RESEARCH ARTICLE OPEN ACCESS

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

Jiahui Fan, MS,* Xiaoguang Li, PhD,* Xueying Yu, MS, Zhenqiu Liu, PhD, Yanfeng Jiang, PhD, Yibin Fang, PhD, Ming Zong, BS, Chen Suo, PhD,† Qiuhong Man, MS,† and Lize Xiong, PhD†

Neurology® 2023;101:e137-e150. doi:10.1212/WNL.0000000000207387

Correspondence
Dr. Xiong
lizexiong@tongji.edu.cn
or Ms. Man
manqiuhong307@163.com
or Dr. Suo
suochen@fudan.edu.cn

Abstract

Background and Objectives

Ischemic stroke (IS), 1 of the 2 main subtypes of stroke, occurs because of brain ischemia caused by 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 a 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 and the attributable risk factors of IS.

Methods

Based on the Global Burden of Disease 2019 database, we used age-standardized mortality rate and disability-adjusted life year to systematically present the geographical distribution and trends of IS disease burden worldwide from 1990 to 2019 by calculating the estimated annual percentage change and to analyze and predict the death number of IS accounted by 7 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 sociodemographic index (SDI) regions. At the same time, a study of attributable risk factors of IS found that 2 behavioral factors, smoking and diet in high sodium, and 5 metabolic factors, including high systolic blood pressure, high low-density lipoprotein cholesterol, kidney dysfunction, high fasting plasma glucose, and a high BMI, are major contributors to the increased disease burden of IS now and in the future.

Discussion

Our study provides the first comprehensive summary for the past 30 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. An inadequate control of the 7 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 IS.

RELATED ARTICLE

Editorial
A Potential Forecast for Ischemic Stroke Burden in 2030: Are We There Yet?
Page 55

*These authors contributed equally to this work as the cofirst authors.

†These authors contributed equally to this work as the cocorresponding authors.

From the Department of Clinical Laboratory (J.F., X.Y., M.Z., Q.M.), Department of Thyroid, Breast and Vascular Surgery (X.L.), Department of Neurovascular Disease (Y.F.), and Department of Anesthesiology and Perioperative Medicine (L.X.), Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine; State Key Laboratory of Genetic Engineering and Collaborative Innovation Center for Genetics and Development, School of Life Sciences (Z.L., Y.J.), Taizhou Institute of Health Sciences (Z.L., Y.J., C.S.), Human Phenome Institute (Z.L., Y.J.), Department of Epidemiology and Key Laboratory of Public Health Safety of Ministry of Education, School of Public Health (C.S.), and Shanghai Institute of Infectious Disease and Biosecurity (C.S.), Fudan University; Translational Research Institute of Brain and Brain-Like Intelligence (L.X.); and Shanghai Key Laboratory of Anesthesiology and Brain Functional Modulation (L.X.), China.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

APC = age-period-cohort; **APD** = absolute percentage deviation; **ASDR** = age-standardized disability-adjusted life year; **ASMR** = age-standardized mortality rate; **ASR** = age-standardized rate; **BAPC** = Bayesian APC; **BMI** = body mass index; **CVD** = cardiovascular disease; **EAPC** = estimated annual percentage change; **FPG** = fasting plasma glucose; **GBD** = Global Burden of Disease; **IS** = ischemic stroke; **LDL** = low-density lipoprotein; **SBP** = systolic blood pressure; **SDI** = sociodemographic index; **UI** = uncertainty interval.

In the past 3 decades, the disease pattern in 80% of developing countries is shifting from communicable to non-communicable 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 IS-related deaths reached 3.29 million, accounting for 50.3% of stroke deaths and 17.7% of all cardiovascular disease (CVD)–related deaths, making the prevention of IS 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 of CVD such as smoking, diet high in sodium, high systolic blood pressure (SBP), high low-density lipoprotein (LDL) cholesterol, kidney dysfunction, high fasting plasma glucose (FPG), and a high body mass index (BMI). This has led to a significant increase in morbidity and mortality from CVD and cerebrovascular diseases, including IS.[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 (ASRs), particularly among people older than 70 years, low income, and a high BMI.[10] However, there are fewer studies on IS, 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 IS and to identify the population at high risk of IS and its attributable risk factors, our study used mortality and disability-adjusted life years of IS within different regions, ages, sexes, and risk factors of 204 countries and territories from 1990 to 2019 in GBD 2019 report database to systematically analyze the burden of IS 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, epidemiologic characteristics, and associated metabolic, environmental, and behavioral risk factors of IS would be highly beneficial to public health professionals as they develop effectively and targeted preventive strategies for reducing the global disease burden from IS.[11]

Methods

Study Data

The sociodemographic index (SDI) for 204 countries and territories is classified into 5 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, the total fertility in those younger than 25 years, and the average education level of people aged 15 years and older, 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 IS, our study used the following parameters to quantify the mortality and disability trends of IS: 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 years by age group from 1990 to 2019 were obtained from the Global Health Data Exchange query tool. Additional data are listed in eMethods (links.lww.com/WNL/C802).

Statistical Analysis

ASRs are estimated using the GBD world population age standard as a reference, following the method described by Ahmad et al.[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 ASR is calculated using the following formula[17]:

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

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), respectively.

Of importance, ASR trends can provide clues to evolving risk factors and shifts in disease patterns.[17] 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 as follows:

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

where $y = \ln(\mathrm{ASR})$ and x = calendar year. And there is $\mathrm{EAPC} = 100 \times (\exp(\beta) - 1)$, where β is the estimated value of the slope b. We also used the abovementioned formula to

calculate the 95% CI, obtained from the fitted regression line.[18] If the estimation of EAPC and its lower boundary of 95% CI were both >0, the ASR was considered to be on the rise. By 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.[19] If the Pearson correlation coefficient was <0 and the p value was ≤0.05, there was a significant negative correlation between the 2 variables.

The 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 3 factors: age, period, and cohort and combining a priori and sample information to derive posterior information. Compared with 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 BAPC model.[20,21] 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 $\widehat{(Y-Y)}/Y \times 100$, where $\hat{Y}$ denotes the predicted value and Y denotes the observed value. We calculated the APD of the BAPC model as 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.[22] The APC model[23] 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, $\alpha_a^{'}$ denotes age effect, $\beta_p^{'}$ denotes period effect, and $\gamma_c^{'}$ 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 $\mu^{'}$, $\alpha_a^{'}$, $\beta_p^{'}$, and $\gamma_c^{'}$, respectively. In this study, we focus on the prediction of Y_{ap}. The identifiability problem of APC models, therefore, does not affect our estimation.[23] We performed a BAPC analysis with an integrated nested Laplace approximation. 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[22]:

$$f(a|k_a) \propto k_a^{\frac{t-2}{2}} \exp\left\{ -\frac{k_a}{2} \sum_{i=3}^{I} [(a_i - a_{i-1}) - (a_{i-1} - a_{i-2})]^2 \right\}$$

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.[24] Considering the smoothing assumption, the BAPC models assume the prior distribution of the period effect as follows:

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

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

Standard Protocol Approvals, Registrations, and Patient Consents

Data used in our study were obtained 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.

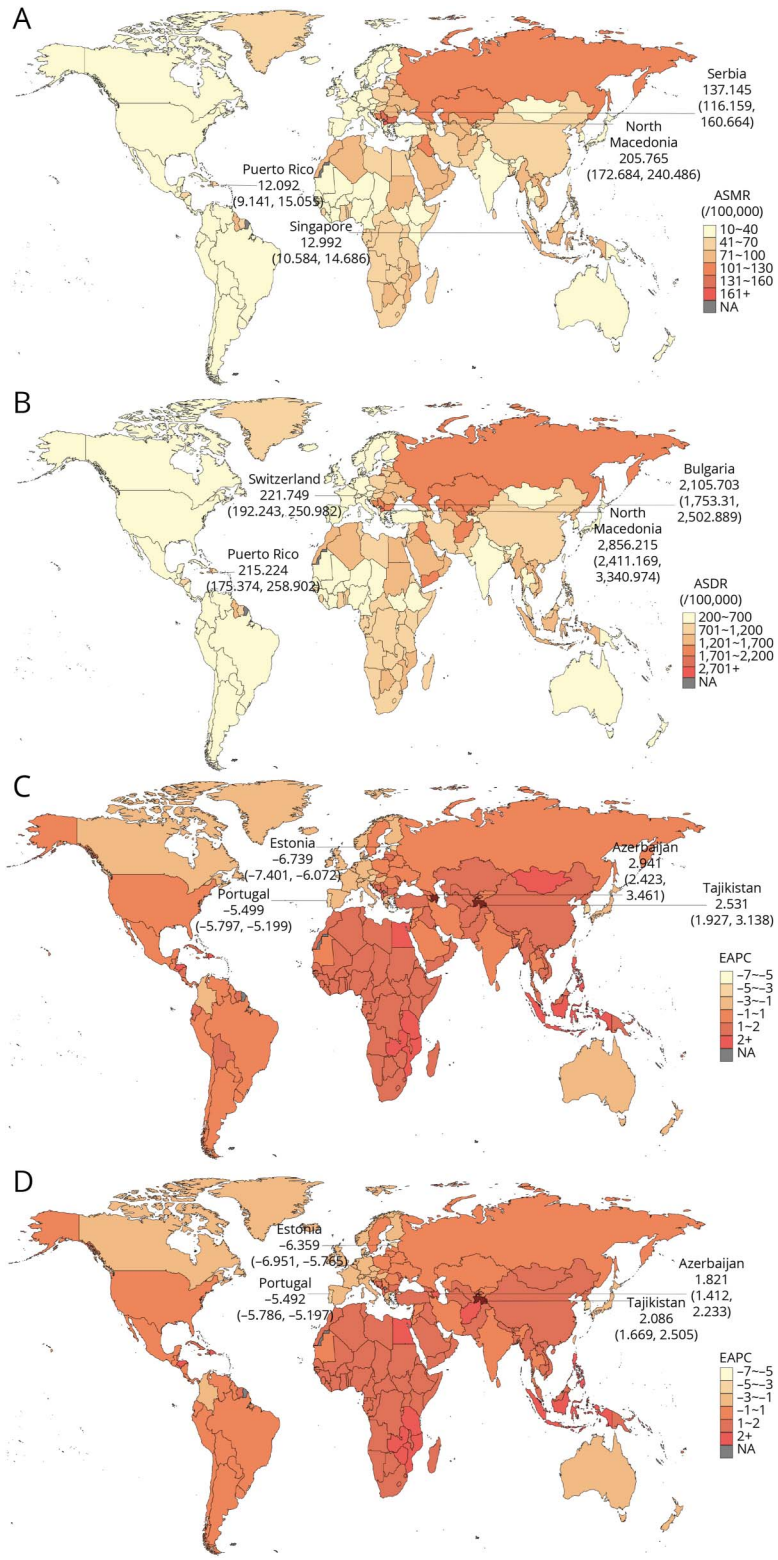
Results

Global Trends in the Distribution of Disease Burden of IS ASMR and ASDR in Different Regions

Overall, the burden of IS decreased over time in most countries, with the burden from IS-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 IS 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 = 2,856.22/100,000, 95% UI 2,411.17/100,000–3,340.97/100,000), and Serbia (ASMR = 137.15/100,000, 95% UI 116.16/100,000–160.66/100,000; ASDR = 1,970.97/100,000, 95% UI 1,674.85/100,000–2,323.13/100,000) (Figure 1, A and B).

Globally, ASMR and ASDR declined in most countries and territories from 1990 to 2019. However, there are still a

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

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) (Table 1 and Figure 1, C and D). All upward trends in ASDR were concentrated in areas with moderate or below SDI.

Table 1 Global ASMR and ASDR of Ischemic Stroke and Their EAPC by Sex, Age, Etiology, SDI Level, and Region

	ASMR/death rate (95% UI)		ASDR/disability-adjusted life years (95% UI)		EAPC (95% CI)	
Characteristics	**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)	1,117.21 (1,038.94–1,202.88)	798.81 (727.51–866.89)	−1.628 (−1.723 to −1.532)	−1.343 (−1.427 to −1.258)
Sex						
Male	68.15 (63.24–75.76)	48.44 (43.68–52.55)	1,171.74 (1,083.49–1,284.96)	878.51 (793.52–956.67)	−1.320 (−1.390 to −1.251)	−1.126 (−1.196 to −1.056)
Female	62.73 (56.43–67.67)	39.12 (34.25–43.01)	1,062.36 (971.82–1,145.19)	726.33 (648.67–798.32)	−1.896 (−2.013 to −1.780)	−1.543 (−1.641 to −1.444)
Age, y						
15–44	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 to −0.753)	−0.444 (−0.497 to −0.391)
45–59	54.58 (50.05–62.09)	38.44 (34.41–42.65)	2,489.24 (2,237.12–2,795.58)	1,925.38 (1,689.20–2,170.18)	−1.361 (−1.483 to −1.239)	−0.989 (−1.076 to −0.903)
60–74	570.58 (530.48–634.17)	388.03 (356.79–418.36)	14,395.38 (13,327.53–15,723.78)	10,474.11 (9,544.93–11,468.37)	−1.707 (−1.904 to −1.509)	−1.429 (−1.585 to −1.274)
75–94	6,715.92 (5,847.45–7,282.45)	4,413.18 (3,758.57–4,818.18)	67,318.77 (59,828.29–72,615.26)	45,894.44 (39,932.98–49,852.05)	−1.682 (−1.776 to −1.589)	−1.498 (−1.572 to −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 to −1.844)	−1.724 (−1.839 to −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 to −1.289)	−1.116 (−1.184 to −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 to −1.623)	−1.345 (−1.427 to −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 to −1.869)	−1.517 (−1.598 to −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 to −1.054)	−0.834 (−0.918 to −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 to −0.913)	−0.456 (−0.564 to −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 to −0.379)	−0.255 (−0.393 to −0.118)
SDI						
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 to −0.170)	−0.264 (−0.307 to −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 to −0.272)	−0.299 (−0.376 to −0.221)
Middle	59.57 (53.46–69.18)	53.21 (46.88–58.74)	1,088.62 (993.06–1,239.26)	982.89 (881.86–1,084.73)	−0.328 (−0.440 to −0.215)	−0.302 (−0.371 to −0.232)
High-middle	97.62 (90.48–102.64)	57.34 (51.31–62.08)	1,609.81 (1,515.40–1,691.81)	993.5 (901.35–1,076.67)	−2.241 (−2.454 to −2.027)	−2.061 (−2.271 to −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 to −3.407)	−2.928 (−3.089 to −2.766)

Continued

Table 1 Global ASMR and ASDR of Ischemic Stroke and Their EAPC by Sex, Age, Etiology, SDI Level, and Region *(continued)*

	ASMR/death rate (95% UI)		ASDR/disability-adjusted life years (95% UI)		EAPC (95% CI)	
Characteristics	**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)**
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 to −4.544)	−3.850 (−4.023 to −3.677)
Central Asia	77.99 (70.95–87.30)	79.43 (71.94–86.85)	1,447.49 (1,320.55–1,627.34)	1,386.79 (1,269.80–1,515.23)	−0.284 (−0.619 to 0.052)	−0.505 (−0.839 to −0.171)
East Asia	64.08 (56.35–76.13)	61.03 (52.42–69.14)	1,195.91 (1,063.63–1,399.61)	1,135.03 (997.93–1,284.34)	−0.075 (−0.252 to 0.102)	−0.116 (−0.236 to 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 to −0.934)	−0.952 (−1.099 to −0.804)
Southeast Asia	62.64 (54.36–71.15)	65.16 (56.18–72.43)	1,139.49 (995.56–1,295.60)	1,175.56 (1,018.24–1,313.00)	0.356 (0.220 to 0.493)	0.277 (0.182 to 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 to −3.498)	−3.563 (−3.777 to −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 to −0.568)	−0.607 (−0.727 to −0.488)
Central Europe	110.3 (102.54–114.86)	66.65 (58.08–74.56)	1,854.04 (1,749.05–1,944.21)	1,087.72 (953.98–1,213.31)	−2.071 (−2.275 to −1.867)	−2.167 (−2.348 to −1.986)
Eastern Europe	155.44 (146.07–160.29)	100.14 (88.29–109.84)	2,556.59 (2,437.97–2,653.61)	1,667.98 (1,502.07–1,837.63)	−2.303 (−2.779 to −1.823)	−2.216 (−2.684 to −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 to −3.791)	−3.810 (−4.025 to −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 to −1.569)	−1.862 (−2.082 to −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 to −2.075)	−2.179 (−2.358 to −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 to −2.221)	−2.434 (−2.606 to −2.261)
Tropical Latin America	79.09 (71.63–83.38)	33.98 (29.68–36.65)	1,318.43 (1,230.00–1,386.46)	561.21 (511.41–599.69)	−2.869 (−3.021 to −2.717)	−2.956 (−3.108 to −2.804)
North Africa and Middle East	69.24 (60.36–77.54)	62.92 (56.28–69.93)	1,297.09 (1,167.48–1,444.89)	1,183.57 (1,060.85–1,307.04)	−0.158 (−0.254 to −0.062)	−0.161 (−0.252 to −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 to −2.357)	−1.838 (−1.979 to −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 to −0.079)	−0.081 (−0.112 to −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 to −0.141)	−0.346 (−0.372 to −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 to 0.405)	0.149 (0.126 to 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 to 1.110)	0.405 (−0.020 to 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 to −0.374)	−0.503 (−0.575 to −0.431)

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

Characteristics of the Distribution of IS Disease Burden in Different Sex and Age Groups

Globally, the absolute number of deaths from IS has increased over the past few decades in both men and women and 16 age groups. Among them, IS-related mortality is higher in men than in women, and the sex difference in the overall burden of IS may increase further. The number of IS deaths in 2019 reached 1,570,000 (95% UI 1,420,000–1,710,000) in male individuals and 1,720,000 (95% UI 1,500,000–1,890,000) in female individuals. 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 female individuals than in male individuals in most regions worldwide from 1990 to 2019; among them, the highest decrease in ASMR in both sexes was in high-income Asia Pacific ($EAPC_{male}$ = −4.541, 95% CI −4.705 to −4.376; $EAPC_{female}$ = −5.127, 95% CI −5.381 to −4.872), and the highest decrease in ASDR in female individuals was in high-income Asia Pacific ($EAPC_{female}$ = −3.847, 95% CI −3.986 to −3.708) and in male individuals was in Australasia ($EAPC_{male}$ = −4.123, 95% CI −4.371 to −3.874). However, it is noteworthy that 4 regions had a higher ASMR and ASDR in female individuals, such as high-income North America ($ASMR_{male}$ = 15.38, $ASMR_{female}$ = 16.72; $ASDR_{male}$ = 339.78, $ASDR_{female}$ = 358.35), and 5 regions had a higher increasing trend in ASMR and ASDR in both sexes, 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 presented in eFigure 1 (links.lww.com/WNL/C802).

Premature death due to IS was more severe in developing countries and regions than in developed countries and regions. The global IS burden tended to increase with age, particularly in those aged 80 years and older age group. Notably, there was a trend toward younger IS in regions with low levels of SDI. Globally, the number of deaths from IS increased across age groups, with the highest increasing trend in the 90–94 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 40–44 age group (EAPC = 0.777, 95% CI 0.629–0.925, Figure 2B). In low-middle SDI regions, the highest increasing trend in IS was the 90–94 age group (EAPC = 1.301, 95% CI 1.116–1.487, Figure 2C). In the middle SDI regions, the 85–89 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 in the 90–94 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).

Distribution Characteristics of IS 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 to 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 IS disease burden (Figure 3).

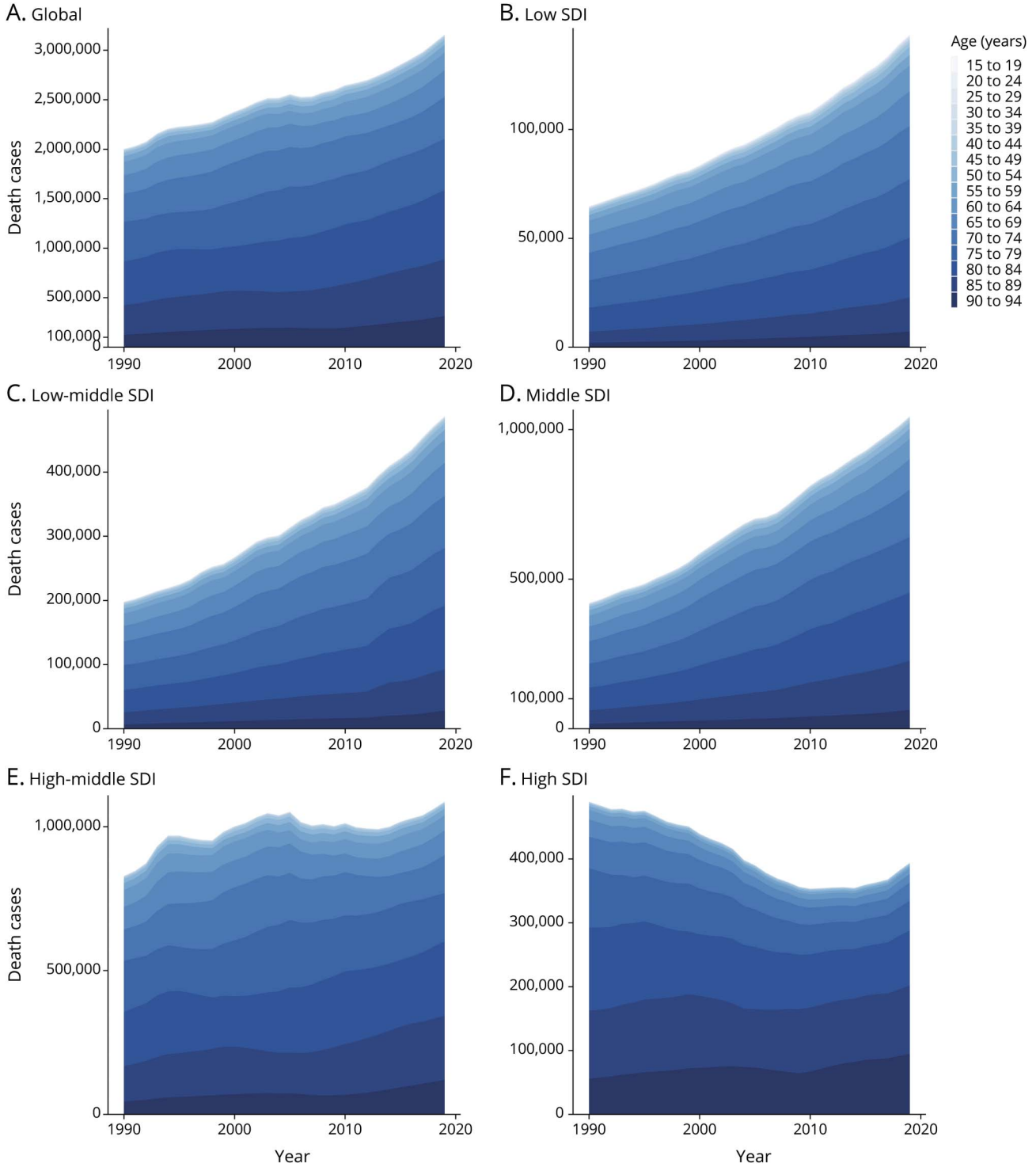
Trends in the Death Burden From IS due to Inadequate Control of 7 Risk Factors

Much of the burden from CVD and cerebrovascular disease is attributable to metabolic, behavioral, environmental, and occupational risk factors. In this study, the behavioral and metabolic factors of smoking, diet high in sodium, a high BMI, high SBP, high LDL cholesterol, kidney dysfunction, and high FPG were the top 7 risk factors for increased death and disability from an IS. 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 FPG. From 1990 to 2019, the rising trend in the burden from an IS caused by 7 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 a 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 SBP occurred mainly in low-middle SDI regions and 4 regions; the rising trend due to high FPG 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 showed separately some regions with less variation in IS burden. Additional data are listed in eFigures 2 and 3 (links.lww.com/WNL/C802).

Among them, the number of deaths caused by smoking increased in 3 older individual groups, including those aged 90–94 years, 85–89 years, and 80–84 years, and 1 youth population group (aged 50–54 years, Figure 4B); the number of deaths caused by a high sodium diet increased in 4 older population groups, including those in the age group of 90–94, 85–89, 80–84, and 75–79 years (Figure 4C); the number of deaths caused by high LDL cholesterol increased in 2 older population groups, including those aged 90–94 and 85–89 years (Figure 4D); the number of deaths caused by kidney dysfunction increased in 3 older population groups, including those aged 90–94, 85–89, and 80–84 years, and 1 youth population group (aged 50–54 years, Figure 4E); the number

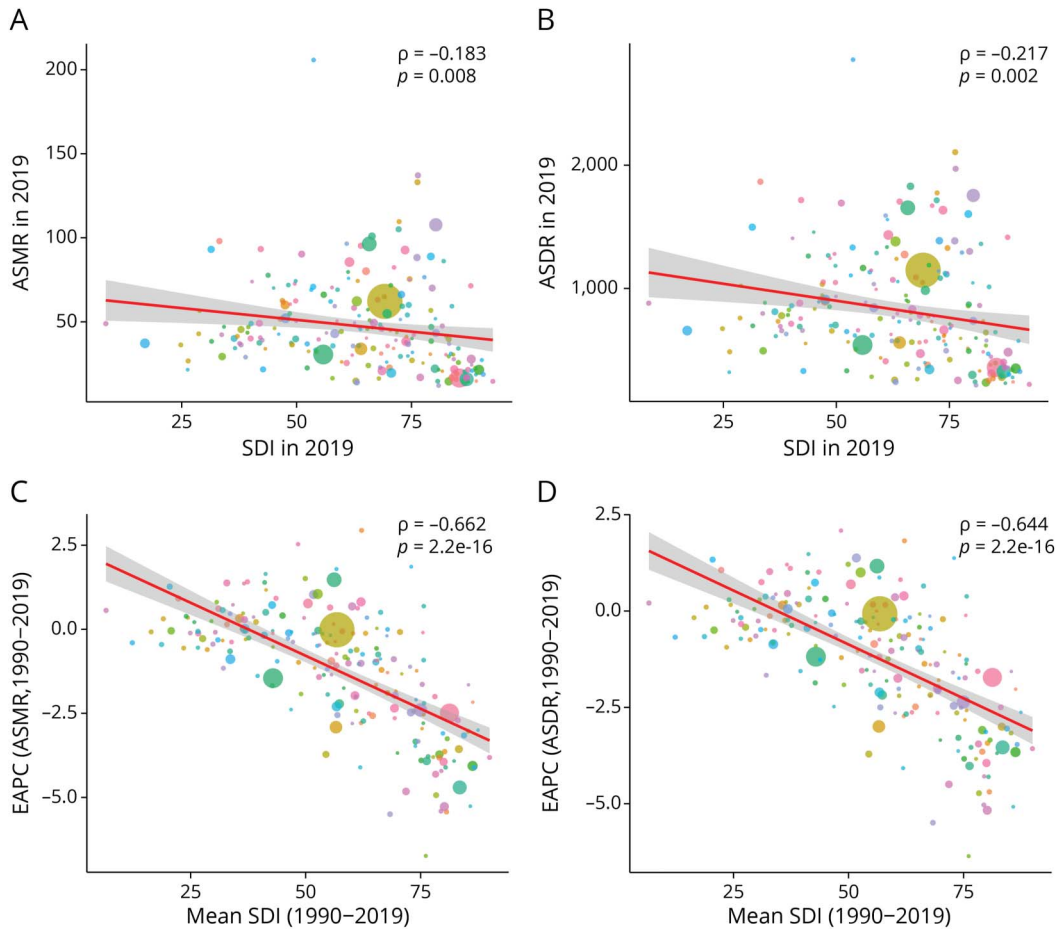
Figure 2 Death Burden Trends From IS in 16 Age Groups and 5 SDI Regions Globally From 1990 to 2019



(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 = sociodemographic index.

of deaths caused by high SBP increased in 2 older population groups, including those in the age group of 90–94 and 85–89 years, and 2 youth population group (aged 50–54 and 45–49 years, Figure 4F); the number of deaths caused by high FPG increased in 2 older population groups, including those aged 90–94 and 85–89 years (Figure 4G); the number of deaths caused by high BMI increased in 2 older population groups, including those aged 90–94 and 85–89 years, and 8 youth population groups, such as those in the age group of 20–24 years (Figure 4H).

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 to 2019 (where circle size represents the number of current cases of ischemic stroke in 2019). ASDR = age-standardized disability-adjusted life year; ASMR = age-standardized mortality rate; EAPC = estimated annual percentage change; SDI = sociodemographic index.

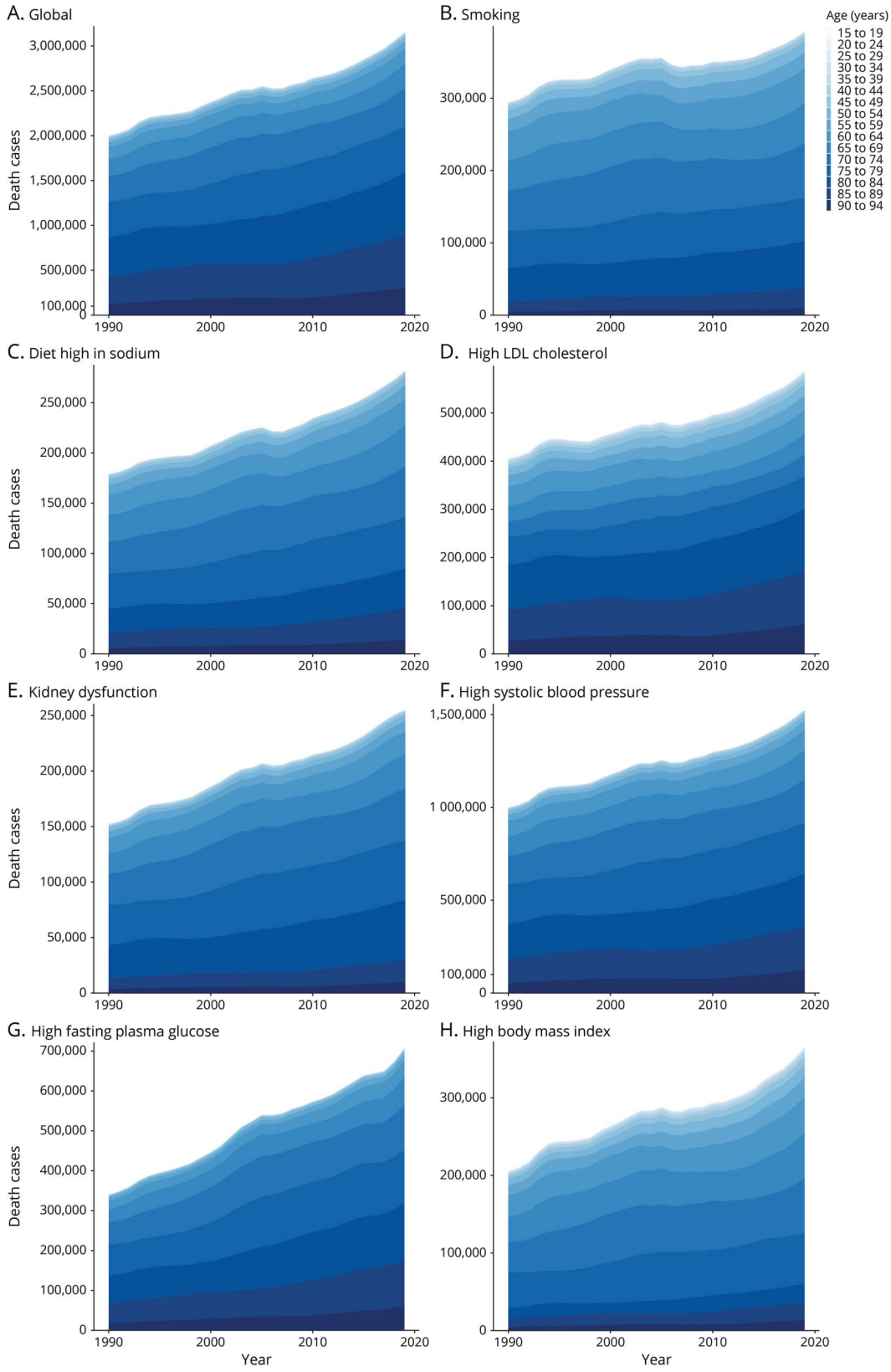
Predicted Trends in the Number of IS Deaths Caused by 7 Risk Factors From 2020 to 2030

This study used the BAPC model to predict that the number of IS deaths caused by the 7 risk factors will continue to increase globally over the next 10 years from 2020 to 2030. From 1990 to 2019, the number of IS 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 IS 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 SBP to 2,408,900 (95% CI 1,066,900–3,750,900) (Figure 5F), high FPG to 1,463,400 (95% CI 580,400–2,346,400) (Figure 5G), and a 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 IS 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 (links.lww.com/WNL/C802).

Discussion

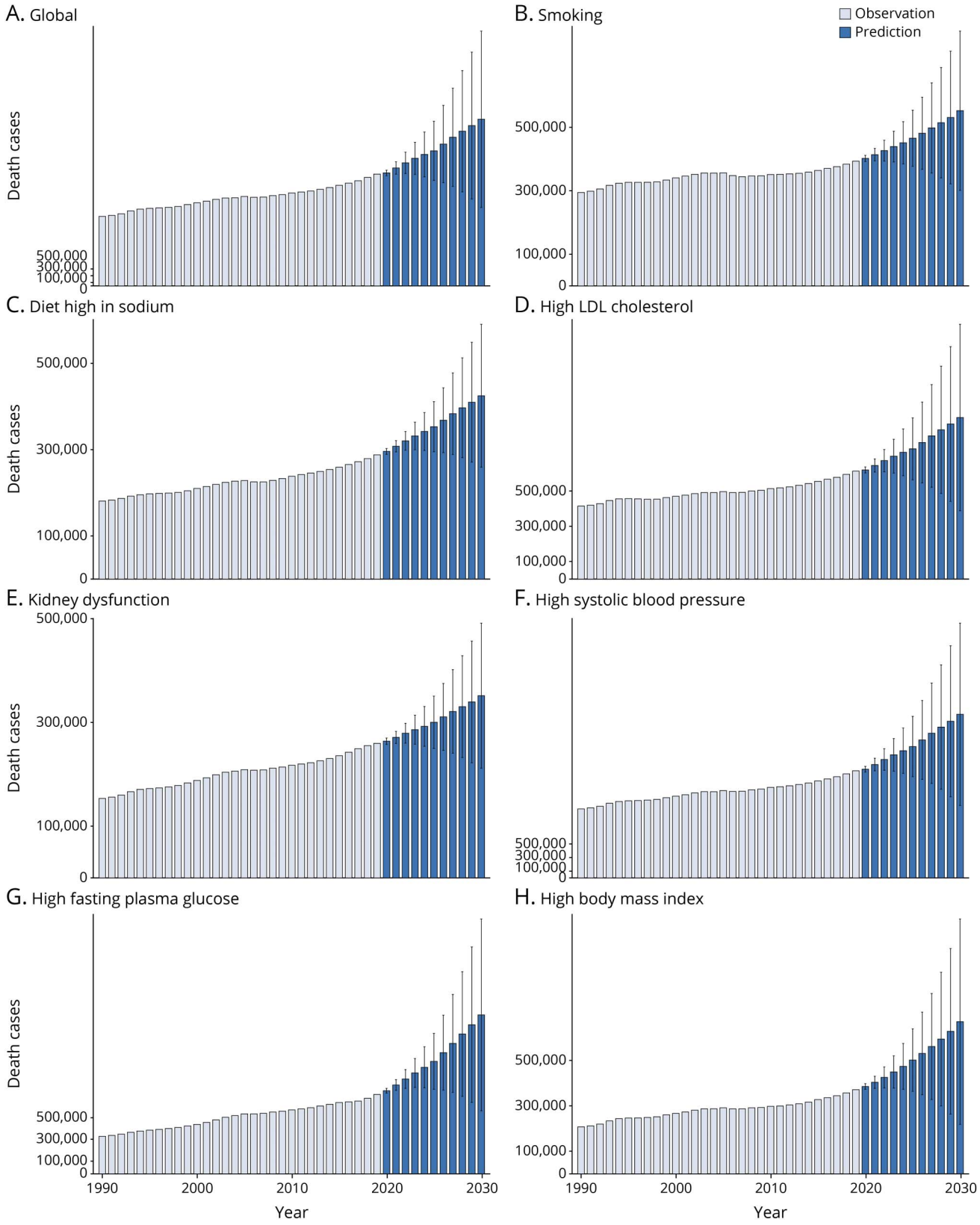
This study is the first systematic and comprehensive description of the disease burden of IS worldwide based on the GBD 2019 dataset and presents the global disease burden and its fraction attributable to inadequate control of risk factors for different levels of SDI and geographic region, sex, and age group, over 30 years from 1990 to 2019, in addition to predicting the situation from 2020 to 2030. Overall, the absolute number of deaths due to IS 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 IS showed consistent downward trends over time, suggesting that population growth and aging are largely responsible. In general,

Figure 4 Global Trends in Death Burden From IS Due to 7 Risk Factors From 1990 to 2019 Across 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 high in 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. BMI = body mass index; IS = ischemic stroke; LDL = low density lipoprotein.

Figure 5 Prediction of Deaths From an IS From 2020 to 2030 Caused by 7 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 a diet high in 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 a high BMI worldwide. BMI = body mass index; IS = ischemic stroke; LDL = low density lipoprotein.

the burden of IS-related deaths is consistent with the trend in the total burden of CVD; however, smoking, diets high in 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 IS toward younger people in developing countries.

At the global and regional levels, the disease burden from IS in developing regions far exceeded that in developed regions. Of interest, the trend toward increased IS 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 IS and increased disease burden,[25-28] 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.[29] To address the critical situation regarding premature death from IS in areas with low SDI levels, prevention strategies for populations at risk of IS should be strengthened and feasible, effective, and affordable clinical management of IS provided.[3]

Over recent decades, rates of death and disability associated with IS have been higher in men than 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 of IS, such as smoking, are more frequent in men than in women and that the incidence of IS 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 IS.[30-32] Several aging-related brain changes are associated with an increased susceptibility to IS in older adults. In addition, differences in risk factors of IS and the mechanisms of ischemic injury between young and older patients mean that older patients with IS are less responsive to treatment and consequently have a worse prognosis.[33] Notably, the trend toward increasing IS 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 IS among women in these regions.[34]

We also examined 7 attributable risk factors that were associated with IS death, including metabolic risk factors (high BMI, high SBP, high LDL cholesterol, kidney dysfunction, and high FPG) and behavioral factors (smoking and diet high in sodium). We found that the death burden from IS due to inadequate control of these risk factors occurred primarily in older patients (older than 80 years) and in areas with lower SDI levels, while the increases in IS due to high FPG 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 IS in younger patients.[35-38] A cohort study of 10 regional populations in China showed that individuals with a high BMI were at an increased risk of stroke.[39] Furthermore, a meta-analysis of 13 large prospective studies of Western patients revealed a 45% increased risk of CVD in individuals with a high BMI.[40] High triglyceride-glucose index levels have also been associated with subclinical cerebral small vessel disease.[41] These results support the hypothesis that high BMI and high FPG are independent risk factors of cerebrovascular disease. The most effective and cost-saving strategy for successfully reducing IS-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 IS deaths will continue to increase over the next 10 years (2020–2030), due to the 7 aforementioned attributable risk factors, with particularly significant increases in IS 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.[42,43] 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, proinflammatory and prothrombotic states, and endothelial dysfunction.[44,45] All these factors represent mechanisms linking the associations of high LDL cholesterol, high BMI, and high FPG with IS. In conclusion, IS 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 IS among younger patients cannot be ignored, and those countries and regions at an increased risk should implement national strategies to control key risk factors.

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

This comprehensive and systematic retrospective summary and prospective prediction study of the global burden of IS and its attributable risk factors over a 4-decade period until 2030 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 epidemiologic studies of IS 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 IS 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 IS 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 IS.

This study has important practical implications for global, regional, and national estimates of the burden of IS 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, healthcare 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 socioeconomic inequalities through appropriate measures, such as legislation and taxation, will be important to reduce CVD and other noncommunicable diseases.

Study Funding

This work was supported by the Ministry of Science and Technology China Brain Initiative Grant (2021ZD0202804), Shanghai Fourth People's Hospital 2021 Annual Discipline Boost Program—Scientific Research Boost Program project (SY-XKZT-2021-1007), Shanghai Fourth People's Hospital 2021 Annual Discipline Boost Program—Talent Boost Program project (SY-XKZT-2021-3008, SY-XKZT-2021-3007), National Key Research and Development Program of China (2019YFC1315804), and Nature Science Foundation of Shanghai (20ZR1405600).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* August 31, 2022. Accepted in final form March 22, 2023. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

Appendix Authors

Name	Location	Contribution
Jiahui Fan, MS	Department of Clinical Laboratory, Shanghai Fourth People's Hospital Affiliated to School of Medicine, Tongji University, China	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Xiaoguang Li, PhD	Department of Thyroid, Breast and Vascular Surgery, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, China	Study concept or design
Xueying Yu, MS	Department of Clinical Laboratory, Shanghai Fourth People's Hospital Affiliated to School of Medicine, Tongji University, China	Analysis or interpretation of data
Zhenqiu Liu, PhD	State Key Laboratory of Genetic Engineering and Collaborative Innovation Center for Genetics and Development, School of Life Sciences, Fudan University; Fudan University Taizhou Institute of Health Sciences; Human Phenome Institute, Fudan University, Shanghai, China	Analysis or interpretation of data
Yanfeng Jiang, PhD	State Key Laboratory of Genetic Engineering and Collaborative Innovation Center for Genetics and Development, School of Life Sciences, Fudan University; Fudan University Taizhou Institute of Health Sciences; Human Phenome Institute, Fudan University, Shanghai, China	Analysis or interpretation of data
Yibin Fang, PhD	Department of Neurovascular Disease, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, China	Analysis or interpretation of data
Ming Zong, BS	Department of Clinical Laboratory, Shanghai Fourth People's Hospital Affiliated to School of Medicine, Tongji University, China	Major role in the acquisition of data
Chen Suo, PhD	Translational Research Institute of Brain and Brain-Like Intelligence, Shanghai Key Laboratory of Anesthesiology and Brain Functional Modulation, Department of Anesthesiology and Perioperative Medicine, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, China	Study concept or design; analysis or interpretation of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Qiuhong Man, MS	Department of Clinical Laboratory, Shanghai Fourth People's Hospital Affiliated to School of Medicine, Tongji University, China	Study concept or design
Lize Xiong, PhD	Fudan University Taizhou Institute of Health Sciences; Shanghai Institute of Infectious Disease and Biosecurity, Fudan University; Department of Epidemiology and Key Laboratory of Public Health Safety of Ministry of Education, School of Public Health, Fudan University, Shanghai, China	Analysis or interpretation of data

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128.
2. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.
3. Phipps MS, Cronin CA. Management of acute ischemic stroke. *BMJ*. 2020;368:l6983.
4. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
5. Ding Q, Liu S, Yao Y, Liu H, Cai T, Han L. Global, regional, and national burden of ischemic stroke, 1990-2019. *Neurology*. 2022;98(3):e279-e290.
6. Wang W, Hu M, Liu H, et al. Global Burden of Disease Study 2019 suggests that metabolic risk factors are the leading drivers of the burden of ischemic heart disease. *Cell Metab*. 2021;33(10):1943-1956.e2.
7. Humphries SE, Morgan L. Genetic risk factors for stroke and carotid atherosclerosis: insights into pathophysiology from candidate gene approaches. *Lancet Neurol*. 2004;3(4):227-235.
8. Song Y, Long Y, Long L, et al. Polymorphism Ala54Thr of fatty acid-binding protein 2 gene is not associated with stroke risk in Han population of Hunan China. *Med Sci Monit*. 2014;20:1751-1757.
9. Tzoulaki I, Elliott P, Kontis V, Ezzati M. Worldwide exposures to cardiovascular risk factors and associated health effects: current knowledge and data gaps. *Circulation*. 2016;133(23):2314-2333.
10. GBD 2019 Stroke Collaborators. Global regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795-820.
11. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(6):1583-1633.
12. Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: findings from the Global Burden of Disease study. *J Psychiatr Res*. 2020;126:134-140.
13. Liu Z, Jiang Y, Yuan H, et al. The trends in incidence of primary liver cancer caused by specific etiologies: results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. *J Hepatol*. 2019;70(4):674-683.
14. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1859-1922.
15. Hankey BF, Ries LA, Kosary CL, et al. Partitioning linear trends in age-adjusted rates. *Cancer Causes Control*. 2000;11(1):31-35.
16. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. *Age Standardization of Rates: A New WHO Standard*. World Health Organization; 2001. Accessed July 2021. who.int/healthinfo/paper31.pdf.
17. Hung GY, Horng JL, Yen HJ, Lee CY, Lin LY. Changing incidence patterns of hepatocellular carcinoma among age groups in Taiwan. *J Hepatol*. 2015;63(6):1390-1396.
18. De Vries E, Schouten LJ, Visser O, Eggermont A, Coebergh J. Rising trends in the incidence of and mortality from cutaneous melanoma in the Netherlands: a Northwest to Southeast gradient? *Eur J Cancer*. 2003;39(10):1439-1446.
19. Fan J, Liu Z, Mao X, et al. Global trends in the incidence and mortality of esophageal cancer from 1990 to 2017. *Cancer Med*. 2020;9(18):6875-6887.
20. Lee TC, Dean CB, Semenciw R. Short-term cancer mortality projections: a comparative study of prediction methods. *Stat Med*. 2011;30(29):3387-3402.
21. Jürgens V, Ess S, Cerny T, Vounatsou P. A Bayesian generalized age-period-cohort power model for cancer projections. *Stat Med*. 2014;33(26):4627-4636.
22. Liu Z, Xu K, Jiang Y, et al. Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: a modelling study. *Int J Epidemiol*. 2021;50(1):128-142.
23. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: age-period-cohort models. *Stat Med*. 1987;6(4):469-481.
24. Riebler A, Held L. Projecting the future burden of cancer: Bayesian age-period-cohort analysis with integrated nested Laplace approximations. *Biom J*. 2017;59(3):531-549.
25. Saposnik G, Jeerakathil T, Selchen D, Baibergenova A, Hachinski V, Kapral MK. Socioeconomic status, hospital volume, and stroke fatality in Canada. *Stroke*. 2008;39(12):3360-3366.
26. Giruparajah M, Bosch J, Vanassche T, et al. Global survey of the diagnostic evaluation and management of cryptogenic ischemic stroke. *Int J Stroke*. 2015;10(7):1031-1036.
27. Jacob MA, Ekker MS, Allach Y, et al. Global differences in risk factors, etiology, and outcome of ischemic stroke in young adults: a worldwide meta-analysis: the GOAL initiative. *Neurology*. 2022;98(6):e573-e588.
28. Aringazina A, Kuandikov T, Arkhipov V. Burden of the cardiovascular diseases in Central Asia. *Cent Asian J Glob Health*. 2018;7(1):321.
29. Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of stroke in Europe: thirty-year projections of incidence, prevalence, deaths, and disability-adjusted life years. *Stroke*. 2020;51(8):2418-2427.
30. Eastern Europe & Central Asia. *Glob Heart*. 2018;13(3):225-229.
31. Man JJ, Beckman JA, Jaffe IZ. Sex as a biological variable in atherosclerosis. *Circ Res*. 2020;126(9):1297-1319.
32. Libby P, Loscalzo J, Ridker PM, et al. Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. *J Am Coll Cardiol*. 2018;72(17):2071-2081.
33. Chen RL, Balami JS, Esiri MM, Chen LK, Buchan AM. Ischemic stroke in the elderly: an overview of evidence. *Nat Rev Neurol*. 2010;6(5):256-265.
34. Gasbarrino K, Di Iorio D, Daskalopoulou SS. Importance of sex and gender in ischaemic stroke and carotid atherosclerotic disease. *Eur Heart J*. 2022;43(6):460-473.
35. Ohlsson C, Bygdell M, Sondén A, Jern C, Rosengren A, Kindblom JM. BMI increase through puberty and adolescence is associated with risk of adult stroke. *Neurology*. 2017;89(4):363-369.
36. Perera KS, De Sa Boasquevisque D, Rao-Melacini P, et al. Evaluating rates of recurrent ischemic stroke among young adults with embolic stroke of undetermined source: the young ESUS longitudinal cohort study. *JAMA Neurol*. 2022;79(5):450-458.
37. Williams LS, Garg BP, Cohen M, Fleck JD, Biller J. Subtypes of ischemic stroke in children and young adults. *Neurology*. 1997;49(6):1541-1545.
38. Putaala J. Ischemic stroke in young adults. *Continuum (Minneap Minn)*. 2020;26(2):386-414.
39. Gao M, Lv J, Yu C, et al. Metabolically healthy obesity, transition to unhealthy metabolic status, and vascular disease in Chinese adults: a cohort study. *PLoS Med*. 2020;17(10):e1003351.
40. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23(9):956-966.
41. Oe M, Fujihara K, Harada-Yamada M, et al. Impact of prior cerebrovascular disease and glucose status on incident cerebrovascular disease in Japanese. *Cardiovasc Diabetol*. 2021;20(1):174.
42. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol*. 2018;17(1):122.
43. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. *Neuron*. 2010;67(2):181-198.
44. Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism*. 2019;92:98-107.
45. Suk SH, Sacco RL, Boden-Albala B, et al. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke*. 2003;34(7):1586-1592.

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

Jiahui Fan, Xiaoguang Li, Xueying Yu, et al.

Neurology 2023;101;e137-e150 Published Online before print May 17, 2023
DOI 10.1212/WNL.0000000000207387