Environmental Research 212 (2022) 113350

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Short-term effects of exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} on ischemic and hemorrhagic stroke incidence in Shandong Province, China

Han Wu [a,1], Bingyin Zhang [b,1], Jing Wei [c,1], Zilong Lu [b], Min Zhao [d], Wenhui Liu [e], Pascal Bovet [f], Xiaolei Guo [b,**], Bo Xi [a,*]

[a] Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[b] Shandong Center for Disease Control and Prevention, and Academy of Preventive Medicine, Shandong University, Jinan, Shandong, China
[c] Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, MD, USA
[d] Department of Nutrition and Food Hygiene, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[e] Information and Data Analysis Lab, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[f] Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

ARTICLE INFO

Keywords:
Particulate matter
Ischemic stroke
Hemorrhagic stroke
Disease burden

ABSTRACT

Background: Short-term exposure to ambient $PM_{2.5}$ and PM_{10} is associated with increased risk of mortality and hospital admissions for stroke. However, there is less evidence regarding the effect of exposure to PM_1 on stroke incidence. We estimated the incidence risk of stroke and the attributable fractions related to short-term exposure to ambient PM_1, $PM_{2.5}$ and PM_{10} in China.
Methods: County-specific incidence of stroke was obtained from health statistics in years 2014–2019. We linked county-level mean daily concentrations of PM_1, $PM_{2.5}$ and PM_{10} with stroke incidence. We used the time stratified case-crossover design to estimate the associations between stroke incidence and exposure to PM_1, $PM_{2.5}$ and PM_{10}. We also estimated the disease burden fractions attributable to PM_1, $PM_{2.5}$, and PM_{10}.
Results: The study included a total of 2,193,954 stroke, from which 1,861,331 were ischemic and 332,623 were hemorrhagic stroke. PM_1, $PM_{2.5}$, and PM_{10} levels were associated with increased risks of total stroke and ischemic stroke at when assessing the associations in exposure at lag0−4 days. The increase of 10 $\mu g/m^3$ in PM_1, $PM_{2.5}$, and PM_{10} was associated with total stroke, and the relative risks were 1.012 (95% confidence interval: 1.008, 1.015), 1.006 (1.004, 1.007) and 1.003 (1.002, 1.004), while the associations with ischemic stroke were 1.013 (1.010, 1.017), 1.006 (1.005, 1.008) and 1.003 (1.002, 1.004), respectively. There was no significant association between PM and risk of hemorrhagic stroke. The attributable fractions of total stroke were 6.9% (5.1%, 8.5%), 5.6% (4.2%, 6.8%) and 5.6% (3.9%, 7.1%) for PM_1, $PM_{2.5}$, and PM_{10}, respectively.
Conclusions: PM_1 showed a stronger association with stroke, with a larger attributable fraction of outcomes, than $PM_{2.5}$ and PM_{10}. Clean air policies should target the whole scope of PM, including PM_1.

1. Introduction

Stroke is one of the leading causes of death worldwide, and there were about 101 million prevalent stroke cases in 2019, which has increased by 85.0% compared with that in 1990 (GBD, 2019 Stroke Collaborators, 2021). It was estimated that the risk of stroke for life-time is approximately 25% after the age of 25 years globally, with a larger lifetime risk in East Asia (38.8%) (Feigin et al., 2018). In China, there are about 2.4 million new strokes annually in recent years and 75% had varying degrees of disability from stroke (Wang et al., 2017a, 2017b).

* Corresponding author. No. 44 Wenhuaxi Road, Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China.
** Corresponding author. No. 16992 Jingshi Road, Shandong Center for Disease Control and Prevention, and Academy of Preventive Medicine, Shandong University, Jinan, Shandong, China.
E-mail addresses: wuhan9281@163.com (H. Wu), 13153785152@163.com (B. Zhang), weijing_rs@163.com (J. Wei), lzllzl22@163.com (Z. Lu), zhaomin1986zm@126.com (M. Zhao), liuwenhui@sdu.edu.cn (W. Liu), pascal.bovet@unisante.ch (P. Bovet), guoxiaolei@126.com (X. Guo), xibo2010@sdu.edu.cn (B. Xi).
[1] Han Wu, Bingyin Zhang, and Jing Wei contributed equally to this study.

https://doi.org/10.1016/j.envres.2022.113350
Received 30 December 2021; Received in revised form 15 April 2022; Accepted 19 April 2022
Available online 27 April 2022

Numerous studies have shown that most stroke-related disability-adjusted life years and premature deaths could be attributed to modifiable risk factors, such as overweight and obesity, diabetes mellitus, hypertension, smoking, and ambient air pollution (GBD, 2019 Stroke Collaborators, 2021; Gan et al., 2021; Jiang et al., 2020). Among various air pollutants, particulate matter (PM) has been shown to be most closely linked to stroke (Niu et al., 2021; Zhao et al., 2017).

PM is composed of a complex mixture of liquid and solid phase particles in different shapes and sizes, with various chemical components (Lu et al., 2021; Zheng et al., 2021). PMs are generally classified into several size fractions based on their aerodynamic diameter, such as PM_{10} (particles with aerodynamic diameter <10 μm), $PM_{2.5}$ (<2.5 μm) and PM_1 (<1 μm) (Lu et al., 2021; Zheng et al., 2021). To date, numerous epidemiological and toxicological studies showed that particles with smaller diameter are more harmful to health (Hu et al., 2018; Yang et al., 2019a; Yin et al., 2020; Zhang et al., 2021; Filep et al., 2016), and positive associations between exposure to $PM_{2.5}$ or PM_{10} in a short-term and stroke mortality have been well documented (Niu et al., 2021; Wang et al., 2014, 2018; Yu et al., 2014). Several recent studies from China have investigated the relationship between PM_1 and stroke mortality and showed a larger effect of PM_1 than $PM_{2.5}$ and PM_{10} (Hu et al., 2018; Yin et al., 2020; Lin et al., 2016).

In China, there is a clearly downward trend of stroke-related mortality among both urban and rural population in the past 30 years, and related stimulative factors were considered to be the improved healthcare coverage, the updated treatment options and modern medical technology (Wang et al., 2017b). On the contrary, the incidence rates of hemorrhagic and ischemic stroke showed an increase trend in recent years, which was because of the rapid socioeconomic, diet and lifestyle transition, and the ubiquitous PM pollution across China (Wang et al., 2020). Therefore, additional studies focusing on stroke morbidity are required to improve our understanding of the acute effects of exposure to PMs (PM_1, $PM_{2.5}$, and PM_{10}) on stroke incidence.

Several studies have examined the association between short-term exposure to $PM_{2.5}$ or PM_{10} with hospital admissions for stroke, and the reported positive associations varied at lag0 to lag5 days (Ban et al., 2021a; Gu et al., 2020; Liu et al., 2017; Tian et al., 2017; Huang et al., 2016). Only two studies additionally explored the effects of exposure to PM_1 on hospital admission for stroke, and inconsistent results were also presented (Zhang et al., 2021; Chen et al., 2020). Using hospital admission for stroke as the outcome of interest may be biased since people may not go to hospital at the day of the symptom or discomfort occur and there is likely a delay between the stroke onset and hospital admission. In addition, hospital admission data may not fully reflect the true incidence rate of local population because of potential selection bias (Liu et al., 2017). Therefore, in previous studies using hospital admission data, the susceptible window for stroke of short-term exposure to PM may be not accurate enough and the adverse effects of PM exposure on stroke incidence may be underestimated. Registry datasets covering all stroke case records from multiple sources may be relatively reliable to reflect the local stroke incidence because of the fewer misclassifications of disease and increased completeness (Butland et al., 2017), but studies relying on population-based registry data are scarce until now (Ban et al., 2021b; Dong et al., 2018; Qian et al., 2019; McClure et al., 2017).

We conducted this epidemiological study to examine the association between short-tern exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} and ischemic and hemorrhagic stroke onset and assess related disease burden, by using population-based registry data from a disease surveillance system which covers the whole residents with an overall population of more than 90 million in 126 counties from Shandong Province, China.

2. Materials and methods

2.1. Study setting

We collected county-level stroke registry data for 126 out of the 136 counties in the Shandong province, China. Shandong province is located in Eastern China, with a generally mild climate (average annual temperature of 11–14 °C. Shandong has 58 urban and 78 rural counties, and the province's total area spans over 158,000 km^2.

2.2. Stroke registry data

Data on county-specific daily incidence of stroke were obtained from the noncommunicable disease registry system operated by the Shandong Center for Disease Control and Prevention (CDC). Patient admissions to all medical institutions in Shandong province, such as private clinics, community health service centers, and public hospitals, with a diagnosis of stroke are obliged to be reported to this registry system. The registry system was initially launched in 2012 with 20 counties as pilot surveillance points, and more and more surveillance points were established afterwards. By 2020, the system had covered 126 of the 136 counties in Shandong. The population in the 126 counties of Shandong, who were considered in this study, correspond to a population of 91 million or 6.4% of the whole population of China.

In this registry system, registry certificates are based on information provided by the attending physician who make a diagnosis for each patient based on the patients' symptoms, inquiries, complaints, and results of medical inspections, and diagnosis is categorized according to the International Classification of Diseases version 10 (ICD-10). In addition, each patient was asked to report when his/her clinical symptom occurred and then the date of symptom occurrence was recorded as the incidence date. Then, the registry certificates will be reported to the registry system in real time. Information on each certificate is validated by professionals in local county CDC within a limit of 7 days, who also check for completeness and coding and quality control of all data is regularly performed. In this study, we focused on all stroke cases recorded to 31 December 2019, including ischemic stroke (ICD-10 code: I63) and hemorrhagic stroke (ICD-10 codes: I60–I61). Information on de-identified cases including sex, age, residence, and incidence date were exported from the registry system. Ethical approval was obtained from the Ethics Review Committee of Public Health, Shandong University (No. LL20211203).

2.3. Air pollution and meteorological data

Daily ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, and O_3 data covering the Shandong province in the years 2014–2019 at a spatial resolution of 0.1° (≈10 km^2) were collected from the ChinaHighAirPollutants (CHAP, available at https://weijing-rs.github.io/product.html). These data were estimated by a developed space-time extremely randomized trees (STET) model, which integrates satellite remote sensing products, atmospheric reanalysis, and ground-based measurements to accomplish model simulation and detailed estimation procedure has been published elsewhere (Wei et al., 2019, 2020, 2021a, 2021b, 2022; Wei, 2021). Briefly, surface daily air pollutant monitoring data in situ observations were obtained from the China National Environmental Monitoring Center. Data from the Moderate Resolution Imaging Spectroradiometer (MODIS) Multi-Angle Implementation of Atmospheric Correction (MAIAC) aerosol optical depth (AOD) product (Lyapustin et al., 2018) were also collected and they were used as the primary inputs to estimate near-surface air pollutant concentrations. In addition, meteorological variables (e.g., temperature, relative humidity, and surface pressure) from the European Centre for Medium-Range Weather Forecasts (ECMWF) Reanalysis product (Hersbach et al., 2020), pollutant emission data from the Multiresolution Emission Inventory for China (MEIC) (Li et al., 2017a), population distribution data from LandScanTM annual population distribution product (Dobson et al., 2000), and land use data (e.g., MODIS land-use cover and Normalized Difference Vegetation Index products, and the Shuttle Radar Topography Mission surface elevation data) were used as auxiliary data to improve estimation accuracy. All the above data were resampled to the same spatial resolution to be consistent with the AOD product (Wei et al., 2019, 2020, 2021a, 2021b, 2022; Wei, 2021). Then, STET models were employed to establish stable estimation models for air pollutant concentrations, and model performance was evaluated using the 10-fold cross-validation approach (Wei et al., 2019, 2020, 2021a, 2021b, 2022; Wei, 2021). The predicted air pollutants levels compare validly with ground-level measurements with a cross-validation coefficient of determination (CV-R^2) of 0.83 and a root-mean-square error (RMSE) of 10.86 μg/m^3 for PM_1, CV-R^2 of 0.91 and RMSE of 12.67 μg/m^3 for $PM_{2.5}$, CV-R^2 of 0.86 and RMSE of 24.34 μg/m^3 for PM_{10}, CV-R^2 of 0.84 and RMSE of 10.07 μg/m^3 for SO_2, and CV-R^2 of 0.87 and RMSE of 17.10 μg/m^3 for O_3 on a daily basis, respectively (Wei et al., 2019, 2020, 2021a, 2021b, 2022). These data have been widely applied in recent epidemiological studies evaluating the impact of exposure to ambient air pollutants on population health in China (Lu et al., 2021; Zheng et al., 2021; Liu et al., 2021; Wang et al., 2021a).

We collected temperature estimates [temperature (T) and dewpoint temperature (DT)] from the ERA5-Land climate reanalysis product supplied by the ECMWF (Hersbach et al., 2020). This product is a gridded reanalysis dataset at 0.25° (≈28 km^2) spatial resolution across the world spanning from 1979 to the present date (Hersbach et al., 2020). ERA5 data has been widely used in recent studies examining the association between meteorological variables and population outcomes (Burkart et al., 2021). We used ERA5 data with an hourly temporal frequency for the Shandong province. The hourly relative humidity (RH) was calculated from the hourly temperature estimates within each grid according to the following formula (Alduchov and Eskridge, 1996):

$$RH = 100*(exp((17.625*DT)/(243.04+DT))/\ exp\ ((17.625*T)/(243.04+T)))$$

This approximation has a relative error of 0.384% or less when used between −40 °C and 50 °C (Alduchov and Eskridge, 1996). Then, the daily average temperature and relative humidity within each location grid were calculated based on hourly data.

2.4. Exposure assessment

For our analysis, the daily means of PM_1, $PM_{2.5}$, PM_{10}, O_3, SO_2, temperature, and relative humidity for each county were estimated by calculating the average of the pixel values weighted by the proportion of the area of the county covered by the pixel, which enhances the spatial representativeness of air pollution and meteorological data for each county. Single-day lag exposures (from lag0 to lag6 days) were calculated. For example, the exposure level at lag0 day was the PM concentration at the day of stroke incidence; the exposure level at lag1 day was the PM concentration at one day prior to the incidence day; and so on. We also estimated the cumulative lag effect which is the overall effect along lags. For example, the effect at lag0−1 day was defined as the cumulative lag effects at lag0 and lag1 days; the effect at lag0−2 day was defined as the cumulative lag effects at lag0, lag1 and lag2 days; and so on.

2.5. Statistical analysis

A three-stage model was applied to analyze the daily count data of stroke. In the first stage, the time stratified case-crossover design was adopted and the associations between stroke incidence and PMs at lag0 to lag6 days were estimated for each included county. In the second stage, the abovementioned associations for the 126 counties were pooled via a random-effect meta-analysis approach. In the third stage, the incidence burden attributable to PM_1, $PM_{2.5}$, and PM_{10} were estimated during the study period.

2.5.1. First stage analysis

The time stratified case-crossover design has been increasingly applied to examine the associations between the acute effects of exposure to air pollutants on health outcomes. By this design, the periods used as reference (control) were the same day of the week, month, and year. This allows to control for time invariant individual confounders (e.g., gender, age, weight and smoking status) in short-term and time-varying confounders in long-term (Peters et al., 2006).

The three types of stroke (total stroke, ischemic stroke, and hemorrhagic stroke) were outcomes of interest, and a conditional Poisson regression (CPR) model was used to examine the association between exposure to PMs and the risk of stroke incidence (Armstrong et al., 2014). Compared with conditional logistic regression models, CPR allows for overdispersion, autocorrelation and varying rate denominators (Armstrong et al., 2014). We incorporated distributed lag non-linear models (DLNMs) in our analyses to determine the effect of lag days, and a cross-basis function was employed to fit the exposure-lag-response association and estimate the cumulative lag effects of air pollutants. In DLNMs, a natural cubic spline with a degree of freedom (*df*) of 3 was used to model the lag-response association and a linear function was used to model the exposure-response association (Gasparrini et al., 2010; Gasparrini, 2014). Natural cubic splines were also included to control the non-linear and lagged effects of meteorological variables, with a df of 3 and a maximum lag of 6 for daily temperature and relative humidity, respectively. A binary variable indexing for public holidays was also adjusted. Single pollutant effects were examined in the main model to avoid the correlation of air pollutants, and the effect estimates for PM_1, $PM_{2.5}$, and PM_{10} were expressed as relative risk (RR) with corresponding 95% confidence intervals (CI) for stroke incidence associated with per 10 mg/m^3 increase in each pollutant. The linear relationship between $PM_{2.5}$ and PM_{10} and risks of ischemic stroke and hemorrhagic stroke has been well documented (Liu et al., 2017; Tian et al., 2017; Ban et al., 2021b), and to test the linearity for exposure-response curves between PM_1 and stroke, a natural cubic spline was used to model the PM_1 terms (df = 3) instead of including linear terms in the above DLNMs, and the exposure-response curves were plotted.

Our preliminary analyses showed that the cumulative effects of PMs tended to be stable at lag0−4 day. Hence, we conducted subgroup analyses at lag0−4 day for PMs, and subgroups were stratified by sex, age (18–64 years, 65–74 years, and ≥75 years), residence region (urban and rural), and season [warm (April to September, mean temperature 23.1 °C) and cool (October to March, mean temperature 6.2 °C)]. We conducted a Z test to examine the statistical significance of the differences between subgroups (Altman and Bland, 2003).

2.5.2. Second stage analysis

In this stage, a meta-analysis was adopted to combine county-specific effect estimates for each of the single lag day and cumulative effect for lag0−1 to lag0−6 day to obtain the overall results. We used a random effect model using the parameters of coefficient and standard error generated from the first-stage model (Viechtbauer, 2010). We performed a meta-regression to examine the association between mean PM levels, population density, and social deprivation index (SDI) at the county level to test the modifying effects of county-level feature on the effect estimates at lag0−4 day (Viechtbauer, 2010). Population density data came from the China's 2010 census survey, and SDI from the 2010 county-level area deprivation index (Wang et al., 2021b). SDI is a well-validated metric of averaged socioeconomic status for residents from each Chinese county (Wang et al., 2021b). The index is a normalized score ranging from −2.71 to 2.92 with higher values indicating greater social deprivation, generated from a principal component analysis of eleven county-level characteristics covering education, income, living conditions, and rural-urban differences (Wang et al., 2021b). Detailed information on this index is provided elsewhere (Wang et al., 2021b).

2.5.3. Third stage analysis

The burden of stroke incidence attributable to PMs was calculated based on the estimated RR at lag0−4 day. The attributable number (AN) of strokes caused by exposure to PM on day *k* were computed according to the following formula (Gasparrini and Leone, 2014):

$$AN_k = N_k^*(RR_k - 1)/RR_k$$

where RR_k was the relative risk of cumulative lag0−4 day associated with the increment in PM level on day k, and N_k was the mean of incidence counts between day *k* and day *k* + 4. Then, the AN_k during the study period was summed up to obtain the total AN, and the corresponding attributable fractions (AF) of stroke incidence were derived by dividing the total AN by total incidence number during the study period.

2.6. Sensitivity analysis

To test the robustness of the findings from the main model using the PM exposure at lag0−4 day, we conducted several analyses. First, we used the PM concentrations at the centroid of each county instead of the weighted mean values of the pixels within each county to serve as the daily exposure level. Second, we used monitored PM data from the China National Environmental Monitoring Center instead of the CHAP data to estimate the daily exposure level. For each district/county, we calculated daily mean levels of PM concentrations averaged across the monitors where available. Third, we restricted the data in years 2017–2019 to make the study period equal across districts/counties. Fourth, we built two-pollutant model by additionally adjusting for $PM_{1-2.5}$ for PM_1, $PM_{2.5-10}$ for $PM_{2.5}$, and SO_2 and O_3 for PM_1, $PM_{2.5}$ and PM_{10}, respectively, aiming to test whether the observed PM-incidence associations were influenced by other fractions of PM or other air pollutants. In DLNMs, they were adjusted by setting a linear function and a maximum lag of 6 days (in a natural cubic spline with a *df* of 3) in the cross-basis functions. The concentrations of $PM_{1-2.5}$ were calculated by subtracting PM_1 from $PM_{2.5}$ and the concentrations of $PM_{2.5-10}$ by subtracting $PM_{2.5}$ from PM_{10} (Chen et al., 2019a). Fifth, we changed the df of natural cubic spline for temperature (4–6 df) and relative humidity (4–6 df), respectively.

Spearman correlation coefficients were applied to assess the correlation among air pollutants and meteorological variables. Categorized variables were described as frequencies with percentages and continuous variables were described as means with standard deviation (SD) as well as their minimum, 25th percentile, median, 75th percentile, and maximum values. All analyses were conducted using R 4.0.3 (The R Project for Statistical Computing, Vienna, Austria). A two-sided P-value < 0.05 was considered statistically significant.

3. Results

During the study period, there was a total of 2,193,954 stroke cases (10 per day), and 1,861,331 cases due to ischemic stroke (9 per day) and 332,623 cases due to hemorrhagic stroke (2 per day) in the 126 included counties (Table 1 and Table 2). There were more stroke cases in males than in females, at age <65 year than older, in urban than in rural area, and during the cool than warm season (Table 1). During the study period, the daily means (SD) of PM_1, $PM_{2.5}$, PM_{10}, temperature and relative humidity were 38.5 (19.4) μg/m^3, 61.7 μg/m^3 (37.3), 113.7 (55.9) μg/m^3, 14.7 (10.3) °C, and 61.6 (17.1) %, respectively. Detailed information regarding the 126 counties is presented in Table S1 and geographical location of them in Figure S1. PM_1, $PM_{2.5}$ and PM_{10} levels were positively correlated with other fractions of PM and SO_2, and negatively correlated with O_3, temperature and relative humidity (except the non-significant correlation between PM_1 and relative humidity, Table S2).

Table 1
Characteristics of study participants.

Variables	Total	Ischemic stroke	Hemorrhagic stroke
Total	2,193,954 (100.0)	1,861,331 (100.0)	332,623 (100.0)
Gender			
Male	1,198,807 (54.6)	1,013,707 (54.5)	185,100 (55.6)
Female	995,147 (45.4)	847,624 (45.5)	147,523 (44.4)
Age (years)			
<65	843,774 (38.5)	696,289 (37.4)	147,485 (44.3)
65–74	700,415 (31.9)	611,609 (32.9)	88,806 (26.7)
≥75	649,765 (29.6)	553,433 (29.7)	96,332 (29.0)
Residence			
Urban	1,358,753 (61.9)	1,158,377 (62.2)	200,376 (60.2)
Rural	835,201 (38.1)	702,954 (37.8)	132,247 (39.8)
Season			
Warm	1,071,570 (48.8)	911,306 (49.0)	160,264 (48.2)
Cool	1,122,384 (51.2)	950,025 (51.0)	172,359 (51.8)

Table 2
Summary statistics of daily ambient air pollutants and meteorological variables and daily stroke incidence.

Variables	Mean ± SD	Minimum	P25	Median	P75	Maximum
PM_1 (μg/m^3)	38.5 ± 19.4	1.0	25.4	33.3	46.2	219.3
$PM_{2.5}$ (μg/m^3)	61.7 ± 37.3	3.1	36.3	51.6	76.0	447.3
PM_{10} (μg/m^3)	113.7 ± 55.9	4.0	73.7	103.0	139.5	725.3
$PM_{1-2.5}$ (μg/m^3)	23.2 ± 20.1	1.0	9.9	18.1	30.2	265.6
$PM_{2.5-10}$ (μg/m^3)	52.0 ± 27.0	1.0	34.1	47.6	63.8	521.5
SO_2 (μg/m^3)	28.8 ± 21.0	2.3	14.6	22.1	36.3	273.4
O_3 (μg/m^3)	99.3 ± 45.4	0.0	63.0	93.0	132.0	369.0
Temperature	14.7 ± 10.3	−15.0	5.2	15.9	24.0	35.3
Relative humidity (%)	61.6 ± 17.1	12.8	48.7	62.4	75.0	100.0
Total stroke	10 ± 7	0	5	9	14	564
Ischemic stroke	9 ± 7	0	4	7	12	558
Hemorrhagic stroke	2 ± 2	0	0	1	2	161

Figure S2 presents the exposure–response relationship for the links between PM_1 with total stroke, ischemic stroke, and hemorrhagic stroke at lag0 day. We observed appropriately linear associations between PM_1 and the relative risks for total stroke and ischemic stroke. There was a slightly departure of the linearity of the association between PM_1 with hemorrhagic stroke and the association was not significant. Fig. 1 presents the effect estimates of PM effects on stroke incidence at lag0 to lag6 day and lag0−1 to lag0−6 day. In the results for single lag day, PM_1 and $PM_{2.5}$ levels were associated with increased risks of total stroke and ischemic stroke at lag0, lag1, lag2, lag3, and lag4 days, and the effect estimates were largest at lag0 day and then attenuated at longer lags. PM_{10} levels were associated with increased risks of total stroke and ischemic stroke at lag1, lag2, lag3, lag4, and lag5 days, and the effect estimate was the largest at lag3 day. A 10 μg/m^3 increase in PM_1, $PM_{2.5}$, and PM_{10} at lag0−4 day was associated with increased risks of stroke (RR: 1.012, 95%CI: 1.008, 1.015, RR: 1.006, 95%CI: 1.004, 1.007, and RR: 1.003, 95%CI: 1.002, 1.004, respectively), and ischemic stroke (RR: 1.013, 1.010, 1.017, RR: 1.006, 95%CI: 1.005, 1.008, and RR: 1.003, 95%CI: 1.002, 1.004, respectively). In addition, PM_1 showed consistently stronger association with total stroke and ischemic stroke than $PM_{2.5}$ and PM_{10} at same lag days. There was no significant association between PM and risk of hemorrhagic stroke.

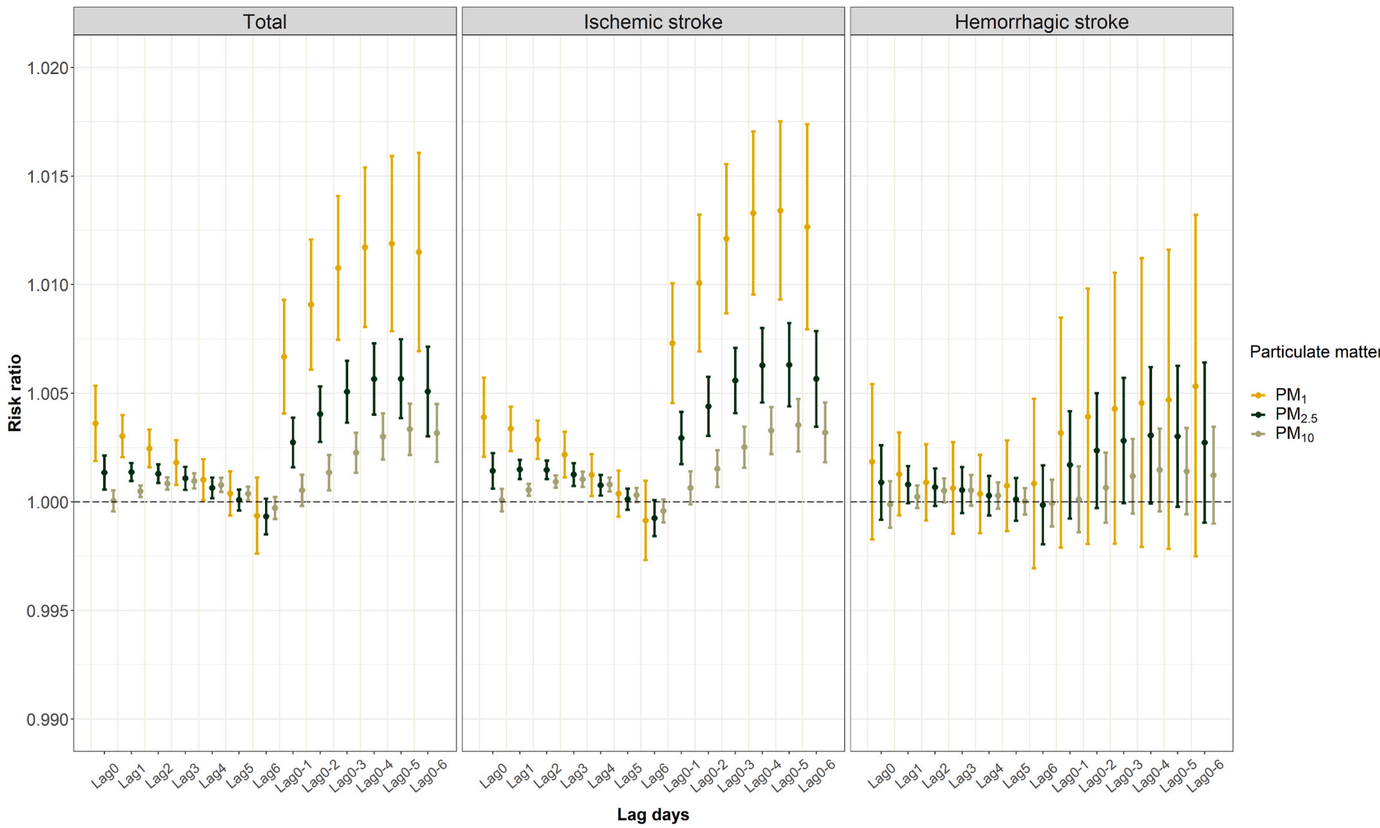

Fig. 1. Pooled relative risk (with 95% confidence interval) in the 126 included counties for stroke, associated with a 10 μg/m^3 increase in PM_1, $PM_{2.5}$, and PM_{10} with different lag time intervals.

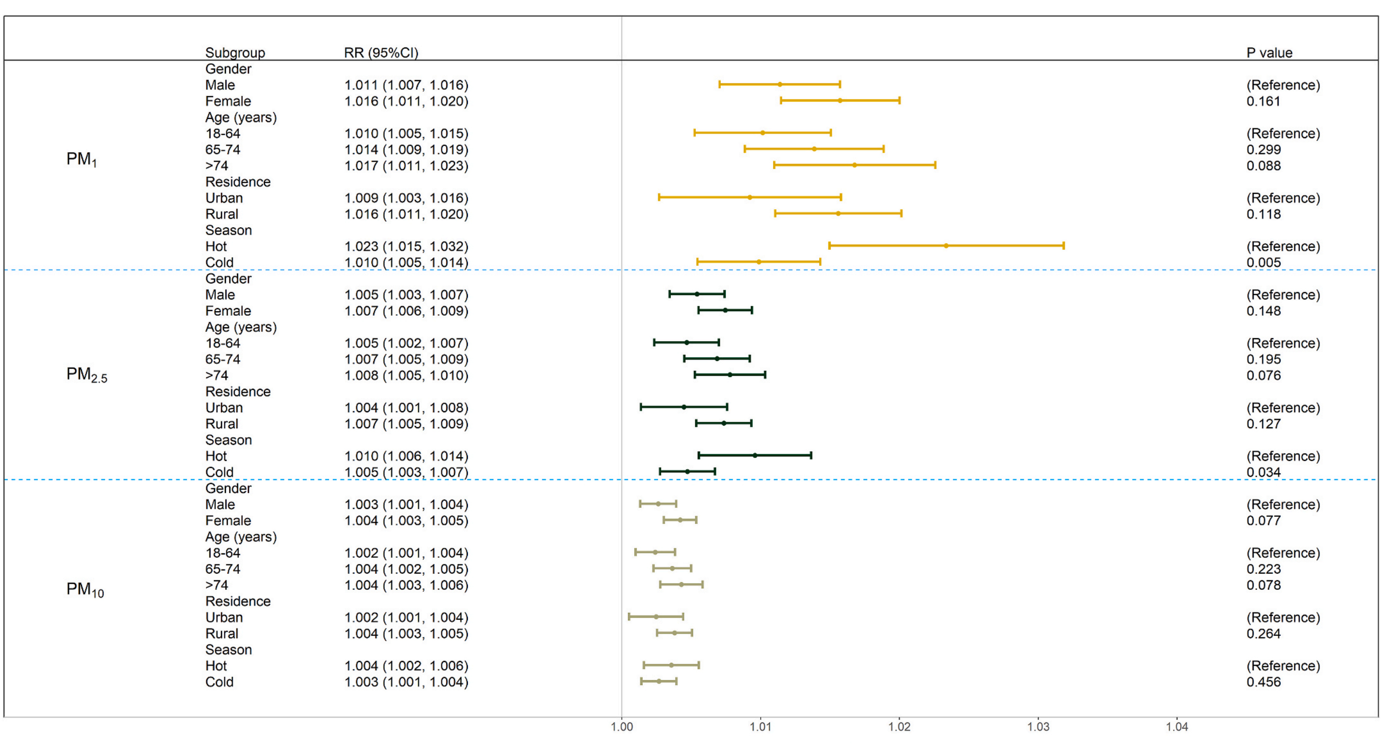

Fig. 2. Pooled relative risk (with 95% confidence interval) for ischemic stroke according to sex, age, and season, associated with a 10 μg/m^3 increase in exposure to PM_1, $PM_{2.5}$, and PM_{10} at lag0−4 day.

Fig. 2 presents the subgroup analyses of the associations between PM_1, $PM_{2.5}$, and PM_{10} with ischemic stroke at lag0−4 days. The association with PM_1, $PM_{2.5}$, and PM_{10} were stronger with ischemic stroke among females than males, among older than younger cases, and during the warm season than cool season, although association were only marginally significant in some instances. For total stroke, results were similar with the above findings (Figure S3), while for hemorrhagic stroke, no significant association was observed for any subgroups (Figure S4).

For the county-level modifiers, SDI seemed to modify the effects of exposure to $PM_{2.5}$ at lag0−4 day for the relations with total stroke and ischemic stroke (Table S3). For each 10 μg/m^3 increase in $PM_{2.5}$, a county with one score higher in local SDI would have increases of 0.6% (95% CI: 0.0%, 1.0%) and 0.6% (95% CI: 0.0%, 1.0%) in daily incidence for total stroke and ischemic stroke, respectively.

Table 3 presents the attributable numbers and attributable fractions of stroke incidence attributable to PM across the 126 counties. Overall, the attributable numbers of total stroke were 32,406 (95% CI: 24,073, 39,543), 26,022 (95% CI: 19,645, 31,684) and 26,127 (95% CI: 18,053, 33,164), and the attributable fractions were 6.9% (95% CI: 5.1%, 8.5%), 5.6% (95% CI: 4.2%, 6.8%) and 5.6% (95% CI: 3.9%, 7.1%) for PM_1, $PM_{2.5}$ and PM_{10}, respectively. The attributable numbers of ischemic stroke were 30,096 (95% CI: 23,349, 35,874), 23,881 (95% CI: 18,481, 28,660) and 23,676 (95% CI: 16,972, 29,516), and the attributable fractions were 7.6% (95% CI: 5.9%, 9.1%), 6.0% (95% CI: 4.7%, 7.2%) and 6.0% (95% CI: 4.3%, 7.4%) for PM_1, $PM_{2.5}$ and PM_{10}, respectively. The attributable numbers and attributable fractions of hemorrhagic stroke were not significant for PM_1, $PM_{2.5}$ or PM_{10} (the 95%CIs cross zero).

Sensitivity analyses along different PM concentrations at the centroid of each county, using monitored air pollution data, using data from years 2017–2019, building two-pollutant models with additionally adjustment for $PM_{1\text{-}2.5}$ for PM_1, $PM_{2.5\text{-}10}$ for $PM_{2.5}$, and SO_2 and O_3 for PM_1, $PM_{2.5}$ and PM_{10}, respectively, as well as changing the df of natural cubic spline for temperature and relative humidity, produced similar effect estimates (Table S4).

4. Discussion

We found that short-term increase in PM_1, $PM_{2.5}$ and PM_{10} levels was associated with increased incidence of total stroke and ischemic stroke at lag0 to lag4 day, while no significant association of PMs with hemorrhagic stroke was observed. The associations for PMs with ischemic stroke were stronger among females, older cases and in warm season. Social deprivation seemed to strengthen the $PM_{2.5}$-stroke association. The association with strokes and the attributable fraction were greater for PM_1 than $PM_{2.5}$ and PM_{10}. These findings have important public health implications for clean air policies, underlining in particular the role of PM_1.

Our findings of positive associations between PM_1, $PM_{2.5}$ and PM_{10} and stroke incidence, and the stronger impact of PM_1 are consistent with several prior studies that had used stroke mortality as the main outcome (Hu et al., 2018; Yin et al., 2020). For example, these studies reported a 0.77%, 0.72% and 0.68% increase in stroke mortality due to per 10 μg/m^3 increase in short-term exposure to PM_1, $PM_{2.5}$ and PM_{10} at lag0−2 day in the Zhejiang province, and a 0.33%, 0.25% and 0.23% increase in stroke mortality due to PM_1, $PM_{2.5}$ and PM_{10} at lag0−1 day in 65 cities of China (Hu et al., 2018; Yin et al., 2020). Some studies using long-term exposures to air pollution found similar results: per 10 μg/m^3 increase in PM_1 and $PM_{2.5}$ was associated with a 0.11% and 0.06% increase in stroke mortality in 33 Chinese communities, and was associated with a 0.05% and 0.03% increase in fatal ischemic stroke mortality across 132 urban hospitals in China (Yang et al., 2019a; Chen et al., 2019b). However, using stroke mortality only as the outcome may underestimate the fractions of population affected by PM, since only a part of stroke incidence can lead to death.

Using hospital admission for stroke data may be a substitute to estimate the health burden of PM exposure on stroke incidence. Only limited studies explored the effects of exposure to PM_1 on hospital admission for stroke, and results are mixed (Zhang et al., 2021; Chen et al., 2020). For instance, a study based on 5 Chinese hospitals showed that a 10 μg/m^3 increase in PM_1, $PM_{2.5}$ and PM_{10} at lag0−1 day was associated with a 1.4%, 0.7% and 0.5% increase in daily hospital admissions for ischemic stroke (Chen et al., 2020), but no association was found in another study (Zhang et al., 2021). Several studies have examined the association between short-term exposure to $PM_{2.5}$ and hospital admissions for ischemic and hemorrhagic strokes, but results were inconsistent, and the reported susceptible lag time interval varied at lag0 to lag5 days (Gu et al., 2020; Liu et al., 2017; Tian et al., 2017, 2019). Another previous study from 10 counties in China, which also used the registry data, found that increases in $PM_{2.5}$ were associated with higher risks of ischemic stroke at lag0, lag0−1, lag0−2, and lag0−3 days, which is consistent with our results (Ban et al., 2021b). However, the authors did not explore the association at longer lags (lag0−4, lag0−5, etc), which does not allow us to make a further comparison. The discrepancies between results across studies may be related to differences in study design (case-crossover or time-series), methodology of estimating PM exposure (averaging the measurements from monitoring sites or integrated data from multiple environmental sources), variations in PM constituents among geographical regions, and analytic models (generalized additive model, conditional logistic regression, or distributed lag model). Moreover, using hospital admissions as the outcome of interest can introduce a bias because there is likely a delay between the onset and hospital admission of stroke patients and not all stroke patients may report to hospital.

A number of pathophysiologic mechanisms can underlie the association between ischemic stroke and short-term exposure to PM. First, inhalation of particulate matters can cause endothelia injury and dysfunction, which may subsequently trigger nonatherosclerotic arteriopathy and small-vessel stroke (Liang et al., 2021). Second, systemic inflammation, oxidative stress, platelet activation, and fibrinolysis disorders caused by exposure to inhaled PM can promote thrombosis and vasoconstriction, and affect the hemodynamic response (Zhu et al., 2021). Third, smaller particles are characterized by a higher surface area to mass ratio and contain higher amounts of adsorbed or condensed toxic compounds per unit mass (Yang et al., 2019b). In addition, Wang et al. used a Multiple-Path Particle Dosimetry model to estimate the deposition of PM in the human respiratory tract, and they found smaller particles more are likely to deposit in the deeper respiratory tract and pulmonary alveoli (Wang et al., 2021c). Moreover, smaller diameter particles may more easily reach and penetrate into the bronchi and even pass through the air-blood barrier and get into the circulatory system (Rossi et al., 2021). The size-depended deposition pattern may partly explain the more adverse effects of smaller vs larger PM on ischemic

Table 3
Attributable number and attributable fractions (with 95% confidence interval) of stroke incidence due to PM_1, $PM_{2.5}$ and PM_{10} at lag0−4 day.

Outcome	Attributable number (cases/year)			Attributable fraction (%)		
	PM_1	$PM_{2.5}$	PM_{10}	PM_1	$PM_{2.5}$	PM_{10}
Total stroke	32,406 (24,073, 39,543)	26,022 (19,645, 31,684)	26,127 (18,053, 33,164)	6.9 (5.1, 8.5)	5.6 (4.2, 6.8)	5.6 (3.9, 7.1)
Ischemic stroke	30,096 (23,349, 35,874)	23,881 (18,481, 28,660)	23,676 (16,972, 29,516)	7.6 (5.9, 9.1)	6.0 (4.7, 7.2)	6.0 (4.3, 7.4)
Hemorrhagic stroke	2281 (−1225, 4850)	2418 (−71, 4354)	2178 (−752, 4433)	3.2 (−1.7, 6.8)	3.4 (−0.1, 6.1)	3.1 (−1.1, 6.2)

stroke (Deng et al., 2019). No significant association between PMs and hemorrhagic stroke was observed in this study, and a recently published review also reported that most of the previous studies found short-term exposure to PM is not associated with hemorrhagic stroke. A study based on 1023 Mexican Americans observed that short-term exposure to $PM_{2.5}$ was associated with elevated levels of low-density lipoprotein cholesterol and total cholesterol (Chen et al., 2016), and two meta-analyses showed that elevated levels of these two metabolic indicators were negatively associated with risk of hemorrhagic stroke (Wang et al., 2013; Xie et al., 2017). Therefore, the different pathophysiologic mechanisms may explain the discrepancy in the association of PM exposure and the two subtypes of stroke. However, the detailed mechanisms are still incompletely understood, which requires further exploration in future studies.

The association between PM and stroke was stronger in females than males, which is consistent with findings from a prior study also using stroke incidence as the outcome based on registry data (Ban et al., 2021b). However, other studies did not find a sex difference (Gu et al., 2020; Chen et al., 2020). A most recent cardiovascular disease screening study based on 1.7 million adults from 141 Chinese counties found a higher prevalence of obesity (26.6% vs. 19.6%), dyslipidemia (61.9% vs. 47.9%), diabetes (63.2% vs. 39.9%), and high blood pressure (98.1% vs. 94.2%) in females than males, which indicating sex may be a modifying factor on the relation between air pollution and stroke (Lu et al., 2019). Furthermore, females exhibited a higher deposition percentage of PM_1 and $PM_{1-2.5}$ in the pulmonary region than in males (Wang et al., 2021c), and it was suggested that females have more reactive airways and subsequently be more sensitive to PM exposure (Hu et al., 2018; Li et al., 2017b). We also found a stronger relation between PM and stroke among older vs younger persons. Such an age difference was also found in a study in China between $PM_{2.5}$ and cardiovascular hospital admissions (Liu et al., 2017). This may be related to the weaker immune response in older vs younger persons. We found a markedly stronger association between PM and stroke during the warm than cool season, consistent with previous studies (Kettunen et al., 2007). Some studies suggested that high temperature was also an independent risk factor for cardiovascular disease (Ravljen et al., 2021), and there may be an interaction between high temperature and PM exposure on stroke (Vered et al., 2020). However, a null association between PM and stroke in warm season or stronger association in the cool season have also been reported in some other studies (Gu et al., 2020; Chen et al., 2020; Dong et al., 2018), which may be attributed to the variety in population susceptibility and in constituent of the PM across regions (Dong et al., 2018; Kettunen et al., 2007).

Results of meta-regression revealed that the adverse effects of $PM_{2.5}$ exposure on stroke appeared to be modified by county-level social deprivation. That is, residents from area with higher social deprivation level may have increased vulnerability to $PM_{2.5}$-induced stroke. A previous study reported that low gross domestic product per capita was associated with increased susceptible to ischemic stroke caused by coarse PM exposure, which is partly in line with our finding (Tian et al., 2019). Social deprivation can reflect the averaged socioeconomic level in a county, and is potentially correlated to local health care and promotion level and air pollution prevention and control level. Therefore, residents in area with relatively high social deprivation level may have more chance of exposure to cardiovascular risk factors and less chance of receiving air pollution prevention information delivered by local government, thus cumulatively increasing their susceptibility to stroke.

We estimated that 7.6%, 6.0%, and 6.0% of all ischemic stroke cases were attributable to short-term exposure to PM_1, $PM_{2.5}$ and PM_{10} in the included counties. Our findings showed that PMs of smaller size might be more important for causing harmful effects than larger ones. Considering the severe PM pollution and the huge amount of population in China, it is crucial to protect the population against PM related health burden. We suggest that the existing global or national air clean policy should be modulated and the public should be alerted to pay more attention to ambient PM_1. The WHO has recently updated their global air quality guideline on daily $PM_{2.5}$ and PM_{10} levels in September 2021 (World Health Organization, 2021), but an expanded environmental standard on PM_1 should be considered in the future.

To our knowledge, this is the first study to examine the association between short-term exposure to PM_1 and stroke using population-based registry data. The registry system covered a total of population of 90.63 million, accounting for 6.4% of the whole population of China. This may make a substantial contribution to provide more robust effect estimates than previous studies collecting hospital admission data based on selected hospitals. Several limitations of this study should however be noted. First, this study is essentially an ecological study, and individual exposure levels were estimated according to weighted mean PM daily concentrations at the county level (i.e. not the actual individual level). Although the sensitivity analyses by using the PM concentrations at the centroid of each county and from monitor stations indicate the results are similar with the main models, exposure measurement errors are inevitable. Second, we lack the data regarding some individual factors known to influence stroke onset, such as weight status, hypertension, active and passive smoking, household fuel type (GBD, 2019 Stroke Collaborators, 2021; Gan et al., 2021; Jiang et al., 2020; Lu et al., 2021). Hence, we could not test the roles, or possibly confounding effects, of these factors. Third, the absence of data on smaller size PM and specific constituents of PM did not allow us to further explore the cardiovascular toxicity of specific aspects of PM. For example, a Danish study revealed that the interquartile range in ultrafine particles ($PM < 0.1$ μm) at lag0−4 day could result in a 21% increase of hospital admissions for several cardiovascular conditions (Andersen et al., 2010). Another recent study suggested that elemental carbon and some metallic elements (e.g., chromium, copper, and zinc) from $PM_{2.5}$ was associated with ischemic stroke.

5. Conclusions

Short-term exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} was associated with increased risk of stroke, with exposure to PM_1 having the strongest effect, and the association were larger in female than males, older vs younger individuals, and during the warm vs cool season. Residents from area with higher social deprivation level may have increased vulnerability to $PM_{2.5}$-induced stroke. In view of persistently severe PM pollution in China, air clean policies should cover the scope of PM_1 and further raise public attention to PM_1 in the future.

Funding

1. National Important Project of the Ministry of Science and Technology in China (grant no. 2017YFC1501404); 2. Innovation Team of "Climbing" Program of Shandong University, and the Youth Team of Humanistic and Social Science of Shandong University (grant no. 20820IFYT1902).

Credit author statement

Han Wu: Formal analysis, Methodology, Visualization, Writing – original draft. **Bingyin Zhang:** Investigation, Data curation, Writing – review & editing. **Jing Wei:** Methodology, Resources, Data curation, Writing – review & editing. **Zilong Lu:** Investigation, Data curation, Writing – review & editing. **Min Zhao:** Formal analysis, Validation, Writing – original draft. **Wenhui Liu:** Software, Writing – review & editing. **Pascal Bovet:** Methodology, Writing – review & editing. **Xiaolei Guo:** Supervision, Resources, Writing – review & editing. **Bo Xi:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113350.

References

Alduchov, O.A., Eskridge, R.E., 1996. Improved magnus form approximation of saturation vapor pressure. J. Appl. Meteorol. 35, 601–609. https://doi.org/10.1175/1520-0450(1996)035<0601:imfaos>2.0.co;2.

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. Bmj 326, 219. https://doi.org/10.1136/bmj.326.7382.219.

Andersen, Z.J., Olsen, T.S., Andersen, K.K., Loft, S., Ketzel, M., Raaschou-Nielsen, O., 2010. Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark. Eur. Heart J. 31, 2034–2040. https://doi.org/10.1093/eurheartj/ehq188.

Armstrong, B.G., Gasparrini, A., Tobias, A., 2014. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. BMC Med. Res. Methodol. 14, 122. https://doi.org/10.1186/1471-2288-14-122.

Ban, J., Ma, R., Zhang, Y., Li, T., 2021a. PM(2.5)-associated risk for cardiovascular hospital admission and related economic burdens in Beijing, China. Sci. Total Environ. 799, 149445. https://doi.org/10.1016/j.scitotenv.2021.149445.

Ban, J., Wang, Q., Ma, R., Zhang, Y., Shi, W., Zhang, Y., Chen, C., Sun, Q., Wang, Y., Guo, X., et al., 2021b. Associations between short-term exposure to PM(2.5) and stroke incidence and mortality in China: a case-crossover study and estimation of the burden. Environ. Pollut. 268, 115743. https://doi.org/10.1016/j.envpol.2020.115743.

Burkart, K.G., Brauer, M., Aravkin, A.Y., Godwin, W.W., Hay, S.I., He, J., Iannucci, V.C., Larson, S.L., Lim, S.S., Liu, J., et al., 2021. Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: a two-part modelling approach applied to the Global Burden of Disease Study. Lancet 398, 685–697. https://doi.org/10.1016/s0140-6736(21)01700-1.

Butland, B.K., Atkinson, R.W., Crichton, S., Barratt, B., Beevers, S., Spiridou, A., Hoang, U., Kelly, F.J., Wolfe, C.D., 2017. Air pollution and the incidence of ischaemic and haemorrhagic stroke in the South London Stroke Register: a case-cross-over analysis. J. Epidemiol. Community Health 71, 707–712. https://doi.org/10.1136/jech-2016-208025.

Chen, Z., Salam, M.T., Toledo-Corral, C., Watanabe, R.M., Xiang, A.H., Buchanan, T.A., Habre, R., Bastain, T.M., Lurmann, F., Wilson, J.P., et al., 2016. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. Diabetes Care 39, 547–554. https://doi.org/10.2337/dc15-1795.

Chen, R., Yin, P., Meng, X., Wang, L., Liu, C., Niu, Y., Liu, Y., Liu, J., Qi, J., You, J., et al., 2019a. Associations between coarse particulate matter air pollution and cause-specific mortality: a nationwide analysis in 272 Chinese cities. Environ. Health Perspect. 127, 17008. https://doi.org/10.1289/ehp2711.

Chen, G., Wang, A., Li, S., Zhao, X., Wang, Y., Li, H., Meng, X., Knibbs, L.D., Bell, M.L., Abramson, M.J., et al., 2019b. Long-term exposure to air pollution and survival after ischemic stroke. Stroke 50, 563–570. https://doi.org/10.1161/strokeaha.118.023264.

Chen, L., Zhang, Y., Zhang, W., Chen, G., Lu, P., Guo, Y., Li, S., 2020. Short-term effect of PM(1) on hospital admission for ischemic stroke: a multi-city case-crossover study in China. Environ. Pollut. 260, 113776. https://doi.org/10.1016/j.envpol.2019.113776.

Deng, Q., Deng, L., Miao, Y., Guo, X., Li, Y., 2019. Particle deposition in the human lung: health implications of particulate matter from different sources. Environ. Res. 169, 237–245. https://doi.org/10.1016/j.envres.2018.11.014.

Dobson, J.E., Bright, E.A., Coleman, P.R., Durfee, R.C., Worley, B.A., 2000. LandScan: a global population database for estimating populations at risk. Photogramm. Eng. Rem. Sens. 66, 849–857.

Dong, H., Yu, Y., Yao, S., Lu, Y., Chen, Z., Li, G., Yao, Y., Yao, X., Wang, S.L., Zhang, Z., 2018. Acute effects of air pollution on ischaemic stroke onset and deaths: a time-series study in Changzhou, China. BMJ Open 8, e020425. https://doi.org/10.1136/bmjopen-2017-020425.

Feigin, V.L., Nguyen, G., Cercy, K., Johnson, C.O., Alam, T., Parmar, P.G., Abajobir, A.A., Abate, K.H., Abd-Allah, F., Abejie, A.N., et al., 2018. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. N. Engl. J. Med. 379, 2429–2437. https://doi.org/10.1056/NEJMoa1804492.

Filep, Á., Fodor, G.H., Kun-Szabó, F., Tiszlavicz, L., Rázga, Z., Bozsó, G., Bozóki, Z., Szabó, G., Peták, F., 2016. Exposure to urban PM1 in rats: development of bronchial inflammation and airway hyperresponsiveness. Respir. Res. 17, 26. https://doi.org/10.1186/s12931-016-0332-9.

Gan, Y., Jiang, H., Room, R., Zhan, Y., Li, L., Lu, K., Wang, C., Chen, S., Liu, J., Yang, Y., et al., 2021. Prevalence and risk factors associated with stroke in China: a nationwide survey of 726,451 adults. Eur. J. Prev. Cardiol. 28, e6–e10. https://doi.org/10.1177/2047487320902324.

Gasparrini, A., 2014. Modeling exposure-lag-response associations with distributed lag non-linear models. Stat. Med. 33, 881–899. https://doi.org/10.1002/sim.5963.

Gasparrini, A., Leone, M., 2014. Attributable risk from distributed lag models. BMC Med. Res. Methodol. 14, 55. https://doi.org/10.1186/1471-2288-14-55.

Gasparrini, A., Armstrong, B., Kenward, M.G., 2010. Distributed lag non-linear models. Stat. Med. 29, 2224–2234. https://doi.org/10.1002/sim.3940.

GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 20, 2021, 795–820. https://doi.org/10.1016/s1474-4422(21)00252-0.

Gu, J., Shi, Y., Chen, N., Wang, H., Chen, T., 2020. Ambient fine particulate matter and hospital admissions for ischemic and hemorrhagic strokes and transient ischemic attack in 248 Chinese cities. Sci. Total Environ. 715, 136896. https://doi.org/10.1016/j.scitotenv.2020.136896.

Hersbach, H., Bell, B., Berrisford, P., Hirahara, S., Horanyi, A., Munoz-Sabater, J., Nicolas, J., Peubey, C., Radu, R., Schepers, D., et al., 2020. The ERA5 global reanalysis. Q. J. R. Meteorol. Soc. 146, 1999–2049. https://doi.org/10.1002/qj.3803.

Hu, K., Guo, Y., Hu, D., Du, R., Yang, X., Zhong, J., Fei, F., Chen, F., Chen, G., Zhao, Q., et al., 2018. Mortality burden attributable to PM(1) in Zhejiang province, China. Environ. Int. 121, 515–522. https://doi.org/10.1016/j.envint.2018.09.033.

Huang, F., Luo, Y., Guo, Y., Tao, L., Xu, Q., Wang, C., Wang, A., Li, X., Guo, J., Yan, A., et al., 2016. Particulate matter and hospital admissions for stroke in Beijing, China: modification effects by ambient temperature. J. Am. Heart Assoc. 5 https://doi.org/10.1161/jaha.116.003437.

Jiang, Y., Lu, H., Man, Q., Liu, Z., Wang, L., Wang, Y., Suo, C., Zhang, T., Jin, L., Dong, Q., et al., 2020. Stroke burden and mortality attributable to ambient fine particulate matter pollution in 195 countries and territories and trend analysis from 1990 to 2017. Environ. Res. 184, 109327. https://doi.org/10.1016/j.envres.2020.109327.

Kettunen, J., Lanki, T., Tiittanen, P., Aalto, P.P., Koskentalo, T., Kulmala, M., Salomaa, V., Pekkanen, J., 2007. Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. Stroke 38, 918–922. https://doi.org/10.1161/01.STR.0000257999.49706.3b.

Li, M., Zhang, Q., Kurokawa, J.I., Woo, J.H., He, K., Lu, Z., Ohara, T., Song, Y., Streets, D. G., Carmichael, G.R., et al., 2017a. MIX: a mosaic Asian anthropogenic emission inventory under the international collaboration framework of the MICS-Asia and HTAP. Atmos. Chem. Phys. 17, 935–963. https://doi.org/10.5194/acp-17-935-2017.

Li, X., Obeidat, M., Zhou, G., Leung, J.M., Tashkin, D., Wise, R., Connett, J., Joubert, P., Bossé, Y., van den Berge, M., et al., 2017b. Responsiveness to ipratropium bromide in male and female patients with mild to moderate chronic obstructive pulmonary disease. EBioMedicine 19, 139–145. https://doi.org/10.1016/j.ebiom.2017.04.020.

Liang, S., Zhao, T., Xu, Q., Duan, J., Sun, Z., 2021. Evaluation of fine particulate matter on vascular endothelial function in vivo and in vitro. Ecotoxicol. Environ. Saf. 222, 112485. https://doi.org/10.1016/j.ecoenv.2021.112485.

Lin, H., Tao, J., Du, Y., Liu, T., Qian, Z., Tian, L., Di, Q., Zeng, W., Xiao, J., Guo, L., et al., 2016. Differentiating the effects of characteristics of PM pollution on mortality from ischemic and hemorrhagic strokes. Int. J. Hyg Environ. Health 219, 204–211. https://doi.org/10.1016/j.ijheh.2015.11.002.

Liu, H., Tian, Y., Xu, Y., Zhang, J., 2017. Ambient particulate matter concentrations and hospitalization for stroke in 26 Chinese cities: a case-crossover study. Stroke 48, 2052–2059. https://doi.org/10.1161/strokeaha.116.016482.

Liu, M., Tang, W., Zhang, Y., Wang, Y., Kangzhuo, B., Li, Y., Liu, X., Xu, S., Ao, L., Wang, Q., et al., 2021. Urban-rural differences in the association between long-term exposure to ambient air pollution and obesity in China. Environ. Res. 201. https://doi.org/10.1016/j.envres.2021.111597.

Lu, J., Lu, Y., Yang, H., Bilige, W., Li, Y., Schulz, W., Masoudi, F.A., Krumholz, H.M., 2019. Characteristics of high cardiovascular risk in 1.7 million Chinese adults. Ann. Intern. Med. 170, 298–308. https://doi.org/10.7326/m18-1932.

Lu, H., Tan, Z., Liu, Z., Wang, L., Wang, Y., Suo, C., Zhang, T., Jin, L., Dong, Q., Cui, M., et al., 2021. Spatiotemporal trends in stroke burden and mortality attributable to household air pollution from solid fuels in 204 countries and territories from 1990 to 2019. Sci. Total Environ. 775, 145839. https://doi.org/10.1016/j.scitotenv.2021.145839.

Lyapustin, A., Wang, Y., Korkin, S., Huang, D., 2018. MODIS Collection 6 MAIAC algorithm. Atmos. Meas. Tech. 11, 5741–5765. https://doi.org/10.5194/amt-11-5741-2018.

McClure, L.A., Loop, M.S., Crosson, W., Kleindorfer, D., Kissela, B., Al-Hamdan, M., 2017. Fine particulate matter (PM(2.5)) and the risk of stroke in the REGARDS cohort. J. Stroke Cerebrovasc. Dis. 26, 1739–1744. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.03.041.

Niu, Z., Liu, F., Yu, H., Wu, S., Xiang, H., 2021. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants. Environ. Health Prev. Med. 26, 15. https://doi.org/10.1186/s12199-021-00937-1.

Peters, A., von Klot, S., Berglind, N., Hörmann, A., Löwel, H., Nyberg, F., Pekkanen, J., Perucci, C.A., Stafoggia, M., Sunyer, J., et al., 2006. Comparison of different methods in analyzing short-term air pollution effects in a cohort study of susceptible individuals. Epidemiol. Perspect. Innovat. 3, 10. https://doi.org/10.1186/1742-5573-3-10.

Qian, Y., Yu, H., Cai, B., Fang, B., Wang, C., 2019. Association between incidence of fatal intracerebral hemorrhagic stroke and fine particulate air pollution. Environ. Health Prev. Med. 24, 38. https://doi.org/10.1186/s12199-019-0793-9.

Ravljen, M., Bajrović, F., Vavpotič, D., 2021. A time series analysis of the relationship between ambient temperature and ischaemic stroke in the Ljubljana area:

immediate, delayed and cumulative effects. BMC Neurol. 21, 23. https://doi.org/10.1186/s12883-021-02044-8.
Rossi, S., Buccarello, A., Caffarra Malvezzi, C., Pinelli, S., Alinovi, R., Guerrero Gerboles, A., Rozzi, G., Leonardi, F., Bollati, V., De Palma, G., et al., 2021. Exposure to nanoparticles derived from diesel particulate filter equipped engine increases vulnerability to arrhythmia in rat hearts. Environ. Pollut. 284, 117163. https://doi.org/10.1016/j.envpol.2021.117163.
Tian, Y., Xiang, X., Wu, Y., Cao, Y., Song, J., Sun, K., Liu, H., Hu, Y., 2017. Fine particulate air pollution and first hospital admissions for ischemic stroke in Beijing, China. Sci. Rep. 7, 3897. https://doi.org/10.1038/s41598-017-04312-5.
Tian, Y., Liu, H., Xiang, X., Zhao, Z., Juan, J., Li, M., Song, J., Cao, Y., Wu, Y., Wang, X., et al., 2019. Ambient coarse particulate matter and hospital admissions for ischemic stroke. Stroke 50, 813–819. https://doi.org/10.1161/strokeaha.118.022687.
Vered, S., Paz, S., Negev, M., Tanne, D., Zucker, I., Weinstein, G., 2020. High ambient temperature in summer and risk of stroke or transient ischemic attack: a national study in Israel. Environ. Res. 187, 109678. https://doi.org/10.1016/j.envres.2020.109678.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Software 36, 1–48. https://doi.org/10.18637/jss.v036.i03.
Wang, X., Dong, Y., Qi, X., Huang, C., Hou, L., 2013. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke 44, 1833–1839. https://doi.org/10.1161/strokeaha.113.001326.
Wang, Y., Eliot, M.N., Wellenius, G.A., 2014. Short-term changes in ambient particulate matter and risk of stroke: a systematic review and meta-analysis. J. Am. Heart Assoc. 3 https://doi.org/10.1161/jaha.114.000983.
Wang, W., Jiang, B., Sun, H., Ru, X., Sun, D., Wang, L., Wang, L., Jiang, Y., Li, Y., Wang, Y., et al., 2017a. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. Circulation 135, 759–771. https://doi.org/10.1161/circulationaha.116.025250.
Wang, W., Wang, D., Liu, H., Sun, H., Jiang, B., Ru, X., Sun, D., Chen, Z., Wang, Y., 2017b. Trend of declining stroke mortality in China: reasons and analysis. Stroke Vasc. Neurol. 2, 132–139. https://doi.org/10.1136/svn-2017-000098.
Wang, X., Qian, Z., Wang, X., Hong, H., Yang, Y., Xu, Y., Xu, X., Yao, Z., Zhang, L., Rolling, C.A., et al., 2018. Estimating the acute effects of fine and coarse particle pollution on stroke mortality of in six Chinese subtropical cities. Environ. Pollut. 239, 812–817. https://doi.org/10.1016/j.envpol.2018.04.102.
Wang, Y., Zhou, L., Guo, J., Wang, Y., Yang, Y., Peng, Q., Gao, Y., Lu, W., 2020. Secular trends of stroke incidence and mortality in China, 1990 to 2016: the global burden of disease study 2016. J. Stroke Cerebrovasc. Dis. 29, 104959. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104959.
Wang, H., Lu, F., Guo, M., Fan, W., Ji, W., Dong, Z., 2021a. Associations between PM1 Exposure and Daily Emergency Department Visits in 19 Hospitals, Beijing. Science of the Total Environment, p. 755. https://doi.org/10.1016/j.scitotenv.2020.142507.
Wang, Z., Chan, K.Y., Poon, A.N., Homma, K., Guo, Y., 2021b. Construction of an area-deprivation index for 2869 counties in China: a census-based approach. J. Epidemiol. Community Health 75, 114–119. https://doi.org/10.1136/jech-2020-214198.
Wang, H., Yin, P., Fan, W., Wang, Y., Dong, Z., Deng, Q., Zhou, M., 2021c. Mortality risk associated with short-term exposure to particulate matter in China: estimating error and implication. Environ. Sci. Technol. 55, 1110–1121. https://doi.org/10.1021/acs.est.0c05095.
Wei, J.L.Z., 2021. ChinaHighSO2: Big Data Seamless 10 Km Ground-Level SO2 Dataset for China (Version 1) [Data Set]. Zenodo. https://doi.org/10.5281/zenodo.4641538.
Wei, J., Li, Z., Guo, J., Sun, L., Huang, W., Xue, W., Fan, T., Cribb, M., 2019. Satellite-derived 1-km-Resolution PM1 concentrations from 2014 to 2018 across China. Environ. Sci. Technol. 53, 13265–13274. https://doi.org/10.1021/acs.est.9b03258.
Wei, J., Li, Z., Cribb, M., Huang, W., Xue, W., Sun, L., Guo, J., Peng, Y., Li, J., Lyapustin, A., et al., 2020. Improved 1 km resolution PM2.5 estimates across China using enhanced space-time extremely randomized trees. Atmos. Chem. Phys. 20, 3273–3289. https://doi.org/10.5194/acp-20-3273-2020.
Wei, J., Li, Z., Xue, W., Sun, L., Fan, T., Liu, L., Su, T., Cribb, M., 2021a. The ChinaHighPM(10) dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China. Environ. Int. 146, 106290. https://doi.org/10.1016/j.envint.2020.106290.
Wei, J., Li, Z., Lyapustin, A., Sun, L., Peng, Y., Xue, W., Su, T., Cribb, M., 2021b. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Rem. Sens. Environ. 252, 112136. https://doi.org/10.1016/j.rse.2020.112136.
Wei, J., Li, Z., Li, K., Dickerson, R.R., Pinker, R.T., Wang, J., Liu, X., Sun, L., Xue, W., Cribb, M., 2022. Full-coverage mapping and spatiotemporal variations of ground-level ozone (O3) pollution from 2013 to 2020 across China. Rem. Sens. Environ. 112775. https://doi.org/10.1016/j.rse.2021.112775.
World Health Organization, 2021. WHO Global Air Quality Guidelines. Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. World Health Organization, Geneva.
Xie, L., Wu, W., Chen, J., Tu, J., Zhou, J., Qi, X., Yin, X., 2017. Cholesterol levels and hemorrhagic stroke risk in East Asian versus non-East Asian populations: a systematic review and meta-analysis. Neurol. 22, 107–115. https://doi.org/10.1097/nrl.0000000000000126.
Yang, B.Y., Guo, Y., Morawska, L., Bloom, M.S., Markevych, I., Heinrich, J., Dharmage, S. C., Knibbs, L.D., Lin, S., Yim, S.H., et al., 2019a. Ambient PM(1) air pollution and cardiovascular disease prevalence: insights from the 33 Communities Chinese Health Study. Environ. Int. 123, 310–317. https://doi.org/10.1016/j.envint.2018.12.012.
Yang, B.Y., Guo, Y., Bloom, M.S., Xiao, X., Qian, Z.M., Liu, E., Howard, S.W., Zhao, T., Wang, S.Q., Li, S., et al., 2019b. Ambient PM(1) air pollution, blood pressure, and hypertension: insights from the 33 Communities Chinese Health Study. Environ. Res. 170, 252–259. https://doi.org/10.1016/j.envres.2018.12.047.
Yin, P., Guo, J., Wang, L., Fan, W., Lu, F., Guo, M., Moreno, S.B.R., Wang, Y., Wang, H., Zhou, M., et al., 2020. Higher risk of cardiovascular disease associated with smaller size-fractioned particulate matter. Environ. Sci. Technol. Lett. 7, 95–101. https://doi.org/10.1021/acs.estlett.9b00735.
Yu, X.B., Su, J.W., Li, X.Y., Chen, G., 2014. Short-term effects of particulate matter on stroke attack: meta-regression and meta-analyses. PLoS One 9, e95682. https://doi.org/10.1371/journal.pone.0095682.
Zhang, Y., Zhang, L., Wei, J., Liu, L., Wang, Y., Liu, J., Zhou, P., Wang, L., Ding, Z., Zhang, Y., 2021. Size-specific Particulate Air Pollution and Hospitalization for Cardiovascular Diseases: A Case-Crossover Study in Shenzhen, China. Atmospheric Environment, p. 251. https://doi.org/10.1016/j.atmosenv.2021.118271.
Zhao, R., Chen, S., Wang, W., Huang, J., Wang, K., Liu, L., Wei, S., 2017. The impact of short-term exposure to air pollutants on the onset of out-of-hospital cardiac arrest: a systematic review and meta-analysis. Int. J. Cardiol. 226, 110–117. https://doi.org/10.1016/j.ijcard.2016.10.053.
Zheng, H., Yi, W., Ding, Z., Xu, Z., Ho, H.C., Cheng, J., Hossain, M.Z., Song, J., Fan, Y., Ni, J., et al., 2021. Evaluation of life expectancy loss associated with submicron and fine particulate matter (PM1 and PM2.5) air pollution in Nanjing, China. Environ. Sci. Pollut. Control Ser. https://doi.org/10.1007/s11356-021-15244-z.
Zhu, X.L., Chen, C., Zhang, B., Ge, Y.H., Wang, W.D., Cai, J., Kan, H.D., 2021. Acute effects of personal exposure to fine particulate matter on salivary and urinary biomarkers of inflammation and oxidative stress in healthy adults. Chemosphere 272. https://doi.org/10.1016/j.chemosphere.2021.129906.