees of freedom for meteorological factors, including mean temperature, relative humidity, air pressure, and wind speed, varying from 3 to between 4 and 6. This adjustment enabled us to observe the impact of different degrees of freedom for these covariates on the association between air pollutants and stroke mortality outcomes. Finally, we employed excess risk to quantify this correlation, which represented the percentage change (*PC%*) in stroke mortality associated with an interquartile range increase in atmospheric pollutant concentration. This is expressed as *PC% =([e^β - 1]×100%)*, along with the 95% confidence interval (95% CI). Statistical significance was determined by a *P-value* of 0.05 for two-tailed tests. All statistical analyses were performed using the "*dlnm*" package to create the DLNM model in R 4.2.3 (The R project for statistical computing, http://www.r-project.org).

The distributions of monthly stroke deaths and meteorological factors in Qingdao are summarized in Table 1, which presents the characteristics of stroke-related mortality based on the collected data. A total of 46,263 patients, including 24,947 males and 21,316 females, died from stroke. The number of patients aged 75 or older (29,975 cases) was higher than that of individuals younger than 75 (16,228 cases). Across all demographic groups, including subgroups by sex and age, the number of deaths during the cold season exceeded those observed in the warm season. Additionally, the distributions of pollutants and meteorological factors in Qingdao are summarized in Supplementary Table S1.

Spearman's correlation analysis results are presented in Table 2. $PM_{2.5}$ exhibited significant positive correlations with precipitation (*rs* = 0.29), while it showed negative correlations with temperature (*rs* = −0.38), wind speed (*rs* = −0.24), and relative humidity (*rs* = −0.03), all with *P-value*s less than 0.01. Similarly, other pollutants displayed weak correlations with meteorological factors. Notably, a positive correlation was also observed between O_3 and temperature (*rs* = 0.66).

Stroke subcategories were stratified to compare mortality risk between two groups exposed to air pollutants. Seasonal stratification was employed to compare the warm and cold seasons with the overall population, as shown in Figure 1. This approach aimed to evaluate the percentage change in stroke mortality risk associated with air pollution exposure. Significant effects on stroke mortality were observed in both the cold and warm seasons. This phenomenon can be attributed to Qingdao's dry and cold winter climate, which facilitates the retention of air pollutants. Additionally, pollutant concentrations tend to be higher during this time, leading to increased pollution levels and greater exposure of residents to harmful substances[10]. Conversely, under the hot and humid conditions of summer, increased blood flow rates may cause individuals to absorb the harmful effects of pollutants more completely. This phenomenon could explain the increased risk of stroke-related mortality in Qingdao during the warm season.

Ischemic stroke exhibited a significantly higher mortality risk and demonstrated increased vulnerability to air pollution (Supplementary Table S2). This aligns with the findings reported by Chen et al., which indicate that short-term exposure to $PM_{2.5}$, PM_{10}, O_3, SO_2, and NO_2 affects the risk of ischemic stroke[5]. Furthermore, our study did not find a significant association between air pollutants and hemorrhagic stroke.

Supplementary Figure S1 presents an analysis of the Lag 0 lead–lag effect on gender and age subgroups based on all-cause stroke mortality data. The results indicate that women exposed to $PM_{2.5}$ and CO face a higher risk of death on Lag 0, with a notable risk increase of 3.82% (95% CI: 0.46%, 7.29%) and 4.96% (95% CI: 0.77%, 9.33%). Men are more susceptible to stroke mortality when exposed to SO_2 and NO_2, with significant effect sizes of 6.02% (95% CI: 1.61%, 10.61%) and 9.84% (95% CI: 4.46%, 15.50%), respectively. Furthermore, the aging group (aged ≥ 75 years) shows a higher risk of stroke mortality due to exposure to $PM_{2.5}$, CO, and O_3, with

Table 1. Characteristics of study participants in Qingdao, China (2014−2019)

Group	Total			HS			IS			Unspecified		
	All	Warm	Cold	All	Warm	Cold	All	Warm	Cold	All	Warm	Cold
All	46263	20208	26055	18661	8284	10377	26368	11388	14980	1234	536	698
Sex												
Male	24947	10969	13978	10491	4685	5806	13806	6004	7802	650	–	–
Female	21316	9239	12077	8170	3599	4571	12562	5384	7178	584	–	–
Age												
Aging	29975	12834	17141	9897	4245	5652	19184	8212	10972	894	–	–
N-aging	16288	7374	8914	8764	4039	4725	7184	3176	4008	340	–	–

Notes. Total, Total stroke; HS, Hemorrhagic Stroke; IS, Ischemic Stroke; Unspecified is Stroke, not specifically bleeding or infarction stroke; aging, individuals aged 75 or older; N-aging, individuals younger than 75; Warm season, April to September; Cold season, October to March of the next year.

Table 2. Spearman Correlation of Air Pollutants in Qingdao, China (2014−2019)

	pr	temp	rh	wind	$PM_{2.5}$	PM_{10}	O_3	CO	SO_2	NO_2
pr	1.00**									
temp	−0.87**	1.00**								
rh	−0.39**	0.36**	1.00**							
wind	−0.06	−0.10**	−0.14**	1.00**						
$PM_{2.5}$	0.29**	−0.38**	−0.03	−0.24**	1.00**					
PM_{10}	0.26**	−0.34**	−0.23**	−0.15**	0.89**	1.00**				
O_3	−0.58**	0.66**	−0.01**	−0.10**	−0.15**	−0.07**	1.00**			
CO	0.42**	−0.52**	−0.09**	−0.27**	0.91**	0.79**	−0.29**	1.00**		
SO_2	0.48**	−0.49**	−0.27**	−0.18**	0.61**	0.56**	−0.27**	0.72**	1.00**	
NO_2	0.40**	−0.47**	−0.34**	−0.41**	0.75**	0.73**	−0.24**	0.82**	0.66**	1.00**

Notes. ** P < 0.001; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤ 2.5μm; PM_{10}, particulate matter with an aerodynamic diameter of ≤ 10μm; CO, carbon monoxide; O_3, ozone; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; pr, daily mean pressure; temp, mean temperature; rh, relative humidity; wind, wind speed.

increases of 2.87% (95% CI: 0.38%, 5.41%), 4.31% (95% CI: 1.20%, 7.51%), and 6.43% (95% CI: 1.26%, 11.85%), respectively. This suggests that older adults, particularly older women, are disproportionately affected by air pollution, resulting in a higher risk of stroke-related mortality. These findings are consistent with previous research[4]. To further explore the long-term effects, we also examined the influence of seasonal factors and their cumulative impact over time, as detailed in Supplementary Table S3 and Figure S2.

Particulate matter, such as $PM_{2.5}$[4] and PM_{10}[5], along with gaseous pollutants such as CO[6] and O_3[9], have been identified as key contributors to stroke mortality in previous studies. However, the impact of seasonal variations on this relationship has not been thoroughly examined. Our study, which accounts for temperature and climatic differences between cold and warm seasons, provides a more nuanced understanding. The stratified analysis in Supplementary Table S3 shows that during the warm season, exposure to $PM_{2.5}$, PM_{10}, CO, and SO_2 is associated with an increased risk of ischemic stroke mortality. The percentage increase in stroke mortality risk associated with these pollutants is 14.37% (95% CI: 2.82%, 27.21%) for $PM_{2.5}$, 12.32% (95% CI: 2.91%, 22.59%) for PM_{10}, 19.05% (95% CI: 4.46%, 35.68%) for CO, and 35.34% (95% CI: 10.41%, 65.89%) for SO_2. Additionally, our findings show that ischemic stroke-related deaths are related to CO and SO_2 exposure, with percentage increases of 13.22% (95% CI: 1.79%, 25.94%) and 21.39% (95% CI: 9.11%, 35.06%), respectively.

Supplementary Figure S2 gives a detailed overview of long-term trends The results from the warm season show a clear upward trend in the risk of ischemic stroke mortality associated with exposure to $PM_{2.5}$, PM_{10}, CO, and SO_2. Notably, the risk of ischemic stroke death is higher during the warm season compared with the cold season. In contrast, our study found no significant correlation between air pollution exposure and the risk of hemorrhagic stroke mortality in either season. However, there is a strong link between air pollution exposure and the risk of death from ischemic stroke, which may appear to contradict previous findings. For example, Chen et al. reported that the risk of stroke-related mortality in Chongqing was mainly observed during the cold season[5]. In contrast, our seasonally adjusted analysis indicates that exposure to pollutants during the warm season poses a greater risk for stroke mortality. This discrepancy could be attributed to the hot and humid conditions prevalent in Qingdao during the warm season.

To ensure the reliability of our findings, we conducted a sensitivity analysis by developing a two-pollutant model and adjusting the *df* from 3 to 4–6 in the single-pollutant model. The two-pollutant model showed a slight reduction in the association between particulate matter exposure and total stroke mortality. However, no significant changes were observed in the relationship between exposure and all-cause stroke mortality (Supplementary Table S4 for details). For example, adjustments for CO on lag

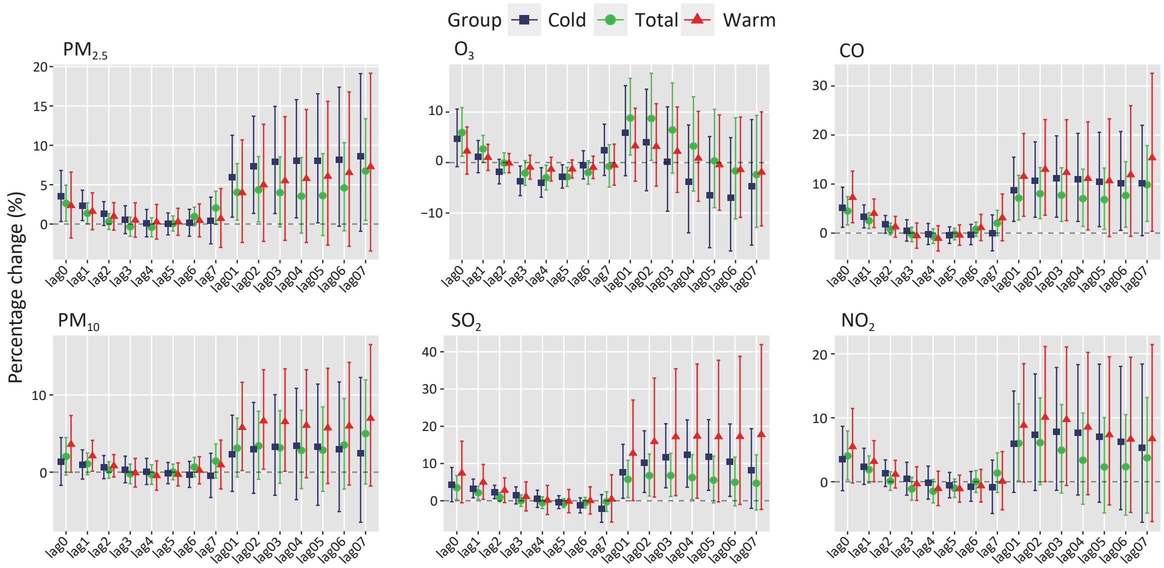

Figure 1. Percentage change (95% confidence interval) in odds of mortality from total stroke associated with an IQR increase of exposure to ambient air pollution during different seasons.

0 days demonstrated minimal variation in the results. When *df* was set to 3, the percentage change was 4.50% (95% CI: 1.65%, 7.43%). This remained consistent at 4.50% (95% CI: 1.68%, 7.48%) with *df* = 4, slightly changed to 4.53% (95% CI: 1.66%, 7.47%) with *df* = 5, and increased to 4.65% (95% CI: 1.78%, 7.60%) with *df* = 6. Our analysis showed that adjusting the covariate *df* from 3 to 4–6 in the single-pollutant model had minimal impact on the association between air pollution and stroke mortality, which confirmed the robustness of our model (Supplementary Figure S3).

Our study has several methodological strengths. First, the use of a case-crossover design effectively minimized confounding bias from time-invariant covariates. Second, our analysis included a large sample size, which consisted of 46,263 stroke cases from Qingdao City between 2014 and 2019. This extensive dataset enhanced the statistical power of our study and improved its sensitivity to detect variations in stroke mortality risk across different subpopulations. Finally, the wide range of air pollutant concentrations observed allowed for a more precise examination of exposure–response relationships.

However, our study has some limitations. First, relying on regional average pollutant exposure levels may lead to exposure misclassification, as individual variations in exposure are not fully captured. Second, despite the advantages of the case-crossover design in reducing time-invariant confounding, our study may still be vulnerable to residual confounding from time-varying individual factors, such as changes in medication use or lifestyle. Lastly, the geographical scope of our study is limited to Qingdao City, which may restrict the generalizability of our findings to other coastal regions with different climatic conditions and population characteristics. It is important to emphasize that these limitations do not undermine our primary conclusions. The use of the case-crossover design in this study effectively addresses individual-level variables and potential biases and ensures that the observed associations between air pollution and stroke mortality risk are both robust and credible. While the external validity may be limited, the internal validity of our findings remains strong. In the future, we plan to integrate the latest stroke data from Qingdao with historical data, and subsequently gather the chemical components of $PM_{2.5}$ to further investigate the factors influencing stroke mortality risk.

Competing Interests The authors declare no competing interests in connection with the work submitted.

Ethics This study obtained ethical approval from the Ethics Review Committee of Qingdao Municipal Center for Disease Control and Prevention (No.202202). The requirement for patient consent was waived owing to the retrospective study design, and prior to analysis, all data in our study were anonymized.

Authors' contributions Jingkai Zhang: Formal analysis, Writing – original draft, Writing – review & editing; Bingling Wang: Data curation, Writing – review & editing; Lu Pan: Investigation, Writing – review & editing;Ge Nan: Methodology, Formal analysis, Visualization;Xiutao Gao: Data curation, Writing – review & editing; Jingya Yin: Methodology, Visualization;Yuan Fang: Investigation, Data curation; Hua Zhang: Methodology, Data curation; Jianjun Zhang: Data curation, Visualization; Yan Ma: Investigation, Data curation; Li Cheng: Methodology, Data curation; Haiping Duan: Funding acquisition, Writing – review & editing. All authors have reviewed the manuscript and approved the final version for publication.

Data sharing The supplementary materials will be available in www.besjournal.com.

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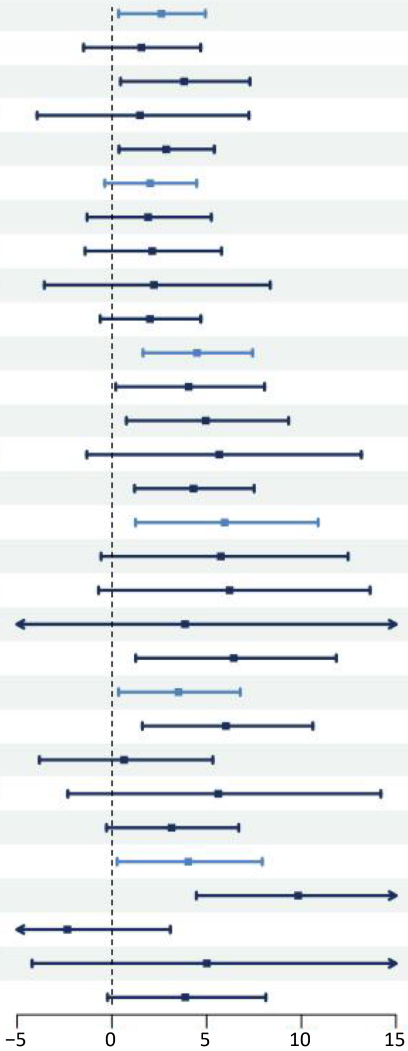
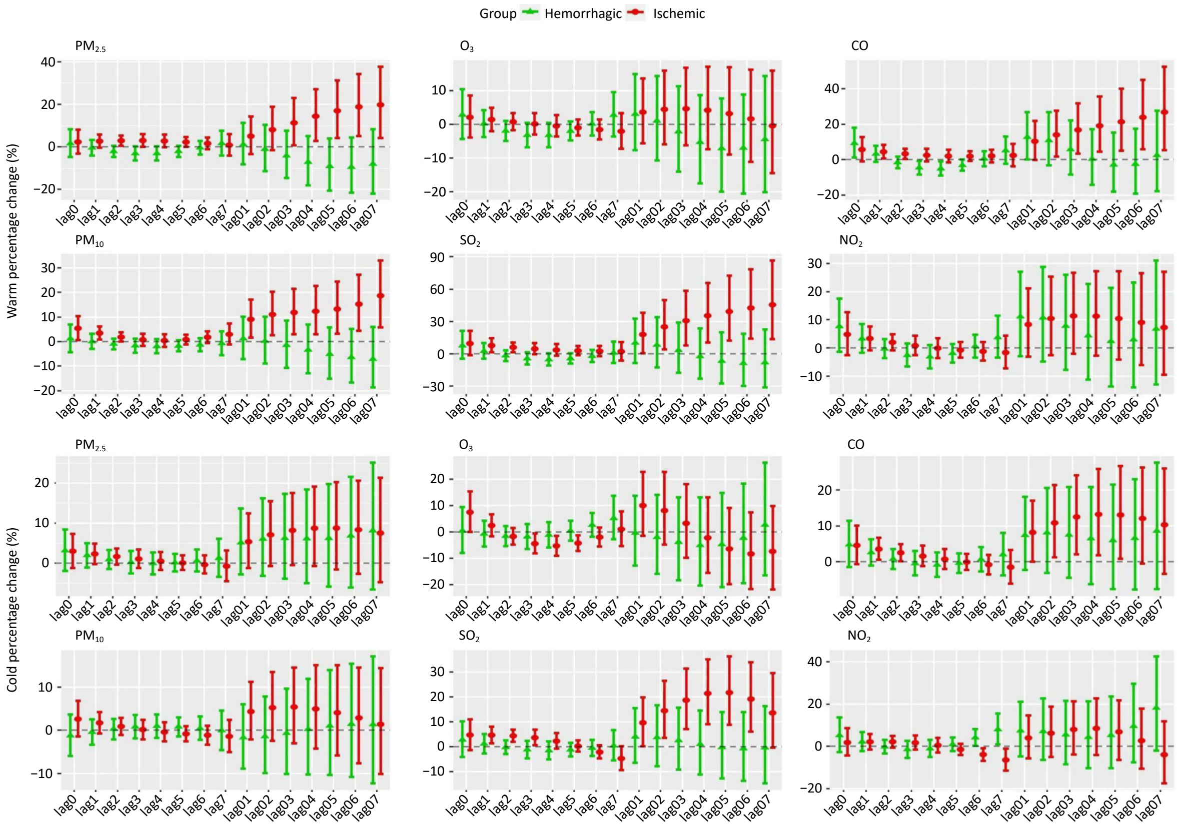
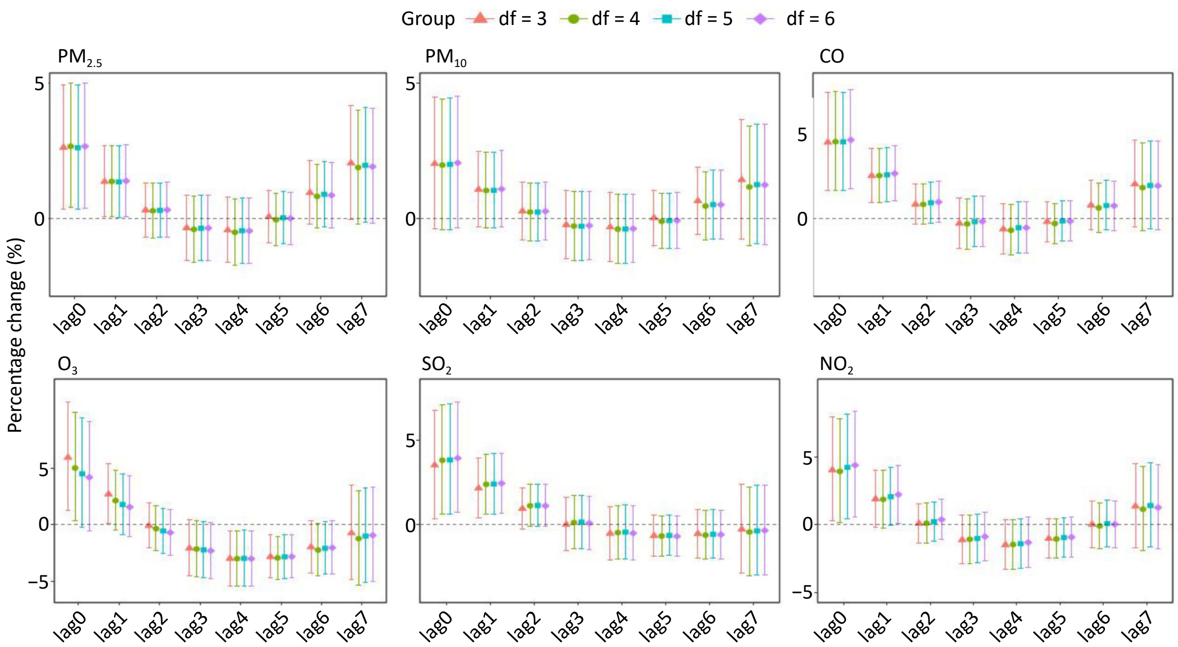
Air pollutants	Group	group	Percentage change(95% CI)	*P*_value
$PM_{2.5}$	Total		2.62 (0.36 to 4.94)	
	Gender	Male	1.56(−1.49 to 4.69)	<0.001
		Female	3.82 (0.46 to 7.29)	
	Age	N-aging	1.49 (−3.94 to 7.24)	<0.001
		Aging	2.87 (0.38 to 5.41)	
PM_{10}	Total		2.02 (−0.37 to 4.48)	
	Gender	Male	1.92(−1.31 to 5.25)	0.747
		Female	2.13 (−1.41 to 5.79)	
	Age	N-aging	2.23 (−3.56 t0 8.36)	0.012
		Aging	2.01(−0.61 to 4.70)	
CO	Total		4.50 (1.65 to 7.43)	
	Gender	Male	4.06 (0.21 to 8.06)	0.856
		Female	4.96 (0.77 to 9.33)	
	Age	N-aging	5.67 (−1.32 to 13.17)	0.018
		Aging	4.31(1.20 to 7.51)	
O_3	Total		5.96(1.25 to 10.89)	
	Gender	Male	5.75 (−0.57 to 12.47)	0.017
		Female	6.22 (−0.70 to 13.63)	
	Age	N-aging	3.86 (−7.19 to 16.23)	<0.001
		Aging	6.43(1.26 to 11.85)	
SO_2	Total		3.52 (0.36 to 6.78)	
	Gender	Male	6.02 (1.61 to 10.61)	<0.001
		Female	0.65 (−3.82 t0 5.33)	
	Age	N-aging	5.62 (−2.32 to 14.20)	<0.001
		Aging	3.15 (−0.28 to 6.70)	
NO_2	Total		4.04 (0.28 to 7.94)	
	Gender	Male	9.84 (4.46 to 15.50)	<0.001
		Female	−2.34 (−7.47 to 3.09)	
	Age	N-aging	5.01(−4.21 to 15.11)	0.008
		Aging	3.87 (−0.22 to 8.13)	



Supplementary Figure S1. ?



Supplementary Figure S2. ?



Supplementary Figure S3. ?