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Global Burden, Risk Factors Analysis, and Prediction Study of Ischemic Stroke, 1990–2030

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Abstract

Purpose: Ischemic stroke (IS), one of the two main subtypes of stroke, occurs due to brain ischemia as a result of thrombosis of a cerebral blood vessel. IS is one of the most important neurovascular causes of death and disability. It is affected by many

risk factors, such as smoking and high body mass index (BMI), which are also critical in the preventive control of other cardiovascular and cerebrovascular diseases. However, there are still few systematic analyses of the current and predicted disease burden, as well as the attributable risk factors for ischemic stroke.

Methods: Based on the GBD2019 database, we used age-standardized mortality rate (ASMR) and disability-adjusted life year (ASDR) to systematically present the geographical distribution and trends of ischemic stroke disease burden worldwide from 1990 to 2019 by calculating the estimated annual percentage change (EAPC), and to analyze and predict the death number of IS accounted by seven major risk factors for 2020-2030.

Results: Between 1990 and 2019, the global number of IS deaths increased from 2.04 million to 3.29 million and is expected to increase further to 4.90 million by 2030. The downward trend was more pronounced in women, young people, and high social-demographic index (SDI) regions. At the same time, a study of attributable risk factors for IS found that two behavioral factors, smoking and diet in high sodium, and five metabolic factors, including high systolic blood pressure, high low-density lipoprotein cholesterol, kidney dysfunction, high fast plasma glucose, and high BMI, are major contributors to the increased disease burden of IS now and in the future.

Conclusions: Our study provides the first comprehensive summary for the last thirty years and the prediction of the global burden of IS and its attributable risk factors until 2030, providing detailed statistics for decision-making on the prevention and control of IS globally. Inadequate control of the seven risk factors would lead to an

increased disease burden of IS in young people, especially in low SDI regions. Our study identifies high-risk populations and helps public health professionals develop targeted preventive strategies to reduce the global disease burden of ischemic stroke.

Keywords

Ischemic stroke; mortality; disability-adjusted life years; estimated annual percentage change; global burden; prediction death cases; age distribution; gender distribution; region distribution; attributable risk factors

Introduction

In the last three decades, the disease pattern in 80% of developing countries is shifting from communicable to noncommunicable diseases, of which stroke is one of the most common debilitating diseases, the second most common cause of death, and the third most common cause of disability-adjusted life-years.[1; 2] Ischemic stroke (IS), accounts for 70% of all strokes, and has a high risk of long-term recurrence. In 2019, the total number of ischemic stroke-related deaths reached 3.29 million, accounting for 50.3% of stroke deaths and 17.7% of all cardiovascular disease-related deaths, making the prevention of ischemic stroke particularly important.[3-5]

Rapid economic development, social progress, changes in social ideology, and population aging has resulted in an increased prevalence of behavioral and metabolic risk factors for cardiovascular disease such as smoking, diet in high sodium, high systolic blood pressure (SBP), high low-density lipoprotein cholesterol (LDL-c), kidney dysfunction, high fast plasma glucose (FPG), and high body mass index (BMI). This has led to a significant increase in morbidity and mortality from cardiovascular

and cerebrovascular diseases, including ischemic stroke.[6-9] A stroke analysis based on the Global Burden of Disease (GBD) 2019 database found that the annual number of strokes and deaths due to stroke increased substantially from 1990 to 2019, despite substantial reductions in age-standardized rates, particularly among people older than 70 years, low-income, and high body-mass index.[10] However, there are fewer studies on ischemic stroke and there is a lack of predictive studies on the number of future deaths attributable to risk factors. To further understand the changing trends of ischemic stroke and to identify the population at high risk of ischemic stroke and its attributable risk factors, our study used mortality and disability-adjusted life years of ischemic stroke within different regions, ages, genders, and risk factors of 204 countries and territories from 1990 to 2019 in GBD 2019 report database to systematically analyze the burden of ischemic stroke and to predict the number of deaths caused by risk factors from 2020 to 2030. A comprehensive and up-to-date study of the disease burden, epidemiological characteristics, and associated metabolic, environmental, and behavioral risk factors for ischemic stroke would be highly beneficial to public health professionals as they develop effectively and targeted preventive strategies for reducing the global disease burden from ischemic stroke.[11]

Methods

Study data

The Socio-Demographic Index (SDI) for 204 countries and territories is classified into five regions based on quintiles: low, low-middle, middle, high-middle, and high.[12; 13] The SDI is closely related to health outcomes and is a composite

indicator for assessing development conditions. It is the geometric mean of the lag distributed income per capita (LDI), the total fertility under 25 years old (TFU25), and the average education level of people aged 15 and over (EDU15+), with possible values ranging from 0 to 1.[14] The world is divided into 21 regions based on geographical location.

Considering the poor prognosis of patients with ischemic stroke, our study used the following parameters to quantify the mortality and disability trends of ischemic stroke: age-standardized mortality rate (ASMR), age-standardized disability-adjusted life year (ASDR), and estimated annual percentage change (EAPC).[15] The ASMR (95% uncertainty interval [UI]) and ASDR (95% UI) stratified by sex, country, and region, and the number of death and disability-adjusted life year by age group from 1990 to 2019 were obtained from the Global Health Data Exchange (GHDx) query tool. Additional data are listed in eMethods in the Supplement.

Statistical analysis

Age-standardized rates are estimated using the GBD world population age standard as a reference, following the method described by Ahmad et al 2001.[16] Direct standardization yields an age-adjusted rate which is a weighted average of age-specific rates. The weighting is intended to represent the relative age distribution. This single aggregated rate reflects the number of events that would be expected to occur in a population with the same age distribution. The direct age-standardized rate is calculated using the following formula:[17]

$$ASR = \frac{\sum_{i=1}^{A} a_i \omega_i}{\sum_{i=1}^{A} \omega_i} \times 10{,}000,$$

where a_i and ω_i denote age-specific rates and the number of persons (or weight) in the same age subgroup of the chosen reference standard population (where *i* denotes the *ith* age class).

Importantly, ASR trends can provide clues to evolving risk factors and shifts in disease patterns.[18] The EAPC is a good indicator for assessing ASR trends. In calculating EAPC from ASR, the calendar year is used as the independent variable to fit a regression line to the natural logarithm of ASR. The formula that was used was:

$$y = a + bx + \varepsilon,$$

where $y = ln\,(ASR)$ and $x = calendar\ year$. And there is $EAPC = 100 \times (exp\,(\beta) - 1)$, where β is the estimated value of the slope b. We also used the above formula to calculate the 95% confidence interval (CI), obtained from the fitted regression line.[19] If the estimation of EAPC and its lower boundary of 95% CI were both > 0, the ASR was considered to be on the rise. In contrast, if the estimation of EAPC and its upper boundary of 95% CI were both < 0, the ASR was considered to be on a downward trend. In addition, EAPC < 0 but its upper boundary of 95% CI > 0, or EAPC > 0 but its lower boundary of 95% CI < 0, that is, the ASR is considered to be on a stable trend when it contains 0 between EAPC and its upper or lower boundary of 95% CI.

Considering that the death registration information is more stable and reliable than incidence registration, the Pearson correlation coefficient between ASMR, ASDR, EAPC, and SDI was calculated.[20] If the Pearson correlation coefficient was < 0 and the *P-value* was ≤ 0.05, there was a significant negative correlation between the two

variables.

Bayesian Age-Period-Cohort (BAPC) is a method for analyzing and predicting trends in disease burden by applying Bayesian formulas to calculate hypothetical probability distributions based on three factors: age, period, and cohort, and combining a priori and sample information to derive posterior information. Compared to methods that estimate the overall parameters from sample statistics only, BAPC is more flexible in the choice of parameters and prior probability distributions, and the predictions are more robust and reliable. We used the absolute percentage deviation (APD) to evaluate the performance of the Bayesian age-period-cohort (BAPC) model.[21; 22] We divided the global death cases dataset into a training set (data from 1990 to 2012) and a test set (data from 2013 to 2019). The APD can be calculated as $(\hat{Y} - Y)/Y \times 100$, where $\hat{Y}$ denotes the predicted value and Y denotes the observed value. We calculated the APD of the BAPC model is 4.11%. The BAPC model has been shown to have a relatively low absolute percentage bias, so we chose it to predict IS deaths by 2030.[23] The APC model [24] assumes that there is a multiplicative effect of age, period, and cohort:

$$Y_{ap} = \mu' \alpha'_a \beta'_p \gamma'_c$$

where Y_{ap} denotes incident case counts, α'_a denotes age effect, β'_p denotes period effect, and γ'_c denotes cohort effect. We used a=1, . . ., A to represent age groups, p=1, . . ., P to represent observation periods, and $c = 5 \times (A - a) + p$ to represent birth cohorts (in this study, A=18, P=30). By using logarithms, this model can be transformed into an additive model:

$$\log(Y_{ap}) = \mu + \alpha_a + \beta_p + \gamma_c$$

where μ, α_a, β_p and γ_c are the logarithms of μ', α'_a, β'_p, and γ'_c, respectively. Here we focus on the prediction of Y_{ap}. The identifiability problem of APC models, therefore, does not affect our estimation.[24] We performed a BAPC analysis with an integrated nested Laplace approximation (INLA). To ensure smoothing, the BAPC model assumes independent mean-zero normal distributions on the second differences of all effects. Specifically, the BAPC model assumes the prior distribution of age effect as follows:[23]

$$f(\alpha|k_\alpha) \propto k_\alpha^{\frac{t-2}{2}} \exp\{-\frac{k_\alpha}{2}\sum_{i=3}^{I}[(\alpha_i - \alpha_{i-1}) - (\alpha_{i-1} - \alpha_{i-2})]^2\}$$

As we are interested in the incident case counts for age group *a*, with a *t* period into the future, the following equation can be applied:

$$\log(Y_{a,p+t}) = \mu + \alpha_a + \beta_{p+t} + \gamma_{c+t} + \delta_{a,p+t}$$

We added an independent random effect $\delta_{a,p+t} \sim N(0, k_\delta^{-1})$ to adjust for overdispersion.[25] Considering the smoothing assumption, the BAPC models assume the prior distribution of the period effect as follows:

$$\beta_{p+t}|\beta_1, \ldots, \beta_p, k_\beta \sim N\{(1+t)\beta_p - t\beta_{p-1}, k_\beta^{-1}(1 + 2^2 + \cdots + t^2)\}$$

All statistics were calculated using the R program (Version 3.6.1).

Standard Protocol Approvals, Registrations, and Patient Consents

The data used in our study came from the GBD database (https://vizhub.healthdata.org/gbd-results/), which is an open-source database without any personal data, so this study was exempt from ethics board review board approval and informed consent of individuals.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

1. Global trends in the distribution of disease burden of ischemic stroke ASMR and ASDR in different regions

Overall, the burden of ischemic stroke decreased over time in most countries, with the burden from ischemic stroke-related deaths in developing regions exceeding that in developed regions. However, it is noteworthy that a small number of developing countries, such as North Macedonia, had a significant upward trend in ASMR and ASDR. In 2019, the highest ASMR and ASDR of ischemic stroke are concentrated in Central Europe, such as North Macedonia (ASMR=205.77/100,000, 95% UI: 172.68/100,000, 240.49/100,000; ASDR=2856.22/100,000, 95% UI: 2411.17/100,000, 3340.97/100,000), and Serbia (ASMR=137.15/100,000, 95% UI: 116.16/100,000, 160.66/100,000; ASDR=1970.97/100,000, 95% UI: 1674.85/100,000, 2323.13/100,000) (Figure 1, A and B).

Globally, ASMR and ASDR declined in the vast majority of countries and territories from 1990 to 2019. However, there are still a few countries and territories with a significant upward trend in ASMR and ASDR, mainly concentrated in Central Asia, such as Azerbaijan ($EAPC_{ASMR}$=2.941, 95% CI: 2.423, 3.461; $EAPC_{ASDR}$=1.822, 95% CI: 1.412, 2.233) and Tajikistan ($EAPC_{ASMR}$=2.531, 95% CI: 1.927, 3.138; $EAPC_{ASDR}$=2.086, 95% CI: 1.670, 2.505) (Table1 and Figure 1, C and D). All upward

trends in ASDR were concentrated in areas with moderate or below SDI.

2. Characteristics of the distribution of ischemic stroke disease burden in different gender and age groups

Globally, the absolute number of deaths from ischemic stroke has increased over the past few decades in both men and women and 16 age groups. Among them, ischemic stroke-related mortality is higher in men than in women, and the gender difference in the overall burden of ischemic stroke may increase further. The number of ischemic stroke deaths in 2019 reached 1,570,000 (95% UI: 1,420,000, 1,710,000) in males and 1,72 0,000 (95% UI: 1,500,000, 1,890,000) in females, respectively. Similarly, ASMR and ASDR at the global and regional levels were higher in men than in women, and the decreasing speed was more pronounced in women than in men. The highest ASMR and ASDR in 2019 were in Eastern Europe for both men and women ($ASMR_{male}$= 111.49, 95%UI: 97.19, 125.47; $ASMR_{female}$= 91.45, 95%UI: 78.50, 103.57; $ASDR_{male}$= 1,978.65, 95% UI: 1,724.07, 2,242.97; $ASDR_{female}$= 1,447.36, 95% UI: 1,269.23, 1,640.56). The decreasing trend in ASMR and ASDR was more pronounced in females than in males in the vast majority of regions worldwide from 1990 to 2019, among them, the highest decrease of ASMR in both genders is High-income Asia Pacific ($EAPC_{male}$= -4.541, 95% CI: -4.705, -4.376; $EAPC_{female}$= -5.127, 95% CI: -5.381, -4.872), and the highest decreasing of ASDR in females is High-income Asia Pacific ($EAPC_{female}$= -3.847, 95% CI: -3.986, -3.708) and in males is Australasia ($EAPC_{male}$= -4.123, 95% CI: -4.371, -3.874). However, it is noteworthy that four regions had a higher ASMR and ASDRs in females, such as

high-income North America (ASMR $_{male}$=15.38, ASMR $_{female}$=16.72; ASDR $_{male}$= 339.78, ASDR $_{female}$= 358.35), and five regions had a higher increasing trend in ASMR and ASDRs in both gender, such as Southeast Asia (EAPC $_{ASMR\text{-}male}$=0.428, 95% CI: 0.304–0.551; EAPC $_{ASDR\text{-}male}$= 0.422, 95% CI: 0.331–0.513; EAPC $_{ASMR\text{-}female}$= 0.283, 95% CI: 0.131–0.436; EAPC $_{ASDR\text{-}female}$= 0.131, 95% CI: 0.022–0.240). Additional data are listed in eFigure 1 in the Supplement.

Premature death due to ischemic stroke was more severe in developing countries and regions than in developed countries and regions. The global ischemic stroke burden tended to increase with age, particularly in the 80 years and older age group. Notably, there was a trend toward younger ischemic stroke in regions with low levels of SDI. Globally, the number of deaths from ischemic stroke increased across age groups, with the highest increasing trend in the 90 to 94 age group (EAPC = 1.133, 95% CI: 0.895, 1.371, Figure 2A). In low SDI regions, the highest increasing trend of deaths was observed in the 40 to 44 age group (EAPC= 0.777, 95% CI: 0.629, 0.925, Figure 2B). In low-middle SDI regions, the highest increasing trend in ischemic stroke was the 90 to 94 age group (EAPC=1.301, 95% CI: 1.116, 1.487, Figure 2C). In the middle SDI regions, the 85 to 89 age group showed the highest increasing trend (EAPC= 1.360, 95% CI: 1.293, 1.428, Figure 2D). And in the high-middle SDI and high SDI regions, the highest increasing trend of deaths was observed both in the 90 to 94 age group (EAPC= 1.882, 95% CI: 1.483–2.283; EAPC=2.527, 95% CI: 2.326–2.729, Figure 2, E and F).

3. Distribution characteristics of ischemic stroke disease burden in regions with different SDI levels

We studied the distribution characteristics of ASMR, ASDR, and their EAPC at different SDI levels. ASMR and ASDR and their EAPC were significantly and negatively correlated with SDI levels in 2019 (ρ = -0.183, p = 0.008; ρ = -0.217, p = 0.002), and from 1990 and 2019 (ρ = -0.662, p = 2.2e-16; ρ = -0.644, p = 2.2e-16). Regions with higher levels of SDI had a smaller upward trend and a larger downward trend in ischemic stroke disease burden (Figure 3).

4. Trends in the death burden from ischemic stroke due to inadequate control of seven risk factors

Much of the burden from cardiovascular and cerebrovascular disease is attributable to metabolic, behavioral, environmental, and occupational risk factors. In this study, the behavioral and metabolic factors of smoking, diet in high sodium, high BMI, high systolic blood pressure, high LDL cholesterol, kidney dysfunction, and high fasting plasma glucose were the top seven risk factors for increased death and disability from an ischemic stroke. There was an increasing trend in disease burden due to these risk factors, with a more pronounced increase in ASMR and ASDR from high BMI and high fasting plasma glucose. From 1990 and 2019, the rising trend in the burden from an ischemic stroke caused by seven risk factors was significantly higher in regions with low levels of SDI than in regions with high levels of SDI. There was also a significant trend toward younger age groups, which we defined as people aged 15-59 years.

Among younger age groups, the rising trend in ASMR and ASDR caused by smoking occurred mainly in Southeast Asia; the rising trend caused by high sodium diet occurred mainly in South Asia, high-income North America, and Oceania; the rising trend due to high LDL cholesterol occurred mainly in North Africa and Middle East; the rising trend due to kidney dysfunction occurred mainly in low SDI, North Africa and Middle East, and Southeast Asia; the rising trend due to high systolic blood pressure occurred mainly in low-middle SDI regions and 4 regions; the rising trend due to high fasting plasma glucose occurred mainly in low SDI, low-middle SDI, middle SDI, and 4 regions; the rising trend due to a high BMI occurred mainly in low SDI, low-middle SDI, and middle SDI regions and 7 regions. In addition, we show separately some regions with less variation in ischemic stroke burden. Additional data are listed in eFigure 2 and eFigure 3 in the Supplement.

Among them, the number of deaths caused by smoking increased in three elderly population groups, including 90 to 94, 85 to 89, and 80 to 84, and one youth population group (50 to 54, Figure 4B); the number of deaths caused by high sodium diet increased in four elderly population groups, including 90 to 94, 85 to 89, 80 to 84, and 75 to 79(Figure 4C); the number of deaths caused by high LDL cholesterol increased in two elderly population groups, including 90 to 94, and 85 to 89(Figure 4D); the number of deaths caused by kidney dysfunction increased in three elderly population groups, including 90 to 94, 85 to 89, and 80 to 84, and one youth population group (50 to 54, Figure 4E); the number of deaths caused by high systolic blood pressure increased in two elderly population groups, including 90 to 94, and 85

to 89, and two youth population group (50 to 54 and 45 to 49, Figure 4F); the number of deaths caused by high fasting plasma glucose increased in two elderly population groups, including 90 to 94, and 85 to 89(Figure 4G); the number of deaths caused by high BMI increased in two elderly population groups, including 90 to 94, and 85 to 89, and eight youth population group, such as 20 to 24(Figure 4H).

5. Predicted trends in the number of ischemic stroke deaths caused by seven risk factors from 2020 to 2030

This study used the BAPC model to predict that the number of ischemic stroke deaths caused by the seven risk factors will continue to increase globally over the next 10 years from 2020 to 2030. From 1990 to 2019, the number of ischemic stroke deaths caused by the 7 risk factors increased globally from 2,049,600 in 1990 to 3,293,300 in 2019. This study predicts a further increase to 4,909,300 in 2030 (95% CI: 2,312,900, 7,505,600) (Figure 5A). The number of ischemic stroke deaths caused by smoking will increase to 552,400 (95% CI: 301,500, 803,300) in 2030 (Figure 5B), a diet high in sodium to 424,800 (95% CI: 259,200, 590,400) (Figure 5C), high LDL cholesterol to 917,300 (95% CI: 388,100, 1,446,600) (Figure 5D), kidney dysfunction to 351,600 (95% CI: 211,700, 491,500) (Figure 5E), high systolic blood pressure to 2,408,900 (95% CI: 1,066,900, 3,750,900) (Figure 5F), high fasting plasma glucose to 1,463,400 (95% CI: 580,400, 2,346,400) (Figure 5G), and high BMI to 670,700 (95% CI: 218,200, 1,123,300) (Figure 5H). In addition, we calculated the combined effect of the 7 risk factors and showed that by 2030, the number of deaths from ischemic stroke under the combined effect of the 7 risk factors reached 6,415,240(2,721,922,

10,108,567). Additional data are listed in eTable 1 and eFigure 4 in the Supplement.

Discussion

This study is the first systematic and comprehensive description of the disease burden of ischemic stroke worldwide based on the 2019GBD dataset and presents the global disease burden and its fraction attributable to inadequate control of risk factors for different levels of SDI and geographic region, sex, and age group, over thirty years from 1990 to 2019, in addition to predicting the situation from 2020 to 2030. Overall, the absolute number of deaths due to ischemic stroke worldwide increased from 2.04 million in 1990 to 3.29 million in 2019, and our prediction analysis indicates that this number could increase to 4.9 million in 2030; however, ASMR and ASDR for ischemic stroke showed consistent downward trends over time, suggesting that population growth and aging are largely responsible. In general, the burden of ischemic stroke-related deaths is consistent with the trend in the total burden of CVD; however, smoking, diets in high sodium, and metabolic risk factors in countries and regions with low levels of SDI have contributed to a notable steady shift in the disease burden of ischemic stroke toward younger people in developing countries.

At the global and regional levels, the disease burden from ischemic stroke in developing regions far exceeded that in developed regions. Interestingly, the trend toward increased ischemic stroke in younger people was more pronounced in areas where SDI was lower. These trends suggest that unequal access to health care and poorer healthcare facilities in developing countries contribute to inferior prognosis in patients with ischemic stroke and increased disease burden,[26-29] consistent with

previous studies showing that most countries in Eastern Europe are predicted to have a higher stroke burden in the future relative to more developed countries in the European Union.[30] To address the critical situation regarding premature death from ischemic stroke in areas with low SDI levels, prevention strategies for populations at risk for ischemic stroke should be strengthened, and feasible, effective, and affordable clinical management of ischemic stroke provided.[3]

Over recent decades, rates of death and disability associated with ischemic stroke have been higher in men than those in women, and there has also been a more pronounced downward trend in women than in men, with the difference likely to increase further in the future. Previous studies have demonstrated that risk factors for ischemic stroke, such as smoking, are more frequent in men than in women, and that the incidence of ischemic stroke due to chronic inflammatory vascular disease, such as atherosclerosis, is higher for men than women; these direct and indirect factors contribute to the sex differences in ischemic stroke.[31-33] Several aging-related brain changes are associated with increased susceptibility to ischemic stroke in older adults. In addition, differences in risk factors for ischemic stroke and in the mechanisms of ischemic injury between young and older patients mean that older patients with ischemic stroke are less responsive to treatment, and consequently have a worse prognosis.[34] Notably, the trend toward increasing ischemic stroke is greater in women in some regions. Unlike men, women often have "atypical" stroke symptoms, and the lack of these "atypical" strokes among women, resulting in a delay in their admission, diagnosis, and treatment, is likely the reason for the higher burden of

ischemic stroke among women in these regions.[35]

We also examined seven attributable risk factors that were associated with ischemic stroke death, including metabolic risk factors (high BMI, high systolic blood pressure, high LDL cholesterol, kidney dysfunction, and high fasting plasma glucose) and behavioral factors (smoking and diet in high sodium). We found that the death burden from ischemic stroke due to inadequate control of these risk factors occurred primarily in older patients (> 80 years old) and in areas with lower SDI levels, while the increases in ischemic stroke due to high fasting plasma glucose and high BMI were particularly pronounced in the younger population. The premature appearance of various risk factors in recent years, due to improved social living standards, has contributed to ischemic stroke in younger patients.[36-39] A cohort study of 10 regional populations in China showed that individuals with a high BMI were at an increased risk of stroke.[40] Further, a meta-analysis of 13 large prospective studies of Western patients revealed a 45% increased risk of cardiovascular disease in individuals with a high BMI.[41] High triglyceride-glucose index levels have also been associated with subclinical cerebral small vessel disease.[42] These results support the hypothesis that high BMI and high fasting plasma glucose are independent risk factors for cerebrovascular disease. The most effective and cost-saving strategy for successfully reducing ischemic stroke-related mortality is to specifically target these risk factors. Controlling the excess burden of death due to high fasting glucose and high BMI should therefore be a global priority.

Our study applied the BAPC model to predict that ischemic stroke deaths will

continue to increase over the next 10 years (2020 to 2030), due to the seven aforementioned attributable risk factors, with particularly significant increases in ischemic stroke deaths due to high LDL cholesterol, high fasting glucose, and high BMI. The potential effects of obesity on the cerebrovascular system include an overload of the structural and functional adaptations of the cerebrovascular system and the effects of adipokines on inflammation and vascular homeostasis. Other stroke risk factors mediate the effects of obesity on the cerebrovascular system, such as dyslipidemia, hypertension, insulin resistance, and hyperglycemia.[43; 44] These cerebrovascular abnormalities usually include both local and systemic changes. Local abnormalities include impaired mitochondrial function, inflammation, hypoxia, and dysregulation of adipokine secretion. Systemic abnormalities include hypertension, abnormal glucose and lipid metabolism, insulin resistance, pro-inflammatory and pro-thrombotic states, and endothelial dysfunction.[45; 46] All of these factors represent mechanisms linking the associations of high LDL cholesterol, high BMI, and high fasting plasma glucose with ischemic stroke. In conclusion, ischemic stroke remains a global public health problem, with the burden of death concentrated in developing countries with low SDI levels. The population in need of priority management is the older adult population; however, the rising trend in ischemic stroke among younger patients cannot be ignored, and those countries and regions at increased risk should implement national strategies to control key risk factors.

Although ischemic stroke is largely preventable, as indicated by the global decline in its incidence, it remained the third leading cause of death and disability

from CVD in 2019. The rising trend in the burden from ischemic stroke caused by attributable risk factors is more pronounced in some developing countries, where the burden from ischemic stroke is high and mortality increased from 1990 to 2019. This suggests that current strategies and measures for the prevention of ischemic stroke are inapplicable or inadequate in these areas, and that universal primary prevention strategies must be implemented worldwide. Without more population-level stroke and cardiovascular disease prevention strategies, the stroke burden is likely to continue to increase, especially in low- and middle-income countries.

To our knowledge, this is the first comprehensive and systematic retrospective summary and prospective prediction study of the global burden of ischemic stroke and its attributable risk factors over a four-decade period until 2030; however, the study has some limitations. First, the low coverage of disease reporting institutions in underdeveloped regions resulted in poor data quality, especially in countries where a lack of original, high-quality epidemiological studies of ischemic stroke affected data quality. In addition, the inability of population data to provide information that individual data can explore, such as interactions between risk factors, limits to some extent the conformity between the results and the true situation. Second, we were unable to obtain data on exposure patterns and distributions of potentially important risk factors, which would facilitate a more detailed analysis of ischemic stroke and allow clearer attribution of changes in the resulting disease burden to population aging or changes in risk factors. Finally, the prediction methods used in our study were based on estimates, rather than observations of ischemic stroke from 1990 to 2019;

hence, the results may be biased by these mathematical methods and should be interpreted with appropriate caution. Nevertheless, our study used the latest information and advanced prediction methods to provide a more comprehensive understanding of trends in ischemic stroke.

This study has important practical implications for global, regional, and national estimates of the burden of ischemic stroke, and provides further analysis of regional differences in attributable risk factors, which will help to better target the identification of high-risk populations. Our findings have implications for the allocation of care resources, health care planning, and the development and implementation of primary prevention interventions for stroke that require support from data, primarily including the reduction of metabolic risk factors (e.g., blood glucose and weight screening and management) and behavioral risk factors (e.g., smoking cessation and improving poor dietary habits). In addition, at the national level, the reduction of poverty and racial and socio-economic inequalities through appropriate measures, such as legislation and taxation, will be important to reduce cardiovascular disease, as well as other non-communicable diseases.

WNL-2023-000238_sup --- http://links.lww.com/WNL/C802

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Table 1. Global ASMR and ASDR of ischemic stroke and their EAPC by gender, age, etiology, SDI level, and region

Characteristics	ASMR/Death Rate (95% UI)		ASDR/Disability adjusted life years (95% UI)		EAPC (95% CI)	
	per 100,000 in 1990	per 100,000 in 2019	per 100,000 in 1990	per 100,000 in 2019	ASMR/Death Rate (1990-2019)	ASDR/Disability adjusted life years (1990-2019)
Overall	65.54(59.89, 71.30)	43.5(39.08, 46.77)	1117.21(1,038.94, 1,202.88)	798.81(727.51, 866.89)	-1.628(-1.723, -1.532)	-1.343(-1.427, -1.258)
Sex						
Male	68.15(63.24, 75.76)	48.44(43.68, 52.55)	1171.74(1,083.49, 1,284.96)	878.51(793.52, 956.67)	-1.320(-1.390, -1.251)	-1.126(-1.196, -1.056)
Female	62.73(56.43, 67.67)	39.12(34.25, 43.01)	1062.36(971.82, 1,145.19)	726.33(648.67, 798.32)	-1.896(-2.013, -1.780)	-1.543(-1.641, -1.444)
Age						
15 to 44 years	6.46(5.77, 7.73)	5.31(4.67, 6.06)	618.59(514.16, 745.83)	558.57(456.17, 675.03)	-0.849(-0.947, -0.753)	-0.444(-0.497, -0.391)
45 to 59 years	54.58(50.05, 62.09)	38.44(34.41, 42.65)	2489.24(2237.12, 2795.58)	1925.38(1689.20, 2170.18)	-1.361(-1.483, -1.239)	-0.989(-1.076, -0.903)
60 to 74 years	570.58(530.48, 634.17)	388.03(356.79, 418.36)	14395.38(13327.53, 15723.78)	10474.11(9544.93, 11468.37)	-1.707(-1.904, -1.509)	-1.429(-1.585, -1.274)
75 to 94 years	6715.92(5847.45, 7282.45)	4413.18(3758.57, 4818.18)	67318.77(59828.29, 72615.26)	45894.44(39932.98, 49852.05)	-1.682(-1.776, -1.589)	-1.498(-1.572, -1.424)
Risk						
Smoking	8.05(7.39, 8.89)	4.89(4.35, 5.43)	185.31(168.58, 204.85)	120.37(107.05, 134.73)	-1.976(-2.108, -1.844)	-1.724(-1.839, -1.670)
Diet high in sodium	5.2(1.45, 11.51)	3.65(0.93, 8.04)	110.03(35.89, 224.66)	82.89(24.78, 168.37)	-1.358(-1.428, -1.289)	-1.116(-1.184, -1.048)
High systolic blood pressure	31.6(23.74, 40.22)	20.53(15.41, 26.10)	563.2(444.68, 680.76)	403.74(318.26, 487.77)	-1.715(-1.808, -1.623)	-1.345(-1.427, -1.262)
High LDL cholesterol	13.29(4.33, 28.03)	8.08(2.80, 16.97)	249.17(130.57, 438.65)	170.21(92.80, 294.74)	-1.959(-2.050, -1.869)	-1.517(-1.598, -1.436)
Kidney dysfunction	4.4(2.60, 6.16)	3.29(1.97, 4.64)	88.86(64.42, 114.68)	72.17(52.71, 93.11)	-1.153(-1.251, -1.054)	-0.834(-0.918, -0.750)
High body-mass index	5.65(2.77, 9.15)	4.61(2.50, 7.29)	138.76(75.23, 215.10)	132.05(80.14, 195.95)	-1.057(-1.201, -0.913)	-0.456(-0.564, -0.347)
High fasting plasma glucose	10.87(5.28, 23.05)	9.56(4.55, 20.78)	182.29(95.92, 344.33)	173.97(90.51, 316.30)	-0.525(-0.672, -0.379)	-0.255(-0.393, -0.118)
Socio-demographic index						
Low	42.86(32.31, 54.87)	40.12(33.13, 48.98)	772.55(624.54, 958.19)	720.34(610.62, 867.08)	-0.241(-0.311, -0.170)	-0.264(-0.307, -0.221)
Low-middle	50.92(42.77, 60.77)	46.26(41.17, 51.32)	879.26(758.65, 1,046.63)	816.32(733.23, 904.22)	-0.391(-0.509, -0.272)	-0.299(-0.376, -0.221)
Middle	59.57(53.46, 69.18)	53.21(46.88, 58.74)	1088.62(993.06, 1,239.26)	982.89(881.86, 1,084.73)	-0.328(-0.440, -0.215)	-0.302(-0.371, -0.232)
High-middle	97.62(90.48, 102.64)	57.34(51.31, 62.08)	1609.81(1,515.40, 1,691.81)	993.5(901.35, 1,076.67)	-2.241(-2.454, -2.027)	-2.061(-2.271, -1.851)

High	48.82(44.28, 51.15)	19.36(16.37, 20.93)	798.05(736.47, 849.49)	371.79(327.55, 413.68)	-3.599(-3.791, -3.407)	-2.928(-3.089, -2.766)
Region						
High-income Asia Pacific	62.01(55.42, 65.58)	17.63(14.12, 19.67)	968.39(884.55, 1,032.17)	352.82(303.27, 401.33)	-4.755(-4.966, -4.544)	-3.850(-4.023, -3.677)
Central Asia	77.99(70.95, 87.30)	79.43(71.94, 86.85)	1447.49(1,320.55, 1,627.34)	1386.79(1,269.80, 1,515.23)	-0.284(-0.619, 0.052)	-0.505(-0.839, -0.171)
East Asia	64.08(56.35, 76.13)	61.03(52.42, 69.14)	1195.91(1,063.63, 1,399.61)	1135.03(997.93, 1,284.34)	-0.075(-0.252, 0.102)	-0.116(-0.236, 0.005)
South Asia	45.61(35.51, 58.83)	35.23(29.96, 40.94)	751.08(602.73, 958.04)	605.29(521.10, 706.71)	-1.172(-1.410, -0.934)	-0.952(-1.099, -0.804)
Southeast Asia	62.64(54.36, 71.15)	65.16(56.18, 72.43)	1139.49(995.56, 1,295.60)	1175.56(1,018.24, 1,313.00)	0.356(0.220, 0.493)	0.277(0.182, 0.372)
Australasia	44.74(39.72, 47.37)	17.49(14.47, 19.47)	658.37(602.28, 701.65)	260.33(226.32, 290.68)	-3.692(-3.885, -3.498)	-3.563(-3.777, -3.349)
Caribbean	47.94(42.76, 52.36)	38.5(33.00, 44.30)	807.49(733.34, 892.77)	662.02(575.72, 760.20)	-0.681(-0.794, -0.568)	-0.607(-0.727, -0.488)
Central Europe	110.3(102.54, 114.86)	66.65(58.08, 74.56)	1854.04(1,749.05, 1,944.21)	1087.72(953.98, 1,213.31)	-2.071(-2.275, -1.867)	-2.167(-2.348, -1.986)
Eastern Europe	155.44(146.07, 160.29)	100.14(88.29, 109.84)	2556.59(2,437.97, 2,653.61)	1667.98(1,502.07, 1,837.63)	-2.303(-2.779, -1.823)	-2.216(-2.684, -1.745)
Western Europe	58.67(53.29, 61.52)	20.6(17.62, 22.39)	850.4(789.10, 893.41)	309.64(275.76, 336.74)	-4.011(-4.230, -3.791)	-3.810(-4.025, -3.594)
Andean Latin America	31.04(26.69, 35.24)	18.77(15.33, 22.68)	525.98(457.90, 593.35)	316.29(268.40, 375.29)	-1.767(-1.965, -1.569)	-1.862(-2.082, -1.641)
Central Latin America	35.8(32.32, 38.03)	19.93(16.81, 22.92)	602.14(559.28, 639.96)	340.17(297.82, 385.12)	-2.241(-2.408, -2.075)	-2.179(-2.358, -1.999)
Southern Latin America	49.03(43.96, 52.99)	24.83(21.81, 27.05)	799.61(727.80, 869.36)	404.42(366.65, 440.48)	-2.409(-2.595, -2.221)	-2.434(-2.606, -2.261)
Tropical Latin America	79.09(71.63, 83.38)	33.98(29.68, 36.65)	1318.43(1,230.00, 1,386.46)	561.21(511.41, 599.69)	-2.869(-3.021, -2.717)	-2.956(-3.108, -2.804)
North Africa and Middle East	69.24(60.36, 77.54)	62.92(56.28, 69.93)	1297.09(1,167.48, 1,444.89)	1183.57(1,060.85, 1,307.04)	-0.158(-0.254, -0.062)	-0.161(-0.252, -0.072)
High-income North America	30.19(26.87, 31.92)	16.36(13.96, 18.01)	565.07(509.09, 617.36)	351.61(303.26, 303.26)	-2.591(-2.824, -2.357)	-1.838(-1.979, -1.697)
Oceania	34.99(26.51, 46.51)	34.63(27.76, 44.74)	749.72(601.73, 955.57)	741.87(610.33, 931.42)	-0.122(-0.164, -0.079)	-0.081(-0.112, -0.050)
Central Sub-Saharan Africa	49.85(36.99, 62.72)	47.85(35.86, 61.41)	906.12(719.82, 1,115.57)	831.15(658.32, 1,040.01)	-0.181(-0.220, -0.141)	-0.346(-0.372, -0.319)
Eastern Sub-Saharan Africa	39.83(31.03, 50.38)	43.43(35.39, 51.18)	748.1(618.08, 922.37)	773.6(651.24, 904.39)	0.364(0.322, 0.405)	0.149(0.126, 0.172)
Southern Sub-Saharan Africa	45.46(39.22, 50.89)	52.39(46.96, 56.44)	820.14(720.94, 904.68)	883.87(803.05, 956.67)	0.642(0.176, 1.110)	0.405(-0.020, 0.831)
Western Sub-Saharan Africa	43.83(36.01, 56.60)	39.19(33.88, 44.76)	796.2(668.43, 1,003.65)	700.79(609.53, 799.59)	-0.454(-0.533, -0.374)	-0.503(-0.575, -0.431)

ASMR, age-standardized rate; ASDR, age-standardized disability-adjusted life year; EAPC, estimated annual percentage change; SDI, socio-demographic index; CI, confidence interval.

Figure 1

The distribution of ASR from ischemic stroke in 204 countries and territories

A. Regional distribution of the ASMR from ischemic stroke in 2019; **B.** Regional distribution of the ASDR from ischemic stroke in 2019; **C.** Regional distribution of trends in ASMR from 1990 to 2019; **D.** Regional distribution of trends in ASDR from 1990 to 2019. ASMR, age-standardized rate; ASDR, age-standardized disability-adjusted life year; EAPC,

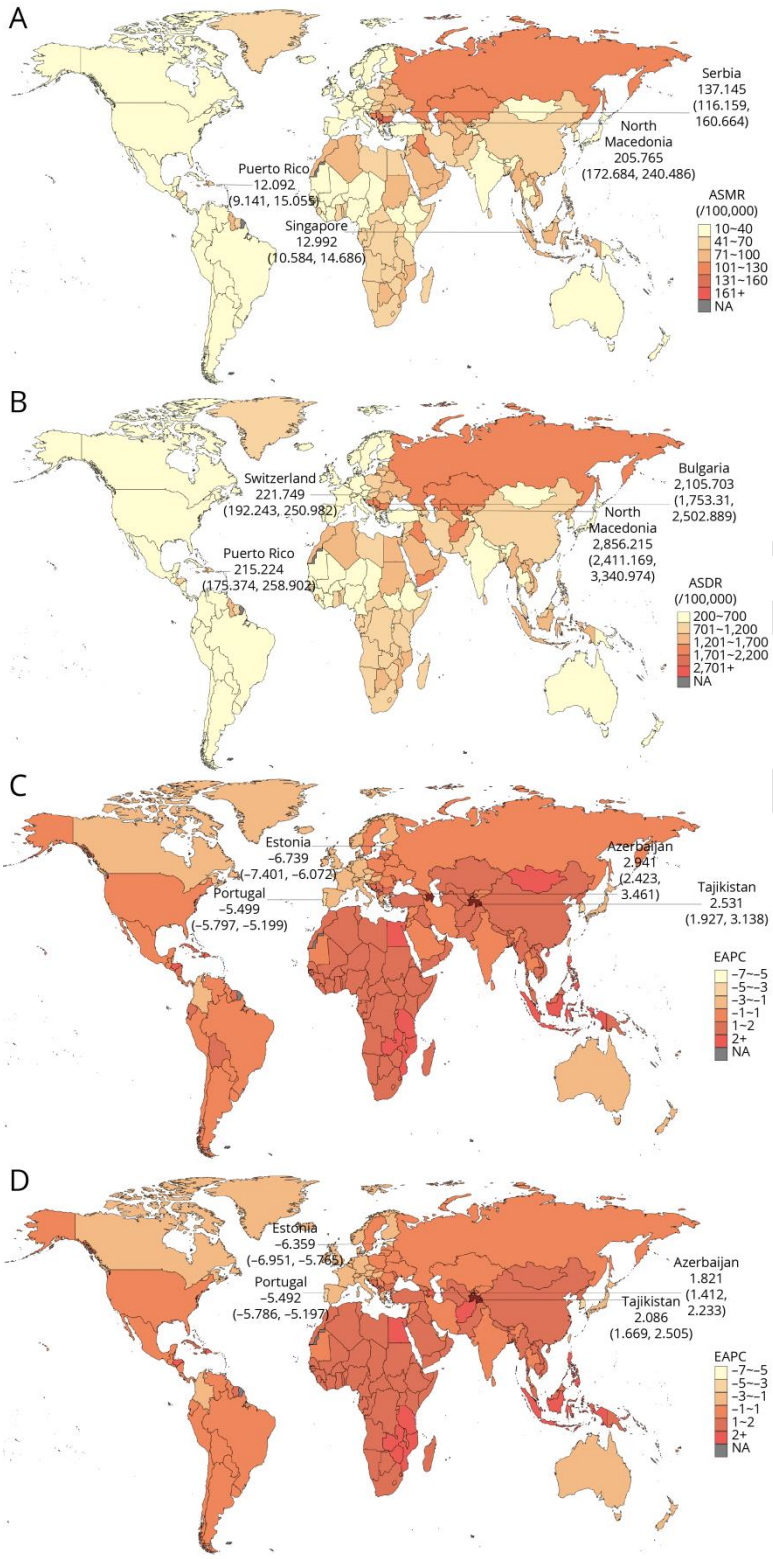


Figure 2

Death burden trends from ischemic stroke in 16 age groups and 5 SDI regions globally from 1990-2019

A. Death burden trends from total IS globally; **B.** Death burden trends in low SDI regions; **C.** Death burden trends in low-middle SDI regions; **D.** Death burden trends in middle SDI regions; **E.** Death burden trends in high-middle SDI regions; **F.** Death burden trends in high SDI regions. IS, ischemic stroke; SDI, socio-demographic index.

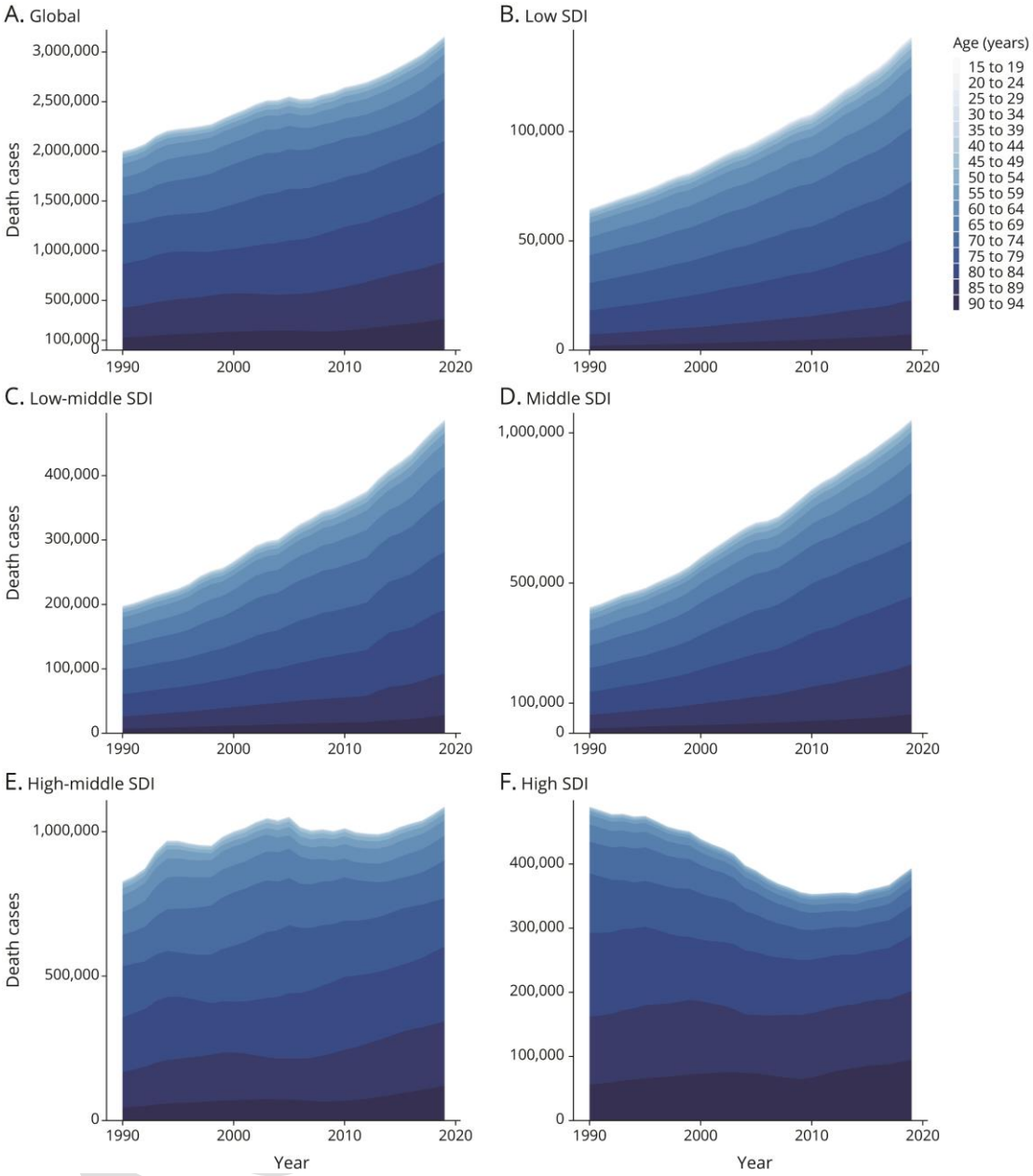


Figure 3

Correlation of ASMR and ASDR and its EAPC with SDI levels

A. Correlation of ASMR with SDI levels in 2019; **B.** Correlation of ASDR with SDI levels in 2019; **C.** Correlation between the trend in ASMR (EAPC) with SDI levels from 1990 to 2019; **D.** Correlation between the trend of ASDR (EAPC) and SDI levels from 1990-2019 (where circle size represents the number of current cases of ischemic stroke in 2019). ASMR, age-standardized rate; ASDR, age-standardized disability-adjusted life year; EAPC, estimated annual percentage change; SDI, socio-demographic index.

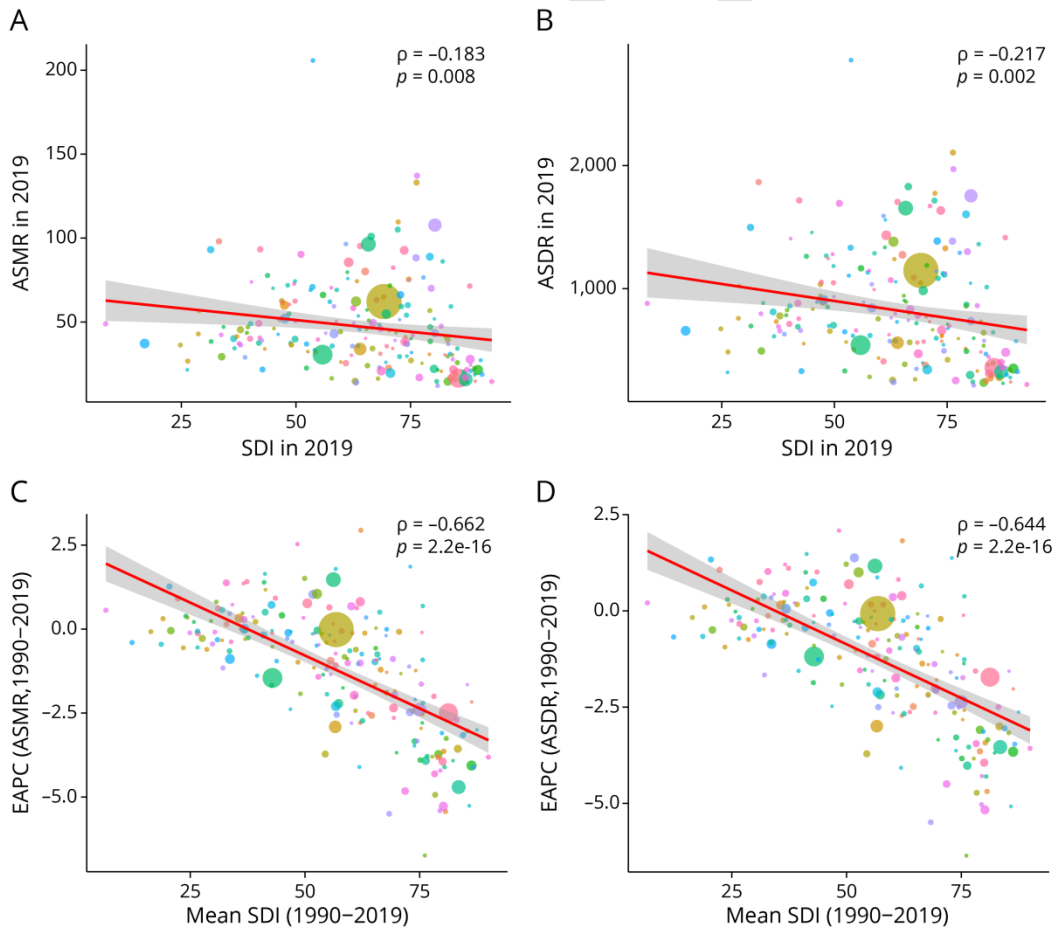


Figure 4

Global trends in death burden from ischemic stroke due to seven risk factors from 1990-2019across 16 age groups

A. Global trends in death burden from IS; **B.** Trends in IS death burden due to smoking; **C.** Trends in IS death burden due to a diet in high sodium; **D.** Trends in IS death burden due to high LDL cholesterol; **E.** Trends in IS death burden due to kidney dysfunction; **F.** Trends in IS death burden due to high systolic blood pressure; **G.** Trends in IS death burden due to high fasting plasma glucose; **H.** Trends in IS death burden due to a high BMI. IS, ischemic stroke; LDL, low density lipoprotein cholesterol; BMI, Body Mass Index.

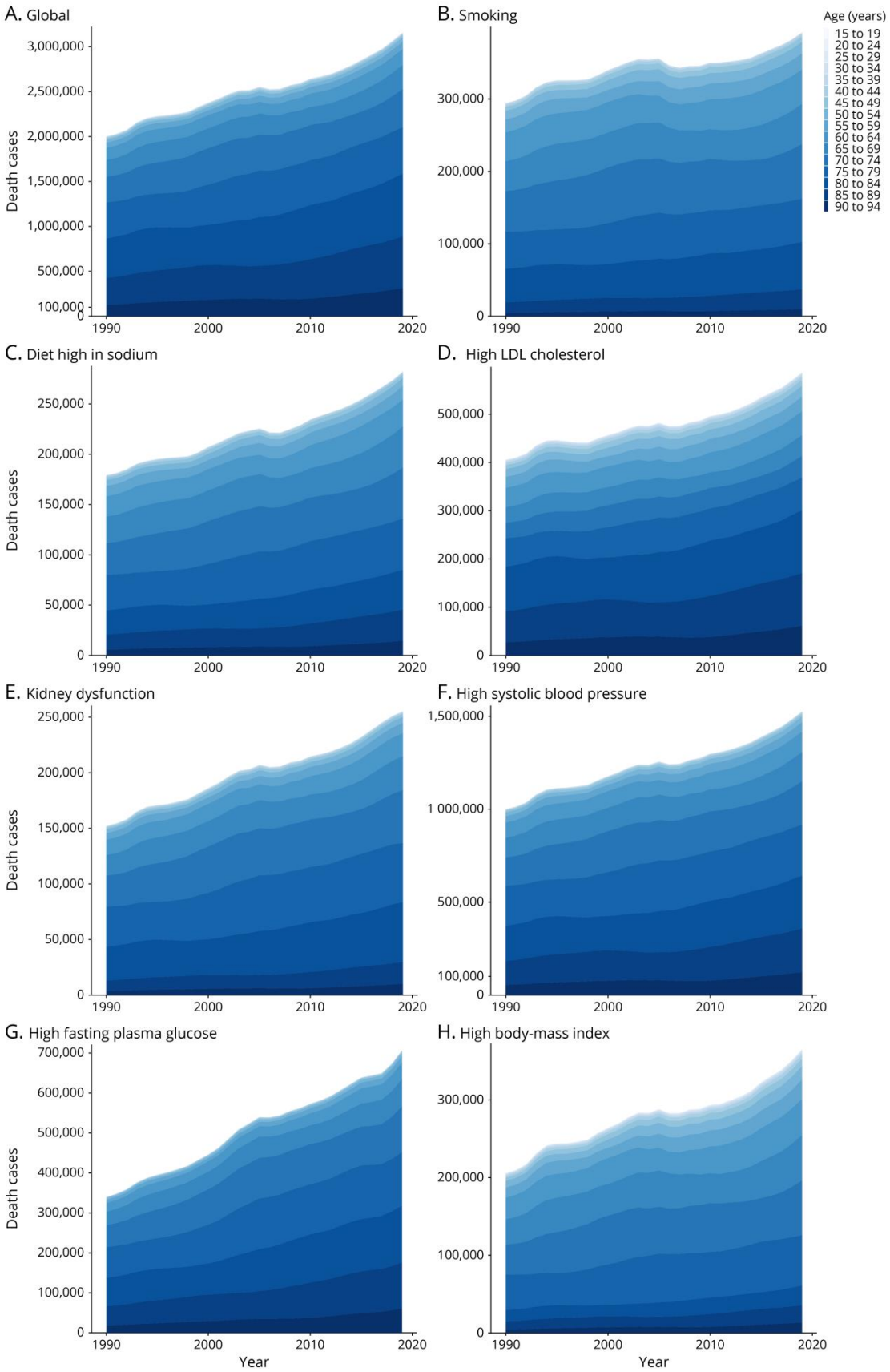
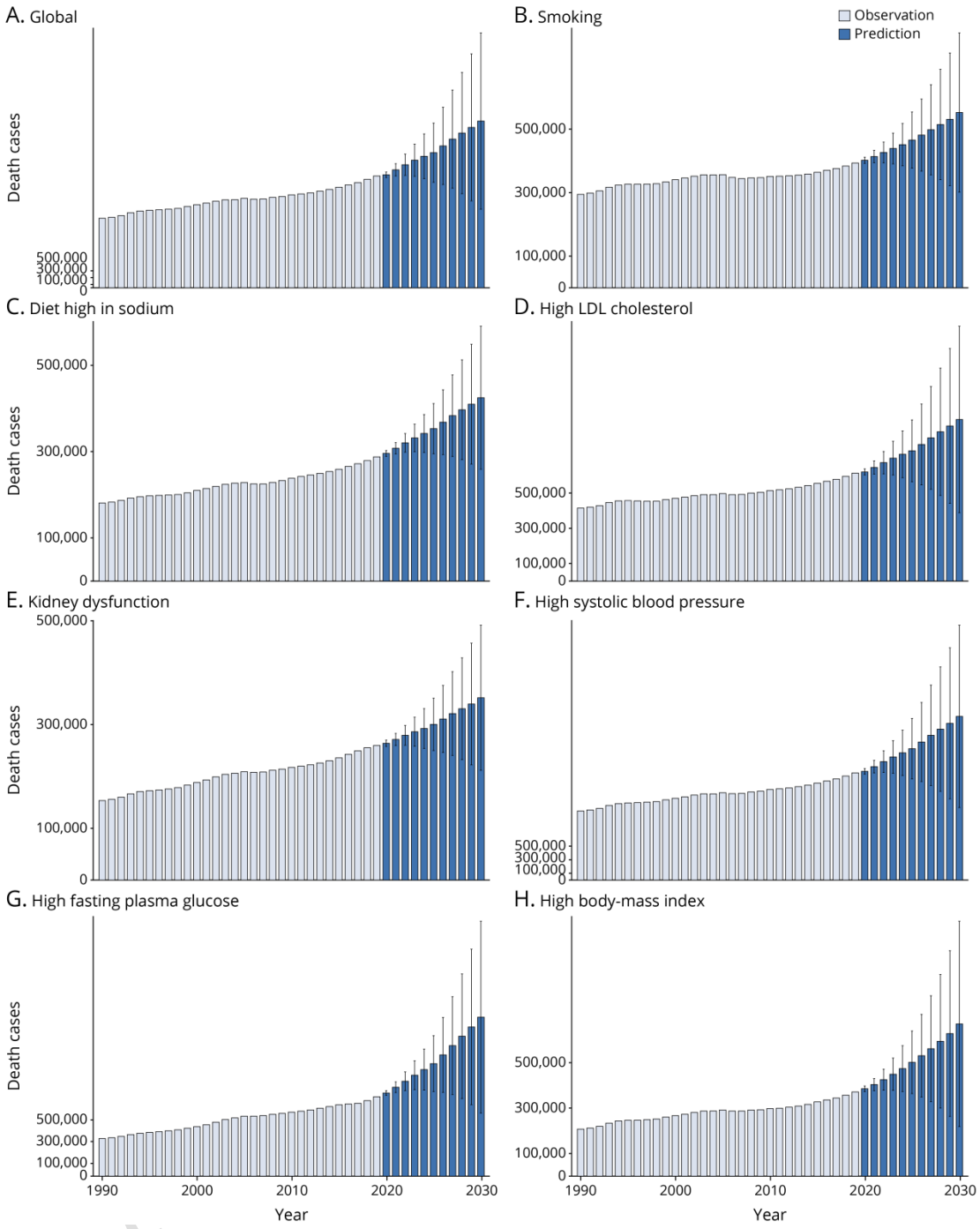
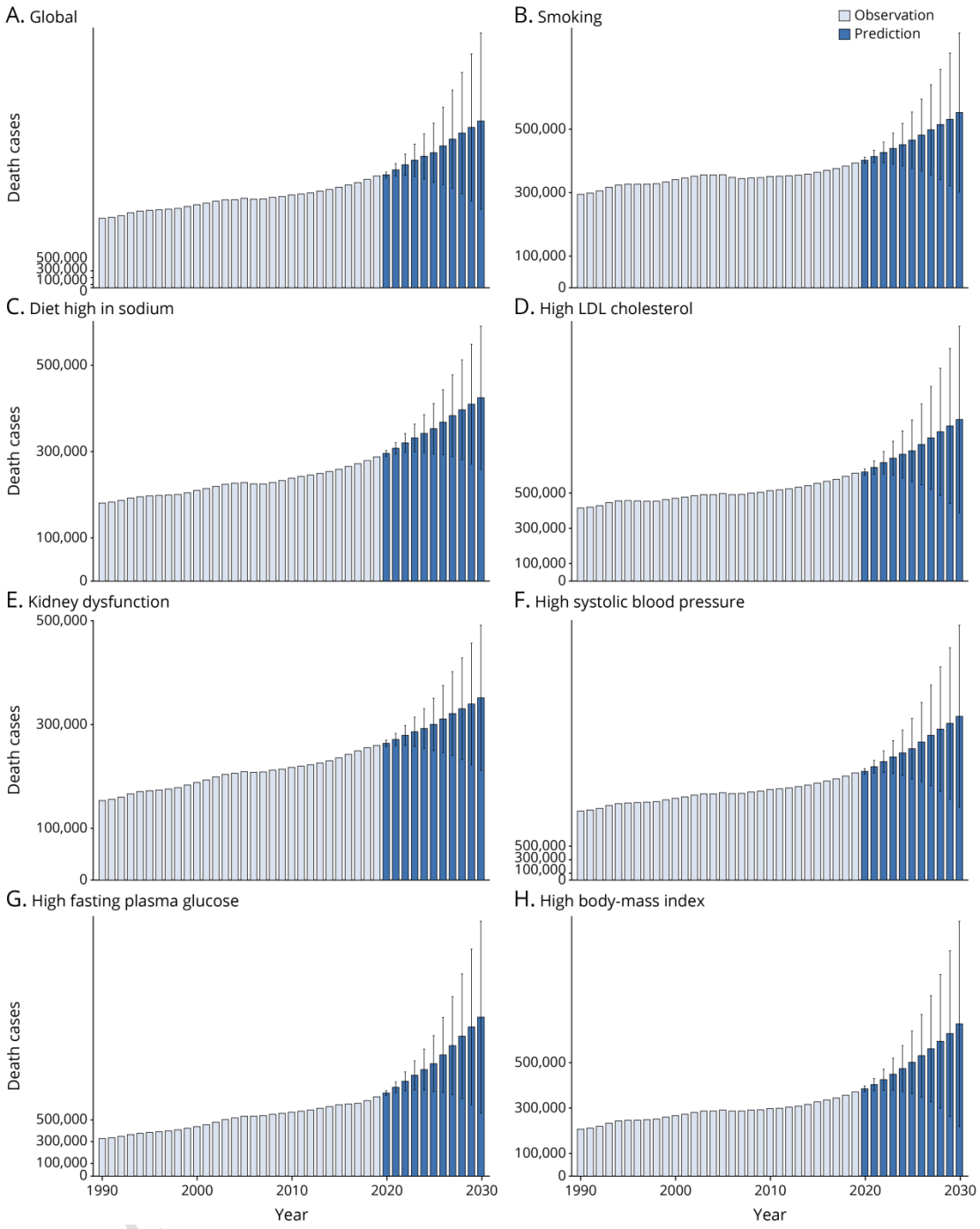


Figure 5

Prediction of deaths from an ischemic stroke from 2020 to 2030 caused by seven risk factors worldwide

A. Prediction of total IS deaths worldwide; **B.** Prediction of IS deaths caused by smoking worldwide; **C.** Prediction of IS deaths caused by diet in high sodium worldwide; **D.** Prediction of IS deaths caused by high LDL cholesterol worldwide; **E.** Prediction of IS deaths caused by kidney dysfunction worldwide; **F.** Prediction of IS deaths caused by high systolic blood pressure worldwide; **G.** Prediction of IS deaths caused by high fasting plasma glucose worldwide; **H.** Prediction of IS deaths caused by high BMI worldwide. IS, ischemic stroke; LDL, low density lipoprotein cholesterol; BMI, Body Mass Index.





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