## **ORIGINAL CONTRIBUTION**

# Hourly Air Pollution Exposure and Emergency Hospital Admissions for Stroke: A Multicenter Case-Crossover Study

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**BACKGROUND:** Daily exposure to ambient air pollution is associated with stroke morbidity and mortality; however, the association between hourly exposure to air pollutants and risk of emergency hospital admissions for stroke and its subtypes remains relatively unexplored.

**METHODS**: We obtained hourly concentrations of fine particulate matter ( $PM_{2.5}$ ), respirable particulate matter ( $PM_{10}$ ), nitrogen dioxide ( $NO_2$ ), sulfur dioxide ( $SO_2$ ), ozone ( $O_3$ ), and carbon monoxide (CO) from the China National Environmental Monitoring Center. We conducted a time-stratified case-crossover study among 86 635 emergency hospital admissions for stroke across 10 hospitals in 3 cities (Jinhua, Hangzhou, and Zhoushan) in Zhejiang province, China, between January 1, 2016 and December 31, 2021. Using a conditional logistic regression combined with a distributed lag linear model, we estimated the association between hourly exposure to multiple air pollutants and risk of emergency hospital admissions for total stroke, ischemic stroke, hemorrhagic stroke, and undetermined type.

**RESULTS:** Hourly exposure to  $PM_{2.5}$ ,  $PM_{10}$ ,  $NO_{2}$ , and  $SO_{2}$  was associated with an increased risk of hospital admissions for total stroke and ischemic stroke. The associations were most pronounced during the concurrent hour of exposure and lasted for  $\approx 2$  hours. We found that the risk was more pronounced among male patients or those aged <65 years old.

**CONCLUSIONS:** Our findings suggest that exposure to  $PM_{2.5'}$ ,  $PM_{10'}$ ,  $NO_{2'}$  and  $SO_{2'}$ , but not CO and  $O_{3'}$  is associated with emergency hospital admissions for total stroke or ischemic stroke shortly after exposure. Implementing targeted pollution emission reduction measures may have significant public health implications in controlling and reducing the burden of stroke.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

Key Words: air pollutants 
sichemic stroke 
morbidity 
nitrogen oxide 
particulate matter

Stroke is a critical global health challenge, ranking among the foremost causes of death. In 2019 alone, there were  $\approx 6.55$  million deaths attributed to stroke, alongside an estimated 143 million disability-adjusted life years lost on a global level. Ischemic stroke and hemorrhagic stroke, the 2 primary types of stroke, accounted for 3.29 and 3.26 million deaths, respectively.<sup>1</sup> The global

burden of stroke (the absolute number of cases) is increasing, particularly in low- and middle-income countries.<sup>2</sup> In China, stroke has been responsible for  $\approx 2.19$  million premature deaths,<sup>3</sup> with a notable impact on the younger and middle-aged adults.<sup>45</sup>

Previous studies suggested that ambient air pollution might play an important role in stroke morbidity

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## Nonstandard Abbreviations and Acronyms

CO ICD-10	carbon monoxide International Classification of Diseases, 10th Revision
NO <sub>2</sub>	nitrogen dioxide
O <sub>3</sub>	ozone
PM <sub>2.5</sub>	fine particulate matter
PM <sub>10</sub>	respirable particulate matter
SO <sub>2</sub>	sulfur dioxide

and mortality.<sup>1,6-11</sup> However, many of these studies have predominantly examined stroke as a whole or investigated the association between daily exposure to air pollution and risk of stroke,<sup>6,12,13</sup> which may be susceptible to ecological fallacy and temporal misclassification of exposures. To overcome these challenges, studies at an hourly level are necessary to better understand the relationship between air pollution exposure and stroke hospital admissions.

The evidence about the association between hourly air pollution exposure and the risk of stroke is limited. One study conducted in Barcelona among 2742 patients with stroke did not find a relationship between hourly PM<sub>25</sub> exposure and ischemic stroke symptom onset over 0 to 23, 24 to 47, and 48 to 72 hours after exposure.14 To our knowledge, there is a scarcity of studies that have examined the associations between hourly exposure to air pollution and specific stroke subtypes, especially in regions with moderate to high levels of air pollution. In China, although air pollution levels have shown some improvement in recent years, the overall average levels of air pollution remain higher than the air quality guidelines set by the World Health Organization. Therefore, it is crucial to investigate the association between hourly exposure to air pollution and the risk of stroke in China.

Accordingly, we aimed to examine the association between hourly exposure to multiple air pollutants and the risk of stroke and its subtypes among 86 635 emergency hospital admissions for stroke across 10 hospitals in 3 cities (Jinhua, Hangzhou, and Zhoushan) in Zhejiang province, China. We also examined whether the association was varied by age, sex, season, city, and time of admission.

## **METHODS**

## **Study Population and Health Outcome**

Emergency care delivered in Zhejiang is typically provided through a network of public hospitals, clinics, and specialized emergency medical centers. Emergency care is covered under China's basic public health insurance schemes, but there could still be out-of-pocket expenses for certain treatments or services. We obtained hourly emergency hospital admissions for stroke across 10 hospitals located in 3 cities (Jinhua, Hangzhou, and Zhoushan) within Zhejiang province from January 1, 2016 to December 31, 2021. We used International Classification of Diseases, 10th Revision (ICD-10) codes to identify cases of stroke (ICD-10: I60-I61 and I63-I64) and stroke subtypes, including ischemic stroke (ICD-10: I63), hemorrhagic stroke (ICD-10: I61), and undetermined type (ICD-10: I60 and I64). The data that support the findings of this study are available from the corresponding author on reasonable request. The study was approved by the institutional review committee of the Zhejiang Provincial Center for Disease Control and Prevention (approval number AF/SC-06/01.0), and informed consent was waived. This study complies with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline (Supplemental Material).

## **Environmental Assessment**

We collected hourly concentrations of fine particulate matter (PM<sub>25</sub>), respirable particulate matter (PM<sub>10</sub>), nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), ozone (O<sub>3</sub>), and carbon monoxide (CO) between January 1, 2016 and December 31, 2021 from the China National Environmental Monitoring Center. We obtained hourly ambient temperature (°C) and relative humidity (%) from the China Meteorological Data Service Center (http://data.cma.cn/). We geocoded the latitude and longitude coordinates of each hospital address and matched them with the nearest monitoring station. In case, where the air pollution data from the nearest station were missing during the specified time period, we obtained the air pollutant data from the second nearest station in the same hours as a replacement.<sup>15</sup> The median distance between the final included monitoring stations and the hospitals was 3.9 km. To control for the potential impact of outliers in the analysis, we removed the highest and lowest 0.1% of hourly concentrations of air pollutants.16

## **Statistical Analyses**

We used a time-stratified case-crossover design to estimate the association between hourly exposure to multiple ambient air pollutants and the risk of emergency hospital admissions for stroke.<sup>17,18</sup> For each patient with stroke, we defined the case period as the specific hour when the patient admitted to the hospital. To select appropriate control periods, we matched the case period by the same hour of the day, day of the week, month, and year.<sup>18</sup> For example, a patient admitted to emergency room for stroke at 2:00 PM on Tuesday, March 15, 2016 would have the index hour of the case period defined as Tuesday, March 15, 2016. The control index hours would be 2:00 PM on all other Tuesdays in March 2016 (specifically, March 1, 8, 22, and 29). By implementing this study design, it can control for seasonality, long-term trends, and potential individual-level confounders.<sup>17</sup>

We used conditional logistic regression models to estimate the associations of exposure to hourly air pollutants with the risk of stroke, ischemic stroke, hemorrhagic stroke, and undetermined type.<sup>19</sup> In the models, we adjusted for public holiday, hourly ambient temperature using a natural cubic spline with 6 *df*, and hourly relative humidity using a natural cubic spline with 3 *df*. We used distributed lag linear modelling framework to fit both linear exposure-response function and nonlinear lagresponse function for air pollutants.<sup>16,20</sup> Based on our preliminary analysis, we selected a maximum lag of 48 hours. To model the lag-response function, we used a natural cubic spline function with 3 internal knots placed at equal intervals on the log scale of lags up to 48 hours. To explore both the acute and delayed effects of air pollutant, we considered lag periods of <1 day (eg, 0–2, 3–12, 13–24, and 0–12 hours), and daily periods, including day 1 (ie, 0–24 hours), day 2 (ie, 25–48 hours), and 0–2 days (ie, 0–48 hours). We expressed results as the percentage excess risk (%) increase in stroke associated with an interquartile range or 10  $\mu$ g/m<sup>3</sup> increase in PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, and 1 mg/m<sup>3</sup> increase in CO.

To examine the exposure-response relationship between hourly exposure to air pollutants and the risk of hospital admissions for stroke, we used a natural cubic spline with 3 *df* to model the exposure-response function and included the same covariates as the main model above.

To identify susceptible subpopulations, we conducted stratified analyses by sex (male versus female), age (<65 versus  $\geq$ 65 years), season (warm [April–September] versus cold [October–March]), city (Jinhua, Hangzhou, and Zhoushan), and time of admission (8 AM–8 PM versus 8 PM–8 AM in the next day). We used 2-sample Z tests to assess whether the differences between subgroups were statistically significant based on a *P*<0.05.

We performed 2 main sensitivity analyses to confirm the robustness of our results. First, to assess the potential confounding of copollutant, we constructed 2-pollutant models. Second, we varied the number of knots in the natural cubic spline of the lag-response function and used 2 and 4 internal knots placed at equal intervals on the log scale of lags up to 48 hours.

We conducted all analyses in R software (version 4.2.2) with the dlnm and survival packages.

## RESULTS

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A total of 86 635 emergency hospital admissions for stroke were documented during the study period, of which 79 478 were ischemic stroke, 3122 were hemorrhagic stroke, and 4035 were undetermined type (Tables S1 and S2; Figure S1). Patients were more likely to be aged >65 years (63.99%), male (53.13%), resided in the Zhoushan area (57.65%), and admitted to hospitals more frequently during the warm season (51.50%) and daytime hours (92.62%; Table 1).

The median distance between the selected hospitals and the air pollutant and meteorologic monitoring station was 3.9 and 17.5 km, respectively (Figure S2). Levels of hourly air pollutants and meteorologic factors are shown in Table S3. The Spearman correlations between air pollutants were generally low to moderate (r<0.5) during both warm and cold seasons (Table S4).

Generally, the association between hourly exposure to air pollutants and risk of hospital admissions for stroke was most pronounced during the concurrent hour of exposure and gradually attenuated over a period of 3 hours. Compared with the other studied lag periods, the associations were strongest at lag 0 to 2 hours, and thus we reported results using a lag period of 0 to 2 hours as the main results (Figure 1).

Exposure to PM2,5, PM10, NO2, and SO2 was associated with an increased risk of hospital admissions for total stroke and ischemic stroke over 0 to 2 hours (Table 2; Table S5). For example, an interquartile range increase in PM2.5, PM10, NO2 and SO2 was associated with an increased risk of hospital admissions for total stroke by 1.86% (95% CI, 0.27%-3.47%), 2.19% (95% CI, 0.64%-3.76%), 3.34% (95% CI, 1.41%-5.31%), and 2.81% (95% CI, 1.15%-4.51%), respectively. The strongest association with ischemic stroke was 3.06% (95% CI, 1.03%-5.14%) for NO, followed by 2.53% (95% CI, 0.79%-4.31%) for SO<sub>0</sub>, 2.25% (95% CI, 0.64%-3.90%) for PM10, and 1.69% (95% CI, 0.03%-3.37%) for PM<sub>2.5</sub>. Furthermore, each interquartile range increase in PM2.5, PM10, O3, and CO over lags 25 to 48 hours was associated with a higher risk of hospital admissions for total stroke and ischemic stroke, respectively (Table S6). We found evidence of an association between NO<sub>2</sub> exposure and undetermined stroke over lags 0 to 24 hours. The Assoc

The exposure-response relationships for the association between  $PM_{2.5}$ ,  $PM_{10}$ ,  $SO_2$ , and  $NO_2$  and risk of hospital admissions for stroke were approximately linear, indicating that the risks of total stroke and ischemic stroke increased with increasing concentration of  $PM_{2.5}$ ,  $PM_{10}$ ,  $SO_2$ , and  $NO_2$  (Figure 2).

Table 1. Characteristics of the Study Population

Baseline characteristics	N (%)				
Age at onset, y					
<65	137 446 (36.0)				
≥65	244 202 (64.0)				
Sex					
Male	202 771 (53.1)				
Female	177 199 (46.4)				
Missing	1678 (0.4)				
Season					
Warm (April-September)	196 533 (51.5)				
Cold (October-March)	185 115 (48.5)				
City					
Hangzhou	110 552 (29.0)				
Zhoushan	220 016 (57.7)				
Jinhua	51 080 (13.4)				
Time of admission					
Daytime	353 486 (92.6)				
Nighttime	28 162 (7.4)				

We defined April-September as the warm season, and October-March as the cold season. We defined 8  $_{\text{PM}}$ -8  $_{\text{PM}}$  as the daytime and 8  $_{\text{PM}}$ -8  $_{\text{AM}}$  the next day as the nighttime.

**ORIGINAL CONTRIBUTION** 

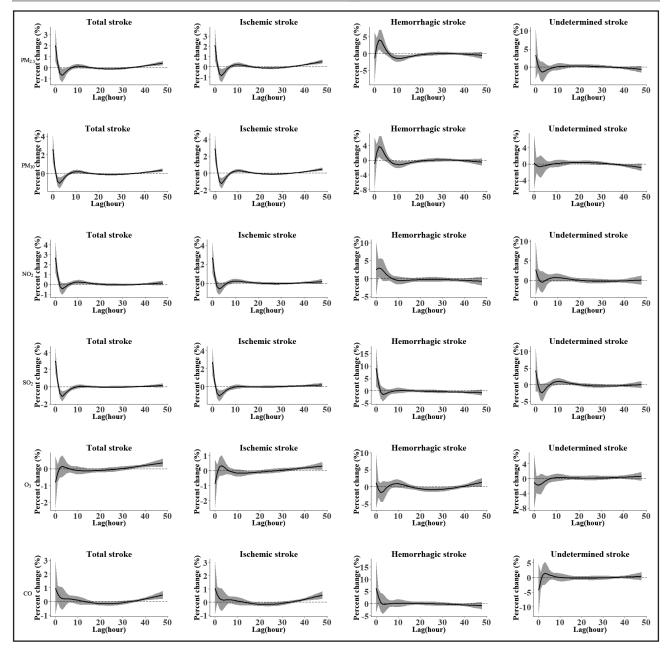


Figure 1. Lag structures for the associations of hospital admissions for stroke with hourly exposure to air pollutants. CO indicates carbon monoxide;  $NO_{2^1}$  nitrogen dioxide;  $O_{3^1}$  ozone;  $PM_{2.5^1}$  fine particulate matter;  $PM_{10^1}$  respirable particulate matter; and  $SO_{2^1}$  sulfur dioxide.

We performed subgroup analysis to test whether the association between air pollution and risk of stroke was more pronounced among subgroups defined by age, sex, season, city, and time of admission. We found that the risk was higher among male patients and those aged <65 years old (Table 3; Table S7).

In sensitivity analyses, our results were not materially different when we additionally adjusted for other air pollutants individually in the 2-pollutant models (Figure S3) or varied the number of knots for the natural cubic spline of the lag-response function and used 2 and 4 internal knots placed at equal intervals on the log scale of lags up to 48 hours (Tables S8; Table S9).

## DISCUSSION

In our analysis of 86 635 emergency department admissions for stroke across 10 hospitals, we found that exposure to  $PM_{2.5}$ ,  $PM_{10}$ ,  $NO_{2'}$  and  $SO_{2}$  was associated with an increased risk of hospital admissions for total stroke and ischemic stroke shortly after exposure. The associations were most pronounced during the concurrent hour of exposure and lasted for  $\approx$ 2 hours. We found that the risk was higher among male patients and patients aged <65 years old.

Using hourly measurement data, we found that exposure to  $\rm PM_{25}$  and  $\rm PM_{10}$  was linked to an increased risk

Air pollutant	Total stroke	stroke Ischemic stroke Hemorrhagic stroke		Undetermined type				
PM <sub>2.5</sub>	1.86 (0.27 to 3.47)	1.69 (0.03 to 3.37)	5.10 (-3.26 to 14.17)	2.90 (-4.22 to 10.55)				
PM <sub>10</sub>	2.19 (0.64 to 3.76)	2.25 (0.64 to 3.90)	4.90 (-2.91 to 13.33)	-0.78 (-7.51 to 6.43)				
NO <sub>2</sub>	3.34 (1.41 to 5.31)	3.06 (1.03 to 5.14)	8.46 (-0.72 to 18.48)	3.41 (-4.49 to 11.96)				
SO <sub>2</sub>	2.81 (1.15 to 4.51)	2.53 (0.79 to 4.31)	11.84 (2.73 to 21.75)	1.92 (-5.14 to 9.52)				
0 <sub>3</sub>	-1.00 (-2.80 to 0.84)	-0.77 (-2.66 to 1.17)	-1.19 (-9.58 to 7.99)	-4.38 (-12.27 to 4.22)				
СО	1.83 (-0.33 to 4.04)	1.90 (-0.36 to 4.21)	9.85 (—1.69 to 22.75)	-4.55 (-13.73 to 5.59)				

 Table 2.
 Percentage Excess Risk of Hospital Admissions for Stroke Associated With an

 Interquartile Range Increase in Air Pollutants Over 0–2 Hours

CO indicates carbon monoxide;  $NO_{2^1}$  nitrogen dioxide;  $O_{3^1}$  ozone;  $PM_{2.5^1}$  fine particulate matter;  $PM_{10^1}$  respirable particulate matter; and  $SO_{2^1}$  sulfur dioxide.

of hospital admissions for total stroke and ischemic stroke. Our findings were generally consistent with previous studies, although most prior studies investigated the association on a daily basis.<sup>21,22</sup> For example, Ban et al<sup>21</sup> reported that the risk of stroke increased by 0.37% (95% CI, 0.15%–0.60%) and the risk of ischemic stroke increased by 0.46% (95% CI, 0.21%-0.72%) associated with 10  $\mu g/m^3$  increase in  $PM_{_{2.5}}$  at lag 0 days among 131 947 patients with stroke in 10 Chinese counties. Using hourly measurement data, a time-stratified casecrossover study conducted in Boston found a positive association between exposure to  $\mathrm{PM}_{_{2.5}}$  or  $\mathrm{NO}_{_2}$  and ischemic stroke over lags 0 to 24 hours.<sup>22</sup> Conversely, a positive association between PM<sub>25</sub> exposure and risk of ischemic stroke was not observed in a large prospective multi-center stroke registry in 8 cities in Canada.<sup>23</sup>

We found a positive association between exposure to NO<sub>2</sub> and SO<sub>2</sub> and risk of hospital admissions for total stroke or ischemic stroke. These findings align with previous studies that investigated the association between NO<sub>2</sub> or SO<sub>2</sub> exposure and risk of total stroke or ischemic stroke at the daily timescale.<sup>6,24,25</sup> For example, a study conducted in the Boston area reported an odds ratio of 1.12 (95% Cl, 1.03–1.22) for ischemic stroke associated with an interquartile range increase in NO<sub>2</sub> over lags 0 to 24 hours.<sup>22</sup> Similarly, in a study of 5257 patients in Canada, Chen et al<sup>26</sup> reported a positive association between exposure to NO<sub>2</sub> and emergency department visits for ischemic stroke at the hourly timescale.

We found no evidence of an association between exposure to  $O_3$  and CO and the risk of hospital admissions for total stroke and ischemic stroke. These results align with a study that utilized data from the Women's Health Initiative, which similarly did not observe any associations between daily exposure to  $O_3$  and CO and stroke and its subtypes.<sup>27</sup> Nevertheless, it is important to note that evidence about the short-term effects of  $O_3$  or CO exposure on total stroke or ischemic stroke has been inconsistent across previous studies.<sup>6,28,29</sup> These discrepancies in findings may be attributed to variations in pollutant concentrations, geographic disparities, population characteristics, pollutant sources and composition, and statistical methods used.<sup>30,31</sup> Recognizing that CO has a higher affinity for hemoglobin, there is a reduction in the hemoglobin's ability to transport oxygen, which causes hypoxia in the brain tissue and damage to the neurological system.<sup>32</sup> Furthermore, both epidemiological and experimental studies have demonstrated that exposure to gaseous pollutants can induce systemic vascular oxidative stress and contribute to thrombus formation, thereby increasing the risk of cardiovascular diseases.<sup>33,34</sup> However, the current body of evidence about the association between exposure to gaseous pollutants at the hourly level and risk of stroke remains limited.

With the exception of SO<sub>2</sub>, we find no evidence of an association between hourly exposure to the 6 air pollutants and the risk of hospital admissions for hemorrhagic stroke or undetermined type of stroke. These findings are consistent with previous studies conducted at the daily level.<sup>21,35</sup> However, it is worth noting that a study among 10 949 patients in Japan found a positive association between PM with an aerodynamic diameter <7 µm (PM<sub>7</sub>) and hemorrhagic stroke, with the highest odds ratio of 1.08 (95% CI, 1.00–1.16) over lags 48 to 72 hours.<sup>36</sup> Meanwhile, a case-crossover study conducted in Zhejiang revealed that SO<sub>2</sub> exposure was linked to a higher risk of hemorrhagic stroke when assessed at the daily level.<sup>9</sup>

Several hypotheses have been proposed to elucidate the potential biological mechanisms through which short-term exposure to air pollutants could play a role in triggering stroke admissions.<sup>37</sup> Both controlled exposure studies in human and animal studies support that just a few hours after exposure to air pollutants, molecular, and cellular pathways associated with stroke onset can be activated. These pathways include processes, such as the induction of oxidative stress, activation of inflammatory pathways, promotion of platelet activation, and the disruption of the autonomic nervous system.<sup>38-44</sup> Acute stroke can be induced by an increase in blood pressure, arrhythmia, or ischemia, all of which can be triggered by the aforementioned molecular and cellular mechanisms.<sup>37</sup>

In our stratified analyses, we found that the relationship between  $PM_{25}$  or  $PM_{10}$  exposure and risk of stroke was more pronounced among male patients, which may be attributed to their greater involvement in outdoor activities and potentially lesser attention to protective measures. Additionally, we found stronger associations **ORIGINAL CONTRIBUTION** 

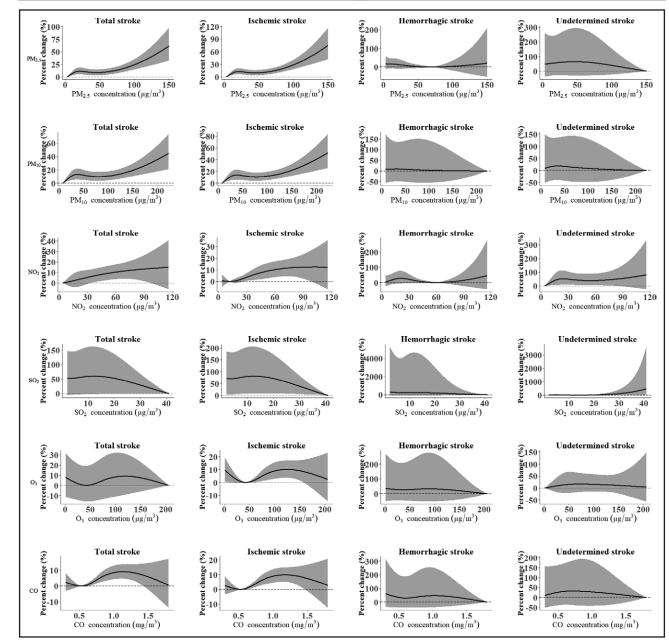


Figure 2. Cumulative exposure-response curves for the associations of hourly exposure to air pollutants with total stroke, ischemic stroke, hemorrhagic stroke, and undetermined type over lags-48 h.

CO indicates carbon monoxide; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, fine particulate matter; PM<sub>10</sub>, respirable particulate matter; and SO<sub>2</sub>, sulfur dioxide.

between PM<sub>10</sub> exposure and stroke among patients aged <65 years old, consistent with findings from a time-series study among 5269 patients in China.<sup>45</sup> The increased vulnerability of younger individuals to the effects of air pollution on stroke risk might be explained by their higher engagement in outdoor activities and exposure to higher levels of air pollution earlier in life compared with older individuals. These variations in susceptibility highlight the importance of implementing effective health protection measures to reduce exposure to air pollution and mitigate the risk of stroke in younger and male populations.

The study also has several limitations. First, our exposure assessment relied on data from the nearest

monitoring site to the hospital address. Although this is a commonly used approach and justified by the practice of promptly sending patients with stroke to the nearest hospital in China, it may not account for localized variations in pollution concentrations. Second, although our study design enables control of time-invariant confounding factors, there remains the possibility of residual confounding arising from time-varying lifestyle-related factors. However, it is unlikely that such confounding would substantially alter our results given that these factors typically do not change significantly within a 1-month period. Third, our study was conducted in Zhejiang province, and as such, the generalizability of our findings to other Chinese

 Table 3.
 Percentage Excess Risk of Hospital Admissions for Stroke Associated With an Interquartile Range Increase in Air

 Pollutants Over Lags 0-2 Hours Stratified by Age, Sex, Season, City, and Time of Admission

Characteristics	PM <sub>2.5</sub>	PM <sub>10</sub>	NO <sub>2</sub>	SO <sub>2</sub>	0 <sub>3</sub>	со			
Sex									
Male	3.40 (1.21 to 5.64)	4.33 (2.18 to 6.53)	3.41 (0.78 to 6.11)	2.39 (0.12 to 4.72)	-1.21 (-3.66 to 1.30)	3.34 (0.34 to 6.42)			
Female	-0.01 (-2.3 to 2.34)	-0.20 (-2.42 to 2.06)	3.23 (0.39 to 6.15)	3.17 (0.72 to 5.68)	-0.62 (-3.29 to 2.13)	0.08 (-3.04 to 3.29)			
Age, y									
<65	3.42 (0.79 to 6.12)	4.88 (2.29 to 7.54)	5.59 (2.34 to 8.93)	3.03 (0.28 to 5.86)	-2.06 (-4.99 to 0.96)	2.34 (-1.24 to 6.05)			
≥65	0.97 (-1.01 to 2.99)	0.65 (-1.26 to 2.61)	2.06 (-0.33 to 4.51)	2.7 (0.61 to 4.83)	-0.36 (-2.64 to 1.97)	1.55 (-1.15 to 4.32)			
Season									
Warm	-0.25 (-3.18 to 2.77)	0.68 (-2.02 to 3.44)	3.42 (0.41 to 6.51)	1.51 (-0.93 to 4.01)	-1.85 (-4.14 to 0.49)	4.64 (0.87 to 8.55)			
Cold	2.54 (0.65 to 4.47)	2.66 (0.76 to 4.58)	3.29 (0.78 to 5.87)	3.62 (1.32 to 5.97)	0.62 (-2.37 to 3.69)	0.38 (-2.25 to 3.08)			
City									
Hangzhou	1.79 (-1.27 to 4.95)	0.70 (-2.34 to 3.84)	5.30 (1.90 to 8.81)	5.37 (2.74 to 8.06)	-2.46 (-5.51 to 0.68)	5.11 (1.06 to 9.32)			
Zhoushan	1.14 (-0.95 to 3.29)	2.06 (0.03 to 4.12)	1.39 (-1.28 to 4.12)	0.19 (-2.38 to 2.82)	0.02 (-2.56 to 2.65)	0.42 (-2.40 to 3.32)			
Jinhua	4.62 (0.42 to 9.01)	4.85 (0.67 to 9.21)	5.62 (0.08 to 11.47)	1.09 (-2.86 to 5.20)	-1.02 (-5.89 to 4.11)	0.29 (-5.94 to 6.92)			
Time of admission									
Daytime	1.79 (0.15 to 3.46)	2.25 (0.66 to 3.87)	3.48 (1.44 to 5.56)	2.69 (0.96 to 4.45)	-0.87 (-2.72 to 1.02)	1.81 (-0.42 to 4.09)			
Nighttime	3.16 (-3.22 to 9.95)	1.83 (-4.45 to 8.51)	2.00 (-4.01 to 8.38)	5.27 (-1.09 to 12.03)	-0.12 (-8.55 to 9.09)	1.67 (-6.98 to 11.12)			

We defined April-September as the warm season and October-March as the cold season. We defined 8 AM-8 PM the daytime and 8 PM-8 AM the next day as the nighttime. CO indicates carbon monoxide; NO<sub>20</sub> nitrogen dioxide; O<sub>30</sub> ozone; PM<sub>250</sub> fine particulate matter; PM<sub>100</sub> respirable particulate matter; and SO<sub>20</sub> sulfur dioxide.

cities or countries may be limited. Further large-scale studies encompassing diverse populations are needed to better understand the effects of air pollution on stroke risk. Fourth, it is important to note that the time of symptom onset preceded the time of the admission, potentially leading to nondifferential exposure misclassification and biasing the relative risk toward the null. Nevertheless, despite these limitations, the utilization of hourly air pollution data and emergency hospital admissions for stroke in our study is a notable strength, which allows for a detailed examination of the sub-daily time process from exposure to stroke admissions, providing a more comprehensive understanding of the temporal relationship.

In conclusion, this time-stratified case-crossover study of 86 635 stroke admissions across 10 hospitals in 3 cities provides compelling evidence that hourly exposure to  $PM_{2.5}$ ,  $PM_{10}$ ,  $NO_{21}$ ,  $SO_{21}$  but not CO, and  $O_3$  was associated with emergency hospital admissions for total stroke or ischemic stroke shortly after exposure. These findings contribute to the growing body of evidence highlighting the detrimental effects of air pollution on stroke.

#### **ARTICLE INFORMATION**

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#### Disclosures

None.

#### **Supplemental Material**

Tables S1–S9 Figures S1–S3

#### REFERENCES

- Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, Abbasifard M, Abbasi-Kangevari M, Abd-Allah F, Abedi V, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20:795–820. doi: 10.1016/S1474-4422(21)00252-0
- Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, Fisher M, Pandian J, Lindsay P. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. *Int J Stroke*. 2022;17:18–29. doi: 10.1177/17474930211065917
- Ma O, Li R, Wang L, Yin P, Wang Y, Yan C, Ren Y, Oian Z, Vaughn MG, McMillin SE, et al. Temporal trend and attributable risk factors of stroke burden in China, 1990–2019: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2021;6:e897–e906. doi: 10.1016/S2468-2667(21)00228-0
- Wang Y, Zhou L, Guo J, Wang Y, Yang Y, Peng Q, Gao Y, Lu W. Secular trends of stroke incidence and mortality in China, 1990 to 2016: The Global Burden of Disease Study 2016. *J Stroke Cerebrovasc Dis.* 2020;29:104959. doi: 10.1016/j.jstrokecerebrovasdis.2020.104959

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- Zhao Y, Hua X, Ren X, Ouyang M, Chen C, Li Y, Yin X, Song P, Chen X, Wu S, et al. Increasing burden of stroke in China: a systematic review and metaanalysis of prevalence, incidence, mortality, and case fatality. *Int J Stroke*. 2022;18:259–267. doi: 10.1177/17474930221135983
- Tian Y, Liu H, Zhao Z, Xiang X, Li M, Juan J, Song J, Cao Y, Wang X, Chen L, et al. Association between ambient air pollution and daily hospital admissions for ischemic stroke: a nationwide time-series analysis. *PLoS Med.* 2018;15:e1002668. doi: 10.1371/journal.pmed.1002668
- Hu W, Chen Y, Chen J. Short-term effect of fine particular matter on daily hospitalizations for ischemic stroke: a time-series study in Yancheng, China. *Ecotoxicol Environ Saf.* 2021;208:111518. doi: 10.1016/j.ecoenv.2020.111518
- Guo Y, Xie X, Lei L, Zhou H, Deng S, Xu Y, Liu Z, Bao J, Peng J, Huang C. Short-term associations between ambient air pollution and stroke hospitalisations: time-series study in Shenzhen, China. *BMJ Open*. 2020;10:e032974. doi: 10.1136/bmjopen-2019-032974
- Xu R, Wang O, Wei J, Lu W, Wang R, Liu T, Wang Y, Fan Z, Li Y, Xu L, et al. Association of short-term exposure to ambient air pollution with mortality from ischemic and hemorrhagic stroke. *Eur J Neurol*. 2022;29:1994–2005. doi: 10.1111/ene.15343
- Wu H, Zhang B, Wei J, Lu Z, Zhao M, Liu W, Bovet P, Guo X, Xi B. Shortterm effects of exposure to ambient PM<sub>1</sub>, PM<sub>25</sub>, and PM<sub>10</sub> on ischemic and hemorrhagic stroke incidence in Shandong Province, China. *Environ Res.* 2022;212:113350. doi: 10.1016/j.envres.2022.113350
- Bont J, Jaganathan S, Dahlquist M, Persson A, Stafoggia M, Ljungman P. Ambient air pollution and cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. *J Intern Med.* 2022;291:779–800. doi: 10.1111/joim.13467
- Tian L, Qiu H, Pun VC, Ho K-F, Chan CS, Yu ITS. Carbon monoxide and stroke: a time series study of ambient air pollution and emergency hospitalizations. Int J Cardiol. 2015;201:4–9. doi: 10.1016/j.ijcard.2015.07.099
- Zhao Y, Guo M, An J, Zhang L, Tan P, Tian X, Liu L, Zhao Z, Wang X, Liu X, et al. Associations between ambient air pollution, meteorology, and daily hospital admissions for ischemic stroke: a time-stratified case-crossover study in Beijing. *Environ Sci Pollut Res Int* 2022;29:53704–53717. doi: 10.1007/s11356-021-18461-8
- 14. Vivanco-Hidalgo RM, Wellenius GA, Basagaña X, Cirach M, González AG, Ceballos P, Zabalza A, Jiménez-Conde J, Soriano-Tarraga C, Giralt-Steinhauer E, et al. Short-term exposure to traffic-related air pollution and ischemic stroke onset in Barcelona, Spain. *Environ Res.* 2018;162:160– 165. doi: 10.1016/j.envres.2017.12.024
- Xue X, Hu J, Peng L, Li H, Jiang Y, Gao C, Chen Y, Chen J, Fu X, Yang L, et al. Low ambient temperature might trigger the symptom onset of pulmonary embolism: a nationwide case-crossover study at hourly level in China. *Sci Total Environ*. 2022;853:158524. doi: 10.1016/j.scitotenv.2022.158524
- Chen R, Jiang Y, Hu J, Chen H, Li H, Meng X, Ji JS, Gao Y, Wang W, Liu C, et al. Hourly air pollutants and acute coronary syndrome onset in 129 million patients. *Circulation*. 2022;145:1749–1760. doi: 10.1161/CIRCULATIONAHA.121.057179
- Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemi*ology. 2001;12:186–192. doi: 10.1097/00001648-200103000-00010
- Carracedo-Martínez E, Taracido M, Tobias A, Saez M, Figueiras A. Casecrossover analysis of air pollution health effects: a systematic review of methodology and application. *Environ Health Perspect*. 2010;118:1173– 1182. doi: 10.1289/ehp.0901485
- Koletsi D, Pandis N. Conditional logistic regression. Am J Orthod Dentofac Orthop. 2017;151:1191–1192. doi: 10.1016/j.ajodo.2017.04.009
- Adebayo-Ojo TC, Wichmann J, Arowosegbe OO, Probst-Hensch N, Schindler C, Künzli N. Short-term joint effects of PM<sub>10</sub>, NO<sub>2</sub> and SO<sub>2</sub> on cardio-respiratory disease hospital admissions in Cape Town, South Africa. *Int J Environ Res Public Health*. 2022;19:8078. doi: 10.3390/ijerph19138078
- Ban J, Wang Q, Ma R, Zhang Y, Shi W, Zhang Y, Chen C, Sun Q, Wang Y, Guo X, et al. Associations between short-term exposure to PM<sub>25</sub> and stroke incidence and mortality in China: a case-crossover study and estimation of the burden. *Environ Pollut*. 2021;268:115743. doi: 10.1016/j.envpol.2020.115743
- Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, Schlaug G, Gold DR, Mittleman MA. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med.* 2012;172:229–234. doi: 10.1001/archinternmed.2011.732
- 23. O'Donnell MJ, Fang J, Mittleman MA, Kapral MK, Wellenius GA; Investigators of the Registry of Canadian Stroke Network. Fine particulate air pollution ( $PM_{25}$ ) and the risk of acute ischemic stroke. *Epidemiology*. 2011;22:422-431. doi: 10.1097/EDE.0b013e3182126580
- 24. Li L, Huang S, Tian Y, Ji J, Zhang Y, Hu J, Lv Z, Liu N, Wang P, Yin P, et al. Short-term exposure to nitrogen dioxide and ischemic stroke incidence in

Shenzhen, China: modification effects by season and temperature. *Ecotoxicol Environ Saf.* 2022;239:113644. doi: 10.1016/j.ecoenv.2022.113644

- Dong H, Yu Y, Yao S, Lu Y, Chen Z, Li G, Yao Y, Yao X, Wang S-L, Zhang Z. Acute effects of air pollution on ischaemic stroke onset and deaths: a timeseries study in Changzhou, China. *BMJ Open.* 2018;8:e020425. doi: 10.1136/bmjopen-2017-020425
- Chen L, Villeneuve PJ, Rowe BH, Liu L, Stieb DM. The air quality health index as a predictor of emergency department visits for ischemic stroke in Edmonton, Canada. J Expo Sci Environ Epidemiol. 2013;24:358–364. doi: 10.1038/jes.2013.82
- Sun S, Stewart JD, Eliot MN, Yanosky JD, Liao D, Tinker LF, Eaton CB, Whitsel EA, Wellenius GA. Short-term exposure to air pollution and incidence of stroke in the women's health initiative. *Environ Int.* 2019;132:105065. doi: 10.1016/j.envint.2019.105065
- Qi X, Wang Z, Guo X, Xia X, Xue J, Jiang G, Gu Y, Han S, Yao Q, Cai Z, et al. Short-term effects of outdoor air pollution on acute ischaemic stroke occurrence: a case-crossover study in Tianjin, China. *Occup Environ Med.* 2020;77:862–867. doi: 10.1136/oemed-2019-106301
- Henrotin JB, Besancenot JP, Bejot Y, Giroud M. Short-term effects of ozone air pollution on ischaemic stroke occurrence: a case-crossover analysis from a 10-year population-based study in Dijon, France. *Occup Environ Med.* 2007;64:439–445. doi: 10.1136/oem.2006.029306
- Chen J, Hoek G. Long-term exposure to PM and all-cause and causespecific mortality: a systematic review and meta-analysis. *Environ Int.* 2020;143:105974. doi: 10.1016/j.envint.2020.105974
- Chen R, Zhang Y, Yang C, Zhao Z, Xu X, Kan H. Acute effect of ambient air pollution on stroke mortality in the China air pollution and health effects study. *Stroke*. 2013;44:954–960. doi: 10.1161/STROKEAHA.111.673442
- Rose JJ, Wang L, Xu Q, McTiernan CF, Shiva S, Tejero J, Gladwin MT. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. *Am J Respir Crit Care Med.* 2017;195:596–606. doi: 10.1164/rccm.201606-1275Cl
- Bourdrel T, Bind M-A, Béjot Y, Morel O, Argacha J-F. Cardiovascular effects of air pollution. Arch 10.1016/j.acvd.2017.05.003
- Liu H, Zhai S, Kong Y, Wang Z, Song G, Song H, Liang L, Liu X, Jiang X, Wu L. Synergistic effects of gaseous pollutants on hospital admissions for cardiovascular disease in Liuzhou, China. *Environ Sci and Pollut Res.* 2021;29:9841–9851. doi: 10.1007/s11356-021-16334-8
- Gu J, Shi Y, Chen N, Wang H, Chen T. Ambient fine particulate matter and hospital admissions for ischemic and hemorrhagic strokes and transient ischemic attack in 248 Chinese cities. *Sci Total Environ*. 2020;715:136896. doi: 10.1016/j.scitotenv.2020.136896
- Yorifuji T, Suzuki E, Kashima S. Cardiovascular emergency hospital visits and hourly changes in air pollution. *Stroke*. 2014;45:1264–1268. doi: 10.1161/STROKEAHA.114.005227
- 37. Kulick ER, Kaufman JD, Sack C. Ambient air pollution and stroke: an updated review. *Stroke*. 2023;54:882–893. doi: 10.1161/STROKEAHA.122.035498
- Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease. J Am Coll Cardiol. 2018;72:2054–2070. doi: 10.1016/j.jacc.2018.07.099
- Seaton A, Godden D, MacNee W, Donaldson K. Particulate air pollution and acute health effects. *Lancet.* 1995;345:176-178. doi: 10.1016/s0140-6736(95)90173-6
- O'Toole TE, Hellmann J, Wheat L, Haberzettl P, Lee J, Conklin DJ, Bhatnagar A, Pope CA. Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. *Circ Res.* 2010;107:200–203. doi: 10.1161/CIRCRESAHA.110.222679
- Wallenborn JG, Schladweiler MC, Nyska A, Johnson JA, Thomas R, Jaskot RH, Richards JH, Ledbetter AD, Kodavanti UP. Cardiopulmonary responses of Wistar Kyoto, spontaneously hypertensive, and stroke-prone spontaneously hypertensive rats to particulate matter (PM) exposure. J Toxicol Environ Health A. 2007;70:1912–1922. doi: 10.1080/15287390701551233
- Gao L, Qin JX, Shi JQ, Jiang T, Wang F, Xie C, Gao Q, Zhi N, Dong Q, Guan YT. Fine particulate matter exposure aggravates ischemic injury via NLRP3 inflammasome activation and pyroptosis. *CNS Neurosci Ther.* 2022;28:1045–1058. doi: 10.1111/cns.13837
- Lee KK, Miller MR, Shah ASV. Air pollution and stroke. J Stroke. 2018;20:2– 11. doi: 10.5853/jos.2017.02894
- Lucking AJ, Lundback M, Mills NL, Faratian D, Barath SL, Pourazar J, Cassee FR, Donaldson K, Boon NA, Badimon JJ, et al. Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J.* 2008;29:3043– 3051. doi: 10.1093/eurheartj/ehn464
- Zeng W, Zhang Y, Wang L, Wei Y, Lu R, Xia J, Chai B, Liang X. Ambient fine particulate pollution and daily morbidity of stroke in Chengdu, China. *PLoS One.* 2018;13:e0206836. doi: 10.1371/journal.pone.0206836