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Long-term exposure to air pollution and survival after ischaemic stroke: The China National Stroke Registry Cohort

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Abstract

Background and Purpose ——China bears a heavy burden of disease due to stroke because of its large population of elderly people and the propensity for stroke. Previous studies have examined the association between air pollution and stroke mortality or hospital admission. However, the global evidence for adverse effects of air pollution on survival after stroke is scarce.

Methods ——We used the first national hospital-based prospective registry cohort of stroke in China, which included 12,291 ischaemic stroke patients who visited hospitals during 2007–2008. All patients were followed for one-year post-stroke. Deaths during the follow-up period were recorded. Participants' three-year pre-stroke exposures to ambient PM_1, $PM_{2.5}$, PM_{10} (particulate matter with aerodynamic diameters ≤1 μm, ≤2.5 μm and ≤10 μm, respectively) and NO_2 (nitrogen dioxide) were estimated by machine learning algorithms with satellite remote sensing, land use information and meteorological data. Cox proportional hazards models were used to examine the association between air pollution and survival after ischaemic stroke.

Results ——In total, 1,649 deaths were identified during the one-year follow-up period. After controlling for potential confounders, significant associations were observed between exposure to PM_1 and $PM_{2.5}$ and incident fatal ischemic stroke. The corresponding HRs (hazard ratios) and 95%CIs (confidence intervals) per 10 μg/m^3 increase in PM_1 and $PM_{2.5}$ were 1.05 (1.02, 1.09) and 1.03 (1.00, 1.06), respectively. No significant association was observed for PM_{10} or NO_2 [HRs and

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95%CIs: 1.01 (1.00, 1.03) and 1.03 (0.99, 1.06), respectively]. Higher HRs (and 95%CIs) were observed for male, elderly and obese individuals.

Conclusions ——Pre-stroke exposure to PM_1 and $PM_{2.5}$ was associated with increased incident fatal ischemic stroke in the year following an ischaemic stroke in China. Improved air quality may be beneficial for people to recover from stroke.

Keywords

Stroke; Epidemiology; Lifestyle and Prevention; Quality and Outcomes; Air pollution; PM_1; $PM_{2.5}$; PM_{10}; NO_2; Stroke survival

Introduction

Stroke is one of major contributors to the global burden of disease, accounting for nearly 5.5 million deaths and 44 million disability-adjusted life-years (DALYs) annually worldwide.[1] The prevalence of stroke is expected to increase markedly in the future, especially in countries with a large elderly population like China.[2] An estimated 2.5 million new cases of stroke occur with approximately 1.6 million deaths from stroke in China every year.[3] Ischaemic stroke is the dominant subtype of stroke in China, accounting for more than 60% of all strokes.[4] Survival after stroke is poor and most cases die within the first year; mortality rates after stroke vary greatly among different regions of the world.[3, 5, 6] Apart from the well-known risk factors for stroke (e.g., hypertension, hyperlipidaemia, diabetes and smoking), environmental risk factors, including air pollution, are of increasing interest.[7–11]

Studies reported higher risk of stroke mortality and hospital admission associated with acute effects of air pollution in China,[12–14] but evidence for long-term effects of air pollution on stroke is very limited, due to limited data on air pollution exposure. One study in South London indicated reduced survival after stroke associated with exposure to high-level air pollution.[15] However, no study has ever examined such associations in China. Previous studies on particulate matter pollution mainly focused on $PM_{2.5}$ and PM_{10} (particulate matter with an aerodynamic diameter ≤2.5 μm and ≤10 μm, respectively). Knowledge of health effects of PM_1 (particulate matter with an aerodynamic diameter ≤1 μm), a major component of $PM_{2.5}$, is very limited. Due to smaller particle size, PM_1 may be more harmful than coarser particles.

Methods

Study population

Stroke cases in this study were obtained through the hospital-based China National Stroke Registry (CNSR). Protocols for the CNSR have been previously reported.[16] In brief, the CNSR included 132 grade II and grade III urban hospitals across mainland China covering all provinces and municipalities. The median number of beds in these hospitals was 800 (5^{th}-95^{th} percentiles: 150–2500). Among these hospitals, 112 (85%) had a stroke out-patient clinic. Neurological rehabilitators from 97 (73%) hospitals, speech therapists from 52 (40%) hospitals and physiotherapists from 45 (34%) hospitals participated in the CNSR. Eligible participants were adult stroke cases who directly visited hospitals within 14 days of a stroke and provided informed consent. Strokes were confirmed by neurologists through brain MRI or CT. In total, 12,291 ischaemic stroke cases with complete geocoded address information who visited hospitals from September 2007 to August 2008 were included in this study. This study was only focused on ischaemic stroke, as it is the dominant subtype of stroke in China. Details of case selection are shown in Figure I in the Supplemental Material. The study was approved by Monash University Human Research Ethics Committee and the central institutional review board at Beijing Tiantan Hospital. Written informed consent was obtained from patients or their legally authorised representatives (e.g., parents, spouses and adult children). The authors declare that all supporting data are available within the article and its online supplementary files.

Data collection and follow-up

Participants, or their authorized representatives, were interviewed by trained investigators after hospital admission. Standard registry forms were used to collect information on prehospital care, post-stroke recovery and severity of stroke. Other participants' information was extracted from their hospital records with informed consent, including demographic characteristics, diagnosis of stroke, medical history, comorbidities, and risk factors for stroke (e.g., hypertension, smoking and alcohol consumption). In addition, participants' insurance information was also collected. Each participant was contacted via telephone by a trained investigator 3 months, 6 months and 12 months after hospital admission. If participants were not able to respond, their relatives or caregivers were contacted. Follow-up data were collected including medication use after stroke, functional and clinical outcomes. In addition, case fatality was further confirmed according to death certificate provided by routine death registration or hospitals. In total, 855 patients (7%) were lost to follow-up during the one-year after hospital admission.

Exposure assessment

Participants' exposure to four air pollutants, PM_1, $PM_{2.5}$, PM_{10} and NO_2 (nitrogen dioxide), were estimated with monitoring data, satellite remote sensing, meteorological and land use information, in addition to other spatial and temporal predictors. Details of data collection and processing were previously reported.[17–19] In addition, please refer to the Supplemental Material for the details. Participants' daily exposure to each air pollutant during three years before stroke were estimated according to their geocoded home address (longitude and latitude) and the onset date of stroke. Daily estimates were aggregated to annual averages.

Statistical analysis

Cox proportional hazards models were used to examine the associations between pre-stroke exposures to air pollutants and survival after ischaemic stroke (p values of proportional hazards assumption test for PM_1, $PM_{2.5}$ and PM_{10} were 0.14, 0.48 and 0.43, respectively). Three types of Cox models were developed. First, a crude model (Model 1) was developed, including the mean concentration of one pollutant during the three years before stroke and a splined term of the interaction of longitude and latitude controlling for potential regional differences in the association.[20] Second, an intermediate model (Model 2) was developed based on the crude model by adding age, sex and body mass index (BMI). Third, a further adjusted model (Model 3) was developed based on the Model 2 by adding socio-economic characteristics (living conditions, educational attainment and health insurance type) and known risk factors for stroke (smoking, alcohol consumption, history of diabetes, hypertension, coronary heart disease or atrial fibrillation) and NIHSS (National Institutes of Health Stroke Scale) score].

As some values of these variables were missing in Model 2 and Model 3 (Table 1), multivariate imputation was used to interpolate the missing values.[21] The multivariate imputation was performed 100 times for in Model 2 and Model 3 with a random seed and the results were pooled. The associations between exposure to air pollutants and survival after stroke were expressed as hazard ratios (HR) and 95% confidence intervals (95%CIs) associated with per 10 μg/m^3 increase in each air pollutant. Additional analyses were performed stratified by sex, age and BMI. The associations between air pollution and survival after stroke were further examined in two-pollutant models (NO_2 and one particulate pollutant). To test the robustness of the results, sensitivity analyses were conducted by including previous one and two years mean exposures to air pollutants, instead of the previous three-year average. Also, subtype of ischaemic stroke (TOAST classification) was included in the sensitivity analyses. All statistical analyses were performed with R software (version 3.3.3, R Development Core Team 2015). Survival analysis and multivariate imputation were performed with the “mgcv” and “mice” R packages, respectively.

Results

The residential locations of all participants are in Figure 1. During the one-year follow-up period, 1,649 deaths and 10,642 survivors were observed. Baseline characteristics of the participants are in Table 1. Compared to deaths, survivors comprised a greater proportion of males, younger and better-educated individuals. In addition, participants who had a less severe stroke and fewer exposures to risk factors (e.g., diabetes and atrial fibrillation) were more likely to survive within one year after stroke. For stroke subtypes, deaths were dominated by large-artery atherosclerosis (62%), followed by cardioembolism (23%) and small-artery occlusion (10%). The proportions of these three subtypes among survivors were 63%, 7% and 25%, respectively.

Estimated exposures to air pollutants during the three years before stroke are summarized in Table 2. Individuals who died had higher levels of exposure than survivors for most air pollutants (except for PM_{10}). Mean exposures to PM_1, $PM_{2.5}$, PM_{10} and NO_2 for people who died were 63.3 μg/m^3, 80.6 μg/m^3, 134.9 μg/m^3 and 50.7 μg/m^3, respectively, while those for survivors were 62.1 μg/m^3, 79.5 μg/m^3, 135.8 μg/m^3 and 49.7 μg/m^3, respectively. Mean exposures to air pollutants for each participant are shown in Figure II-V in the Supplemental Material. Participants with high level of exposure to air pollutants were located in the North China Plain (Hebei, Shandong and Henan), while those with low level of exposure were located in remote areas of Southern and Western China (e.g., Hainan, Yunnan and Xinjiang).

The associations between exposures to air pollutants and survival after ischaemic stroke are shown in Figure 2. In the crude models (Model 1), exposure to PM_1, $PM_{2.5}$ and NO_2 were significantly associated with an increased risk of death from ischaemic stroke and the HRs (95%CI) per 10 μg/m^3 increase in air pollutants were 1.06 (1.03, 1.10), 1.04 (1.01, 1.08) and 1.04 (1.00, 1.08), respectively. Exposure to PM_{10} was not significantly associated with risk of death. After controlling for other potential confounders (Model 3, adjusted results are also in Figure 2), significant associations between PM_1 and $PM_{2.5}$ and death from stroke were also observed; the corresponding HRs (95%CIs) were 1.05 (1.02, 1.09) and 1.03 (1.00, 1.06), respectively. However, no significant adjusted associations were found for PM_{10} or NO_2. The adjusted results of Model 3 were consistent with those from Model 2.

The results for two-pollutant models are shown in Table 3. A larger estimated effect of PM_1 on death from ischaemic stroke was observed [HR and 95%CI: 1.08 (1.03, 1.14)], while weaker associations were present for other air pollutants. The results of stratified analyses using Model 3 are shown in Table 4. When the analysis was stratified by sex, age and BMI, PM_1 was more strongly associated with stroke among male, elderly and obese patients. For example, HRs (95%CIs) associated with PM_1 exposure were 1.06 (1.02, 1.11) and 1.04 (0.99, 1.08) among male and females, respectively, and they were 1.07 (1.02, 1.12) and 1.01 (0.96, 1.06) among obese and normal weight patients, respectively. No significant associations were observed for other pollutants. The results for stratified analyses using Model 1 and Model 2 are shown in Table II-III in the Supplemental Material.

The results of sensitivity analyses are shown in Table IV of the Supplemental Material. Changing the exposure assessment windows to the previous one or two years' mean exposures or including subtype of ischaemic stroke did not substantially change the results.

Discussion

To the best of our knowledge, this is the first study to evaluate the association between long-term exposure to air pollution and survival after stroke in China. The existing studies of air pollution and stroke in China mainly focused on the acute effects of air pollution on stroke mortality and hospital admissions.[13, 22] Studies in China on air pollution and survival after stroke have been challenging for two reasons. First, data on survival after stroke are very limited in China, and the existing studies are small in scale. Second, regulatory ground-level measurements of air pollutants (e.g., $PM_{2.5}$) at the national level were not available prior to 2013, which made it difficult to assess an individual's long-term exposure.

A study conducted in South London reported that exposures to PM_{10} and NO_2 were significantly associated with increased risk of death from stroke [HRs and 95%CIs associated per 10 μg/m^3 increase in air pollutants: 1.52 (1.06, 2.18) and 1.28 (1.11, 1.48), respectively].[15] In our study, we found that exposures to these two pollutants were not significantly associated with the risk of death. These contrasting results may be due to several aspects, including study design, sample size, and exposure assessment. Previous studies also reported long-term air pollution was associated with incidence of stroke. For example, a cohort study conducted in 36 U.S. metropolitan areas illustrated long-term exposure to $PM_{2.5}$ increased the incidence of stroke in women [HR and 95%CI associated per 10 μg/m^3 increase in $PM_{2.5}$: 1.28 (1.02, 1.61)].[23] A cohort study conducted in Korea also stated increased risk of ischaemic stroke associated with long-term exposure to $PM_{2.5}$ [HR and 95%CI associated per 1 μg/m^3 increase in $PM_{2.5}$: 1.45 (1.31, 1.61)].[24]

Several potential mechanisms may explain the association between air pollution and survival after stroke. Exposure to air pollution can impair vascular function leading to raised blood pressure and plasma viscosity.[25–27] It has been suggested that exposure to ambient particulate matter pollution was associated with increased coagulability by provoking alveolar inflammation and triggering the release of inflammatory cytokines.[28] In addition, stroke patients may be more susceptible to air pollution compared to healthy people and particulate matter pollution may trigger a recurrence and complications of stroke.[11] Our results might be explained by the excess early mortality associated to air pollution, as most deaths (62%) in this study occurred within 3 month after ischaemic stroke. Exposure to air pollution was associated with acute complications of stroke (e.g., respiratory infection and venous thromboembolism) leading to lower early survival.[29, 30]

Due to its large population and the propensity for stroke, China bears the highest burden of stroke globally.[31] Cerebrovascular disease is now the dominant cause of death among the elderly population in China.[2] Coinciding with rapid economic growth and urbanization, the proportion of the population aged ≥65 years has been increasing for decades,[32] and is predicted to reach 25% by 2050.[33, 34] China is therefore expected to face an even greater burden of stroke in the future. Our results suggest that more effective policies to curb the severe air pollution in China may reduce the burden of survival after stroke. Additionally, stroke patients might be a particularly susceptible to air pollution and the cleaner air could be beneficial for people recovering from stroke.

We found higher HRs associated with PM_1 than coarser particles, although the differences may not be significant. The health effects of smaller particles may be more significant than coarse particles, as they contain most of toxins generated in combustion and they are able to penetrate deeper and stay longer in the lung.[35, 36] Currently studies on PM_1 are very limited, due to lack of monitoring data. In future, more studies should focus on the health effects of PM_1 and relevant biological mechanisms. Based on these studies, standards for PM_1 should be proposed.

Our study has several strengths. Firstly, as the CNSR is the first national prospective stroke registry in China supported by Ministry of Health, the study population is characterized with broad geographic coverage and high quality of diagnosis.[16] Secondly, a wide range of covariates were considered in our analysis particularly including several risk factors for stroke and a smoothed term of location to control for the potential geographical variation.[20] Finally, individual long-term exposures to air pollution were estimated with satellite remote sensing and a random forests approach which showed high predictive ability and several other strengths over traditional methods.[37, 38]

Our study has several limitations. Previous studies reported that patients' income was related to their stroke care.[39, 40] This variable was not included in our final model, as there was a high fraction of missing values due to a privacy issue. However, the complete values of income in this study were highly correlated with health insurance type and educational level.

We had no access to ground measuring data of air pollutants prior to 2014, and as the consequence of it, the final model cannot be validated during the whole study period. However, this method has been used by previous studies in China and Western countries indicating the PM-AOD and NO_2-OMI relationships do not remarkably change over time.[41–43] As CNSR only included grade II and grade III urban hospitals, the results of this study may have better representativeness of urban or developed areas than rural or less developed areas of China. In addition, the stroke cases in this study were not evenly distributed geographically with far fewer cases in western and northern China. Finally, some post-stroke factors might be also associated with the survival that we did not consider in this study. For example, we had no access to patients' mobility information after stroke which might be linked with changed exposure to air pollution. Also, acute stroke management was another factor related to survival after stroke.[44] However, it involved a wide range of variables that could not be controlled by only statistical model.

5. Conclusions

In this study, we found that people living in more heavily air polluted areas had higher risk of death in the 12 months after ischaemic stroke. Fine particles (PM_1 and $PM_{2.5}$) appeared to be more harmful than other pollutants for stroke patients. More studies should focus on health effects of PM_1 and these studies will provide valuable information for policy-makers to propose standards for PM_1. Moreover, studies are needed to explore the associations between air pollution and the recovery from stroke and the role of smaller particles in these associations. Abatement of air pollution may contribute to the recovery of stroke patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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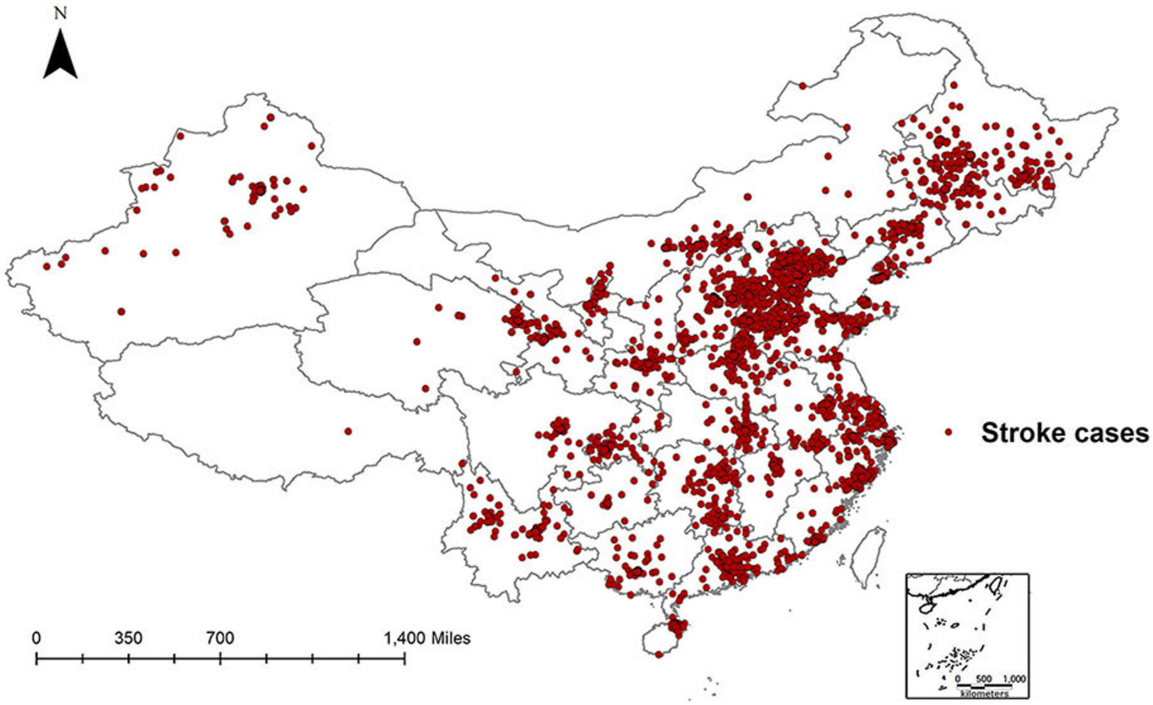

Figure 1.

Locations of 12,291 ischaemic stroke patients included in this study.

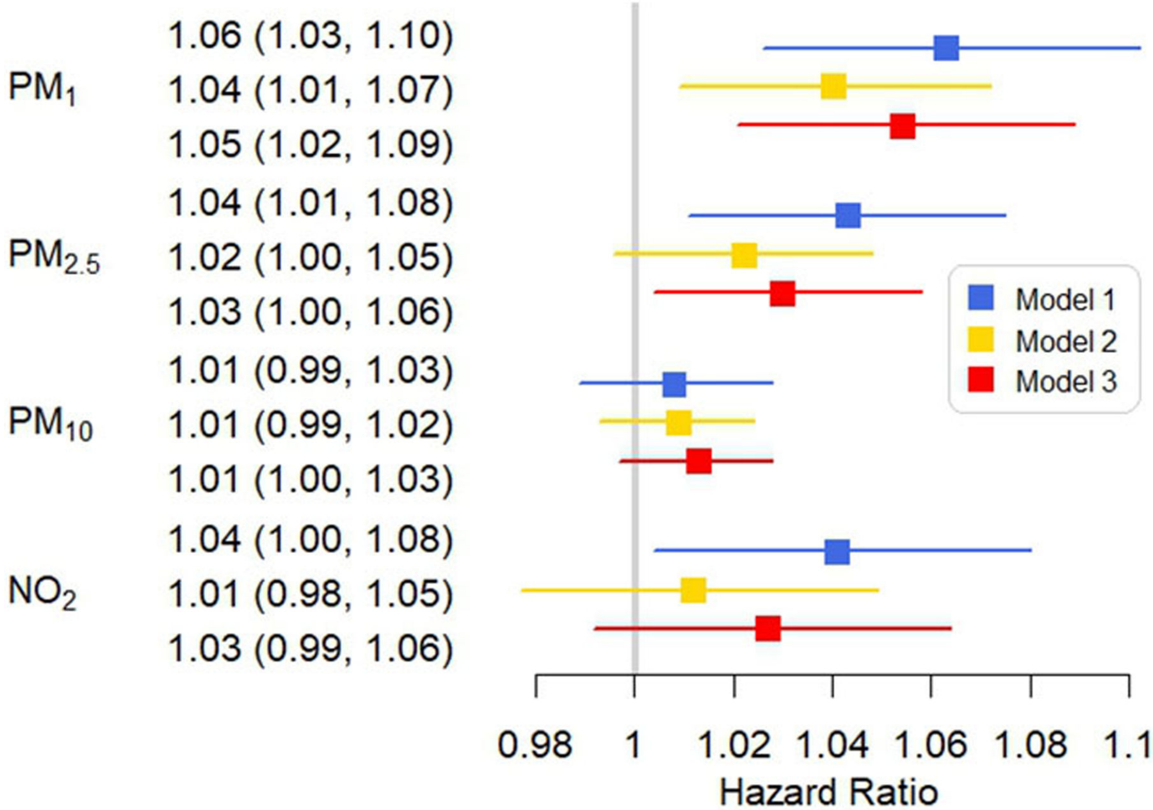

Figure 2.

Hazard ratios (and 95% confidence intervals) of death from ischaemic stroke associated with per 10 μg/m^3 increase in mean exposures to air pollutants during three years before stroke.

Note: Model 1 included mean level of one pollutant and a smooth term of the interaction of longitude and latitude. Model 2 included all variables in the Model 1 and added age, sex and BMI. Model 3 included all variables shown in Table 1.

Table 1.

Baseline characteristics of deaths and survivors after ischaemic stroke during one-year follow-up period.

Variables	All cases		Deaths		Survivors		*p* value*
	N	%	N	%	N	%	
Sex							< 0.01
Male	7579	62%	869	53%	6710	63%	
Female	4712	38%	780	47%	3932	37%	
Age (years, Mean+SD)	65.5	12.3	72.5	11.4	64.4	12.1	
BMI (kg/m^2)							< 0.01
<18.5	456	4%	109	7%	347	3%	
18.5–24	4799	39%	619	38%	4180	39%	
≥ 24	5858	48%	647	39%	5211	49%	
Missing values	1178	10%	274	17%	904	8%	
Living condition							< 0.01
Live alone	440	4%	82	5%	358	3%	
Live with others	11697	95%	1524	92%	10173	96%	
Live in nursing home	50	0%	20	1%	30	0%	
Missing values	104	1%	23	1%	81	1%	
Educational attainment							< 0.01
University	1166	9%	92	6%	1074	10%	
Senior high school	2233	18%	217	13%	2016	19%	
Junior high school	2899	24%	319	19%	2580	24%	
Junior school	3036	25%	447	27%	2589	24%	
Illiterate	1649	13%	369	22%	1280	12%	
Missing values	1308	11%	205	12%	1103	10%	
Health insurance type							< 0.01
Urban workers or commercial insurance	6574	53%	877	53%	5697	54%	
Government expense	855	7%	77	5%	778	7%	
Rural cooperative insurance	2026	16%	284	17%	1742	16%	
Others	2508	20%	357	22%	2151	20%	
Missing values	328	3%	54	3%	274	3%	
NIHSS score							< 0.01
Mean + Median	6.8	4.0	14.2	12.0	5.6	4.0	
≤ 4	6171	50%	365	22%	5806	55%	
5–16	4814	39%	603	37%	4211	40%	
16–21	606	5%	240	15%	366	3%	
≥ 21	700	6%	441	27%	259	2%	
Diabetes							< 0.01
Yes	3457	28%	1224	74%	2233	21%	
No	8574	70%	380	23%	8194	77%	
Missing values	260	2%	45	3%	215	2%	
Hypertension							0.33

Variables	All cases		Deaths		Survivors		*p* value*
	N	%	N	%	N	%	
Yes	7722	63%	1050	64%	6672	63%	
No	4353	35%	564	34%	3789	36%	
Missing values	216	2%	35	2%	181	2%	
Coronary heart disease							< 0.01
Yes	1772	14%	338	20%	1434	13%	
No	10519	86%	1311	80%	9208	87%	
Atrial fibrillation							<0.01
Yes	907	7%	307	19%	600	6%	
No	11384	93%	1342	81%	10042	94%	
Family history of stroke							< 0.01
Yes	1507	12%	149	9%	1358	13%	
No	9994	81%	1367	83%	8627	81%	
Missing values	790	6%	133	8%	657	6%	
Smoking							< 0.01
Non-smoker	7078	58%	1092	66%	5986	56%	
Ex-smoker	1609	13%	215	13%	1394	13%	
Current smoker	3280	27%	287	17%	2993	28%	
Missing values	324	3%	55	3%	269	3%	
Alcohol consumption							< 0.01
Never	8194	67%	1236	75%	6958	65%	
Current	3315	27%	279	17%	3036	29%	
Former	580	5%	90	5%	490	5%	
Missing values	202	2%	44	3%	158	1%	
In total	12291	100%	1649	100%	10642	100%	

*: p values for chi-squared test or Mann-Whitney U test

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Table 2.

A summary of participants' exposures to air pollutants (μg/m^3) during three years before stroke.

Pollutants	Mean	Quartiles					*p* value*
		Q0	Q25	Q50	Q75	Q100	
PM_1							< 0.01
Deaths	63.3	12.8	51.1	62.8	63.3	105.6	
Survivors	62.1	13.4	49.7	61.0	78.4	108.5	
$PM_{2.5}$							0.02
Deaths	80.6	20.6	64.5	82.9	99.6	129.6	
Survivors	79.5	20.1	63.0	81.0	98.2	131.5	
PM_{10}							0.56
Deaths	134.9	41.4	109.0	131.6	162.9	221.6	
Survivors	135.8	37.6	109.2	134.6	163.7	222.6	
NO_2							< 0.01
Deaths	50.7	13.2	39.1	54.7	63.1	80.9	
Survivors	49.7	11.3	38.4	52.0	61.8	81.6	

* *p* value of Mann-Whitney U test for distribution differences between deaths and survivors.

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Table 3.

Hazard ratios (and 95% confidence intervals) of death after ischaemic stroke associated with per 10 μg/m^3 increase in air pollutants in two-pollutant models.

Pollutants	**PM_1 + NO_2**	**$PM_{2.5}$ + NO_2**	**PM_{10} + NO_2**
PM_1	1.08 (1.03, 1.14)	-	-
$PM_{2.5}$	-	1.03 (0.99, 1.08)	-
PM_{10}	-	-	1.01 (0.99, 1.03)
NO_2	0.96 (0.91, 1.01)	0.99 (0.94, 1.05)	1.02 (0.97, 1.07)

Note: The two-pollutant models adjusted for all variables shown in Table 1.

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Table 4.

Hazard ratios (and 95% confidence intervals) of death after ischaemic stroke associated with per 10 μg/m^3 increase in air pollutants in stratified analyses using Model 3.

Variables	PM_1	$PM_{2.5}$	PM_{10}	NO_2
Sex				
Male	1.06 (1.02, 1.11)	1.03 (0.99, 1.07)	1.01 (0.99, 1.03)	1.03 (0.98, 1.08)
Female	1.04 (0.99, 1.08)	1.02 (0.99, 1.06)	1.01 (0.99, 1.04)	1.02 (0.97, 1.07)
Age (years)				
<65	1.06 (0.99, 1.12)	1.03 (0.97, 1.08)	1.02 (0.99, 1.06)	1.02 (0.95, 1.10)
65–75	1.04 (0.99, 1.10)	1.03 (0.99, 1.08)	1.02 (0.99, 1.05)	1.04 (0.97, 1.10)
>=75	1.06 (1.01, 1.11)	1.03 (0.99, 1.08)	1.00 (0.98, 1.03)	1.03 (0.98, 1.08)
BMI (kg/m^2)				
<24	1.01 (0.96, 1.06)	1.00 (0.96, 1.04)	0.99 (0.97, 1.02)	0.98 (0.93, 1.03)
≥24	1.07 (1.02, 1.12)	1.04 (1.00, 1.09)	1.02 (1.00, 1.04)	1.05 (0.99, 1.11)

Note: Model 3 adjusted for all variables shown in Table 1.