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Spatiotemporal Trends of Stroke Burden Attributable to Ambient $PM_{2.5}$ in 204 Countries and Territories, 1990–2019

A Global Analysis

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Abstract

Background and Objectives

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 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 disability-adjusted life years 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 male patients, in the middle SDI regions, and for intracerebral hemorrhage (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% CI −0.05 to 0.24) and 0.31 (95% CI 0.18–0.44), respectively. The significant increases of ASMR and ASDR were observed in the low, low-middle, and middle SDI regions, and for ICH. However, a decreasing trend was observed in high and middle-high SDI regions, and for subarachnoid hemorrhage.

Discussion

The global burden of stroke attributable to ambient $PM_{2.5}$ showed an increasing trend over the past 30 years, especially in male patients, 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.

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Glossary

ASDR = age-standardized disability-adjusted life-year rate; **ASMR** = age-standardized mortality rate; **ASR** = age-standardized rate; **DALY** = disability-adjusted life year; **EAPC** = estimated annual percentage change; **GBD** = Global Burden of Disease; **ICH** = intracerebral hemorrhage; **IS** = ischemic stroke; **$PM_{2.5}$** = particulate matter; **SAH** = subarachnoid hemorrhage; **SDI** = sociodemographic index; **UI** = uncertainty interval; **WHO** = World Health Organization; **YLD** = year lived with disability; **YLL** = year of life lost.

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 2 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.

Methods

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, was obtained from the Global Health Data Exchange.[7] Data from a total of 204 countries and territories were available, which were 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 female patients younger than 25 years, the education level of people aged 15 years or older, and the lagged gross domestic product 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 at an interval of 5 years and 1 group aged 95 years or older.

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 of ≤2.5 μm (μg/m^3), which was evaluated using chemical transport models, ground-level monitoring, and satellite in grids at 0.1° × 0.1° spatial resolution. The Bayesian hierarchical model and Gaussian processes were used to calculate the population-weighted national-level 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 3 pathologic subtypes of stroke: IS was defined as an attack of neurologic 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 SAH 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 nonlinear 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 (YLLs) because of premature death and years

Table 1 Stroke Burden Attributable to Ambient Particulate Matter in 1990 and 2019 and Its Temporal Trends From 1990 to 2019

	1990			2019			EAPC	
Characteristics	**Incident cases, n × 10^3 (95% UI)**	**ASMR per 100,000, n (95% UI)**	**ASDR per 100,000, n (95% UI)**	**Incident cases, n × 10^3 (95% UI)**	**ASMR per 100,000, n (95% UI)**	**ASDR per 100,000, n (95% UI)**	**ASMR**	**ASDR**
Global	508 (350.1–684.2)	14 (9.6–18.6)	319.3 (219.5–433.5)	1,143.4 (945.5–1,336.4)	14.3 (11.8–16.6)	348.1 (283.3–404.4)	0.09 (−0.05 to 0.24)	0.31 (0.18 to 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 to −0.19)	0.01 (−0.09 to 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 to 0.58)	0.53 (0.37 to 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 to 0.87)	0.57 (0.31 to 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 to 0)	0.41 (0.35 to 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 to −1.62)	−1.48 (−1.76 to −1.19)
SDI								
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 to −3.87)	−3.14 (−3.27 to −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 to −0.99)	−1.09 (−1.35 to −0.83)
Middle SDI	156.8 (92.1–239)	17.3 (10.2–26.1)	400.5 (235.1–603.2)	515.6 (420.3–599.8)	22.6 (18.5–26.3)	520.1 (428.5–602.3)	1.04 (0.73 to 1.36)	1 (0.74 to 1.27)
Low-middle SDI	43.3 (19.2–79.2)	8.2 (3.7–14.8)	191.2 (84.7–352)	216.2 (152.4–276.3)	16.9 (11.9–21.6)	403.9 (286.7–512.6)	2.75 (2.66 to 2.84)	2.85 (2.75 to 2.94)
Low SDI	11.1 (3.9–24.3)	5.3 (1.9–11.3)	124.7 (43.4–273)	47.2 (28.7–70)	10 (6.1–14.8)	238.6 (144.8–355.1)	2.51 (2.33 to 2.7)	2.55 (2.36 to 2.74)
Region								
Andean Latin America	1.9 (0.9–3.2)	9.2 (4.3–15.9)	234 (108.9–398.2)	3.3 (2.3–4.5)	6 (4.1–8.2)	155.2 (107.2–208.1)	−1.48 (−1.83 to −1.12)	−1.43 (−1.77 to −1.08)
Australasia	0.5 (0.1–1.2)	2.2 (0.2–5.3)	46.4 (5.3–112.1)	0.3 (0.1–0.7)	0.6 (0.2–1.2)	14.7 (3.6–27.7)	−4.77 (−5.03 to −4.51)	−4.36 (−4.62 to −4.09)
Caribbean	2 (0.9–3.7)	8 (3.4–14.5)	193 (81.8–349.8)	3.9 (2.1–6.3)	7.5 (4.2–12.2)	185.9 (102.6–300.4)	−0.14 (−0.31 to 0.03)	−0.08 (−0.27 to 0.11)
Central Asia	8.6 (4.5–14.4)	19.6 (10.2–32.9)	476.6 (249.5–789.1)	17.7 (12.6–23.3)	26.9 (19.5–35.4)	630.7 (455.1–827.3)	0.74 (0.38 to 1.09)	0.58 (0.24 to 0.91)
Central Europe	36.8 (20.3–55.3)	26.4 (14.5–39.8)	589.8 (327.2–875.3)	27.5 (22.5–33.3)	12.4 (10.1–14.9)	271.5 (223.1–326.6)	−3.06 (−3.33 to −2.79)	−3.15 (−3.41 to −2.89)
Central Latin America	6.4 (3.2–10.6)	8.2 (4.1–13.7)	195 (100.2–317.7)	12 (8.9–15.2)	5.2 (3.9–6.6)	129.2 (97.7–164)	−2 (−2.18 to −1.81)	−1.83 (−2.02 to −1.64)
Central Sub-Saharan Africa	1.1 (0.4–2.6)	5.8 (1.9–13.4)	135.9 (42.4–319.5)	4.5 (2.2–8)	9.8 (4.9–17.1)	229.4 (112.1–405.7)	1.59 (1.15 to 2.03)	1.58 (1.14 to 2.03)
East Asia	166.8 (79.2–280.4)	22.4 (10.7–37.6)	487.5 (230.6–820.6)	553 (446.5–659.2)	29 (23.4–34.5)	639.1 (518.3–758.7)	1.1 (0.69 to 1.51)	1.11 (0.76 to 1.46)
Eastern Europe	65.8 (29.9–109.1)	25 (11.4–41.2)	540.7 (252.6–875.2)	37 (22.8–52.2)	10.7 (6.7–15.1)	252.1 (157.3–353.2)	−3.4 (−3.93 to −2.87)	−3.08 (−3.62 to −2.54)

Continued

Table 1 Stroke Burden Attributable to Ambient Particulate Matter in 1990 and 2019 and Its Temporal Trends From 1990 to 2019 *(continued)*

Characteristics	1990			2019			EAPC	
	Incident cases, n × 10^3 (95% UI)	ASMR per 100,000, n (95% UI)	ASDR per 100,000, n (95% UI)	Incident cases, n × 10^3 (95% UI)	ASMR per 100,000, n (95% UI)	ASDR per 100,000, n (95% UI)	ASMR	ASDR
Eastern Sub-Saharan Africa	2.2 (0.8–5.3)	3.3 (1.1–7.6)	79.5 (27.3–187.7)	9.2 (4.9–15.3)	6.3 (3.3–10.5)	146.7 (79.5–245.5)	2.65 (2.49 to 2.82)	2.46 (2.31 to 2.62)
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 to −4.02)	−3.46 (−3.79 to −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 to −4.49)	−4.21 (−4.47 to −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 to 0.27)	0.12 (−0.01 to 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 to 1.11)	1.07 (0.96 to 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 to 2.26)	2.36 (2.24 to 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 to 1.54)	1.16 (0.87 to 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 to −2.53)	−2.9 (−3.14 to −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 to 1.31)	0.37 (−0.07 to 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 to −2.77)	−3.15 (−3.37 to −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 to −5.26)	−5.06 (−5.16 to −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 to 2.41)	2.26 (2.08 to 2.43)

Abbreviations: ASDR = age-standardized disability-adjusted life-year rate; ASMR = age-standardized mortality rate; EAPC = estimated annual percentage change; SDI = sociodemographic index; UI = uncertainty interval.

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: $\ln(ASR) = a + bx + c$, where x = calendar year. The EAPC was calculated as $EAPC = 100\times(\exp(b) - 1)$, 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. By 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 (version 4.1.3; R Core Team, Vienna, Austria). A 2-sided $p < 0.05$ was considered as statistical significance.

Standard Protocol Approvals, Registrations, and Patient Consents

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 on reasonable request.

Result

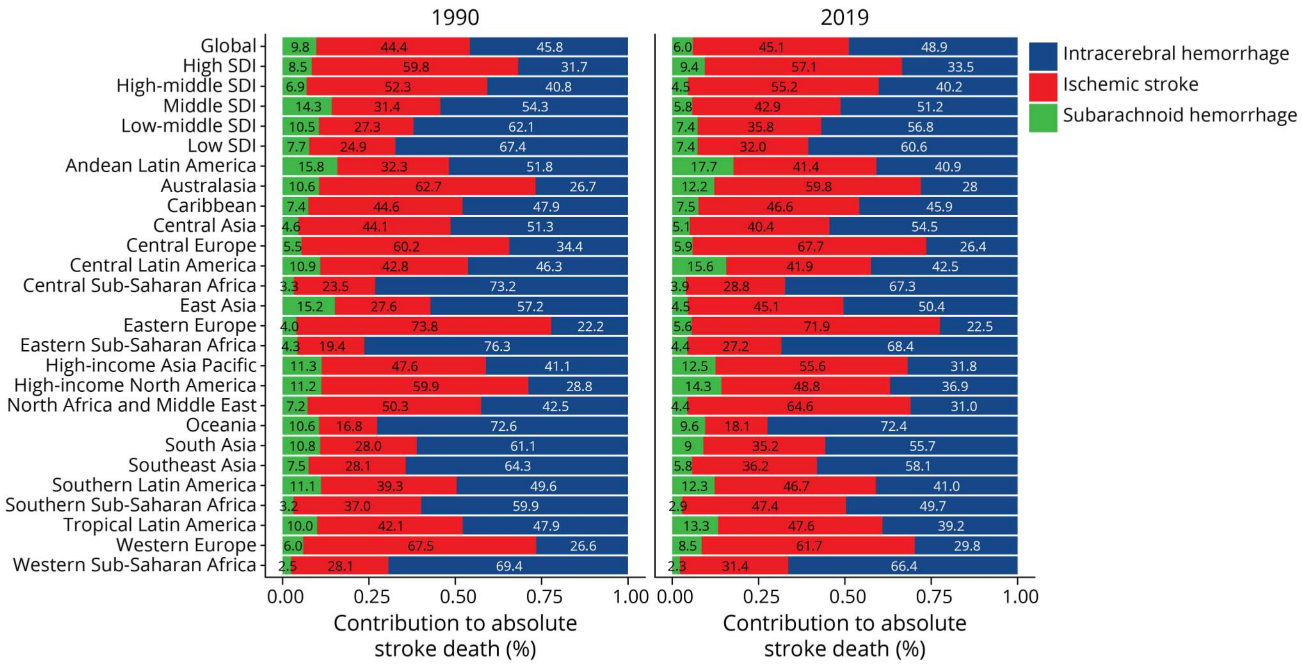
Global Spatial Patterns of Stroke Burden Attributable to Ambient $PM_{2.5}$ in 2019

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% uncertainty interval (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 numbers of stroke ASMR and ASDR in high and low SDI regions were smaller than those in the other 3 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%). However, 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 2, A and C). By 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 2, A 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-

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



SDI = sociodemographic index.

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, and Western Europe) (Figure 1).

Additional information on the spatial patterns of stroke burden attributable to ambient $PM_{2.5}$ at the national level is presented in eAppendix 1 (links.lww.com/WNL/C944).

Global Burden of Stroke Attributable to Ambient $PM_{2.5}$ by Sex and Age in 2019

Globally, the numbers of death and DALYs of stroke attributable to ambient $PM_{2.5}$ in male patients were both higher than those in female patients in 2019 (Table 1, Figure 3), so were ICH, IS, and SAH (eFigures 1–3, links.lww.com/WNL/C933, links.lww.com/WNL/C934, links.lww.com/WNL/C935). 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 increasing trend with age but decreased after 85 years old. In parallel, the rates of death and DALYs in male patients were also higher than those in female patients.

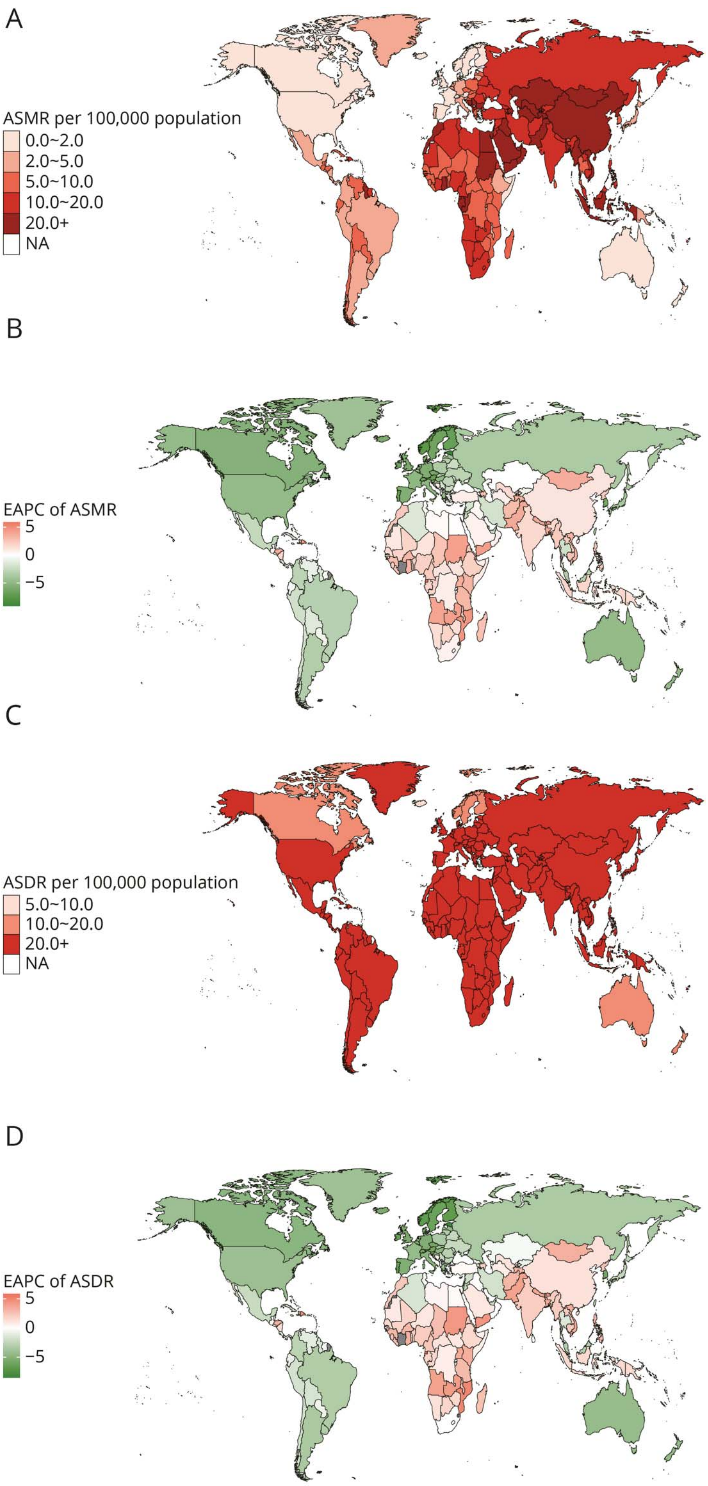
Relationship Between SDI and Stroke Burden Attributable to Ambient $PM_{2.5}$

Figure 4 presents 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 and SDI, with ASMR gradually increasing when SDI <0.45 but rapidly increasing 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 was associated with lower SDI in 2019 (correlation coefficient −0.35 for EAPC of ASMR and −0.35 for EAPC of ASDR) (eFigure 4, links.lww.com/WNL/C936).

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 numbers 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 increasing trend from 1990 to 2019 (EAPC 0.09%, 95% CI −0.05% to 0.24%), although this change was not statistically significant (Table 1). By 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 numbers of ASMR and ASDR in 2019 were all increased in comparison with 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

Figure 2 Spatial Distribution of Stroke Burden Attributable to Ambient Particulate Matter in 204 Countries and Territories

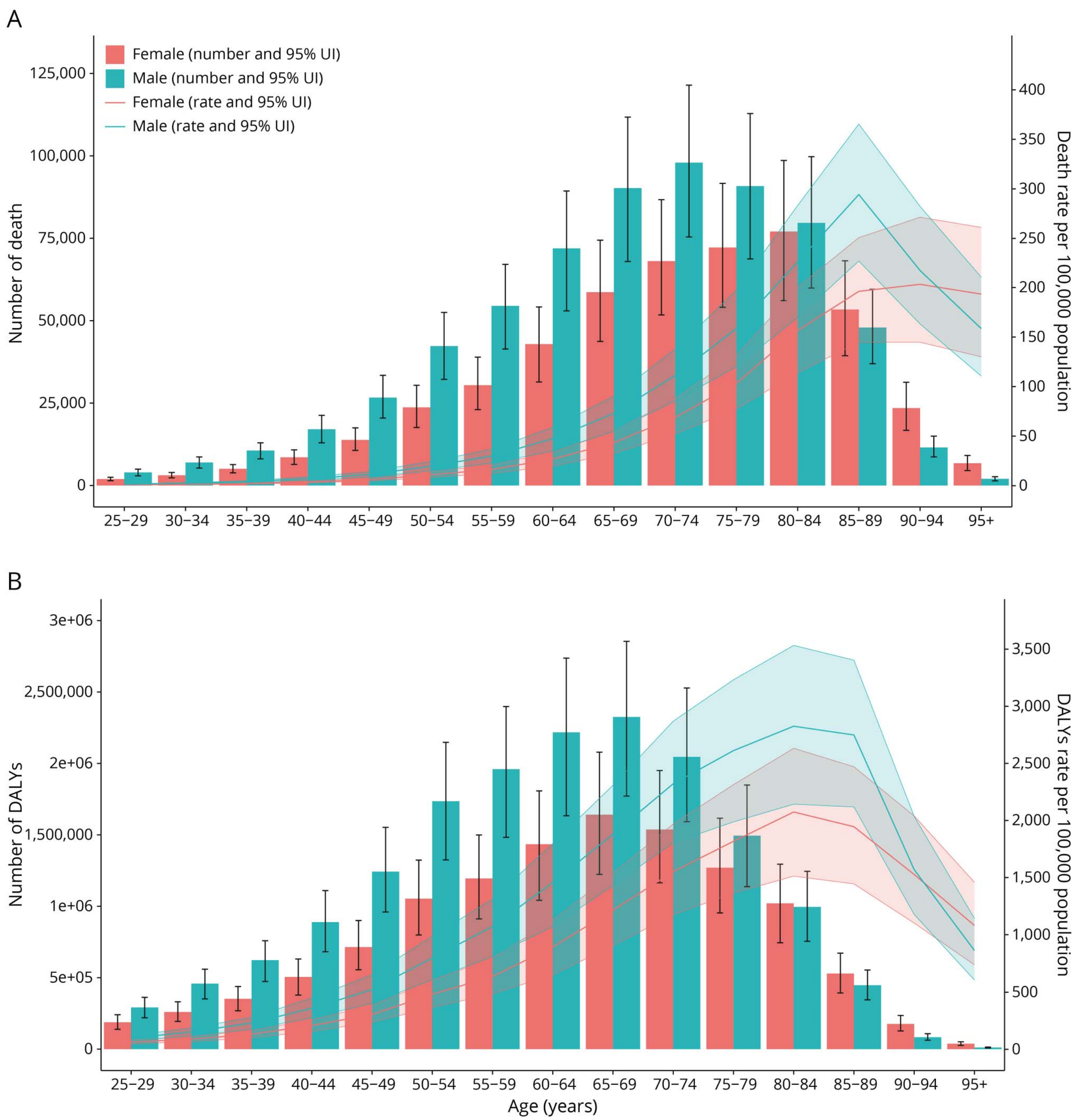


(A) The ASMR of stroke burden attributable to ambient particulate matter in 2019. (B) The EAPC of stroke ASMR from 1990 to 2019. (C) The ASDR of stroke burden attributable to ambient particulate matter in 2019. (D) The EAPC of stroke ASMR from 1990 to 2019. ASDR = age-standardized disability-adjusted life-year rate; ASMR = age-standardized mortality rate; EAPC = estimated annual percentage change; NA = not available.

0.57% (95% CI 0.31%–0.83%), respectively, during 1990–2019 (Table 1). For IS, although 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%), whereas the ASDR increased by an average of 0.41% (95% CI 0.35%–0.46%). For SAH, both the ASMR and the 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 region 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]

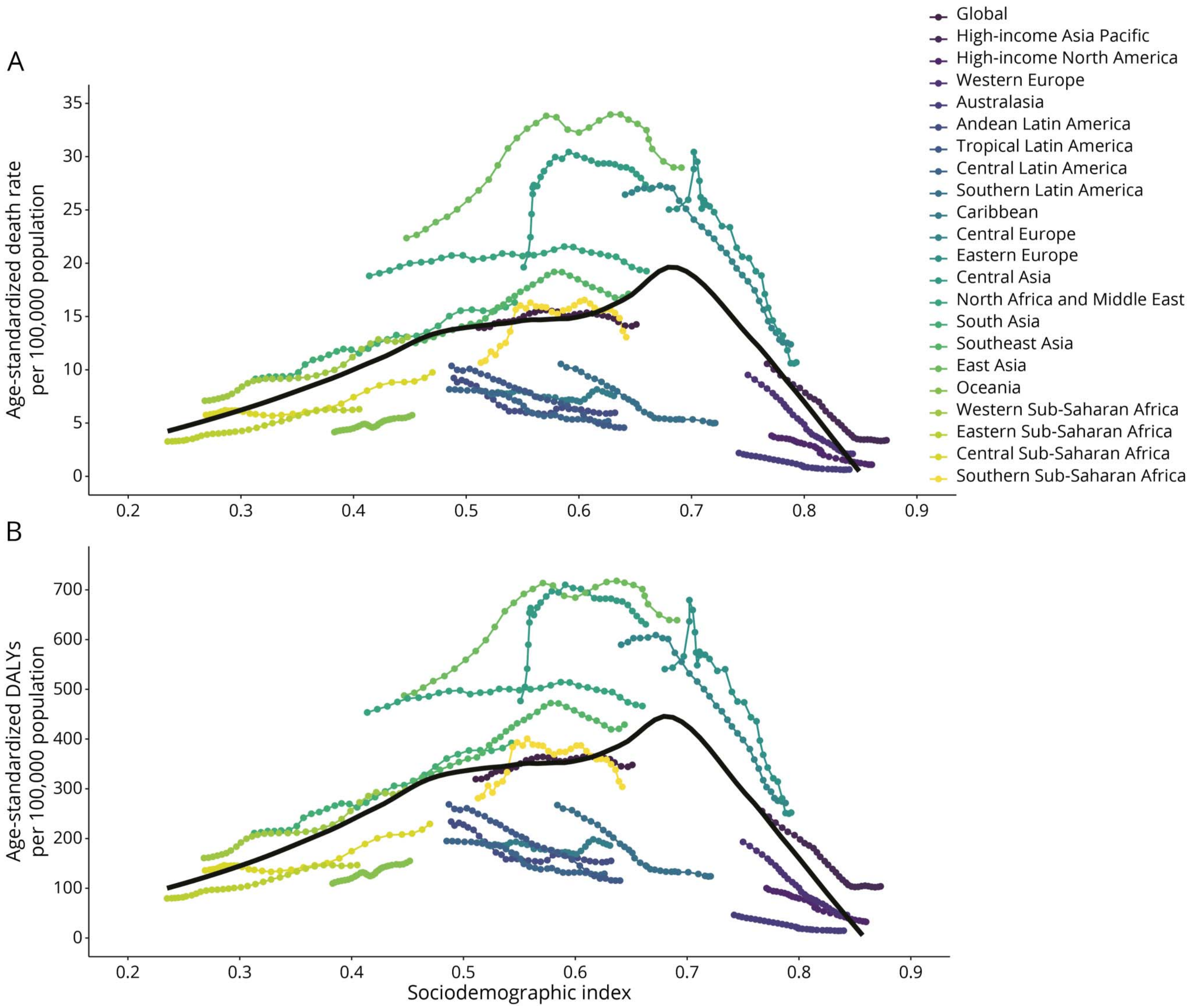
Figure 3 Age-Specific Numbers and Rates of Deaths (A) and DALYs (B) of Stroke Attributable to Ambient Particulate Matter by Sex, in 2019



DALY = disability-adjusted life year; UI = uncertainty interval.

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, whereas a generally linear decreasing trend in high SDI regions (EAPC [95% CI] −4.01 [−4.16 to −3.87] for ASMR and −3.14 [−3.27 to −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 decreasing trend from 1990 to 2014 and became decrease rapidly since 2014 (EAPC [95% CI] −1.27 [−1.55 to −0.99] for ASMR and −1.09 [−1.35 to −0.83] for ASDR, respectively). Similarly, ICH and IS also showed an increasing trend in low, low-middle, and middle SDI regions, but a

Figure 4 Age-Standardized Rates of Stroke Death (A) and DALY (B) Attributable to Ambient Particulate Matter by Sociodemographic Index in 2019



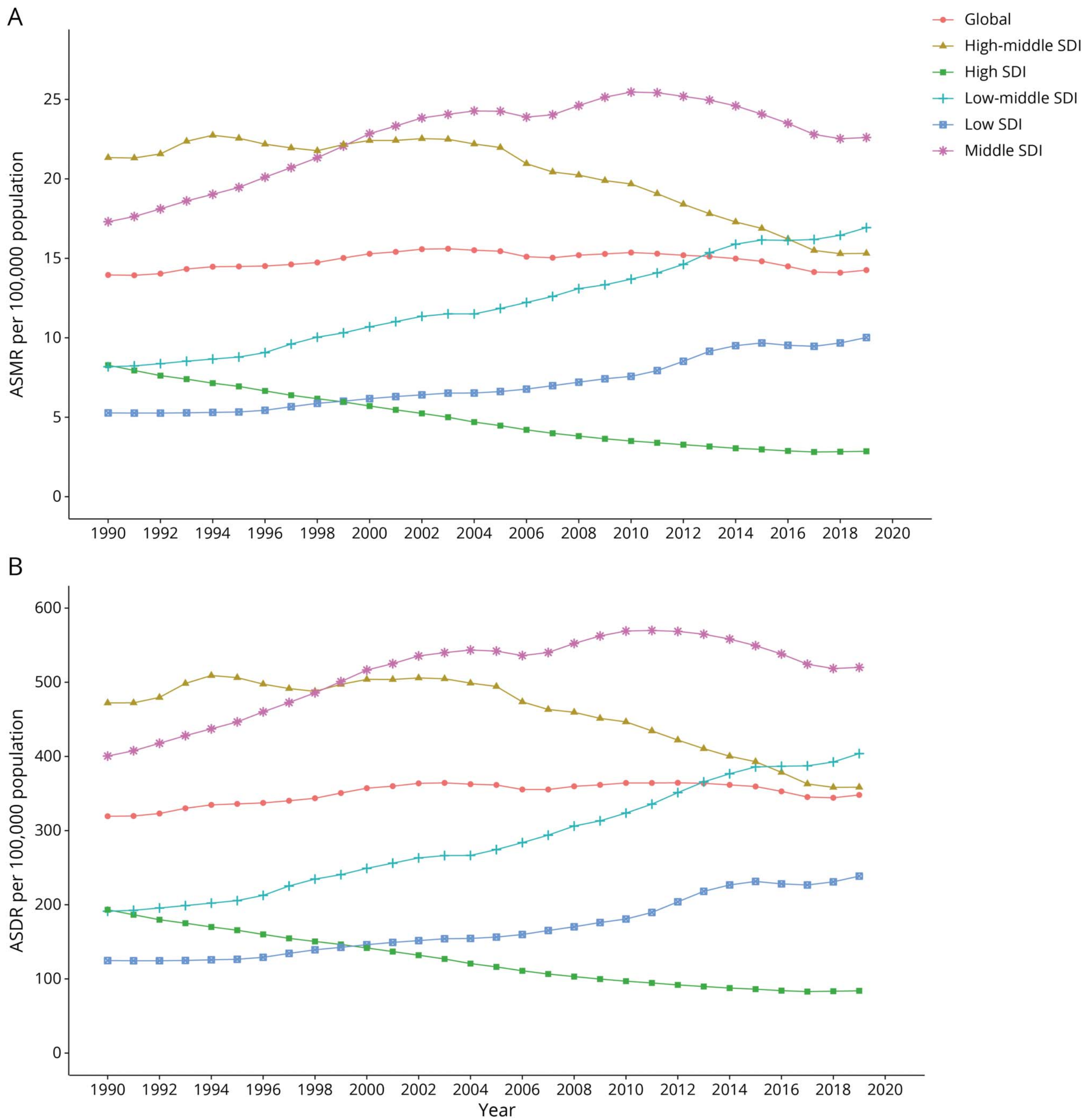
DALY = disability-adjusted life year.

decreasing trend in high and middle-high regions (eTables 1 and 2, links.lww.com/WNL/C943, eFigures 5 and 6, links.lww.com/WNL/C937, links.lww.com/WNL/C938). However, SAH showed an increasing trend in low and low-middle SDI regions, but a decreasing trend in high, middle-high, and middle SDI regions (eTable 3, eFigure 7, links.lww.com/WNL/C939). 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). By contrast, the ASMRs decreased in 10 regions with the largest decrease in Western Europe (EAPC [95% CI] −5.37 [−5.48 to −5.26]), followed by high-income North America (EAPC [95% CI] −4.82 [−5.15 to −4.49]) and Australasia (EAPC [95% CI] −4.77 [−5.03 to −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, links.lww.com/WNL/C943).

Additional information on the EAPCs in ASMR and ASDR of stroke burden attributable to ambient $PM_{2.5}$ from 1990 to 2019

Figure 5 Temporal Trends in ASMR (per 100,000 Population) (A) and ASDR (per 100,000 Population) (B) for Stroke Associated With Ambient Particulate Matter in Global and SDI Regions, 1990–2019



ASDR = age-standardized disability-adjusted life-year rate; ASMR = age-standardized mortality rate; SDI = sociodemographic index.

at the national level is presented in eTable 4 (links.lww.com/WNL/C943) and eFigures 8–10 (links.lww.com/WNL/C940, links.lww.com/WNL/C941, links.lww.com/WNL/C942).

Discussion

This study evaluated 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 male patients than in female patients, 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, whereas 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 increasing trend in 87 and 84 of 204 countries or regions, respectively. However, a decreasing trend was observed in 103 and 104 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 United States demonstrated that every interquartile range increase in the yearly mean ambient $PM_{2.5}$ (3.7 μg/m^3) was associated with a 2.2% (95% CI 1.7%–2.8%) increase in risk of incident stroke.[15] The UK Biobank study suggested that every 5 μg/m^3 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 μg/m^3 increase in daily average ambient $PM_{2.5}$ was associated with 0.34% (95% CI 0.20%–0.48%) increase in hospital admissions for IS.[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 $PM_{2.5}$ 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 $PM_{2.5}$ exposure. What's more, the GBD study used nonlinear risk functions for ambient $PM_{2.5}$ exposure and stroke burden, which were downward concave and monotonically increasing the most biologically plausible shapes of the $PM_{2.5}$ risk curve,[8] thus providing a more accurate estimate for $PM_{2.5}$-related disease burden.

The exact mechanism how $PM_{2.5}$ contributes to stroke remains unclear. Previous studies have suggested that air pollutants can have an adverse effect 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 $PM_{2.5}$ has 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 $PM_{2.5}$ 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 male patients than that in female patients, which was consistent with previous studies.[15,16] Several potential factors can explain the sex heterogeneity of stroke burden attributable to ambient $PM_{2.5}$. First, in comparison with female patients, male patients stay longer outside and had more chance to be exposed to ambient $PM_{2.5}$. Second, male patients had higher ventilation volume and greater particle deposition per unit time, which may lead to male patients being more sensitive to vascular inflammation caused by $PM_{2.5}$.[22] In addition, male patients were more likely being exposed to other stroke-related risk factors, such as smoking and drinking,[3] which could affect 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 increasing 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. Although previous studies suggested that air pollutants can activate systemic inflammation and oxidative stress, leading to endothelial dysfunction,[23,24] 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 increasing trend from 1990 to 2019, whereas 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.[16,25]

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 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 $PM_{2.5}$.[26-28] 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] In addition, 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 inversed 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 was also 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.[29]

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, whereas a decreasing 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. It is more important that 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.[30] Another possible explanation is that less access to health services in low SDI countries may result in underreport of stroke burden,[31,32] 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. Although 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 PM_{10}, NO_2, and SO_2 were not available, it is difficult for us to distinguish whether the observed burden was specifically caused by $PM_{2.5}$ or a combination of the pollutants. Third, $PM_{2.5}$ exposure was estimated using the 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.

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 male patients, 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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