RESEARCH ARTICLE

Association of Ambient Particulate Matter Pollution of Different Sizes With In-Hospital Case Fatality Among Stroke Patients in China

Miao Cai, PhD, Shiyu Zhang, BM, Xiaojun Lin, PhD, Zhengmin Qian, PhD, Stephen Edward McMillin, PhD, Yin Yang, PhD, Zilong Zhang, PhD, Jay Pan, PhD,* and Hualiang Lin, PhD*

Neurology® 2022;98:e2474-e2486. doi:10.1212/WNL.0000000000200546

Correspondence
Dr. Lin
linhualiang@
mail.sysu.edu.cn

RELATED ARTICLE

Editorial
Ambient Pollution and Stroke: Time to Clear the Air on Causal Mechanisms
Page 1003

Abstract

Background and Objectives

To characterize the association of ambient particulate matter (PM) pollution of different sizes (PM ≤1 μm in aerodynamic diameter [PM_1], $PM_{2.5}$, and PM_{10}) with in-hospital case fatality among patients with stroke in China.

Methods

We collected hospitalizations due to stroke in 4 provinces in China from 2013 to 2019. Seven-day and annual averages of PM prior to hospitalization were estimated using bilinear interpolation and residential addresses. Associations with in-hospital case fatality were estimated using random-effects logistic regression models. Potential reducible fraction and the number of fatalities attributed to PM were estimated using a counterfactual approach.

Results

Among 3,109,634 stroke hospitalizations (mean age 67.23 years [SD 12.22]; 1,765,644 [56.78%] male), we identified 32,140 in-hospital stroke fatalities (case fatality rate 1.03%). Each 10 $\mu g/m^3$ increase in 7-day average (short-term) exposure to PM was associated with increased in-hospital case fatality: odds ratios (ORs) were 1.058 (95% CI 1.047–1.068) for PM_1, 1.037 (95% CI 1.031–1.043) for $PM_{2.5}$, and 1.025 (95% CI 1.021–1.029) for PM_{10}. Similar but larger ORs were observed for annual averages (long-term): 1.240 (95% CI 1.217–1.265) for PM_1, 1.105 (95% CI 1.094–1.116) for $PM_{2.5}$, and 1.090 (95% CI 1.082–1.099) for PM_{10}. In counterfactual analyses, PM_{10} was associated with the largest potential reducible fraction in in-hospital case fatality (10% [95% CI 8.3–11.7] for short-term exposure and 21.1% [19.1%–23%] for long-term exposure), followed by PM_1 and $PM_{2.5}$.

Discussion

PM pollution is a risk factor for in-hospital stroke-related deaths. Strategies that target reducing PM pollution may improve the health outcomes of patients with stroke.

*These authors contributed equally to this work as co-corresponding authors.

From the Department of Epidemiology (M.C., S.Z., Y.Y., Z.Z., H.L.), School of Public Health, Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong; HEOA Group, West China School of Public Health and West China Fourth Hospital (X.L., J.P.), and Institute for Healthy Cities and West China Research Center for Rural Health Development (X.L., J.P.), Sichuan University, Chengdu, China; and Department of Epidemiology and Biostatistics (Z.Q.) and School of Social Work (S.E.M.), College for Public Health & Social Justice, Saint Louis University, MO.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CHAP = China High Air Pollutant; **ICD-10** = International Classification of Diseases, 10th Edition; **LMIC** = low- and middle-income country; **OR** = odds ratio; **PM** = particulate matter.

As of 2017, stroke was the second leading cause of death across the globe.[1] Strokes predominantly afflict low- and middle-income countries (LMICs), which account for 70% of stroke incidence and 87% of both stroke-related deaths and disability-adjusted life-years.[2] In China specifically, stroke led to ≈2.19 million fatalities and 45.9 million disability-adjusted life years in 2019.[3]

Stroke results in substantial morbidity and case fatality within hospitals. The risk of in-hospital case fatality among patients with stroke is a result of clinical treatment, demographics, comorbidities, health behaviors, and environmental factors.[4-6] Obtaining a deeper understanding of these risk factors and the magnitude of their effects may help reduce in-hospital case fatalities and improve the outcomes of hospitalized patients with stroke in China, while also potentially informing the management and prevention of stroke mortality in other LMICs.

Exposure to particulate matter (PM) has been widely associated with the incidence, hospitalization, and mortality of stroke,[5-7] yet few studies have examined how different particle sizes affect the case fatality of hospitalized patients with stroke. Evidence supporting the association of PM and in-hospital stroke case fatality is particularly scarce in China, where both a high burden of stroke and air pollutants have been reported.[8-10] The widespread adoption of an electronic medical records system in China in recent years can be translated into valuable insights on PM and stroke in-hospital case fatality for China and other LMICs, keep national and global estimates of disease burden up to date, and strengthen future environmental policies.

In this study, we collected data on ≈3.1 million stroke hospitalizations in 4 provinces of China and estimated individual-level exposure to PM pollutants in the week prior to hospitalization, as well as the annual average at residential addresses. Our aims were to characterize the associations of both short-term and long-term exposure to PM ≤1 μm in aerodynamic diameter (PM_1), $PM_{2.5}$, and PM_{10} with the risk of in-hospital case fatality of stroke in China and the associated attributable burden.

Methods

Data Sources

We used de-identified hospital electronic medical records from 4 provinces in China (Figure 1): Sichuan, Shanxi, Guangxi, and Guangdong (Zhanjiang city only). The 4 provinces were selected based on the availability of datasets. The data collection periods were different for the 4 provinces: January 1, 2013, to December 31, 2018, in Shanxi; January 1, 2018, to December 31, 2019, for Sichuan; January 1, 2013, to December 31, 2016, for Guangxi and Guangdong (Zhanjiang). These data sets were queried from electronic medical record databases managed by provincial health information departments, covering almost all patients hospitalized in tertiary and secondary hospitals, as well as some primary hospitals in the sample provinces and cities.[11-17] The database includes patient demographics and socioeconomic variables, codes and text descriptions for clinical diagnoses and procedures, and current residential addresses.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was an analysis of routinely collected data and considered a minimal risk observational study under the Revised Common Rule, and consequently the requirement for informed consent was waived. The study was approved by the institutional review board of the School of Public Health, Sun Yat-sen University.

Inclusion and Exclusion Criteria for Stroke Cases

Stroke cases were identified using principal inpatient diagnosis ICD-10 codes that were previously validated and reported to have high positive predictive value for identifying stroke cases.[18-20] Ischemic stroke was identified using primary diagnosis ICD-10 codes I63.x and H34.1; hemorrhagic stroke was identified by primary diagnosis ICD-10 codes I60.x, I61.x, and G45.x; unspecified stroke was identified using ICD-10 code I64.x.

We excluded patients younger than 18 years or with missing information on age, sex, or ethnicity (n = 1,219) as well as those without residential location information or outside of the sample provinces (n = 47,959). The final sample included 3,109,634 stroke cases collected in the 4 provinces (Figure 1).

Outcomes

The primary outcome of interest is in-hospital case fatality,[21] defined as fatality within the time of hospitalization. This variable was recorded in the field "discharge status" by physicians in the electronic medical records.

Exposure Data

We used the 10 × 10 km grid China High Air Pollutants (CHAP) daily data set as the data source for assessing exposure to air pollutants.[22-25] CHAP is a long-term, full-coverage, high-resolution, high-accuracy, ground-level air pollutant data source. It uses a combination of advanced satellite remote sensing and space–time models, achieving a high cross-validation coefficient of determination of 0.89 and low root mean square error of 10.33 μg/m^3.[22-25] This data set includes daily concentrations of PM_1, $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO in China from 2013 to 2020, with the exception of 2013, when PM_1 was not recorded.

In addition, PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO were measured in daily average concentrations, while O_3 was measured using maximum 8-hour averages. In sensitivity analyses, we also measured the residential air pollution using a much higher resolution CHAP, a 1 × 1 km annual average data set of the 7 air pollutants, and re-estimated the models for long-term exposure.

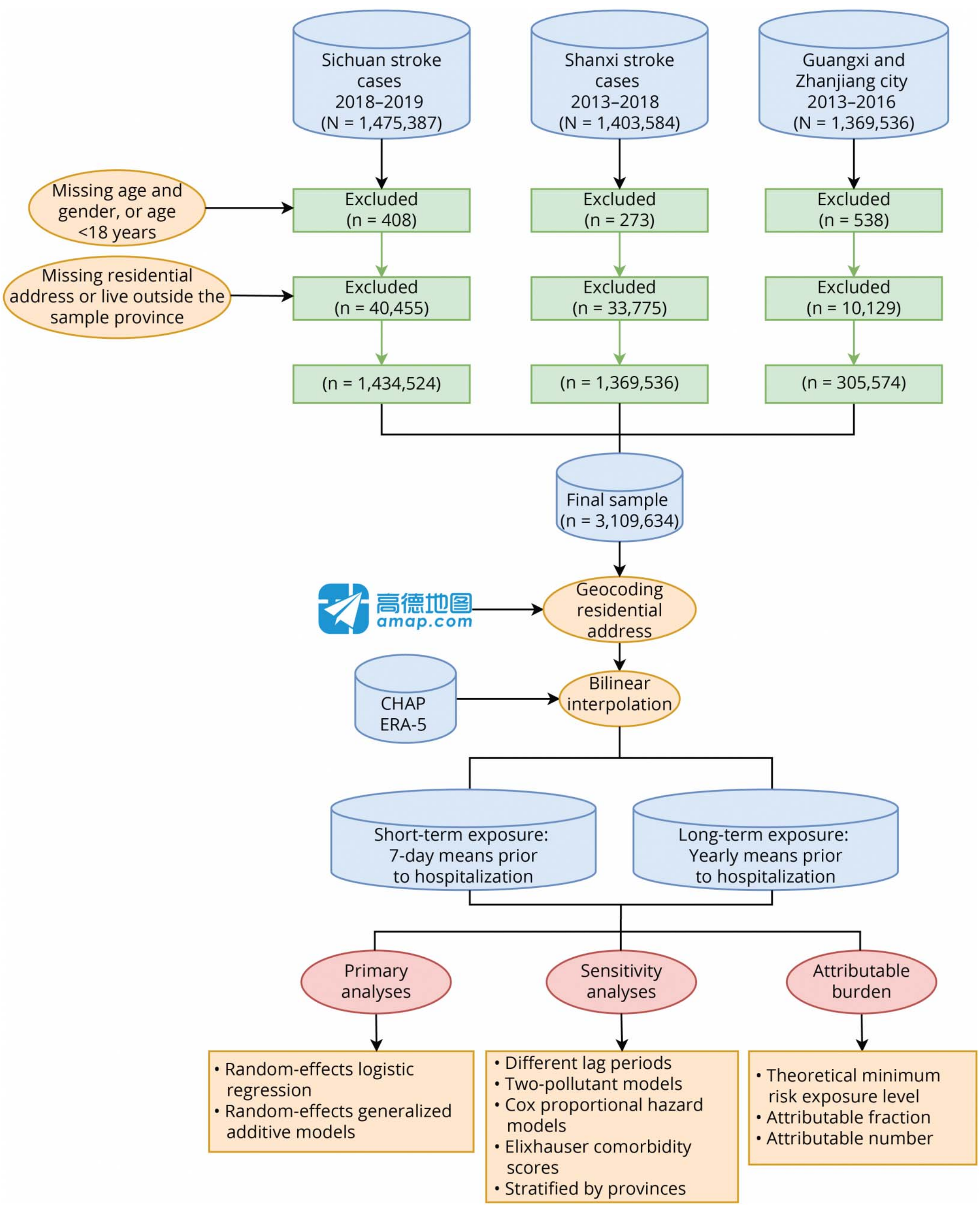
We also obtained daily data on meteorologic variables (temperature and relative humidity) measured at 10 × 10 km grids from the fifth generation of European Reanalysis (ERA5)–Land reanalysis data set.[26] The ERA5 is a high-resolution and long-span dataset for meteorologic variables, estimated using state-of-the-art land surface modeling techniques.

Matching Stroke Cases With Exposure Using Bilinear Interpolation Approach

We used a 2-stage assessment strategy to evaluate individual-level exposure to pollutants and meteorologic variables for the stroke cases.

In the first stage, we obtained the latitudes and longitudes of each patient using the residential address and then a

Figure 1 Flowchart for Sample Inclusion, Exclusion, Exposure Measurements, and Statistical Analyses



CHAP = China High Air Pollutant; ERA5 = the fifth generation of European Reanalysis.

geocoding programming interface provided by amap (also known as Gaode map),[27] a leading mapping, navigation, and location-based service provider in China. The accuracy of residential addresses and geocoding was enhanced by including the province and cities identified using the patient's postal code. Cases with latitudes and longitudes located outside the provinces were excluded to eliminate bias caused by outlier locations.

In the second stage, we used bilinear interpolation to estimate the exposure to pollutants and meteorologic variables. This algorithm enhanced the spatial resolution of environmental variables at a specific location by calculating a weighted average of the nearest 4 grids.[28] The closer air pollutant and meteorologic variables grids were to the location of the cases, the larger the associated weights associated with the grids. In locations where fewer than 4 grids were available (for example, islands or coastal cities), we used given available grids and recalculated the weights so that the weights sum up to unity. These outliers accounted for less than 1% of our sample and they had at least one measure of a nearby air pollution level, so we decided to include them in our final sample.

Short-Term and Long-Term Exposure to PM

Short-term exposure to PM air pollution was defined as the 7-day average of PM prior to the day of hospitalization. We also used alternative measures of lag 0 to lag 7 and moving averages of PM in sensitivity analyses. PM air pollution within hospitals was not accounted for in this study because data on indoor air pollution were not available. CHAP is a satellite image-based air pollution source and it is essentially a measure of outdoor air pollution. Inpatient departments in Chinese hospitals are generally equipped with air conditioners, which can substantially reduce the level of PM air pollution within hospitals compared with outdoor air pollution.[29]

Because the adverse effects of pollution on in-hospital fatalities among patients with stroke may be attributable to long-term exposure, we further assessed the annual (365 days) average exposure to major pollutants prior to the day of hospitalization as long-term exposure to PM pollution.

Covariates

We considered several covariates in the analysis, including demographics (age, sex, and ethnicity), socioeconomic status (marital status and occupation), and comorbidities. Self-reported ethnicity was classified as Han or non-Han Chinese. Marital status was categorized as married, unmarried, widowed, divorced, or other. Occupation was classified as public institution, private institution, farmer, jobless, retired, or other. Missing data for marital status and occupation were imputed using the highest-frequency category (married for marital status and farmer for occupation). We also included a set of comorbidities including hypertension, diabetes, congestive heart failure, cardiac arrhythmias, peripheral vascular disorders, liver disease, and stroke subtypes (ischemic, hemorrhagic, and unspecified stroke), which were selected based on relevance to both air pollution and in-hospital fatality. These comorbidities were identified using ICD-10 codes from patient diagnosis fields and were further enhanced by text matching using regular expressions in clinical diagnosis descriptions.[4,30] Hospital level was coded as tertiary or non-tertiary.[11] Intracranial procedure was identified using ICD-9 procedure codes and key words matching in procedure text description. We included 7-day averages of the meteorologic variables (temperature and relative humidity) prior to the day of hospitalization as the environmental covariates in all models.

Statistical Analyses

We calculated the frequency for categorical variables and means and SDs for continuous variables for the overall sample and stratified by in-hospital fatality. We constructed random-effects logistic regression models where the provinces and cities were included as random intercepts to account for clustering among observations. To estimate the exposure–response curves, we further constructed random-effects logistic regression models where the continuous pollutant variables were included as natural cubic splines with knots specified at each quartile.[31] Temperature and relative humidity (7-day means prior to hospitalization) were included as natural cubic splines with knots specified at each quartile in all models.

To estimate the potential reducible fractions and number of in-hospital case fatalities associated with the exposures, we predicted the number of fatalities based on our main random-effects logistic regression models and a counterfactual scenario. The scenario was set to be hypothetical levels of each size of PM that achieved the optimal fifth percentile in the entire sample.[32-34] If the observed levels of PM were lower than the fifth percentile, they were kept the same in the scenario. We did not use the guideline levels specified by the WHO[35] as there were no guideline levels for either 24-hour or 1-year PM_1. The differences between the observed and predicted number of fatalities (using the fifth percentiles of PM_1, $PM_{2.5}$, and PM_{10}) were used to represent the potential reducible number of fatalities attributable to PM_1, $PM_{2.5}$, and PM_{10}, respectively. The potential reducible fractions were then calculated by dividing these differences between the observed and predicted number of fatalities by the observed total number of fatalities. The associated 95% CIs were estimated using a bootstrap method, with 1,000 replicate samples produced for each model.[15]

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline. The effect estimates were considered statistically significant if the *p* values were lower than 0.05 or the CIs excluded unity. The computations were performed on the Ohio Supercomputer Center platform. We used statistical computing environment R 4.0.2 for all data cleaning, analyses, and visualization.[36] A flowchart of data inclusion and exclusion, data processing, statistical modeling, and sensitivity analyses is provided in Figure 1.

Sensitivity Analyses

We performed several sensitivity analyses to assess the robustness of results to the lags of exposure measurement, gaseous air pollutants, model specification, and missing comorbidity confounding. First, we assessed different lags (lag 0 to lag 7) and moving averages (MA01 to MA07) of short-term exposure to PM using the bilinear interpolation approach. Second, we performed several 2-pollutant models by further including each of the gaseous air pollutants (O_3, NO_2, SO_2, and CO). Third, to assess the robustness of results in different model specifications, we included the time to in-hospital fatality starting from hospitalization as the outcome and re-estimated the results using Cox proportional hazard models. For nonevent hospitalizations, we used the length of stay within hospitals as the follow-up period. Fourth, in main analyses, we included only a few comorbidity dummy variables that were most relevant to stroke or in-hospital fatalities and may be prone to bias caused by missing comorbidities. To have a more comprehensive capture of comorbidities and their weights, we alternatively adjusted for Elixhauser comorbidity scores,[37-39] which were weighted summation of 31 comorbidities and showed high predictive performance for in-hospital case fatality in Chinese samples.[15] Fifth, to test the robustness of our exposure resolution, we assessed the long-term exposure to the pollution for each case using a much finer resolution annual 1 × 1 km CHAP data set as the alternative data source for air pollutants,[22,24] and the main models and sensitivity analyses models were re-estimated using these high-resolution grids. The 1 × 1 km exposure data were not used in our primary results because daily exposure at this resolution is not currently available. Sixth, to examine the robustness of results to samples with incomplete covariate information, we conducted our models among participants (n = 2,321,628, 74.7% of the full sample) who had complete occupation and marital status (not equal to other category) and full 4 grids of exposure.

Data Availability

The original data cannot be shared because they include private patient address information. The secondary data, analysis results, and R code may be shared at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Characteristics of the Sample Stroke Cases

The final full sample included 3,109,634 stroke cases, among which 1,434,524 (46.1%) were from Sichuan province, 1,369,536 (44.0%) from Shanxi province, and 305,574 (9.8%) from Guangxi province and Zhanjiang city. Figure 2 presents the geographic distribution of the sample stroke cases. There were 32,140 in-hospital fatalities, resulting in a case fatality rate of 1.03%. Temporal trends of the stroke hospitalizations and case fatality rate by year and month are shown in eFigure 1 (links.lww.com/WNL/B983).

The 7-day average (short-term) level of PM prior to the day of hospitalization was 31.38 (SD 17.43) μg/m^3 for PM_1, 45.43 (SD 25.80) μg/m^3 for $PM_{2.5}$, and 78.75 (SD 38.24) μg/m^3 PM_{10} (Table 1). Similarly, the annual average (long-term) level of PM prior to the year of hospitalization was 32.98 (8.27) μg/m^3 for PM_1, 49.08 (12.32) μg/m^3 for $PM_{2.5}$, and 87.32 (17.66) μg/m^3 PM_{10}. At the time of hospitalization, the patients who experienced in-hospital fatalities were more likely to be older adults, male, Han Chinese, retired, unmarried, widowed, or divorced; to have experienced hemorrhagic stroke; or to have comorbidities (Table 1).

Associations of PM_1, $PM_{2.5}$, and PM_{10} With In-Hospital Stroke Case Fatality

We observed that each 10 μg/m^3 increment in 7-day averages of PM prior to hospitalization were significantly associated with stroke fatality: odds ratios (ORs) 1.058 (95% CI 1.047–1.068) for PM_1, 1.037 (95% CI 1.031–1.043) for $PM_{2.5}$, and 1.025 (95% CI 1.021–1.029) for PM_{10} (Table 2). Similar patterns of ORs can be observed for annual average concentration of PM: 1.240 (95% CI 1.217–1.265) for PM_1, 1.105 (95% CI 1.094–1.116) for $PM_{2.5}$, and 1.090 (95% CI 1.082–1.099) for PM_{10}. When stratified by stroke subtypes, we found that the associations of PM pollution and in-hospital case fatality were consistently larger among patients with ischemic stroke than those among patients with hemorrhagic stroke (Table 2). In summary, we found that the effect sizes of each 10 μg/m^3 increase in PM were larger in smaller PM than those in larger PM, and the effect sizes of PM measured using annual averages were larger than those measured using 7-day averages.

Figure 3 presents the exposure–response relationships between short-term and long-term exposure to PM and ORs of in-hospital case fatality. For the short-term exposure (Figure 3A), we observed a consistent concave-down trend of the nonlinear associations with the risk of in-hospital fatality. Similarly, we also observed a concave-down trend for annual means of PM_1 and PM_{10} with the risk of in-hospital fatality, except that the trend for annual exposure to $PM_{2.5}$ with in-hospital fatality was a slight concave-up relationship (Figure 3B).

Sensitivity Analyses

Table 3 demonstrates the results of sensitivity analyses. The results were highly consistent with the primary analyses (1) using Elixhauser comorbidity score as a more comprehensive measurement of comorbidities than the 6 comorbidity dummy variables in the main models, (2) using Cox proportional hazard model to re-estimate the results, and (3) when stratified by different provinces. We observed a consistent trend that the effect sizes per 10 μg/m^3 increment in PM pollutants were larger in PM of smaller sizes, and effect sizes of annual means were larger than those of daily means. When stratified by different provinces, we still observed the general pattern of smaller PM associated with larger effect sizes.

In 2-pollutant models using different lags (lag 0 to lag 7) and moving averages (MA01 to MA07) for 7-day and annual averages of exposure to PM (eFigure 2 and eTable 1, links.lww.com/WNL/B983), we observed a consistent pattern that both short-term and long-term exposure to PM were associated with elevated risk of stroke case fatality when CO, O_3, and SO_2 were included in the model sequentially. The 2-pollutant models when controlling for NO_2 showed null or extremely slight protective association of PM, which may be subject to the strong association between NO_2 and PM_1, $PM_{2.5}$, and PM_{10} (eFigure 3).

When the exposure to PM was measured at yearly 1 × 1 km resolution grids, the results for main models and sensitivity analysis models (eTable 2, links.lww.com/WNL/B983) were highly consistent with those of 365-day averages, shown in Table 2. Results of sensitivity analyses in which participants with incomplete occupation and marital status were excluded are shown in eTable 3, and the results revealed a consistent pattern that ORs per 10 μg/m^3 increment were larger for PM with smaller sizes.

Potential Reducible In-Hospital Fatalities Attributable to PM Air Pollution

The total potential reducible in-hospital fatalities are a product of the toxicity of PM (ORs per 10 μg/m^3 increment in PM) and potential reducible level of PM. Although previous analyses showed that the effect sizes of 10 μg/m^3 increases were larger for smaller PM (OR: PM_1 > $PM_{2.5}$ > PM_{10}), the potential reducible in-hospital fatalities may not exhibit a similar trend because the distributions of PM_1, $PM_{2.5}$, and PM_{10} vary substantially (Figure 4, C and D). For example, the averages of short-term exposure to PM_1, $PM_{2.5}$, and PM_{10} were 31.4, 45.4, and 78.8 μg/m^3 (Table 1), and the corresponding fifth percentiles were 12.6, 17.7, and 31.3 μg/m^3 (Figure 4C and eTable 4, links.lww.com/WNL/B983), representing 18.8, 27.7, and 47.5 μg/m^3 potential level of reduction for PM_1, $PM_{2.5}$, and PM_{10} in our counterfactual scenarios, respectively.

Figure 4, A and B, and eTable 4 (links.lww.com/WNL/B983) present the potential reducible fraction and number of in-hospital fatalities associated with PM_1, $PM_{2.5}$, and PM_{10}. PM_{10} was associated with the largest potential reducible fraction and number (10% [95% CI 8.3–11.7] and 3,199 [2,653–3,746] fatalities for short-term exposure; 21.1% [95% CI 19.1–23] and 6,766 [95% CI 6,139–7,393] fatalities for long-term exposure), followed by PM_1 (9.4% [95% CI 7.5–11.3] and 3,013 [95% CI 2,403–3,624] fatalities for short-term exposure; 18.4% [95% CI 16.7–20.2] and 5,917 [95% CI 5,354–6,479] fatalities for long-term exposure), and $PM_{2.5}$

Figure 2 Location of the 4 Sample Provinces (Sichuan, Shanxi, Guangxi, and Guangdong [Zhanjiang City Only]) and the Geographic Distribution of the Stroke Hospitalizations in the 4 Provinces

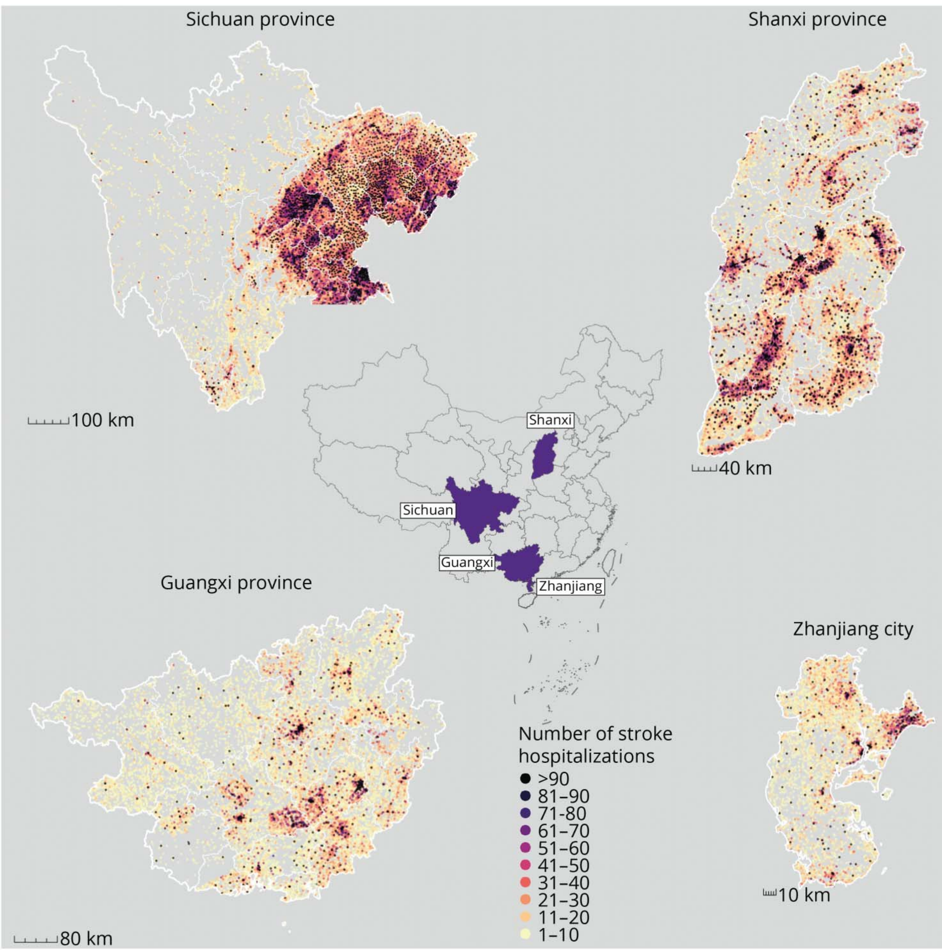


Table 1 In-Hospital Outcomes, Environmental Variables, and Patient Characteristics by Case Fatality

Characteristic	Overall (n = 3,109,634)	Case fatality		*p* Value
		No (n = 3,077,494)	Yes (n = 32,140)	
In-hospital outcomes				
Case fatality	32,140 (1.03)			
7-day moving averages of air pollutants and meteorologic variables prior to hospitalization				
PM_1, μg/m^3	31.38 (17.43)	31.38 (17.45)	31.40 (16.18)	0.78
$PM_{2.5}$, μg/m^3	45.43 (25.80)	45.42 (25.78)	46.55 (26.79)	<0.001
PM_{10}, μg/m^3	78.75 (38.24)	78.78 (38.23)	75.68 (38.24)	<0.001
Temperature, °C	14.91 (8.98)	14.90 (8.98)	15.47 (8.35)	<0.001
Relative humidity, %	65.90 (16.25)	65.85 (16.27)	70.56 (13.86)	<0.001
Annual exposure to PM prior to hospitalization				
PM_1, μg/m^3	32.98 (8.27)	32.99 (8.28)	32.12 (7.28)	<0.001
$PM_{2.5}$, μg/m^3	49.08 (12.32)	49.06 (12.32)	51.01 (12.64)	<0.001
PM_{10}, μg/m^3	87.32 (17.66)	87.34 (17.66)	85.47 (17.36)	<0.001
Patient demographics and socioeconomic status				
Age, y	67.23 (12.22)	67.21 (12.19)	70.00 (14.72)	<0.001
Sex				<0.001
Female	1,343,990 (43.22)	1,332,093 (43.28)	11,897 (37.02)	
Male	1,765,644 (56.78)	1,745,401 (56.72)	20,243 (62.98)	
Ethnicity				0.091
Han	3,074,784 (98.88)	3,042,972 (98.88)	31,812 (98.98)	
Non-Han	34,850 (1.12)	34,522 (1.12)	328 (1.02)	
Occupation				<0.001
Public institution	81,987 (2.64)	81,037 (2.63)	950 (2.96)	
Private institution	184,542 (5.93)	182,379 (5.93)	2,163 (6.73)	
Farmer	1,643,981 (52.87)	1,631,369 (53.01)	12,612 (39.24)	
Jobless	81,526 (2.62)	80,520 (2.62)	1,006 (3.13)	
Retired	377,263 (12.13)	371,278 (12.06)	5,985 (18.62)	
Other	740,335 (23.81)	730,911 (23.75)	9,424 (29.32)	
Marital status				<0.001
Married	2,593,695 (83.41)	2,568,707 (83.47)	24,988 (77.75)	
Unmarried	86,244 (2.77)	84,016 (2.73)	2,228 (6.93)	
Widowed	150,583 (4.84)	147,969 (4.81)	2,614 (8.13)	
Divorced	39,532 (1.27)	38,387 (1.25)	1,145 (3.56)	
Other	239,580 (7.70)	238,415 (7.75)	1,165 (3.62)	
Stroke type				<0.001
Hemorrhagic	764,414 (24.58)	746,417 (24.25)	17,997 (56.00)	
Ischemic	2,206,840 (70.97)	2,194,499 (71.31)	12,341 (38.40)	
Unspecified	138,380 (4.45)	136,578 (4.44)	1,802 (5.61)	

Continued

Table 1 In-Hospital Outcomes, Environmental Variables, and Patient Characteristics by Case Fatality *(continued)*

Characteristic	Overall (n = 3,109,634)	Case fatality No (n = 3,077,494)	Case fatality Yes (n = 32,140)	*p* Value
Comorbidities and procedures				
Hypertension	1,618,594 (52.05)	1,601,874 (52.05)	16,720 (52.02)	0.922
Diabetes	414,174 (13.32)	409,208 (13.30)	4,966 (15.45)	<0.001
Congestive heart failure	106,403 (3.42)	103,177 (3.35)	3,226 (10.04)	<0.001
Cardiac arrhythmias	163,320 (5.25)	159,560 (5.18)	3,760 (11.70)	<0.001
Peripheral vascular disorders	287,697 (9.25)	286,714 (9.32)	983 (3.06)	<0.001
Liver disease	85,032 (2.73)	83,638 (2.72)	1,394 (4.34)	<0.001
Elixhauser comorbidity score	4.06 (3.94)	4.04 (3.91)	5.81 (5.96)	<0.001
Intracranial procedure	52,766 (1.70)	50,103 (1.63)	2,663 (8.29)	<0.001
Hospital level				
Nontertiary	1,664,400 (53.52)	1,649,484 (53.60)	14,916 (46.41)	<0.001
Tertiary	1,445,234 (46.48)	1,428,010 (46.40)	17,224 (53.59)	

Abbreviations: PM = particulate matter; PM_1 = ambient particulate matter with diameter ≤2.5 μm.
Values are n (%) or mean (SD).

(9.2% [95% CI 7.6–10.9] and 2,962 [95% CI 2,432–3,493] fatalities for short-term exposure; 17.4% [95% CI 15.4–19.3] and 5,579 [95% CI 4,953–6,206] fatalities for long-term exposure). Long-term exposure to PM was associated with around twice the potential reducible fraction and number of in-hospital case fatalities compared with short-term exposure.

Discussion

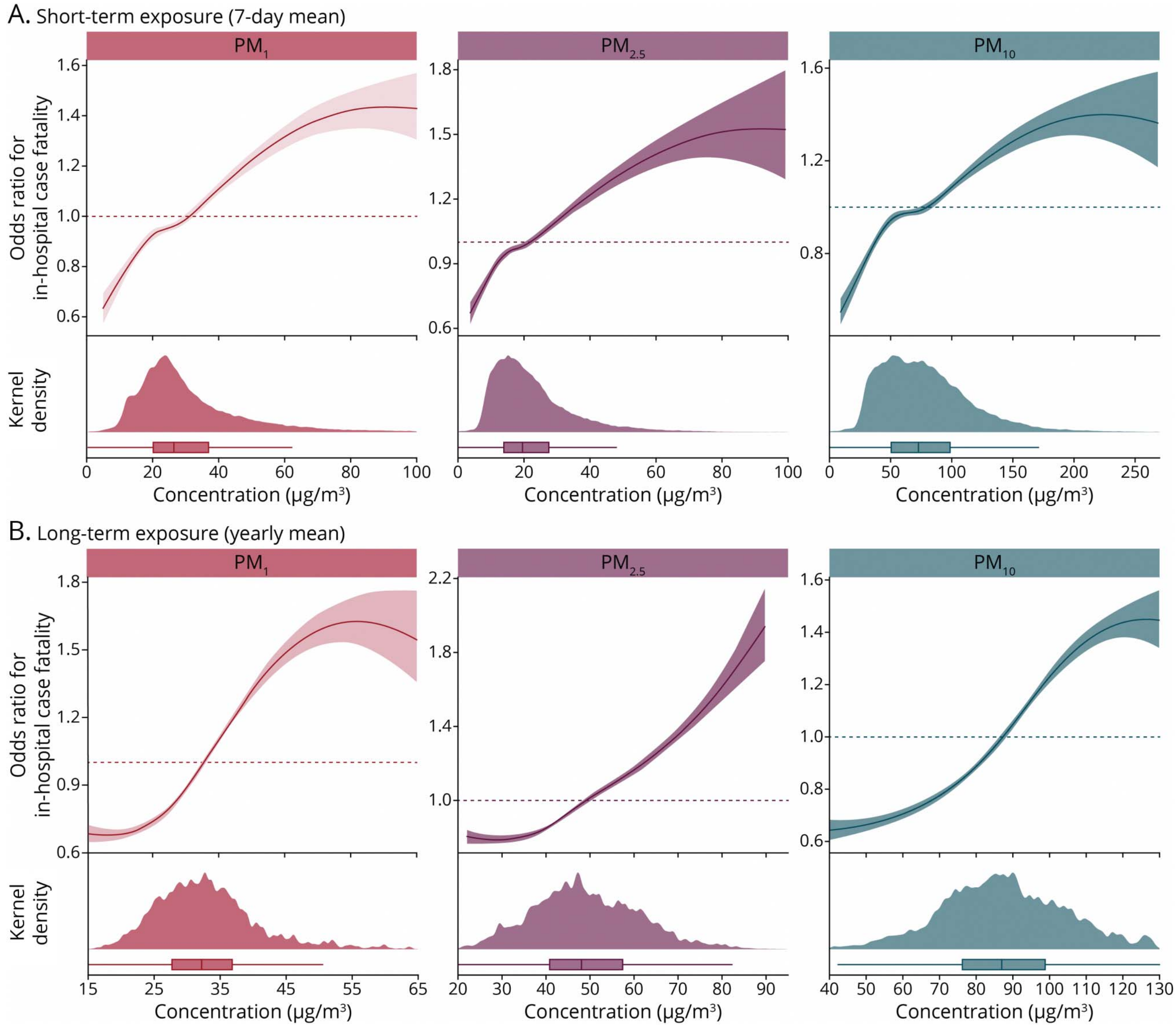
Based on the sample of 3,109,634 hospitalized stroke cases in 4 provinces of China, we found robust evidence that exposure to ambient PM of different sizes was associated with an increased risk of in-hospital case fatality. We observed a graded

Table 2 Association of 10 μg/m^3 Increase in PM_1, $PM_{2.5}$, or PM_{10} With In-Hospital Stroke Fatality Among 3,109,634 Stroke Hospitalizations in China

	PM_1	$PM_{2.5}$	PM_{10}
Main models			
7-day mean (short-term)	1.058 (1.047–1.068)	1.037 (1.031–1.043)	1.025 (1.021–1.029)
Annual mean (long-term)	1.240 (1.217–1.265)	1.105 (1.094–1.116)	1.090 (1.082–1.099)
Models stratified by stroke types			
7-day mean (short-term)			
Ischemic (n = 2,206,840)	1.066 (1.050–1.083)	1.044 (1.035–1.053)	1.031 (1.025–1.038)
Hemorrhagic (n = 764,414)	1.046 (1.032–1.060)	1.022 (1.014–1.030)	1.012 (1.007–1.018)
Unspecified (n = 138,380)	1.059 (1.010–1.110)	1.055 (1.028–1.084)	1.037 (1.017–1.056)
Annual mean (long-term)			
Ischemic (n = 2,206,840)	1.238 (1.206–1.271)	1.118 (1.100–1.136)	1.089 (1.075–1.103)
Hemorrhagic (n = 764,414)	1.232 (1.194–1.272)	1.070 (1.056–1.085)	1.071 (1.059–1.082)
Unspecified (n = 138,380)	1.279 (1.174–1.392)	1.174 (1.126–1.224)	1.164 (1.124–1.206)

Abbreviation: PM = particulate matter.
Values are odds ratio (95% CI).

Figure 3 Exposure–Response Relationships Between Short-Term and Long-Term Exposure to Particulate Matter and Odds Ratios of In-Hospital Case Fatality



Exposure–response relationships of (A) short-term and (B) long-term exposure to PM_1, $PM_{2.5}$, and PM_{10} with stroke in-hospital case fatality (upper panels), as well as the kernel density curves and boxplots of PM_1, $PM_{2.5}$, and PM_{10} distribution of sample cases (lower panels). The pollutants were measured as 7-day means prior to hospitalization and annual means prior to the year of hospitalization. The daily and annual pollution data were assessed using 10 × 10 km grids. The pollutants were trimmed at 0.1-th percentiles to avoid excessively large CIs and abnormally nonlinear patterns due to small sample sizes. The solid lines with shaded bands in the upper panels indicate the changes in odds ratios of in-hospital stroke case fatality and their 95% CIs, respectively. PM = particulate matter.

increase in the risk of in-hospital fatality when the sizes of PM were smaller. The associations of PM and in-hospital case fatality were stronger among patients with ischemic stroke than those among patients with hemorrhagic stroke. Long-term exposure to PM was associated with a higher risk of in-hospital fatality. These findings were consistent and robust in multiple sensitivity analyses including those using multiple lags and moving averages of exposure, alternating the pollutant models and statistical models, comorbidity adjustments, and resolution of exposure grids, as well as subgroups analyses in different provinces. Counterfactual analyses suggested that PM_{10} was associated with the largest reducible fraction of in-hospital fatality, followed by PM_1, and $PM_{2.5}$.

Our study supports the longstanding assumption that exposure to smaller PM is more harmful than exposure to larger PM.[40-42] Our study includes measurements of PM_1, which may be small enough to be inhaled deeply into lungs, pass through lung tissue, penetrate biological membranes, and circulate in the bloodstream.[41] Previous toxicologic experiments also supported the assumption that smaller PM exhibits larger toxicity per unit increment than that of larger particles through various mechanisms such as oxidative stress and vascular inflammation.[40-42] Among hospitalized patients with stroke, who are generally sicker than patients with stroke without hospitalization, ambient PM pollution may increase the risk of death through recurrent cerebrovascular events or

Table 3 Exposure–Response Relationships Between Short-Term and Long-Term Exposure to Particulate Matter and Odds Ratios of In-Hospital Case Fatality

	PM_1	$PM_{2.5}$	PM_{10}
Short-term association using 7-day mean of air pollutants			
Elixhauser comorbidity score, OR	1.056 (1.046–1.067)	1.036 (1.030–1.041)	1.024 (1.020–1.028)
Cox proportional hazard model, HR	1.042 (1.032–1.052)	1.027 (1.022–1.033)	1.017 (1.013–1.020)
By different provinces and cities			
Sichuan (n = 1,434,524), OR	1.050 (1.035–1.065)	1.022 (1.015–1.030)	1.017 (1.011–1.023)
Shanxi (n = 1,369,536), OR	1.033 (1.013–1.053)	1.042 (1.030–1.053)	1.019 (1.011–1.027)
Guangxi and Zhanjiang (n = 305,574), OR	1.147 (1.116–1.179)	1.091 (1.074–1.108)	1.065 (1.052–1.077)
Long-term association using annual mean of air pollutants			
Elixhauser comorbidity score, OR	1.242 (1.218–1.266)	1.104 (1.093–1.115)	1.091 (1.083–1.010)
Cox proportional hazard model, HR	1.170 (1.148–1.192)	1.077 (1.067–1.188)	1.071 (1.063–1.080)
By different provinces and cities			
Sichuan (n = 1,434,524), OR	1.236 (1.205–1.269)	1.107 (1.089–1.124)	1.102 (1.089–1.114)
Shanxi (n = 1,369,536), OR	1.185 (1.135–1.237)	1.098 (1.072–1.124)	1.075 (1.058–1.093)
Guangxi and Zhanjiang (n = 305,574), OR	1.378 (1.302–1.457)	1.233 (1.198–1.270)	1.154 (1.130–1.178)

Abbreviations: HR = hazard ratio; OR = odds ratio; PM = particulate matter.
95% CIs presented in parentheses.

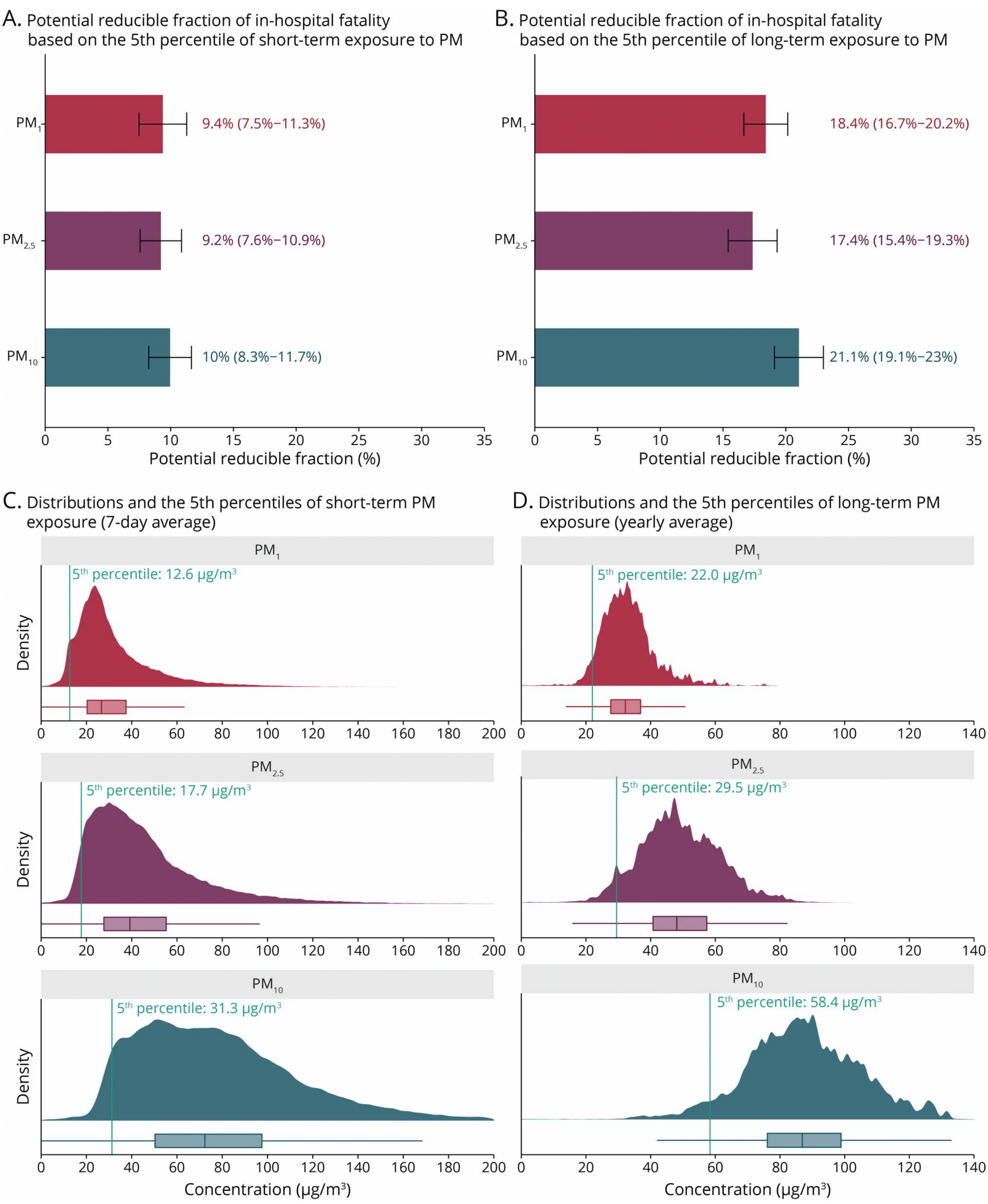
other complications.[43] Our epidemiologic results also show that the PM and in-hospital mortality association were stronger among patients with ischemic stroke than patients with hemorrhagic stroke; this may increase the likelihood of biological pathways specific to ischemic stroke including vascular inflammation, changing vasomotor tone, and accelerating atherosclerosis.[44-46] However, the biological mechanism underlying our observed association among patients with hospitalized stroke is not clear and remains to be investigated.

Although our logistic regressions showed larger effect sizes per 10 μg/m^3 increase in smaller PM, the results of the counterfactual analyses indicated that PM_{10} was associated with the largest potential reducible number of in-hospital fatalities and fractions. These seemingly contradictory results are caused by the stark difference in the distribution of PM_1, $PM_{2.5}$, and PM_{10}. Compared with a more concentrated distribution of smaller PM, the distribution of larger PM was more diffuse on the higher end, which led to more potential for reduction in PM in counterfactual scenarios of the fifth percentile. The fifth percentiles of annual exposure to PM in this study (29.5 μg/m^3 for $PM_{2.5}$ and 58.4 μg/m^3 for PM_{10}) were higher than the WHO guideline (10 μg/m^3 for $PM_{2.5}$ and 20 μg/m^3 for PM_{10}) and the European guideline (20 μg/m^3 for $PM_{2.5}$ and 40 μg/m^3 for PM_{10}).[35] This indicates that setting the counterfactual thresholds to levels commensurate with those specified by the European guidelines (20 μg/m^3 for $PM_{2.5}$ and 40 μg/m^3 for PM_{10}, much lower than our fifth percentile) will result in greater potential reducible fraction and number of stroke fatalities within hospitals.

The results of counterfactual analyses indicate that ambient PM_{10} was associated with a larger burden of stroke in-hospital case fatality compared with smaller PM including PM_1 and $PM_{2.5}$. The results suggest that public health policy efforts should consider targeting reducing ambient PM_{10} instead of focusing on smaller PM (PM_1 and $PM_{2.5}$); this may have more public health benefits on reducing stroke in-hospital case fatality and ameliorating the health outcomes of hospitalized patients with stroke. Although PM_1 showed larger effect sizes for in-hospital case fatality, the level of PM_1 pollution was low compared with that of PM_{10} in our sample and the overall health benefits of reducing PM_1 may not be as effective as those of reducing PM_{10}.

Compared with previous studies that investigated case fatality rate among patients with stroke, the in-hospital case fatality rate in this study appears to be relatively low (1.03%). For example, Zhang et al. reported that the 1-month case fatality rate of ischemic stroke in Asia was 10.8% (95% CI 8.3–13.5).[47] Another study showed the rate of in-hospital death or discharge against medical advice was 8.3% among 3 million stroke inpatients from 1,853 tertiary Chinese hospitals in 2018.[48] Three reasons may explain the low case fatality rate in our study. First, our study included hospitalized patients with stroke in primary, secondary, and tertiary hospitals in the 4 sample provinces in China. Tertiary hospitals primarily focus on the treatment and

Figure 4 Potential Reducible Fraction of In-Hospital Stroke Case Fatality Attributable to Short-Term and Long-Term Ambient PM_1, $PM_{2.5}$, and PM_{10} Based on a Counterfactual Scenario of the 5th Percentiles of Air Pollutant Distributions



(A–D) Potential reducible fractions and distributions. The error bars in A and B are the 95% CIs calculated based on 1,000 bootstrap samples. PM = particulate matter.

care of acute stroke; primary and secondary hospitals (53.5% of the total sample were hospitalized in nontertiary hospitals) play a major role in stroke rehabilitation and care for nonsevere stroke,[11] and these patients had lower case fatality rate. Second, there may be recurrent hospitalizations in our sample, which may expand the denominator (the number of participants at risk) and dilute the case fatality rate. Third, many patients with stroke at terminal status would prefer to die at home than in hospitals owing to the Chinese culture of strong family ties and hospice care[16]; this would also lead to low in-hospital case fatality rates in our sample.

The study has a few limitations. The sample hospitalized stroke cases were collected at the convenience of data accessibility and may have limited generalizability to hospitalized stroke cases in other provinces in China. Although we accounted for several known covariates, we cannot exclude the possibility of missing covariate bias. For example, our study did not adjust for a few covariates including smoking status, body mass index, and the severity of stroke. The exposure was measured at the current residential addresses, so we were unable to account for exposure in previous residential addresses within the past year, indoor exposure to air pollutants during the hospitalization period, or occupational exposure at nonresidential addresses. Although we re-estimated the results using Cox proportional hazard models in sensitivity analyses, the follow-up periods were computed using in-hospital length of stay and were relatively short. In addition, we cannot capture the outcomes of the nonfatality cases after they were discharged from hospitals. In-hospital case fatality has very specific setting and the biological mechanism underlying the positive association in this study is unclear and remains to be investigated.

Compared with Europe and North America, the level of air pollution in this study is high (annual $PM_{2.5}$ was around 50 $\mu g/m^3$), and evidence on exposure to air pollution and stroke case fatality is scarce using individual-level data at this elevated level of air pollution. The estimated association of ambient PM and stroke mortality in China suggest efforts to reduce PM air pollution may help ameliorate in-hospital outcomes of people with stroke in developing countries, where the level of air pollution and the burden of stroke mortality are high.[49] To our knowledge, this is the first study that investigates the relationship between exposure to PM of varied sizes and in-hospital case fatality among a large multiprovince sample of patients with stroke. The association of exposure to air pollution and stroke mortality has been well reported, but we have not found any evidence of exposure to air pollution and in-hospital case fatality among patients with stroke at individual level. A key strength of the study is the large sample size and individual-level data with >3 million stroke cases, spanning multiple provinces in central, western, and southern China.

Among 3.1 million stroke hospitalizations in China, exposure to PM was consistently associated with increased risk of in-hospital case fatality, where smaller PM and long-term exposure to PM exhibited larger toxicity. The results suggest that prioritizing efforts to reduce the level of PM air pollution may improve the health outcomes of people hospitalized with stroke.

Acknowledgment

The authors thank the Health Commissions of Sichuan, Shanxi, Guangxi, and Guangdong provinces for granting access to data for research. This work was supported by the Ohio Supercomputer Center (PMIU 0180). The data providers and funders had no role in the design, data analyses and interpretation, manuscript development, or submission.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* September 17, 2021. Accepted in final form March 2, 2022. Submitted and externally peer reviewed. The handling editor was Brad Worrall, MD, MSc.

Appendix Authors

Name	Location	Contribution
Miao Cai, PhD	Department of Epidemiology, School of Public Health, Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Shiyu Zhang	Department of Epidemiology, School of Public Health, Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Xiaojun Lin, PhD	HEOA Group, West China School of Public Health and West China Fourth Hospital, Sichuan University; Institute for Healthy Cities and West China Research Center for Rural Health Development, Sichuan University, Chengdu, Sichuan, China	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Zhengmin Qian, PhD	Department of Epidemiology and Biostatistics, College for Public Health & Social Justice, Saint Louis University, MO	Drafting/revision of the manuscript for content, including medical writing for content
Stephen Edward McMillin, PhD	School of Social Work, College for Public Health and Social Justice, Saint Louis University, MO	Drafting/revision of the manuscript for content, including medical writing for content
Yin Yang, PhD	Department of Epidemiology, School of Public Health, Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content

Continued

Appendix *(continued)*

Name	Location	Contribution
Zilong Zhang, PhD	Department of Epidemiology, School of Public Health, Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content
Jay Pan, PhD	HEOA Group, West China School of Public Health and West China Fourth Hospital, Sichuan University; Institute for Healthy Cities and West China Research Center for Rural Health Development, Sichuan University, Chengdu, Sichuan, China	Major role in the acquisition of data
Hualiang Lin, PhD	Department of Epidemiology, School of Public Health, Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

References

1. Global Burden of Disease Study Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018; 392(10159):1736-1788.
2. Lanas F, Seron P. Facing the stroke burden worldwide. *Lancet Glob Health.* 2021;9(3): e235–e236.
3. Ma Q, Li R, Wang L, 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(12):e897–e906.
4. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. *Circ Res.* 2017;120(3):472-495.
5. Mateen FJ, Brook RD. Air pollution as an emerging global risk factor for stroke. *JAMA.* 2011;305(12):1240-1241.
6. Shah AS, Lee KK, McAllister DA, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ.* 2015;350:h1295.
7. Tian Y, Liu H, Zhao Z, et al. Association between ambient air pollution and daily hospital admissions for ischemic stroke: a nationwide time-series analysis. *PLoS Med.* 2018;15(10):e1002668.
8. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation.* 2017;135(8):759-771.
9. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2019;394(10204):1145-1158.
10. Yin P, Brauer M, Cohen AJ, et al. The effect of air pollution on deaths, disease burden, and life expectancy across China and its provinces, 1990-2017: an analysis for the Global Burden of Disease Study 2017. *Lancet Planet Health* 2020;4(9):e386–e398.
11. Cai M, Liu E, Tao H, Qian Z, Lin X, Cheng Z. Does level of hospital matter? A study of mortality of acute myocardial infarction patients in Shanxi, China. *Am J Med Qual.* 2018;33(2):185-192.
12. Cai M, Liu E, Li W. Rural versus urban patients: benchmarking the outcomes of patients with acute myocardial infarction in Shanxi, China from 2013 to 2017. *Int J Environ Res Public Health.* 2018(9):15.
13. Lin X, Cai M, Tao H, et al. Insurance status, inhospital mortality and length of stay in hospitalised patients in Shanxi, China: a cross-sectional study. *BMJ Open* 2017;7(7):e015884.
14. Lu L, Pan J. The association of hospital competition with inpatient costs of stroke: evidence from China. *Soc Sci Med.* 2019;230:234-245.
15. Cai M, Liu E, Zhang R, et al. Comparing the performance of Charlson and Elixhauser comorbidity indices to predict in-hospital mortality among a Chinese population. *Clin Epidemiol.* 2020;12:307-316.
16. Cai M, Liu E, Tao H, et al. Does a medical consortium influence health outcomes of hospitalized cancer patients? An integrated care model in Shanxi, China. *Int J Integr Care* 2018;18(2):7.
17. Lin X, Green JC, Xian H, Cai M, Skrzypek J, Tao H. Holiday and weekend effects on mortality for acute myocardial infarction in Shanxi, China: a cross-sectional study. *Int J Public Health* 2020;65(6):847-857.
18. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, Revisions 9 and 10. *Stroke.* 2005;36(8):1776-1781.
19. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of diagnostic codes for acute stroke in administrative databases: a systematic review. *PLoS One* 2015;10(8):e0135834.
20. Hammond G, Luke AA, Elson L, Towfighi A, Joynt Maddox KE. Urban-rural inequities in acute stroke care and in-hospital mortality. *Stroke.* 2020;51(7):2131-2138.
21. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project: World Health Organization monitoring trends and determinants in cardiovascular disease. *Stroke.* 1995;26(3):361-367.
22. Wei J, Li Z, Cribb M, et al. Improved 1 km resolution PM 2.5 estimates across China using enhanced space–time extremely randomized trees. *Atmos Chem Phys.* 2020; 20(6):3273-3289.
23. Wei J, Li Z, Guo J, et al. Satellite-derived 1-km-resolution PM1 concentrations from 2014 to 2018 across China. *Environ Sci Technol.* 2019;53(22):13265-13274.
24. Wei J, Li Z, Lyapustin A, et al. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. *Remote Sensing Environ.* 2021;252:112136.
25. Wei J, Li Z, Xue W, et al. The ChinaHighPM10 dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China. *Environ Int.* 2021;146: 106290.
26. Muñoz-Sabater J, Dutra E, Agustí-Panareda A, et al. ERA5-Land: a state-of-the-art global reanalysis dataset for land applications. *Earth Syst Sci Data Discuss.* 2021;2021: 1-50.
27. A map developer guideline: geocode/reverse geocode: a map open-source platform. Accessed July 21, 2021. lbs.amap.com/api/webservice/guide/api/georegeo
28. Dong L, Li S, Yang J, Shi W, Zhang L. Investigating the performance of satellite-based models in estimating the surface PM2.5 over China. *Chemosphere.* 2020;256: 127051.
29. Lin LY, Chuang HC, Liu IJ, Chen HW, Chuang KJ. Reducing indoor air pollution by air conditioning is associated with improvements in cardiovascular health among the general population. *Sci Total Environ.* 2013;463-464:176-181.
30. Cai M, Xie Y, Bowe B, et al. Temporal trends in incidence rates of lower extremity amputation and associated risk factors among patients using Veterans Health Administration services from 2008 to 2018. *JAMA Netw Open.* 2021;4(1):e2033953.
31. Cai M, Zhang B, Yang R, et al. Association between maternal outdoor physical exercise and the risk of preterm birth: a case-control study in Wuhan, China. *BMC Pregnancy Childbirth.* 2021;21(1):206.
32. Bowe B, Artimovich E, Xie Y, Yan Y, Cai M, Al-Aly Z. The global and national burden of chronic kidney disease attributable to ambient fine particulate matter air pollution: a modelling study. *BMJ Glob Health.* 2020;5(3):e002063.
33. Xie Y, Bowe B, Yan Y, Cai M, Al-Aly Z. County-level contextual characteristics and disparities in life expectancy. *Mayo Clin Proc.* 2021;96(1):92-104.
34. Cai M, Bowe B, Xie Y, Al-Aly Z. Temporal trends of COVID-19 mortality and hospitalisation rates: an observational cohort study from the US Department of Veterans Affairs. *BMJ Open* 2021;11(8):e047369.
35. World Health Organization. Application of guidelines in policy formulation: particulate matter, ozone, nitrogen dioxide and sulfur dioxide. In: *Air Quality Guidelines Global Update 2005*. World Health Organization; 2006:173-188.
36. R Core Team. *R: A Language and Environment for Statistical Computing*; 2013.
37. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care.* 1998;36(1):8-27.
38. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11): 1130-1139.
39. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care.* 2009;47(6):626-633.
40. Wang X, Hart JE, Liu Q, Wu S, Nan H, Laden F. Association of particulate matter air pollution with leukocyte mitochondrial DNA copy number. *Environ Int.* 2020;141: 105761.
41. Ohlwein S, Kappeler R, Kutlar Joss M, Kunzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. *Int J Public Health.* 2019;64(4):547-559.
42. Bhargava A, Tamrakar S, Aglawe A, et al. Ultrafine particulate matter impairs mitochondrial redox homeostasis and activates phosphatidylinositol 3-kinase mediated DNA damage responses in lymphocytes. *Environ Pollut.* 2018;234:406-419.
43. Kettunen J, Lanki T, Tiittanen P, et al. Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. *Stroke.* 2007; 38(3):918-922.
44. Qiu H, Sun S, Tsang H, et al. Fine particulate matter exposure and incidence of stroke: a cohort study in Hong Kong. *Neurology.* 2017;88(18):1709-1717.
45. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA.* 2005;294(23): 3003-3010.
46. Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol.* 2002;39(6): 935-942.
47. Zhang R, Wang Y, Fang J, Yu M, Wang Y, Liu G. Worldwide 1-month case fatality of ischaemic stroke and the temporal trend. *Stroke Vasc Neurol.* 2020 Dec;5(4): 353-360.
48. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: a report from the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol.* 2020;5(3): 211-239.
49. Al-Aly Z, Bowe B. The road ahead for research on air pollution and kidney disease. *J Am Soc Nephrol.* 2021;32(2):260-262.