

ORIGINAL ARTICLE

Association of short-term exposure to ambient air pollution with mortality from ischemic and hemorrhagic stroke

Ruijun Xu¹ | Qingqing Wang² | Jing Wei³ | Wenfeng Lu^{4,5} | Rui Wang⁶ |
Tingting Liu¹ | Yaqi Wang¹ | Zhaoyu Fan¹ | Yingxin Li¹ | Luxi Xu¹ | Chunxiang Shi⁷ |
Guo Li⁸ | Gongbo Chen⁹ | Lan Zhang¹⁰ | Yun Zhou^{4,5} | Yuewei Liu¹ | Hong Sun²

¹Department of Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China

²Department of Environment and Health, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China

³Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, Maryland, USA

⁴State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

⁵Department of Preventive Medicine, School of Public Health, Guangzhou Medical University, Guangzhou, China

⁶Luohu District Chronic Disease Hospital, Shenzhen, China

⁷Meteorological Data Laboratory, National Meteorological Information Center, Beijing, China

⁸Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁹Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, Guangzhou, China

¹⁰Institute of Chronic Noncommunicable Disease Control and Prevention, Hubei Provincial Center for Disease Control and Prevention, Wuhan, China

Correspondence

Yuewei Liu, Department of Epidemiology,
School of Public Health, Sun Yat-sen
University, 74 Zhongshan Second Road,
Guangzhou, Guangdong 510080, China.
Email: liuyuewei@mail.sysu.edu.cn

Hong Sun, Department of Environment
and Health, Jiangsu Provincial Center
for Disease Control and Prevention, 172
Jiangsu Road, Nanjing, Jiangsu 210009,
China.

Email: hongsun@jscdc.cn

Funding information

Hebei Provincial Health Commission
in China, Grant/Award Number:
WJ2019Z016; National Natural Science
Foundation of China, Grant/Award
Number: 81773479 and 91743205;
Jiangsu Social Development Project,
Grant/Award Number: BE2018745

Abstract

Background: Short-term exposure to ambient air pollution has been linked to increased risk of stroke mortality, but its adverse effects on mortality from specific types of stroke including ischemic stroke and hemorrhagic stroke remain poorly understood.

Methods: Using the China National Mortality Surveillance System, we conducted a time-stratified case-crossover study among 412,567 stroke deaths in Jiangsu province, China during 2015–2019. Residential daily PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ exposure concentrations were extracted from the ChinaHighAirPollutants dataset for each subject. Conditional logistic regression models were performed to conduct exposure-response analyses.

Results: Each 10 µg/m³ increase of PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ was respectively associated with a 1.44%, 0.93%, 5.55%, 2.90%, 0.148%, and 0.54% increase in odds of mortality from ischemic stroke, which was significantly stronger than that from hemorrhagic stroke (percent change in odds: 0.74%, 0.51%, 3.11%, 1.15%, 0.090%, and 0.10%). The excess fraction of ischemic stroke mortality associated with PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ exposure was 6.90%, 6.48%, 8.21%, 8.61%, 9.67%, and 4.76%, respectively, which was also significantly higher than that of hemorrhagic stroke mortality (excess fraction: 3.49%, 3.48%, 4.69%, 3.48%, 5.86%, and 0.88%). These differences in adverse effects generally remained across sex, age, and season.

Conclusions: Short-term exposure to ambient air pollution was significantly associated with increased risk of both ischemic and hemorrhagic stroke mortality and posed considerable excess mortality. Our results suggest that air pollution exposure may lead to

Ruijun Xu and Qingqing Wang contributed equally to this work.

substantially greater adverse effects on mortality from ischemic stroke than that from hemorrhagic stroke.

KEY WORDS

air pollution, case-crossover study, hemorrhagic stroke, ischemic stroke, mortality

INTRODUCTION

As a leading cause of death and acquired disability in adults, stroke has emerged as a critical global issue especially in low- and middle-income countries [1]. According to estimates from the Global Burden of Disease Study, the global burden of stroke had risen steadily since 1990, reaching 6.55 million deaths and 143 million disability-adjusted life-years (DALYs) in 2019 [2]. China has been experiencing the highest burden of stroke since 1990, with 2.19 million deaths and 45.9 million DALYs in 2019. As ambient air pollution is considered as an important modifiable risk factor of stroke mortality, it is important to quantitatively assess its association with risk of stroke mortality and estimate its corresponding excess mortality [3,4].

Extensive previous studies have reported that short-term exposure to particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) [5–13], particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}) [3,4,6,12–15], sulfur dioxide (SO_2) [3,4,15,16], nitrogen dioxide (NO_2) [3,4,10,13,15,17–19], carbon monoxide (CO) [4,9,20], and/or ozone (O_3) [4,13,21] was associated with stroke mortality. As two main types of stroke, ischemic stroke and hemorrhagic stroke have different patterns of incidence and prognosis. While ischemic stroke accounts for over 85% of all stroke events, hemorrhagic stroke generally has a worse prognosis (fatality rate: 25%–30% in high-income, 30%–48% in low- and middle-income countries) [22]. Because the pathophysiological mechanism of ischemic stroke is substantially different from that of hemorrhagic stroke, it is possible that the acute adverse effects of ambient air pollution vary across types of stroke, which may be of great clinical and public health significance but has been less studied [23]. To date, only a limited number of studies have separately investigated the association of short-term exposure to air pollution with ischemic and hemorrhagic stroke, and the results remain inconclusive due to lack of statistical tests [10–12,15,24–28]. In addition, the excess mortality of ischemic and hemorrhagic stroke associated with short-term exposure to ambient air pollution has not been assessed and compared, which hindered the researchers from drawing a clear conclusion.

Therefore, we conducted a stratified case-crossover study of over 0.4 million stroke deaths in Jiangsu province, China during 2015–2019 to quantitatively access and compare the association of short-term exposure to ambient $\text{PM}_{2.5}$, PM_{10} , SO_2 , NO_2 , CO , and O_3 with mortality from ischemic and hemorrhagic stroke. The excess

mortality of these two types of stroke associated with ambient air pollution was further estimated.

METHODS

Study population

From the China National Mortality Surveillance System, we identified 412,567 deaths from stroke (including 212,088 ischemic stroke and 157,056 hemorrhagic stroke) in Jiangsu province, China during 2015–2019 (Figure 1). Personal data on sex, date of birth, race, date of death, and residential address were collected for each subject. As an eastern-central coastal province of China, Jiangsu province covers an area of 107,200 km^2 , and had a population of 84.7 million in 2020. This study was approved by the Ethical Committee of the School of Public Health, Sun Yat-sen University with a waiver of informed consent.

Outcomes

We used the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) to code mortality from stroke as the underlying cause of death. The primary outcomes were mortality from ischemic stroke (ICD-10 code: I63) and hemorrhagic stroke (I60–I62). We also investigated mortality from total stroke (I60–I64) in the analysis.

Study design

We estimated the association between short-term exposure to ambient air pollution and stroke mortality using a time-stratified case-crossover design, in which each case served as its own control by assessing referent exposures on days before or after the date of death. For each death, we defined the day of death as the case day, while the control days were defined as days with the same day of week, month, and year as the case day. For example, if a subject died on January 15, 2018 (Monday), January 15, 2018 was defined as the case day while all other Mondays in January 2018 (January 1, 8, 22, and 29, 2018) were defined as the control days. According to this approach, each case day was matched for three or four control days.

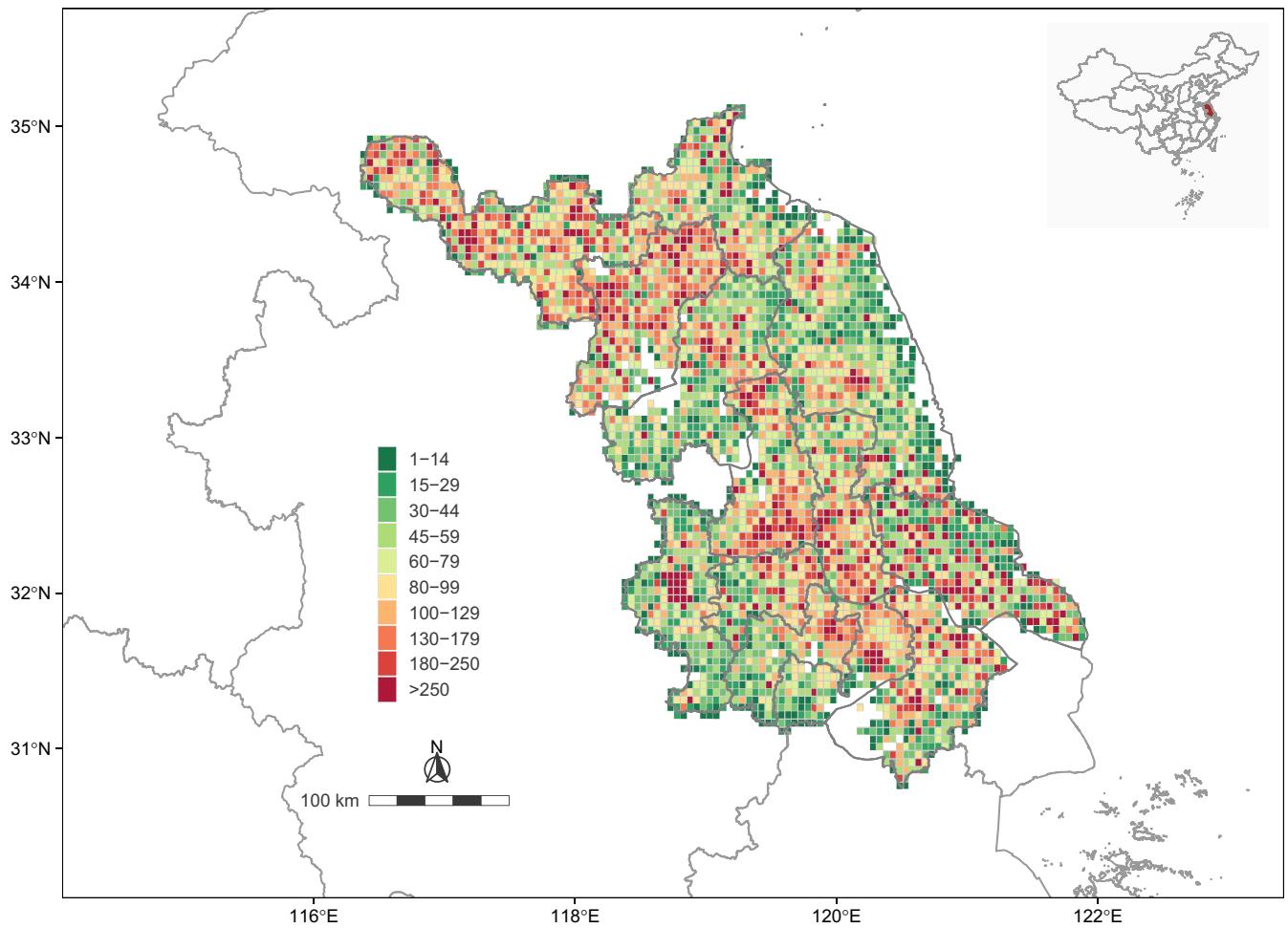


FIGURE 1 Spatial distribution of the study population in Jiangsu province, China, 2015–2019. The grids with different colors indicate the number of stroke deaths at a 5 km × 5 km spatial resolution

This design can control the effects of seasonality, day of week, long-term trends, and individual-level time-invariant confounders [29].

Exposure assessment

Daily gridded data (spatial resolution: 10 km × 10 km) on PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ concentrations were collected from the ChinaHighAirPollutants (CHAP) dataset, which has been known as a long-term, full-coverage, high-resolution, and high-quality near-surface air pollutants dataset in China. This dataset was generated from our proposed Space-Time Extra-Trees (STET) model combining with big data including ground measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations [30–33]. The cross-validation coefficient of determination (R^2) for PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ was 0.91, 0.88, 0.84, 0.84, 0.80, and 0.87, respectively. For each death, we extracted 24-h average PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and maximum 8-h moving average O₃ concentrations on each of the case and control days at the geocoded residential address. Single-day lag exposures (from lag 0 to lag 6 days) and moving average day lag

exposures (from lag 01 to lag 06 days) were used to examine the acute effects of ambient air pollution on stroke mortality. For example, lag 0 day exposure refers to the exposure on the same day of death; lag 1 day exposure was defined as the exposure on the previous day of death; and lag 01 day exposure was defined as the mean of exposure on the same day of death and 1 day prior. Because the association of exposure with stroke mortality may vary across different lag periods, we used the lag period with the strongest association for each air pollutant in the main analyses [34].

Covariates

Daily gridded data (spatial resolution: 0.0625° × 0.0625°) on meteorological conditions including 24-h average temperature (°C) and relative humidity (%) during 2015–2019 were obtained from the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0) [35,36]. We extracted meteorological condition values on the case and control days at the geocoded residential address for each death. Exposure to 24-h average

temperature and relative humidity were assessed by calculating the mean value on the same day of death and 3 days prior (lag 03 days) [37]. Because individual-level covariates (e.g., age, sex, race, genetics, lifestyles) were unlikely to change across the case and control days, we did not consider them as potential confounders in the analyses.

Statistical analysis

We employed conditional logistic regression models to quantify exposure-response associations. Percent change in odds ([odds ratio-1] × 100%) of mortality and its 95% confidence interval (CI) were estimated for each 10 µg/m³ increase of exposure to each air pollutant. All models were adjusted for exposure (lag 03 days) to temperature and relative humidity using a natural spline function with 6 degrees of freedom (df) and 3 df, respectively. In addition, we included exposure to each air pollutant as a natural cubic spline function (df = 3) in the model and plotted exposure-response curves to elucidate the shape of associations. To compare the association of air pollution with ischemic and hemorrhagic stroke mortality, we performed two-sample z-tests based on their point estimates β (ln odds ratio) and standard errors (SEs) [38]:

$$z = \frac{\beta_1 - \beta_2}{\sqrt{SE_1^2 + SE_2^2}}$$

To estimate the excess mortality of stroke associated with air pollution exposure, we calculated the excess fraction of mortality and number of excess deaths using the following formulas [39]:

$$\text{Excess fraction} = \frac{\sum_{i=1}^N 1 - \frac{1}{e^{\beta(C_i - C_0)}}}{N} \times 100\%$$

$$\text{Number of excess deaths} = \text{Excess fraction} \times N$$

where β is the point estimate for each air pollutant; N is the total number of stroke deaths; C_i is the pollutant concentration on each case day with concentration that exceeded C_0 ; C_0 is the counterfactual exposure distribution, which was defined as the theoretical minimum risk exposure level in calculating the overall excess mortality [40], or the referent pollutant concentration according to the World Health Organization (WHO) air quality guidelines [41] and the ambient air quality standards in China (Grade II in GB 3095-2012) [42] in calculating the avoidable excess mortality, which means the reducible excess mortality in the future if the current levels of exposure were reduced to a given air quality standard [43]. We used two-sample z-tests to examine the difference of excess fraction for mortality from ischemic and hemorrhagic stroke.

We conducted subgroup analyses by sex (male, female), age (<80, ≥80 years), and season (warm: April to November, cool: December to March) to examine the difference of the association of ambient air pollution with mortality from ischemic and hemorrhagic stroke and further compare the excess fraction of these two types of stroke.

Sensitivity analyses were conducted to examine the robustness of our results. First, we fitted two-pollutant models by including each of the other pollutants in the same model and used likelihood ratio tests to examine the difference between the nested single- and two-pollutant models. Second, we calculated the excess fraction of mortality from total, ischemic, and hemorrhagic stroke using the risk estimates of each air pollutant in lag 01 day. Third, we adjusted for exposure to two meteorological conditions using natural spline functions with 3 df in the analysis. All data analyses were performed using R (version 4.0.2). All statistical tests were two-sided, and a $p < 0.05$ was considered statistically significant.

RESULTS

During the study period, we identified a total of 412,567 stroke deaths, including 212,088 (51.4%) deaths from ischemic stroke and 157,056 (38.1%) deaths from hemorrhagic stroke. Of these death cases, 50.8% were male; 99.8% were Han race; 52.3% died at 80 years or older; 60.6% were married; and 51.2% died in warm season (Table 1).

Overall, the mean exposure to PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ was 54.8 µg/m³, 90.6 µg/m³, 18.2 µg/m³, 35.7 µg/m³, 0.91 mg/m³, and 100.4 µg/m³, respectively (Table 2). The spatial distributions of ambient PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ in Jiangsu province, China, during 2015–2019 is shown in Figure S1. Exposure to PM_{2.5}, PM₁₀, SO₂, NO₂, and CO was significantly and positively correlated, whereas O₃ exposure was negatively correlated with all other air pollutants (all pairwise p values <0.05; Figure S2).

Each 10 µg/m³ increase of exposure to PM_{2.5} (lag 04 days), PM₁₀ (lag 04 days), SO₂ (lag 06 days), NO₂ (lag 04 days), CO (lag 03 days), and O₃ (lag 02 days) was significantly associated with a 1.18% (95% CI: 0.96%, 1.40%), 0.79% (95% CI: 0.63%, 0.94%), 4.55% (95% CI: 3.50%, 5.62%), 2.18% (95% CI: 1.69%, 2.67%), 0.125% (95% CI: 0.103%, 0.148%), and 0.37% (95% CI: 0.18%, 0.57%) increase in odds of mortality from total stroke (all $p < 0.05$; Figure 2, Tables S1–S4). The percent change in odds of mortality from ischemic stroke was 1.44% (95% CI: 1.14%, 1.74%), 0.93% (95% CI: 0.72%, 1.14%), 5.55% (95% CI: 4.08%, 7.05%), 2.90% (95% CI: 2.22%, 3.60%), 0.148% (95% CI: 0.117%, 0.178%), and 0.54% (95% CI: 0.27%, 0.82%), respectively, which were all significantly higher than that from hemorrhagic stroke (percent change in odds: 0.74% [95% CI: 0.37%, 1.11%], 0.51% [95% CI: 0.26%, 0.77%], 3.11% [95% CI: 1.41%, 4.83%], 1.15% [95% CI: 0.35%, 1.95%], 0.090% [95% CI: 0.053%, 0.126%], and 0.10% [95% CI: -0.22%, 0.41%]; all p for difference <0.05; Table S4). All these exposure-response associations were almost linear, and there were no potential risk thresholds at low exposure levels (Figure S3). In two-pollutant models, the association of exposure to all air pollutants with mortality from total stroke and ischemic stroke, as well as exposure to PM_{2.5}, PM₁₀, SO₂, and CO with mortality from hemorrhagic stroke, remained similar or became slightly weaker, while the association of exposure to NO₂ with hemorrhagic stroke mortality decreased significantly (Table S5).

TABLE 1 Characteristics of the study population in Jiangsu province, China, 2015–2019

Characteristic	Total stroke	Type of stroke	
		Ischemic stroke	Hemorrhagic stroke
Deaths (case days), n (%)	412,567 (100)	212,088 (51.4)	157,056 (38.1)
Control days, n	1,400,547	719,766	533,488
Age (years), %			
Mean (SD)	78.2 (11.6)	80.5 (9.6)	74.2 (13.2)
Median (IQR)	80.6 (13.8)	82.0 (11.4)	76.9 (17.8)
<80	196,608 (47.7)	86,172 (40.6)	94,495 (60.2)
≥80	215,959 (52.3)	125,916 (59.4)	62,561 (39.8)
Sex, n (%)			
Male	209,387 (50.8)	103,192 (48.7)	86,103 (54.8)
Female	203,180 (49.2)	108,896 (51.3)	70,953 (45.2)
Race, n (%)			
Han	411,675 (99.8)	211,574 (99.8)	156,734 (99.8)
Other	892 (0.2)	514 (0.2)	322 (0.2)
Marital status, n (%)			
Married	250,135 (60.6)	124,592 (58.7)	105,031 (66.9)
Widowed	147,223 (35.7)	81,041 (38.2)	45,102 (28.7)
Unmarried	10,654 (2.6)	4390 (2.1)	4850 (3.1)
Divorced	3301 (0.8)	1351 (0.6)	1635 (1.0)
Unknown	1254 (0.3)	714 (0.3)	438 (0.3)
Season at death ^a , n (%)			
Warm	211,136 (51.2)	106,208 (50.1)	83,176 (53.0)
Cool	201,431 (48.8)	105,880 (49.9)	73,880 (47.0)

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

^aWarm season: April to November; cool season: December to March.

Overall, the excess fraction associated with exposure to PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ was 5.57%, 5.34%, 6.78%, 6.52%, 8.15%, and 3.29%, respectively, corresponding to 22,980, 22,021, 27,983, 26,911, 33,631, and 13,590 deaths (Figure 3 and Table S6). Reducing daily air pollutant concentrations to the WHO guideline levels (24-h average PM_{2.5}: 25 µg/m³; 24-h average PM₁₀: 50 µg/m³; 24-h average SO₂: 20 µg/m³; maximum 8-h moving average O₃: 100 µg/m³), the excess fraction associated with exposure to PM_{2.5}, PM₁₀, SO₂, and O₃ remained 3.41%, 3.16%, 1.23%, and 0.59%, respectively; while the excess fraction was 0.50%, 0.15%, 0%, 0.003%, 0%, and 0.06%, respectively, if the PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃ concentrations were reduced to the standard levels in China (24-h average PM_{2.5}: 75 µg/m³; 24-h average PM₁₀: 150 µg/m³; 24-h average SO₂: 150 µg/m³; 24-h average NO₂: 80 µg/m³; 24-h average CO: 4 mg/m³; maximum 8-h moving average O₃: 160 µg/m³). For each air pollutant, the overall excess fraction of mortality from ischemic stroke was significantly higher than that from hemorrhagic stroke (all *p* < 0.05).

The results of subgroup analyses by sex, age, and season are shown in Tables 3 and 4, and Table S7. Overall, stronger association for short-term exposure to air pollutants was observed for ischemic stroke mortality compared with hemorrhagic stroke mortality

across sex, age, and season, though some of the associations became insignificant. Similarly, the excess mortality of ischemic stroke associated with air pollutants exposure was generally higher than that of mortality from hemorrhagic stroke. Based on the risk estimates in lag 01 day, the associations and excess fractions of ischemic stroke mortality were significantly higher than those of hemorrhagic stroke mortality for all air pollutants except SO₂ and O₃ (Table S8). Adjusting for both temperature and relative humidity using natural splines with 3 *df* in the analysis yielded similar results (Figures S4–S5).

DISCUSSION

In this large case-crossover study, we found significantly stronger association of short-term exposure to ambient air pollution with mortality from ischemic stroke than that from hemorrhagic stroke. An estimated 6.90%, 6.48%, 8.21%, 8.61%, 9.67%, and 4.76% of deaths from ischemic stroke were associated with short-term exposure to PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃, respectively, which was significantly higher than that from hemorrhagic stroke (excess fraction: 3.49%, 3.48%, 4.69%, 3.48%, 5.86%, and 0.88%). The

TABLE 2 Distribution of exposure to ambient air pollution and meteorological conditions on the day of stroke death in Jiangsu province, China, 2015–2019

Parameter	Mean	SD	Min	Percentile					
				5th	25th	50th	75th	95th	Max
Total stroke									
PM _{2.5} , µg/m ³	54.8	31.8	3.2	19.7	32.4	46.7	68.6	118.2	316.5
PM ₁₀ , µg/m ³	90.6	45.2	6.1	36.6	57.3	81.4	113.5	177.5	729.7
SO ₂ , µg/m ³	18.2	10.5	1.8	6.7	11.0	15.7	22.5	38.2	153.3
NO ₂ , µg/m ³	35.7	14.8	3.2	17.2	25.0	32.7	43.5	63.8	145.4
CO, mg/m ³	0.91	0.31	0.20	0.53	0.69	0.84	1.06	1.52	3.67
O ₃ , µg/m ³	100.4	42.2	4.5	45.4	67.6	92.2	128.0	179.2	332.4
Temperature, °C	14.8	9.4	-7.5	1.2	6.2	14.6	23.1	29.6	35.8
Relative humidity, %	73.5	11.1	24.7	52.9	66.4	74.9	82.1	89.1	95.7
Ischemic stroke									
PM _{2.5} , µg/m ³	56.0	32.5	3.3	20.0	33.0	47.8	70.2	120.8	316.0
PM ₁₀ , µg/m ³	92.8	46.1	6.6	37.3	58.8	83.6	116.3	181.2	725.6
SO ₂ , µg/m ³	18.3	10.8	1.9	6.7	10.9	15.7	22.6	39.0	131.3
NO ₂ , µg/m ³	35.8	14.7	3.2	17.3	25.1	32.9	43.8	63.6	145.4
CO, mg/m ³	0.92	0.32	0.22	0.54	0.70	0.85	1.07	1.55	3.67
O ₃ , µg/m ³	100.2	42.6	4.5	45.0	66.9	91.7	128.4	179.5	310.8
Temperature, °C	14.6	9.5	-7.5	0.9	5.9	14.2	23.0	29.6	35.8
Relative humidity, %	73.0	11.3	25.8	52.2	65.7	74.4	81.8	88.9	95.7
Hemorrhagic stroke									
PM _{2.5} , µg/m ³	53.9	31.2	3.2	19.6	32.0	46.0	67.2	116.2	316.5
PM ₁₀ , µg/m ³	89.6	44.8	6.1	36.3	56.6	80.3	112.1	175.9	729.7
SO ₂ , µg/m ³	18.1	10.5	1.8	6.7	10.9	15.7	22.4	37.8	128.7
NO ₂ , µg/m ³	35.4	14.7	4.0	17.1	24.8	32.5	43.1	63.5	129.8
CO, mg/m ³	0.91	0.31	0.20	0.53	0.69	0.84	1.05	1.51	3.47
O ₃ , µg/m ³	100.9	42.0	4.7	45.8	68.3	93.2	128.4	178.8	332.4
Temperature, °C	15.1	9.3	-7.0	1.5	6.6	15.2	23.2	29.5	35.8
Relative humidity, %	73.7	11.0	24.7	53.3	66.7	75.1	82.2	89.2	95.7

Abbreviations: CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM₁₀, particulate matter with an aerodynamic diameter ≤10 µm; PM_{2.5}, particulate matter with an aerodynamic diameter ≤2.5 µm; SD, standard deviation; SO₂, sulfur dioxide.

differences in these associations and excess fractions generally remained across sex, age, and season. We estimated that reducing pollutant exposures to the WHO guideline levels could help avoid up to 4.30% and 2.11% of ischemic stroke deaths and hemorrhagic stroke deaths, respectively.

Consistent with results from most previous studies, we found that short-term exposure to ambient air pollution was associated with increased risk of total stroke mortality [3–5,16,17,20,21]. In addition, we found significant associations for mortality with both ischemic and hemorrhagic stroke, a finding that was also reported by three Chinese studies in Guangdong province (PM_{2.5} and PM₁₀), Beijing (PM_{2.5}), and Shanghai (SO₂ and NO₂) [12,15,25]; in contrast, the other studies in Japan, China, and Korea did not identify a significant association of exposure to certain air pollutants with ischemic and/or hemorrhagic stroke mortality [10,11,26,27]. The inconsistency of these findings may be due to several reasons, including: (1)

insufficient sample size especially for hemorrhagic stroke mortality; (2) heterogeneous study population; (3) various air pollution exposure levels; and (4) different strategies for exposure assessment.

This is the first study to systematically investigate the excess mortality of ischemic and hemorrhagic stroke associated with short-term exposure to ambient air pollution. We found novel and consistent evidence that the excess mortality of both ischemic and hemorrhagic stroke was substantial, and that the excess mortality of ischemic stroke was much higher than that from hemorrhagic stroke. Consistent with the findings that the association between air pollution and mortality from ischemic stroke was stronger than that from hemorrhagic stroke, this result provided further evidence that ambient air pollution causes considerably greater acute adverse effects on mortality from ischemic stroke. Given the heavy disease burden of mortality from stroke, these findings highlight the urgent need for both policy practitioners and individuals to take effective

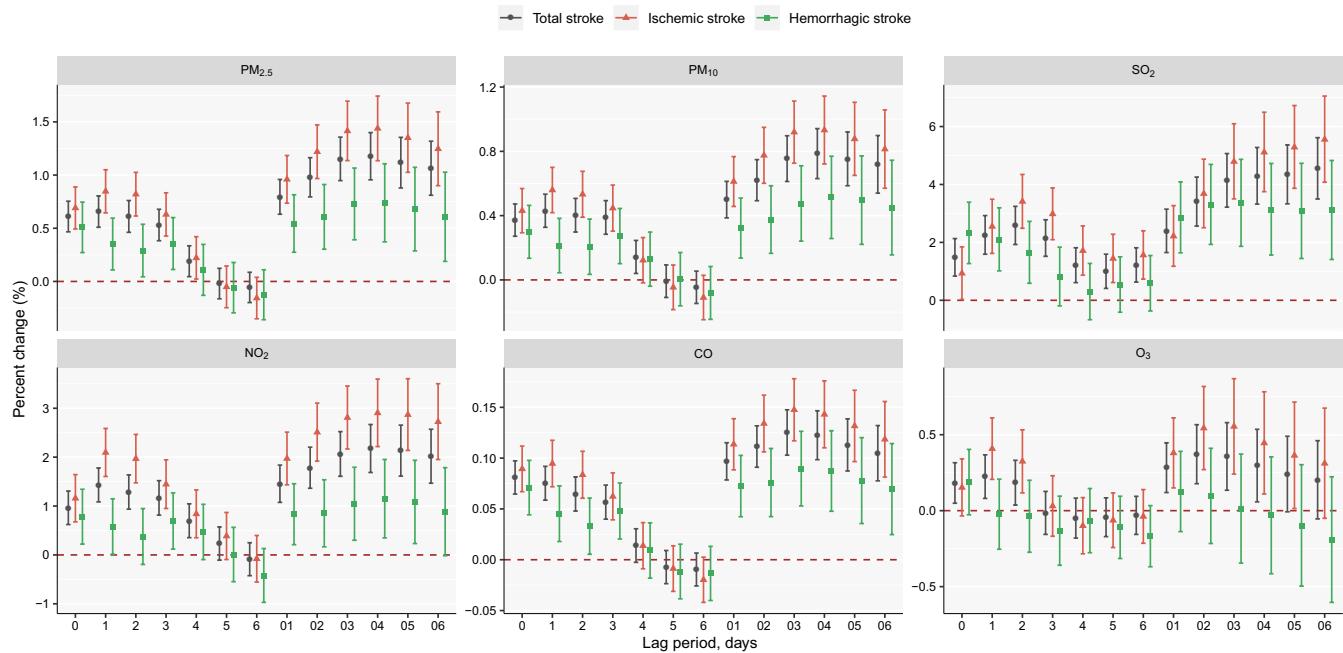


FIGURE 2 Percent change (95% confidence interval) in odds of mortality from total stroke, ischemic stroke, and hemorrhagic stroke associated with each $10 \mu\text{g}/\text{m}^3$ increase of exposure to ambient air pollution. CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$; PM₁₀, particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$; SO₂, sulfur dioxide

measures to reduce ambient air pollutant exposures, especially in preventing premature deaths from ischemic stroke. In addition, our results provide useful clues for clinical practitioners to improve the treatment of specific types of stroke by taking into consideration the effects of air pollution.

To date, the underlying biological mechanisms on how short-term exposure to air pollution triggers mortality from ischemic and hemorrhagic stroke remain unclear. It has been proposed that inhaled air pollutants can acutely trigger local and systemic inflammation [44], endothelial injury [45], alterations in cerebrovascular hemodynamics [46], and enhance blood coagulation and plasma viscosity, which may further lead to atherosclerosis [47], thrombus formation [48] and finally trigger ischemic stroke death, especially among patients with preexisting ischemic cardiovascular diseases (e.g., myocardial infarction) [49]. For hemorrhagic stroke, air pollution can lead to direct ischemic damage to blood vessels, vasoconstriction, or hypertension and induce the rupture of atherosclerotic plaques [10], and trigger death. Note that the existing proposed mechanisms by which air pollutants might trigger hemorrhagic stroke were mainly related to the development and progression of vascular ischemic, which plays a central role in the occurrence of ischemic stroke [23]. In addition, compared with ischemic stroke, the much higher case fatality rate of hemorrhagic stroke might obscure the acute adverse effects of ambient air pollution and could possibly be one of the reasons for the observed weaker effects on hemorrhagic stroke. Further studies are needed to clarify the potential biological mechanisms of different associations between air pollution and mortality from ischemic and hemorrhagic stroke.

One unique strength of our study is the large sample size, which provided us with sufficient statistical power to estimate the association for mortality from specific types of stroke separately. Note that the association for mortality from hemorrhagic stroke in our study had wider 95% CIs, which may partly explain why most previous studies reported null associations for hemorrhagic stroke mortality. Second, because China was experiencing severe air pollution problems during the study period, the wide range of air pollutant concentrations in Jiangsu province offered us unique opportunities to systematically elucidate the exposure-response association between short-term exposure to air pollution and stroke mortality. Third, we employed a case-crossover design to take advantage of individual-level exposure assessment based on the residential address and validated gridded air pollution datasets with a reasonably high spatial resolution ($10 \text{ km} \times 10 \text{ km}$), which could provide more accurate exposure assessment in comparison with that in previous studies. Previous time-series studies typically used the mean daily air pollutant concentration at all monitoring stations in a city as the city-wide exposure level on a given date, while previous case-crossover studies used city-wide exposure or daily concentration at the nearest monitoring station of residential address. All these monitoring station-based exposure assessments relied on a sufficiently short distance (e.g., within 25 km) between residential addresses and monitoring stations. Because the gridded datasets had a full coverage of Jiangsu province and did not have missing values, we were able to include all individuals who lived in Jiangsu province in the analysis.

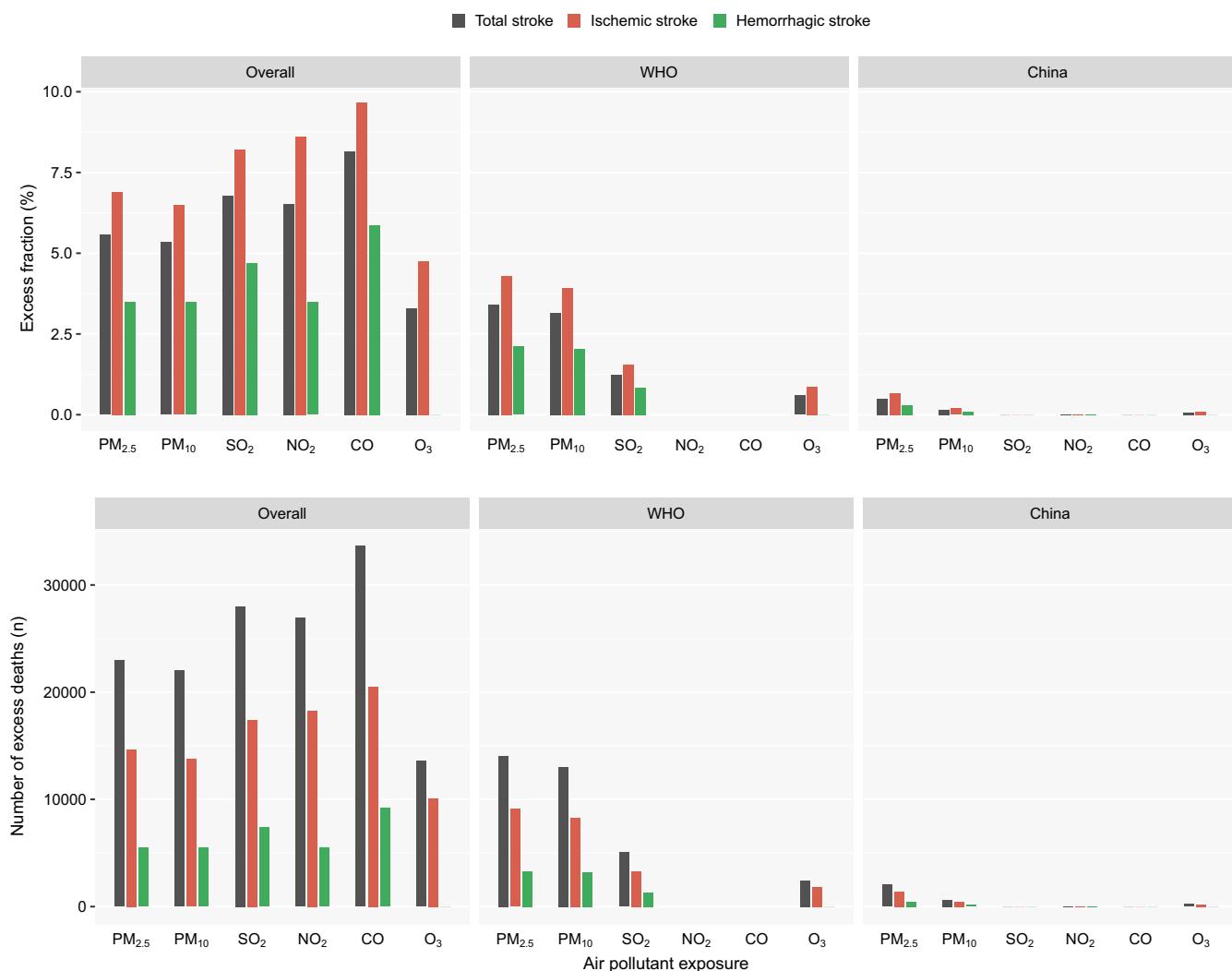


FIGURE 3 Estimated excess fraction and number of excess deaths from total stroke, ischemic stroke and hemorrhagic stroke associated with short-term exposure to ambient air pollution in Jiangsu province, China, 2015–2019. For each air pollutant in each panel, the three bars from left to right represent the estimated excess fraction or number of excess deaths from total stroke, ischemic stroke, and hemorrhagic stroke, respectively. CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$; PM₁₀, particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$; SO₂, sulfur dioxide; WHO, World Health Organization

Our study also has some limitations. First, as in most previous studies on this topic, we were unable to measure actual personal exposure to ambient air pollution directly but estimated individual-level air pollutant exposure by extracting air pollutant data from a validated gridded air quality dataset. Because we did not have data on personal activity (e.g., staying indoors, wearing masks, using air purifiers, and/or air conditioning), exposure misclassification might have been introduced; however, the exposure misclassification tended to be nondifferential and the estimated associations were unlikely to be significantly biased [50]. Second, although the case-crossover study design helped us account for time-invariant individual-level confounders, and we adjusted for some time-variant variables (i.e., meteorological conditions) in the model, residual or unmeasured confounding was still possible. Third, because short-term exposure to most air pollutants were highly or moderately correlated, we were unable to adequately conduct multi-pollutant

models and distinguish their respective adverse effects on stroke mortality. Fourth, due to lack of data, we were unable to account for influenza epidemics, which could possibly induce inaccurate estimates. Fifth, we did not have information on the number of vascular risk factors and therefore were unable to adjust them in this analysis. However, this was unlikely to significantly confound our estimates because the number of vascular risk factors would not materially change within a month. Finally, this study was conducted in a single province in China. Although the base population was up to 84.7 million, caution should be exercised in generalizing our results to other populations.

In conclusion, we found that short-term exposure to ambient air pollution was associated with increased risk of mortality from both ischemic and hemorrhagic stroke, which posed a considerable excess mortality. In addition, our results suggest that air pollution exposure causes substantially greater adverse effects on mortality

TABLE 3 Percent change (95% confidence interval) in odds of mortality from ischemic and hemorrhagic stroke associated with each $10 \mu\text{g}/\text{m}^3$ increase in exposure to ambient air pollution by sex, age, and season subgroups

Subgroup	Percent change, % (95% CI)				
	PM _{2.5}	PM ₁₀	SO ₂	NO ₂	CO
Sex, male					O ₃
Ischemic stroke	1.25 (0.82, 1.68)	0.78 (0.48, 1.08)	5.69 (3.59, 7.84) ^a	2.62 (1.64, 3.62) ^a	0.136 (0.093, 0.180)
Hemorrhagic stroke	0.61 (0.12, 1.10)	0.46 (0.11, 0.80)	1.78 (-0.49, 4.09)	0.79 (-0.28, 1.87)	0.094 (0.045, 0.144)
Sex, female					
Ischemic stroke	1.62 (1.19, 2.05) ^a	1.08 (0.78, 1.37) ^a	5.39 (3.33, 7.50)	3.16 (2.20, 4.13) ^a	0.159 (0.116, 0.201) ^a
Hemorrhagic stroke	0.90 (0.35, 1.45)	0.58 (0.20, 0.97)	4.68 (2.14, 7.29)	1.59 (0.39, 2.80)	0.084 (0.029, 0.139)
Age, <80 years					
Ischemic stroke	1.39 (0.91, 1.87) ^a	0.97 (0.63, 1.30) ^a	3.77 (1.50, 6.08)	2.61 (1.50, 3.74) ^a	0.156 (0.108, 0.205) ^a
Hemorrhagic stroke	0.52 (0.05, 0.997)	0.35 (0.02, 0.68)	2.64 (0.44, 4.88)	0.59 (-0.45, 1.64)	0.063 (0.015, 0.111)
Age, ≥80 years					
Ischemic stroke	1.47 (1.08, 1.87)	0.91 (0.64, 1.19)	6.84 (4.89, 8.82)	3.11 (2.23, 3.99)	0.142 (0.103, 0.182)
Hemorrhagic stroke	1.06 (0.48, 1.64)	0.76 (0.35, 1.17)	3.74 (1.09, 6.46)	1.94 (0.69, 3.19)	0.128 (0.071, 0.186)
Season, warm					
Ischemic stroke	2.41 (1.68, 3.15) ^a	1.30 (0.88, 1.72) ^a	7.38 (4.14, 10.73) ^a	4.30 (2.74, 5.89) ^a	0.21 (0.14, 0.28) ^a
Hemorrhagic stroke	0.06 (-0.75, 0.88)	0.26 (-0.23, 0.75)	0.87 (-2.47, 4.32)	-0.02 (-1.68, 1.67)	0.05 (-0.02, 0.13)
Season, cool					
Ischemic stroke	1.15 (0.81, 1.49)	0.76 (0.51, 1.01)	5.50 (3.81, 7.22)	2.63 (1.86, 3.41)	0.12 (0.09, 0.15)
Hemorrhagic stroke	0.86 (0.44, 1.27)	0.61 (0.31, 0.92)	4.77 (2.75, 6.82)	1.71 (0.79, 2.64)	0.09 (0.05, 0.14)

Abbreviations: CI, confidence interval; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM₁₀, particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$; SO₂, sulfur dioxide.

^a $p < 0.05$ compared with the percent change in odds of mortality from hemorrhagic stroke.

TABLE 4 Excess fraction of mortality from ischemic and hemorrhagic stroke associated with short-term exposure to ambient air pollution by sex, age, and season subgroups

Subgroup	Excess fraction, % (95% CI)					O_3
	$\text{PM}_{2.5}$	PM_{10}	SO_2	NO_2	CO	
Sex, male						
Ischemic stroke	6.07 (4.04, 8.05) ^a	5.51 (3.45, 7.52)	8.44 (5.49, 11.27) ^a	7.84 (5.01, 10.57) ^a	8.99 (6.22, 11.66)	2.77 (-0.72, 6.11)
Hemorrhagic stroke	2.89 (0.56, 5.14)	3.10 (0.77, 5.36)	2.73 (-0.77, 6.08)	2.41 (-0.89, 5.59)	6.16 (2.99, 9.22)	1.18 (-2.69, 4.89)
Sex, female						
Ischemic stroke	7.68 (5.75, 9.57) ^a	7.38 (5.42, 9.29) ^a	7.95 (5.06, 10.72)	9.31 (6.62, 11.92) ^a	10.31 (7.65, 12.88) ^a	6.63 (3.40, 9.73) ^a
Hemorrhagic stroke	4.21 (1.67, 6.66)	3.94 (1.39, 6.41)	6.93 (3.29, 10.38)	4.76 (1.21, 8.17)	5.48 (1.93, 8.88)	0.45 (-3.88, 4.58)
Age, <80 years						
Ischemic stroke	6.71 (4.48, 8.88) ^a	6.78 (4.52, 8.96) ^a	5.77 (2.39, 9.00)	7.70 (4.53, 10.75) ^a	10.23 (7.20, 13.15) ^a	4.19 (0.36, 7.85) ^a
Hemorrhagic stroke	2.47 (0.23, 4.65)	2.41 (0.16, 4.59)	3.98 (0.69, 7.12)	1.79 (-1.41, 4.88)	4.16 (1.04, 7.17)	-0.87 (-4.68, 2.77)
Age, ≥80 years						
Ischemic stroke	7.04 (5.24, 8.80)	6.29 (4.46, 8.08)	9.86 (7.26, 12.36)	9.26 (6.78, 11.65)	9.33 (6.86, 11.73)	5.09 (2.07, 8.00)
Hemorrhagic stroke	4.98 (2.32, 7.55)	5.09 (2.42, 7.67)	5.66 (1.72, 9.39)	5.84 (2.15, 9.37)	8.30 (4.68, 11.77)	3.40 (-1.03, 7.60)
Season, warm						
Ischemic stroke	7.77 (5.51, 9.96) ^a	6.53 (4.48, 8.51) ^a	8.75 (5.11, 12.22) ^a	9.40 (6.16, 12.52) ^a	10.62 (7.37, 13.74) ^a	7.47 (3.89, 10.91) ^a
Hemorrhagic stroke	0.20 (-2.41, 2.73)	1.32 (-1.22, 3.77)	1.14 (-3.39, 5.42)	-0.06 (-4.32, 4.01)	2.84 (-1.23, 6.73)	-1.84 (-6.34, 2.46)
Season, cool						
Ischemic stroke	7.32 (5.23, 9.35)	6.73 (4.60, 8.81)	9.49 (6.76, 12.11)	9.21 (6.62, 11.71)	9.47 (6.83, 12.03)	-6.60 (-10.60, -2.76)
Hemorrhagic stroke	5.19 (2.73, 7.58)	5.27 (2.69, 7.78)	8.24 (4.91, 11.41)	6.26 (2.97, 9.44)	7.40 (4.11, 10.56)	-3.97 (-8.74, 0.57)

Abbreviations: CI, confidence interval; CO, carbon monoxide; NO_2 , nitrogen dioxide; O_3 , ozone; PM_{10} , particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$; SO_2 , sulfur dioxide.

^a $p < 0.05$ compared with excess fraction of mortality from hemorrhagic stroke.

from ischemic stroke than that from hemorrhagic stroke. These findings highlight the need for general population, clinical, and policy practitioners to take effective measures to reduce air pollution exposure to prevent stroke mortality, especially for individuals with higher risk of ischemic stroke. Further studies are needed to confirm our findings in other populations and to elucidate the underlying biological mechanisms.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (grants 81773479 and 91743205), the Hubei Provincial Health Commission in China (grant WJ2019Z016), and the Jiangsu Social Development Project (grant BE2018745).

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Ruijun Xu: Formal analysis (equal); Methodology (equal); Visualization (equal); Writing – original draft (lead); Writing – review & editing (lead). **Qingqing Wang:** Formal analysis (equal); Methodology (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Jing Wei:** Data curation (equal); Formal analysis (equal); Methodology (equal); Validation (equal). **Wenfeng Lu:** Writing – review & editing (supporting). **Rui Wang:** Writing – review & editing (supporting). **Tingting Liu:** Writing – review & editing (supporting). **Yaqi Wang:** Writing – review & editing (supporting). **Zhaoyu Fan:** Writing – review & editing (supporting). **Yingxin Li:** Writing – review & editing (supporting). **Luxi Xu:** Writing – review & editing (supporting). **Chunxiang Shi:** Data curation (equal). **Guo Li:** Writing – review & editing (supporting). **Gongbo Chen:** Writing – review & editing (supporting). **Lan Zhang:** Writing – review & editing (supporting). **Yun Zhou:** Writing – review & editing (supporting). **Yuewei Liu:** Conceptualization (lead); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Hong Sun:** Conceptualization (supporting); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (lead); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY STATEMENT

The air pollution data were obtained from the CHAP dataset, which was available at <https://weijing-rs.github.io/product.html>. The meteorological condition data were obtained from the CLDAS (version 2.0), which was available at the National Meteorological Information Center in China (<http://data.cma.cn>). The surveillance data on mortality from stroke used in this study are not publicly available.

ORCID

Yuewei Liu  <https://orcid.org/0000-0001-5970-4262>

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Xu R, Wang Q, Wei J, et al. Association of short-term exposure to ambient air pollution with mortality from ischemic and hemorrhagic stroke. *Eur J Neurol*. 2022;00:1-12. doi:[10.1111/ene.15343](https://doi.org/10.1111/ene.15343)