Science of the Total Environment 886 (2023) 163988

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Submicron particle exposure and stroke hospitalization: An individual-level case-crossover study in Guangzhou, China, 2014–2018

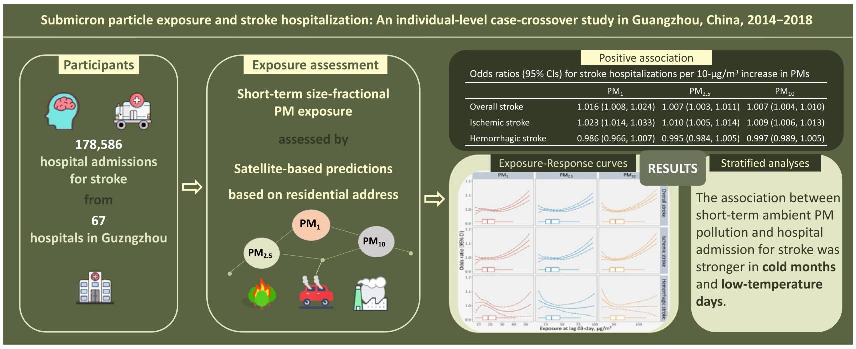
Murui Zheng [a,1], Zhouxin Yin [b,c,1], Jing Wei [d], Yong Yu [e], Kai Wang [b], Yang Yuan [b], Yaiqi Wang [b], Liansheng Zhang [b,*], Fang Wang [f,**], Yunquan Zhang [b,*]

[a] Department of Community Health, Guangzhou Center for Disease Control and Prevention, Guangzhou 510440, China
[b] Institute of Social Development and Health Management, Hubei Province Key Laboratory of Occupational Hazard Identification and Control, School of Public Health, Wuhan University of Science and Technology, Wuhan 430065, China
[c] School of Public Health and Emergency Management, Southern University of Science and Technology, Shenzhen 518055, China
[d] Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park 20742, USA
[e] School of Public Health, Hubei University of Medicine, Shiyan 442000, China
[f] School of Public Health, Xuzhou Medical University, Xuzhou 221004, Jiangsu, China

HIGHLIGHTS

- An individual-level case-crossover study of ~0.17 million stroke cases from 67 large hospitals in Guangzhou, China.
- Short-term exposure to PMs increased risks of hospitalization for overall and ischemic stroke.
- PM_1 exhibited greater risk effects compared with $PM_{2.5}$ and PM_{10}.
- Significant effects of PMs exposure on stroke were only detected in cold months and low-temperature days.

GRAPHICAL ABSTRACT


Submicron particle exposure and stroke hospitalization: An individual-level case-crossover study in Guangzhou, China, 2014–2018

Participants

178,586 hospital admissions for stroke from 67 hospitals in Guznzghou

Exposure assessment

Short-term size-fractional PM exposure assessed by Satellite-based predictions based on residential address

Positive association

Odds ratios (95% CIs) for stroke hospitalizations per 10-μg/m³ increase in PMs

	PM_1	$PM_{2.5}$	PM_{10}
Overall stroke	1.016 (1.008, 1.024)	1.007 (1.003, 1.011)	1.007 (1.004, 1.010)
Ischemic stroke	1.023 (1.014, 1.033)	1.010 (1.005, 1.014)	1.009 (1.006, 1.013)
Hemorrhagic stroke	0.986 (0.966, 1.007)	0.995 (0.984, 1.005)	0.997 (0.989, 1.005)

RESULTS

Exposure-Response curves

Stratified analyses

The association between short-term ambient PM pollution and hospital admission for stroke was stronger in **cold months** and **low-temperature days**.

ARTICLE INFO

Editor: Pavlos Kassomenos

Keywords:
PM_1
Particulate matter
Hospital admission
Stroke
Case-crossover study

ABSTRACT

Background: Short-term exposure to ambient $PM_{2.5}$ and PM_{10} (particulate matter with aerodynamic diameters ≤ 2.5 μm and 10 μm, respectively) has been linked with hospitalization and mortality from stroke. However, the effect of PM_1 (≤ 1 μm) exposure on the risk of hospitalization from stroke and its subtypes has rarely been investigated, in particular, on the basis of fine-scale exposure assessment at the individual level.
Methods: We collected data on hospital admissions due to stroke and its subtypes in Guangzhou, China from January 1, 2014 to December 31, 2018. Daily exposures to PM_1, $PM_{2.5}$, and PM_{10} were assessed from satellite-derived estimates at a 1-km^2 spatial resolution based on residential addresses. A time-stratified case-crossover analysis combined with a conditional logistic regression model was performed to examine the associations of stroke hospitalization risks with short-term exposure to size-fractional particles. We conducted stratified analyses by sex, age, season, and ambient temperature.
Results: A total of 178,586 stroke hospitalizations were recorded during the study period, among which 141,709 cases were ischemic stroke and 25,255 cases were hemorrhagic stroke. The mean concentrations on the day of hospitalization were 20.0 μg/m^3 (control days: 19.9 μg/m^3) for PM_1, 37.6 μg/m^3 (37.4 μg/m^3) for $PM_{2.5}$, and 59.3 μg/m^3 (59.0 μg/m^3) for PM_{10}. Short-term exposure to size-fractional particles was significantly associated with increased risks of hospital admission for overall stroke and ischemic stroke, whereas null or negative associations were observed for hemorrhagic

---

* Corresponding authors at: School of Public Health, Wuhan University of Science and Technology, Wuhan 430065, China.
** Correspondence to: F. Wang, School of Public Health, Xuzhou Medical University, Xuzhou 221004, Jiangsu, China.
E-mail addresses: zhangliansheng@wust.edu.cn (L. Zhang), fwang@xzhmu.edu.cn (F. Wang), YunquanZhang@wust.edu.cn (Y. Zhang).

[1] Murui Zheng and Zhouxin Yin are co-first authors who contributed equally to this paper.

http://dx.doi.org/10.1016/j.scitotenv.2023.163988
Received 30 December 2022; Received in revised form 30 April 2023; Accepted 2 May 2023

stroke. Compared with $PM_{2.5}$ and PM_{10}, PM_1 was associated with greater excess risks of stroke hospitalizations. For each 10-μg/m^3 increase in PM_1, $PM_{2.5}$, and PM_{10} exposure at lag 03-day, the odds ratios were 1.016 (95% confidence interval: 1.008, 1.024), 1.007 (1.003, 1.011), and 1.007 (1.004, 1.010) for overall stroke hospitalization, and were 1.023 (1.014, 1.033), 1.010 (1.005, 1.014), and 1.009 (1.006, 1.013) for ischemic stroke, respectively. These associations were robust to co-pollutant adjustments and did not vary by sex and age, while significantly elevated risks were identified in cold months (October to March of the next year) and low-temperature days (<23.8 °C) only.

Conclusions: Short-term exposure to particulate matter air pollution, particularly PM_1, was associated with increased risks of hospitalization for overall stroke and ischemic stroke.

1. Introduction

Stroke is a complex and multi-factorial disease resulting from a combination of genetic and environmental risk factors. Extensive epidemiological and toxicological studies have revealed that short-term exposure to ambient particulate matter (PM), mainly inhalable PM (PM_{10}, PM with an aerodynamic diameter ≤ 10 μm) and fine PM ($PM_{2.5}$, PM with an aerodynamic diameter ≤ 2.5 μm), is associated with an elevated risk of morbidity and mortality from stroke worldwide (Shah et al., 2015; Verhoeven et al., 2021). Recently, there is emerging evidence pointing out that PM with smaller sizes might pose stronger adverse effects on cardiovascular diseases and the observed $PM_{2.5}$-induced effects are dominantly attributable to submicron PM (PM_1, PM with an aerodynamic diameter ≤ 1 μm) (Chen et al., 2017; Hu et al., 2018; Lin et al., 2016). However, the relationship between PM_1 exposure and the risk of stroke remained largely unstudied, owing primarily to the scarcity of routine PM_1 monitoring data.

Several time-series or case-crossover investigations associated short-term PM_1 exposure with stroke incidence (Wu et al., 2022), hospitalization (Chen et al., 2020; Liu et al., 2022), and mortality (Hu et al., 2018; Perez et al., 2009; Yin et al., 2020) in highly polluted regions, while exposure assessment of these studies largely relied on regional average PM concentrations or sparse fixed stations. Despite high accuracy at specific locations, station-based PM measurements failed to reveal the spatiotemporal variations of individual residential-level exposure (Wang et al., 2013b), which may result in exposure misclassification and bias the health effect estimation (Baxter et al., 2013; Wei et al., 2022). In addition, limited research has been carried out to distinguish the impacts of size-fractional PMs on different stroke types, hindering a comprehensive understanding of their underlying biological mechanisms. To support evidence-based policymaking, systematic evaluations using high-resolution pollutant data sets that link individual-level PM_1 exposure with stroke and its subtypes are urgently required.

Therefore, we conducted a case-crossover study at the individual level by enrolling ~0.17 million stroke cases in Guangzhou, China from 2014 to 2018. This analysis aimed to examine the associations between short-term exposure to size-fractional particles (PM_1, $PM_{2.5}$, PM_{10}) and risks of hospitalization for stroke and its subtypes. We also explored the susceptible sub-populations and the seasonal pattern by carrying out stratified analyses across different sexes, age groups, seasons, and temperature days.

2. Materials and methods

2.1. Study area and population

Located in the Pearl River Delta region, Guangzhou (112°57′–114°3′ E, 22°26′–23°56′ N) is the third largest city in China covering an area of approximately 7434.4 km^2. The primary landform types in Guangzhou City are hilly lands in the north and east, and alluvial plains in the south, with the terrain high in the northeast while low in the southwest. This study was conducted among permanent residents in Guangzhou and the population distribution was shown in Fig. S1.

2.2. Stroke hospital admission data

Stroke hospital admission data in our study were extracted from the Guangzhou Cardio- and Cerebrovascular Disease Event Surveillance System, which was established to monitor stroke and other cardio- and cerebrovascular events in Guangzhou (Guo et al., 2017). In order to collect case data to the greatest extent, we recruited class 2 and class 3 hospitals with the ability of diagnosis and treatment of stroke, excluding hospitals that were not specialized in cerebrovascular diseases, such as pediatric, obstetric, orthopedic, and other specialized hospitals. Finally, a total of 67 hospitals that were widely distributed in Guangzhou were included (Fig. S1). All hospitals adopted a unified guideline and standard for the diagnosis of stroke. Hospital admission data for stroke were abstracted by trained staff of the Guangzhou Center for Disease Control and Prevent using a standardized operation procedure, and relevant information including demographics, and clinical symptoms were collected. All stroke cases were coded according to the International Classification of Diseases, Tenth Revision (ICD-10) as follows: overall stroke (I60–I69), ischemic stroke (I63), and hemorrhagic stroke (I60–I61).

We obtained 178,586 stroke hospital admission records from 67 hospitals in Guangzhou between January 1, 2014 and December 31, 2018. For each case, we extracted 1) patient demographics including sex, age, and ethnicity; 2) principal diagnosis codes; 3) inpatient admission date; 4) current residential addresses and household registration addresses. We geocoded the residential address of each patient into latitude and longitude, and if the current residential address was missing (<0.2%), the household registration address was used. The spatial distribution of the included cases was illustrated in Fig. 1.

2.3. Exposure assessment

Satellite-derived estimates for daily gridded particulate air pollution data with a 1-km^2 spatial resolution from 2014 to 2018 were collected from the ChinaHighAirPollutants (CHAP) dataset, which has been widely validated and adopted in environmental health studies. Briefly, by well incorporating space-time models and advanced satellite remote sensing, CHAP showed superior performance in estimating daily PM concentrations with a cross-validation coefficient of determination (CV-R^2) of 0.77 and a root-mean-square error (RMSE) of 14.6 μg/m^3 for PM_1 (Wei et al., 2019a), CV-R^2 of 0.92 and RMSE of 10.76 μg/m^3 for $PM_{2.5}$ (Wei et al., 2021b), and CV-R^2 of 0.9 and RMSE of 21.12 μg/m^3 for PM_{10} (Wei et al., 2021a). Gridded gaseous pollutants (i.e., SO_2, NO_2, O_3, and CO) at 10-km^2 spatial resolutions were also obtained from the CHAP dataset (https://weijing-rs.github.io/product.html, accessed on April 30, 2023). More modeling details could be found in prior publications. To account for confounding effects of weather conditions, we extracted daily data on mean temperature and relative humidity at a 10-km^2 spatial resolution from European Center for Medium-Range Weather Forecasts (https://cds.climate.copernicus.eu, accessed on April 30, 2023) for the same study period. With these high-resolution predictions, we assigned environmental exposures geographically to each stroke case according to their residence and admission date.

2.4. Statistical analysis

A time-stratified case-crossover approach was applied to estimate associations between short-term changes in PM concentrations and hospital admissions for stroke. The case-crossover design has been broadly adopted in environmental epidemiology to evaluate acute health effects of exposure to

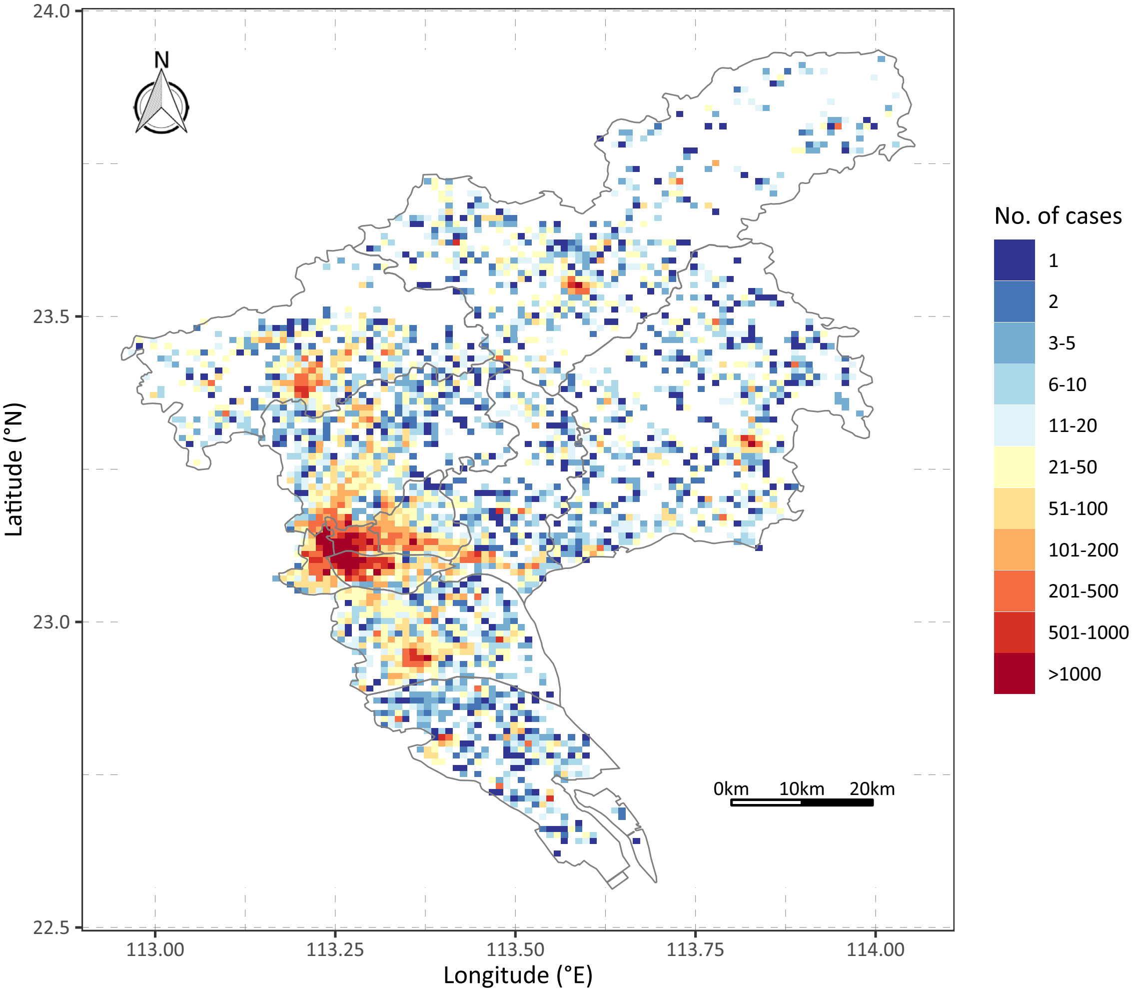


Fig. 1. Spatial distribution of the stroke cases in Guangzhou, China, 2014 to 2018.

air pollution (Verhoeven et al., 2021; Wei et al., 2019b). This approach features that each case serves as his/her own control, and so confounders related to individual characteristics that are unlikely to vary within a short period, such as demographic, socioeconomic, and some behavioral risk factors, are inherently well controlled. For each stroke case, date of hospital admission was defined as the case day. The control days were derived from the same calendar year, month, and day of the week (before or after the case day) as the corresponding case to control for day of week, long-term trends, and seasonal effects in hospital admissions and air pollutants (i.e., if a case occurs on the first Wednesday of September 2016, the control days are all other Wednesdays in September 2016) (Levy et al., 2001). Each case day had three or four matching control days. The associations between PM exposures and the risks of hospitalization for stroke were then assessed by comparing the levels of exposure for each case on the case day with their levels on control days. For the current study, 606,890 control days were selected for 178,586 hospital admissions for overall stroke.

For each pollutant, we performed a conditional logistic regression to separately evaluate the exposure-response (E-R) relationship of short-term PM exposure with hospitalization for 3 types of stroke (i.e., overall stroke, ischemic stroke, and hemorrhagic stroke) of interest. To characterize the lag patterns, we assessed exposures at single-lag days (lag 0-day to lag 4-day) and moving-average exposures on the same and previous days of each hospitalization (lag 01-day to lag 04-day). We applied a natural cubic spline (NCS) function with 3 degrees of freedom (*df*) for terms of average temperature at lag 03-day and relative humidity on the current day, so as to eliminate potential nonlinear confounding effects of meteorological conditions. These modeling parameters were empirically chosen in accordance with prior studies (Tian et al., 2018; Zhang et al., 2020). To compare the effects of size-fractional PMs exposure on stroke hospitalization based on comparable contrasts, we assessed odds ratios (ORs) and their 95% confidence intervals (CIs) per 10-μg/m^3 or interquartile range (IQR) increase in PMs concentrations. We depicted the E-R curves between size-fractional PMs and stroke hospitalization risks by smoothing exposures using NCS terms with 3 *df*.

To examine whether certain subpopulations suffered greatly from PM-related health risks, we conducted several subgroup analyses stratified by sex (male, female), age group (0–74, 75+ years), and season of admission (warm, cold). Specifically, we defined the warm season as the month of admission from April to September, and the cold season as the month from October to March of the next year. Furthermore, to investigate the potential effect modification of ambient temperature, we divided subjects into low- and high-temperature days using the median temperature (23.8 °C) as the binary cutoff. We examined between-group differences via 2-sample z-tests by comparing subgroup-specific regression coefficients (β = ln odds ratio) and corresponding standard errors (SE) derived from conditional logistic models (Altman and Bland, 2003).

Multiple sensitivity analyses were performed to check the robustness of our results. First, we applied multipollutant analyses by additionally including one of gaseous pollutants (i.e., SO_2, NO_2, O_3, and CO) and four pollutants simultaneously in the main model to eliminate potential confounding effects by other air pollutants. Second, we changed the *df* (s) from 3 to 4, 5, and 6 of NCS functions for temperature and relative humidity.

Statistical analyses were performed using R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria), with the “survival” package for conditional logistic regression analysis and the “splines” package for NCS smoothing. A *P* value of <0.05 was considered statistically significant for all two-sided tests.

3. Results

Table 1 summarizes the descriptive statistics of stroke cases included in this study. From 2014 to 2018, we recorded a total of 178,586 hospital admission cases for overall stroke in Guangzhou, including 141,709 cases for ischemic stroke and 25,255 cases for hemorrhagic stroke. For overall stroke, 56.1% of the hospital admissions were males, more than half (56.6%) were under 75 years of age, and 50.2% occurred in warm months.

The concentrations of particulate air pollutants on case days tended to be slightly higher than those on control days, with average estimates of 20.0 μg/m^3 versus 19.9 μg/m^3 for PM_1, 37.6 μg/m^3 versus 37.4 μg/m^3 for $PM_{2.5}$, 59.3 μg/m^3 versus 59.0 μg/m^3 for PM_{10}, respectively (Table 2). Size-fractional PMs were positively and highly correlated (Spearman *r*: 0.90–0.96), while relatively weaker or negative correlations were observed between PMs and gaseous pollutants (Fig. S2).

Fig. 2 presents the associations of PMs exposures with hospital admission for stroke across various lag days. Ambient exposures to size-fractional particles (PM_1, $PM_{2.5}$, and PM_{10}) were all significantly associated with increased risks of hospital admission for overall and ischemic stroke. In contrast, null or negative effects of PMs exposure were observed for hemorrhagic stroke, except for PM_{10} exposure at lag 4-day. Size-fractional PMs exhibited highly similar lag patterns in associations with overall and ischemic stroke, wherein excess risks were seen immediately on the concurrent day and lasted until lag 3-day or lag 4-day. In comparison with $PM_{2.5}$ and PM_{10}, both a 10-μg/m^3 or an IQR increase of PM_1 yielded larger effects on stroke hospitalizations (Tables S1 & S2). For instance, each 10-μg/m^3 increase in PM_1 exposure at lag 03-day was accordingly associated with an OR of 1.016 (95% CI, 1.008–1.024) for overall stroke, corresponding to ORs of 1.007 (95% CI, 1.003–1.011) and 1.007 (95% CI, 1.004–1.010) related to $PM_{2.5}$ and PM_{10} exposure, respectively. E-R associations between PM concentrations at lag 03-day and stroke risks were depicted in Fig. 3. In general, largely similar shapes of curves were seen in associations of size-fractional PMs with overall and ischemic stroke, consistently showing a sharp increase of risk at higher concentrations only (e.g., >25 μg/m^3 for PM_1).

Table 3 estimates subgroup-specific ORs of stroke hospital admission associated with PM exposures, stratified by sex, age at admission, season of admission, and ambient temperature. The magnitudes of associations were generally comparable across different sex and age groups. We identified a clear seasonal pattern for PM-related risks of hospitalization for overall stroke and ischemic stroke, with significant effects being found in the cold months only. For instance, for per 10-μg/m^3 rise in PM_1 exposure at lag 03-day, the ORs for hospital admission for overall stroke were 1.022 (95% CI, 1.012–1.031) in the cold season and 0.987 (95% CI, 0.969–1.006) in the warm season. In stratified analysis by ambient temperature, we also observed significantly stronger PM-stroke associations in

Table 2
Summary distributions of exposure to ambient air pollutants and meteorological conditions on case days and control days.

Variables	Mean	SD	Percentile				
			5th	25th	50th	75th	95th
On case days (n = 178,586)							
Air pollutant							
PM_1, μg/m^3	20.0	11.2	7.9	12.3	17.1	24.6	42.5
$PM_{2.5}$, μg/m^3	37.6	21.0	14.7	22.7	32.5	47.3	76.3
PM_{10}, μg/m^3	59.3	28.4	26.7	39.3	52.4	72.9	112.9
SO_2, μg/m^3	13.2	5.8	6.4	9.3	11.8	15.7	24.4
NO_2, μg/m^3	42.3	18.0	21.4	30.2	38.4	50.1	76.9
CO, mg/m^3	0.9	0.2	0.6	0.7	0.8	1.0	1.3
O_3, μg/m^3	93.0	49.0	23.6	55.9	87.3	123.2	182.1
Meteorological condition							
Temperature, °C	22.5	5.8	12.0	18.1	23.8	27.4	29.6
Relative humidity, %	69.0	12.9	44.2	62.0	70.0	78.1	88.3
On control days (n = 606,890)							
Air pollutant							
PM_1, μg/m^3	19.9	11.0	7.9	12.3	17.1	24.4	42.2
$PM_{2.5}$, μg/m^3	37.4	20.8	14.6	22.6	32.4	47.0	76.4
PM_{10}, μg/m^3	59.0	28.1	26.7	39.2	52.3	72.4	112.9
SO_2, μg/m^3	13.2	5.8	6.4	9.3	11.8	15.7	24.4
NO_2, μg/m^3	42.2	17.5	21.5	30.2	38.4	50.0	76.0
CO, mg/m^3	0.9	0.2	0.6	0.7	0.8	1.0	1.3
O_3, μg/m^3	93.1	49.4	22.9	55.5	87.5	123.8	182.8
Meteorological condition							
Temperature, °C	22.5	5.9	11.9	18.1	23.9	27.4	29.6
Relative humidity, %	69.0	13.0	43.9	61.8	70.0	78.3	88.4

Abbreviations: SD, standard deviation; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone.

Table 1
Basic characteristics of the stroke cases, 2014 to 2018.

Characteristics	Values, No. (%)		
	Overall stroke	Ischemic stroke	Hemorrhagic stroke
Stroke cases	178,586 (100.0)	141,709 (100.0)	25,255 (100.0)
Sex			
Male	100,098 (56.1)	78,368 (55.3)	15,107 (59.8)
Female	78,488 (43.9)	63,341 (44.7)	10,148 (40.2)
Age at admission, years, mean ± SD	70.8 ± 12.4	71.7 ± 11.7	65.4 ± 14.8
<65 years	53,528 (30.0)	38,755 (27.3)	11,728 (46.4)
65–74 years	47,540 (26.6)	38,737 (27.3)	5734 (22.7)
75–84 years	56,223 (31.5)	46,544 (32.8)	5821 (23)
≥85 years	21,243 (11.9)	17,635 (12.4)	1963 (7.8)
Unknown	52 (<0.1)	38 (<0.1)	9 (<0.1)
Ethnicity			
Han	177,303 (99.3)	140,681 (99.3)	25,076 (99.3)
Others	1283 (0.7)	1028 (0.7)	179 (0.7)
Marital status			
Never married	2453 (1.4)	1475 (1.0)	808 (3.2)
Married	166,694 (93.3)	132,753 (93.7)	23,032 (91.2)
Divorced or widowed	6315 (3.5)	5028 (3.5)	883 (3.5)
Unknown	3124 (1.7)	2453 (1.7)	532 (2.1)
Season of admission			
Warm (April to September)	89,595 (50.2)	72,053 (50.8)	11,533 (45.7)
Cold (January to March, October to December)	88,991 (49.8)	69,656 (49.2)	13,722 (54.3)

Note: The sum of proportions may not equal 100% due to the use of rounding-off method. Abbreviation: SD, standard deviation.

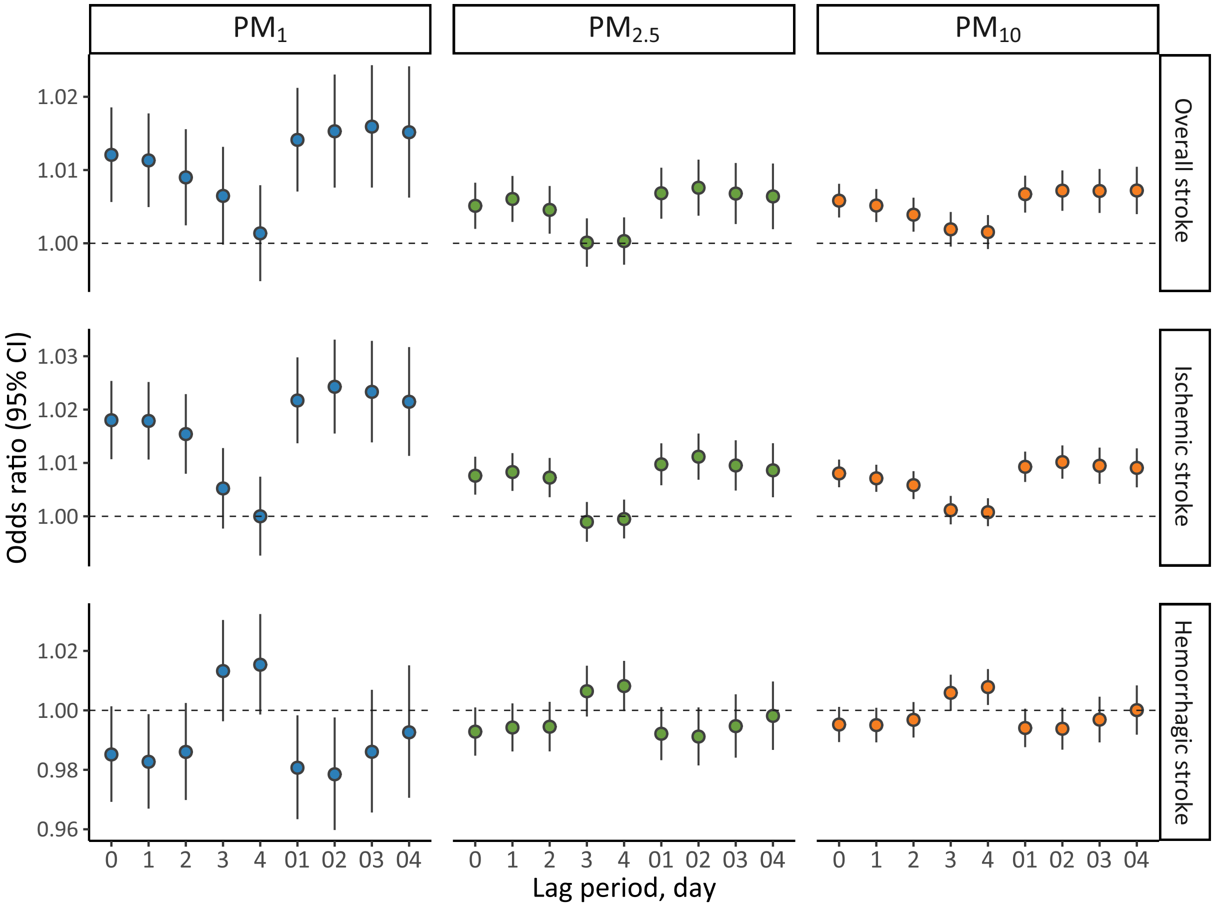


Fig. 2. Odds ratios (95% CIs) of hospitalization for stroke and its subtypes associated with per 10-μg/m^3 increase in exposure to PM$_1$, PM$_{2.5}$, and PM$_{10}$ at various lag days. Abbreviations: CI, confidence interval; PM$_1$, particulate matter with aerodynamic diameter ≤1 μm; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM$_{10}$, particulate matter with aerodynamic diameter ≤10 μm.

low-temperature days than in high-temperature days (P <0.04 for between-group differences).

In our sensitivity analyses, the results remained generally stable after introducing gaseous pollutants separately or simultaneously for additional modeling adjustments, suggesting minimal confounding from each other (Table S3). Overall, the estimates were largely unchanged when using different *df* (s) for NCS smoothing of temperature and humidity.

4. Discussion

In this large individual-level case-crossover study of 178,586 stroke cases in Guangzhou, we observed that short-term particulate air pollution exposures increased the risk of hospital admission for overall and ischemic stroke, whereas null or negative effects of PMs exposure on hemorrhagic stroke were detected. The effect estimates were greater for PM$_1$ compared with PM$_{2.5}$ and PM$_{10}$. Significant effects of PMs exposures on stroke hospitalization were only detected in cold months and low-temperature days. Our findings may have some implications in better understanding of cerebrovascular health impacts associated with size-fractional particles and evidence-based policymaking for stroke preventive strategies in highly polluted days.

Several multi-city studies in China have provided evidence of positive relationships between ambient PM$_1$ exposure and stroke incidence in 5 Third-grade class-A hospitals (Chen et al., 2020), 292 cities nationwide (Liu et al., 2022), and 126 out of the 136 counties in Shandong Province (Wu et al., 2022), respectively. These studies reported an increased risk of 0.53–1.2% for overall stroke and 0.67–1.4% for ischemic stroke, in relation to a 10-μg/m^3 rise in PM$_1$, respectively, which was slightly lower than our estimates (1.6% for overall stroke and 2.3% for ischemic stroke). One reason could be that we firstly evaluated the adverse impacts of acute exposure to PM$_1$ on stroke admissions by applying a fine-scale exposure assessment approach based on residential address of each subject. This provided a more accurate assessment of individual-level exposure than prior studies which utilized sparse fixed stations or county-level mean concentrations to measure individual exposure levels (Baxter et al., 2013). For more intuitive comparisons, we reran the main model by using city-level average PM concentrations measured at the supersite as the substitute for population-level PM exposure. The analysis results showed that using station-based PM measurements might underestimate the PM-stroke associations compared with satellite-based predictions, which supported the above conjecture (Fig. S3). A simulation study also suggested that the use of ambient predictions with a finer spatial resolution will result in smaller bias (Wei et al., 2022). Therefore, we call for more research leveraging more sophisticated analyses and precise exposure assessments to explore PM$_1$-stroke associations.

Our study strengthened the notion that PM$_1$ exposure could induce more deleterious health effects compared with PM$_{2.5}$ and PM$_{10}$. We provided comparative risk assessments of size-fractional PMs on stroke hospitalization and the greater impacts of PM$_1$ were consistent with several prior studies on stroke mortality (Hu et al., 2018; Yin et al., 2020), hospital admission (Chen et al., 2020; Liu et al., 2022), recurrence (Cai et al., 2023; Liu et al., 2022), prevalence (Yang et al., 2019), and 1-year survival after ischemic stroke (Chen et al., 2019). Very recently, a 4-province study in China also showed that short- and long-term exposures to size-fractional particles were associated with increased in-hospital case fatality among stroke patients, where smaller PM exhibited larger toxicity (Cai et al.,

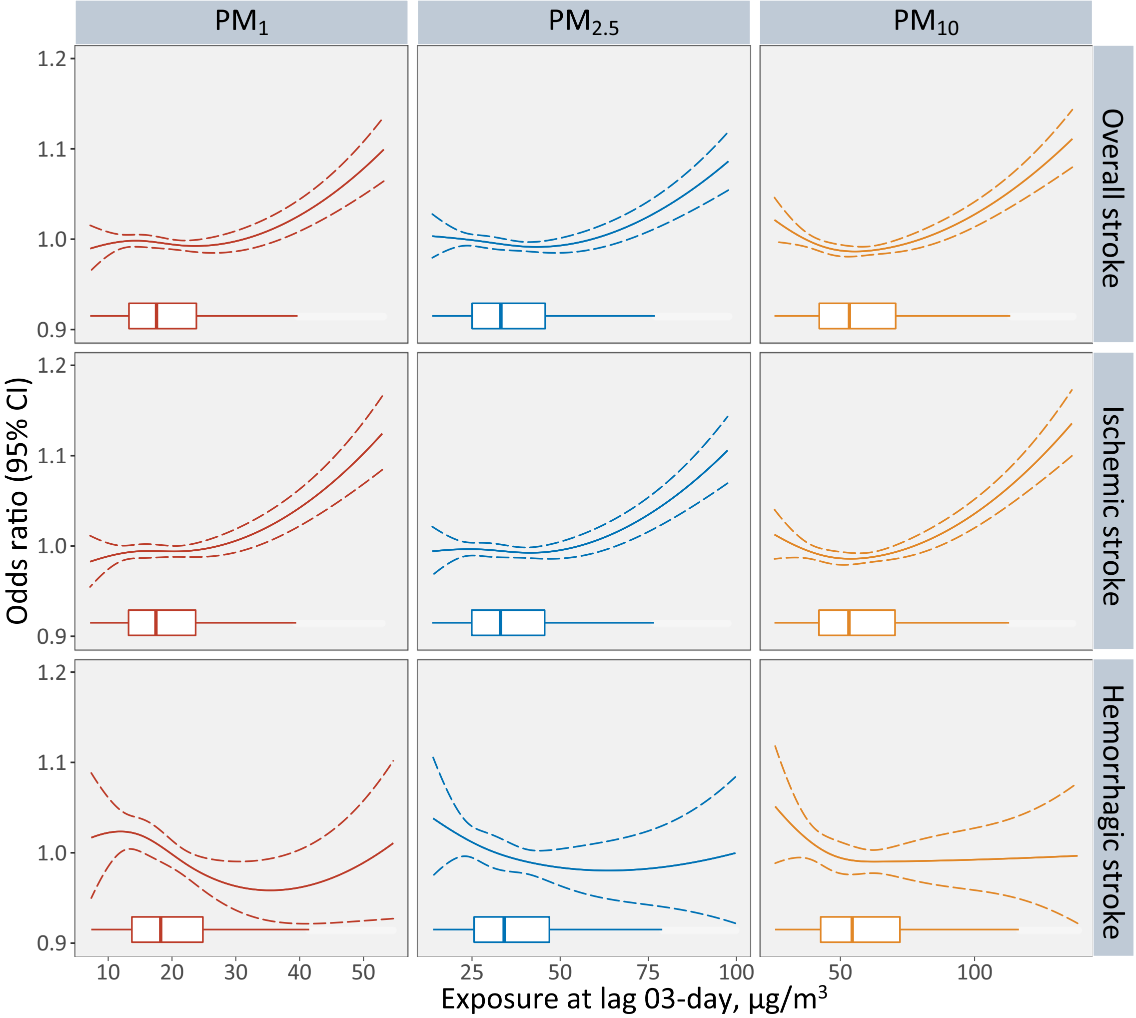


Fig. 3. Exposure-response relationships of PM_1, $PM_{2.5}$ and PM_{10} exposure at lag 03-day with hospital admission for stroke and its subtypes. Abbreviations: CI, confidence interval; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

2022). Furthermore, some studies found significant adverse effects of ultrafine particles (UFPs, particles with aerodynamic diameters ≤0.1 μm), the smallest fraction of ambient PM, on stroke (Andersen et al., 2010; Kettunen et al., 2007; Perez et al., 2009). For instance, a case-crossover study from Copenhagen, Denmark reported that short-term exposure to UFPs was associated with hospital admissions for ischemic stroke without atrial fibrillation (Andersen et al., 2010), while weak associations were observed with PM_{10}. The underlying mechanism may be that its small particle size and large surface area to mass ratio enable them to deposit in deeper respiratory tract and carry more toxins (Zou et al., 2017). Moreover, evidence shows that the smaller the size of particles, the easier the passage into the systemic circulation and the greater the toxicity through mechanisms of oxidative stress and inflammation (Manigrasso et al., 2020; Valavanidis et al., 2008). The expanding evidence demonstrated great importance of mitigating particulate matter air pollution and formulating the air quality standards of smaller particles including PM_1 and ultrafine particles in China.

We found differential effect directions of PMs on stroke subtypes. This finding was consistent with most prior studies which reported that exposure to particulate matter was significantly associated with an increased risk of hospitalization and mortality for ischemic stroke, but not with hemorrhagic stroke (Liu et al., 2017; Tian et al., 2019). Several pathophysiologic mechanisms have been proposed for the PM-induced effects on stroke, such as inflammation, vasoconstriction, blood coagulation, and atherosclerosis (Sun et al., 2005; Suwa et al., 2002), which might be more likely to provoke ischemic stroke rather than hemorrhagic stroke. In a study including 1023 Mexican Americans, short-term exposure to $PM_{2.5}$ was linked to higher total cholesterol and low-density lipoprotein cholesterol (Chen et al., 2016), while two systematic reviews and meta-analyses reported negative associations between these two metabolic indicators and hemorrhagic stroke (Wang et al., 2013a; Xie et al., 2017). This provided the biological plausible explanation for the negative relationship between PM exposure and hemorrhagic stroke. More detailed mechanisms of disparate effects of PM exposure on two subtypes of stroke are still warranted to explore in the future.

Studies showed mixed results for effect modification by sex and age in PM-stroke analyses. Our study reported comparable effect sizes of stroke risk associated with size-fractional PM exposure for male and female, suggesting no clear sex difference. Largely similar findings were observed in several multi-city studies in China (Chen et al., 2020; Gu et al., 2020; Tian et al., 2018), nonetheless, a few studies have also reported sex differences in the effects of particulate matter exposures on stroke (Wu et al., 2022; Yang et al., 2019). The source of differences in the adverse effects of particle exposures among different sexes have not been fully clarified to date and need more sophisticated researches to explore. Consistent with most prior studies (Ho et al., 2018; Tian et al., 2018; Wu et al., 2022), we found that patients older than 75 years had a higher estimated risk of stroke hospital admission, although between-group differences did

Table 3

Subgroup-specific odds ratios (95% CIs) for hospital admission associated with per 10-μg/m^3 increase in exposure to size-fractional particles at lag 03-day, stratified by sex, age, season and ambient temperature.

Exposure	Overall stroke		Ischemic stroke		Hemorrhagic stroke	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
PM_1						
Sex		0.76		1.00		0.19
Male	1.017 (1.006, 1.028)		1.023 (1.011, 1.036)		0.998 (0.971, 1.025)	
Female	1.014 (1.002, 1.027)		1.023 (1.009, 1.038)		0.970 (0.938, 1.002)	
Age, years		0.33		0.85		0.58
<75	1.012 (1.001, 1.023)		1.023 (1.010, 1.036)		0.989 (0.965, 1.015)	
≥75	1.021 (1.008, 1.034)		1.025 (1.011, 1.039)		0.977 (0.940, 1.015)	
Season		0.001		0.003		0.44
Cold	1.022(1.012, 1.031)		1.030(1.019, 1.041)		0.988(0.965, 1.011)	
Warm	0.987(0.969, 1.006)		0.994(0.974, 1.015)		0.966(0.919, 1.017)	
Temperature		<0.001		<0.001		0.85
Low (<50th)	1.032 (1.023, 1.041)		1.043 (1.033, 1.054)		0.980 (0.959, 1.002)	
High (≥50th)	0.986 (0.969, 1.004)		0.989 (0.993, 1.008)		0.985 (0.939, 1.034)	
$PM_{2.5}$						
Sex		0.89		0.99		0.37
Male	1.007 (1.001, 1.013)		1.009 (1.003, 1.016)		0.999 (0.985, 1.013)	
Female	1.006 (1.000, 1.013)		1.010 (1.003, 1.017)		0.989 (0.973, 1.006)	
Age, years		0.54		0.93		0.33
<75	1.006 (1.000, 1.011)		1.010 (1.003, 1.016)		0.998 (0.985, 1.011)	
≥75	1.008 (1.002, 1.015)		1.009 (1.002, 1.016)		0.987 (0.968, 1.006)	
Season		0.02		0.02		0.69
Cold	1.009 (1.004, 1.014)		1.012 (1.007, 1.018)		0.992 (0.980, 1.004)	
Warm	0.997 (0.988, 1.005)		0.998 (0.988, 1.008)		0.998 (0.974, 1.022)	
Temperature		0.03		0.003		0.04
Low (<50th)	1.013 (1.009, 1.018)		1.019 (1.013, 1.024)		0.986 (0.975, 0.997)	
High (≥50th)	1.003 (0.994, 1.011)		1.002 (0.993, 1.012)		1.013 (0.990, 1,036)	
PM_{10}						
Sex		0.67		0.83		0.96
Male	1.006 (1.002, 1.011)		1.009 (1.005, 1.014)		0.997 (0.987, 1.007)	
Female	1.008 (1.003, 1.012)		1.010 (1.005, 1.015)		0.997 (0.985, 1.009)	
Age, years		0.26		0.69		0.37
<75	1.005 (1.001, 1.010)		1.009 (1.004, 1.013)		0.999 (0.990, 1.009)	
≥75	1.009 (1.005, 1.014)		1.010 (1.005, 1.015)		0.991 (0.978, 1.005)	
Season		0.13		0.09		0.49
Cold	1.008 (1.004, 1.011)		1.011 (1.007, 1.015)		0.995 (0.986, 1.003)	
Warm	1.002 (0.996, 1.008)		1.003 (0.996, 1.010)		1.001 (0.984, 1.019)	
Temperature		0.009		<0.001		0.07
Low (<50th)	1.012 (1.009, 1.015)		1.016 (1.013, 1.020)		0.991 (0.983, 0.999)	
High (≥50th)	1.003 (0.997, 1.009)		1.003 (0.996, 1.010)		1.008 (0.991, 1.025)	

Abbreviations: OR, odds ratio; CI, confidence interval; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

Note: *P*-value <0.05 indicates statistically significant effect heterogeneity between subgroups.

not reach statistical significance. It has been widely reported that older individuals are more susceptible to air pollution, which might be due to their poorer respiratory function and ventilation and thus a higher deposition rate of PM in the airway (Franchini and Mannucci, 2011). In addition, older adults are more likely to have other cardiovascular risk factors, which may contribute to increased PM-related risk of stroke. Notably, considering that older adults tend to spend more time indoors, ambient PM measurements may fail to fully capture individual exposure levels and be slightly overestimated in older adults (Verhoeven et al., 2021). Further investigation is clearly needed to assess whether subpopulations experience higher risks of stroke associated with PMs exposures, so as to guide the preventive actions against particulate air pollution.

We observed distinct seasonal disparity in stroke risks relating to ambient PM exposure, with significant increases detected in the cold months only. This may be related to the relatively higher particulate concentrations in cold season than in warm season (e.g., 31.7 μg/m^3 versus 20.6 μg/m^3 for PM_1), as the associations were stronger at higher concentrations of PM (Fig. 3). The seasonal heterogeneity may also be explained by variation in chemical components and exposure patterns (Bell et al., 2008). In addition, we also found some evidence for effect modification by ambient temperature in our stratified analyses, with higher PM-related hospitalization risks for stroke observed in low-temperature days. This added another possible explanation to seasonal differences in PM-hospitalization associations. Our finding was concordant with several prior studies conducted in China (Chen et al., 2020; Hu et al., 2021), the United States (Bell et al., 2008; Bell et al., 2015), and Europe (Yitshak-Sade et al., 2018), while there were also contradictory evidence (Chen et al., 2013; Peng et al., 2005; Yin et al., 2020). For example, a multi-city time-series study in Zhejiang province found that PM_1 exposure was more strongly associated with all-cause and cardiovascular mortality in the warm season than in the cold season (Hu et al., 2018). This is still an ongoing debate on seasonal patterns in PM-stroke associations, which merits continuous efforts in further epidemiological and experimental studies.

There are several limitations for this study. First, we failed to consider time intervals between the date of onset and the date of hospitalization of stroke patients, while most patients were admitted to the hospital within the first 6 h of stroke occurrence in China (Fang et al., 2011). Second, due to the unavailability of indoor air pollution and cases' time-activity patterns, air pollutant concentrations at the individual residence were used as surrogate exposures. This might lead to non-differential exposure misclassification to some extent, but it usually biases the PM-associated health effects towards the null direction. Third, we had no access to information on specific PM sources and chemical components, which might be helpful for comparing the toxicity of size-fractional particles (Lin et al., 2016). Fourth, although time-invariant factors (e.g., sex, race, genetics, and lifestyle) and time-varying weather conditions could be well controlled by the case-crossover design, residual confounders (e.g., medication use) might still possibly bias the estimated association. In addition, although we included as many hospitals as possible where patients in Guangzhou City might be admitted, there may still be some selection bias. Our findings should be generalized with care given that this is a single-city study.

5. Conclusions

In summary, we identified compelling evidence for associations between short-term exposures to size-fractional particulate matter and increased risks of hospitalization for overall stroke and ischemic stroke, but not for hemorrhagic stroke in Guangzhou, China from 2014 to 2018. A greater magnitude of associations was observed for PM_1 compared with $PM_{2.5}$ and PM_{10}. Significant adverse effects of PMs were mainly detected during cold months and in low-temperature days. The findings of this study could be helpful in better understanding of cerebrovascular health effects associated with air pollution and provide population-based insights into underlying biological mechanisms, underscoring continued efforts to control particulate air pollution and prevent PM-induced stroke.

CRediT authorship contribution statement

Murui Zheng: Methodology, Data curation, Resources, Writing - review & editing; **Zhouxin Yin**: Formal analysis, Methodology, Software, Writing - original draft, Writing - review & editing, Visualization; **Jing Wei**: Methodology, Data curation, Resources; **Yong Yu**: Data curation, Resources; **Kai Wang**: Writing - review & editing; **Yang Yuan**: Writing - review & editing; **Yaiqi Wang**: Writing - review & editing, Visualization; **Liansheng Zhang**: Methodology, Supervision, Writing - review & editing; **Fang Wang:** Writing - review & editing, Supervision; **Yunquan Zhang**: Conceptualization, Formal analysis, Methodology, Software, Visualization, Data curation, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition. All authors read and approved the final manuscript.

Data availability

Data will be made available on request.

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.

Acknowledgments

This study was supported by the Hubei Provincial Natural Science Foundation of China (Grant No. 2021CFB032) and "The 14th Five Year Plan" Hubei Provincial Advantaged Characteristic Disciplines (Groups) Project of Wuhan University of Science and Technology (Grant No. 2023C0102). We appreciate the anonymous reviewers whose insightful comments and suggestions contributed to the considerable improvement in manuscript quality.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163988.

References

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. BMJ 326, 219. https://doi.org/10.1136/bmj.326.7382.219.

Andersen, Z.J., Olsen, T.S., Andersen, K.K., et al., 2010. Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen. Denmark Eur. Heart J. 31, 2034–2040. https://doi.org/10.1093/eurheartj/ehq188.

Baxter, L.K., Dionisio, K.L., Burke, J., et al., 2013. Exposure prediction approaches used in air pollution epidemiology studies: key findings and future recommendations. J. Expo. Sci. Environ. Epidemiol. 23, 654–659. https://doi.org/10.1038/jes.2013.62.

Bell, M.L., Ebisu, K., Peng, R.D., et al., 2008. Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999–2005. Am. J. Epidemiol. 168, 1301–1310. https://doi.org/10.1093/aje/kwn252.

Bell, M.L., Son, J.Y., Peng, R.D., et al., 2015. Ambient $PM_{2.5}$ and risk of hospital admissions: do risks differ for men and women? Epidemiology 26, 575–579. https://doi.org/10.1097/EDE.0000000000000310.

Cai, M., Lin, X., Wang, X., et al., 2023. Ambient particulate matter pollution of different sizes associated with recurrent stroke hospitalization in China: a cohort study of 1.07 million stroke patients. Sci. Total Environ. 856, 159104. https://doi.org/10.1016/j.scitotenv.2022.159104.

Cai, M., Zhang, S., Lin, X., et al., 2022. Association of ambient particulate matter pollution of different sizes with in-hospital case fatality among stroke patients in China. Neurology https://doi.org/10.1212/WNL.0000000000200546.

Chen, G., Li, S., Zhang, Y., et al., 2017. Effects of ambient PM_1 air pollution on daily emergency hospital visits in China: an epidemiological study. Lancet Planet. Health 1, e221–e229. https://doi.org/10.1016/S2542-5196(17)30100-6.

Chen, G., Wang, A., Li, S., et al., 2019. Long-term exposure to air pollution and survival after ischemic stroke. Stroke 50, 563–570. https://doi.org/10.1161/STROKEAHA.118.023264.

Chen, L., Zhang, Y., Zhang, W., et al., 2020. Short-term effect of PM_1 on hospital admission for ischemic stroke: a multi-city case-crossover study in China. Environ. Pollut. 260, 113776. https://doi.org/10.1016/j.envpol.2019.113776.

Chen, R., Peng, R.D., Meng, X., et al., 2013. Seasonal variation in the acute effect of particulate air pollution on mortality in the China Air Pollution and Health Effects Study (CAPES). Sci. Total Environ. 450–451, 259–265. https://doi.org/10.1016/j.scitotenv.2013.02.040.

Chen, Z., Salam, M.T., Toledo-Corral, C., et al., 2016. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. Diabetes Care 39, 547–554. https://doi.org/10.2337/dc15-1795.

Fang, J., Yan, W., Jiang, G.X., et al., 2011. Time interval between stroke onset and hospital arrival in acute ischemic stroke patients in Shanghai, China. Clin. Neurol. Neurosurg. 113, 85–88. https://doi.org/10.1016/j.clineuro.2010.09.004.

Franchini, M., Mannucci, P.M., 2011. Thrombogenicity and cardiovascular effects of ambient air pollution. Blood 118, 2405–2412. https://doi.org/10.1182/blood-2011-04-343111.

Gu, J., Shi, Y., Chen, N., et al., 2020. Ambient fine particulate matter and hospital admissions for ischemic and hemorrhagic strokes and transient ischemic attack in 248 Chinese cities. Sci. Total Environ. 715, 136896. https://doi.org/10.1016/j.scitotenv.2020.136896.

Guo, P., Zheng, M., Feng, W., et al., 2017. Effects of ambient temperature on stroke hospital admissions: results from a time-series analysis of 104,432 strokes in Guangzhou, China. Sci. Total Environ. 580, 307–315. https://doi.org/10.1016/j.scitotenv.2016.11.093.

Ho, A.F.W., Zheng, H., De Silva, D.A., et al., 2018. The Relationship Between Ambient Air Pollution and Acute Ischemic Stroke: A Time-Stratified Case-Crossover Study in a City-State with Seasonal Exposure to the Southeast Asian Haze Problem. Ann. Emerg. Med. 72, 591–601. https://doi.org/10.1016/j.annemergmed.2018.06.037.

Hu, K., Guo, Y., Hu, D., et al., 2018. Mortality burden attributable to PM_1 in Zhejiang province, China. Environ. Int. 121, 515–522. https://doi.org/10.1016/j.envint.2018.09.033.

Hu, W., Chen, Y., Chen, J., 2021. Short-term effect of fine particular matter on daily hospitalizations for ischemic stroke: a time-series study in Yancheng, China. Ecotoxicol. Environ. Saf. 208, 111518. https://doi.org/10.1016/j.ecoenv.2020.111518.

Kettunen, J., Lanki, T., Tiittanen, P., et al., 2007. Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. Stroke 38, 918–922. https://doi.org/10.1161/01.STR.0000257999.49706.3b.

Levy, D., Lumley, T., Sheppard, L., et al., 2001. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology 12, 186–192. https://doi.org/10.1097/00001648-200103000-00010.

Lin, H., Tao, J., Du, Y., et al., 2016. Particle size and chemical constituents of ambient particulate pollution associated with cardiovascular mortality in Guangzhou, China. Environ. Pollut. 208, 758–766. https://doi.org/10.1016/j.envpol.2015.10.056.

Liu, H., Tian, Y., Xu, Y., et al., 2017. Ambient particulate matter concentrations and hospitalization for stroke in 26 Chinese cities: a case-crossover study. Stroke 48, 2052–2059. https://doi.org/10.1161/STROKEAHA.116.016482.

Liu, T., Jiang, Y., Hu, J., et al., 2022. Association of ambient PM_1 with hospital admission and recurrence of stroke in China. Sci. Total Environ. 828, 154131. https://doi.org/10.1016/j.scitotenv.2022.154131.

Manigrasso, M., Costabile, F., Liberto, L.D., et al., 2020. Size resolved aerosol respiratory doses in a Mediterranean urban area: from PM_{10} to ultrafine particles. Environ. Int. 141, 105714. https://doi.org/10.1016/j.envint.2020.105714.

Peng, R.D., Dominici, F., Pastor-Barriuso, R., et al., 2005. Seasonal analyses of air pollution and mortality in 100 US cities. Am. J. Epidemiol. 161, 585–594. https://doi.org/10.1093/aje/kwi075.

Perez, L., Medina-Ramón, M., Künzli, N., et al., 2009. Size fractionate particulate matter, vehicle traffic, and case-specific daily mortality in Barcelona, Spain. Environ. Sci. Technol. 43, 4707–4714. https://doi.org/10.1021/es8031488.

Shah, A.S., Lee, K.K., McAllister, D.A., et al., 2015. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ 350, h1295. https://doi.org/10.1136/bmj.h1295.

Sun, Q., Wang, A., Jin, X., et al., 2005. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA 294, 3003–3010. https://doi.org/10.1001/jama.294.23.3003.

Suwa, T., Hogg, J.C., Quinlan, K.B., et al., 2002. Particulate air pollution induces progression of atherosclerosis journal of the American college. Cardiology 39, 935–942. https://doi.org/10.1016/s0735-1097(02)01715-1.

Tian, Y., Liu, H., Wu, Y., et al., 2019. Association between ambient fine particulate pollution and hospital admissions for cause specific cardiovascular disease: time series study in 184 major Chinese cities. BMJ 367, l6572. https://doi.org/10.1136/bmj.l6572.

Tian, Y., Liu, H., Zhao, Z., et al., 2018. Association between ambient air pollution and daily hospital admissions for ischemic stroke: a nationwide time-series analysis. PLoS Med. 15, e1002668. https://doi.org/10.1371/journal.pmed.1002668.

Valavanidis, A., Fiotakis, K., Vlachogianni, T., 2008. Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev. 26, 339–362. https://doi.org/10.1080/10590500802494538.

Verhoeven, J.I., Allach, Y., Vaartjes, I.C.H., et al., 2021. Ambient air pollution and the risk of ischaemic and haemorrhagic stroke. Lancet Planet. Health 5, e542–e552. https://doi.org/10.1016/S2542-5196(21)00145-5.

Wang, X., Dong, Y., Qi, X., et al., 2013a. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke 44, 1833–1839. https://doi.org/10.1161/strokeaha.113.001326.

Wang, Z., Liu, Y., Hu, M., et al., 2013b. Acute health impacts of airborne particles estimated from satellite remote sensing. Environ. Int. 51, 150–159. https://doi.org/10.1016/j.envint.2012.10.011.

Wei, J., Li, Z., Guo, J., et al., 2019a. Satellite-derived 1-km-resolution PM_1 concentrations from 2014 to 2018 across China. Environ. Sci. Technol. 53, 13265–13274. https://doi.org/10.1021/acs.est.9b03258.

Wei, J., Li, Z., Xue, W., et al., 2021a. The ChinaHighPM_{10} dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China. Environ. Int. 146, 106290. https://doi.org/10.1016/j.envint.2020.106290.

Wei, J., Li, Z.Q., Lyapustin, A., et al., 2021b. Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens. Environ. 252, 112136.

Wei, Y., Qiu, X., Yazdi, M.D., et al., 2022. The impact of exposure measurement error on the estimated concentration-response relationship between long-term exposure to $PM_{2.5}$ and mortality. Environ. Health Perspect. 130, 77006. https://doi.org/10.1289/EHP10389.

Wei, Y., Wang, Y., Di, Q., et al., 2019b. Short term exposure to fine particulate matter and hospital admission risks and costs in the medicare population: time stratified, case crossover study. BMJ 367, l6258. https://doi.org/10.1136/bmj.l6258.

Wu, H., Zhang, B., Wei, J., et al., 2022. Short-term effects of exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} on ischemic and hemorrhagic stroke incidence in Shandong Province, China. Environ. Res. 212, 113350. https://doi.org/10.1016/j.envres.2022.113350.

Xie, L., Wu, W., Chen, J., et al., 2017. Cholesterol Levels and Hemorrhagic Stroke Risk in East Asian Versus Non-East Asian Populations: A Systematic Review and Meta-Analysis. Neurologist 22, 107–115. https://doi.org/10.1097/nrl.0000000000000126.

Yang, B.Y., Guo, Y., Morawska, L., et al., 2019. Ambient PM_1 air pollution and cardiovascular disease prevalence: insights from the 33 communities Chinese health study. Environ. Int. 123, 310–317. https://doi.org/10.1016/j.envint.2018.12.012.

Yin, P., Guo, J., Wang, L., et al., 2020. Higher risk of cardiovascular disease associated with smaller size-fractioned particulate matter. Environ. Sci. Technol. Lett. 7, 95–101. https://doi.org/10.1021/acs.estlett.9b00735.

Yitshak-Sade, M., Bobb, J.F., Schwartz, J.D., et al., 2018. The association between short and long-term exposure to $PM_{2.5}$ and temperature and hospital admissions in New England and the synergistic effect of the short-term exposures. Sci. Total Environ. 639, 868–875. https://doi.org/10.1016/j.scitotenv.2018.05.181.

Zhang, Y., Ding, Z., Xiang, Q., et al., 2020. Short-term effects of ambient PM_1 and $PM_{2.5}$ air pollution on hospital admission for respiratory diseases: case-crossover evidence from Shenzhen, China. Int. J. Hyg. Environ. Health 224, 113418. https://doi.org/10.1016/j.ijheh.2019.11.001.

Zou, Y., Wu, Y., Wang, Y., et al., 2017. Physicochemical properties, in vitro cytotoxic and genotoxic effects of $PM_{1.0}$ and $PM_{2.5}$ from Shanghai, China. Environ. Sci. Pollut. Res. Int. 24, 19508–19516. https://doi.org/10.1007/s11356-017-9626-9.