Fine Particulate Matter Exposure and Incidence of Stroke: a Cohort Study in Hong Kong

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Author Contributions:

HQ and LT defined the research theme and wrote the manuscript; HQ and SS analyzed the data and interpreted the results; HT worked on data cleaning and preliminary analyses; CMW set up the method for exposure assessment; RSL and CMS set up the cohort, CMS and LT reviewed/revised the manuscript and approved the submission.

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Glossary:

ICD-9 = International Classification of Diseases, 9th version; HR = hazard ratio; PM= particulate matter air pollution; $PM_{2.5}$ = fine particulate matter with aerodynamic diameter less than 2.5 microns; SEC = surface extinction coefficients; TPU = tertiary planning units.

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Abstract

Objectives: We aimed to assess the association of long-term residential exposure to fine particulate matter with aerodynamic diameter less than 2.5 microns ($PM_{2.5}$) with the incidence of stroke and its major subtypes.

Methods: We ascertained the first occurrence of emergency hospital admission for stroke in a Hong Kong Chinese cohort of 66,820 older people (65+ years) who enrolled during 1998-2001 (baseline) and were followed up to 31 December 2010. High resolution (1 × 1 km) yearly mean concentrations of $PM_{2.5}$ were predicted from local monitoring data and U.S. National Aeronautics and Space Administration satellite data using linear regression. Baseline residential $PM_{2.5}$ exposure was used as a proxy for long-term exposure. We used Cox proportional hazards to evaluate the risk of incident stroke associated with $PM_{2.5}$ exposure adjusted for potential confounders, including individual and neighborhood factors.

Results: Over a mean follow-up of 9.4 years, we ascertained 6,733 cases of incident stroke, of which 3,526 (52.4%) were ischemic, and 1,175 (17.5%) were hemorrhagic. The hazard ratio for every 10 $\mu g/m^3$ higher $PM_{2.5}$ concentration was statistically significant as 1.21 (95% confidence interval (CI) 1.04 to 1.41) for ischemic and non-statistically significant as 0.90 (95% CI 0.70 to 1.17) for hemorrhagic stroke in fully adjusted Model 3. The estimates for ischemic stroke were higher in older participants (>70 years), the less educated and in men for current smokers.

Conclusions: Long-term $PM_{2.5}$ exposure was associated with the higher risk of incident ischemic stroke, but the association with incident hemorrhagic stroke was less clear.

Key Words: Emergency hospital admission; Incidence; Ischemic stroke; Hemorrhagic stroke; Long-term residential exposure; Fine particulate matter

Introduction

Particulate matter (PM) air pollution plays a causal role in cardiovascular morbidity and mortality, according to a definitive scientific statement from the American Heart Association.[1] Many epidemiological studies have demonstrated higher risk of stroke associated with both short-term[2,3] and long-term PM exposure.[4–8] Nevertheless, stroke is heterogeneous in nature and etiology; with different risk profiles for ischemic and hemorrhagic stroke,[9] making it important and informative to consider them separately. Few studies have examined the effects of PM air pollution on different types of stroke, with somewhat mixed results; in Western countries, the risks of air pollution are greater for ischemic than hemorrhagic stroke,[10–12] but some studies from Asia have found that air pollution only affected hemorrhagic stroke[13] or intracerebral hemorrhage as well as ischemic stroke.[14,15] Few studies linking long-term PM exposure to the incidence of stroke by subtype have been conducted.[10,16,17]

Risk factors for stroke, including hypertension, current smoking, abdominal obesity, diet, alcohol intake and physical activity, account for more than 80% of the global risk of stroke (ischemic and intracerebral hemorrhagic), based on a case-control study in 22 countries.[18] Air pollution has been proposed as an emerging global risk factor for stroke.[9] In this study, in a population with low levels of smoking and alcohol use, but high levels of exposure to $PM_{2.5}$[19], we assessed the association of long-term residential exposure to $PM_{2.5}$ with the incidence of overall, ischemic and hemorrhagic stroke. Hong Kong is an ideal place to study these associations because hemorrhagic stroke is relatively common[20] and high levels of public housing mean less residential segregation[21], and thereby less confounding by social-economic position. We also assessed whether the associations varied by age, sex, socio-economic position and/or smoking to identify vulnerable subpopulations.

Methods

Study population

A total of 66,820 older adults aged 65 years or above was enrolled by the Elderly Health Service (EHS) of the Department of Health in Hong Kong from July 1998 to December 2001. Elderly

Health Centres (EHC) located in each of the 18 districts in Hong Kong provide health assessments, using standardized and structured interviews, and comprehensive clinical examinations. Information on socio-demographics, lifestyle, and disease history was collected by doctors and nurses, as described previously.[19] The participants account for about 9% of the older people in Hong Kong.[19] The cohort was set up to promote understanding of aging in this developed non-Western setting where the patterns of common chronic diseases and their determinants may differ from those in the West.

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and the ethics committee of the Department of Health. This is an analysis of routinely collected data, the participants implicitly agreed to their data being used for research by using the service.

Exposure model and Estimation of residential exposure to $PM_{2.5}$

We assessed $PM_{2.5}$ exposure from satellite-based aerosol optical depth (AOD) recordings and monitoring data from ground-based stations.[22] AOD, a measure indicating $PM_{2.5}$ levels in the troposphere, was retrieved for Hong Kong from remote sensing imaging by National Aeronautics and Space Administration (NASA)'s two Earth Observing System satellites.[23] We estimated surface extinction coefficients (SEC) from AOD at 1×1 kilometer (km) resolution, after controlling for humidity and rainy days.[24] The missing SEC data (15.7%) mainly due to cloud cover problems were replaced by multiple imputation procedure.[22] Four general monitoring stations, maintained by the Environmental Protection Department (EPD) in Hong Kong, continuously monitor $PM_{2.5}$ concentrations. Annual mean $PM_{2.5}$ concentrations from 1998 to 2010 for each general monitoring station were averaged from hourly concentrations and then regressed on annual SEC. For each year between 1998 and 2010 annual $PM_{2.5}$ exposures at the residential location of each participant, based on geo-coded anonymized address, were obtained using the same exposure model with annual SEC as the explanatory variable. In this Hong Kong cohort of older people, about 13.3% changed their residential address during the period 1998 to 2010. We used $PM_{2.5}$ exposure in the year of recruitment for each participant to

approximate long-term exposure in the main analyses.[22] $PM_{2.5}$ exposure year by year as a time-varying variable was used in a sensitivity analysis,[4] taking into account changes in residential address.

Health endpoints: Incidence of stroke and its subtypes

We obtained stroke incidence by subtype from 1998 to 2010 from hospitalization records via record linkage to the electronic health record system of the Hospital Authority, which manages all 42 public hospitals in the entire territory of Hong Kong. All hospital discharges are coded using the International Classification of Diseases, Ninth Revision (ICD-9): 430-436,[25] with hemorrhagic stroke defined as ICD-9 430, 431, ischemic stroke as ICD-9 433, 434, and unspecified stroke as ICD-9 436. We ascertained the first occurrence of emergency hospital admissions (admissions through the accident and emergency services) for stroke and its major subtypes as the incident cases.

Individual, ecological and environmental covariates

We identified potential confounders from the literature as possible common causes of $PM_{2.5}$ exposure and stroke. On this basis age, sex, body mass index (BMI), physical exercise, socio-economic position (education and personal monthly expenditure) were considered as potential confounders, because these might result in residence in a location more prone to air pollution. To characterize differences between residential areas more fully, we also included neighborhood tertiary education, monthly domestic household income, and percentage of older people (aged 65+) based on 197 small areas from the 2001 census, called Tertiary Planning Units (TPU). We also included the percentage of smokers (aged 15+) in the 18 districts of Hong Kong to indicate the exposure to environmental tobacco smoke (ETS), as previous studies suggest.[22,26] We also collected information on active chronic diseases and medication use at baseline. We defined self-reported active diseases as self-reported hypertension, heart disease, diabetes, chronic obstructive pulmonary disease (COPD)/asthma, or cerebrovascular accident. We used three models to estimate the hazard ratios (HR) for every 10 $\mu g/m^3$ higher $PM_{2.5}$ concentration adjusted for different sets of potential confounders. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for BMI, physical exercise, education,

monthly expenditure, and self-reported active diseases. Model 3 was additionally adjusted for smoking status, alcohol use, medication use, and neighborhood level factors including the percentage of older people, the proportion with tertiary education and proportion with income ≥ US$ 1923/month, and the smoking rate at the district level. Model 3 does not include self-reported active diseases, such as hypertension and diabetes, as confounders because these could be mediators of the associations of air pollution with stroke. All confounders were included in the models as the baseline values considered as time-independent variables.[8]

Statistical analysis

We used Cox proportional hazards to estimate the adjusted association of long-term exposure to $PM_{2.5}$ with incidence of stroke overall and by subtype.[4] Follow-up time from baseline (time to event) was used as the timescale, which was from date of recruitment to date of first hospital admission for stroke, date of death or was censored at the end of follow-up on 2010-12-31. We used the estimated $PM_{2.5}$ exposure at baseline (enrollment from 1998 to 2001) as a time-independent variable to represent long-term exposure in the main analyses.[22] The Cox proportional hazard assumption was tested using the 'cox.zph' function in 'survival' package in R. The exposure-response relation of $PM_{2.5}$ with stroke overall and by subtype was plotted using a natural cubic spline with three degrees of freedom for $PM_{2.5}$ exposure term in Model 3.[22] Linearity was tested by comparing the fit of the linear and the spline model using the log likelihood ratio Chi-square test.[27]

To assess potential effect modification, we conducted subgroup analyses stratified by age (≤70 or >70), gender (male or female), education level (below primary, primary, or secondary and above), and smoking status (never smoker, former smoker, or current smoker). The p-value for the interaction was obtained from the interaction of each potential effect modifier with $PM_{2.5}$ in model 3.

To assure detection of long-term associations and to control for competing diseases, we performed sensitivity analyses excluding participants with incident stroke or death in the first year after entry, or excluding those with self-reported cerebrovascular accident at baseline.[22] As air pollution exposure may be related to exposures across the life course, we also conducted

a sensitivity analysis with attained age as the underlying timescale while adjusting for calendar year of enrollment. Using attained age as the time scale provides flexible control for age while avoiding the need to include age as a confounder.[28] Considering $PM_{2.5}$ exposure may vary from year to year, a time-dependent model for yearly $PM_{2.5}$ exposure from 1998 to 2010 was used in sensitivity analysis.[4]

All analyses were conducted in R statistical environment version 3.3.0, with packages 'survival' for survival analysis to estimate the hazard ratio, 'rms' for regression modeling strategies and 'Hmisc' for plotting the exposure-response relationship curve.

Results

A total of 66,820 older people were enrolled in the initial study cohort. After excluding 1,932 (2.9%) people without sufficient address information for geocoding, 3,420 (5.1%) with wrong geo-coding or without $PM_{2.5}$ exposure estimates due to lack of satellite data, and 21 (0.03%) with missing covariates, a final sample of 61,447 (92.0%) was included in the analyses.

The correlation between the annual $PM_{2.5}$ concentrations obtained from the general monitoring stations and from the adjusted satellite-based SEC on dry days in the same 1×1 km grid during the years 1998 to 2010 was 0.625 (p-value < 0.001). The mean estimated annual $PM_{2.5}$ concentration in the baseline year was 35.8 $\mu g/m^3$ with a standard deviation of 2.4 $\mu g/m^3$.

The spatial distribution of the 61,447 participants included in this study is shown in Figure-1. Over a mean follow-up of 9.4 years (a total of 578,464.7 person-years) we observed 6,733 cases of incidence stroke with an incident rate of 11.6 cases per 1,000 person-years in this cohort of older people from Hong Kong. Most strokes (52.4%) were ischemic, 26.5% were unspecified and 17.5% were hemorrhagic.

In this cohort of older people, the mean age at entry was 72 years and about 65.9% were women. 5,907 (9.6%) were current smokers and 11,871 (19.3%) were former smokers. 8,461 (13.8%) were former or regular drinkers, and 44,252 (72%) did daily physical exercise. Most participants (82.9%) had primary school education or below. About half the participants took

regular medication (53.1%) and reported active diseases (48.9%), including hypertension, heart disease, diabetes, COPD/asthma, or a cerebrovascular accident (Table 1).

Effects of particulate matter air pollution

In all three models $PM_{2.5}$ was clearly associated with higher stroke incidence (Table-2) with fairly similar estimates. The HR for every 10 $\mu g/m^3$ higher $PM_{2.5}$ concentration was 1.14 (95% confidence interval (CI): 1.02-1.27) for all incident stroke in Model 3. Long-term $PM_{2.5}$ exposure had different associations by stroke subtype, with a statistically significant HR (1.21, 95% CI: 1.04, 1.41) for ischemic stroke and no significant association for hemorrhagic stroke (HR 0.90, 95% CI: 0.70, 1.17). $PM_{2.5}$ was also strongly associated with unspecified stroke. Sensitivity analysis excluding participants with incident stroke or death in the first year after entry, a self-reported cerebrovascular accident at baseline or using attained age as the underlying timescale gave similar findings (Table-3). However, using a time-dependent exposure of yearly $PM_{2.5}$ from 1998 to 2010 gave less consistent estimates by stroke subtype, although the estimate for ischemic stroke remained similar (Table-3). Comparison of the linear and spline models suggested the exposure-response relationship was essentially linear for all incident stroke, ischemic stroke, and unspecified stroke subtypes but not for hemorrhagic stroke (Supplemental Figure-e1).

Effect modification for long-term $PM_{2.5}$ exposure

Table-4 shows the associations of $PM_{2.5}$ exposure with incident stroke and its subtypes in Model 3 stratified by age, gender, education and smoking status. The association of $PM_{2.5}$ with stroke varied by age and the association was only evident for those aged >70 years. Some of the other associations varied by strata but there was no other evidence of differences by strata (p-values for interaction >0.05). The point estimates for ischemic stroke appeared higher in older people, the less educated and in men for current smokers albeit with wide confidence intervals.

Discussion

In an under-studied non-Western population exposed to high levels of air pollution, we found higher risks of incident stroke, ischemic stroke, and unspecified stroke (mostly likely ischemic stroke[29]) associated with long-term $PM_{2.5}$ exposure. This finding is consistent with a previous meta-analysis of 11 cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE) which suggested a 19% higher risk of incident stroke per 5 $\mu g/m^3$ increment in $PM_{2.5}$ exposure.[8] Our study also adds by showing that the exposure-response relationships were essentially linear for overall stroke, ischemic and unspecified stroke, and by showing that the association of $PM_{2.5}$ exposure with hemorrhagic stroke was less clear.

While some previous studies have linked $PM_{2.5}$ to a higher risk of incident stroke[6-8], the evidence is not always consistent, as in the all-male Health Professionals cohort[17] and some other cohorts from the United States[4] and Sweden.[5] These differences may have arisen from different exposure assessment models and exposure windows, different population characteristics, and/or different atmospheric environments with different air pollution characteristics and weather factors. We also found that long-term $PM_{2.5}$ exposure was associated with a higher risk of ischemic but not clearly with hemorrhagic stroke, consistent with a large cohort study from Denmark[11] and a small-area level ecological study from London (UK).[10] A Canadian study observed associations of long-term $PM_{2.5}$ exposure with both hemorrhagic and non-hemorrhagic stroke subtypes,[16] however, the estimates of risk diminished after controlling for ecological measures of income and deprivation.

The biological mechanisms linking long-term PM exposure with chronic damage to the cerebrovascular system may occur through several pathways. Particulate matter might increase blood pressure through disrupting hemodynamic balance favoring vasoconstriction and augmenting release of various pro-oxidative, inflammatory mediators.[30] However, this would suggest, if anything, a greater effect on hemorrhagic than ischemic stroke. Long-term exposure to PM may induce acceleration of atherosclerosis, alter vasomotor tone and cause vascular inflammation,[31,32] which might be more specific to ischemic stroke. Finally, $PM_{2.5}$ may promote blood coagulation[33], which would be more likely to provoke ischemic than hemorrhagic stroke.

However, the mechanisms underlying the differential effects of long-term $PM_{2.5}$ exposure on ischemic and hemorrhagic stroke subtypes is still not clear and needs to be further studied.

The effect of long-term $PM_{2.5}$ exposure tended to be greater at older ages and appeared to have higher point estimates for the less educated and in men for current smokers. Greater effects of PM on mortality and morbidity have previously been observed in the elderly.[34] People with lower education may have to live in more polluted areas, generating greater vulnerability to PM exposure.[35] The stronger association in current smokers suggests a synergist effect of long-term $PM_{2.5}$ exposure and smoking on stroke, which has been observed before.[11,36] Baseline smoking rates for this elderly cohort were 20.5% in men and 4.0% in women. Lifetime smoking exposure raises the risk of carotid atherosclerosis,[37] so smokers may be more susceptible to the effects of $PM_{2.5}$ exposure. However, in ESCAPE, based on 11 European cohorts, associations with long-term $PM_{2.5}$ exposure were only evident among never-smokers.[8] Differences between studies may relate to varying demographic characteristics, smoking rates, pollution levels, and ascertainment of stroke outcomes in these cohorts.[8,9]

We took advantage of a very large cohort, where we were able to control for a number of individual and neighborhood level confounders, nevertheless limitations exist. First, residual confounding is possible. For example, we did not have information on traffic noise or fast food restaurant density which have been linked to both $PM_{2.5}$ exposure and stroke.[38,39] Second, we obtained hospitalization records for the participants from 1998 to 2010 and used the first admission for stroke during this period as the incident stroke. Hospitalization records prior to 1998 are not available so we could not identify participants who had previously had a stroke, which may distort the association we found. Sensitivity analysis excluding the participants with incident stroke or death in the first year after entry, or excluding those with a self-reported cerebrovascular accident at baseline gave similar estimates. Third, the participants were enrolled at a preventive service, so they may be more health-conscious and perhaps less susceptible to the effects of air pollution than the general elderly population,[19] which might make our estimates conservative. Fourth, hemorrhagic stroke is less common than ischemic stroke, and was only 17.5% of strokes, giving less power to detect the risk of this type of stroke. Fifth, we used exposure to $PM_{2.5}$ at the residential location to approximate exposure to $PM_{2.5}$,

which previous studies have suggested is a valid proxy for long-term exposure.[7,40] Results were similar for all stroke, ischemic stroke and unspecified stroke using time-varying exposures, although the point estimate for hemorrhagic stroke was somewhat different but in both analyses indicated no clear association. Sixth, baseline residential exposure to $PM_{2.5}$ pollution was estimated from the relation between local monitoring data measured by the Hong Kong Environmental Protection Department and SEC data from NASA satellites. About 15.7% of SEC data was missing due to cloud cover which may bias the exposure assessment, although we imputed such SEC data using multiple imputation.[22] Seventh, short-term $PM_{2.5}$ changes are an established risk factor for stroke,[2,3] so the effects of long-term $PM_{2.5}$ exposure could be due to its correlation with short-term $PM_{2.5}$ changes. Such confounding is unlikely because long-term exposure contrasts are established geographically in cohort studies while the short-term exposure contrasts are usually constructed temporally in time-series studies. Last but not least, the data used to verify the estimation model for $PM_{2.5}$ was from four monitoring stations. Further study with $PM_{2.5}$ data measured at a larger number of monitoring stations or using different approaches for exposure modeling could improve the accuracy of the exposure assessment and help confirm the health effects of long-term PM exposure on stroke and its subtypes.

This study adds to the evidence base that long-term residential $PM_{2.5}$ exposure increases the risk of incident ischemic stroke in older people. The association of $PM_{2.5}$ with hemorrhagic stroke was less clear.

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Figure legend:

Figure-1 Spatial distribution of the patients in the Elderly Health Services cohort in Hong Kong (n=61,447) at baseline (1998-2000) by stroke occurrence

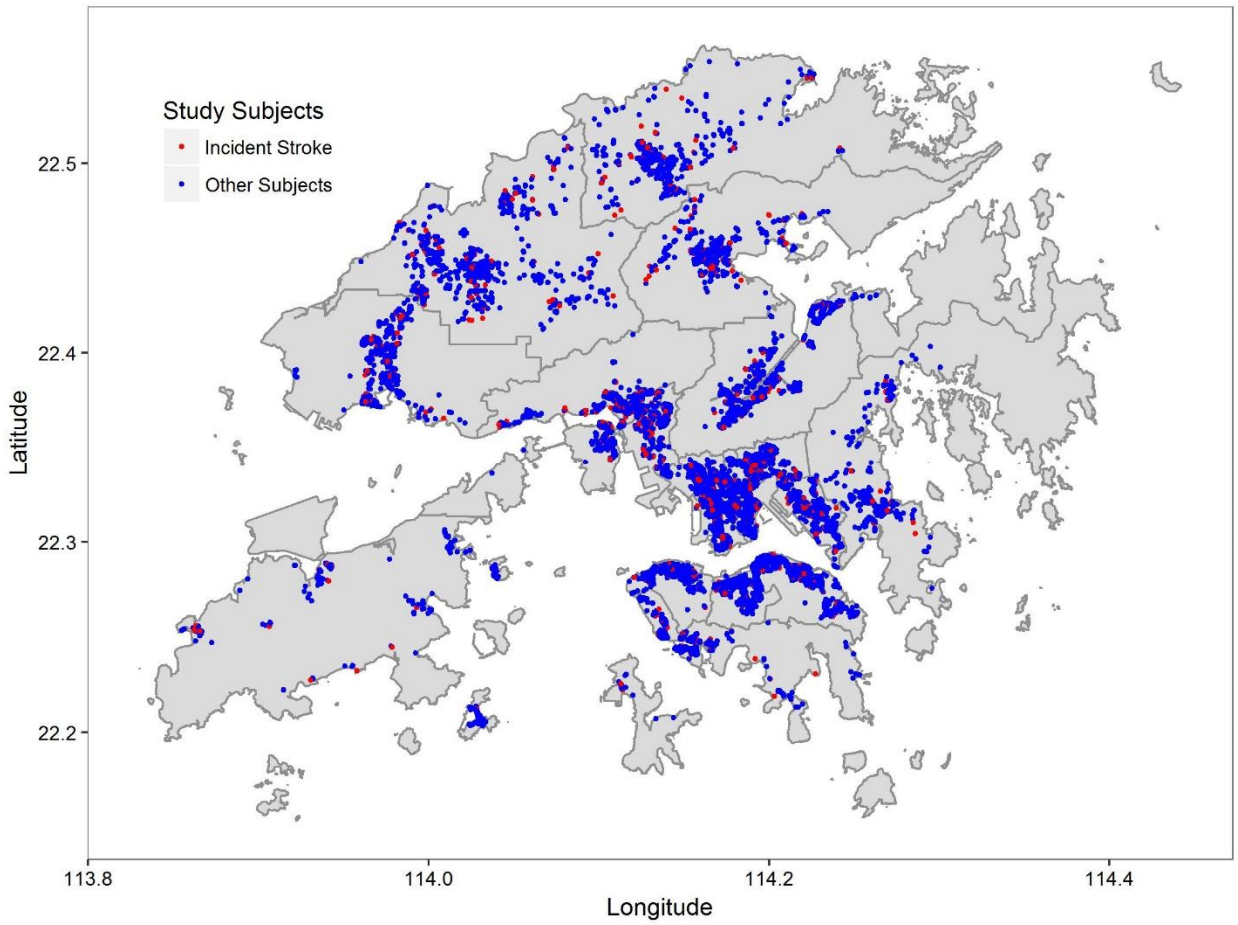

Table-1 Descriptive characteristics of the Elderly Health Services cohort (n=61,447) at baseline (1998-2000) by $PM_{2.5}$ exposure ($\mu g/m^3$)

Characteristic	All Patient (n=61,447)	$PM_{2.5}$ exposure* Low (n=30,828)	High (n=30,619)
PM2.5 concentrations ($\mu g/m^3$)(Mean±SD)	35.8 ± 2.4	33.9 ± 1.5	37.7 ± 1.5
Incident stroke (N (%))	6,733 (11.0)	3,269 (10.6)	3,464 (11.3)
Hemorrhagic Stroke	1,175 (1.9)	593 (1.9)	582 (1.9)
Ischemic Stroke	3,526 (5.7)	1,699 (5.5)	1,827 (6.0)
Unspecific Stroke	1,785 (2.9)	860 (2.8)	925 (3.0)
Individual-level covariates			
Age at entry (N (%))			
≤ 70 years	29,038 (47.3)	14,801 (48.0)	14,237 (46.5)
> 70 years	32,409 (52.7)	16,027 (52.0)	16,382 (53.5)
Gender (N (%))			
Male	20,933 (34.1)	10,579 (34.3)	10,354 (33.8)
Female	40,514 (65.9)	20,249 (65.7)	20,265 (66.2)
BMI quartiles (N (%))			
1st [<21.6]	14,168 (23.1)	6,948 (22.5)	7,220 (23.6)
2nd – 3rd [21.6-26.3]	31,179 (50.7)	15,529 (50.4)	15,650 (51.1)
4th [>26.3]	16,100 (26.2)	8,351 (27.1)	7,749 (25.3)
Smoking status (N (%))			
Never	43,669 (71.1)	22,031 (71.5)	21,638 (70.7)
Former	11,871 (19.3)	5,896 (19.1)	5,975 (19.5)
Current	5,907 (9.6)	2,901 (9.4)	3,006 (9.8)
Alcohol drinking (N (%))			
Never/Social drinker	52,986 (86.2)	26,597 (86.3)	26,389 (86.2)
Former/Regular drinker	8,461 (13.8)	4,231 (13.7)	4,230 (13.8)
Exercise in days/week (N (%))			
Never [0]	9,406 (15.3)	4,335 (14.1)	5,071 (16.6)
Medium [1-6]	7,789 (12.7)	3,862 (12.5)	3,927 (12.8)
High [7]	44,252 (72.0)	22,631 (73.4)	21,621 (70.6)
Education (N (%))			
Below primary	28,242 (46.0)	14,455 (46.9)	13,787 (45.0)
Primary	22,656 (36.9)	10,967 (35.6)	11,689 (38.2)
Secondary or above	10,549 (17.2)	5,406 (17.5)	5,143 (16.8)
Expenses/month in US$ (N (%))			
Low [<128]	10,122 (16.5)	4,338 (14.1)	5,784 (18.9)
Medium [128-384]	42,152 (68.6)	21,554 (69.9)	20,598 (67.3)
High [≥385]	9,173 (14.9)	4,936 (16.0)	4,237 (13.8)
Medication taken (N (%))			
Yes	32,628 (53.1)	14,518 (47.1)	14,301 (46.7)
No	28,819 (46.9)	16,310 (52.9)	16,318 (53.3)
Active Diseases# (N (%))			
Yes	30,052 (48.9)	15,903 (51.6)	15,492 (50.6)
No	31,395 (51.1)	14,925 (48.4)	15,127 (49.4)
TPU level covariates			
Prevalence of age≥65 (mean)	12.10	11.38	12.84
Prevalence of tertiary education (mean)	12.98	13.38	12.59
Prevalence of income≥US$1,923/m (mean)	59.50	61.93	57.04
District level covariate			
Smoking rate (mean)	11.55	11.49	11.61

*: High and low $PM_{2.5}$ exposure was defined by using the median (=35.7756 $\mu g/m^3$) as the cutoff point.

#: Active diseases were defined as self-reported hypertension, heart diseases, diabetes, COPD/asthma, or cerebrovascular accident at baseline.

Table-2: Association of 10μg/m^3 of $PM_{2.5}$ at baseline (1998-2000), i.e., time-independent, with incident stroke (time to first emergency hospitalization) from 1998 to 2012, overall and by subtype, in the Elderly Health Services cohort (n=61,447)

Incidence Cases	N	Hazard Ratio	P-Value
Model 1			
Stroke	6733	1.17 (1.06, 1.29)	0.002
Hemorrhagic Stroke	1175	0.99 (0.78, 1.26)	0.927
Ischemic Stroke	3526	1.19 (1.04, 1.37)	0.012
Unspecified Stroke	1785	1.40 (1.15, 1.70)	< 0.001
Model 2			
Stroke	6733	1.18 (1.07, 1.31)	0.001
Hemorrhagic Stroke	1175	0.97 (0.77, 1.24)	0.833
Ischemic Stroke	3526	1.22 (1.06, 1.40)	0.006
Unspecified Stroke	1785	1.44 (1.19, 1.75)	< 0.001
Model 3			
Stroke	6733	1.14 (1.02, 1.27)	0.020
Hemorrhagic Stroke	1175	0.90 (0.70, 1.17)	0.448
Ischemic Stroke	3526	1.21 (1.04, 1.41)	0.012
Unspecified Stroke	1785	1.31 (1.05, 1.62)	0.015

Model 1 adjusted for age and sex;
Model 2 adjusted for what we consider to be confounders: BMI, physical exercise, education, monthly expenses, and self-reported active diseases including hypertension, heart diseases, diabetes, COPD/asthma, or cerebrovascular accident at baseline;
Model 3 adjusted for confounders in model 2 except self-reported active diseases, and other studies consider to be confounders: smoking status, alcohol drinking, medication taken, the TPU level covariates (prevalence of age>=65, tertiary education and income ≥ US$ 1923/m) and smoking rate at district level; all covariates were included in the model as fixed values at baseline.

Table-3 Sensitivity analyses in Model 3 for the association of 10μg/m^3 of $PM_{2.5}$ at baseline (1998-2000) with incident stroke (time to first emergency hospitalization) from 1998 to 2012, overall and by subtype, in the Elderly Health Services cohort (n=61,447)

Sensitivity analysis	N	HR (95% CI)	p-value
Excluding those with incident stroke (n=630) or death (n=230) in the first year			
All Stroke	6103	1.15 (1.02, 1.29)	0.019
Hemorrhagic Stroke	1070	0.91 (0.69, 1.20)	0.489
Ischemic Stroke	3326	1.22 (1.04, 1.42)	0.012
Unspecified Stroke	1418	1.34 (1.05, 1.70)	0.017
Excluding those with self-reported cerebrovascular accident at baseline (n=1817)			
All Stroke	6244	1.12 (1.00, 1.26)	0.044
Hemorrhagic Stroke	1089	0.87 (0.66, 1.14)	0.314
Ischemic Stroke	3274	1.20 (1.03, 1.41)	0.019
Unspecified Stroke	1616	1.28 (1.02, 1.60)	0.031
With attained age rather than time to event as the underlying timescale			
All Stroke	6733	1.11 (1.00, 1.24)	0.060
Hemorrhagic Stroke	1175	0.89 (0.68, 1.15)	0.365
Ischemic Stroke	3526	1.19 (1.03, 1.38)	0.022
Unspecified Stroke	1785	1.24 (1.00, 1.54)	0.045
With yearly $PM_{2.5}$ exposure as a time-varying exposure from 1998 to 2010			
All Stroke	6723	1.20 (1.06, 1.37)	0.005
Hemorrhagic Stroke	1175	1.22 (0.90, 1.65)	0.210
Ischemic Stroke	3516	1.19 (1.00, 1.41)	0.050
Unspecified Stroke	1785	1.25 (0.96, 1.62)	0.095

Table-4 The association of 10μg/m^3 of $PM_{2.5}$ at baseline (1998-2000), i.e., time-independent, with incident stroke (time to first emergency hospitalization) from 1998 to 2012, overall and by subtype, stratified by age, gender, smoking status and education in the Elderly Health Services cohort (n=61,447) using Model 3

Stratified Characteristic	All Stroke		Hemorrhage Stroke		Ischemic Stroke	
	N	HR (95%CI)	N	HR (95%CI)	N	HR (95%CI)
Age						
Age≤70	2334	0.97 (0.81, 1.17)	419	0.94 (0.60, 1.45)	1242	1.14 (0.89, 1.47)
Age>70	4399	1.23 (1.08, 1.41)*	756	0.88 (0.64, 1.22)	2284	1.25 (1.04, 1.50)
Gender						
Male	2485	1.15 (0.96, 1.37)	424	1.24 (0.81, 1.91)	1256	1.28 (1.00, 1.64)
Female	4248	1.14 (0.99, 1.31)	751	0.76 (0.55, 1.06)	2270	1.18 (0.98, 1.43)
Education						
Below Primary	3291	1.21 (1.04, 1.42)	581	0.96 (0.66, 1.39)	1742	1.34 (1.09, 1.66)
Primary	2438	1.08 (0.90, 1.29)	427	0.94 (0.61, 1.46)	1265	1.05 (0.82, 1.36)
Secondary or above	1004	1.09 (0.82, 1.44)	167	0.69 (0.35, 1.38)	519	1.25 (0.85, 1.84)
Smoking status in male						
Never smoker	906	1.10 (0.82, 1.47)	153	1.02 (0.50, 2.06)	452	1.28 (0.85, 1.94)
Former smoker	1046	1.14 (0.87, 1.51)	172	1.36 (0.69, 2.68)	523	1.07 (0.72, 1.58)
Current smoker	533	1.25 (0.85, 1.84)	99	1.50 (0.61, 3.69)	281	1.83 (1.07, 3.13)
Smoking status in female						
Never smoker	3675	1.12 (0.96, 1.29)	628	0.80 (0.56, 1.15)	1999	1.16 (0.95, 1.41)
Former smoker	394	1.31 (0.83, 2.05)	76	0.50 (0.17, 1.42)	199	1.34 (0.71, 2.54)
Current smoker	179	1.40 (0.73, 2.71)	47	0.86 (0.23, 3.13)	72	1.72 (0.62, 4.78)

*: p-value for interaction between $PM_{2.5}$ exposure and age group is 0.047 for all stroke, while p values for the other interactions in this table are all >0.05. Statistically significant hazard ratios are in bold.