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Ambient particulate matter pollution of different sizes associated with recurrent stroke hospitalization in China: A cohort study of 1.07 million stroke patients

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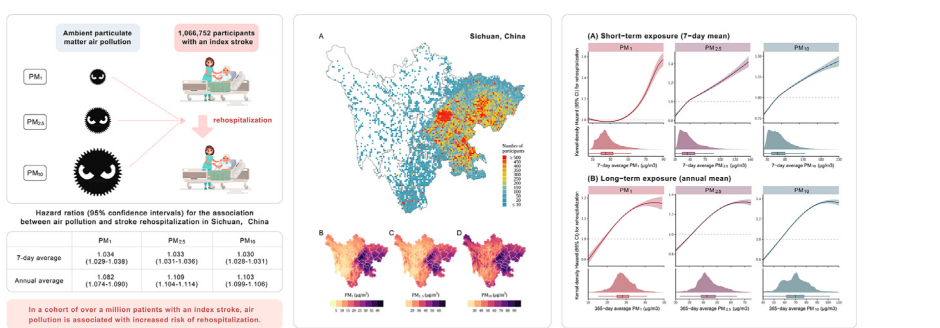
HIGHLIGHTS

- A longitudinal cohort of >1 million participants with an index stroke hospitalization in Sichuan, China.
- Bilinear interpolation was used to enhance the precision of ambient particulate matter measurement.
- Ambient particulate matter of different sizes is associated with significantly elevated risk of stroke rehospitalization.
- The associations were stronger in those who were female, of minority ethnicity, and had an ischemic stroke.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: To estimate the associations between ambient particulate matter (PM) pollution of different sizes (PM_1, $PM_{2.5}$, and PM_{10}) and risk of rehospitalization among stroke patients, as well as the attributable burden in China.
Methods: We built a cohort of 1,066,752 participants with an index stroke hospitalization in Sichuan, China from 2017 to 2019. Seven-day and annual average exposures to PM pollution prior to the date of the index hospitalization were linked with residential address using a bilinear interpolation approach. Cox proportional hazard models were constructed to assess the association between ambient PM and the risk of rehospitalization. The burden of stroke rehospitalization was estimated using a counterfactual approach.
Results: 245,457 (23.0 %) participants experienced rehospitalization during a mean of 1.15 years (SD: 0.90 years) of

Abbreviations: CHAP, China High Air Pollutants; CI, confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases, Tenth Edition; ID, identification number; NRCMS, the New Rural Cooperative Medical Scheme; PM, particulate matter; SD, standard deviation; TMREL, theoretical minimum risk exposure level; UEBMI, the Urban Employee Basic Medical Insurance; URBMI, the Urban Resident Basic Medical Insurance; WHO, World Health Organization.

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follow-up. Seven-day average concentrations of PM were associated with increased risk of rehospitalization: the hazard ratios (HRs) per 10 μg/m^3 were 1.034 (95 % confidence interval [CI]: 1.029–1.038) for PM_1, 1.033 (1.031–1.036) for $PM_{2.5}$, and 1.030 (1.028–1.031) for PM_{10}; the hazard ratios were larger for annual average concentrations: 1.082 (1.074–1.090) for PM_1, 1.109 (1.104–1.114) for $PM_{2.5}$, and 1.103 (1.099–1.106) for PM_{10}. The associations were stronger in participants who were female, of minority ethnicity (non-Han Chinese), who suffered from an ischemic stroke, and those admitted under normal conditions. Population attributable fractions for stroke rehospitalization ranged from 4.66 % (95 % CI: 1.69 % to 7.63 %) for the 7-day average of PM_1 to 17.05 % (14.27 % to 19.83 %) for the annual average of PM_{10}; the reducible average cost of rehospitalization per participant attributable to PM ranged from 492.09 (178.19 to 806) RMB for the 7-day average of PM_1 to 1801.65 (1507.89 to 2095.41) RMB for the annual average of PM_{10}.

Conclusions: Ambient PM pollution may increase the risk of rehospitalization in stroke patients and is responsible for a significant burden of stroke rehospitalization.

1. Introduction

Stroke is the second-leading cause of morbidity and mortality worldwide in 2019, causing 6.55 million deaths and 143 million disability-adjusted life years (G. B. D. Stroke Collaborators, 2021). The burden of stroke is disproportionally high in low- and middle-income countries due to a lack of public health intervention and medical care, as well as a greater prevalence of stroke risk factors (G. B. D. Stroke Collaborators, 2021; Owolabi et al., 2022; Wu et al., 2019). Survivors of an index stroke hospitalization often experience a greater functional decline and have multiple comorbidities and complications, and are therefore more vulnerable to subsequent recurrent hospital admissions (Chen et al., 2020; Lakshminarayan et al., 2011; Lin et al., 2011). Reducing unnecessary rehospitalization is a prioritized way to improve the prognosis for patients and slash medical expenses for a preponderance of medical providers (Boutwell et al., 2020).

Elevated ambient particulate matter (PM) pollution has been widely associated with increased risks of incidence, hospitalization, and mortality of stroke (Cai et al., 2022; Huang et al., 2019; Lin et al., 2017; Qiu et al., 2017; Ruan et al., 2020; Shah et al., 2015; Tian et al., 2022; Tian et al., 2018; Verhoeven et al., 2021). However, to our knowledge, no prior study has examined the association between ambient PM air pollution of different sizes and recurrent hospitalization in patients with stroke. Exposure to PM air pollution is associated with immune system disturbances, systemic inflammation, and hypercoagulability (Bowe et al., 2021; Pope et al., 2016; Rajagopalan et al., 2018), as well as the incidence of cardiopulmonary events (Eze et al., 2015; Yang et al., 2020), which may induce the occurrences of rehospitalization among patients hospitalized with stroke. The evidence above together supports the plausibility of the hypothesis that exposure to ambient PM air pollution may be associated with an elevated risk of stroke rehospitalization.

In this study, we assembled a province-wide longitudinal cohort of 1,066,752 patients who had their index stroke hospitalization in Sichuan Province, China. We aimed to examine the relationship between ambient PM pollution (PM_1, $PM_{2.5}$ and PM_{10}) and the risk of stroke rehospitalization, build the exposure-response functions to characterize the nonlinear shape of the associations, and estimate the burden of rehospitalizations (number and fraction of rehospitalization, total hospitalization cost, and cost per patient) attributable to ambient PM pollution.

2. Methods

2.1. Data source

Individual-level data for hospitalized stroke patients were obtained from a province-wide hospitalized electronic medical database from January 1, 2017 to December 31, 2019 (Deng and Pan, 2019; Lin et al., 2021; Lu and Pan, 2019). The database, standardized by the former Ministry of Health in China, continuously and regularly collects information on demographic characteristics, clinical diagnoses (*International Classification of Diseases, Tenth Edition* [ICD-10]) codes, surgical procedures, residential address, discharge status, medical cost of hospitalized patients in Sichuan Province, China (Cai et al., 2018b; Cai et al., 2018c; Lin et al., 2018). Patient's unique identification number (ID) was converted into pseudo-IDs to identify unique patients before the study team had access to the data. The study was approved by the institutional review board of Sichuan University.

2.2. Cohort construction

We identified unique patients who experienced and survived their index stroke hospitalization in Sichuan Province between January 1, 2017 and December 31, 2019. An index hospitalization was defined as the total number of hospitalizations being equal to one and the principal diagnosis code of their hospitalization being stroke. Stroke patients were identified with principal inpatient ICD-10 diagnosis codes that matched previously validated codes: ischemic stroke: I63.x and H34.1; hemorrhagic stroke: I60.x, I61.x, and G45.x; unspecified stroke: I64.x (Hammond et al., 2020; Kokotailo and Hill, 2005; McCormick et al., 2015). We excluded patients with missing pseudo-IDs, residential addresses or covariates, as well as those whose index stroke hospitalization cannot be tracked. A total of 40,863 (3.7 %) stroke hospitalizations were excluded, yielding an analytical cohort of 1,066,752 hospitalized stroke patients. Participants were followed up until the occurrences of rehospitalization, death, or administrative end of follow-up on December 31, 2019, whichever came first.

2.3. Outcomes

The primary outcomes of this study included time until the occurrence of the first recurrent hospital admission and the total inpatient costs of the first recurrent hospital admission. Rehospitalizations were identified by matching the pseudo-IDs, and time until rehospitalization was calculated as the difference between the date of the recurrent hospital admission and the discharge date of the index hospitalization.

2.4. Air pollution exposure

Daily ambient concentrations of PM_1, $PM_{2.5}$, and PM_{10} with full spatial coverage were obtained from the China High Air Pollutants (CHAP, available at https://weijing-rs.github.io/product.html) data set (10 km × 10 km grids). The exposure data were estimated using a combination of space-time machine learning models, satellite remote sensing techniques, and ground-based measurements, yielding highly accurate and stable estimates of ground-level air pollutants (cross-validation R^2: 0.83 for PM_1, 0.91 for $PM_{2.5}$, and 0.86 for PM_{10}; root mean square error: 9.25 μg/m^3 for PM_1, 12.67 μg/m^3 for $PM_{2.5}$, and 24.34 μg/m^3 for PM_{10}) (Wei et al., 2019; Wei et al., 2020; Wei et al., 2021a; Wei et al., 2021b). Patients' residential addresses were geocoded into latitude and longitude data using the application programming interface provided by amap (also known as Gaode map) (Amap open-source platform, 2022), a leading commercial-use mapping and navigation service provider in China.

The concentrations of PM_1, $PM_{2.5}$, and PM_{10} were estimated using a bilinear interpolation approach (Cai et al., 2022; Liu et al., 2022). We identified four grids closest to the residential address of each participant and assigned a weight to each of the four grids based on the distance from the residential address to the grids. The final concentration was determined by calculating the weighted average of the four closest grids, where closer grids had larger weights. Short-term exposure to air pollution was defined as the 7-day average prior to the day of the index hospitalization, and long-term exposure to air pollution was calculated as the annual (365 days) mean concentration prior to the date of the index hospitalization.

2.5. Covariates

We selected a set of covariates based on previously published studies and data availability (Cai et al., 2021a; Lin et al., 2018). The covariates were evaluated based on the data at index hospitalization. Age, sex, ethnicity (Han Chinese and minorities), marital status (married, single, widowed, divorced, and other), and occupation (public sector, private sector, agriculture, unemployed, and retired) were included as demographic and socioeconomic variables (Cai et al., 2018a). Insurance coverage was categorized as the Urban Employee Basic Medical Insurance (UEBMI), the Urban Resident Basic Medical Insurance (URBMI), the New Rural Cooperative Medical Scheme (NRCMS), and self-payment (Lin et al., 2017). We also controlled for common comorbidities including stroke subtypes (ischemic, hemorrhagic, and unspecified stroke), hypertension, diabetes, congestive heart failure, cardiac arrhythmias, peripheral vascular disorders, and chronic pulmonary disease (Cai et al., 2021b). Admission severity was defined by the doctor or nurse at the time of index hospitalization, and it included normal, emergent, and dangerous. Daily data on temperature and relative humidity were measured at 9 km × 9 km resolutions from the fifth generation of European ReAnalysis (ERA5)-Land reanalysis data set (Muñoz-Sabater et al., 2021). 7-day averages of temperature and relative humidity were controlled for as natural cubic splines with four degrees of freedom.

2.6. Statistical analyses

Characteristics of the overall cohort and by rehospitalization status were reported as mean (standard deviations, SD) or frequency (percent). We constructed Cox proportional hazard models to estimate the association of baseline ambient exposure to PM_1, $PM_{2.5}$, and PM_{10} with the risk of rehospitalization with full adjustment of the covariates. We did not test the proportional hazard assumption because it is unnecessary and expected to be unmet in this large cohort study of over one million participants (Stensrud and Hernan, 2020). In this study, a hazard ratio (HR) is interpreted as a weighted average of the true HR during the follow-up. To characterize the exposure-response curves and assess any potential nonlinearity, we re-constructed the Cox regression models with the concentration of air pollutants included as natural cubic splines and generated the marginal effect plots. The unadjusted and adjusted HRs and 95 % confidence intervals (95 % CIs) were reported separately for short-term and long-term exposures.

To estimate the potential reducible number and fraction of rehospitalization attributed to PM_1, $PM_{2.5}$, and PM_{10}, we predicted the number of rehospitalization based on our main multivariable Cox regression models and a counterfactual scenario of air pollutant concentrations. The counterfactual scenario was set to be hypothetical concentrations of PM that achieved the optimal 5th percentiles in the cohort, which are also known as the theoretical minimum risk exposure level (TMREL) in the methodologies of the Global Burden of Disease studies (Bowe et al., 2020; Cohen et al., 2017; Xie et al., 2021). If the actual levels of PM for the participants were lower than the 5th percentiles, they were kept the same in the counterfactual scenario. The guideline levels specified by the World Health Organization (WHO) (World Health Organization, 2021) were not used in this study as there were no guideline levels for either 24-h or one-year PM_1. The differences between the observed and predicted number of rehospitalizations (using the 5th percentiles of PM_1, $PM_{2.5}$, and PM_{10}) while other covariates remained unchanged were used to represent the potential reducible number of rehospitalizations attributable to PM_1, $PM_{2.5}$, and PM_{10}, respectively. The potential reducible fractions were computed as dividing the attributable number of rehospitalizations by the observed total number of rehospitalizations; similarly, the potential reducible inpatient costs were evaluated as the product of the number of rehospitalizations and average inpatient cost of rehospitalizations. The associated 95 % CIs were estimated based on the prediction intervals generated by the Cox regression models.

We assessed potential effect modification of the association between ambient PM pollution and the risk of rehospitalization by age group, sex, ethnicity, stroke subtypes, and admission severity by conducting formal interaction analyses. The statistical significance of the interaction analyses was determined by adding interaction terms for each subgroup variable in separate models, and the *p*-values for the joint significance with multiple subgroups were determined using analysis of variance.

All statistical tests were two-sided, and HRs of which the 95 % CIs excluded unity were considered statistically significant. The data cleaning, statistical modeling, and data visualization were conducted in statistical computing environment R 4.1.2 (R Core Team, 2013). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.7. Sensitivity analyses

We conducted several sensitivity analyses to test the robustness of the findings to alternative exposure measurement, outcome definition, and covariate sets. (A) To test the consistency of results on short-term exposure to varying lag periods, we assessed short-term exposure to PM pollution using different lag periods (a lag of 0 day to 7 days and moving averages of a lag of 0–1 days to a lag of 0–7 days; for example, lag 02 is the average exposure between two days prior to the day of hospitalization and the day of hospitalization) and estimated the models. (B) To assess the robustness of long-term exposure assessment, we leveraged a CHAP annual data set with a much higher spatial resolution of 1 km × 1 km grids as the alternative data source for ambient PM_1, $PM_{2.5}$, and PM_{10} (Wei et al., 2020; Wei et al., 2021a) and estimated our main models; this data source is not used in our main models because it is available only for annual means and daily data at 1 km × 1 km grids were not yet available at the time of this study. (C) Because 30-day readmission has been widely acknowledged as an important metric for quality of care (Bambhroliya et al., 2018; Leppert et al., 2020), we estimated the association between ambient PM pollution and rehospitalization within and beyond 30 days respectively. (D) To capture more comorbidities as covariate while mitigating the issue of including too many covariates, we adjusted for Elixhauser comorbidity scores (Elixhauser et al., 1998; Quan et al., 2005; van Walraven et al., 2009) as an alternative measure of comorbidities, which were numeric values of weighted summation of 31 comorbidities and showed overall good prediction accuracy of in-hospital health outcomes in China (Cai et al., 2020). (E) To further test the sensitivity of results to unmeasured confounding and measure the strength of causality, we calculated the E-value for each of our univariate and multivariable Cox proportional hazard models. E-value is defined as the minimum strength of association that an unmeasured confounder would be needed to explain away the observed exposure-outcome association, conditional on the observed covariates (Mathur et al., 2018; VanderWeele and Ding, 2017; VanderWeele et al., 2019). E-value examines the extent of an observed association to potential unmeasured confounding. The minimum value of E-value is one. The greater the magnitude of E-value is, the more likely the causal relationship between the exposure and the outcome is, and the less likely this relationship is subject to unmeasured confounding. (F) To check the regional differences by different smaller administrative areas, we constructed separate models by cities and autonomous prefectures (21 geographical units).

3. Results

3.1. Characteristics of the hospitalized stroke cohort

We identified 1,066,752 unique hospitalized patients with the primary diagnosis of stroke between January 1, 2017 and December 31, 2019. The participants were followed up for a mean of 1.15 years (SD: 0.90 years). In the overall cohort during the follow-up period, 245,457 (23.0 %) participants had a recurrent hospital admission; 75,094 participants had a rehospitalization within 30 days of their index hospitalization, which accounted for 7.0 % of the overall cohort and 30.6 % of the participants who had rehospitalization. Of participants who experienced rehospitalization, the mean length to rehospitalization was 188.77 (SD: 216.93) days, and the average cost of a rehospitalization was 8370.60 RMB (around 1238.85 US dollars). A map of the spatial distribution of the participants in Sichuan Province is presented in Fig. 1A.

Demographic, health, and environmental characteristics of the participants overall and by rehospitalization status are reported in Table 1. The annual average levels of PM_1, $PM_{2.5}$, and PM_{10} experienced by the participants were 28.16, 43.78, and 69.94 μg/m^3. Maps of the gridded data on annual means of PM_1, $PM_{2.5}$, and PM_{10} in the year of 2017 are shown in Fig. 1B to D. The 7-day and annual average concentrations of ambient PM pollution in the recurrent hospitalization group were significantly higher than those in the group who did not experience recurrent admission (Table 1). Participants who experienced recurrent hospitalization were more likely to be male, Han Chinese, unmarried, agricultural worker, had emergent conditions at admission, and had a higher prevalence of hypertension and diabetes. Characteristics of study participants by rehospitalization within and beyond 30 days are shown in Table S1.

3.2. Association between PM pollution and rehospitalization in patients who experienced an index stroke hospitalization

Table 2 presents the unadjusted and fully adjusted HRs on the association of ambient PM air pollution and the risk of rehospitalization estimated with Cox proportional hazard models, where short-term and long-term exposures were defined at baseline as 7-day average and annual average concentrations prior to the index hospitalization. Each 10 μg/m^3 increment in 7-day average concentration of ambient PM air pollution was associated with significant increases in risk of rehospitalization in fully adjusted models: the HRs were 1.034 (95 % CI: 1.029–1.038) for PM_1, 1.033 (1.031–1.036) for $PM_{2.5}$, and 1.030 (1.028–1.031) for PM_{10}; larger effect

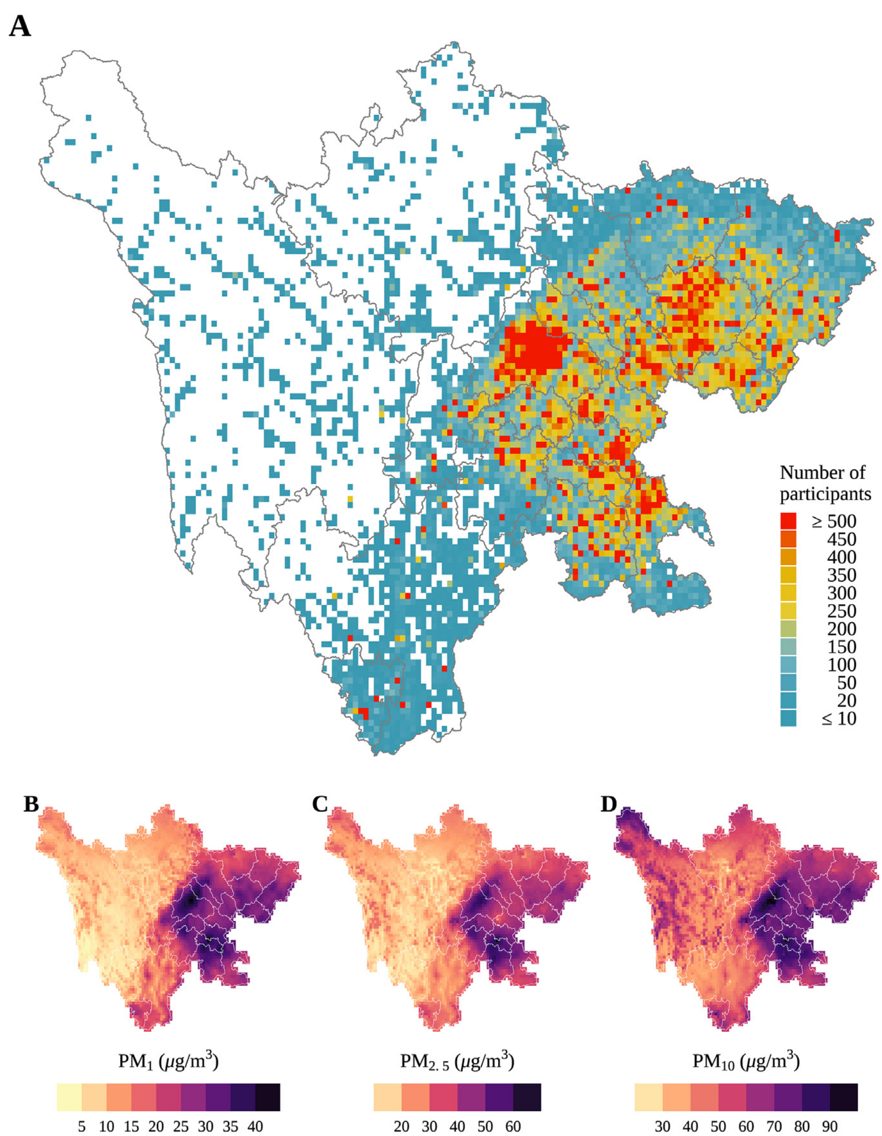

Fig. 1. (A) Map of the cohort participants in Sichuan Province, China. Each grid is at approximately 10 km × 10 km scale; (B–D) Maps of annual average concentrations of PM_1, $PM_{2.5}$, and PM_{10} at 10 km × 10 km resolution in Sichuan, China, 2017.

Table 1
Characteristics and environmental exposure of the overall cohort and by recurrent hospitalization.

Characteristics	Overall n = 1,066,752	Recurrent hospitalization	
		No n = 821,295 (77.0 %)	Yes n = 245,457 (23.0 %)
Outcomes			
Follow-up days, mean (SD)	419.41 (326.94)	488.35 (322.68)	188.77 (216.93)
30-day rehospitalization, n (%)	75,094 (7.0 %)		75,094 (30.6 %)
Medical costs, RMB, mean (SD)[a]			
Index hospitalization	11,008.47 (20,113.21)	10,947.75 (19,989.32)	11,211.62 (20,521.04)
Recurrent hospitalization			8370.60 (14,839.88)
Particulate matter air pollutants, 7-day average, mean (SD), μg/m^3			
PM_1	27.83 (12.69)	27.66 (12.39)	28.24 (13.37)
$PM_{2.5}$	40.73 (22.92)	40.19 (22.49)	42.04 (23.88)
PM_{10}	65.05 (31.41)	64.09 (30.82)	67.36 (32.68)
Particulate matter air pollutants, annual average, mean (SD), μg/m^3			
PM_1	28.16 (5.64)	28.02 (5.66)	28.51 (5.57)
$PM_{2.5}$	43.78 (8.97)	43.36 (8.93)	44.80 (8.97)
PM_{10}	69.94 (12.53)	69.20 (12.56)	71.73 (12.26)
Age, years, mean (SD)	69.37 (11.79)	69.37 (11.98)	69.40 (11.13)
Sex, n (%)			
Female	499,109 (46.79)	392,405 (47.78)	106,704 (43.47)
Male	567,643 (53.21)	428,890 (52.22)	138,753 (56.53)
Ethnicity, n (%)			
Han	1,049,917 (98.42)	807,408 (98.31)	242,509 (98.80)
Non-Han	16,835 (1.58)	13,887 (1.69)	2948 (1.20)
Marital status, n (%)			
Married	915,985 (85.87)	705,499 (85.90)	210,486 (85.75)
Unmarried	39,937 (3.74)	28,331 (3.45)	11,606 (4.73)
Widowed	69,273 (6.49)	54,945 (6.69)	14,328 (5.84)
Divorced	16,311 (1.53)	12,746 (1.55)	3565 (1.45)
Other	25,246 (2.37)	19,774 (2.41)	5472 (2.23)
Occupation, n (%)			
Public sector	25,887 (2.43)	20,481 (2.49)	5406 (2.20)
Private sector	56,616 (5.31)	44,186 (5.38)	12,430 (5.06)
Agriculture	527,813 (49.48)	404,887 (49.30)	122,926 (50.08)
Unemployed	27,393 (2.57)	21,226 (2.58)	6167 (2.51)
Retired	96,298 (9.03)	71,995 (8.77)	24,303 (9.90)
Other	332,745 (31.19)	258,520 (31.48)	74,225 (30.24)
Insurance, n (%)			
URBMI	564,157 (52.89)	437,272 (53.24)	126,885 (51.69)
UEBMI	221,998 (20.81)	168,409 (20.51)	53,589 (21.83)
NRCMS	219,665 (20.59)	165,655 (20.17)	54,010 (22.00)
Self-payment	60,932 (5.71)	49,959 (6.08)	10,973 (4.47)
Severity at admission, n (%)			
Normal	750,090 (70.32)	583,822 (71.09)	166,268 (67.74)
Emergent	213,521 (20.02)	156,064 (19.00)	57,457 (23.41)
Dangerous	103,141 (9.67)	81,409 (9.91)	21,732 (8.85)
Stroke type, n (%)			
Hemorrhagic	226,089 (21.19)	181,487 (22.10)	44,602 (18.17)
Ischemic	822,641 (77.12)	625,806 (76.20)	196,835 (80.19)
Unspecified	18,022 (1.69)	14,002 (1.70)	4020 (1.64)
Comorbidities, n (%)			
Hypertension	612,400 (57.41)	466,487 (56.80)	145,913 (59.45)
Diabetes	170,861 (16.02)	128,176 (15.61)	42,685 (17.39)
Congestive heart failure	77,156 (7.23)	60,451 (7.36)	16,705 (6.81)
Cardiac arrhythmias	90,485 (8.48)	71,012 (8.65)	19,473 (7.93)
Peripheral vascular disorders	145,862 (13.67)	113,560 (13.83)	32,302 (13.16)
Chronic pulmonary disease	153,066 (14.35)	120,006 (14.61)	33,060 (13.47)
Elixhauser comorbidity index, mean (SD)	4.09 (5.52)	4.18 (5.58)	3.77 (5.29)
Meteorological variables, mean (SD)			
Temperature, °C	17.09 (7.36)	17.10 (7.34)	17.08 (7.41)
Relative humidity, %	75.08 (7.87)	75.22 (7.91)	74.60 (7.73)

SD: standard deviation, PM: particulate matter, UEBMI: the Urban Employee Basic Medical Insurance, URBMI: the Urban Resident Basic Medical Insurance, NRCMS: the New Rural Cooperative Medical Scheme.
[a] 1 RMB ≈ 0.148 USD in 2017.

sizes of HR were found on the association between annual average concentration of ambient PM air pollution and stroke rehospitalization: 1.082 (1.074–1.090) for PM_1, 1.109 (1.104–1.114) for $PM_{2.5}$, and 1.103 (1.099–1.106) for PM_{10}. In unadjusted models, we observed a similar pattern with a smaller magnitude of HRs and the associated 95 % CIs.

Fig. 2 shows the concentration-response relationships between short-term (2A) and long-term (2B) exposure to ambient PM air pollution and hazard of stroke rehospitalization. The association between short-term exposure to PM_1 and rehospitalization exhibited a slightly increasing gradient, while the association of short-term exposure to $PM_{2.5}$ and PM_{10} with rehospitalization showed a consistent increasing trend with decreasing gradient. The association between long-term exposure to PM and risk of rehospitalization manifested a consistently increasing trend with decreasing gradient: the risk of stroke rehospitalization attenuated at higher levels of PM.

Fig. 3 and Table S2 presents the HRs for the association of PM_1, $PM_{2.5}$, and PM_{10} with the risk of stroke rehospitalization by age groups, sex, ethnicity, stroke subtypes, and admission severity, and the *p*-values for effect

Table 2
Association of each 10 μg/m^3 increase in PM_1, $PM_{2.5}$, and PM_{10} with the risk of rehospitalization in a cohort of 1.07 million hospitalized stroke patients in Sichuan, China.

Pollutants[†]	PM_1		$PM_{2.5}$		PM_{10}	
	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value
Unadjusted models						
7-day average	1.023 (1.020–1.026)	<0.001	1.020 (1.019–1.022)	<0.001	1.019 (1.018–1.020)	<0.001
Annual average	1.079 (1.072–1.086)	<0.001	1.104 (1.099–1.108)	<0.001	1.094 (1.091–1.097)	<0.001
Fully adjusted models[‡]						
7-day average	1.034 (1.029–1.038)	<0.001	1.033 (1.031–1.036)	<0.001	1.030 (1.028–1.031)	<0.001
Annual average	1.082 (1.074–1.090)	<0.001	1.109 (1.104–1.114)	<0.001	1.103 (1.099–1.106)	<0.001

HR: hazard ratio, 95 % CI: 95 % confidence interval.
[†] The air pollutants were measured at baseline prior to the index hospitalization.
[‡] Fully adjusted models controlled for age, sex, ethnicity, marital status, occupation, medical insurance, severity at admission, stroke subtype, hypertension, diabetes, congestive heart failure, cardiac arrhythmias, peripheral vascular disorders, and chronic pulmonary disease; temperature and relative humidity were included as natural cubic splines with 5 degrees of freedom.

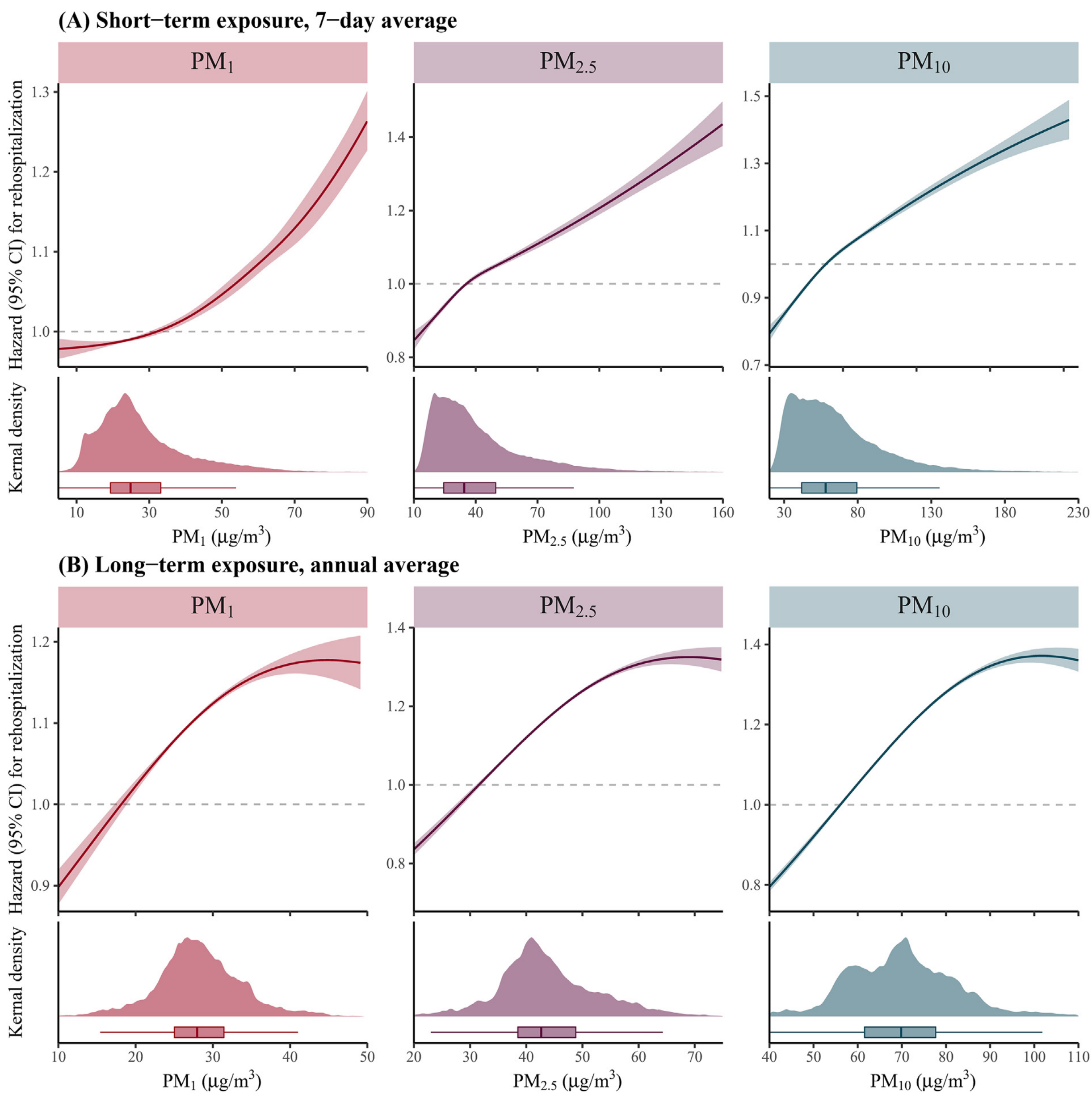

Fig. 2. Nonlinear exposure-response relationships of short-term (A) and long-term (B) exposure to PM_1, $PM_{2.5}$, PM_{10} with stroke rehospitalization (upper panels) in a cohort of 1.07 million hospitalized stroke patients, as well as the kernel density curves and boxplots of PM_1, $PM_{2.5}$, PM_{10} (lower panels). The pollutants were measured as 7-day (short-term) and annual averages (long-term) prior to the index hospitalization. The daily and annual concentrations of air pollution were assessed using 10 × 10 km satellite-based grids data. The air pollutants were trimmed at the 0.1-th percentiles to avoid excessively large confidence intervals and deviant nonlinear patterns due to small sample sizes. The solid lines with shaded bands in nonlinear curves indicate the changes in hazards of stroke rehospitalization and their 95 % confidence intervals, respectively.

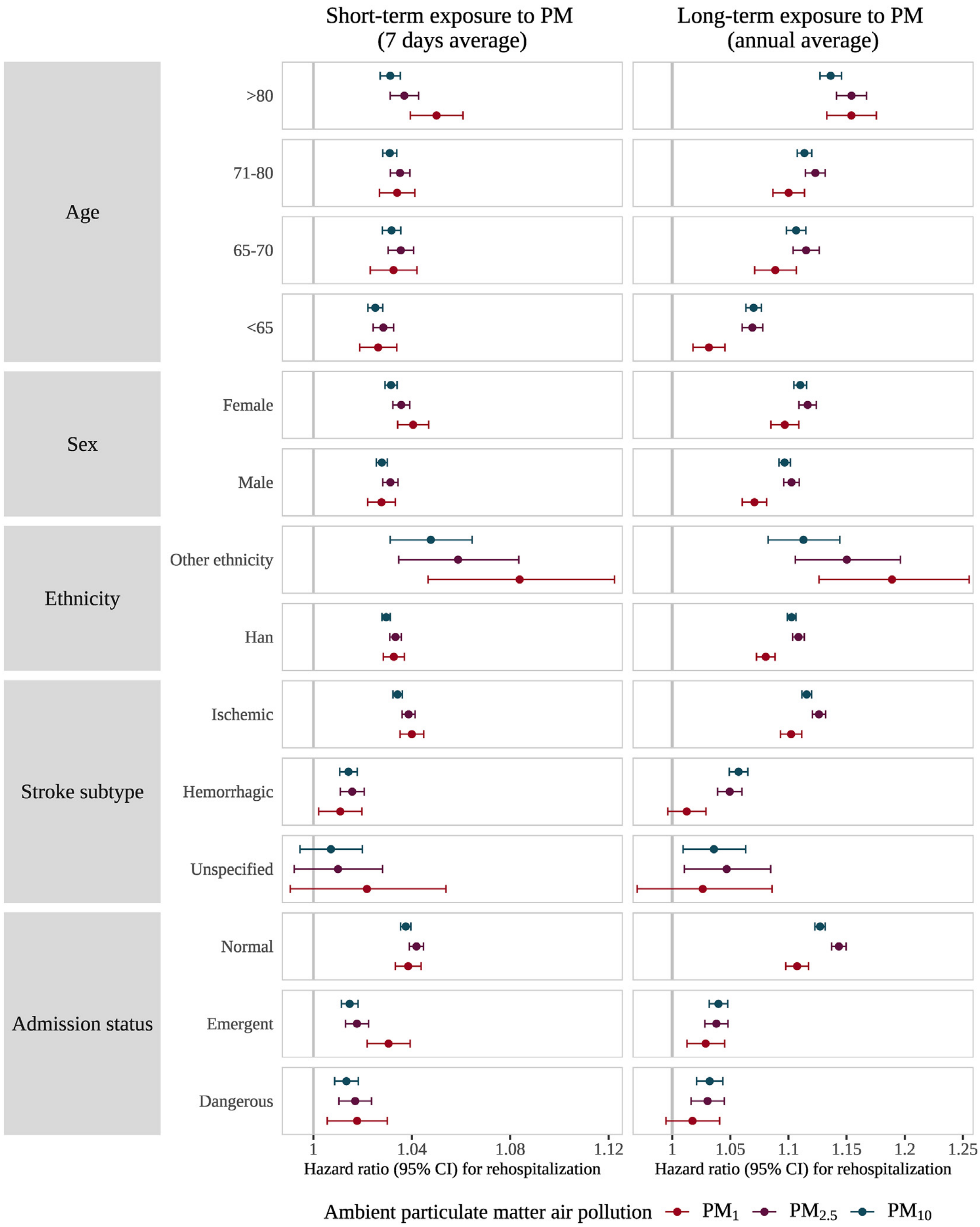

Fig. 3. Associations between PM pollution and recurrent stroke hospital admission by age, sex, ethnicity, stroke subtype, and admission status.

modification are included in Table S2. The association between short-term ambient PM pollution and stroke rehospitalization was stronger in participants who were female, of minority ethnicity (non-Han Chinese), with ischemic stroke, and those who had normal condition at admission; similarly, the association between long-term exposure to PM and rehospitalization were enhanced among older patients, females, those of minority ethnicity (non-Han Chinese), patients who had ischemic stroke, and those with normal condition at admission.

3.3. Sensitivity analyses

We conducted the following sensitivity analyses to test the robustness of the findings. (A) To test different lag periods for short-term exposure definition, we assigned short-term exposure to PM pollution for each participant using varying lag periods (lag 0 to lag 7 and moving averages of lag 0–1 to lag 0–7); the HRs for short-term PM pollution at lag 0 to lag 7 showed a consistently and significantly positive association with stroke rehospitalization (Fig. S1). (B) To assess the robustness of the results on long-term exposure at different measurement resolutions, we assessed annual average concentrations of PM at 1 km × 1 km grids; Table 3 shows that the results remained consistently significant, and the magnitude of relative risk estimates (HRs) was increased compared to the main results using air pollution measured at 10 km × 10 km grids. (C) Considering the clinical implication of 30-day readmission, we further estimated two different models in which the outcomes were redefined into rehospitalizations within 30 days and beyond 30 days; the results suggest that PM pollution was associated with a higher risk of stroke rehospitalization beyond 30 days compared to the association for rehospitalization within 30-days (Table 3). (D) To capture a more comprehensive set of comorbidities as covariates, we adopted the Elixhauser comorbidity score approach that was a weighted average

Table 3
Sensitivity analyses of the association between short-term and long-term exposure to PM pollution (10 μg/m^3 increase) and the risk of rehospitalization in a cohort of 1.03 million hospitalized stroke patients in Sichuan, China.

	PM_1	$PM_{2.5}$	PM_{10}
Alternative exposure measurement: using 1 km × 1 km exposure measurement			
Annual mean, HR (95 % CI)	1.149 (1.131–1.167)	1.123 (1.115–1.132)	1.113 (1.107–1.119)
Alternative outcome definition			
7-day average concentration of PM air pollution, HR (95 % CI)			
Rehospitalization within 30 days, n = 163,170	1.022 (1.017–1.028)	1.019 (1.014–1.023)	1.014 (1.010–1.017)
Rehospitalization beyond 30 days, n = 147,407	1.069 (1.063–1.075)	1.071 (1.068–1.074)	1.065 (1.063–1.067)
Annual average concentration of PM air pollution, HR (95 % CI)			
Rehospitalization within 30 days, n = 163,170	0.995 (0.961–1.008)	0.991 (0.981–1.000)	0.996 (0.990–1.003)
Rehospitalization beyond 30 days, n = 147,407	1.305 (1.292–1.317)	1.341 (1.333–1.348)	1.314 (1.308–1.320)
Alternative covariate sets: controlling for Elixhauser comorbidity index			
7-day mean, HR (95 % CI)	1.034 (1.029–1.038)	1.033 (1.031–1.035)	1.029 (1.028–1.031)
Annual mean, HR (95 % CI)	1.083 (1.075–1.091)	1.108 (1.103–1.113)	1.101 (1.098–1.105)

PM: particulate matter, HR: hazard ratio, 95 % CI: 95 % confidence interval.
All models controlled for age, sex, ethnicity, marital status, occupation, medical insurance, severity at admission, stroke subtype, hypertension, diabetes, congestive heart failure, cardiac arrhythmias, peripheral vascular disorders, and chronic pulmonary disease; temperature and relative humidity were included as natural cubic splines with 5 degrees of freedom.

of a more comprehensive list of 31 comorbidities (Cai et al., 2020), and the results remained relatively unchanged (Table 3). (E) To assess the robustness of the HR estimates to unmeasured confounding, we further calculated E-values for our univariate and multivariable Cox proportional hazard models and overall evidence for causality (Table S3); the E-values for short-term exposure to PM pollution ranges between 1.13 and 1.18 while those for long-term exposure to PM pollution were between 1.29 and 1.36, suggesting that the associations between PM pollution and stroke rehospitalization were unlikely to be biased by a strong unmeasured confounder; this implies a plausible evidence for causal relationships (VanderWeele and Ding, 2017; VanderWeele et al., 2019). (F) To test the sensitivity of results to different administrative areas, we conducted separate analyses in subgroups of all the 18 cities and 3 autonomous prefectures in Sichuan (Table S4); the results showed some geographical variability in HR estimates but remained highly consistent with the main findings.

3.4. Attributable burden of stroke rehospitalization due to ambient PM pollution

Utilizing the approaches specified by the Global Burden of Diseases, we estimated the burden of stroke rehospitalizations attributable to ambient PM pollution — avoidable burden of stroke rehospitalizations if the concentrations of PM air pollution were no higher than the TMRELs. The TMRELs were defined as the optimal 5th percentiles of each pollutant in the overall cohort (Table 4 and Fig. 4). The median (IQR) and the 5th percentile of PM pollutants, reducible number and fraction of rehospitalizations, total reducible cost of rehospitalizations, and average cost of rehospitalization per patient attributable to PM are presented in Table 4.

The population attributable fractions of short-term exposure to PM pollution for stroke rehospitalization were 4.66 % (95 % CI: 1.69 % to 7.63 %) for PM_1, 7.36 % (4.45 % to 10.28 %) for $PM_{2.5}$, and 9.86 % (6.97 % to 12.74 %) for PM_{10} (Table 4 and Fig. 4); those of long-term exposure to PM pollution were 6.86 % (3.93 % to 9.8 %) for PM_1, 13.36 % (10.53 % to 16.19 %) for $PM_{2.5}$, 17.05 % (14.27 % to 19.83 %) for PM_{10} (Table 4 and Fig. 4). The reducible average costs of rehospitalization per participant attributable to PM air pollution ranged from 492.09 (95 % CI: 178.19 to 806) RMB per patient for short-term exposure to PM_1 to 1801.65 (1507.89 to 2095.41) RMB per patient for long-term exposure to PM_{10}. The total reducible costs of rehospitalization attributable to PM air pollution ranged from 152,833,102.25 (95 % CI: 55,342,321.29 to 250,323,883.21) RMB for short-term exposure to PM_1 to 559,551,528.68 (468,316,466.72 to 650,786,590.65) RMB for long-term exposure to PM_{10}.

Table 4
Reducible burden of stroke rehospitalization attributable to short-term and long-term exposure to PM pollution in a cohort of 1.07 million stroke patients in Sichuan, China.

	Median (IQR), μg/m^3	Counterfactual TMREL 5th percentiles, μg/m^3	Reducible number of rehospitalizations	Reducible fraction of rehospitalizations	Total reducible cost of rehospitalization, RMB†	Reducible cost of rehospitalization per patient, RMB†
Short-term exposure (7-day average)						
PM_1	24.89 (19.30 to 33.23)	12.5	14,461.65 (5236.7 to 23,686.6)	4.66 % (1.69 % to 7.63 %)	152,833,102.25 (55,342,321.29 to 250,323,883.21)	492.09 (178.19 to 806)
$PM_{2.5}$	34.39 (24.38 to 49.82)	16.85	22,871.43 (13,817.43 to 31,925.44)	7.36 % (4.45 % to 10.28 %)	241,709,063.08 (146,024,850.59 to 337,393,275.56)	778.26 (470.17 to 1086.34)
PM_{10}	58.29 (41.92 to 79.62)	29.45	30,613.15 (21,656.75 to 39,569.54)	9.86 % (6.97 % to 12.74 %)	323,524,754.83 (228,872,094.28 to 418,177,415.37)	1041.69 (736.93 to 1346.45)
Long-term exposure (annual average)						
PM_1	27.93 (25.00 to 31.40)	18.95	21,318.63 (12,201.22 to 30,436.04)	6.86 % (3.93 % to 9.8 %)	225,298,735.94 (128,944,442.6 to 321,653,029.27)	725.42 (415.18 to 1035.66)
$PM_{2.5}$	42.61 (38.41 to 48.81)	30.27	41,480.47 (32,688.46 to 50,272.49)	13.36 % (10.53 % to 16.19 %)	438,372,430.15 (345,457,019.84 to 531,287,840.47)	1411.48 (1112.31 to 1710.65)
PM_{10}	69.74 (61.34 to 77.67)	51.64	52,946.90 (44,313.89 to 61,579.91)	17.05 % (14.27 % to 19.83 %)	559,551,528.68 (468,316,466.72 to 650,786,590.65)	1801.65 (1507.89 to 2095.41)

All models controlled for age, sex, ethnicity, marital status, occupation, medical insurance, severity at admission, stroke subtype, hypertension, diabetes, congestive heart failure, cardiac arrhythmias, peripheral vascular disorders, and chronic pulmonary disease; temperature and relative humidity were included as natural cubic splines with 5 degrees of freedom.
IQR: interquartile range, TMREL: theoretical minimum risk exposure level, PM: particulate matter, RMB: Renminbi (Chinese currency).
† 1 RMB ≈ 0.148 USD in 2017.

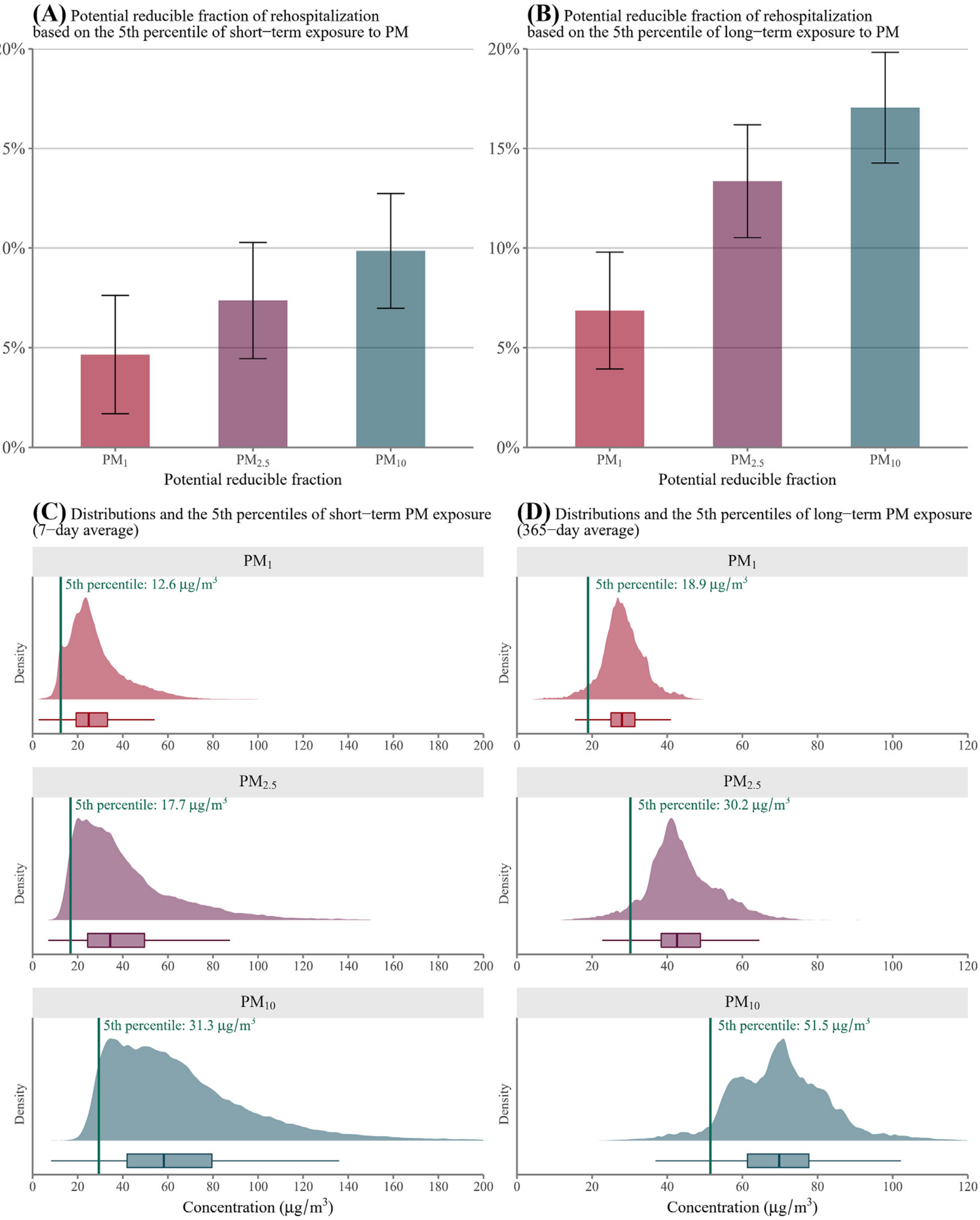

Fig. 4. Potential reducible fraction of recurrent stroke hospital admission based on a counterfactual scenario of the 5th percentiles of PM_1, $PM_{2.5}$, and PM_{10} in a cohort of 1.07 million hospitalized stroke patients in Sichuan, China.

4. Discussion

In this province-wide longitudinal cohort of 1,066,752 participants with an index stroke hospitalization in Sichuan, China, elevated levels of short-term (7-day average) and long-term (annual average) ambient PM air pollution (PM_1, $PM_{2.5}$, and PM_{10}) were associated with an increased risk of rehospitalization. The associations were stronger in females, minority ethnicity (non-Han Chinese), participants with ischemic stroke, and those who had normal condition at admission. Further spline analyses revealed increasing but slightly "concave-down" nonlinear associations between ambient PM air pollution and rehospitalization. The results remained consistent in sensitivity analyses including altering the exposure measurement at different lag periods and spatial resolution, stratifying the outcomes by readmissions within and beyond 30 days, replacing the covariate set with a numeric comorbidity score, and testing the potential influence of unmeasured confounding using E-values. Counterfactual analyses revealed substantial burden of stroke rehospitalization attributable to PM air pollution. The evidence taken together suggests that ambient PM air pollution is a significant risk factor for rehospitalization in stroke patients.

Although numerous studies have reported the associations of ambient PM air pollution with the incidence, hospitalization, and mortality of stroke (Huang et al., 2019; Ljungman et al., 2019; Qiu et al., 2017; Shah et al., 2015; Tian et al., 2018; Cai et al., 2022; Tian et al., 2022; Verhoeven et al., 2021), the association with stroke rehospitalization have not yet been reported. Our study highlights elevated concentrations of both short-term and long-term ambient PM air pollution as a newly recognized risk factor for stroke recurrent hospitalization. This relationship is supported by biological mechanisms including immune system disturbances and increased systemic inflammation induced by small particles translocated in systemic circulation, which may further release pro-oxidative and pro-inflammatory indicators (Pope et al., 2016; Rajagopalan et al., 2018). These pathophysiological mechanisms may in turn increase the likelihood of vulnerability to plaque and thrombogenicity among stroke patients who experienced an index hospitalization, which may necessitate recurrent hospital admission and other adverse outcomes.

Stroke is a leading cause of mortality and morbidity in China, causing 3.94 million incident cases of stroke, 45.9 million stroke DALYs and 2.19 million deaths in 2019 (Ma et al., 2021; Tu et al., 2022). Although the air quality in China has been substantially improved by implementing tough clean air policies in the recent decade (Zhang et al., 2019), PM air pollution in China (annual average in 2020: 38.84 μg/m^3) remain regularly higher than the air quality guideline levels recommended by the WHO (5 μg/m^3) (World Health Organization, 2021) and those in Western countries (7.66 μg/m^3 in the United States in 2019) (Al-Aly and Bowe, 2021). Our counterfactual analyses found that 17.05 % (95 % CI: 14.27 % to 19.83 %) of stroke rehospitalization and an average of 1801.65 RMB (95 % CI: 1507.89 to 2095.41) is attributable to long-term exposure to PM_{10} if the 5th percentile of TMREL (51.64 μg/m^3) could be achieved. These results underscore the benefits of improving the health outcomes for stroke patients after an index hospitalization (Clery et al., 2021) and easing the burden of medical system by reducing air pollution.

The concentration response function shows a substantial increase in risk of recurrent stroke hospital admission at lower levels of pollutants, while exhibits a modestly increasing trend at higher levels of pollution. This pattern is consistent with most prior studies that investigated the relationship between air pollution and health outcomes. The shape of the exposure-response curves suggests that a considerable reduction in ambient air pollution is needed in China to mitigate the adverse health outcomes of stroke. The characterization of exposure-response curves in this study is valuable, as a majority of the world's population resides in areas that have pollution levels much higher than those recommended by the WHO, but evidence generated by large cohort studies in these areas is scarce.

Sichuan Province is known to have many Tibetan residents, a socioeconomically disadvantaged group who live in sparsely populated northern and western parts of the province. Our results suggest that older age, female, minority ethnicity, ischemic stroke, and normal admission severity may strengthen the association between ambient PM pollution and the risk of rehospitalization in stroke patients. These results indicate that these vulnerable populations may be more susceptible to stroke rehospitalization even at the same concentrations of ambient PM pollution, which presents the problem of environmental pollution inequity (Al-Aly, 2021; O'Carroll and Dumitrascu, 2022; Tarko et al., 2022). Our findings also suggest that national and provincial policies are needed to mitigate deleterious effects of air pollution on the susceptible population and improve environmental justice (Cai et al., 2022; Robinson et al., 2022; Walker, 2012).

A key strength of the study is the large sample size and individual-level data on over one million participants with an index stroke hospitalization, spanning multiple years in Western China. To our knowledge, this is the first study that investigates the relationship between exposure to PM of varied sizes and rehospitalization in stroke patients. Compared to Europe and North America, the concentrations of air pollution in our study were relatively high (annual concentration of $PM_{2.5}$ in this study was around 50 μg/m^3), and evidence on exposure to air pollution and stroke outcomes is scarce using large individual-level data at this exceedingly high level of air pollution. The estimated association of ambient PM with rehospitalization in China suggests that policy efforts to lower PM air pollution may reduce the burden of rehospitalization in stroke patients in developing countries, where the concentration of air pollution and the burden of stroke mortality are increasingly high. The advances in satellite-based measurement of ground-level air pollution allow us to investigate smaller sized air pollution (PM_1) in this study.

The study has a few limitations. The cohort was built using hospitalized stroke patients in Sichuan province and may be limited in representing hospitalized stroke patients in other provinces in China. Although we accounted for several known covariates, we cannot exclude the possibility of unmeasured covariate such as BMI, smoking, and the level of disability. In addition, the exposure was measured at fixed residential addresses, so we were not able to account for indoor exposure to air pollutants and varying exposures at non-residential addresses. The mean follow-up period was 1.15 years, limiting the insights on the association with stroke rehospitalization in the long run. The study utilized the hospitalized patient's database in Sichuan Province, and the patients who were admitted in hospitals in other provinces were not tracked and were subject to the issue of missing follow-up information. Cox proportional hazard models used in this study can only assess the time to the first recurrent event and ignore all subsequent events. Examining the relationship between air pollution and multiple recurrent events would need more sophisticated statistical models such as a point process model (Cai et al., 2022).

In conclusion, we provided evidence for positive relationships of short-term and long-term exposure to ambient PM air pollution with rehospitalization in stroke patients. The associations were stronger among those at older age, female, of minority ethnicity, with ischemic stroke, and those who had a normal condition at admission. Counterfactual analyses estimated that a substantial fraction of rehospitalization and the associated medical costs were attributable to PM air pollution.

CRediT authorship contribution statement

Dr. Cai and Dr. X. Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Cai, X. Lin, Pan, H. Lin.

Acquisition, analysis, or interpretation of data: Cai, X. Lin, Wei, Pan, H. Lin.

Drafting of the manuscript: Cai, X. Lin, Pan, H. Lin.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Cai, X. Lin.

Administrative, technical, or material support: Wei, Pan, H. Lin.

Supervision: Pan, H. Lin.

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Data availability

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.159104.

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