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Spatiotemporal Trends of Stroke Burden Attributable to Ambient PM2.5 in 204 Countries and Territories, 1990–2019: A Global Analysis

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Abstract

Background: Previous studies suggested that long-term exposure to ambient fine particulate matter (PM_{2.5}) is associated with increased risk of stroke. However, limited studies evaluated the stroke burden attributable to ambient PM_{2.5} globally, especially comprising across different regions, countries, and social-economic levels. We thus conducted this study to estimate the spatial and temporal trends of ambient PM_{2.5} related stroke burden by sex, age, and subtypes from 1990 to 2019 at global, regional, and national levels.

Methods: Information on the ambient PM_{2.5}-related stroke burden from 1990 to 2019 was obtained from the Global Burden of Disease (GBD) study 2019. The burdens of stroke attributable to ambient PM_{2.5} [i.e., age-standardized mortality rate (ASMR) and age-standardized disability-adjusted life year rate (ASDR)] were estimated by sex, age, and subtypes from 1990 to 2019 at global, regional, and national levels. The estimated annual percentage change (EAPC) was used to evaluate the changing trends of ASDR

and ASMR attributable to ambient PM_{2.5} from 1990 to 2019. The Spearman correlation coefficient was used to examine the correlation between sociodemographic index (SDI) and EAPC of ASMR and ASDR at the national level.

Results: In 2019, the global ambient PM_{2.5}-related stroke mortality and DALYs were 1.14 million and 28.74 million, respectively, with the corresponding ASDR and ASMR of 348.1 and 14.3 per 100,000 population, respectively. The ASDR and ASMR increased with age, and were highest among males, in the middle SDI regions, and for ICH. From 1990 to 2019, the absolute death number of stroke attributable to ambient PM_{2.5} and the corresponding ASMR and ASDR were both in an increasing trend. The corresponding EAPCs in ASMR and ASDR were 0.09 (95% confidence interval [CI]: -0.05 to 0.24) and 0.31 (95% CI: 0.18 to 0.44), respectively. The significant increases of ASMR and ASDR were observed in the low, low-middle, and middle SDI regions, and for ICH. While, a decrease trend was observed in high and middle-high SDI regions, and for SAH.

Conclusion: The global burden of stroke attributable to ambient PM_{2.5} showed an increasing trend over the past 30-year, especially in males, low-income countries, and for ICH. Continued efforts on reducing the level of ambient PM_{2.5} are necessary to reduce the burden of stroke.

Key Words: Stroke; Air pollution; Disability-adjusted life years (DALYs); Mortality

Introduction

Stroke, a leading cause of mortality and disability, has been considered to confer a series of disease burden and substantial economic costs.^{1,2} Previous studies from the Global burden of disease (GBD) collaborators suggested that stroke accounted for approximately 6.55 million deaths and 143 million disability-adjusted life-years (DALYs) globally in 2019.³ In addition, approximately 90% of the stroke related disease burden can be attributed to modifiable risk factors, such as air pollution, smoking, low physical activity, and metabolic risk factors.³ Interventions targeting these risk factors have been proven to be cost-effective in reducing the heavy burden of stroke on human health and the economy.⁴

Air pollution, especially fine particulate matter (PM_{2.5}) is a major public health problem. Although the exposure to PM_{2.5} air pollution shows an overall declining trend in most developed regions, 99% of the world's population are still residing in regions where the air quality exceeds the World Health Organization (WHO) limits.⁵ The two common sources of PM_{2.5} are ambient air pollution from traffic emissions and industrious as well as household air pollution from solid fuels. The GBD collaborators found that the combined effects of ambient and household PM_{2.5} were associated with 6.5 million premature deaths in 2019, and 4.2 million of them could be ascribed to ambient PM_{2.5}.⁶ Previous study showed that more than 24% of PM_{2.5}-related premature death was due to stroke in 2019,³ and ambient PM_{2.5} ranked

as the fourth leading risk factor of stroke.³ Therefore, it is important to develop effective prevention strategies based on the different spatial and temporal distributions to reduce ambient PM_{2.5} related stroke burden. However, there is no study evaluating the spatial and temporal trends of stroke burden attributable to ambient PM_{2.5} globally. We thus conducted this study to estimate the spatial and temporal trends of ambient PM_{2.5} related stroke burden by sex and age from 1990 to 2019 at global, regional, and national levels.

Method

Data source

Information on the global burden of stroke and its subtype (intracerebral hemorrhage[ICH], ischemic stroke[IS], and subarachnoid hemorrhage[SAH]) attributable to ambient PM_{2.5} from 1990 to 2019, by country, region and sex were obtained from the Global Health Data Exchange (GHDx).⁷ Data from a total of 204 countries and territories were available, which was separated into 5 regions according to the sociodemographic index (SDI) regions: high, high-middle, middle, low-middle, and low SDI regions. The SDI is a composite indicator to reflect the development of a specific region, which was calculated according to the total fertility rate among females younger than 25 years, the education level of people aged ≥15 years old, and the lagged GPD per capita. The SDI ranges from 0 to 1, and 0 represents the lowest development level and 1 represents the highest development level.⁸ What's more,

these countries were also categorized into 21 regions according to the geography (Table 1). For stratified analysis, age was grouped into 15 age groups, including 14 age groups between 25 and 94 years old at an interval of 5 year-old, and one group aged ≥ 95 year-old.

Ambient PM_{2.5} pollution exposure assessment

The level of ambient PM_{2.5} pollution used in GBD was the population weighted annual average concentrations of particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($\mu\text{g}/\text{m}^3$), which was evaluated using chemical transport models, ground level monitoring, and satellite in grids at $0.1^\circ \times 0.1^\circ$ spatial resolution. The Bayesian hierarchical model and Gaussian processes were used to calculate the population weighted national or sub-national level average exposure according to the modeling framework of the Data Integration Model for Air Quality.⁹

Estimated stroke burden due to ambient PM_{2.5}

The methods of stroke burden estimations have been described in previous studies.^{3,8} Briefly, stroke death was defined according to the WHO clinical criteria, as a clinical symptom (usually focal) of rapidly developing brain dysfunction that persists for more than 24 hours or leading to death. The GBD 2019 included three pathological subtypes of stroke: IS was defined as an attack of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction; ICH was defined as nontraumatic stroke

with a focal collection of blood in the brain; and SAH was defined as a stroke caused by brain subarachnoid hemorrhage without trauma. Transient ischemic attacks were not estimated.

The comparative risk assessment framework was adopted by GBD 2019 to evaluate the attributable deaths and DALYs.⁸ In brief, all case-control, cohort, and randomized clinical trial studies published before March 31, 2018, which evaluated the relationship between ambient PM_{2.5} and stroke burden, were quantitatively synthesized. The meta regression Bayesian, regularized, trimmed (MR-BRT) splines were selected to fit the non-linear risk curves of ambient PM_{2.5} and stroke based on the pooled results. DALYs were calculated as the sum of years of life lost due to premature death (YLLs) and years lived with disability (YLDs). YLLs were calculated by multiplying the number of deaths by age under a standard life expectancy at each age. YLDs were calculated by multiplying the number of people living with stroke by a disability weight, which was measured on a scale from 0 to 1 where 0 indicates a state of full health and 1 indicates death. For a specific sequelae of disease, the disability weight is constant. The GBD site provided death, DALY, YLD, and YLL and we used the DALYs and death of stroke attributable to ambient PM_{2.5} in this study.

Statistical analysis

The age-standardized rate (ASR) of disability-adjusted life years (ASDR) and mortality (ASMR) were used to quantify the temporal trends of stroke burden attributable to ambient PM_{2.5} at different levels, such as national, regional, and subtypes.¹⁰ The ASR is necessary for comprising different populations with different age structure and the same population at different periods. The estimated annual percentage change (EAPC) was used to evaluate the trends in ASDR or ASMR attributable to ambient PM_{2.5} from 1990 to 2019. A regression line was fitted to natural logarithm of ASR: $\ln(\text{ASR})=a+bx+c$, where x =calendar year. The EAPC were calculated as $\text{EAPC}=100 \times [\exp(b)-1]$ and its 95% confidence interval (CI) was derived from the regression model. The ASR was considered to be in an increasing trend when both the estimated value of EAPC and the lower limit of its corresponding 95% CI were larger than 0. In contrast, the ASR was considered to be in a decreasing trend when both the estimated value of EAPC and the upper limit of its corresponding 95% CI were smaller than 0. Otherwise, it was considered as to be stable. In addition, we examined the relationship of ASDR and ASMR with SDI by regions. The Spearman correlation coefficient was used to examine the correlation between SDI and EAPC of ASMR and ASDR at the national level. All statistical analyses were performed using R program (R core team, Version 4.1.3). A two-sided $P < 0.05$ was considered as statistical significance.

Standard protocol approvals, registrations, and patient consent

This study was deemed nonregulated by the Institutional Ethics Committee of Zhengzhou University because only publicly available and aggregate data were used. Informed consent was not needed because no identifiable information was included in the analysis.

Data availability

The data and analytical methods of this study are available from the corresponding author upon reasonable request.

Result

Global spatial patterns of stroke burden attributable to ambient PM_{2.5} in 2019

Globally, in 2019, the absolute numbers of stroke death, ASMR, and ASDR attributable to ambient PM_{2.5} were approximately 1.14 million, 14.3 per 100,000 population, and 348.1 per 100,000 population respectively (Table 1). Of these, approximately a half (45.8%) of stroke death was due to ICH (Table 1, Figure. 1). The highest stroke burden was observed in ICH [6.8 (95% UI: 5.5-8.1) per 100,000 population for ASMR, and 174.8 (95% UI: 140.1-206.0) per 100,000 population for ASDR, respectively], followed by IS [6.6 (95% UI: 5.5-7.7) per 100,000 population

for ASMR, and 146.2 (95% UI: 119.8-171.2) per 100,000 population for ASDR, respectively] and SAH [0.8 (95% UI: 0.7-1.0) per 100,000 population for ASMR, and 27.1 (95% UI: 21.3-32.7) per 100,000 population for ASDR, respectively].

For SDI regions, the number of stroke ASMR and ASDR in high, and low SDI regions were smaller than those in the other three SDI regions, with the smallest number in the high SDI regions in 2019 (Table 1). ICH accounts for the highest proportion of number of stroke death in low, low-middle, and middle SDI regions (low SDI regions: 60.6%; low-middle SDI regions: 56.8%; middle SDI regions: 51.2%). While IS was the leading contributor to the number of stroke death in high and high-middle SDI regions (high SDI regions: 57.1%; high-middle SDI regions: 55.2%) (Figure. 1).

For the geographical level, East Asia had the largest number of stroke ASMR [29 (95% UI: 23.4-34.5) per 100,000 population] and ASDR [639.1 (95% UI: 518.3-758.7) per 100,000 population] attributable to ambient PM_{2.5}, followed by Central Asia [26.9 (95% UI: 19.5-35.4) per 100,000 population for ASMR, and 630.7 (95% UI: 455.1-827.3) per 100,000 population for ASDR, respectively] and North Africa and Middle East [19.3 (95% UI: 16.1-22.8) per 100,000 population for ASMR, and 466.4 (95% UI: 391.1-553.9) per 100,000 population for ASDR, respectively] (Table 1, Figure 2A and C). In contrast, the lowest numbers of stroke ASMR and ASDR attributable to ambient PM_{2.5} were observed in Australasia [0.6 (95% UI: 0.2-1.2) per 100,000

population for ASMR, and 14.7 (95% UI: 3.6-27.7) per 100,000 population for ASDR, respectively], followed by High-income North America [1.1 (95% UI: 0.6-1.7) per 100,000 population for ASMR, and 32.4 (95% UI: 17.3-49.7) per 100,000 population for ASDR, respectively] and Western Europe [2.1 (95% UI: 1.5-2.7) per 100,000 population for ASMR, and 46.2 (95% UI: 34.0-59.8) per 100,000 population for ASDR, respectively] (Table 1, Figure 2A and C). The absolute number of stroke death attributable to ambient PM_{2.5} was highest in East Asia [533×10^3 (95% UI: 446.5×10^3 - 659.2×10^3)], followed by South Asia [213.9×10^3 (95% UI: 159.5×10^3 - 267.4×10^3)] and Southeast Asia [96.7×10^3 (95% UI: 72.8×10^3 - 121.2×10^3)], while the lowest numbers were observed in Australasia [0.3×10^3 (95% UI: 0.1×10^3 - 0.7×10^3)], followed by Oceania [0.4×10^3 (95% UI: 0.1×10^3 - 0.9×10^3)] and Andean Latin America [3.3×10^3 (95% UI: 2.3×10^3 - 4.5×10^3)] (Table 1). ICH was the leading contributor to death of stroke attributable to ambient PM_{2.5} in 10 regions (including Central Asia, Central Latin America, Central Sub-Saharan Africa, East Asia, Eastern Sub-Saharan Africa, Oceania, South Asia, Southeast Asia, Southern Sub-Saharan Africa, and Western Sub-Saharan Africa), and IS was the leading contributor in 11 other regions (including Andean Latin America, Australasia, Caribbean, Central Europe, Eastern Europe, High-income Asia Pacific, High-income North America, North Africa and Middle East, Southern Latin America, Tropical Latin America, Western Europe) (Figure 1).

Additional information on the spatial patterns of stroke burden attributable to ambient

PM_{2.5} at national level are presented in eAppendix 1.

Global burden of stroke attributable to ambient PM_{2.5} by sex and age in 2019

Globally, the number of death and DALYs of stroke attributable to ambient PM_{2.5} in males were both higher than those in females in 2019 (Table 1, Figure 3), so were ICH, IS and SAH (eFigures 1-3). The age-specific rates of death and DALYs of stroke attributable to ambient PM_{2.5} are presented in Figure 3. The rate of death and DALYs of stroke attributable to ambient PM_{2.5} generally showed an increase trend with age, but decreased after 85 years old. In parallel, the rate of death and DALYs in males were also higher than those in females.

Relationship between SDI and stroke burden attributable to ambient PM_{2.5}

Figure 4 described the relationships between the ASMR and ASDR of stroke attributable to ambient PM_{2.5} with SDI from 1990 to 2019 in 21 regions of the world classified by GBD. Each colored line represents the time trend of the specified region. Each dot represents a specific year in the region. The results suggested an inversed “U” relationship between ASMR with SDI, with ASMR gradually increase when SDI < 0.45 but rapidly increase when SDI > 0.7. The similar results were observed for the relationship between ASDR and SDI. The Spearman correlation suggested that EAPC

of ASMR and ASDR were both negatively correlated with SDI in 2019 (correlation coefficient: -0.35 for EAPC of ASMR, -0.35 for EAPC of ASDR). (eFigure 4)

Temporal trends of stroke burden attributable to ambient PM_{2.5} from 1990 to 2019

At the global level, ASMR of stroke burden attributable to ambient PM_{2.5} slightly increased 2.1% from 14 per 100,000 population in 1990 to 14.3 per 100,000 population in 2019. In parallel, the absolute number of stroke death and ASDR attributable to ambient PM_{2.5} were also increased (Table 1). The EAPC of ASMR suggested that the change of ASMR was in an increase trend from 1990 to 2019 (EAPC 0.09%, 95% CI -0.05% to 0.24%), even though this change was not statistically significant (Table 1). In contrast, the ASDR of stroke burden attributable to ambient PM_{2.5} increased significantly by an average of 0.31% (95% CI 0.18%–0.44%) from 1990 to 2019 (Table 1). As to ICH, the absolute death number, ASMR and ASDR in 2019 were all increased in comparison to 1990 (Table 1). The EAPC showed that the ASMR and ASDR increased by an average of 0.57% (95% CI 0.26%–0.87%) and 0.57% (95% CI 0.31%–0.83%), respectively, during 1990-2019 (Table 1). For IS, even though the absolute death number and ASDR increased, the ASMR decreased. The EAPC showed that the ASMR of IS decreased by an average of 0.05% (95% CI 0.0%–0.11%), while the ASDR increased by an average of 0.41% (95% CI 0.35%–0.46%). For SAH, both the ASMR and ASDR decrease although the absolute death number increased. The ASMR and ASDR decreased by an average of 1.98% (95%

CI 1.62%–2.33%) and 1.48% (95% CI 1.19%–1.76%), respectively (Table 1).

At the SDI regions level, a generally linear increasing trend in ASMR and ASDR of stroke burden attributable to ambient PM_{2.5} was observed in low [EAPC (95% CI): 2.51 (2.33-2.70) for ASMR, and 2.55 (2.36-2.74) for ASDR, respectively] and low-middle [EAPC (95% CI): 2.75 (2.66-2.84) for ASMR, and 2.85 (2.75-2.94) for ASDR, respectively] SDI regions from 1990 to 2019, while a generally linear decreasing trend in high SDI regions [EAPC (95% CI): -4.01 (-4.16--3.87) for ASMR, and -3.14 (-3.27--3.01) for ASDR, respectively] in the same period (Table 1, Figure 5). However, in middle SDI regions, we found that the ASMR and ASDR of stroke attributable to ambient PM_{2.5} rose firstly before 2010, and began to slightly decrease thereafter [EAPC (95% CI): 1.04 (0.73-1.36) for ASMR, and 1.00(0.74-1.27) for ASDR, respectively]. In high-middle SDI regions, the ASMR and ASDR of stroke attributable to ambient PM_{2.5} showed a slight decrease trend from 1990 to 2014, and became decrease rapidly since 2014 [EAPC (95% CI): -1.27 (-1.55--0.99) for ASMR, and -1.09 (-1.35--0.83) for ASDR, respectively]. Similarly, ICH and IS also showed an increase trend in low, low-middle, and middle SDI regions, but decrease trend in high and middle-high regions (eTables 1-2, eFigures 5-6). However, SAH showed an increase trend in low and low-middle SDI regions, but decrease trend in high, middle-high, and middle SDI regions (eTable 3, eFigure 7). The largest increases in ASMR of stroke subtypes were attributed to ICH and IS in the low-middle SDI regions, while the largest increase attributed to SAH was observed in low SDI regions

(eTables 1-3, eFigures 5-7)

For the geographical regions, ASMRs of stroke burden attributable to ambient PM_{2.5} increased in 9 regions, with the largest increase in Eastern Sub-Saharan Africa [EAPC (95% CI): 2.65 (2.49-2.82)], followed by Western Sub-Saharan Africa [EAPC (95% CI): 2.23 (2.05-2.41)] and South Asia [EAPC (95% CI): 2.14 (2.02-2.26)] (Table 1, Figure 2B). In contrast, the ASMRs decreased in 10 regions with the largest decrease in Western Europe [EAPC (95% CI): -5.37 (-5.48--5.26)], followed by High-income North America [EAPC (95% CI): -4.82 (-5.15--4.49)] and Australasia [EAPC (95% CI): -4.77 (-5.03--4.51)] (Table 1, Figure 2B). Similarly, the most pronounced increases of ASMRs due to ICH, IS or SAH were also observed in Eastern Sub-Saharan Africa, and the highest declines of ASMRs due to ICH, IS and SAH were detected in Western Europe. However, the most pronounced decrease of ASMR due to SAH was observed in East Asia (eTables 1-3).

Additional information on the EAPCs in ASMR and ASDR of stroke burden attributable to ambient PM_{2.5} from 1990 to 2019 at the national level are presented in eTable 4 and eFigures 8-10.

Discussion

To the best of our knowledge, this is the first study to evaluate the spatiotemporal trends of stroke burden attributable to ambient PM_{2.5} at global, regional, and national levels. At the global level, in 2019, the burden of stroke attributable to ambient PM_{2.5} pollution was highest in middle SDI regions, higher in males than in females, and the main types of burden were ICH. From 1990 to 2019, the absolute death number of stroke attributable to ambient PM_{2.5} and the corresponding ASMR and ASDR were both in an increasing trend. The significant increases of ASMR and ASDR were observed in the low, low-middle, and middle SDI regions, and for ICH, while a decreasing trend was observed in high and middle-high SDI regions, and for SAH. Among 204 countries and regions, the ASMR and ASDR of stroke attributable to ambient PM_{2.5} showed an increase trend in 87 and 84 out of 204 countries or regions, respectively. While a decrease trend was observed in 103 and 104 out of 204 countries or regions, respectively.

Several previous studies have investigated the relationship between ambient PM_{2.5} and risk of stroke.¹¹⁻¹⁶ For instance, a nationwide population-based cohort study in the USA demonstrated that every interquartile range (IQR) increase in the yearly mean ambient PM_{2.5} (3.7 µg/m³) was associated with a 2.2% [95% confidence intervals (CI): 1.7%-2.8%] increase in risk of incident stroke.¹⁵ The UK Biobank study suggested that every 5 µg/m³ increase in annual average ambient PM_{2.5} was associated with 24%

increased risk of incident stroke [(95% CI:10%- 40%).¹⁶ Another study in China suggested that every 10 $\mu\text{g}/\text{m}^3$ increase in daily average ambient $\text{PM}_{2.5}$ was associated with 0.34% (95% CI: 0.20% to 0.48%) increase in hospital admissions for ischemic stroke.¹¹ However, most of these studies were limited to specific regions or countries, or only provided time-series estimates, this study comprehensively evaluated the long-term trend of the stroke burden attributable to ambient $\text{PM}_{2.5}$ at the global level. In addition, our study relied on a large number of studies and effect estimates, which have been combined and integrated across a wide range of ambient $\text{PM}_{2.5}$ exposure. What's more, the GBD study used non-linear risk functions for ambient $\text{PM}_{2.5}$ exposure and stroke burden, which were downward concave and monotonically increasing, the most biologically plausible shapes of the $\text{PM}_{2.5}$ risk curve,⁸ thus providing a more accurate estimate for $\text{PM}_{2.5}$ related disease burden.

The exact mechanism how $\text{PM}_{2.5}$ contribute to stroke remains unclear. Previous studies have suggested that air pollutants can have an adverse effects on vascular endothelial function and can increase the activity of sympathetic nervous system, leading to vasoconstriction, increased blood pressure, ischemia, and thrombosis.¹⁷⁻¹⁹ Moreover, even slightly increase in the level of $\text{PM}_{2.5}$ have been demonstrated to be associated with the changes of hemodynamics, including decreased cerebral blood flow and increased cerebrovascular resistance.²⁰ Another potential pathway for the effect of air pollution on stroke is that exposure to $\text{PM}_{2.5}$ can increase the risk of atrial arrhythmias, which can lead to thromboembolic events.²¹

We found that the burden of stroke attributable to ambient PM_{2.5} was higher in males than that in females, which was consistent with previous studies.^{15, 22} Several potential factors can explain the sex heterogeneity of stroke burden attributable to ambient PM_{2.5}. First, in comparison with females, males stay longer outside and had more chance to be exposed to ambient PM_{2.5}. Second, males had higher ventilation volume and greater particle deposition per unit time, which may lead to males being more sensitive to vascular inflammation caused by PM_{2.5}.²³ In addition, males were more likely being exposed to other stroke-related risk factors, such as smoking and drinking,³ which could have an effect on the interactions of PM_{2.5}-stroke relationship. We also found that the burden of stroke attributable to ambient PM_{2.5} showed a generally increase trend with age, which could be ascribed to the accumulated longer exposure to PM_{2.5}, and increasing prevalence of incident stroke in elderly population.⁷

In most SDI and geographical regions, ICH and IS accounted for a higher proportion of stroke burden attributable to ambient PM_{2.5} than SAH. Even though previous studies suggested that air pollutants can activate systemic inflammation and oxidative stress, leading to endothelial dysfunction,^{24, 25} the exact mechanism by which PM_{2.5} affects different stroke subtypes is not clear. Therefore, it is difficult to directly compare the effect size of PM_{2.5} on different subtypes on stroke. In addition, the stroke subtype of ICH showed a significant increase trend from 1990 to 2019, while the IS and SAH showed a decreased trend. However, the proportion of ICH decreased

in most regions, which might be due to the changes in the exposure levels of other risk factors, such as lifestyle and metabolic factors.^{22, 26}

The stroke burden attributable to ambient PM_{2.5} varies across the world in 2019. Lower SDI ranked countries including most countries in Asia and Africa, had higher ASMR and ASDR of PM_{2.5}-related stroke burden than those high SDI ranked countries. The difference might be due to the different levels of ambient PM_{2.5} and SDI. High levels of ambient PM_{2.5} exposure and several factors associated with low SDI (i.e., low education level and economic development, poor health care and prevention programme, and lack of health awareness) may have interactively contributed to a heavy stroke burden due to ambient PM_{2.5}²⁷⁻²⁹. For example, the urban expansion and rapid industrial development have exacerbated the air pollution situation in South Asia, which in turn led to a heavy stroke burden related to ambient PM_{2.5}. In addition, countries in the high-SDI regions paid more attention to the air pollution control, which made the ambient PM_{2.5} to be controlled at a low level.⁹ What's more, low SDI ranked countries lacked effective intervention for stroke and health care due to the severe poverty, leading to increased stroke burden.⁴ We also found that the stroke burden attributable to ambient PM_{2.5} showed an inversed "U" relationship with SDI, which may be attributed to the inverse U-relationship between ambient PM_{2.5} and socioeconomic development, with an increasing trend of PM_{2.5} exposure in low to middle SDI regions but a decreasing trend in high SDI regions.⁸ This also was consistent with the opinion of Environmental Kuznets Curve, which

suggested that environment quality deteriorates in the early stages of economic growth, but improves after a certain level of economic growth.³⁰

In parallel to the spatial pattern of stroke burden attributable to ambient PM_{2.5}, the temporal trend of both ASMR and ASDR of ambient PM_{2.5}-related stroke burden showed an increasing trend in low, low-middle, and middle SDI regions, while a decrease trend in high and middle high SDI regions, from 1990 to 2019. The governments' efforts to improve air quality, as well as advanced healthcare systems and high health awareness among populations could contribute to the lower burden of ambient PM_{2.5} related stroke burden in high-SDI countries. More importantly, low-income and middle-income countries had a more pronounced stroke burden than that in high-income countries,⁸ partially due to the increase in PM_{2.5} emissions caused by the increase of urbanization industrialization and car ownership, and the decrease of the greenness of vegetation.³¹ Another possible explanation is that less access to health services in low SDI countries may result in under-report of stroke burden,^{32,33} which might lead to the underestimation of stroke burden in low SDI countries. Therefore, controlling air quality is still an urgent need to prevent stroke, especially in low SDI countries.

This study provides a comprehensive estimation of spatial and temporal trend in stroke burden attributable to ambient PM_{2.5} at global, regional, and national levels.

Even though we used data by a systematic and comprehensive database, several

limitations should be mentioned. First, the burden of stroke might have been underestimated since several types of stroke, such as silent strokes, were not recorded in the GBD. Second, due to the data for other pollutants such as PM₁₀, NO₂, and SO₂ was not available, it is difficult for us to distinguish whether the observed burden were specifically caused by PM_{2.5} or a combination of the pollutants. Third, PM_{2.5} exposure was estimated using residential ZIP code but not the exact home address, which may bias the estimation of exposure levels. However, the method criteria and data inclusion for GBD are consistent across all countries, thus the bias seems random which reduced these limitations when comparing indicators across countries.⁹ Fourth, both the exposure and health outcome data used in this study were based on GBD 2019 estimates, but not real data. This is more prominent in low and middle-income countries, which usually have limited health data. Therefore, in those data-limited countries, estimates depend heavily on predictive covariates and trends in neighboring countries, thus preventing unambiguous inferences, especially for causality inferences. Finally, there may be residual confounding due to unknown or unmeasured confounders in the studies included in the GBD 2019, which could affect the assessment of the risk curves.

Conclusion

In conclusion, this study systematically estimated the temporal and spatial trends of the stroke burden attributable to ambient PM_{2.5}. The global burden of stroke attributable to PM_{2.5} showed an increasing trend over the past 30-years, especially in

males, low-income countries, and for ICH. Continued efforts on reducing the level of ambient PM_{2.5} are urgently needed to reduce the burden of stroke.

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Table 1. Stroke burden attributable to ambient particulate matter in 1990 and 2019, and its temporal trends from 1990 to 2019

Characteristics	1990			2019			EAPC	
	Incident cases No.×10 ³ (95% UI)	ASMR per 100,000 No. (95% UI)	ASDR per 100,000 No. (95% UI)	Incident cases No.×10 ³ (95% UI)	ASMR per 100,000 No. (95% UI)	ASDR per 100,000 No. (95% UI)	ASMR	ASDR
Global	508 (350.1-684.2)	14 (9.6-18.6)	319.3 (219.5-433.5)	1143.4 (945.5-1336.4)	14.3 (11.8-16.6)	348.1 (283.3-404.4)	0.09 (-0.05-0.24)	0.31 (0.18-0.44)
Sex								
Female	241.6 (168.6-326.1)	12 (8.3-16.1)	267.5 (185.1-366.3)	489.2 (390.7-590.7)	11.2 (8.9-13.5)	274.3 (220.6-329.4)	-0.31 (-0.43--0.19)	0.01 (-0.09-0.11)
Male	266.5 (179.4-361.7)	16.3 (11.1-21.9)	376 (254-511.4)	654.1 (534.3-777.2)	17.8 (14.6-21.2)	428.1 (348.7-505.8)	0.4 (0.22-0.58)	0.53 (0.37-0.69)
Subtype								
Intracerebral hemorrhage	232.8 (151.3-329.2)	6 (3.9-8.5)	152.2 (98.8-215.4)	558.5 (450.7-660.2)	6.8 (5.5-8.1)	174.8 (140.1-206)	0.57 (0.26-0.87)	0.57 (0.31-0.83)
Ischemic stroke	225.6 (160.1-290.6)	6.7 (4.8-8.6)	130.8 (93.2-169.8)	516 (428.8-605.1)	6.6 (5.5-7.7)	146.2 (119.8-171.2)	-0.05 (-0.11-0)	0.41 (0.35-0.46)
Subarachnoid hemorrhage	49.7 (28.6-77)	1.2 (0.7-1.9)	36.3 (22.1-54.9)	68.8 (54.5-83.2)	0.8 (0.7-1)	27.1 (21.3-32.7)	-1.98 (-2.33--1.62)	-1.48 (-1.76--1.19)
Socio-demographic index								
High SDI	87.1 (57.3-119.2)	8.3 (5.4-11.3)	193.3 (129.1-259.2)	55.7 (42.3-70.2)	2.9 (2.2-3.6)	83.9 (65.7-103.4)	-4.01 (-4.16--3.87)	-3.14 (-3.27--3.01)
High-middle SDI	209.6 (147.4-274.8)	21.3 (14.9-27.9)	472.2 (330.9-616)	308.3 (257-360.1)	15.3 (12.8-17.9)	358.5 (301.1-415.9)	-1.27 (-1.55--0.99)	-1.09 (-1.35--0.83)
Middle SDI	156.8	17.3	400.5	515.6	22.6	520.1	1.04	1

		(92.1-239)	(10.2-26.1)	(235.1-603.2)	(420.3-599.8)	(18.5-26.3)	(428.5-602.3)	(0.73-1.36)	(0.74-1.27)
Low-middle SDI		43.3	8.2 (3.7-14.8)	191.2	216.2	16.9	403.9	2.75	2.85
		(19.2-79.2)		(84.7-352)	(152.4-276.3)	(11.9-21.6)	(286.7-512.6)	(2.66-2.84)	(2.75-2.94)
Low SDI		11.1	5.3 (1.9-11.3)	124.7	47.2 (28.7-70)	10 (6.1-14.8)	238.6	2.51	2.55
		(3.9-24.3)		(43.4-273)			(144.8-355.1)	(2.33-2.7)	(2.36-2.74)
Region									
Andean	Latin	1.9 (0.9-3.2)	9.2 (4.3-15.9)	234	3.3 (2.3-4.5)	6 (4.1-8.2)	155.2	-1.48	-1.43
America				(108.9-398.2)			(107.2-208.1)	(-1.83--1.12)	(-1.77--1.08)
Australasia		0.5 (0.1-1.2)	2.2 (0.2-5.3)	46.4	0.3 (0.1-0.7)	0.6 (0.2-1.2)	14.7 (3.6-27.7)	-4.77	-4.36
				(5.3-112.1)				(-5.03--4.51)	(-4.62--4.09)
Caribbean		2 (0.9-3.7)	8 (3.4-14.5)	193	3.9 (2.1-6.3)	7.5 (4.2-12.2)	185.9	-0.14	-0.08
				(81.8-349.8)			(102.6-300.4)	(-0.31-0.03)	(-0.27-0.11)
Central Asia		8.6 (4.5-14.4)	19.6	476.6	17.7	26.9	630.7	0.74	0.58
			(10.2-32.9)	(249.5-789.1)	(12.6-23.3)	(19.5-35.4)	(455.1-827.3)	(0.38-1.09)	(0.24-0.91)
Central Europe		36.8	26.4	589.8	27.5	12.4	271.5	-3.06	-3.15
		(20.3-55.3)	(14.5-39.8)	(327.2-875.3)	(22.5-33.3)	(10.1-14.9)	(223.1-326.6)	(-3.33--2.79)	(-3.41--2.89)
Central	Latin	6.4 (3.2-10.6)	8.2 (4.1-13.7)	195	12 (8.9-15.2)	5.2 (3.9-6.6)	129.2	-2	-1.83
America				(100.2-317.7)			(97.7-164)	(-2.18--1.81)	(-2.02--1.64)
Central		1.1 (0.4-2.6)	5.8 (1.9-13.4)	135.9	4.5 (2.2-8)	9.8 (4.9-17.1)	229.4	1.59	1.58
Sub-Saharan				(42.4-319.5)			(112.1-405.7)	(1.15-2.03)	(1.14-2.03)
Africa									
East Asia		166.8	22.4	487.5	553	29 (23.4-34.5)	639.1	1.1	1.11
		(79.2-280.4)	(10.7-37.6)	(230.6-820.6)	(446.5-659.2)		(518.3-758.7)	(0.69-1.51)	(0.76-1.46)
Eastern Europe		65.8	25 (11.4-41.2)	540.7	37 (22.8-52.2)	10.7 (6.7-15.1)	252.1	-3.4	-3.08
		(29.9-109.1)		(252.6-875.2)			(157.3-353.2)	(-3.93--2.87)	(-3.62--2.54)
Eastern		2.2 (0.8-5.3)	3.3 (1.1-7.6)	79.5	9.2 (4.9-15.3)	6.3 (3.3-10.5)	146.7	2.65	2.46
Sub-Saharan				(27.3-187.7)			(79.5-245.5)	(2.49-2.82)	(2.31-2.62)
Africa									

High-income Asia Pacific	20 (8.7-34.4)	10.6 (4.5-18.3)	255.2 (111.1-430.6)	16.7 (11.8-22.3)	3.4 (2.5-4.5)	103.8 (76.8-135.9)	-4.38 (-4.74--4.02)	-3.46 (-3.79--3.14)
High-income North America	13.8 (5.1-26)	3.8 (1.4-7.2)	100.2 (38.2-183.1)	7.1 (3.7-10.9)	1.1 (0.6-1.7)	32.4 (17.3-49.7)	-4.82 (-5.15--4.49)	-4.21 (-4.47--3.94)
North Africa and Middle East	28.6 (22.3-36.3)	18.8 (14.6-24)	453.5 (356.5-572)	74.9 (62.6-89.2)	19.3 (16.1-22.8)	466.4 (391.1-553.9)	0.13 (-0.02-0.27)	0.12 (-0.01-0.25)
Oceania	0.1 (0-0.3)	4.2 (1.2-10.8)	109.6 (31.4-282.8)	0.4 (0.1-0.9)	5.7 (1.8-13.3)	154.9 (48.3-361.6)	0.99 (0.87-1.11)	1.07 (0.96-1.19)
South Asia	44.9 (19.6-82.2)	9.1 (4-16.7)	210.9 (92.2-384.7)	213.9 (159.5-267.4)	16.3 (12.2-20.4)	392.2 (293.8-488.4)	2.14 (2.02-2.26)	2.36 (2.24-2.49)
Southeast Asia	29.3 (13.5-52.7)	12.5 (5.7-22.3)	316 (146-569.3)	96.7 (72.8-121.2)	17.1 (12.8-21.4)	429 (325.3-534.3)	1.22 (0.91-1.54)	1.16 (0.87-1.45)
Southern Latin America	4.7 (2-8.3)	10.5 (4.4-18.6)	267.3 (115.1-463.7)	4.2 (2.9-5.6)	5 (3.5-6.6)	124.1 (87.1-163.6)	-2.78 (-3.03--2.53)	-2.9 (-3.14--2.65)
Southern Sub-Saharan Africa	2.8 (2-3.7)	10.7 (7.6-14)	280.9 (202.1-364.9)	6.6 (5.1-8.2)	13.1 (10-16.3)	304 (235.4-375)	0.83 (0.36-1.31)	0.37 (-0.07-0.8)
Tropical Latin America	9.2 (4.2-16.3)	10.4 (4.8-18.4)	268.6 (123.9-470.3)	10.8 (7.6-14.3)	4.6 (3.2-6)	115.4 (81.8-151.4)	-3.01 (-3.24--2.77)	-3.15 (-3.37--2.92)
Western Europe	57 (26.2-95.1)	9.5 (4.4-15.9)	193.1 (89.3-321)	22.3 (16.1-29.2)	2.1 (1.5-2.7)	46.2 (34-59.8)	-5.37 (-5.48--5.26)	-5.06 (-5.16--4.96)
Western Sub-Saharan Africa	5.4 (2.4-10.7)	7.1 (3.2-13.7)	160.8 (71.4-318.4)	21.4 (13.5-30.4)	13.1 (8.4-18.5)	298 (188.3-425.5)	2.23 (2.05-2.41)	2.26 (2.08-2.43)

ASMR: age-standardized mortality rate; ASDR: age-standardized disability-adjusted life year rate; EAPC: estimated annual percentage change

Figure Legends

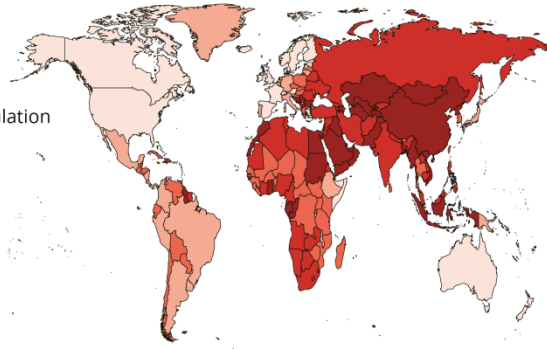
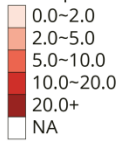
Figure 1. Contribution of intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage to absolute stroke death number attributable to ambient particulate matter globally and by region, in 1990 and 2019.



Figure 2. Spatial distribution of stroke burden attributable to ambient particulate matter in 204 countries and territories. (A) The ASMR of stroke burden attributable to ambient particulate matter in 2019; (B) The EAPC of stroke ASMR from 1990 to 2019; (C) The ASDR of stroke burden attributable to ambient particulate matter in 2019; (D) The EAPC of stroke ASMR from 1990 to 2019.

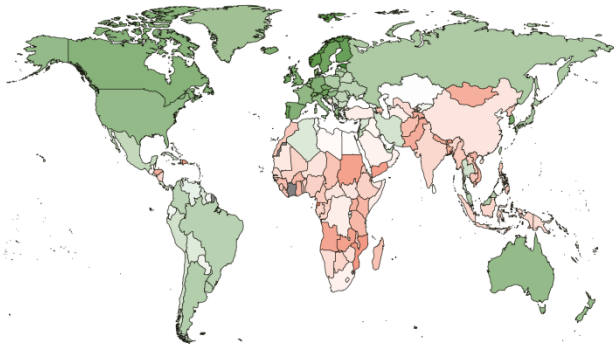
A

ASMR per 100,000 population



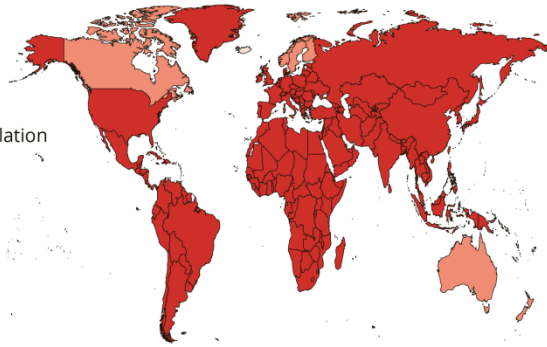
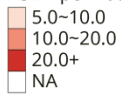
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EAPC of ASMR



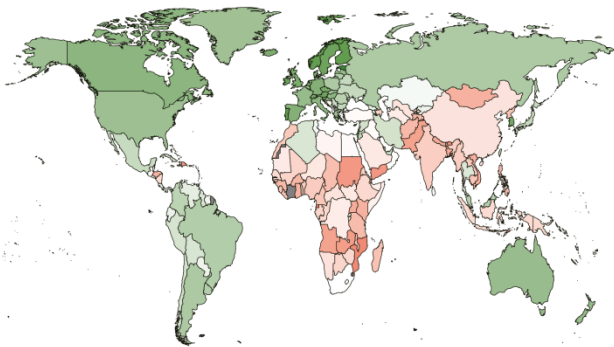
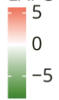
C

ASDR per 100,000 population



D

EAPC of ASDR



LED

Figure 3. Age-specific numbers and rates of deaths (A) and DALYs (B) of stroke attributable to ambient particulate matter by sex, in 2019.

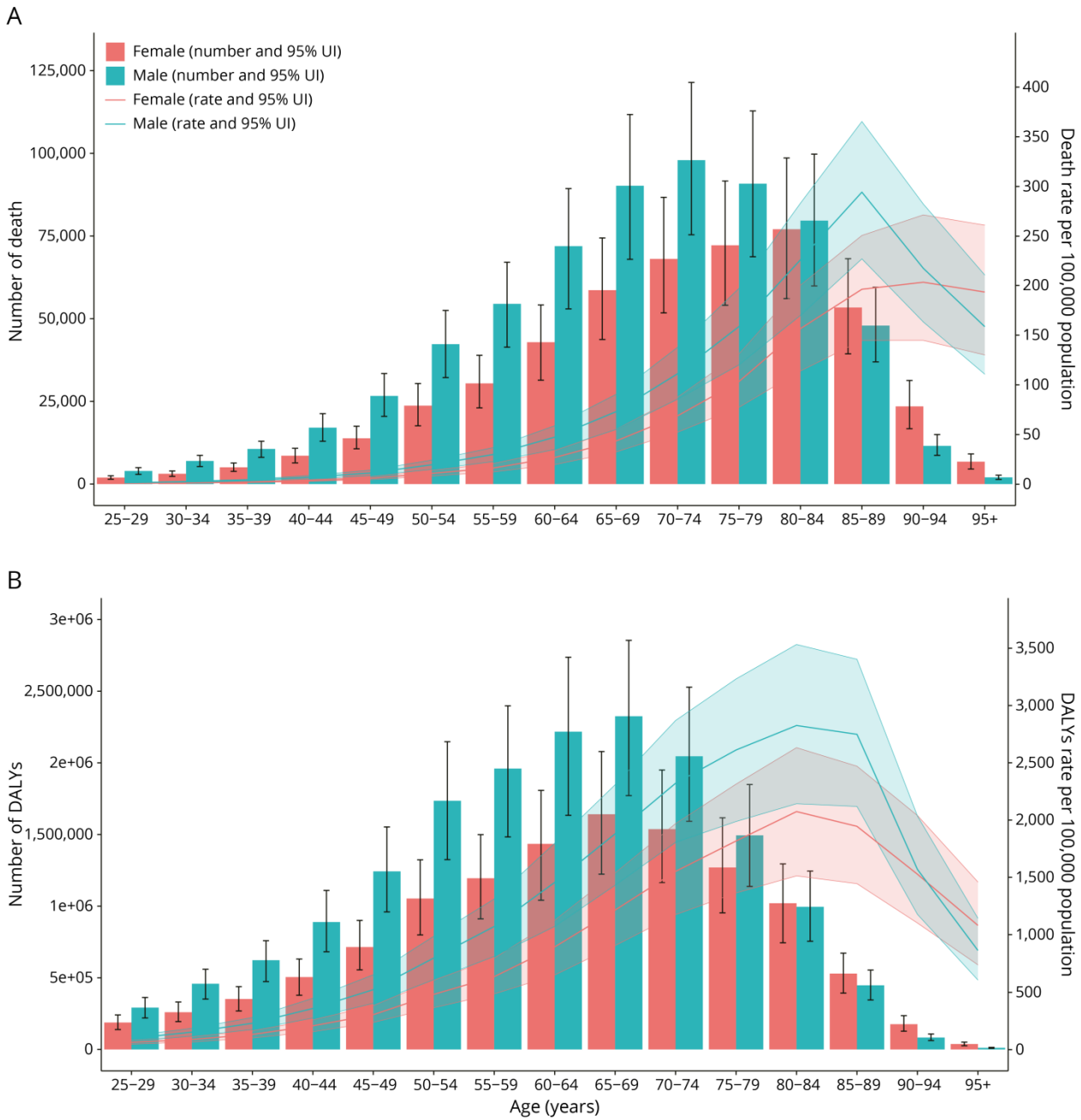


Figure 4. Age-standardized rates of stroke death (A) and DALY (B) attributable to ambient particulate matter by Socio-demographic Index in 2019.

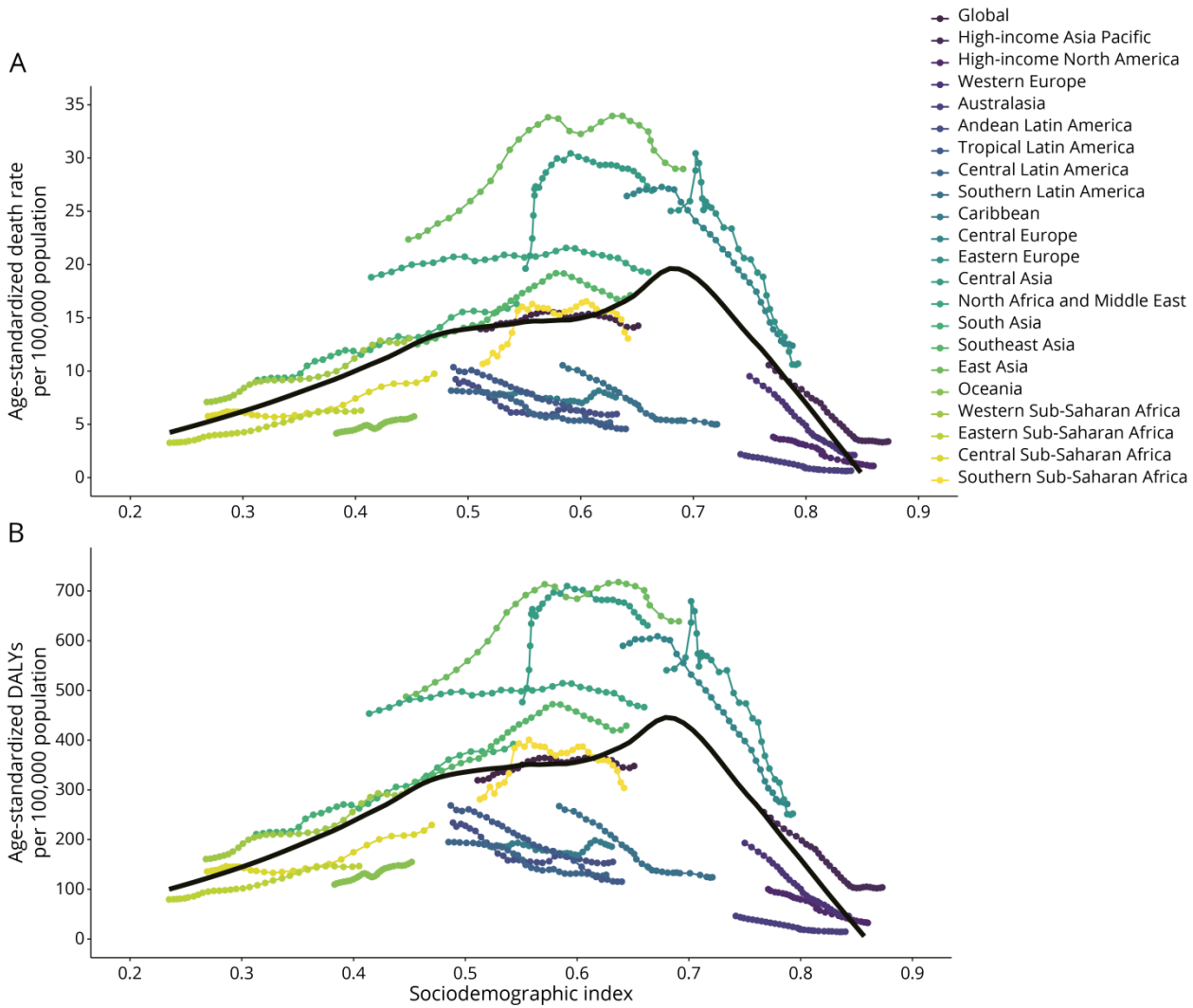
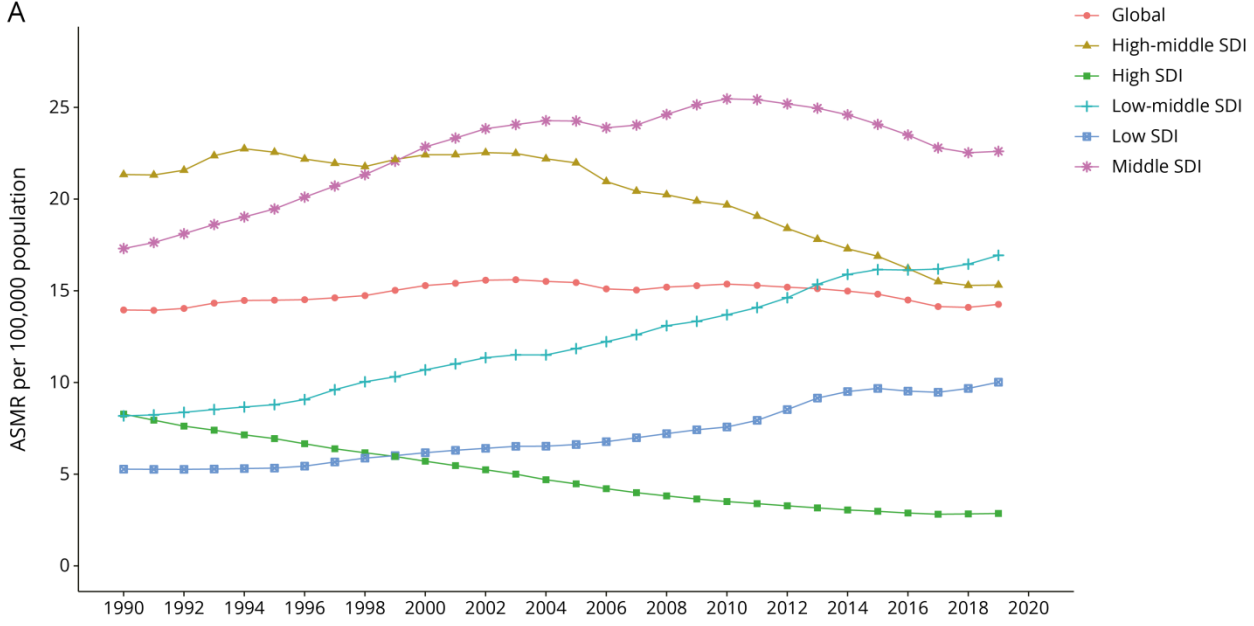
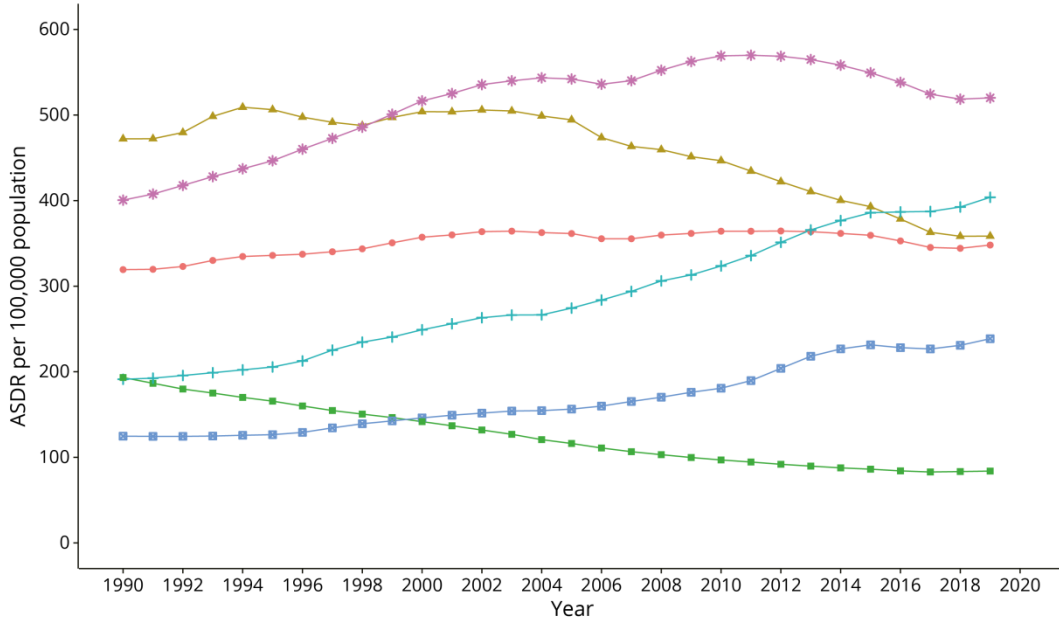


Figure 5. Temporal trends in age-standardized mortality rate (per 100,000 Population) (A) and age-standardized DALYs rate (per 100,000 Population) (B) for stroke associated with ambient particulate matter in global and SDI regions, 1990–2019.

A



B



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Spatiotemporal Trends of Stroke Burden Attributable to Ambient PM2.5 in 204 Countries and Territories, 1990–2019: A Global Analysis

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