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Air pollution and stroke hospitalization in the Beibu Gulf Region of China: A case-crossover analysis

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A R T I C L E I N F O

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A B S T R A C T

Background: The relationship between air pollution and stroke has been extensively studied, however, the evidence regarding the association between air pollution and hospitalization due to stroke and its subtypes in coastal areas of China is limited.
Objective: To estimate the associations between air pollution and hospitalizations of stroke and its subtypes in the Beibu Gulf Region of China.
Methods: We conducted a time-stratified case-crossover study in 15 cities in Beibu Gulf Region in China from 2013 to 2016. Exposures to PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO on the case and control days were assessed at residential addresses using bilinear interpolation. Conditional logistic regressions were constructed to estimate city-specific associations adjusting for meteorological factors and public holidays. Meta-analysis was further conducted to pool all city-level estimates.
Results: There were 271,394 case days and 922,305 control days. The odds ratios (ORs) for stroke hospitalizations associated with each interquartile range (IQR) increase in 2-day averages of SO_2 (IQR: 10.8 μg/m^3), NO_2 (IQR: 11.2 μg/m^3), and PM_{10} (IQR: 37 μg/m^3) were 1.047 (95 % CI [confidence interval]: 1.015–1.080), 1.040 (95 % CI: 1.027–1.053), and 1.018 (95 % CI: 1.004–1.033), respectively. The associations with hospitalizations of ischemic stroke were significant for all seven pollutants, while the association with hemorrhagic stroke was significant only for CO. The associations of SO_2, NO_2, and O_3 with stroke hospitalization were significantly stronger in the cool season.
Conclusions: Short-term increase in SO_2, NO_2, and PM_{10} might be important triggers of stroke hospitalization. All seven air pollutants were associated with ischemic stroke hospitalization, while only CO was associated with hemorrhagic stroke hospitalization. These results should be considered in public health policy.

1. Introduction

Stroke is a major contributor to global mortality, with China experiencing both a high incidence of stroke and severe ambient air pollution (Feigin et al., 2021; Kan et al., 2012). In 2019, it was estimated that 2.19 million deaths and 45.9 million disability-adjusted life years (DALYs) could be attributed to stroke (Ma et al., 2021). The major risk factors for stroke were smoking, high body mass index, air pollution, high systolic blood pressure, and high fasting plasma glucose (Feigin et al., 2021). As air pollution is a modifiable risk factor that is independent of individual

Abbreviations: PM_1, particulate matter with aerodynamic diameter less than 1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter less than 10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; CO, carbon monoxide; IQR, interquartile range; CI, confidence interval; ORs, odds ratios; VIF, variance inflation factor; DALYs, disability-adjusted life years.

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behavior, improving air quality has the potential to play a crucial role in reducing the incidence of stroke (Tian et al., 2022, 2018).

Numerous studies have explored the relationship between air pollution and stroke in China, but these studies focused on one single city, a specific outcome, or some subtype of stroke (Cai et al., 2022; Guo et al., 2017, 2020; Liu et al., 2017; Qi et al., 2020; Qian et al., 2013; Shen et al., 2020; Tian et al., 2018; Weng et al., 2021; Wing et al., 2017). Ischemic and hemorrhagic stroke have different pathophysiological mechanisms, it is possible that the acute adverse effects of air pollution vary across types of stroke (Xu et al., 2022). Besides, it is possible that different particle sizes may play differential effects in this association but has not been fully studied. Furthermore, previous studies were mainly conducted in heavily polluted areas of China, while there is limited research conducted in less polluted areas of China.

The Beibu Gulf Region in Southwest China, a developing industrial area, includes 15 cities, 14 of which are located in Guangxi province and the remaining one is in Guangdong province (Zhanjiang city). This region has several unique characteristics. First, this region has a mix of subtropical and tropical monsoon climates, characterized by dry and mild winters, as well as wet and hot summers. Therefore, the temperature, relative humidity, and composition of air pollutants are different from those in northern regions. Second, a broad spectrum of air pollutant concentrations in the Beibu Gulf Region provides unique opportunities to study the associations with stroke hospitalization. Third, the Beibu Gulf Region is ethnically diverse, with ethnic minorities accounting for 37.52 % of its total population and far exceeding the national average of 8.5 %.

To better understand the potential health effects of air pollution in a population with a high percentage of ethnic minorities and relatively low concentrations of air pollution, we estimated the associations between short-term air pollution and stroke hospitalization in the Beibu Gulf Region of China using a time-stratified case-crossover study design.

2. Methods

2.1. Data sources

Daily admissions for stroke were derived from tertiary and secondary hospitals in the study area, which were collected by the local Health Commission from 2013 to 2016 (Cai et al., 2018, 2020). For each hospitalization, we extracted sociodemographic characteristics (age, sex, date of birth), the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis codes (outpatient and emergency diagnosis, principal diagnosis code, and up to two secondary diagnosis codes), length of stay, discharge outcomes, and current residential addresses from hospital electronic medical records. Patients with a principal diagnosis of stroke were included, while those who had missing information on age, sex, and whose residential location was outside of the study area were excluded (Fig. 1). ICD-10 codes of the primary diagnosis were used to identify the hospitalized cases for stroke (I60-I69), hemorrhagic stroke (I60-I62), ischemic stroke (I63) and unspecified stroke (I64-I69) (Huang et al., 2019), respectively. Informed consent was waived because this study was an observational study using routinely collected data and all patient identifiers were excluded prior to the study team had access to the data.

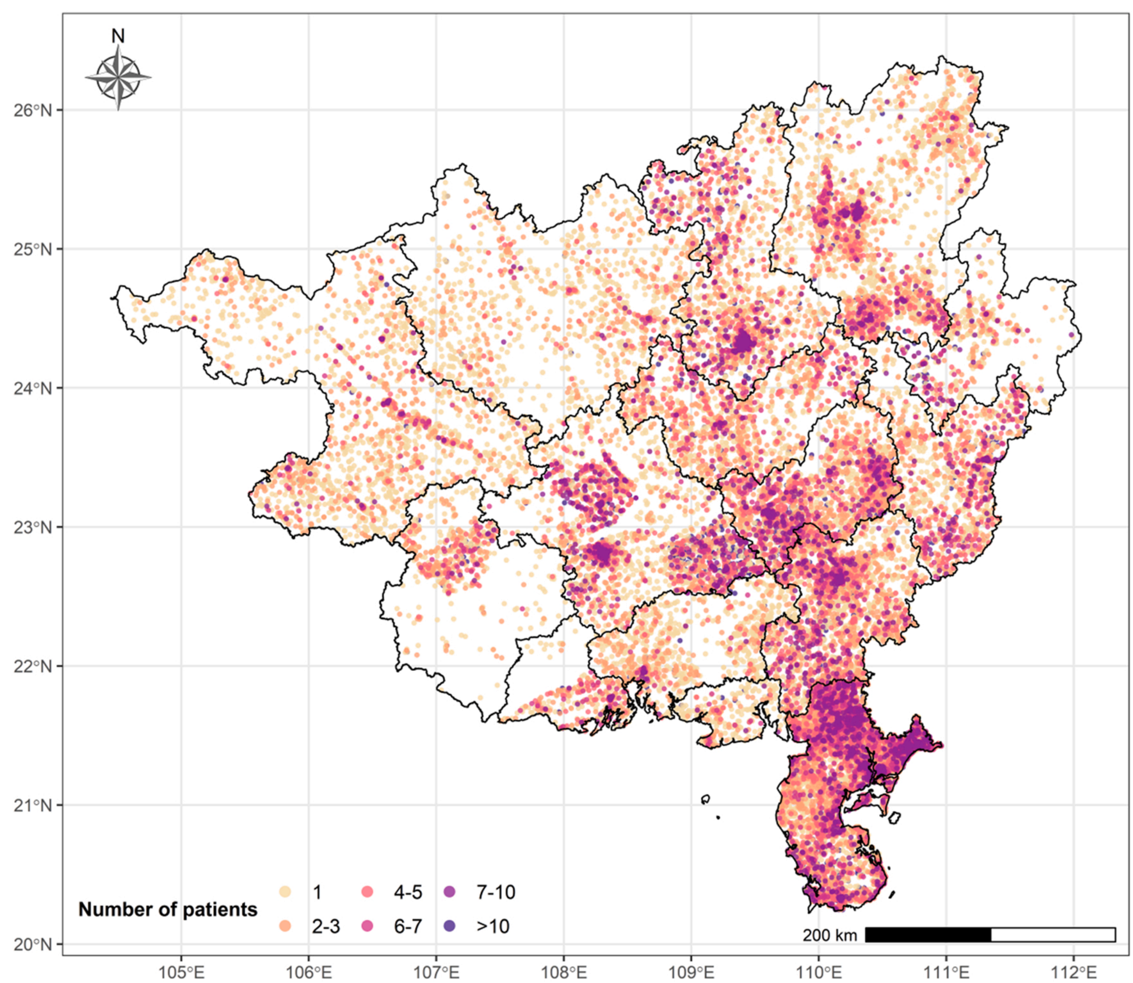

Fig. 1. The geographic distribution of stroke hospitalizations in Beibu Gulf Region, China, 2013–2016.

2.2. Air pollution and meteorological factors

The air pollution data and its quality control have been described previously (Cai et al., 2022). Briefly, we obtained 24-hour mean concentrations of PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and maximum 8-hour mean concentrations of O_3 from the 10 × 10 km grid China High Air Pollutants (CHAP) daily data set. This data set includes daily concentrations of PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO in China from 2013 to 2020. The cross-validation coefficients of determination (R^2) for PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO were 0.77, 0.92, 0.90, 0.84, 0.84, 0.87, and 0.80, respectively (Wei et al., 2019, 2022a, 2021a, 2021b, 2022b). To control for the meteorological conditions, temperature (°C) and relative humidity (%) were collected at 10 × 10 km grids from the fifth generation of European ReAnalysis (ERA5)-Land reanalysis data set (Liu et al., 2022).

A two-stage data analyses was used to evaluate individual-level exposure to various air pollutants and meteorological variables for each stroke case. First, we estimated the latitudes and longitudes of each home address by Gaode map. Then, we estimated the pollutants' concentration and meteorological variables using bilinear interpolation. This algorithm enhanced the spatial resolution of environmental variables at a specific location by calculating a weighted average of the nearest 4 grids. The closer air pollutant and meteorological variable grids were to the location of the cases, the larger the associated weights were for the grids (Cai et al., 2023a, 2023b).

2.3. Study design

We used a time-stratified case-crossover study design. This design is ideal for adjusting for individual-level characteristics and potential confounders that remain temporally constant because each participant serves as his/her own control (Sun et al., 2019). We compared the level of exposure on the case day (the day of stroke hospitalization) with the levels on control days both before and after the case day but within the same month to control for the effects of time trends, seasonality, and day of the week. (Sun et al., 2019). For example, a given exposure for a case occurring on Tuesday, 8 June would be compared to the exposure occurring on all other Tuesdays in June (i.e. 1 June, 15 June, 22 June, and 29 June) (Shoraka et al., 2022). Therefore, the estimates represent the acute triggering effect of air pollution on the stroke hospitalization (Cai et al., 2023c; Liu et al., 2022). This approach ensured that there are 3 or 4 control days matched to each stroke hospitalization (case day). We chose 922,305 control days for the 271,394 stroke cases in the analyses.

2.4. Statistical analyses

Spearman's correlation coefficients were computed to present the pairwise correlation between exposure variables. The statistical models were conducted in two steps. First, we used conditional logistic regressions to estimate the city-specific odds ratios of stroke hospital admission per an interquartile range (IQR) increase in each air pollutant. Temperature, relative humidity, and public holidays were incorporated in the model as time-varying covariates. We adjusted for the nonlinear and delayed effects of meteorological variables by fitting natural cubic splines with 3 degrees of freedom (df) for the 4-day moving average temperature and relative humidity (Lin et al., 2016). Then, we included a pollutant using a natural cubic spline function (df = 3) to plot the exposure-response curves (Liu et al., 2019). Our data analyses showed that the estimated effects were representative at lag01 day and stable, and it was also used extensively in previous studies. Hence, we reported estimates using the lag 01 (2-day moving average of current and previous day) in our main results (Kim et al., 2018; Liu et al., 2021). In the second stage, we applied meta-analyses using random-effects models to combine all city-level estimates. This approach provides a flexible tool to pool risk estimates while accounting for within-city statistical error and between-city variability (heterogeneity) of the 'true' risks (Lin et al., 2016).

We also stratified data by sex (male and female), age (<65 and ≥65 yrs), and season (warm: April to September and cool: October to March) to identify any potential effect modifications. The differences of risk estimates by subgroups were tested using a Z-test (Altman and Bland, 2003).

Several sensitivity analyses were conducted. We conducted several two-pollutant models, in which each of the seven air pollutants was further adjusted with another pollutant in the same model. In the two-pollutant models, we examined possible multicollinearity based on the variance inflation factor (VIF), and we did not conduct two-pollutant models with a VIF ≥ 5 to avoid model fitting issues (O'Brien, 2007). To evaluate the robustness of the associations at different length of exposure window, various lag intervals of the exposure were considered. We estimated the effects at different exposure windows, including single-day lags from lag0 to lag7 and moving average of multi-day lags of lag01 (the day and previous one day) and lag07 (the day and previous seven days).

Statistical computing environment R (version 4.1.3) (Team, 2021) was used to analyze and visualize the data. R package "survival" was used to construct conditional logistic regressions and "metafor" was used to conduct meta-analyses.

3. Results

3.1. Descriptive results

Our analysis included 271,394 case days and 922,305 control days. Among 271,394 hospital admissions with a confirmed diagnosis of stroke, 39,732 (14.6 %) were hemorrhagic stroke, and 158,775 (58.5 %) were ischemic stroke. Compared to patients who experienced a hemorrhagic stroke, those with an ischemic stroke were older and more likely to be hospitalized in the warm seasons (Table 1).

The mean concentrations of pollutants on the day of hospitalization were 25.0 μg/m^3 for PM_1, 37.9 μg/m^3 for $PM_{2.5}$, 58.9 μg/m^3 for PM_{10}, 17.2 μg/m^3 for SO_2, 20.9 μg/m^3 for NO_2, 74.8 μg/m^3 for O^3 and 0.96 mg/m^3 for CO (Table 2). Compared with the National Ambient Air Quality Standards of China released in 2012 (annual mean standards are 35 μg/m^3 for $PM_{2.5}$, 70 μg/m^3 for PM_{10}, 60 μg/m^3 for SO_2, 40 μg/m^3 for NO_2, 4 mg/m^3 for CO, and maximum 8-hour mean standards are 160 μg/m^3 for O_3), the mean concentrations of $PM_{2.5}$ slightly exceeded the national standards, while the other pollutants were within the guideline levels, indicating relatively low concentrations of air

Table 1
Demographic characteristics of stroke admissions in the Beibu Gulf Region, China,2013–2016.

Variable	Total stroke	Hemorrhagic stroke	Ischemic stroke
Hospital admissions, n (%)	271,394	39,732 (14.6)	158,775 (58.5)
Gender, n (%)			
Male	160,450 (59.1)	24,926(62.7)	96,287(60.6)
Female	110,944 (40.9)	14,806(37.3)	62,488(39.4)
Age			
Mean ± SD, yr	67.4 ± 14.2	60.6 ± 17.0	68.6 ± 12.2
<65 yr (%)	102,971 (37.9)	22,331(56.2)	55,633(35.0)
≥65 yr (%)	168,423 (62.1)	17,401(43.8)	103,142(65.0)
Season, n (%)			
Cool	128,539 (47.4)	21,998(55.4)	74,105(46.7)
Warm	142,855 (52.6)	17,734(44.6)	84,670(53.3)

Abbreviations: SD, standard deviation.

Table 2
Summary statistics for air pollutants concentrations and meteorological variables on case and control days in the Beibu Gulf Region, China.

Variable	Mean	SD	Percentile			IQR
			P_{25}	P_{50}	P_{75}	
On case days (n = 271,394)						
Air pollutant						
O_3 (μg/m^3)	74.8	30.3	54.7	73.1	93.3	38.6
PM_1 (μg/m^3)	25.0	14.2	15.2	21.8	31.8	16.6
$PM_{2.5}$ (μg/m^3)	37.9	24.8	21.1	32.1	48.2	27.0
PM_{10} (μg/m^3)	58.9	34.4	36.5	51.0	73.5	37.0
SO_2 (μg/m^3)	17.2	10.0	10.5	15.7	21.3	10.8
NO_2 (μg/m^3)	20.9	10.6	14.4	19.2	25.6	11.2
CO (mg/m^3)	0.96	0.31	0.80	0.95	1.12	0.32
Meteorological condition						
Temperature (℃)	20.2	7.7	14.8	22.7	26.5	11.8
Relative humidity, (%)	73.1	20.7	68.7	79.7	85.8	17.1
On control days (n = 922,305)						
Air pollutant						
O_3 (μg/m^3)	74.9	30.6	54.5	73.2	93.8	39.2
PM_1 (μg/m^3)	25.0	14.2	15.2	21.8	31.8	16.6
$PM_{2.5}$ (μg/m^3)	37.9	24.9	21.1	32.1	48.1	27.0
PM_{10} (μg/m^3)	58.9	34.6	36.5	51.0	73.5	36.9
SO_2 (μg/m^3)	17.2	10.0	10.5	15.7	21.3	10.8
NO_2 (μg/m^3)	20.9	10.5	14.4	19.2	25.6	11.2
CO (mg/m^3)	0.96	0.31	0.80	0.95	1.12	0.32
Meteorological condition						
Temperature (℃)	20.2	7.7	14.7	22.7	26.6	11.8
Relative humidity, (%)	73.0	20.8	68.6	79.7	85.8	17.22

Abbreviations: SD, standard deviation; IQR, interquartile range.

pollution. All air pollutants were intercorrelated and also correlated with temperature and relative humidity (Fig. S1).

3.2. Short-term associations of air pollutants with stroke hospitalization

Short-term exposure to PM_{10}, SO_2, and NO_2 was positively associated with stroke hospitalization (Fig. 2). The ORs per IQR increment in 2-day average were 1.018 (95 % CI: 1.004–1.033) for PM_{10} (IQR: 37 μg/m^3), 1.047 (95 % CI: 1.015–1.080) for SO_2 (IQR: 10.8 μg/m^3), and 1.040 (95 % CI: 1.027–1.053) for NO_2 (IQR: 11.2 μg/m^3). The remaining associations were positive but not significant, and they were 1.010 (95 % CI, 0.992–1.028) for PM_1 (IQR: 16.6 μg/m^3), 1.011 (95 % CI: 0.996–1.026) for $PM_{2.5}$ (IQR: 27 μg/m^3), 1.006 (95 % CI: 0.987–1.026) for O_3 (IQR: 38.6 μg/m^3), and 1.016 (95 % CI: 0.998–1.034) for CO (IQR: 0.32 mg/m^3).

When stratified by stroke subtypes, the air pollutants were associated with hospitalizations of ischemic stroke; the ORs were 1.025 (95 % CI: 1.011–1.040) for PM_1, 1.021 (95 % CI: 1.007–1.034) for $PM_{2.5}$, 1.029 (95 % CI: 1.016–1.042) for PM_{10}, 1.056 (95 % CI: 1.019–1.093) for SO_2, 1.052 (95 % CI: 1.033–1.071) for NO_2, 1.017 (9 5% CI: 1.002–1.033) for O_3, and 1.022 (95 % CI: 1.006–1.038) for CO. For hemorrhagic stroke, the associations remained significantly positive for CO (OR: 1.031; 95 % CI: 1.004–1.059), but were significantly negative for PM_1 (OR: 0.962; 95 % CI: 0.936–0.989) and PM_{10} (OR: 0.972; 95 % CI: 0.949–0.996); the rest of associations were negative and insignificant, they were 0.979 (95 % CI: 0.955–1.004) for $PM_{2.5,}$ 0.995 (95 % CI: 0.969–1.021) for SO_2, 0.980 (95 % CI: 0.954–1.007) for NO_2, and 0.970 (95 % CI: 0.938–1.003) for O_3 (Fig. 2).

The curves of PM rose rapidly at low levels and then increased slightly at higher concentrations (Fig. 3). In addition, the concentration-response curves of NO_2 and SO_2 were similar: they were flat at low levels and then increased dramatically and almost linearly positive at high levels, whereas the curves for CO and O_3 suggested a linear rise at low levels but remained flat at high levels. The concentration-response curves by stroke subtypes are shown in Fig. S2.

3.3. Short-term associations between SO_2, $NO_{2,}$ O_3 and stroke were stronger in cool season

Table 3 presents the associations between 2-day average (lag 01) air pollutant exposure levels and stroke subtypes admissions stratified by sex, age, and season. For SO_2, $NO_{2,}$ and $O_{3,}$ we observed stronger associations in cool seasons (all $P < 0.05$). We observed the same stronger association only between SO_2 and the hospitalization of hemorrhagic stroke ($P < 0.05$). No other significant effect modifications were identified by sex, age, or season ($P > 0.05$), but we found that exposure to particulate pollutants (PM_1, $PM_{2.5}$ and PM_{10}) increased the risk of ischemic stroke in women older than 65 years and increased the risk of hemorrhagic stroke in men older than 65 years.

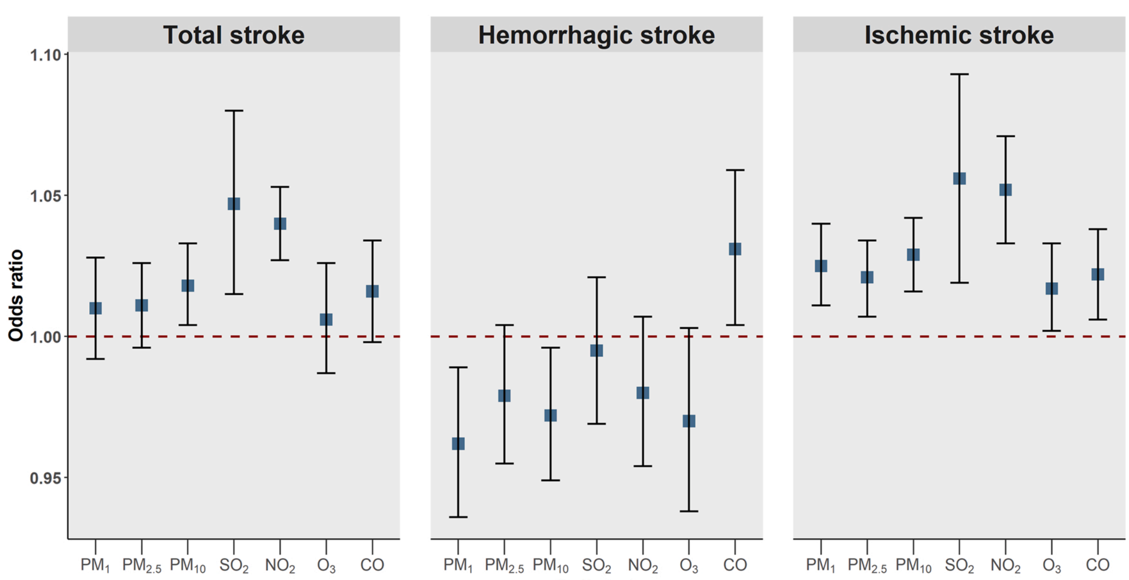

Fig. 2. Combined odds ratios (ORs) and 95 % confidence intervals (CIs) in hospital admissions for stroke associated with an interquartile range (IQR) increase in short-term (2-day average) exposure to PM_1(16.6 μg/m^3), $PM_{2.5}$ (27 μg/m^3), PM_{10}(37 μg/m^3), SO_2 (10.8 μg/m^3), NO_2 (11.2 μg/m^3), O_3 (38.6 μg/m^3), and CO (0.32 mg/m^3) in the Beibu Gulf Region, China.

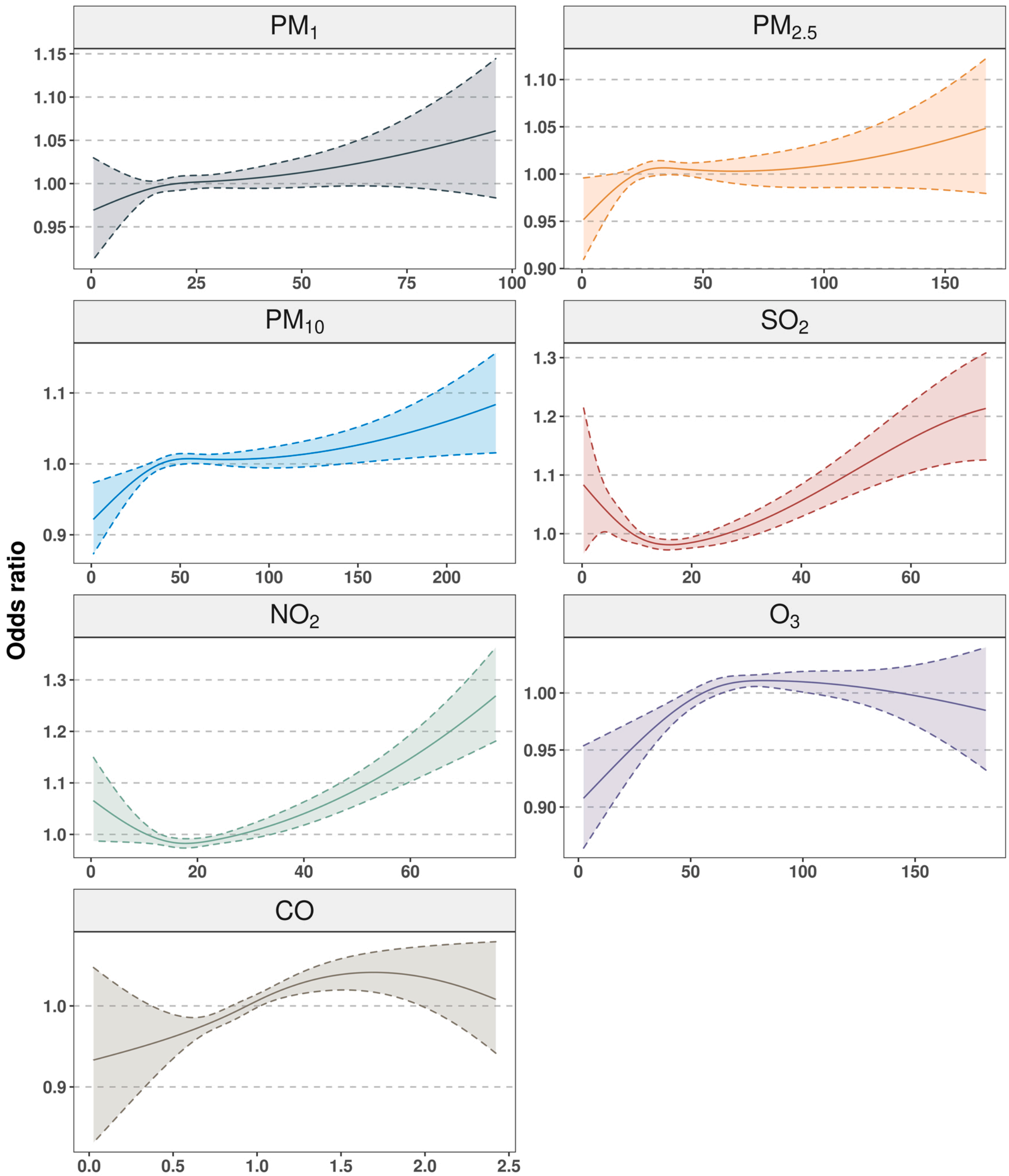

Fig. 3. Exposure-response curves on the associations of PM_1 (μg/m[3]), $PM_{2.5}$ (μg/m[3]), PM_{10} (μg/m[3]), SO_2 (μg/m[3]), NO_2 (μg/m[3]), O_3 (μg/m[3]), CO (mg/m[3]) with hospital admissions for stroke. The pollutants were trimmed at 0.1-th percentiles in order to prevent excessively large confidence intervals and abnormally nonlinear patterns resulting from small sample sizes. The solid lines with shaded bands represent the odds ratio of hospital admissions and their corresponding 95 % confidence intervals, respectively.

3.4. Sensitivity analysis

In two-pollutant models, the pattern of associations in two-pollutant models was generally consistent with that of single-pollutant models (Table S2). In particular, the associations between air pollution and stroke were strengthened after accounting for NO_2 in the model, while the ORs for PM_{10} were attenuated after further adjusting for NO_2 for all and ischemic stroke. For example, the ORs for any stroke hospitalization per an IQR increase in short-term exposure to PM_{10} decreased from 1.018 (95 % CI, 1.004–1.033) to 0.990 (95 % CI, 0.957–1.023) when NO_2 was added into the model. A similar decreasing pattern was observed in the OR of ischemic stroke with PM_{10} after further adjustment of NO_2 (OR=1.029, 95 % CI: 1.016–1.042 to OR=0.992, 95 % CI: 0.966–1.018). Fig. S3 shows the associations of short-term exposure to air pollutants at different exposure windows with stroke hospitalizations. For ischemic stroke, the ORs of almost all pollutants decreased with the increasing lag days and moving average days. Conversely, the ORs for hemorrhagic stroke increased as we used longer periods of exposure window (Fig.S3).

4. Discussion

In this multiyear analysis of stroke hospitalizations in the Beibu Gulf Region, significant associations between short-term exposure to SO_2,

Table 3
ORs (95 % CIs) for stroke admissions per an IQR increase in air pollutants stratified by sex, age, and season.

Pollutant	Variable	PM_1		$PM_{2.5}$		PM_{10}		SO_2		NO_2		O_3		CO	
		OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value
Total Stroke	Sex														
	M	1.016 (0.994, 1.037)	0.506	1.012 (0.997, 1.028)	0.769	1.021 (1.003, 1.038)	0.683	1.047 (1.010, 1.085)	0.574	1.039 (1.024, 1.055)	0.978	1.009 (0.986, 1.032)	0.744	1.012 (0.997, 1.027)	0.281
	F	1.004 (0.980, 1.030)		1.008 (0.986, 1.031)		1.015 (0.995, 1.036)		1.033 (1.005, 1.063)		1.039 (1.021, 1.058)		1.003 (0.977, 1.029)		1.030 (1.001, 1.059)	
	Age														
	<65	1.000 (0.976, 1.024)	0.245	1.004 (0.988, 1.021)	0.29	1.011 (0.995, 1.027)	0.284	1.040 (1.005, 1.078)	0.756	1.037 (1.019, 1.055)	0.665	1.003 (0.982, 1.024)	0.719	1.027 (1.003, 1.052)	0.359
	≥65	1.019 (0.997, 1.042)		1.017 (0.999, 1.035)		1.025 (1.004, 1.047)		1.049 (1.009, 1.091)		1.043 (1.023, 1.063)		1.008 (0.986, 1.031)		1.013 (0.994, 1.032)	
	Season														
	Cool	1.009 (0.989, 1.030)	0.617	1.012 (0.996, 1.028)	0.704	1.024 (1.008, 1.040)	0.295	**1.075 (1.033, 1.119)**	**0**	**1.058 (1.040, 1.077)**	**0**	**1.026 (1.002, 1.050)**	**0.01**	1.024 (1.006, 1.042)	0.79
	Warm	0.998 (0.959, 1.038)		1.003 (0.963, 1.045)		0.998 (0.954, 1.044)		**0.973 (0.939, 1.007)**		**0.977 (0.944, 1.012)**		**0.987 (0.970, 1.004)**		1.020 (0.997, 1.043)	
Hemorrhagic Stroke	Sex														
	M	0.966 (0.933, 1.000)	0.68	0.984 (0.954, 1.015)	0.668	0.973 (0.943, 1.003)	0.972	0.999 (0.967, 1.033)	0.661	0.982 (0.949, 1.015)	0.876	0.954 (0.910, 1.000)	0.188	1.031 (0.997, 1.066)	0.972
	F	0.955 (0.912, 0.999)		0.972 (0.93, 1.016)		0.972 (0.932, 1.013)		0.987 (0.944, 1.032)		0.977 (0.934, 1.022)		0.998 (0.952, 1.046)		1.032 (0.989, 1.077)	
	Age														
	<65	0.957 (0.920, 0.995)	0.72	0.974 (0.943, 1.007)	0.653	0.970 (0.939, 1.002)	0.824	0.994 (0.961, 1.029)	0.98	0.977 (0.943, 1.013)	0.774	0.975 (0.938, 1.013)	0.675	1.029 (0.991, 1.069)	0.854
	≥65	0.972 (0.902, 1.047)		0.992 (0.924, 1.066)		0.978 (0.919, 1.041)		0.995 (0.955, 1.037)		0.985 (0.945, 1.027)		0.963 (0.922, 1.005)		1.034 (0.995, 1.076)	
	Season														
	Cool	0.962 (0.931, 0.993)	0.797	0.983 (0.957, 1.011)	0.488	0.983 (0.957, 1.01)	0.122	**1.016 (0.985, 1.047)**	**0.013**	0.989 (0.960, 1.018)	0.081	0.991 (0.954, 1.030)	0.155	1.030 (0.999, 1.061)	0.402
	Warm	0.953 (0.894, 1.015)		0.952 (0.874, 1.038)		0.926 (0.862, 0.994)		**0.902 (0.825, 0.985)**		0.917 (0.847, 0.993)		0.947 (0.900, 0.995)		1.059 (0.999, 1.122)	
Ischemic Stroke	Sex														
	M	1.022 (1.004, 1.041)	0.728	1.018 (1.001, 1.035)	0.546	1.029 (1.01, 1.049)	0.991	1.047 (1.008, 1.088)	0.962	1.052 (1.028, 1.076)	0.899	1.020 (1.002, 1.039)	0.664	1.009 (0.992, 1.027)	0.072
	F	1.028 (1.001, 1.055)		1.026 (1.005, 1.048)		1.030 (1.008, 1.051)		1.048 (1.015, 1.083)		1.049 (1.026, 1.074)		1.013 (0.989, 1.037)		1.042 (1.011, 1.074)	
	Age														
	<65	1.024 (1.000, 1.049)	0.933	1.020 (0.998, 1.043)	0.945	1.029 (1.007, 1.051)	0.96	1.066 (1.027, 1.105)	0.361	1.060 (1.035, 1.085)	0.433	1.005 (0.978, 1.033)	0.252	1.034 (1.012, 1.058)	0.252
	≥65	1.026 (1.007, 1.044)		1.021 (1.004, 1.038)		1.028 (1.012, 1.045)		1.040 (1.004, 1.078)		1.046 (1.021, 1.071)		1.024 (1.006, 1.042)		1.017 (0.998, 1.036)	
	Season														
	Cool	1.025 (1.005, 1.045)	0.537	1.023 (1.008, 1.038)	0.583	1.032 (1.016, 1.047)	0.541	**1.083 (1.035, 1.135)**	**0.004**	**1.072 (1.049, 1.096)**	**0**	**1.036 (1.011, 1.063)**	**0.019**	1.029 (1.01, 1.049)	0.503
	Warm	1.012 (0.977, 1.048)		1.010 (0.970, 1.053)		1.019 (0.983, 1.057)		**0.994 (0.960, 1.029)**		**0.990 (0.954, 1.027)**		**0.997 (0.977, 1.017)**		1.018 (0.993, 1.044)	

Abbreviations: ORs, odds ratios; CIs, confidence intervals; IQR, interquartile range; M, male; F, female.

NO_2, and PM_{10} and stroke hospitalizations were observed. All air pollutants presented a positive and significant association with hospitalizations of ischemic stroke. Additionally, it was found that the associations between SO_2, NO_2, and PM_{10} and stroke hospitalization were moderated by season. This study provided new evidence on the associations between short-term exposure to air pollutants and stroke hospitalization among a Chinese population with a high proportion of ethnic minorities and a relatively low level of air pollution.

The observed associations between NO_2, SO_2, and PM_{10} and stroke hospitalizations in this study were consistent with those of several previous studies. However, compared with previous studies, the odds ratios in this study appear to be lower (NO_2:1.040; SO_2:1.047; PM_{10}:1.018). For example, Fisher et al. reported that the ORs of ischemic stroke associated with PM_{10} were 1.26 (1.03, 1.55), and associations were elevated for nonsmokers, aspirin nonusers, and those without a history of high cholesterol (Fisher et al., 2019). Another study showed the ORs were 1.50 (1.12, 2.01) for NO_2 in the warm season, and associations were stronger for those with a history of stroke, heart disease, and taking medication for diabetes (Villeneuve et al., 2012). Two reasons may explain the low ORs in our study. First, our study was conducted in areas with relatively low levels of pollution in China. Second, the odds ratio for stroke may be higher in individuals with pre-existing medical conditions, particularly in older patients with cardiovascular diseases.

This study also provided new insights into the relationship between air pollution and stroke. First, we observed a significant association between PM_1 and hospital admissions for ischemic stroke. As PM_1 is characterized with smaller size and higher surface to volume ratio, it contains more toxins and can penetrate deeper into the lung even circulate in the bloodstream. So, it may be more harmful than $PM_{2.5}$ and PM_{10} as previous studies have suggested(Chen et al., 2020; Wu et al., 2022). Our study did not find such a trend, possibly because the level of particulate pollution in our sample was lower than that in other studies. The results suggest that it is more beneficial for public health policy makers to consider targeting reducing ambient PM_{10} instead of focusing on smaller PM (PM_1 and $PM_{2.5}$). Besides, we found that the associations between CO (lag 01) and hemorrhagic stroke were statistically significant. Only one prior study has also reported a similar association between CO and hemorrhagic stroke, such finding has been limited to lag1 period and warm season (Villeneuve et al., 2006). A previous animal-model study indicated that CO had vasodilation, neurotransmission, inhibition of platelet aggregation, and anti-smooth muscle proliferation (Kamat et al., 2019), and it may damage vessels through these pathways leading to hemorrhagic stroke. Overall, our finding suggests that more attention should be paid to CO to prevent hemorrhagic stroke hospitalization.

Identifying vulnerable sub-populations has significant scientific and public health implications, as it suggests that targeted and personal preventive measures for these potentially susceptible populations may lead to better health benefits (Tian et al., 2018). In this study, we found that O_3, $SO_{2,}$ and NO_2 had stronger effect in the cool seasons. Zhao et al. reported stronger associations of $PM_{2.5}$ and PM_{10} in the cool season, and similarly, Dong et al. reported stronger associations of NO_2 and SO_2 in the cool season (Dong et al., 2018; Zhao et al., 2022). The seasonal pattern in our study might be attributable to worse diffusion conditions of pollutants in the cool season than that in the warm season (Zhao et al., 2022). A prior report suggested arterial thrombosis could be worsen by cold temperature. Thus, ischemic stroke could occur more often in cool days (Hong et al., 2003). These findings may have implications for those already at high risk for stroke, who live in high air pollution zones: colder seasons may necessitate more rigorous implementation pollution avoidance measures.

Several potential mechanistic pathways have been proposed to explain the observed association in this study: systemic inflammation, oxidative stress, thrombosis, artery calcification, and vascular endothelial dysfunction (Niu et al., 2021; Weng et al., 2021). There are some mechanistic differences between particulate matter and gaseous pollutants. For particulate matter, vascular dysfunction likely plays a pivotal role in the mechanisms for air pollution related stroke (Brook et al., 2009). It was hypothesized that exposure to PM causes a significant increase in diastolic blood pressure and impairs endothelial function(Brook et al., 2009), which may further lead to stroke hospitalizations. Gaseous pollutants can penetrate blood-brain barrier to cause cerebral ischemia (Chen et al., 2019) through excitotoxicity and endothelial and inflammatory responses (Dong et al., 2018).

Our study had several notable strengths. First, we use bilinear interpolation to assess individual-level exposure based on the patient's home address, which enhances the accuracy of exposure measurement. Second, we adopted a case-crossover design, which reduces the confounding bias caused by time-invariant covariates (Liu et al., 2021). Third, we included more than 270,000 cases from 2013 to 2016, which provided a large statistical power to detect differences in stroke hospitalization risks in potentially vulnerable populations (Di et al., 2017). Fourth, there were a wide concentration range of air pollutants which provided an ideal study opportunity to examine the exposure response relationships (Wang et al., 2021). Finally, we were able to analyze a large sample from the Beibu Gulf Region, which could provide new insights into the relationship between pollution and stroke in this ethnically diverse region of China.

Our study also had some limitations. First, although a high-accuracy method was applied to assess personal exposure at residential addresses, exposure misclassification cannot be entirely excluded as we had no data on whether the address remained fixed in seven days before hospitalization (Royé et al., 2019). However, this issue is less of a concern because patients with stroke are older and restricted in physical activity and they are less likely to move extensively. Secondly, while the case-crossover study design allowed us to control for time-invariant confounders, our study was still subject to residual confounding from time-varying individual factors (He et al., 2022). Additionally, the data used were derived from 15 medium and small cities, which may limit the generalizability to larger cities (Liu et al., 2017). Fourth, we were not able to identify the re-admissions for the same patients from the available data. Fifth, we were not able to investigate the estimates influenced by the pre-existing diseases because the Health Commission collected only a limited number of variables (age, sex, residential address, hospitalization diagnosis, and information about medical expense). Nonetheless, we want to note that missing these variables do not influence our main findings as these individual-level variables have been cancelled out using the case-crossover design in this study. Finally, 26.9% of patients in this study were not categorized further by stroke subtype, which could affect the subtype specific associations.

5. Conclusion

The study suggested that short-term increases in SO_2, $NO_{2,}$ and PM_{10} concentrations were associated with increased risks of stroke hospitalization in a Chinese population with a high percentage of minority ethnicity groups. All seven air pollutants were associated with hospitalizations of ischemic stroke. We also found a positive significant association between CO and hospitalizations of hemorrhagic stroke. The associations of SO_2, NO_2, and O_3 with stroke hospitalization were significantly stronger in cool seasons. The findings urge a greater awareness of reducing the exposure to SO_2, $NO_{2,}$ and PM_{10}. The improved air quality may mitigate the adverse health effects on elderly populations especially in cool seasons. Our findings contribute to the limited literature concerning the effect of air pollution on stroke in Southwest China, where air pollution is less severe. Further study is required to examine the effect of air pollution on more specific stroke subtypes or other diseases in the same place.

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CRediT authorship contribution statement

Meijun Li: Conceptualization, Methodology, Software, Writing – original draft. **Randall C. Edgell:** Writing – review & editing. **Jing Wei:** Methodology. **Haopeng Li:** Methodology, Software. **Zhengmin (Min) Qian:** Writing – review & editing. **Jin Feng:** Software. **Fei Tian:** Software. **Xiaojie Wang:** Supervision, Project administration. **Qinghua Xin:** Supervision, Project administration. **Miao Cai:** Supervision, Project administration, Writing – review & editing. **Hualiang Lin:** Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.114814.

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.114814.

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