Original Contribution

Ambient Particulate Matter Concentrations and Hospitalization for Stroke in 26 Chinese Cities

A Case-Crossover Study

Hui Liu, PhD*; Yaohua Tian, BS*; Yan Xu, MD; Jun Zhang, MD

Background and Purpose—Little is known about the short-term health impacts of particulate matter (PM) on stroke in China. We, therefore, conducted a time-stratified case-crossover study to examine the association between ambient PM and hospital admissions for stroke in 26 Chinese cities.

Methods—We identified hospital admissions for stroke by using electronic hospitalization summary reports from January 1, 2014 through December, 31 2015. We applied conditional logistic regression to explore the association between PM and hospital admissions for stroke. We also assessed the effect modification of stroke risk by geographical region, sex, and age.

Results—Hospital admissions for ischemic (n=278 980) and hemorrhagic (69 399) strokes were examined separately. For ischemic stroke, both $PM_{2.5}$ and PM_{10} had the strongest effect at lag 3 days, with an interquartile range increase in $PM_{2.5}$ (47.5 μg/m^3) and PM_{10} (76.9 μg/m^3) significantly associated with a 1.0% (95% confidence interval, 0.7%–1.4%) and 0.8% (95% confidence interval, 0.3%–1.3%) increase in admissions for ischemic stroke, respectively. In northern China where PM pollution is more severe, the risk estimates for both $PM_{2.5}$ and PM_{10} were larger than those in southern China in all lag structures. An interquartile range increase in $PM_{2.5}$ and PM_{10} in northern China corresponded to a 1.0% (95% confidence interval, 0.7%–1.4%) and 0.7% (95% confidence interval, 0.3%–1.2%) increase in ischemic stroke admissions at lag 3 days, respectively. For hemorrhagic stroke, no significant association was observed with PM in the 26 cities.

Conclusions—This study suggests that short-term elevations in PM may increase the risk of ischemic but not hemorrhagic stroke. The associations of PM with ischemic stroke are stronger in northern China than in the south. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016482.)**

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Key Words: China ■ hospitalization ■ particulate matter ■ quality control ■ stroke

Stroke

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Stroke is the second leading cause of death and the third major cause of adult disability worldwide, accounting for an estimated 6.5 million deaths and 113 million disability-adjusted life-years in 2013.[1] In China, stroke is the commonest cause of death and adult disability. It has been estimated that ≈2.5 million new cases of stroke are diagnosed, and 1.6 million people die from stroke annually in China.[2,3] Although several prevention strategies have been implemented in recent decades,[4,5] the incidence of stroke continues to increase in low- and middle-income countries owing to rapid growth and aging of the population and changes in lifestyle and environmental factors.[1] In addition, stroke is responsible for considerable human suffering and substantial healthcare costs.[2,6] It is therefore of great importance to enhance primary prevention efforts aimed at reducing the incidence of stroke from the public health perspective.

There is increasing evidence suggesting a close, quantitative relationship between exposure to air pollution and increases in mortality and hospital admissions owing to stroke.[7–9] Air pollution is a heterogeneous, complex mixture consisting of both gaseous pollutants and particulate matters (PMs). Identification of the specific air pollutants that contribute most to an increased risk of stroke has important implications for evidence-based policy making, specific intervention, and a better understanding of the underlying mechanisms of such an association. Epidemiological and toxicological studies have suggested that ambient PM and, in particular, fine PM ($PM_{2.5}$, particles with an aerodynamic diameter ≤2.5 μm) may have strong adverse health effects.[10–12] However, only a limited number of studies have explored the association between $PM_{2.5}$ and the risk of stroke. These studies have had inconstant findings, owing primarily to the lack of $PM_{2.5}$ monitoring data.[13–15] Furthermore,

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previous studies have primarily been conducted in Western countries. However, because of substantial differences among these studies in the levels of air pollution, characteristics of PM, weather patterns, and population susceptibility, there remains a need to evaluate the health effects of PM on stroke in developing countries.

With rapid industrialization and growing energy consumption during the past several decades, air pollution has become a major environmental issue in China.[16–18] The serious air pollution has attracted extensive public concern because of its huge adverse health impacts. The Global Burden of Diseases 2010 study estimated that air pollution is responsible for ≈1.2 million premature deaths and 25 million disability-adjusted life-years each year in China.[19] Although 2 studies have recently been conducted to examine the associations between $PM_{2.5}$ and mortality or hospital admissions for stroke in China, a weakness of these studies was their focus on a single city[20,21]; consequently, the generalizability of these findings is uncertain. China is very vast, and the air quality differs widely between southern and northern China, which is defined by the line formed by the Huai River and Qinling Mountain range. Generally, ambient PM concentrations in northern China are much higher than those in southern China, mainly owing to coal burning and differences in climate and geographical conditions and in the industrial structures.[22,23] Several studies have suggested that the health effects of air pollution among individuals in northern China are substantially greater than those in southern China.[24–26]

The aims of this study were to examine the association of PM with hospital admissions for stroke in 26 large Chinese cities during 2014 to 2015 and to determine whether this association differed between southern and northern China, by using a time-stratified case-crossover design.

Materials and Methods

Study Population

The data on daily admissions for stroke used in this study were sourced from electronic hospitalization summary reports of the top-ranked hospitals (grade 3A) in care, safety, and quality as evaluated by the National Hospital Performance Evaluation Project of the National Healthcare Data Center of China. The standard ranking system considers several aspects, including hospital infrastructure, medical service and management, technical level and efficiency, and quality and safety of clinical care. The medical information recorded on the hospitalization summary report includes basic demographics (sex and age), dates of admission and discharge, hospitalization and discharge diagnoses in Chinese and their corresponding International Classification of Diseases, 10th Revision (ICD-10) codes, treatments (mainly surgical information), discharge status (survival status, drug allergy, and hospitalization infection), and financial costs.

We identified admissions for ischemic stroke (ICD-10 code I63) and hemorrhagic stroke (ICD-10 codes I61 and I62) from January 1, 2014 to December 31, 2015, on the basis of the principal diagnosis using ICD-10 codes. To ensure the diagnostic validity of stroke, we also used the corresponding Chinese diagnoses to check the identified admissions. Individuals aged <18 years were excluded from this study. In total, we identified 278 980 and 69 399 hospital admissions for ischemic and hemorrhagic strokes, respectively, from 26 large cities in China. These included all the 4 municipalities, 21 of 28 provincial capital cities, and Dalian city, shown in Figure I in the online-only Data Supplement.

Air Pollution and Meteorologic Data

Data on air pollution, including levels of $PM_{2.5}$, PM <10 µm in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO) between January 1, 2014, and December 31, 2015, were obtained from the National Air Pollution Monitoring System, which is run by the Ministry of Environmental Protection. There are 4 to 15 ambient air-monitoring stations in each city. To fulfill the quality assurance and quality control programs mandated by the Chinese government, each monitoring station must provide hourly air pollution data to the China National Air Pollution Monitoring System. For each city, we obtained the daily (24 hours) mean concentrations for pollutants averaged across the air pollution monitoring stations.[27] To allow the adjustment for weather conditions, meteorologic data of daily 24-hour average temperature (°C) and relative humidity (%) monitored at meteorologic observatories in each city were obtained from the Chinese Meteorologic Bureau.

Study Design

We performed pooled analyses, for which observations for all cities were combined. Each city has a special indicator in the data set. Associations between ambient PM concentrations and stroke were investigated using a time-stratified case-crossover study design. In this design, cases serve as their own controls by using exposure on the days before or after the case period, in the same city.[28] For each case of stroke, ambient PM exposure on the case day (the day of hospital admission for stroke) was compared with exposure on a series of referent days occurring on the same days of the week within the same month and year as the case day. This approach can control for the influence of day of the week, seasonal and long-term trends, and slowly varying individual-level risk factors (eg, sex, genetics).

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Statistical Analysis

Spearman's correlation tests were used to examine the associations among exposure variables. Conditional logistic regression was applied to estimate the associations between PM and stroke. For adjustment of the delayed and nonlinear effects of temperature and humidity, we used the distributed lag nonlinear models with 3 degrees of freedom in the natural cubic splines and a maximum lag of 3 days.[29] To control the spatial variations in health effects of meteorology, interactions between meteorology and cities were also included in the model. We also incorporated public holiday in the model. The results are reported as the percentage change and 95% confidence interval (CI) in the daily stroke admissions per interquartile range (IQR) increase in PM concentration. Smoothing function was applied to graphically analyze the exposure–response association between $PM_{2.5}$ concentration and stroke hospitalizations.

To examine the temporal association of PM concentration with stroke, we fitted the models with different lag structures from the current day (lag0) to ≤5 lag days (lag5). Considering that single-day lag models may underestimate the effect of pollutant,[30] we also estimated associations with 3-day (lag0–2) and 6-day (lag0–5) moving average PM concentrations.

We examined potential confounding by other air pollutants by applying 2-pollutant models adjusted for CO, NO_2, or SO_2. Stratified analyses were used to examine whether associations differed by geographical region (southern and northern China), sex, and age (≥65 years and <65 years). Stratified models were compared using a Z test.[31]

All analyses were conducted using R programming language (V.3.2.2, R Development Core Team). All statistical tests were 2-sided, and $P<0.05$ was considered statistically significant.

Results

There were 278 980 hospital admissions for ischemic stroke and 69 399 admissions for hemorrhagic stroke that formed

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Table 1. Demographic Characteristics of Stroke Admissions

Variable	Ischemic Stroke	Hemorrhagic Stroke
Total	278 980	69 399
Sex		
Male (%)	177 313 (63.6)	47 179 (68.0)
Female (%)	101 667 (36.4)	22 220 (32.0)
Age, y (mean±SD)	64.9±12.8	59.0±14.2
<65 (%)	136 590 (49.0)	45 156 (65.1)
≥65 (%)	142 390 (51.0)	24 243 (34.9)
Geographic region		
Southern China (%)	78 022 (28.0)	27 653 (39.8)
Northern China (%)	200 958 (72.0)	41 746 (60.2)

the basis for this study (Table 1). The mean ages (SD) at admission for ischemic and hemorrhagic strokes were 64.9 years (12.8 years) and 59.0 years (14.2 years), respectively. For ischemic stroke, there were 63.6% male patients, 51.0% elderly patients (≥65 years old), and 72.0% of patients were from northern China. For hemorrhagic stroke, there were 68.0% male patients, 34.9% elderly patients, and 60.2% of patients were in northern China.

Air Pollution and Meteorologic Variables

Summary statistics of air pollutants and meteorologic variables in the 26 Chinese cities during the study period (2014–2015) are presented in Table 2. The means (SD) of air pollutants were 63.5 μg/m³ (50.6 μg/m³) for $PM_{2.5}$, 106.8 μg/m³ (71.9 μg/m³) for PM_{10}, 29.6 μg/m³ (32.6 μg/m³) for SO_2, 44.1 μg/m³ (19.4 μg/m³) for NO_2, and 1.15 μg/m³ (0.63 μg/m³) for CO. Means (SD) of temperature and relative humidity were 14.5°C (10.9°C) and 69.2% (33.2%), respectively. The levels of $PM_{2.5}$ and PM_{10} concentrations in northern China were much higher than those in southern China.

$PM_{2.5}$ was highly and positively correlated with PM_{10} (correlation coefficient r=0.87, P<0.001). The daily average concentrations of $PM_{2.5}$ and PM_{10} were moderately and positively correlated with CO, NO_2, and SO_2 (r=0.54–0.68, P<0.001). In general, air pollutant concentrations were negatively correlated with temperature and humidity (r=−0.5 to 0.02; Table I in the online-only Data Supplement).

Associations Between Air Pollution and Stroke

There were clear exposure–response associations between the 6-day (lag0–5) moving average $PM_{2.5}$ and PM_{10} concentrations and ischemic stroke hospitalizations in the 26 cities (Figure 1). Table 3 shows percentage changes with 95% CIs in ischemic and hemorrhagic stroke admissions associated with

Table 2. Summary Statistics for Air Pollutants Concentrations and Meteorologic Variables

Variable	Mean±SD	Minimum	Percentile			Maximum	IQR
			25th	50th	75th		
$PM_{2.5}$, μg/m³	63.5±50.6	5.1	31.5	49.4	79.0	897.5	47.5
Southern China	53.6±37.6	5.1	28.3	44.0	66.9	543.5	38.6
Northern China	71.4±57.9	5.2	34.7	54.5	88.4	897.5	53.7
PM_{10}, μg/m³	106.8±71.9	7.4	58.3	89.4	135.2	977.3	76.9
Southern China	84.3±50.4	7.4	49.6	72.6	107.2	614.8	57.6
Northern China	127.1±82.2	8.9	73.1	108.4	158.8	977.3	85.7
SO_2, μg/m³	29.6±32.6	1.9	11.4	18.8	33.6	316.9	22.2
Southern China	18.8±12.6	2.0	10.8	15.9	23.4	217.0	12.6
Northern China	39.6±41.2	1.9	12.5	25.4	50.8	316.9	38.3
NO_2, μg/m³	44.1±19.4	4.5	30.0	40.2	54.1	175.8	24.1
Southern China	41.3±17.6	4.5	28.4	37.8	50.7	175.8	22.3
Northern China	46.6±20.6	5.6	31.8	42.8	57.2	170.9	25.4
CO, mg/m³	1.15±0.63	0.14	0.76	0.99	1.32	8.41	0.56
Southern China	1.00±0.35	0.25	0.77	0.95	1.16	5.93	0.39
Northern China	1.28±0.78	0.14	0.76	1.07	1.57	8.41	0.81
Temperature(°C)	14.5±10.9	−25.7	7.0	16.4	23.3	35.5	16.3
Southern China	18.1±8.1	−12.2	11.8	19.4	24.6	35.3	12.8
Northern China	11.2±12.0	−25.7	1.9	12.8	21.5	35.5	19.6
Relative humidity (%)	69.2±33.2	8	53	69	80	97	27
Southern China	75.3±13.5	16	68	77	85	97	17
Northern China	62.0±45.4	8	42	57	71	95	53

IQR indicates interquartile range.

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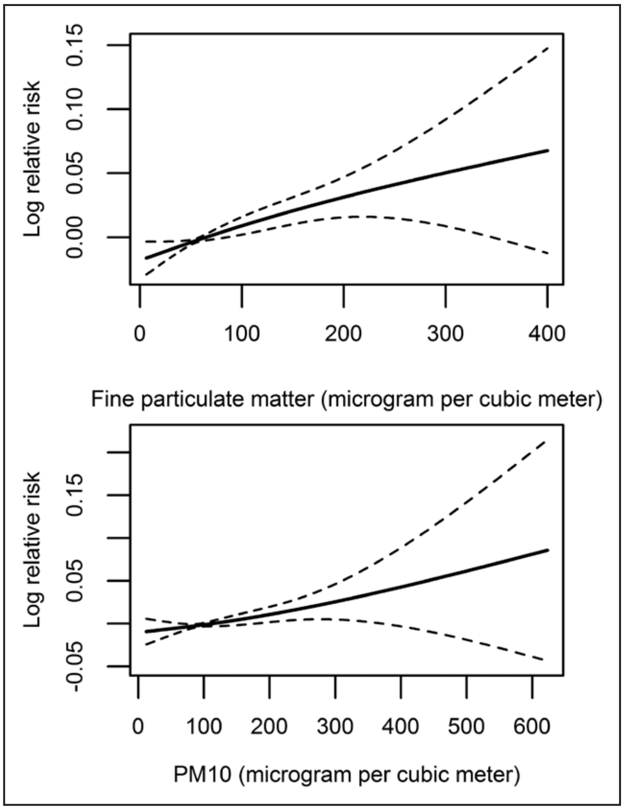

Figure 1. The exposure–response curve of 6-d (lag0–5) moving average fine particulate matter ($PM_{2.5}$, **top**) and PM_{10} concentrations (**bottom**; degree of freedom=3) and ischemic stroke hospitalizations in 26 cities. The *x* axis is the 6-d (lag0–5) moving average PM concentrations (μg/m³). *y* axis is the predicted log (relative risk), after adjusting for temperature and relative humidity, is shown by the solid line, and the dotted lines represent the 95% confidence interval.

an IQR increase in $PM_{2.5}$ (47.5 μg/m³) and PM_{10} (76.9 μg/m³) concentrations for different lag structures. Positive associations between $PM_{2.5}$ and ischemic stroke were observed at lag 2, 3, 4, 5, and 0 to 5 days, and a significant association in relation to PM_{10} was observed at lag 2, 3, 4, and 0 to 5 days. Both $PM_{2.5}$ and PM_{10} had the highest impact at lag 3 days. An IQR increase in $PM_{2.5}$ and PM_{10} concentrations at lag 3 days corresponded to a 1.0% (95% CI, 0.7%–1.4%) and 0.8% (95% CI, 0.3%–1.3%) increase in ischemic stroke admissions, respectively. Consistent results were observed for ischemic stroke, whereas no association with hemorrhagic stroke was detected.

Figure 2 shows the associations between PM concentration and ischemic stroke, stratified by geographical region. Associations with both $PM_{2.5}$ and PM_{10} were stronger in northern China than in southern China. In northern China, an IQR increase in $PM_{2.5}$ and PM_{10} concentrations at lag 3 days was associated with a 1.0% (95% CI, 0.7%–1.4%) and 0.7% (95% CI, 0.3%–1.2%) increase in ischemic stroke admissions, respectively.

We did not find evidence for effect modification by age or sex in all lag structures (all $P>0.05$; Figure II in the online-only Data Supplement). The percentage changes with 95% CIs for PM concentration at lag 0 to 5 days did not substantially change when adjusted for CO, NO_2, or SO_2 in the 2-pollutant models (Table 4).

Discussion

Our analysis summarizes the results from 26 large Chinese cities concerning the short-term effects of ambient PM pollution on stroke. To the best of our knowledge, this is the largest epidemiological study worldwide to date to examine the association of PM with stroke. This study showed that short-term increases in $PM_{2.5}$ and PM_{10} were significantly associated with an increased risk of ischemic stroke. In contrast, no evidence of an association with $PM_{2.5}$ or PM_{10} was found for hemorrhagic stroke. We observed effect modification by region, with significantly higher risk estimates in northern China.

Comparable epidemiological research from around the world has yielded inconsistent results on the association between exposure to PM and ischemic stroke. In Canada, a multicity study involving 9202 patients failed to find a significant association of $PM_{2.5}$ levels with ischemic stroke risk, in contrast to the positive findings in our study.[32] However, 2 studies conducted in the United States demonstrated that $PM_{2.5}$ was significantly associated with increased risk of ischemic stroke/transient ischemic attacks, even with $PM_{2.5}$ concentrations ranging well below the current US National Ambient Air Quality Standards.[14,15] In East Asia, a time-series study in Taipei City suggested a nonsignificant increase in emergency hospital admissions for stroke related to $PM_{2.5}$ or PM_{10}.[13] A recent multicenter hospital-based study, including 6885 ischemic stroke patients in Japan, found that each 10 μg/m³ increase in $PM_{2.5}$ was significantly associated with a 2% increased occurrence of ischemic stroke at lag 0 to 1 days.[33] In line with our findings, 2 recent studies performed in the Chinese cities of Guangzhou and Beijing also observed significant associations between PM and mortality or hospital admissions owing to stroke.[20,21] The heterogeneity of findings obtained in different parts of the world may reflect differences in the levels of pollution, population susceptibility, characteristics of pollutants, and the outcome definitions.

Consistent with most previous studies, we observed no statistically significant associations for hemorrhagic stroke.[9,21,34] The putative pathophysiologic mechanisms of PM-related cardiovascular effects and differences in the causes of hemorrhagic and ischemic strokes may be responsible for the stronger association with ischemic stroke than hemorrhagic stroke in our study. It has been demonstrated that exposure to ambient PM pollution could adversely affect vascular endothelial function, the activity of the sympathetic nervous system, and systemic inflammation, leading to vasoconstriction, increased plasma viscosity, and a risk of blood clotting and thrombosis.[35–37] These pathophysiologic changes are more closely related to the development and progression of ischemic stroke than hemorrhagic stroke.

We observed that $PM_{2.5}$ has a greater adverse effect on both ischemic and hemorrhagic strokes than PM_{10}, which is consistent with previous reports. For example, a time-stratified case-crossover study found that an IQR increase in the same-day $PM_{2.5}$ (82.0 μg/m³) and PM_{10} (93.5 μg/m³) corresponded to a 1.26% (95% CI, 0.30%–2.23%) and 1.18% (95% CI, 0.19%–2.17%) increase in hospital admissions for ischemic stroke, respectively.[21] A meta-analysis that combined the estimates from 103 studies using either admission or mortality data

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Table 3. Percentage Change With 95% CI in Ischemic and Hemorrhagic Stroke Admissions Associated With an Interquartile Range Increases in $PM_{2.5}$ (47.5 μg/m³) and PM_{10} (76.9 μg/m³) Concentration for Different Lag Structures

Lag Days	Ischemic Stroke			Hemorrhagic Stroke		
	Percentage Change	95% CI	*P* Value	Percentage Change	95% CI	*P* Value
$PM_{2.5}$						
Lag 0 d	0.1	−0.4 to 0.3	0.658	0	−0.7 to 0.8	0.942
Lag 1 d	0	−0.3 to 0.4	0.913	0.1	−0.7 to 0.8	0.886
Lag 2 d	0.8	0.4 to 1.1	<0.001	0.6	−0.1 to 1.3	0.118
Lag 3 d	1.0	0.7 to 1.4	<0.001	0.3	−0.4 to 1.1	0.371
Lag 4 d	0.9	0.6 to 1.3	<0.001	0.2	−0.5 to 1.0	0.534
Lag 5 d	0.4	0 to 0.8	0.028	0.4	−0.3 to 1.1	0.301
Lag 0–2 d	0.4	−0.1 to 0.8	0.116	0.3	−0.6 to 1.3	0.469
Lag 0–5 d	1.1	0.6 to 1.7	<0.001	0.6	−0.5 to 1.7	0.284
PM_{10}						
Lag 0 d	−0.1	−0.5 to 0.4	0.737	−0.4	−1.4 to 0.5	0.366
Lag 1 d	−0.2	−0.6 to 0.3	0.432	−0.4	−1.3 to 0.5	0.351
Lag 2 d	0.6	0.1 to 1.0	0.014	0.4	−0.6 to 1.3	0.452
Lag 3 d	0.8	0.3 to 1.3	<0.001	0.1	−0.8 to 1.0	0.819
Lag 4 d	0.7	0.3 to 1.1	0.001	0.3	−0.7 to 1.2	0.584
Lag 5 d	0.2	−0.1 to 0.6	0.435	0.3	−0.7 to 1.2	0.574
Lag 0–2 d	0.2	−0.4 to 0.7	0.592	−0.3	−1.4 to 0.9	0.654
Lag 0–5 d	0.8	0.3 to 1.5	0.009	0	−1.3 to 1.5	0.951

CI indicates confidence interval.

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indicated that a 10 μg/m³ increment of $PM_{2.5}$ and PM_{10} was significantly associated with a 1.1% (95% CI, 1.1%–1.2%) and 0.3% (95% CI, 0.2%–0.4%) higher risk of stroke, respectively. It is now generally accepted that $PM_{2.5}$ may have greater toxicity than PM_{10} because smaller particles can deposit more deeply into lungs; these also have a greater surface area, and thus, potentially larger concentrations of adsorbed or condensed toxic air pollutants per unit mass.[11,12,38]

The estimated effects for $PM_{2.5}$ in relation to ischemic stroke were larger and stronger in northern China than those in southern China. This geographical difference is consistent with the effect modification by region on associations between PM and stroke observed in previous studies.[13–15,20,21,32,33] There are several possible explanations for the geographical differences in health effects with respect to ambient PM pollution. First, the greater adverse effect may partly be attributable to the relatively higher level of PM pollution in northern China. In this study, the overall mean daily concentrations of $PM_{2.5}$ and PM_{10} were about 33.2% and 51.2% higher in northern China, respectively, than in the south. The dramatic difference in the PM concentration between southern and northern China observed in this study is consistent with previous reports.[22,26] Chen et al[26] evaluated the impact of exposure to total suspended particulates on life expectancy in 90 cities of China. They found that ambient concentrations of total suspended particulates are 55% higher, and life expectancies are 5.5 years (95% CI, 0.8–10.2 years) lower in northern China owing to increased incidence of cardiorespiratory mortality (and little effect on other causes). In general, the PM level is higher in the north, whereas levels of gaseous pollutants, including CO and NO_2, are similar between the 2 regions,[39] which was also shown in this study. Therefore, it is plausible that PMs are a crucial factor in determining the health effects caused by air pollution. This hypothesis is supported by previous findings. For example, Zhang et al[24] investigated the health effects caused by PM pollution in 111 Chinese cities and observed that these effects were much greater in cities with higher PM_{10} levels. However, very few studies have examined geographical differences in the effects of ambient particulate pollution on cardiorespiratory diseases. To the best of our knowledge, ours is the first study to investigate differences in the association of air pollution with stroke between southern and northern China. The greater effects of PM pollution on stroke in northern China could partly explain the shorter life expectancies in the north of the country.[26] Second, the geographical difference in the incidence of stroke may also contribute to effect modification by region. A recent nationwide population-based survey of 480 687 adults indicated that there is a north-to-south gradient in stroke in China, with the highest annual incidence rate observed in Northeast (365 per 100 000 person-years) and the lowest in Southwest (154 per 100 000 person-years).[40] The lower incidence of stroke in southern China leads to larger imprecision in the estimates.[8] In addition, the differences in the characteristics of PM weather patterns, and population

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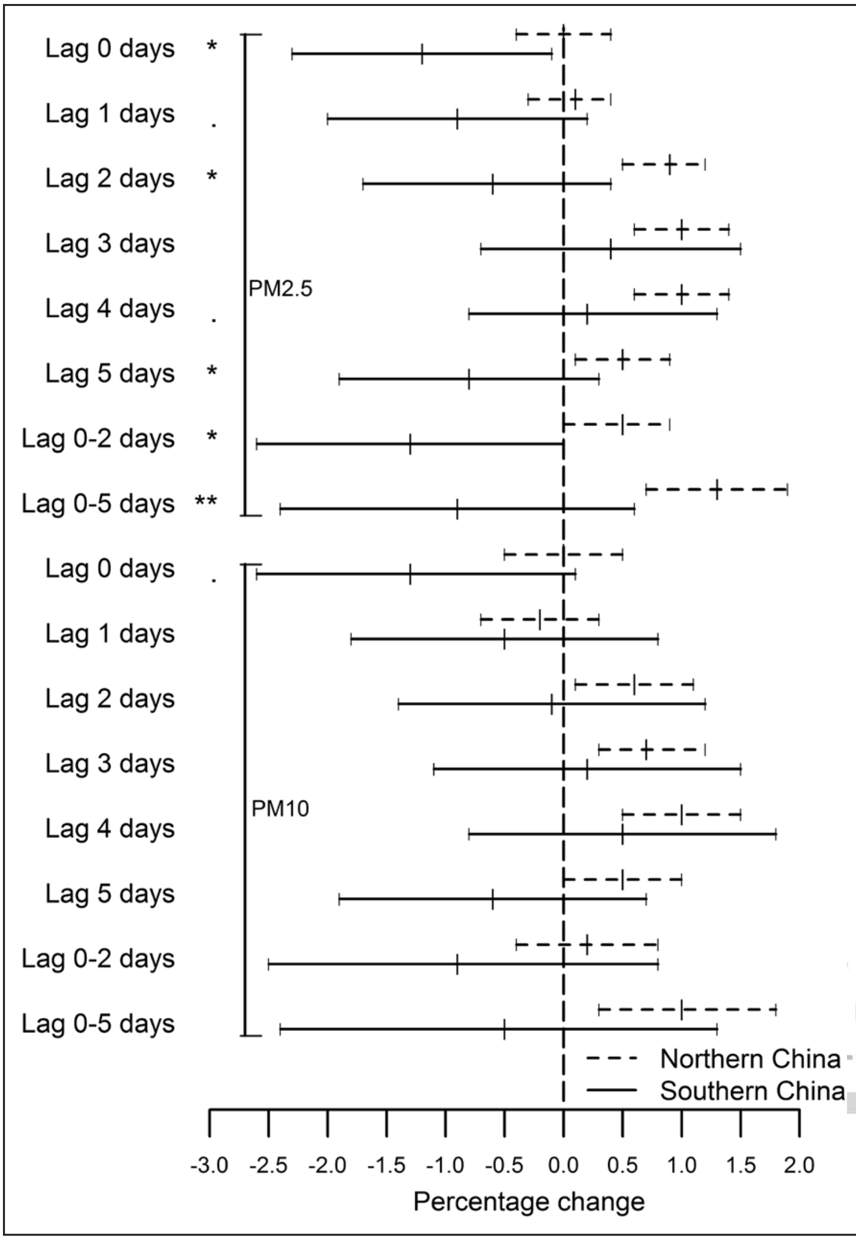

Figure 2. Percentage change with 95% confidence interval in ischemic stroke admissions associated with an interquartile range increase in $PM_{2.5}$ (47.5 µg/m^3) and PM_{10} (76.9 µg/m^3) concentrations stratified by region. ▪$P<0.1$, *$P<0.05$, **$P<0.01$, P value obtained from Z test for the difference between the 2 risk estimates derived from subgroup analysis. PM indicates particulate matter.

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susceptibility between southern and northern China may also account for the variation in the magnitude of risk estimates. Therefore, future studies are warranted to confirm the existence of geographical differences in health effects with respect to ambient PM pollution.

Our study had some potential limitations. First, the study was confined to large cities; thus, the association of interest in smaller cities was unclear. However, it has been demonstrated that the variability of PM levels in cities of different sizes is limited.[22] Ambient PM pollution is a national environmental issue in China. In addition, the use of citywide air pollutant mass concentrations as proxies for personal exposure can be expected to cause exposure measurement error, resulting in the underestimation of pollutant effects.[41] In this study, we fitted 2-pollutant models to examine the robustness of the associations between PM and stroke. However, the collinearity among the pollutants added uncertainty to the interpretation of the results and limited our ability to isolate the independent effects of PM on stroke,[42] and additional studies are needed to identify the specific air pollutant which is directly responsible for increased risk of stroke. Therefore, our results of 2-pollutant models should be interpreted with caution. Finally, the potential misclassifications for the diseases diagnosis should be considered when interpreting the findings. However, as all the hospitals included in this study were reputable university-teaching hospitals in China, technical level in these hospitals is of reasonably high quality. They have a high reputation for quality in all aspects of health care, including treatment, diagnosis, coding, hospital management, and electronic medical record systems. The Beijing Municipal Health Bureau had conducted a quality control study and found that over 95% of diagnostic codes recorded on the hospitalization summary report were accurate according to manual examinations of electronic medical records.[43] In addition, we used the corresponding Chinese diagnoses to check the identified admissions. Natural

Table 4. Percentage Change With 95% CI in Ischemic Stroke Admissions Associated With an Interquartile Range Increases in $PM_{2.5}$ (47.5 μg/m³) and PM_{10} (76.9 μg/m³) Concentration at Lag 0 to 5 Days in 2-Pollutant Models

Variable	Adjust SO_2	Adjust NO_2	Adjust CO
Overall			
$PM_{2.5}$	1.1 (0.6 to 1.7)	1.0 (0.5 to 1.6)	1.1 (0.5 to 1.7)
PM_{10}	0.9 (0.2 to 1.6)	0.7 (0 to 1.5)	0.8 (0.1 to 1.5)
Northern China			
$PM_{2.5}$	1.3 (0.7 to 1.9)	1.1 (0.5 to 1.7)	1.2 (0.6 to 1.8)
PM_{10}	1.0 (0.2 to 1.7)	0.6 (0 to 1.3)	0.8 (0 to 1.6)
Southern China			
$PM_{2.5}$	−0.8 (−2.3 to 0.8)	−0.5 (−2.1 to 1.1)	−0.1 (−1.8 to 1.6)
PM_{10}	−0.2 (−2.2 to 1.8)	2.4 (−1.8 to 2.3)	0.5 (−1.5 to 2.6)

CI indicates confidence interval.

language processing has been suggested to be an efficient method for identifying cases in large clinical databases.[44,45] By using both ICD-10 codes and corresponding patient diagnoses to identify eligible hospital admissions for stroke, it was possible to significantly reduce the impact of coding inaccuracy.

In conclusion, our results indicated that short-term elevations in the levels of $PM_{2.5}$ and PM_{10} are significantly associated with increased risk of ischemic stroke in the 26 Chinese cities studied. We also observed effect modification by region, with significantly stronger associations in northern China. Further studies are needed to confirm our findings and to explore potential biological mechanisms.

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Disclosures

None.

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ONLINE SUPPLEMENT

Ambient Particulate Matter Concentrations and Hospitalization for Stroke in 26 Chinese Cities: A Case-Crossover Study

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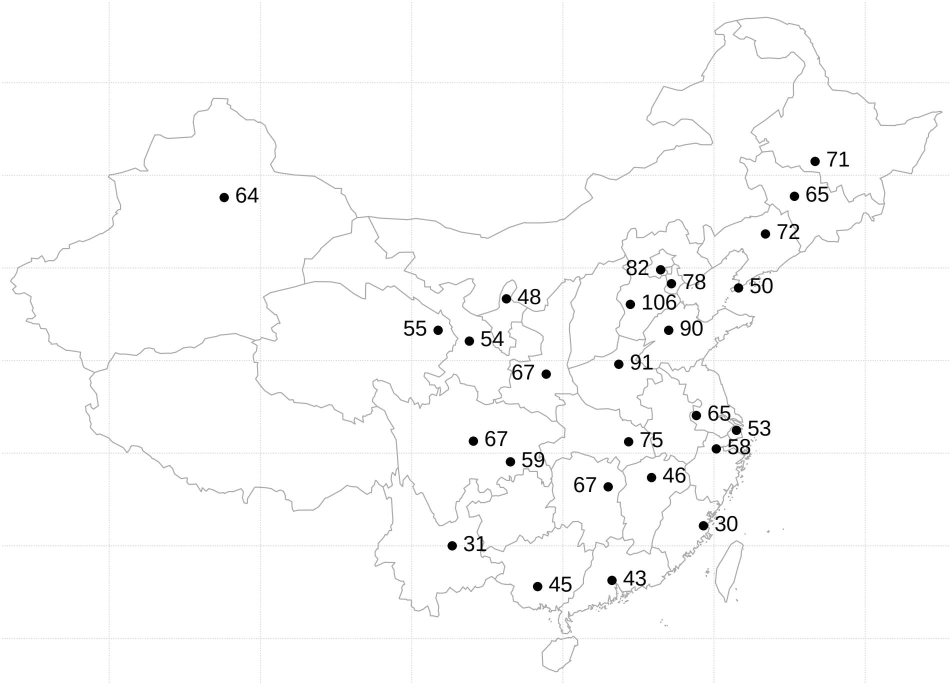
Supplemental Table I. Spearman correlation coefficients among the exposure variables.

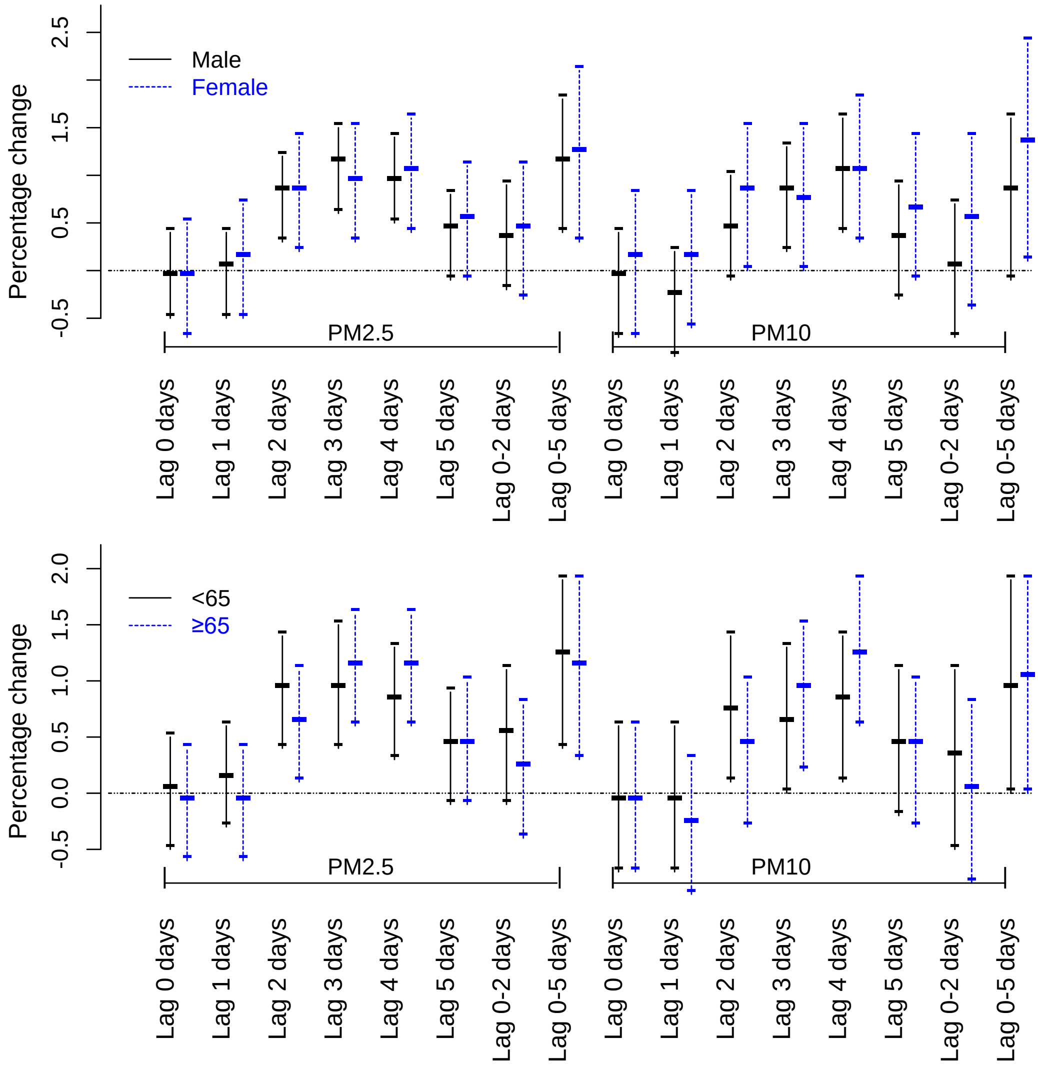
Variables	$PM_{2.5}$	PM_{10}	NO_2	SO_2	CO	Temp	RH
$PM_{2.5}$	1.00	0.87*	0.67*	0.61*	0.68*	-0.32*	-0.08*
PM_{10}	—	1.00*	0.64*	0.63*	0.60*	-0.27*	-0.33*
NO_2	—	—	1.00	0.54*	0.59*	-0.36*	-0.11*
SO_2	—	—	—	1.00	0.55*	-0.51*	-0.36*
CO	—	—	—	—	1.00	-0.37*	0.02†
Temp	—	—	—	—	—	1.00	0.18*
RH	—	—	—	—	—	—	1.00

*$P < 0.001$

†$P < 0.05$



Supplemental Figure I. Locations of the 26 Chinese cities in this study. The Arabic numeral for each city indicated the average daily $PM_{2.5}$ concentration over the study period (2014–2015).



Supplemental Figure II. Percentage change with 95% CI in ischemic stroke admissions associated with an interquartile range increase in $PM_{2.5}$ (47.5 μg/m^3) and PM_{10} (76.9μg/m^3) concentrations stratified by gender and age.