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Long-term exposure to ambient $PM_{2.5}$ and stroke mortality among urban residents in northern China

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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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2021.112063.

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Abstract

Evidence is still limited for the role of long-term $PM_{2.5}$ exposure in cerebrovascular diseases among residents in high pollution regions. The study is aimed to investigate the long-term effects of $PM_{2.5}$ exposure on stroke mortality, and further explore the effect modification of temperature variation on the $PM_{2.5}$-mortality association in northern China. Based on a cohort data with an average follow-up of 9.8 years among 38,435 urban adults, high-resolution estimates of $PM_{2.5}$ derived from a satellite-based model were assigned to each participant. A Cox regression model with time-varying exposures and strata of geographic regions was employed to assess the risks of stroke mortality associated with $PM_{2.5}$, after adjusting for individual risk factors. The cross-product term of $PM_{2.5}$ exposure and annual temperature range was further added into the regression model to test whether the long-term temperature variation would modify the association of $PM_{2.5}$ with stroke mortality. Among the study participants, the annual mean level of $PM_{2.5}$ concentration was 66.3 $\mu g/m^3$ ranging from 39.0 $\mu g/m^3$ to 100.6 $\mu g/m^3$. For each 10 $\mu g/m^3$ increment in $PM_{2.5}$, the hazard ratio (HR) was 1.31 (95% CI: 1.04–1.65) for stroke mortality after multivariable adjustment. In addition, the HRs of $PM_{2.5}$ decreased gradually as the increase of annual temperature range with the HRs of 1.95 (95% CI: 1.36–2.81), 1.53 (95% CI: 1.06–2.22), and 1.11 (95% CI: 0.75–1.63) in the low, middle, and high group of annual temperature range, respectively. The findings provided further evidence of long-term $PM_{2.5}$ exposure on stroke mortality in high-exposure settings such as northern China, and also highlighted the view that assessing the adverse health effects of air pollution might not ignore the role of temperature variations in the context of climate change.

Keywords

Satellite-based model; Population-based cohort; Stroke mortality; Long-term exposure; Temperature variation

1. Introduction

Stroke is one of great threats to global health, contributing to approximate 6.2 million deaths worldwide and 2.1 million deaths in China (GBD 2017 Causes of Death Collaborators, 2018; Institute for Health Metrics and Evaluation, 2020). Also the modifiable risk factors such as hypertension, obesity and physical inactivity, which were closely related to risk of stroke, have not been well controlled during the past decades (GBD 2015 Risk Factors Collaborators, 2016). In addition to these well-known risk factors, increasing observational and experimental studies found that pollution of fine particulate matter (particulate matter with aerodynamic diameter ≤ 2.5 μm, $PM_{2.5}$) might serve as a novel risk factor for stroke and other cardiovascular diseases (Brook et al., 2010; Rajagopalan et al., 2018). Most of population-based studies documented risks of hospital admission or mortality of stroke associated with short-term ambient $PM_{2.5}$ exposure (Tian et al., 2018, 2019b; Shah et al., 2015). However, the evidence on cerebrovascular damage linked to long-term $PM_{2.5}$ exposure was still limited. Based on the literature review of two meta-analysis studies (Yuan et al., 2019; Chen and Hoek, 2020), six epidemiology studies were conducted in Asian

regions, and others mainly derived from European and North American countries where annual concentrations of ambient $PM_{2.5}$ were usually not over 35 μg/m^3 (Yuan et al., 2019; Chen and Hoek, 2020). Considering the uncertainties and heterogeneities of current findings (Yuan et al., 2019; Chen and Hoek, 2020), the exposure-response relationships derived from studies with relatively low levels of $PM_{2.5}$ might not directly extended to those in high pollution regions. In addition, several studies conducted in the concentration range of 50–100 μg/m^3 showed inconsistent results between long-term $PM_{2.5}$ exposure and stroke risks (Huang et al., 2019; Chen et al., 2019; Yang et al., 2018). Thus research evidence focusing on the chronic effect of $PM_{2.5}$ exposure on stroke need further accumulated, especially among people living in high pollution settings, which is important to obtain accurate estimations in cerebrovascular disease burden attributable to global exposure range of $PM_{2.5}$.

In China, ambient air pollution has emerged as one of top risk factors contributing to cardiovascular disease burdens in 2017 (Institute for Health Metrics and Evaluation, 2020). Recently, two studies in mainland China observed long-term exposure to $PM_{2.5}$ significantly associated with incidence and/or mortality of stroke (Huang et al., 2019; Chen et al., 2019), although one of the studies was conducted among ischemic stroke patients with only 1-year follow-up (Chen et al., 2019). Another publication conducted in Hong Kong, China, reported non-significant association of long-term $PM_{2.5}$ exposure with cerebrovascular mortality in an elderly cohort (Yang et al., 2018). To illustrate the $PM_{2.5}$-stroke relationship accurately, these research evidence still need validated independently from longitudinal cohort data with wide range of $PM_{2.5}$ exposure. In addition, a few studies illustrated that effects of short-term $PM_{2.5}$ exposure on cardiovascular events could be modified by ambient temperature (Chen et al., 2018; Qian et al., 2008; Yitshak-Sade et al., 2018), while two studies both reported increased effects of long-term $PM_{2.5}$ pollution on natural-cause mortality were modified by an increase in annual or seasonal average temperature (Kioumourtzoglou et al., 2016; Wang et al., 2016). However, few studies have examined the role of annual temperature variation in effect modification for the association of long-term $PM_{2.5}$ exposure with stroke mortality, considering potential interaction roles of air pollution and temperature.

In this study, combining the satellite-based $PM_{2.5}$ exposure estimates with a cohort data among urban adults, we aimed to investigate the relationship between stroke mortality and long-term exposure to ambient $PM_{2.5}$ in northern China, and examined the potential effect modification of annual temperature range in the context of global climate change.

2. Materials and methods

2.1. Study design and participants

The cohort study is proposed to investigate the relationship between long-term exposure to air pollution and health among adults who lived in northern China (Zhang et al., 2014; Chen et al., 2016; Shan et al., 2020). Details of the study population have been described in Supplemental Methods. In this study, 113 deceased participants before 2000 were excluded because the satellite-based estimation of ambient $PM_{2.5}$ data in China was available after 2000. Furthermore, 506 participants with stroke or cancer at baseline were excluded, and 295 were excluded due to covariates data missing, finally leaving 38,140 participants for the

analysis. A flow chart showed the inclusion and exclusion of the study population (Supplemental Fig. 1).

The study has been approved by the ethics committee of the coordinating center of Tianjin Medical University. Written informed consent was signed by each participant before surveys conducted.

2.2. Exposure and health data collection

The ambient $PM_{2.5}$ levels in China were estimated using a satellite-based spatiotemporal model, and the detailed methodology of the model has been published elsewhere (Xiao et al., 2018; Liang et al., 2020b).

The demographic, socio-economic, and lifestyle information at baseline were collected by trained interviewers using standardized questionnaires. For death cases, local investigators used questionnaires to record the date, location and cause of death provided by next of kin. All mortality information was also crosschecked based on death certificates from the databases in local Centers for Disease Control and Prevention (CDCs). The causes of death were coded based on the International Classification of Diseases, tenth revision (I60–I69 for stroke).

Description for the features of modeling, estimations of individual exposure to ambient $PM_{2.5}$, and health data collection could be found in Supplemental Methods.

2.3. Statistical analysis

Baseline characteristics of study populations were presented as percentages for categorical variables or mean ± standard derivation for continuous variables. The association between long-term exposure to $PM_{2.5}$ and stroke mortality was assessed using a Cox proportional hazards model with time-varying exposure of $PM_{2.5}$ on 1-year scale, considering changes of annual average $PM_{2.5}$ levels during the follow-up period (Andersen and Gill, 1982). In addition, the Cox regression analysis was performed with a stratum variable of four residential cities as the indicator addressing potential variations due to geographic regions, and used time-on-study as the time scale (i.e., time since baseline to follow-up). The other covariates were included gradually in the following multi-variable adjustment models: Model 1 adjusting for age and sex; Model 2 further adjusting for education level and personal income; Model 3 additionally adjusting for BMI, smoke, drink, and exercise; and Model 4 additionally adjusting for medical history of hypertension and diabetes. The association estimate from Model 4 was reported as the main result after fully adjusting for individual cardiovascular covariates, based on recommendations from previous works (Yuan et al., 2019; Huang et al., 2019; Miller et al., 2007).

Subgroup analyses were performed based on Model 4, and stratified by age, sex, education, personal monthly income, smoking and alcohol drinking status. We further examined the multiplicative interactions of $PM_{2.5}$ exposure and each characteristic factor by introducing a cross-product term in the Cox model. In addition, several sensitivity analyses were performed to test robustness of results. First, to minimize the potential bias, we excluded individuals with cardiovascular diseases at baseline, and repeated the Cox regression

analysis. Second, the hazard ratios (HRs) were re-calculated after excluding participants who reported occupational exposure with particulate matter at baseline. Third, based on the Model 4, we additionally adjusted covariates of dietary frequencies, including seafood, red meat, poultry, vegetable, and fruit consumption at baseline which were classified into three groups: low (no more than once a week), moderate (two or three times per week), and high (equal to or more than four times a week).

Last, we examined whether the annual range of ambient temperature would modify the effect estimation for the association between long-term exposure to $PM_{2.5}$ and stroke mortality. The annual temperature range was classified into low (24.6 °C–28.5 °C), middle (28.5 °C–30.6 °C), and high (30.6 °C–40.0 °C) groups, according to the cutoff points of tertiles. Based on the Model 4, main effects of $PM_{2.5}$ and tertiles of annual temperature range were both included along with other covariates, and the multiplicative interaction term of annual $PM_{2.5}$ exposure and annual temperature range was tested for the significance of effect modification.

All of the analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The tests of significance were two sided with *P*-value < 0.05.

3. Results

3.1. Descriptive analysis of the study participants

During the average follow-up of 9.8 years, 254 deaths of stroke were observed among the eligible 38,140 Chinese participants. The study participants were on average 44.0 years of age, and 50.2% were women. In addition, over 50% and 38% of men were smokers and alcohol drinkers, respectively, which were much higher than those proportions of women. The detailed baseline characteristics of the study participants were shown in Table 1, and descriptions of city-specific characteristics in Supplemental Table 1.

3.2. Associations between long-term exposure to $PM_{2.5}$ and stroke mortality

The average level of annual exposure to $PM_{2.5}$ was 66.3 $\mu g/m^3$ with the range from 39.0 $\mu g/m^3$ to 100.6 $\mu g/m^3$. The temporal trends of annual $PM_{2.5}$ levels and annual temperature ranges by city and calendar year were shown in Supplemental Fig. 2. Based on the Cox regression models with various multivariable adjustments, Table 2 represented the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association of long-term $PM_{2.5}$ exposure with stroke mortality. In the Model 4, the risk of stroke death was significantly elevated with a HR of 1.31 (95% CI, 1.04–1.65) per 10 $\mu g/m^3$ increase of $PM_{2.5}$ concentration after adjusting for age, sex, education level, personal income, BMI, smoke, drink, physical activity, and medical history of hypertension and diabetes at baseline. In addition, when the $PM_{2.5}$ concentrations were categorized using the quartile cutoff points of 58.5 $\mu g/m^3$, 63.6 $\mu g/m^3$, and 75.1 $\mu g/m^3$, higher risks of stroke mortality were also observed with HRs of 1.38 (95% CI, 0.91–2.10), 1.42 (95% CI, 0.96–2.10), and 1.60 (95% CI, 1.08–2.35) for the second, third, and fourth quarter group, respectively, compared with the first

quarter as reference (Supplemental Table 2). The trend testing of HRs across the quarters was significant ($P = 0.020$).

3.3. Subgroup and sensitivity analyses

The associations between long-term exposure to $PM_{2.5}$ and stroke mortality across different subgroups were displayed stratified by age, sex and education levels in Table 3. The risk of stroke mortality linked to long-term $PM_{2.5}$ exposure seemed higher among elder, women, and people with low level of education. The estimates of HRs were similar among other subgroups categorized by personal income, smoking, and alcohol drinking. However, we did not observed significant interactions between $PM_{2.5}$ exposure and those individual factors of demographic or behavior characteristics (P-value for interaction ≥0.05).

In the sensitivity analysis, the HRs for the $PM_{2.5}$-stroke mortality associations were 1.29 (95%CI, 1.02–1.64) and 1.32 (95%CI, 1.04–1.68) after removing participants with cardiovascular disease at baseline and those with self-reported occupational particulate exposure, respectively (Table 4). When dietary factors were further adjusted in the multivariate regression model (Model 5), the result kept consistent with the main analysis (Model 4). Moreover, we removed the strata of cities and directly added an indicator variable of four residential cities as a covariate into the Cox model, which showed little change with HR of 1.31 (95%CI, 1.04–1.65). In addition, residents within the same neighborhoods may share similar socioeconomic status and environmental factors. Thus, we used a shared frailty model by which cluster effect of residential neighborhoods were incorporated into the Cox regression analysis, and the HR of association was 1.31 (95%CI, 1.04–1.66) which was close to the main result. Overall, the results of sensitivity analyses did not show substantial changes in association estimations of long-term $PM_{2.5}$ exposure with stroke mortality.

3.4. Effect modification of annual temperature range for the association between $PM_{2.5}$ and stroke mortality

The mean level for annual range of temperature exposure among the study participants were 30.4 °C (minimum to maximum: 24.6–40.0 °C). After adding the annual range of temperature as a continuous covariate into the Cox regression model, the risk of stroke mortality was still associated significantly with each 10 μg/m^3 increase of $PM_{2.5}$, and the HR (95% CI) slightly increased to 1.35 (95% CI, 1.04–1.77). The participants were further categorized into three subgroups according to the tertiles of annual temperature range. Fig. 1 illustrated that HRs for the associations of long-term $PM_{2.5}$ exposure with stroke mortality decreased gradually as the increment of annual temperature range. The effect modification of annual temperature range was significant by testing the cross-product term of annual $PM_{2.5}$ exposure and tertiles of annual temperature range ($P = 0.048$).

4. Discussion

Using the cohort data collected from 2000 to 2009 among 38,140 participants, a significant association of long-term exposure to $PM_{2.5}$ with stroke mortality was observed in northern China, where the urban residents had been living in high-polluted environments with the annual average level of $PM_{2.5}$ ranging from 39.0 μg/m^3 to 100.6 μg/m^3. In addition, the

study observed that the effect estimation for the $PM_{2.5}$-stroke mortality association was strengthened when the annual range of ambient temperature kept at low level. These findings highlighted the importance of assessing the health effects attributable to air pollution and climate change jointly in future research works.

Air pollution has been considered as a great threat to global public health, and particulate matter pollution has exhibited extensive adverse effects to cardiovascular and cerebrovascular functions (Manisalidis et al., 2020; Burnett et al., 2018). Many studies have documented the short-term exposure to particulate matter was significantly associated with elevated risks of stroke mortality (Shah et al., 2015), but the evidence of long-term exposure to $PM_{2.5}$ was still limited, especially in high pollution settings. One recent meta-analysis pooled 16 cohort studies to obtain an overall association between stroke mortality and long-term exposure to $PM_{2.5}$ with the HR of 1.11(95% CI: 1.04, 1.18) per 10 $\mu g/m^3$ increase of $PM_{2.5}$ (Chen and Hoek, 2020). However, 13 of those studies have been conducted in North American or European countries, where the annual mean levels of $PM_{2.5}$ exposure were often less than 35 $\mu g/m^3$. In addition, only 5 original studies of the 16 cohorts included in the meta-analysis showed significant positive associations along with substantial heterogeneities of the pooled result (I^2 = 84.7%). To the best of our knowledge, effect estimations of associations between stroke mortality and long-term exposure to $PM_{2.5}$ were inadequate among populations exposed to high-polluted settings such as in mainland China. Two population-based prospective cohort studies in mainland China have examined the risks of stroke deaths associated with long-term $PM_{2.5}$ exposure, the mean levels of which reached to 43.7 $\mu g/m^3$ (range: 4.2 $\mu g/m^3$ – 83.8 $\mu g/m^3$) for the Chinese Male Cohort and 67.4 $\mu g/m^3$ (range: 25.5 $\mu g/m^3$–114.0 $\mu g/m^3$) for the study of Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) (Liang et al., 2020a; Yin et al., 2017). The Chinese Male Cohort observed risk of stroke mortality elevated for a 10 $\mu g/m^3$ increase with a HR of 1.14 (95% CI, 1.13–1.16) (Yin et al., 2017), but the study was only recruited male participants (Niu et al., 1998). The China-PAR study covered 15 provinces across China with an average follow-up of 7.6 years among 116,792 participants, which reported the HR of stroke mortality was 1.10 (95% CI, 1.05–1.18) for a 10 $\mu g/m^3$ increase of $PM_{2.5}$ (Liang et al., 2020a). The two works did not report the specific HRs of stroke mortality stratified by regions (northern vs southern China), while it is known that average $PM_{2.5}$ concentrations were much higher in the northern than other regions in China (He et al., 2017). Our study was conducted in four northern cities of China among over 38,000 urban participants, and observed a relative higher HR of 1.31 (95% CI, 1.04–1.65) for the association of long-term $PM_{2.5}$ exposure with stroke mortality. To diminish potential confounding maximally, we have adjusted demographics, BMI, smoke, drink, physical activity, and medical history in Model 4 (Table 2) and available dietary information in Model 5 (Table 4). The association results were robust in the multivariate analyses. We also used the stratified Cox regression model with a stratum variable of the four cities, which allowed us to control potential heterogeneities of study regions assuming distinct baseline hazard function for each stratum (Kleinbaum, 1996). As one of sensitivity analyses, if the variable of four cities was added as a covariate into the Cox model without the strata, the result was almost the same to the primary analysis with the HR of 1.31 (95% CI, 1.04–1.65).

In addition, after a series of sensitive analyses, the estimations for HRs seemed no substantial changes in our data (Table 4), although a slight overestimation for the association might exist considering the relatively narrow range of $PM_{2.5}$ exposure (39.0 μg/m^3–100.6 μg/m^3) in this study, compared with aforementioned studies of the Chinese Male Cohort and the China-PAR cohort. More evidence derived from high polluted regions will be warranted in future to obtain robust estimations for the stroke mortality-$PM_{2.5}$ associations.

In the subgroup analysis, we did not find significant differences in the association estimations between $PM_{2.5}$ concentrations and stroke mortality stratified by either demographic factors (e.g., age and sex) or individual behavior characteristics (e.g., smoke and drink). Interestingly, it is observed that the annual temperature range significantly modified the effect of stroke mortality- $PM_{2.5}$ association. Numerous studies highlighted the impacts of climate change on human health (Bernard et al., 2001), and pervious researches mainly focused on the short-term temperature change related to stroke events (Takumi et al., 2015; Tian et al., 2019a; Pan et al., 1995; Vered et al., 2020). Impacts of long-term temperature change on stroke mortality have not been fully understood yet. For the health effects of long-term temperature change, several researches documented increases in annual temperature were significantly associated with elevated fasting blood glucose and obesity (Wallwork et al., 2017; Yang et al., 2015; Valdes et al., 2014), which were metabolic risk factors for stroke. A few studies also suggested that higher temperature standard deviation was associated with increased natural-cause mortality (Shi et al., 2015, 2016). Some plausible mechanisms explaining these associations included direct effects of temperature variability on cardiovascular systems, and changes in population behavior such as more time spent indoor. Additionally, several case-crossover or time-series studies observed the short-term temperature change could modify the acute effects of particulate matter on cardiovascular events (Chen et al., 2015; Huang et al., 2016; Li et al., 2015; Sun et al., 2015), but less is known about the role of long-term temperature variation in the association between $PM_{2.5}$ and stroke. Based on the cohort data, this study found that the annual temperature range also affected the health effects of $PM_{2.5}$ in long run, and the association between $PM_{2.5}$ and stroke mortality was enhanced when the annual range of temperature was relatively low (< 28.5 °C) among the study participants. Although evidence is still limited in the interactions of temperature variability and air pollution on long-term health outcomes, the findings suggested that assessing chronic health effects linked to air pollution might not ignore the role of long-term temperature change. Further studies need more concerns on the disease burdens attributable to ambient air pollution and temperature jointly in the context of global climate change.

The understanding of biological mechanisms underlying $PM_{2.5}$-mediated cerebrovascular risk is still evolving. In general, inhaled $PM_{2.5}$ may stimulate mediators of oxidative stress, or initiating inflammatory responses, while some ultrafine particles may penetrate into the circulatory system leading to direct deleterious effects (Rajagopalan et al., 2018). Animal toxicological and human epidemiological studies also suggested that fine particulate pollutants could provoke vascular endothelial dysfunction, enhance blood coagulation, and promote artery calcification (Franchini and Mannucci, 2011; Kaufman et al., 2016; Tornqvist et al., 2007). These pathophysiologic pathways may be related to the development of stroke and increased risk of stroke mortality associated with long-term $PM_{2.5}$ exposure. In

addition, extreme temperature variations plausibly contributed to cardiovascular damages by increasing amount of free radicals, inducing neuronal apoptotic signal transduction, and even elevating blood pressure and heart rate (Gostimirovic et al., 2020). In future, we still need bio-molecular evidence supporting the specific and joint influences of long-term $PM_{2.5}$ pollution and temperature variation in cerebrovascular functions.

One of strengths in the current study is that the cohort data were collected from general Chinese participants with a long period of follow-up. Uniformed protocols and questionnaires with strict training for interviewers with strict quality control guaranteed the data quality from multiple survey centers, where the residents had a relatively high exposure of $PM_{2.5}$. In addition, the high-resolution (1-km) $PM_{2.5}$ estimates we used were derived from an ensemble machine-learning spatiotemporal model, which had improved the accuracy of ambient $PM_{2.5}$ exposure estimation (Xiao et al., 2018; Liang et al., 2020b).

Despite the strengths above, several limitations should be addressed. First, the particulate matter is a complex mixture and chemical compositions of $PM_{2.5}$ may vary in different regions of China (Wang et al., 2014; Zhu et al., 2018), nevertheless we did not collect the detailed composition data of $PM_{2.5}$ among the study participants. Although all of the study participants were from four northern cities of China, it still needs cautions with effect estimations in the current study, and specific cerebrovascular damages related to different particulate compositions need investigations in future. Second, some known confounders such as fasting lipids and glucose were not available in the baseline survey, although the covariates of demographics, lifestyle, and medical history had been adjusted in regression models stepwise and the results seemed robust for the $PM_{2.5}$-stroke mortality relationship. Third, the analysis did not consider the indoor air pollutants, such as solid fuel use, which may also contribute to long-term health effects (Arku et al., 2018; Yu et al., 2018, 2020). Fourth, the mechanism for the interaction of long-term exposure to $PM_{2.5}$ pollution and temperature range is still unclear. It is inferred that a larger annual temperature range might be a marker for a more severe winter with heavier indoor air pollution due to solid fuel use, or a marker for more time spent indoors with less physical activity. More validated studies are expected with more careful and accurate measurements for exposure and potential confounders. Last, the results of subgroup analyses should be cautiously treated, especially in the subgroups of age and education level due to some unbalanced distributions across the four study cities. Independent multi-center studies with uniformed participants' characteristics should be conducted in the future to obtain robust subgroup-specific associations and to identify people more susceptible to long-term air pollution.

5. Conclusion

In sum, this extended follow-up study provided direct evidence that long-term exposure to $PM_{2.5}$ will significantly increase stroke mortality under the high concentrations of $PM_{2.5}$ pollution in northern China. The findings also supported that the strength of association between stroke mortality and air pollution could be modified by annual temperature range. Despite of existed uncertainties, these new findings expand our understanding in the excess mortality linked to long-term $PM_{2.5}$ exposure and temperature variations. More solid evidence on the adverse health effects related to air pollution and climate change will

promote us to take more targeted and efficient reactions to issues of environment and health, especially in those fast industrializing countries such as China.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Abbreviations list:

$PM_{2.5}$	particulate matter with aerodynamic diameter ≤ 2.5 μm
HR	hazard ratio
China-PAR	Prediction for Atherosclerotic Cardiovascular Disease Risk in China

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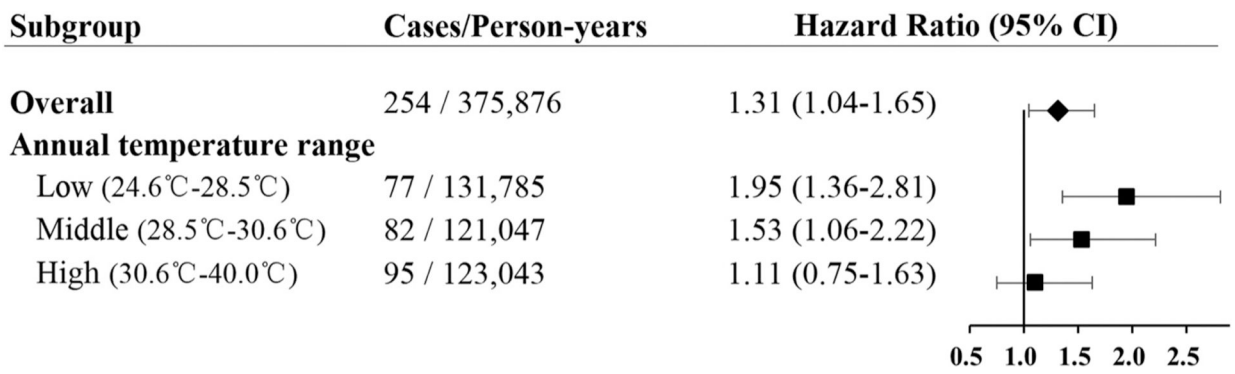

Fig. 1.

Adjusted hazard ratio (95% CI) of stroke mortality per 10 μg/m^3 increase of $PM_{2.5}$ across different groups of annual temperature range. The annual temperature range was classified into the Low, Middle, and High groups using tertiles as cutoff points. The rhombus and square markers represent the point estimations of hazard ratios, and the black bars represent 95% CIs.

Table 1

Baseline characteristics of 38,140 participants in the cohort study.

Characteristics	Total	Male	Female
Participants (n)	38,140	18,990	19,150
Age, y	43.96 ± 13.68	43.74 ± 13.66	44.18 ± 13.69
Education (%)			
≥ high school level	16,434 (43.09)	8749 (46.07)	7685 (40.13)
Personal monthly income (%)			
≥ 500 Yuan	20,927 (54.87)	12,406 (65.33)	8521 (44.50)
BMI, kg/m^2	22.63 ± 2.95	22.66 ± 2.79	22.60 ± 3.11
Physical activity (%)	19,102 (50.08)	9214 (48.52)	9888 (51.63)
Occupational exposure (%)	2746 (7.20)	1694 (8.92)	1052 (5.49)
Smokers (%)	10,629 (27.87)	9580 (50.45)	1049 (5.48)
Alcohol drinkers (%)	7718 (20.24)	7221 (38.03)	497 (2.60)
Hypertension (%)	3942 (10.34)	1827 (9.62)	2115 (11.04)
Diabetes (%)	1620 (4.25)	737 (3.88)	883 (4.61)

Table 2

Adjusted hazard ratio (95% CI) of stroke mortality associated with each 10 μg/m^3 increase in $PM_{2.5}$ levels.

Items	Number	Hazard Ratio (95%CI)	*p*-value
Death cases of stroke	254		
Follow-up (person-years)	375,876		
Model 1[a]		1.27 (1.01–1.60)	0.044
Model 2[b]		1.29 (1.02–1.63)	0.031
Model 3[c]		1.31 (1.04–1.64)	0.023
Model 4[d]		1.31 (1.04–1.65)	0.020

[a]Model 1: adjusted for age and sex.

[b]Model 2: Model 1 + adjusted for education and personal monthly income (< 500 Yuan vs ≥ 500 Yuan).

[c]Model 3: Model 2 + adjusted for BMI, smoke (yes vs no), drink (yes vs no), and physical activity (inactive vs active).

[d]Model 4: Model 3 + adjusted for history of hypertension (yes vs no) and diabetes (yes vs no).

Table 3

Subgroup analyses for hazard ratios (95% CIs) of stroke mortality associated with each 10 μg/m^3 increase in $PM_{2.5}$ levels.

Subgroup	No. of deaths	Person-years of follow-up	Hazard ratio (95%CI)[a]	*p*-value for interaction
Age				
< 65	101	339,598	1.00 (0.68–1.47)	
≥ 65	153	35,750	1.58 (1.17–2.13)	0.716
Sex				
Men	163	186,434	1.24 (0.93–1.66)	
Women	91	189,442	1.48 (1.01–2.19)	0.143
Education				
< high school level	209	212,962	1.36 (1.05–1.75)	
≥ high school level	45	162,913	1.18 (0.68–2.05)	0.639

[a]Covariates in the multivariable-adjusted models included age, sex, education, personal monthly income, BMI, smoke, alcohol drink, physical activity, history of hypertension and diabetes.

Table 4

Sensitivity analyses for associations of stroke mortality with 10 μg/m^3 increase in $PM_{2.5}$.

Sensitivity analysis	No. of Deaths	Person-years of follow-up	Hazard ratio (95% CI)	*p*-value
Excluding 2118 participants with CVD at baseline				
Cox Regression Model 4[a]	244	355,178	1.29 (1.02–1.64)	0.032
Excluding 2746 participants with occupational particulate matter exposure at baseline				
Cox Regression Model 4[a]	235	348,854	1.32 (1.04–1.68)	0.022
Adjusting for dietary factors in addition to the covariates of Model 4				
Cox Regression Model 5[b]	254	375,876	1.31 (1.04–1.66)	0.022

[a]Model 4: adjusted for age, sex, education, personal monthly income (< 500 Yuan vs ≥ 500 Yuan), BMI, smoke (yes vs no), drink (yes vs no), physical activity (inactive vs active), history of hypertension (yes vs no) and diabetes (yes vs no).

[b]Model 5: Model 4 + dietary frequency per week (i.e., low, moderate, or high) for red meat, poultry, seafood, vegetable, and fruit.