



Effect of short-term exposure to air pollution on ischemic stroke incidence and mortality: a five-year time-series study in Jining, China

Yaohui Kong^{1,*}, Wenhua Duan^{2,*}, Zi Zhang¹, Peizhen Zhou¹, Mei Wang², Jing Zhang³ and Wenjun Wang^{1,4}

¹ School of Public Health, North China University of Science and Technology, Tangshan, China

² Jining Center for Disease Control and Prevention, Jining, China

³ School of Clinical Medicine, Jining Medical University, Jining, China

⁴ Weifang Nursing Vocational College, Weifang, China

* These authors contributed equally to this work.

ABSTRACT

Background. Short-term exposure to air pollutants is associated with an increased risk of ischemic stroke incidence and mortality. However, there is a lack of research based on data from disease surveillance systems. This study used disease surveillance system data to quantitatively analyze the association between air pollution and ischemic stroke incidence and mortality in Jining, China.

Methods. The stroke registration system of the Jining City Center for Disease Control and Prevention (CDC) includes information on confirmed stroke cases reported by all medical institutions in the jurisdiction, covering a population of 8.9 million. Generalized linear regression models combined with distributed lag nonlinear models (DLNM) were used to determine the association between air pollutants and ischemic stroke incidence and mortality. Stratified analyses by sex, age, and season were also conducted.

Results. During the study period (January 1, 2018, to December 31, 2022), there were 209,949 ischemic stroke incidence cases and 23,565 ischemic stroke-related deaths. There were more ischemic stroke incidence and death cases in males compared to females. The number of incidence cases was higher in the warm season (52.6%) than in the cold season (47.4%), while this pattern was reversed for the number of deaths, with a higher number of deaths in the cold season (55.9%) than in the warm season (44.1%). This study showed that exposure to particulate matter (PM_{2.5} and PM₁₀), nitrogen dioxide (NO₂), and carbon monoxide (CO) was associated with ischemic stroke incidence, and exposure to PM_{2.5}, PM₁₀, sulfur dioxide (SO₂), and CO was associated with ischemic stroke mortality. The relative risks (RRs, with 95% CIs) for ischemic stroke incidence at the maximum single-lag effect day for each interquartile range (IQR) increment for PM_{2.5}, PM₁₀, NO₂, and CO were 1.007 (1.001–1.014), 1.004 (1.000–1.008), 1.031 (1.011–1.051), and 1.008 (1.001–1.015), respectively. The RRs (with 95% CIs) for mortality for PM_{2.5}, PM₁₀, SO₂, and CO were 1.049 (1.025–1.073), 1.031 (1.014–1.048), 1.021 (1.001–1.041), and 1.044 (1.017–1.071), respectively. Furthermore, the association between air pollution and ischemic stroke incidence risk was modified by age and season. Individuals aged >75 years were more vulnerable to

Submitted 5 February 2025

Accepted 6 October 2025

Published 6 November 2025

Corresponding authors

Jing Zhang, zhangj1976@163.com

Wenjun Wang, wwjun1973@163.com

Academic editor

Worradorn Phairuang

Additional Information and
Declarations can be found on
page 15

DOI 10.7717/peerj.20298

© Copyright
2025 Kong et al.

Distributed under
Creative Commons CC-BY-NC 4.0

OPEN ACCESS

SO₂-induced ischemic stroke incidence risk, and PM_{2.5} and CO were more harmful in the cold season.

Conclusion. These findings suggest that short-term exposure to PM_{2.5}, PM₁₀, SO₂, NO₂, and CO leads to increased ischemic stroke morbidity and mortality. The elderly population, as well as the general population, should be better protected during the cold season.

Subjects Neurology, Public Health, Environmental Health

Keywords Air pollution, Ischemic stroke, Incidence, Death, Short-term exposure

INTRODUCTION

Stroke, also known as cerebrovascular accident (CVA), has a rapid onset. In 2021, there were 11.9 million new stroke events, representing the third leading cause of deaths worldwide after ischemic heart disease and COVID-19. Ischemic stroke constituted the largest proportion of all incident strokes (7.8 million, or 65.3%), followed by intracerebral hemorrhage. Rates of incident and fatal stroke were highest for ischemic stroke (92.4 per 100,000 and 44.2 per 100,000, respectively; [Collaborators, 2021](#)). Unlike the decline in age-standardized stroke incidence and mortality in recent years in developed countries, developing countries have experienced a dramatic increase in stroke incidence and mortality due to significant population aging, with 70% of stroke incidence and 87% of stroke-related deaths occurring in low- and middle-income countries ([Bell et al., 2017](#)). Therefore, the variability of stroke risk factors should be identified among countries with different levels of economic development.

Large cohort studies have shown that, in addition to high blood pressure, smoking, and physical inactivity, air pollution is associated with stroke, and this relationship may be stronger in low- and middle-income countries ([Sarker et al., 2015](#)). The molecular mechanisms by which air pollution contributes to stroke incidence and mortality are complex, and this complexity is exacerbated by pollutant interactions. In previous studies, air pollutants, including particulate matter pollutants (PM_x), sulfur dioxide (SO₂), carbon monoxide (CO), and nitrogen dioxide (NO₂), have been shown to affect stroke incidence, prognosis, and death by causing oxidative stress and systemic inflammatory responses, promoting atherosclerosis formation, damaging vascular endothelial cells, increasing blood viscosity and thrombosis, and causing cardiac arrhythmias and elevated blood pressure ([Bobb et al., 2015](#); [Liang et al., 2014](#); [Nemmar et al., 2011](#); [Thomson et al., 2007](#)).

Current epidemiologic studies of the association between air pollution and stroke are deficient, resulting in large discrepancies or even conflicting conclusions ([Baum et al., 2017](#); [Butland et al., 2017](#); [Mecocci et al., 2018](#); [Wellenius & Joel Schwartz, 2005](#)). Using stroke admissions as the outcome of interest may be biased because people may not go to the hospital on the same day they experience symptoms or discomfort, and there may be a delay between stroke onset and admission. In addition, due to potential selection bias, admission data may not fully reflect the true incidence of the disease in the local population ([Ban et al., 2021](#); [Chen et al., 2022](#)). Registry datasets covering all stroke case records from

multiple sources may be relatively reliable in reflecting local stroke incidence because of decreased misclassification of disease and improved completeness; however, to date, there have been few studies based on population-based registry data (*Butland et al., 2017*). In addition, racial stratification, geographic differences, and varying levels of pollution due to differences in industrial infrastructure all contribute to the wide variation in study results (*Chen et al., 2014; Scheers et al., 2015; Wang, Liu & Li, 2016*).

Understanding the relationship between air pollution and ischemic stroke is crucial for public health policymaking and the development of effective intervention strategies aimed at reducing the burden of stroke. In this context, the current epidemiologic study used population-based registry data from the disease surveillance system in a highly polluted area with a robust coal industry to examine the association between short-term exposure to air pollutants and stroke incidence and mortality and to explore the potential effects of gender, age, and season.

MATERIALS & METHODS

Study area and data collection

Jining is located in the southwest of Shandong Province, East China, covering an area of 11,100 km² with a permanent population of 8.9 million in 2022. The coal-containing area of Jining exceeds 3,920 km², accounting for more than 1/3 of the total land area of the city, and is one of the eight major coal-based cities in China. Coal and its derivative industries have introduced substantial pollution to the environment of Jining. Although the government has taken active measures to combat air pollution in recent years, the air quality of Jining still ranked second to last in Shandong Province in 2022 (*Chiu et al., 2023*).

Daily ischemic stroke incidence data were sourced from the stroke registration system of the Jining Centers for Disease Control and Prevention (CDC). This system requires all medical facilities including hospitals, clinics, and community health centers within the jurisdiction to provide timely reports on cases diagnosed as stroke. Stroke deaths that did not involve hospitalization were also included. The registration data includes basic patient information, clinical symptoms, and medical examination results that are categorized according to the International Classification of Diseases version 10 (ICD-10). The date of the occurrence of clinical symptoms is recorded as the incidence date. The time frame of this study was from January 1, 2018 to December 31, 2022, and the study population consisted of all ischemic stroke (ICD code: I63) cases recorded in the system. The private information of patients, such as name, ID number, and medical insurance number, was not collected during data export.

Environmental data and exposure assessment

Air pollution data including PM_{2.5}, PM₁₀, SO₂, NO₂, and CO were obtained from the China Air Quality Online Monitoring and Analysis Platform or the National Urban Air Quality Real-time Publishing Platform, covering six air quality monitoring stations in Jining City (<http://www.cnemc.cn/sssj/>). Data measurements were in accordance with Chinese National Quality Control (GB3095-2012) protocols. The 24-hour average concentration of

a pollutant was used to represent the daily exposure level for each individual. Daily mean temperature was sourced from the National Meteorological Information Center of China. Single-day lag exposures and cumulative lag effects were calculated. For example, the effect at lag 0–1 day was defined as the single-day lagged effect for the lag 0 day and lag 1 day. The effect at lag 02 day was defined as the cumulative lagged effect of lag 0, lag 1, and lag 2 days. The effect at lag 01–02 was defined as the effect at the lag 01 and lag 02 days.

Statistical analysis

Daily ischemic stroke incidence and mortality, concentration of air pollutants, and temperature were established as time series and expressed as maximum (Max), minimum (Min), median (Median), mean (Mean), standard deviation (SD), and interquartile range (IQR). Spearman's correlation coefficient was used to estimate the relationship between pollutants and temperature. The effects of air pollutants on ischemic stroke are lagged and nonlinear, and distributed lag nonlinear models (DLNMs) were used to estimate the exposure-lag effect of short-term air pollution exposure on ischemic stroke incidence and mortality ([Ban et al., 2021](#); [Gasparrini, Armstrong & Kenward, 2010](#)). Since the daily ischemic stroke incidence and death data are quantitative data and are small probability events, the DLNM combined with a quasi-Poisson regression model was applied. The model is as follows:

$$\log[E(Y_t)] = \alpha + cb(\text{pollutant}_t) + cb(\text{Mean Temp}_t) + ns(\text{time}, df = 7 * \text{years}) + \beta * \text{DOW} + \gamma * \text{holiday}$$

where Y_t is the expected value of incidence or mortality on day t ; α is the intercept term; cb is the cross-basis function; pollutant is air pollution, and Mean Temp_t is mean temperature. There is often a lagged effect between air temperature and health outcomes, so the parameter settings used in this study for temperature confounding control were consistent with those for pollutants, using both linear and natural cubic spline fits to the lag-response relationship and the respective association with the ending exposure-response relationships, with degrees of freedom (df) set to 3. The nonlinear relationship between air pollution and ischemic stroke was explored through a natural cubic spline function ($df = 3$) when the cumulative effect appeared to be strongest. The variable ns (time , $df = 7 * \text{years}$) represents a degree of freedom of 7 per year for controlling for long term trends and seasonality. DOW denotes the day of the week, and holiday denotes the effect of the holiday that both variables were included as dummy variables.

Studies have shown that the duration of cardiovascular effects of air pollution generally lasts 1–5 days. To fully examine the lag effect, the maximum number of lag days in the crossbasis was set at 7 days in this study. A single-pollutant model was used to assess the association between air pollution and ischemic stroke incidence or mortality to avoid air pollutant correlation. The risk estimates for air pollutants were expressed as relative risks (RRs) with their 95% confidence intervals (CIs) in ischemic stroke incidence and mortality when the concentration of each air pollutant increases by per interquartile range (IQR).

Effect modification

Stratified analyses by age (≤ 75 years, > 75 years), sex (male, female), and season (cold season, October to March; warm season, April to September) were performed to explore potential effect modifiers of associations. A subsequent z test was performed to determine whether significant differences existed between subgroups (Altman & Bland, 2003; Liu et al., 2021).

Sensitivity analysis

The robustness of the results was determined in the sensitivity analysis by fitting a two-pollutant model (incorporating pollutants with correlation coefficients < 0.6 to avoid covariance), varying the degrees of freedom of the natural cubic spline function for time ($df = 6-8$) and temperature ($df = 4-6$). All analyses were conducted through R (version 4.3.1, R Institute for Statistical Computing, Vienna, Austria) and related packages like “dlnm” and “splines”. A two-sided P -value < 0.05 was considered statistically significant.

Ethical approval

This study was approved by the Ethics Committee of the Jining Center for Disease Control and Prevention. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research/review board (IRB)-IRB Number: (2024-005). Study participation only required verbal informed consent, which was obtained from all subjects who participated in this study and was approved by the ethics committee.

RESULTS

Population and exposure characteristics

During the study period (January 1, 2018 to December 31, 2022), there were 209,949 ischemic stroke incidence cases and 23,565 ischemic stroke-related death cases. There were more ischemic stroke incidence and death cases in males than in females. The number of incidence cases was higher in the warm season (52.6%) than in the cold season (47.4%), while this pattern was reversed for the number of deaths, with a higher number in the cold season (55.9%) than in the warm season (44.1%). During the study period, the daily mean (with maximum) values of $PM_{2.5}$, PM_{10} , SO_2 , CO, NO_2 , and temperature were 50.6 (241.1) $\mu g/m^3$, 89.3 (1017.1) $\mu g/m^3$, 31.1 (108.3) $\mu g/m^3$, 0.9 (2.8) mg/m^3 , 14.1 (49.8) $\mu g/m^3$ and 16.8 (36.2) $^{\circ}C$, respectively. Detailed information is presented in Table 1. The concentrations of each air pollutant (including $PM_{2.5}$, PM_{10} , SO_2 , CO, and NO_2) showed obvious cyclical changes during the study period, with high concentrations in the cold season and low concentrations in the warm season, consistent with the changes in atmospheric dispersion conditions and pollutant sources (Fig. S1). The SO_2 concentration peaked in 2018 and began to gradually decrease, due to the strict control of industrial pollution sources in Jining, especially the upgrading of desulfurization measures related to the coal burning industry. There were positive correlations between $PM_{2.5}$, PM_{10} , NO_2 , CO, and SO_2 (Pearson’s r range: 0.39–0.77; $PM_{2.5}$ was strongly correlated with PM_{10} and CO, Pearson’s $r > 0.7$) and all pollutants showed negative correlations with temperature. (Table 2).

Table 1 Distribution of air pollutants, temperature and ischemic stroke cases in Jining, China (2018–2022).

Variables			Mean ± SD	Min	P25	P50	P75	P95	Max
Air pollutants									
	PM _{2.5} (μg/m ³)		50.6 ± 34.2	3.7	27.7	40.8	62.4	123.9	241.1
	PM ₁₀ (μg/m ³)		89.3 ± 57.8	8.7	55.2	76.5	108.5	180.8	1,017.1
	SO ₂ (μg/m ³)		31.1 ± 16.2	4.7	18.5	26.8	42.0	62.2	108.3
	CO (mg/m ³)		0.9 ± 0.3	0.2	0.7	0.8	1.0	1.4	2.8
	NO ₂ (μg/m ³)		14.1 ± 6.9	2.4	9.3	12.5	17.5	27.6	49.8
Meteorological factor									
	Temperature (°C)		16.8 ± 9.8	−7.49	8.4	17.3	25.7	30.3	36.2
Ischemic stroke cases									
Total									
	Incidence	209,949	114.98 ± 32.34	34.0	92.0	114.0	135.0	168.0	338.0
	Death	23,565	12.91 ± 8.03	1	8.0	12.0	17.0	25.0	180.0
Sex									
Male	Incidence	120,264	65.86 ± 19.65	16.0	52.0	64.0	78.0	99.0	211.0
	Death	13,549	7.42 ± 5.13	0	4.0	7.0	10.0	15.0	110.0
Female	Incidence	89,685	49.12 ± 14.76	13.0	39.0	49.0	58.0	75.0	141.0
	Death	10,016	5.49 ± 3.83	0	3.0	5.0	7.0	12.0	70.0
Age									
≤75	Incidence	148,558	81.36 ± 23.47	22.0	65.0	80.0	95.0	119.0	247.0
	Death	9,937	5.44 ± 4.22	0	3.0	5.0	7.0	12.0	108.0
>75	Incidence	61,391	33.62 ± 10.87	9.0	26.0	33.0	40.0	51.7	100.0
	Death	13,628	7.46 ± 4.92	0	4.0	7.0	10.0	15.0	72.0
Season									
Warm	Incidence	110,515	120.78 ± 32.65	34.0	98.0	119.0	140.0	172.0	325.0
	Death	10,401	11.37 ± 5.77	0	7.0	11.0	15.0	22.2	35.0
Cold	Incidence	99,434	109.15 ± 30.96	44.0	87.0	106.0	127.0	164.0	338.0
	Death	13,164	14.45 ± 9.55	1	9.0	13.0	19.0	27.0	180.0

Table 2 Spearman’s correlation coefficients between air pollutants and temperature.

Variables	PM _{2.5}	PM ₁₀	NO ₂	CO	SO ₂	Temperature
PM _{2.5}	1.00					
PM ₁₀	0.75**	1.00				
NO ₂	0.66**	0.52**	1.00			
CO	0.77**	0.57**	0.58**	1.00		
SO ₂	0.39**	0.40**	0.54**	0.39**	1.00	
Temperature	−0.51**	−0.36**	−0.55**	−0.29**	−0.34**	1.00

Notes.
***P* < 0.01.

Association between air pollution and ischemic stroke incidence and mortality

In the single-day pollutant model (Fig. 1), after adjusting for the effect of temperature, the single-day lagged structures showed that exposure to PM_{2.5} (at lag 2–3 day), PM₁₀ (at

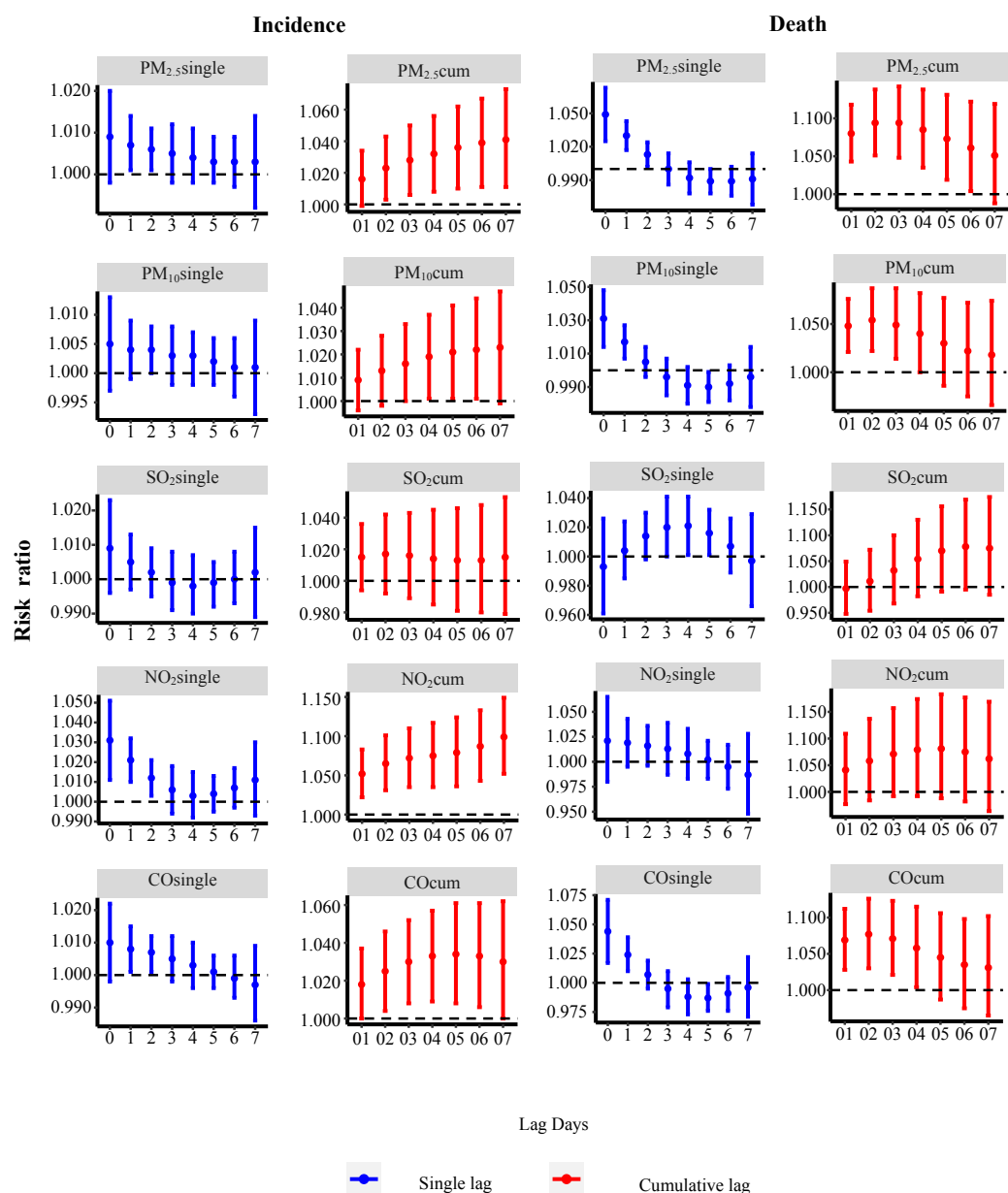


Figure 1 Relative risk of ischemic stroke incidence or death associated with air pollution in a single or cumulative lag day structure. RRs and 95% CIs were calculated for each IQR increment.

[Full-size DOI: 10.7717/peerj.20298/fig-1](https://doi.org/10.7717/peerj.20298/fig-1)

lag 3 day), NO₂ (at lag 0–3 day), and CO (at lag 2–3 day) was associated with ischemic stroke incidence, and PM_{2.5} (at lag 0–2 day), PM₁₀ (at lag 0–1 day), SO₂ (at lag 3–5 day), and CO (at lag 0–1 day) were associated with ischemic stroke mortality. The RRs (with 95% CIs) for ischemic stroke incidence at the maximum single-lag effect day for each IQR increment for PM_{2.5}, PM₁₀, NO₂, and CO were 1.007 (1.001–1.014), 1.004 (1.000–1.008), 1.031 (1.011–1.051), and 1.008 (1.001–1.015), respectively; the RRs (with 95% CIs) for mortality for PM_{2.5}, PM₁₀, SO₂, and CO were 1.049 (1.025–1.073), 1.031 (1.014–1.048),

1.021 (1.001–1.041), and 1.044 (1.017–1.071), respectively. Cumulative lagged structures showed that exposure to PM_{2.5} (at lag02–07 day), PM₁₀ (at lag03–06 day), NO₂ (at lag01–07 day), and CO (at lag02–06 day) was associated with ischemic stroke incidence, and that PM_{2.5} (lag01–06 day), PM₁₀ (lag 01–03 day), and CO (lag 01–04 day) were associated with ischemic stroke mortality. The RRs (95% CIs) of ischemic stroke incidence at the maximum cumulative-lag effect day for each IQR increment in air pollutant concentration for PM_{2.5}, PM₁₀, NO₂, and CO were 1.041 (1.011–1.073), 1.022 (1.001–1.044), 1.099 (1.052–1.149), and 1.034 (1.008–1.061), respectively; the RRs (95% CIs) of mortality for PM_{2.5}, PM₁₀, and CO were 1.094 (1.051–1.138), 1.054 (1.022–1.087), and 1.077 (1.030–1.126), respectively.

Subgroup analyses of the association between air pollution and ischemic stroke incidence or mortality

The association between air pollution and the incidence or mortality of ischemic stroke was investigated through subgroup analysis based on sex, age, and season of incidence time, to determine the potential modifying effects of these variables.

Figures 2 and 3 illustrate a positive association between the risk of ischemic stroke incidence and NO₂ that was observed in both male and female subgroups, as well as between stroke incidence and PM_{2.5} in the male subgroup. The >75-year-old subgroup and ≤75-year-old subgroup showed positive associations between NO₂ (at lag0–2) and, similarly, exposure to SO₂ showed a positive association with the incidence of ischemic stroke in the >75-year-old group (lag03, lag04, lag05, lag06, lag07), while no association was observed in the ≤75-year-old group, indicating a modification effect of age (all $P < 0.05$). Subgroup analysis based on the season of incidence showed a positive association between the risk of ischemic stroke incidence and NO₂ at lag0–2 in the cold season and lag6–7 in the warm season. In addition, the risk of ischemic stroke incidence showed a positive association with PM_{2.5} at lag1 in the cold season and with CO at lag1 in the warm season. Furthermore, the season of incidence showed modification effects, with the population being more sensitive to exposure to PM_{2.5} (lag1, lag02, lag03, lag04) and CO (lag1, lag02, lag03) in the cold season (all $P < 0.05$). For ischemic stroke mortality, results were similar to the above findings (Figs. S2–S3); however, sex, age, and season of mortality did not show a modifying effect.

Sensitivity analyses

The results of the sensitivity analysis are presented in Tables 3 and 4. Using the same pollutant exposure and ischemic stroke incidence and mortality data, a two-pollutant model was constructed. After adjusting for exposure to other pollutants, there was no significant change in the association between the individual pollutants and ischemic stroke incidence or mortality (Table 3). Changing the df value did not have a substantial impact on the association between air pollutant and ischemic stroke incidence or mortality (Table 4).

DISCUSSION

Air pollution causes serious health problems and economic burdens globally, with many studies linking it to cardiovascular and respiratory diseases, among others. Research on the

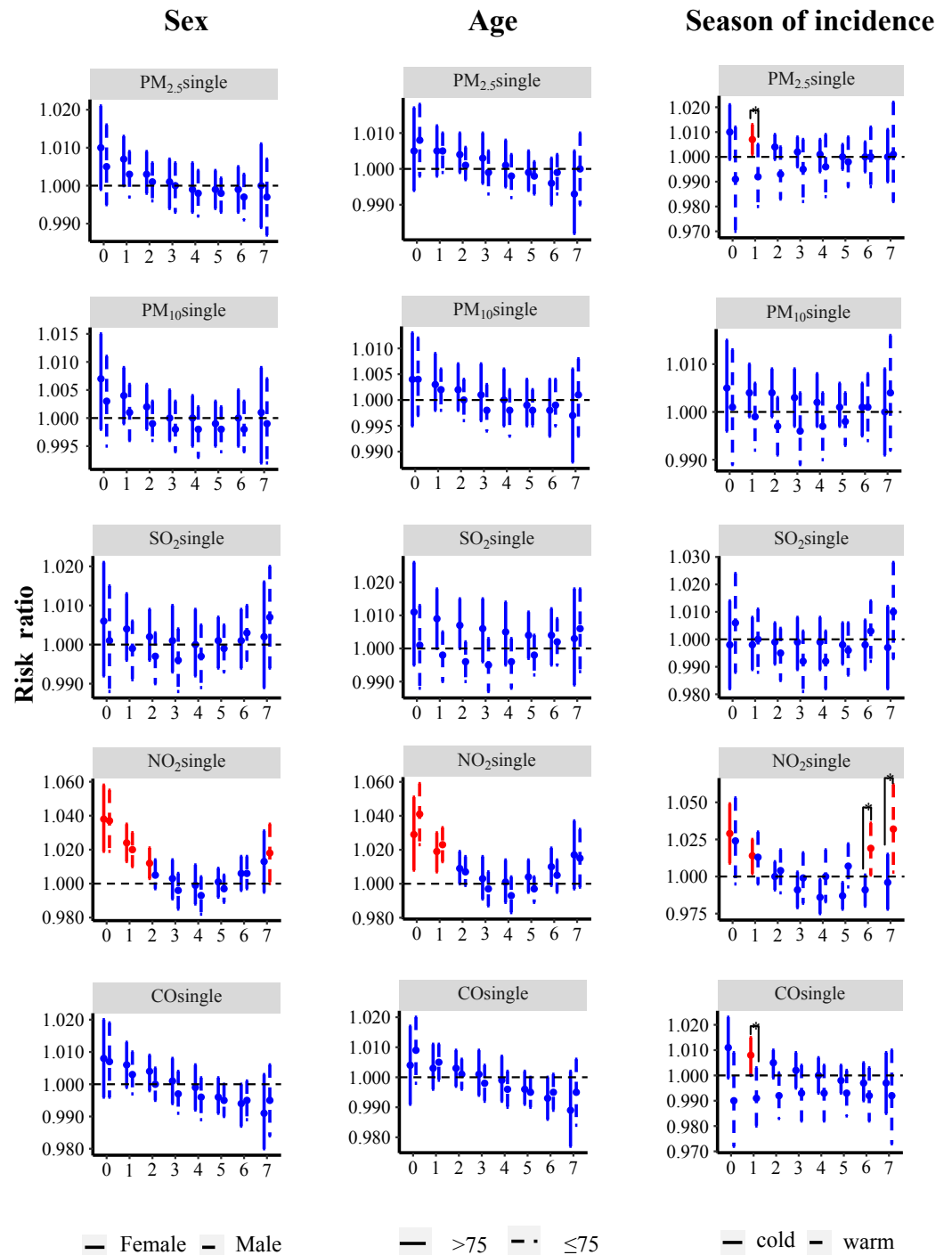


Figure 2 Relative risk of ischemic stroke incidence associated with air pollution exposure stratified by sex, age, and season of incidence in a single lag day structure. Red color indicates the association was significant. * Indicates significant difference between two subgroups. RRs and 95% CIs were calculated for each IQR increment.

Full-size [DOI: 10.7717/peerj.20298/fig-2](https://doi.org/10.7717/peerj.20298/fig-2)

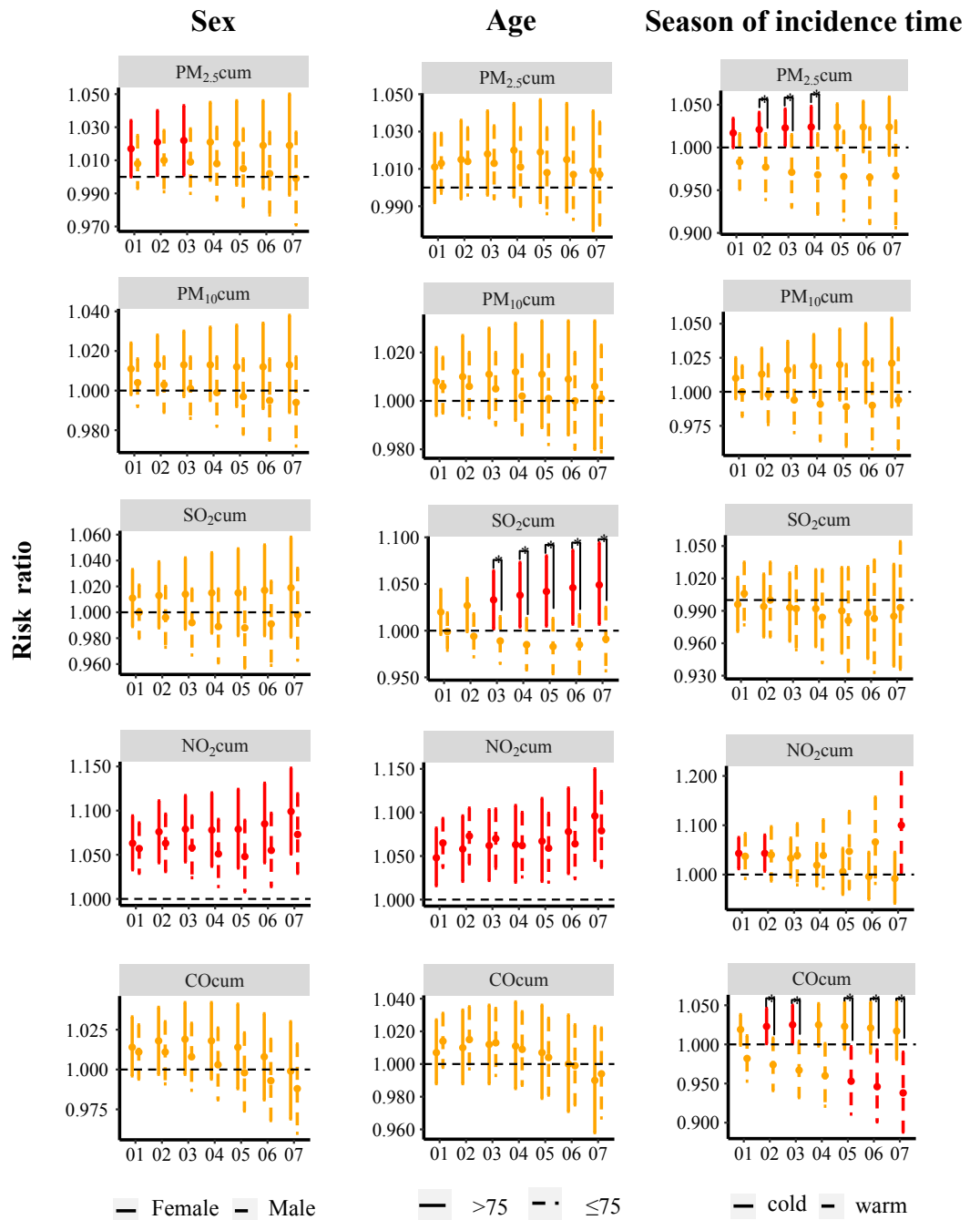


Figure 3 Relative risk of ischemic stroke incidence associated with air pollution exposure stratified by sex, age, and season of incidence in a cumulative day structure. Red color indicates the association was significant. * Indicates a significant difference between two subgroups. RRs and 95% CIs were calculated for each IQR increment.

Full-size [DOI: 10.7717/peerj.20298/fig-3](https://doi.org/10.7717/peerj.20298/fig-3)

Table 3 Relative RRs (with 95% CIs) of ischemic stroke incidence or death associated with air pollution for each IQR increment in a two-pollutant model.

		RR (95% CI) ^a	P value	RR (95% CI) ^b	P value
PM _{2.5}	null	1.041 (1.011–1.073)		1.094 (1.051–1.138)	
	SO ₂	1.043 (1.011–1.075)	0.952	1.094 (1.050–1.139)	0.990
	NO ₂	1.015 (0.981–1.050)	0.575	1.101 (1.052–1.152)	0.847
PM ₁₀	null	1.022 (1.001–1.044)		1.054 (1.022–1.087)	
	SO ₂	1.021 (0.999–1.044)	0.962	1.054 (1.022–1.088)	0.979
	NO ₂	1.002 (0.978–1.026)	0.224	1.048 (1.014–1.084)	0.818
	CO	1.014 (0.990–1.039)	0.625	1.041 (1.006–1.077)	0.596
NO ₂	null	1.099 (1.052–1.149)		1.081 (0.988–1.183)	
	CO	1.105 (1.048–1.164)	0.891	1.039 (0.931–1.159)	0.582
	SO ₂	1.116 (1.061–1.173)	0.661	1.059 (0.958–1.171)	0.768
CO	null	1.034 (1.008–1.061)		1.077 (1.030–1.126)	
	SO ₂	1.035 (1.008–1.062)	0.970	1.079 (1.031–1.129)	0.963

Notes.

^aIschemic stroke incidence.

^bIschemic stroke death.

Table 4 Relative RRs (with 95% CIs) of ischemic stroke incidence or death associated with air pollution for each IQR increment by different degree of freedom (df) for time and temperature (T).

		df	PM _{2.5}	PM ₁₀	SO ₂	NO ₂	CO
Incidence	time	6	1.047 (1.016–1.078)	1.021 (1.000–1.043)	1.015 (0.990–1.040)	1.107 (1.060–1.155)	1.034 (1.009–1.061)
		8	1.037 (1.007–1.068)	1.022 (1.001–1.044)	1.013 (0.988–1.037)	1.092 (1.044–1.143)	1.029 (1.003–1.056)
		9	1.035 (1.004–1.066)	1.021 (1.000–1.043)	1.016 (0.990–1.042)	1.085 (1.035–1.136)	1.028 (1.002–1.054)
	T	4	1.037 (1.007–1.068)	1.021 (1.000–1.043)	1.009 (0.984–1.033)	1.082 (1.036–1.131)	1.036 (1.011–1.063)
		5	1.046 (1.015–1.077)	1.023 (1.002–1.045)	1.006 (0.982–1.031)	1.085 (1.039–1.134)	1.042 (1.016–1.069)
		6	1.040 (1.009–1.073)	1.023 (1.001–1.045)	1.006 (0.981–1.030)	1.079 (1.033–1.128)	1.039 (1.013–1.066)
Death	time	6	1.096 (1.053–1.140)	1.054 (1.022–1.086)	1.021 (1.001–1.041)	1.075 (0.984–1.175)	1.079 (1.033–1.128)
		8	1.091 (1.049–1.136)	1.054 (1.021–1.087)	1.022 (1.002–1.042)	1.090 (0.994–1.195)	1.074 (1.027–1.123)
		9	1.089 (1.046–1.133)	1.054 (1.022–1.087)	1.022 (1.002–1.042)	1.091 (0.993–1.199)	1.073 (1.026–1.123)
	T	4	1.089 (1.046–1.133)	1.050 (1.018–1.083)	1.021 (1.001–1.041)	1.072 (0.98–1.1730)	1.071 (1.024–1.120)
		5	1.090 (1.047–1.134)	1.051 (1.019–1.084)	1.022 (1.002–1.042)	1.076 (0.983–1.177)	1.071 (1.024–1.121)
		6	1.086 (1.043–1.130)	1.052 (1.019–1.085)	1.022 (1.002–1.043)	1.074 (0.982–1.175)	1.069 (1.022–1.118)

association between stroke and air pollution continues to intensify. Ischemic stroke is the most common stroke subtype and is characterized by arterial blockage leading to reduced blood flow to brain tissue. This time-series study investigated the association between multiple air pollutants and ischemic stroke in a total of 209,949 patients with ischemic stroke incidence and 23,565 patients with ischemic stroke death between 2018 and 2022. This study found that air pollutants contribute to ischemic stroke incidence and mortality, while age, sex, and season of exposure can influence the effect of pollutants.

In this study, PM_{2.5}, PM₁₀, SO₂, and CO were associated with ischemic stroke mortality. This is consistent with previous studies. [Hu et al. \(2018\)](#) reported that for every 10 µg/m³ increment in PM_{2.5} and PM₁₀ concentrations on days lag0–2, the risk of stroke mortality in

the exposed population increased by 0.72% and 0.68%, respectively. Similarly, in another study in southeast Chengdu, for every one unit increment in $PM_{2.5}$ and PM_{10} exposure, the risk of stroke mortality for days lag0–10 increased by 0.25 and 0.14, respectively ([Luo et al., 2019](#)). Long-term exposure to air pollutants can also lead to similar results, with a prospective cohort trajectory analysis showing that for long-term exposure to $PM_{2.5}$, the hazard ratios for direct transition from health to mortality for each five $\mu g/m^3$ increment in pollutant concentration were 1.30 (1.21, 1.40); ([Tian et al., 2022](#)). Using mortality data as an outcome underestimates the impact of environmental pollution on stroke. Deaths due to acute stroke episodes tend to occur rapidly, and some patients are not included in the stroke death population because the diagnostic process stops at the prehospital emergency stage, prior to systematic imaging and laboratory diagnosis. Thus, hospitalization rates better reflect the impact of air pollutants on exposed populations than mortality rate. In a study based on data from three hospitals in Chongqing, it was shown that for each IQR increment increase in the concentrations of $PM_{2.5}$, PM_{10} , and SO_2 , the hospitalization rate of ischemic stroke increased by 1.2%, 1.0% and 4.8%, respectively ([Chen et al., 2022](#)). In contrast, another study based on a population in the coastal Beibu Gulf region of China did not show significant associations between PM_1 or $PM_{2.5}$ and stroke hospitalization rates ([Chen et al., 2022](#); [Li et al., 2023](#)). Similar to the Beibu Gulf region of China, Ireland has relatively low levels of air pollution, and a study in Ireland by [Byrne et al. \(2020\)](#) showed no significant association between stroke admissions and any individual air pollutant. Excluding differences in study design (case-crossover or time-series) and air pollutant concentration levels, the use of hospitalization data may still produce unpredictable bias. There is a time lag between the onset of symptoms and hospitalization, and this lag is influenced by the level of economic development of the region. Healthcare performance of stroke patients varies by socioeconomic status ([Kim et al., 2021](#); [Li et al., 2023](#)). The government-led disease surveillance and registry system covers all levels of hospitals and community health centers. Compared with collecting admission data from selected hospitals, this system accounts for people of different income levels, and the data collection is more robust. In the current study, population-based disease surveillance system data were used to determine incidence rates rather than using hospitalization registry data from selected hospitals, allowing for more stability. The results showed that exposure to $PM_{2.5}$, PM_{10} , NO_2 , and CO was associated with the incidence of ischemic stroke. This is similar to the results of a recent meta-analysis ([Toubasi & Al-Sayegh, 2023](#)).

Exposure to particulate matter pollutants of different particle sizes is associated with different levels of risk for ischemic stroke incidence and mortality. In the current study, $PM_{2.5}$ was associated with higher stroke incidence and mortality rate compared to PM_{10} . Studies have shown that particulate pollutants with smaller particle sizes are more likely to enter the alveoli through respiration and cross the air-blood barrier into the circulatory system ([Manojkumar, Srimuruganandam & Nagendra, 2019](#); [Wang et al., 2021](#)). This discussion on pollutant particle size is not applicable to all environments, and no such trend was found in the study by [Li et al. \(2023\)](#). This contradiction may be attributable to differences in pollutant concentrations in the study area. For cities with higher air pollution

concentrations, public health policymakers should consider focusing on smaller particulate matter (like $PM_{2.5}$ and PM_1).

Unlike $PM_{2.5}$ and PM_{10} , this study did not find a significant effect of SO_2 on the development of ischemic stroke in the overall population. However, further subgroup analyses showed that SO_2 was significantly associated with ischemic stroke in those >75 years of age, whereas there was no significant association in those ≤ 75 years of age. This study also shows that age plays a modifying role in ischemic stroke-related mortality. This conclusion is supported by the available evidence that older individuals are more sensitive to air pollutants than younger populations ([Luo et al., 2022](#)). This may be related to lower immune responses and more prevalent comorbid underlying diseases in older individuals. Aging itself is one of the risk factors for poorer prognosis after stroke, and the rate of aging is a better indicator of the risk of stroke incidence than the age of the individual ([Shao et al., 2020](#)). In this study, season had a similar modifying effect on stroke incidence, and this may be attributed to poor diffusion conditions of pollutants during the cold season ([Xu et al., 2022b](#)). The physiological basis of the increase effect of air pollutants on stroke incidence during the cold season may be related to elevated blood pressure in the body and arterial thrombosis, which are both worsened by cold temperatures ([Hong et al., 2003](#); [Liu et al., 2021](#); [Wang et al., 2016](#)). The elderly population should have increased awareness of the risk of stroke incidence associated with air pollution, especially in winter when air pollutant concentrations are higher. However, not all epidemiologic studies are consistent in their findings. Studies from Israel and Poland support the conclusion that young people are more sensitive to air pollutants ([Sade et al., 2015](#); [Świączkowski et al., 2025](#)). The study from Israel was conducted in a desert area, and the main pollutant was natural dust, whereas in the study from Poland the air pollution contained high levels of benzo(alpha)pyrene [B(a)P], which is quite different from the composition of the air pollutants in the current study. As mentioned above, both studies used hospital admission data rather than disease registry data, especially since only one hospital was covered in the study by [Sade et al. \(2015\)](#). This may lead to a large selection bias, with low rates of post-stroke morbidity treatment in the elderly population in relatively economically disadvantaged areas and a high rate of post-stroke morbidity and mortality in elderly patients further reducing admission rates.

The association between air pollution and ischemic stroke was stronger in females compared with males, and this is consistent with the results of certain previous study ([Ban et al., 2021](#)). However, in another study that did not rely on disease surveillance system registry data, ischemic stroke hospitalization due to air pollution was more strongly associated with male patients ([Lv et al., 2023](#)). This has again prompted researchers to emphasize the importance of obtaining data based on disease surveillance systems rather than focusing solely on registry data from selected hospitals. According to the World Stroke Organization (WSO), the proportion of stroke patients is higher in females (56% in 2019) than in males ([Feigin et al., 2022](#)), and females have a higher lifetime risk of stroke and worse stroke outcomes ([Seshadri et al., 2006](#); [Xu et al., 2022a](#)). Hypertension is one of the most important risk factors for stroke. The dramatic increase in the prevalence of hypertension in postmenopausal females and the fact that stroke risk in females begins at a lower systolic

blood pressure (SBP) threshold compared to males may increase the susceptibility to stroke in the female population (*Ji et al., 2021; Mills et al., 2016*). Additionally, specific risk factors in the female population such as pregnancy and exogenous estrogen intake also increase the risk of stroke (*Swartz et al., 2017; Xu et al., 2015*). To summarize, women, especially those of advanced age, are more susceptible to blood pressure, metabolic disorders, and abnormal hormone levels, ultimately increasing the risk of stroke associated with air pollution.

Most of the previous research on this topic examined the effect of air pollution on either stroke incidence or mortality in specific populations, and studies have rarely included both outcomes. By using the DLNM, this study more intuitively explores these relationships. This study found an earlier increase in the risk of air pollution-related stroke mortality prior to the increased risk of air pollution-related stroke incidence. The risk of ischemic stroke-related mortality due to $PM_{2.5}$, PM_{10} , and CO increases at lag0, excluding NO_2 . This again suggests that health policy makers should address the loss of life due to air pollution-related stroke. In the single-day lagged structures, a strong association was found between NO_2 and the risk of stroke incidence, but only a tiny association between NO_2 and the risk of stroke mortality was observed. *Tian et al. (2022)* retrieved 318,752 subjects from the UK Biobank to study the effects of particulate matter pollutants (PMx) and nitrogen oxides (NOx) on the various stages of stroke progression and showed that, for every five $\mu g/m^3$ increment in $PM_{2.5}$ and NO_2 , there was a 30% and 3% increase, respectively, in the risk of the population transitioning from a healthy state to mortality, and that NO_2 associated with stroke deaths with minimal intensity. In another study, death rates after intravenous thrombolysis (IVT) for stroke were highly associated with short-term exposure to particulate matter (PM), but not to NO_2 (*Cappellari et al., 2018*). The health effects of short-term exposure to NO_2 have been systematically reviewed by *Hesterberg et al. (2009)* who concluded that the concentration at which NO_2 produces extrapulmonary effects is generally higher than 1–2 ppm (about 2,000–4,000 $\mu g/m^3$ at standard state). In *Zhu et al. (2012)* the nitrogen dioxide concentration was set to extremely high levels, far exceeding real-world concentrations. The maximum concentration in the current study was only 49.8 $\mu g/m^3$, which is much lower than the 2,000 $\mu g/m^3$ that may produce extrapulmonary hazards. Additionally, in the current study, NO_2 was no longer associated with stroke incidence in a two-pollutant model adjusted for $PM_{2.5}$ and PM_{10} separately. It is reasonable to doubt whether there is a real association of NO_2 with stroke incidence or whether this association is due to collinearity. Additional evidence from clinical studies is still needed to address this issue.

As discussed above, collinearity may confound the effect of NO_2 , representing one of the limitations of this study. *Li et al. (2022)* investigated the health effects of air pollution mixtures on the overall death rate in the elderly individuals using Bayesian kernel machine regression (BKMR). This model allows for flexible capture of joint effects of mixture components, thereby capturing potential interactions and nonlinear effects. Future studies may consider using alternative machine learning models to distinguish between the impact of individual pollutants and the overall effect of mixtures on stroke incidence or mortality, thus providing more robust evidence for health decision-making.

CONCLUSIONS

In this time series study involving 209,949 individuals registered in the disease surveillance systems dataset, short-term exposure to air pollution (PM_{2.5}, PM₁₀, SO₂, NO₂, and CO) was significantly associated with the increased risk of ischemic stroke incidence and mortality. Elderly populations are more sensitive to exposure to air pollution and have a higher risk of ischemic stroke incidence and mortality compared to the non-elderly. In addition to age factors, this study shows that air pollutants have a different impact on the incidence of stroke in different genders, with the association between air pollution and ischemic stroke being stronger in women than in men. It is particularly important to address the impact of air pollution on the elderly and women in clinical practice.

ACKNOWLEDGEMENTS

We thank the Jining Center for Disease Control and Prevention for providing the data on ischemic stroke.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

This work was funded by the Healthy Shandong Construction Unveiled Key Project (No. 2024-29). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors:
Healthy Shandong Construction Unveiled Key Project: No. 2024-29.

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Yaohui Kong conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Wenhua Duan performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Zi Zhang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Peizhen Zhou analyzed the data, prepared figures and/or tables, and approved the final draft.
- Mei Wang analyzed the data, prepared figures and/or tables, and approved the final draft.
- Jing Zhang conceived and designed the experiments, authored or reviewed drafts of the article, and approved the final draft.

- Wenjun Wang conceived and designed the experiments, authored or reviewed drafts of the article, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

This study was approved by the Ethics Committee of Jining Center for Disease Control and Prevention, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research/review board (IRB)-IRB Number: (2024-005).

Data Availability

The following information was supplied regarding data availability:

The code and raw data are available in the [Supplemental Files](#).

Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.20298#supplemental-information>.

REFERENCES

- Altman DG, Bland JM. 2003. Interaction revisited: the difference between two estimates. *BMJ* 326:219 DOI 10.1136/bmj.326.7382.219.
- Ban J, Wang Q, Ma R, Zhang Y, Shi W, Zhang Y, Chen C, Sun Q, Wang Y, Guo X, Li T. 2021. Associations between short-term exposure to PM2.5 and stroke incidence and mortality in China: a case-crossover study and estimation of the burden. *Environmental Pollution* 268:115743 DOI 10.1016/j.envpol.2020.115743.
- Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. 2017. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based *post-hoc* analysis of heterogeneous treatment effects in the Look AHEAD trial. *Lancet Diabetes Endocrinology* 5:808–815 DOI 10.1016/S2213-8587(17)30176-6.
- Bell S, Daskalopoulou M, Rapsomaniki E, George J, Britton A, Bobak M, Casas JP, Dale CE, Denaxas S, Shah AD, Hemingway H. 2017. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ* 356:j909 DOI 10.1136/bmj.j909.
- Bobb JF, Valeri L, Henn BC, Christiani DC, Wright RO, Mazumdar M, Godleski JJ, Coull BA. 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. *Biostatistics* 16:493–508 DOI 10.1093/biostatistics/kxu058.
- Butland BK, Atkinson RW, Crichton S, Barratt B, Beevers S, Spiridou A, Hoang U, Kelly FJ, Wolfe CD. 2017. Air pollution and the incidence of ischaemic and haemorrhagic stroke in the South London stroke register: a case-cross-over analysis. *Journal of Epidemiology and Community Health* 71:707–712 DOI 10.1136/jech-2016-208025.

- Byrne CP, Bennett KE, Hickey A, Kavanagh P, Broderick B, O'Mahony M, Williams DJ. 2020. Short-term air pollution as a risk for stroke admission: a time-series analysis. *Cerebrovascular Diseases* 49:404–411 DOI 10.1159/000510080.
- Cappellari M, Turcato G, Zannoni M, Forlivesi S, Maccagnani A, Bonora A, Ricci G, Salvagno GL, Cervellin G, Bonetti B, Lippi G. 2018. Association between short- and medium-term air pollution exposure and risk of mortality after intravenous thrombolysis for stroke. *Journal of Thrombosis and Thrombolysis* 45:293–299 DOI 10.1007/s11239-017-1589-7.
- Chen GY, Chen CL, Tuan HY, Yuan PX, Li KC, Yang HJ, Hu YC. 2014. Graphene oxide triggers toll-like receptors/autophagy responses *in vitro* and inhibits tumor growth *in vivo*. *Advanced Healthcare Materials* 3:1486–1495 DOI 10.1002/adhm.201300591.
- Chen H, Cheng Z, Li M, Luo P, Duan Y, Fan J, Xu Y, Pu K, Zhou L. 2022. Ambient air pollution and hospitalizations for ischemic stroke: a time series analysis using a distributed lag nonlinear model in Chongqing, China. *Frontiers in Public Health* 9:762597 DOI 10.3389/fpubh.2021.762597.
- Chiu Y-HM, Wilson A, Hsu H-HL, Jamal H, Mathews N, Kloog I, Schwartz J, Bellinger DC, Xhani N, Wright RO, Coull BA, Wright RJ. 2023. Prenatal ambient air pollutant mixture exposure and neurodevelopment in urban children in the Northeastern United States. *Environmental Research* 233:116394 DOI 10.1016/j.envres.2023.116394.
- Collaborators GS. 2021. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurology* 20:795–820 DOI 10.1016/S1474-4422(21)00252-0.
- Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, Fisher M, Pandian J, Lindsay P. 2022. World stroke organization (WSO): global stroke fact sheet 2022. *International Journal of Stroke* 17:18–29 DOI 10.1177/17474930211065917.
- Gasparrini A, Armstrong B, Kenward MG. 2010. Distributed lag non-linear models. *Statistics in Medicine* 29:2224–2234 DOI 10.1002/sim.3940.
- Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA. 2009. Critical review of the human data on short-term nitrogen dioxide (NO2) exposures: evidence for NO2 no-effect levels. *Critical Reviews in Toxicology* 39:743–781 DOI 10.3109/10408440903294945.
- Hong Y-C, Rha J-H, Lee J-T, Ha E-H, Kwon H-J, Kim H. 2003. Ischemic stroke associated with decrease in temperature. *Epidemiology* 14:473–478 DOI 10.1097/01.ede.0000078420.82023.e3.
- Hu K, Guo Y, Hu D, Du R, Yang X, Zhong J, Fei F, Chen F, Chen G, Zhao Q, Yang J, Zhang Y, Chen Q, Ye T, Li S, Qi J. 2018. Mortality burden attributable to PM1 in Zhejiang province, China. *Environment International* 121:515–522 DOI 10.1016/j.envint.2018.09.033.
- Ji H, Niiranen TJ, Rader F, Henglin M, Kim A, Ebinger JE, Claggett B, Merz CNB, Cheng S. 2021. Sex differences in blood pressure associations with cardiovascular outcomes. *Circulation* 143:761–763 DOI 10.1161/CIRCULATIONAHA.120.049360.

- Kim J, Yang KH, Choi AR, Kang MY, Kim HJ, Lee H, Lee JY. 2021. Healthcare quality assessments: no guarantees of same outcomes for different socio-economic stroke patients. *International Journal for Quality in Health Care* 33:mzab081 DOI 10.1093/intqhc/mzab081.
- Li H, Deng W, Small R, Schwartz J, Liu J, Shi L. 2022. Health effects of air pollutant mixtures on overall mortality among the elderly population using bayesian kernel machine regression (BKMR). *Chemosphere* 286:131566 DOI 10.1016/j.chemosphere.2021.131566.
- Li M, Edgell RC, Wei J, Li H, Qian ZM, Feng J, Tian F, Wang X, Xin Q, Cai M, Lin H. 2023. Air pollution and stroke hospitalization in the Beibu Gulf Region of China: a case-crossover analysis. *Ecotoxicology and Environmental Safety* 255:114814 DOI 10.1016/j.ecoenv.2023.114814.
- Liang R, Zhang B, Zhao X, Ruan Y, Lian H, Fan Z. 2014. Effect of exposure to PM2.5 on blood pressure: a systematic review and meta-analysis. *Journal of Hypertension* 32:2130–2140 DOI 10.1097/HJH.0000000000000342.
- Liu Q, Shkirkova K, Lamorie-Foote K, Connor M, Patel A, Babadjouni R, Huuskonen M, Montagne A, Baertsch H, Zhang H, Chen J-C, Mack WJ, Walcott BP, Zlokovic BV, Sioutas C, Morgan TE, Finch CE, Mack WJ. 2021. Air pollution particulate matter exposure and chronic cerebral hypoperfusion and measures of white matter injury in a murine model. *Environmental Health Perspectives* 129:87006 DOI 10.1289/EHP8792.
- Luo L, Dai Y, Zhang F, Chen M, Chen F, Qing F. 2019. Time series analysis of ambient air pollution effects on dynamic stroke mortality. *International Journal of Health Planning and Management* 35:79–103 DOI 10.1002/hpm.2821.
- Luo H, Zhang Q, Yu K, Meng X, Kan H, Chen R. 2022. Long-term exposure to ambient air pollution is a risk factor for trajectory of cardiometabolic multimorbidity: a prospective study in the UK Biobank. *EBioMedicine* 84:104282 DOI 10.1016/j.ebiom.2022.104282.
- Lv X, Shi W, Yuan K, Zhang Y, Cao W, Li C, Xu L, Wu L, Sun S, Hong F. 2023. Hourly air pollution exposure and emergency hospital admissions for stroke: a multicenter case-crossover study. *Stroke* 54:3038–3045 DOI 10.1161/STROKEAHA.123.044191.
- Manojkumar N, Srimuruganandam B, Nagendra SMS. 2019. Application of multiple-path particle dosimetry model for quantifying age specified deposition of particulate matter in human airway. *Ecotoxicology and Environmental Safety* 168:241–248 DOI 10.1016/j.ecoenv.2018.10.091.
- Mecocci P, Boccardi V, Cecchetti R, Bastiani P, Scamosci M, Ruggiero C, Baroni M. 2018. A long journey into aging, brain aging, and Alzheimer’s disease following the oxidative stress tracks. *Journal of Alzheimer’s Disease* 62:1319–1335 DOI 10.3233/JAD-170732.
- Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. 2016. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 134:441–450 DOI 10.1161/CIRCULATIONAHA.115.018912.

- Nemmar A, Zia S, Subramaniyan D, Fahim MA, Ali BH. 2011. Exacerbation of thrombotic events by diesel exhaust particle in mouse model of hypertension. *Toxicology* 285:39–45 DOI 10.1016/j.tox.2011.03.018.
- Sade MY, Novack V, Ifergane G, Horev A, Kloog I. 2015. Air pollution and ischemic stroke among young adults. *Stroke* 46:3348–3353 DOI 10.1161/STROKEAHA.115.010992.
- Sarker D, Ang JE, Baird R, Kristeleit R, Shah K, Moreno V, Clarke PA, Raynaud FI, Levy G, Ware JA, Mazina K, Lin R, Wu J, Fredrickson J, Spoerke JM, Lackner MR, Yan Y, Friedman LS, Kaye SB, Derynck MK, Workman P, Bono JSd. 2015. First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. *Clinical Cancer Research* 21:77–86 DOI 10.1158/1078-0432.CCR-14-0947.
- Scheers H, Jacobs L, Casas L, Nemery B, Nawrot TS. 2015. Long-term exposure to particulate matter air pollution is a risk factor for stroke. *Stroke* 46:3058–3066 DOI 10.1161/STROKEAHA.115.009913.
- Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. 2006. The lifetime risk of stroke: estimates from the Framingham study. *Stroke* 37:345–350 DOI 10.1161/01.STR.0000199613.38911.b2.
- Shao A, Lin D, Wang L, Tu S, Lenahan C, Zhang J. 2020. Oxidative stress at the crossroads of aging, stroke and depression. *Aging and Disease* 11:1537–1566 DOI 10.14336/AD.2020.0225.
- Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, McClure JA, Lindsay MP. 2017. The incidence of pregnancy-related stroke: a systematic review and meta-analysis. *International Journal of Stroke* 12:687–697 DOI 10.1177/1747493017723271.
- Świączkowski M, Lip GYH, Kurasz A, Dąbrowski EJ, Tomaszuk-Kazberuk A, Kamiński JW, Struzewska J, Dobrzycki S, Kuźma Ł. 2025. Association between exposure to air pollution and increased ischemic stroke incidence: a retrospective population-based cohort study (EP-PARTICLES study). *European Journal of Cardiovascular Prevention and Rehabilitation* 32:276–287 DOI 10.1093/eurjpc/zwae301.
- Thomson EM, Kumarathasan P, Calderón-Garcidueñas L, Vincent R. 2007. Air pollution alters brain and pituitary endothelin-1 and inducible nitric oxide synthase gene expression. *Environmental Research* 105:224–233 DOI 10.1016/j.envres.2007.06.005.
- Tian F, Cai M, Li H, Qian ZM, Chen L, Zou H, Zhang Z, Wang C, Xian H, McMillin SE, Lin H. 2022. Air pollution associated with incident stroke, poststroke cardiovascular events, and death: a trajectory analysis of a prospective cohort. *Neurology* 99:e2474–e2484 DOI 10.1212/WNL.0000000000201316.
- Toubasi A, Al-Sayegh TN. 2023. Short-term exposure to air pollution and ischemic stroke: a systematic review and meta-analysis. *Neurology* 101:e1922–e1932 DOI 10.1212/WNL.0000000000207856.
- Wang X, Cao Y, Hong D, Zheng D, Richtering S, Sandset EC, Leong TH, Arima H, Islam S, Salam A, Anderson C, Robinson T, Hackett ML. 2016. Ambient temperature

- and stroke occurrence: a systematic review and meta-analysis. *International Journal of Environmental Research and Public Health* **13**:698 DOI [10.3390/ijerph13070698](https://doi.org/10.3390/ijerph13070698).
- Wang Y, Liu T, Li H. 2016.** Enhancement of triptolide-loaded micelles on tumorigenicity inhibition of human ovarian cancer. *Journal of Biomaterials Science, Polymer Edition* **27**:545–556 DOI [10.1080/09205063.2015.1131667](https://doi.org/10.1080/09205063.2015.1131667).
- Wang H, Yin P, Fan W, Wang Y, Dong Z, Deng Q, Zhou M. 2021.** Mortality risk associated with short-term exposure to particulate matter in China: estimating error and implication. *Environmental Science & Technology* **55**:1110–1121 DOI [10.1021/acs.est.0c05095](https://doi.org/10.1021/acs.est.0c05095).
- Wellenius GA, Joel Schwartz MAM. 2005.** Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke* **36**:2549–2553 DOI [10.1161/01.STR.0000189687.78760.47](https://doi.org/10.1161/01.STR.0000189687.78760.47).
- Xu Z, Li Y, Tang S, Huang X, Chen T. 2015.** Current use of oral contraceptives and the risk of first-ever ischemic stroke: a meta-analysis of observational studies. *Thrombosis Research* **136**:52–60 DOI [10.1016/j.thromres.2015.04.021](https://doi.org/10.1016/j.thromres.2015.04.021).
- Xu R, Li Z, Zhu X, Guo C, Su Q, Peng J, Wang Z, Qian Y, Li X, Xu Q, Wei Y. 2022b.** Acute effects of exposure to fine particulate matter and ozone on lung function, inflammation and oxidative stress in healthy adults. *Ecotoxicology and Environmental Safety* **243**:114013 DOI [10.1016/j.ecoenv.2022.114013](https://doi.org/10.1016/j.ecoenv.2022.114013).
- Xu M, Vallejo AA, Calvete CC, Rudd A, Wolfe C, O’Connell MDL, Douiri A. 2022a.** Stroke outcomes in women: a population-based cohort study. *Stroke* **53**:3072–3081 DOI [10.1161/STROKEAHA.121.037829](https://doi.org/10.1161/STROKEAHA.121.037829).
- Zhu N, Li H, Han M, Guo L, Chen L, Yun Y, Guo Z, Li G, Sang N. 2012.** Environmental nitrogen dioxide (NO₂) exposure influences development and progression of ischemic stroke. *Toxicology Letters* **214**:120–130 DOI [10.1016/j.toxlet.2012.08.021](https://doi.org/10.1016/j.toxlet.2012.08.021).