The Global Burden of Hemorrhagic Stroke

A Summary of Findings From the GBD 2010 Study

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ABSTRACT

This report summarizes the findings of the GBD 2010 (Global Burden of Diseases, Injuries, and Risk Factors) study for hemorrhagic stroke (HS). Multiple databases were searched for relevant studies published between 1990 and 2010. The GBD 2010 study provided standardized estimates of the incidence, mortality, mortality-to-incidence ratios (MIR), and disability-adjusted life years (DALY) lost for HS (including intracerebral hemorrhage and subarachnoid hemorrhage) by age, sex, and income level (high-income countries [HIC]; low- and middle-income countries [LMIC]) for 21 GBD 2010 regions in 1990, 2005, and 2010. In 2010, there were 5.3 million cases of HS and over 3.0 million deaths due to HS. There was a 47% increase worldwide in the absolute number of HS cases. The largest proportion of HS incident cases (80%) and deaths (63%) occurred in LMIC countries. There were 62.8 million DALY lost (86% in LMIC) due to HS. The overall age-standardized incidence rate of HS per 100,000 person-years in 2010 was 48.41 (95% confidence interval [CI]: 45.44 to 52.13) in HIC and 99.43 (95% CI: 85.37 to 116.28) in LMIC, and 81.52 (95% CI: 72.27 to 92.82) globally. The age-standardized incidence of HS increased by 18.5% worldwide between 1990 and 2010. In HIC, there was a reduction in incidence of HS by 8% (95% CI: 1% to 15%), mortality by 38% (95% CI: 32% to 43%), DALY by 39% (95% CI: 32% to 44%), and MIR by 27% (95% CI: 19% to 35%) in the last 2 decades. In LMIC countries, there was a significant increase in the incidence of HS by 22% (95% CI: 5% to 30%), whereas there was a significant reduction in mortality rates of 23% (95% CI: -3% to 36%), DALY lost of 25% (95% CI: 7% to 38%), and MIR by 36% (95% CI: 16% to 49%). There were significant regional differences in incidence rates of HS, with the highest rates in LMIC regions such as sub-Saharan Africa and East Asia, and lowest rates in High Income North America and Western Europe. The worldwide burden of HS has increased over the last 2 decades in terms of absolute numbers of HS incident events. The majority of the burden of HS is borne by LMIC. Rates for HS incidence, mortality, and DALY lost, as well as MIR decreased in the past 2 decades in HIC, but increased significantly in LMIC countries, particularly in those patients $\leq$75 years. HS affected people at a younger age in LMIC than in HIC. The lowest incidence and mortality rates in 2010 were in High Income North America, Australasia, and Western Europe, whereas the highest rates were in Central Asia, Southeast Asia, and sub-Saharan Africa. These results suggest that reducing the burden of HS is a priority particularly in LMIC. The GBD 2010 findings may be a useful resource for planning strategies to reduce the global burden of HS.

Hemorrhagic stroke (HS), including primary intracerebral and subarachnoid hemorrhage, accounts for 10% to 27% of strokes worldwide [1], yet because of its high case fatality rate, it contributes to a high proportion of stroke deaths, with a 30-day case fatality rate of >50% for intracerebral hemorrhage and around 45% for subarachnoid hemorrhage [2]. HS has poor short- and long-term prognoses with the risk of death increasing with increasing age [3]. Those who survive 28 days have a 4.5-fold increased risk of death, compared with risk of ischemic strokes (IS), within the first year. HS are associated with higher rates of mortality risk and greater stroke severity than IS are [4,5].

During the past few decades, there has been an increase in life expectancy worldwide, along with a shift from death and disability related to communicable diseases and undernutrition to those related to chronic noncommunicable conditions such as stroke and heart disease [6]. Industrialization and urbanization in developing countries have led to the increased prevalence of adverse

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The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, or any other government entity.
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dietary risk factors, increased smoking, and harmful use of alcohol [7]. This epidemiologic transition [8] may have contributed to increased disparities in stroke burden between low- and middle-income countries (LMIC) and high-income countries (HIC). Importantly, it has been shown in a recent study that whereas the secular trends for IS and ischemic heart disease are similar, they differ from that for HS [9]. An accurate evaluation of stroke burden by its pathological subtypes is essential for planning well-informed and targeted prevention and treatment strategies to reduce stroke burden worldwide.

The GBD 2010 (Global Burden of Diseases, Injuries, and Risk Factors) study was a systematic analysis of the global, comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and country income level in 21 world regions for 1990, 2005, and 2010 [10]. The GBD 2010 [11,12] provided standardized estimates of the incidence; mortality; mortality-to-incidence ratios (MIR), a measure of stroke case fatality; and disability-adjusted life years (DALY), a measure of population health burden from stroke, for total stroke, and the first GBD estimates for IS and HS separately by age, sex, and country income level [11,12]. The purpose of this report is to summarize the main findings for the burden of HS from the GBD 2010 study [11].

METHODS

Multiple databases (MEDLINE, Embase, Scopus, LILACS [Literatura Latino-Americana e do Caribe em Ciências da Saúde], PubMed, Science Direct, Global Health Database, and regional databases) were searched for relevant studies published between 1990 and 2010. Studies were included for data extraction and analysis if they used the World Health Organization definition of stroke, reported methods for ascertaining stroke cases, distinguished between first-ever stroke and recurrent stroke (only incident strokes were included in these analyses), reported an age-specific epidemiologic parameter of interest and the population denominator (i.e., stroke incidence and/or prevalence in 5- or 10-year age bands) with sufficient detail to enable an estimate of age-adjusted parameters. Incidence studies from HIC required complete stroke case ascertainment, whereas less rigorous stroke case ascertainment was allowed for studies from LMIC in which no other relevant data were otherwise available. Pathological types of stroke were analyzed only for studies that had computed tomography of the head, magnetic resonance imaging within 2 weeks of stroke onset, or brain autopsy findings available for $\geq$70% of stroke cases. All age groups were included in the analysis. To estimate the mortality rate, the GBD mortality database and an ensemble cause of death modeling approach were used [10,12,13]. MIR was used as an ecological proxy estimation of stroke case fatality, because incidence and mortality data could not be linked at the level of individual cases. MIR was calculated as the ratio of the number of deaths to the number of new cases of stroke within a specified period. DALY are used as a summary measure of population health burden and are the sum of years of life lost due to death and years lived with disability [14]. Years of life lost is the product of the number of deaths at each age by a standard life expectancy at that age according to standard life tables. The reference for life expectancy was made by the least observed mortality rate of each age group among countries in 2010. Years lived with disability is the prevalence of the disease multiplied by the disability weight for that disease. The disability weight is calculated on the basis of the level of health loss for the disease and reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death) [14]. Each DALY is a year of healthy life lost due to disease, impairment, or death. Age-standardized incidence and mortality rates per 100,000 person-years and estimates of DALY lost per 100,000 people were calculated with the direct method of standardization with the World Health Organization standard population as a reference. The GBD 2010 analytical technique DisMod-MR was used to estimate the overall number of incident strokes and the number of HS [10]. As the majority of data were for incidence and 28-day case fatality, DisMod-MR estimated the prevalence of acute stroke (28 days) by taking incidence of stroke, 28-day case fatality plus a high remission to keep duration, by definition, of acute stroke sequelae, under 30 days. Uncertainty of each step was tracked by saving and following 1,000 draws of the posterior distribution of results from each step including prevalence, disability weight, reference life expectancy, envelope of all-cause mortality, and stroke mortality. Mean and credible interval of the posterior distribution for each outcome measure was calculated using final 1,000 draws. The detailed methodology for calculating all these estimates in the GBD 2010 project has been described elsewhere [10,12].

RESULTS

Worldwide, there were 5.3 million cases of HS in 2010 and the largest proportion (80%) of these occurred in LMIC countries, in contrast with IS, of which 63% occurred in LMIC. There were over 3.0 million HS deaths (84% in LMIC), and 62.8 million DALY lost (86% in LMIC) due to HS.

The overall age-standardized incidence rate of HS per 100,000 person-years in 2010 was 48.41 (95% CI: 45.44 to 52.13) in HIC, 99.43 (95% CI: 85.37 to 116.28) in LMIC, and 81.52 (95% CI: 72.27 to 92.82) globally (Table 1). There were large variations in age-standardized incidence and mortality rates by 21 GBD regions. The highest incidences of HS in 2010 were in the Central Asia and East Asia regions (101 to 158 per 100,000 person-years) and East and Southern sub-Saharan Africa (73 to 101 per 100,000 person-years). The lowest HS incidence rates were in High Income North America, Central and Andean Latin America, Western Europe, and Oceania

TABLE 1. Age-standardized annual incidence and mortality rates (per 100,000 person-years), MIR, and DALY lost for HS in HIC, LMIC, and globally in 1990, 2005, and 2010

	Number	1990	Number	2005	Number	2010	p Value*
HIC							
Incidence	844,105	53.30 (49.44–57.25)	974,336	49.12 (45.75–52.84)	1,050,985	48.81 (45.44–52.13)	0.032
MIR		0.652 (0.589–0.729)		0.551 (0.492–0.628)		0.476 (0.430–0.546)	<0.001
DALY	10,500,007	695.26 (629.69–753.52)	9,840,594	529.78 (484.51–582.25)	8,569,255	425.13 (385.67–470.63)	<0.001
Mortality	549,858	32.65 (29.95–35.68)	536,700	24.55 (22.67–27.37)	499,809	20.25 (18.57–22.91)	<0.001
LMIC							
Incidence	1,996,072	81.40 (69.54–94.31)	3,662,492	98.80 (84.77–115.66)	4,274,013	99.43 (85.37–116.28)	0.040
MIR		0.932 (0.708–1.177)		0.668 (0.534–0.822)		0.595 (0.470–0.729)	<0.001
DALY	43,382,156	1,614.23 (1,292.98–1,946.36)	53,539,196	1,363.83 (1,154.83–1,580.73)	54,273,644	1,207.21 (1,024.82–1,408.04)	<0.001
Mortality	1,869,514	80.37 (63.72–96.98)	2,446,397	69.29 (58.11–81.26)	2,538,954	61.93 (52.53–72.34)	<0.001
Global							
Incidence	2,840,177	69.36 (62.46–77.18)	4,636,828	80.33 (71.40–91.69)	5,324,997	81.52 (72.27–92.82)	0.033
MIR		0.847 (0.692–1.009)		0.643 (0.536–0.766)		0.571 (0.471–0.676)	<0.001
DALY	53,882,164	1,266.94 (1,068.41–1,484.26)	63,379,792	1,081.81 (935.41–1,234.23)	62,842,896	956.22 (827.57–1,104.44)	<0.001
Mortality	2,419,372	59.66 (50.61–69.71)	2,983,097	51.61 (44.68–59.07)	3,038,763	46.14 (40.13–53.15)	<0.001

Values are rates (95% confidence intervals). DALY, disability-adjusted life years lost; HIC, high-income countries; HS, hemorrhagic stroke; LMIC, low- and middle-income countries; MIR, mortality-to-incidence ratio.

*The p value considers the trend in rates between the 1990 and 2010 points only.

(25 to 40 per 100,000 person-years). At the country level, age-standardized incidence of HS was lowest in Qatar (14.55) and highest in China (159.81). The highest mortality rate among the 21 GBD regions was in Southeast Asia, 90.12 (95% CI: 80.42 to 98.70).The highest mortality rate for male patients was in Southeast Asia, 104.98 (95% CI: 87.81 to 121.57) and highest in Southeast Asia for female patients, 77.49 (95% CI: 67.99 to 85.96) (Fig. 1). The lowest mortality rate was High Income North America for both male patients, 9.56 (95% CI: 7.13 to 11.35), and female patients, 9.14 (95% CI: 7.52 to 10.35). The age-standardized mortality rate per 100,000 person-years was lowest in the United States at 9.64 and highest in Mongolia at 210.56. DALY lost due to HS per 100,000 people ranged from 178.20 in Switzerland to 4,118.90 in Mongolia.

Between 1990 and 2010, there was an increase in the absolute numbers of incident HS in LMIC of 114%, and a 24% increase in HIC, and a 47% increase globally. The age-standardized incidence of HS increased by 18.5% worldwide between 1990 and 2010. However, there were differing trends in stroke burden by country income level over the last 2 decades (Fig. 2). In HIC, incidence of HS reduced by 8% (95% CI: 1% to 15%), mortality by 38% (95% CI: 32% to 43%), DALY by 39% (95% CI: 32% to 44%), and MIR by 27% (95% CI: 19% to 35%). In LMIC, there was a 22% (95% CI: 5% to 30%) increase in the incidence of HS. There was a significant reduction in mortality rates of 23% (95% CI: -3% to 36%), DALY lost of 25% (95% CI: 7% to 38%), and MIR by 36% (95% CI: 16% to 49%) in LMIC.

Trends in HS burden for different age groups varied for LMIC and HIC (Fig. 3). There was a significant reduction (14.6%, $p = 0.046$) globally in the incidence of HS in the older age group ($\geq$75 years). However, in LMIC, there was a 19% (95% CI: 5% to 30%) increase in the incidence of HS in those $<$75 years. In particular, in people ages 20 to 64 years, the incidence of HS in LMIC increased significantly by 40.8% ($p = 0.001$) versus a 6.9% increase in the same age group in HIC. The mean age of people for incident HS was 69.1 $\pm$ 0.15 years in HIC compared with 63.8 $\pm$ 0.13 years in LMIC. In 2010, the mean age at fatal HS in HIC was 74.8 $\pm$ 0.32 years and was also higher by 6 years than in LMIC at 68.9 $\pm$ 0.31 years. Globally, in 2010, the mean age at HS incidence at 65.1 $\pm$ 0.15 years was 8 years younger than the mean age at IS at 73.1 $\pm$ 0.10 years, and age at death for HS was 9.5 years younger than for IS deaths.

Trends in HS burden varied between the 21 GBD regions. The greatest increases in HS rates between 1990 and 2010 were seen in eastern and central Europe, North and sub-Saharan Africa, and the Middle East, whereas significant reductions were noted in North America, western Europe, and tropical and southern Latin America. MIR for HS was lowest in High Income North America, whereas Oceania had the highest (0.94 to 1.27).

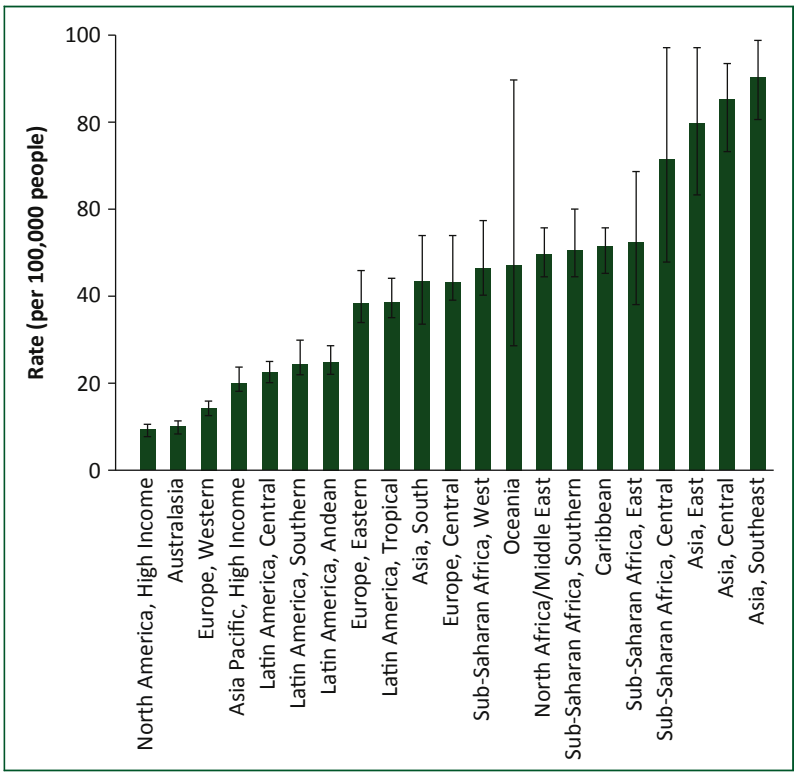

FIGURE 1. Age-standardized mortality rates of HS by 21 GBD regions in 2010. There were large variations in mortality rates in the 21 GBD regions. The highest mortality rates in 2010 were in Southeast Asia, Central Asia, and East Asia, (79.58 to 90.12 per 100,000 people), while the lowest incidence rates were in High Income North America, Australasia, and Western Europe (9.38 to 14.26 per 100,000 person-years). GBD, Global Burden of Diseases, Injuries, and Risk Factors study; HS, hemorrhagic stroke.

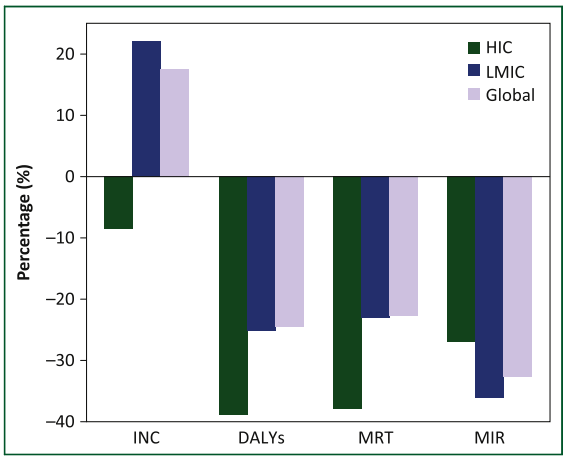

FIGURE 2. Percentage of global change in HS burden from 1990 to 2010. HS incidence rates declined in HIC and increased in LMIC and globally. Mortality rates and DALY lost were reduced significantly in HIC, and there was a trend toward a reduction on LMIC. MIR were significantly decreased in HIC, LMIC, and globally. DALY, disability-adjusted life years lost; HIC, high-income countries; HS, hemorrhagic stroke; INC, age-standardized incidence rates; LMIC, low- and middle-income countries; MIR, mortality-to-incidence ratio; MRT, age-standardized mortality rates.

DISCUSSION

The GBD 2010 study found that the global burden of HS in terms of absolute numbers of incident cases, deaths, and DALY lost in 2010 is substantial, and that the bulk of stroke burden is disproportionately due to HS rather than to IS [11]. HS burden is significantly higher in LMIC than in HIC. As shown in the GBD 2010 studies for stroke burden by subtypes [11], compared with IS, incident HS occurred at a younger age on average, with the mean age of around one-half of those affected being <65 years of age. Age-standardized rates of HS incidence, mortality, and DALY lost have declined in HIC, in both younger and older age groups. In contrast, there was a significant increase in the incidence rates of HS in LMIC, particularly in the younger age groups (20 to 64 years) in the past 2 decades.

An encouraging finding was the decline in age-standardized mortality rates, DALY lost, and MIR for HS in LMIC. This may reflect some changes toward better access to acute treatment and antihypertensive medication within some regions of LMIC [15,16]. Wide regional differences in stroke burden by subtype have been reported in countries such as China [17], possibly reflecting the effect of socioeconomic and risk factor exposure heterogeneity on HS burden.

A recent meta-analysis found that there was no decrease in intracerebral hemorrhage incidence worldwide between 1980 and 2008 and both incidence and case fatality increased with age, with no decrease in case fatality seen over the study period [18]. However, another study found an increase in HS incidence in people ≥75 years [19]. Previous studies have also shown that HS occurs at a younger age than IS does and the risk of intracerebral hemorrhage in hypertensive people is greater if they are not compliant with antihypertensive medication or are smokers [20–22]. Our results are in line with other studies that have shown that the burden of HS relative to IS has increased in LMIC in many countries with poor access to medical care and hypertension control [23].

Several factors may bring about the increasing disparities between regions of different income level [6]. Hypertension is the most important risk factor for HS [24,25], and other important risk factors include smoking and excessive alcohol intake [26]. The increased prevalence of risk factors such as smoking [27,28] and harmful use of alcohol [29,30] are also likely to be major contributors to the disproportionate increase in HS burden in LMIC. The significant disparity of HS burden in LMIC compared with HIC could also be attributed to differences in awareness of stroke risk factors and low accessibility to diagnostic and

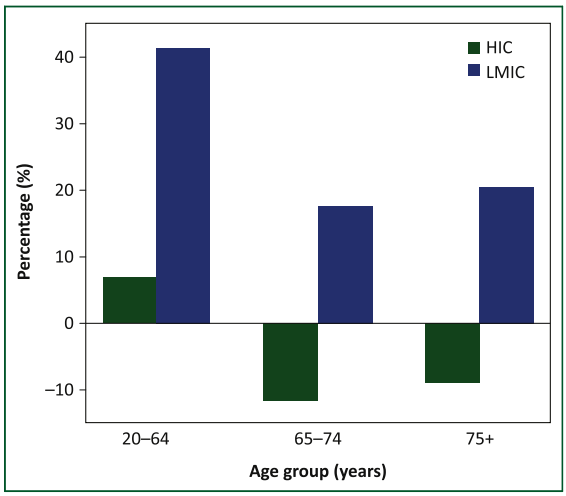

FIGURE 3. Percentage of change in stroke burden from 1990 to 2010 by age group. Age-standardized rates of HS increased significantly particularly in younger age groups (20 to 64 years) by 40.8% in LMIC countries, while the incidence of HS reduced in HIC in people over 65 years of age. Abbreviations as in Figures 1 and 2.

therapeutic interventions for the prevention and treatment of HS [31]. An aging population has contributed to increased incidence of both HS and IS. Whereas regional and temporal trends of IS are similar to those of ischemic heart disease, the trends for HS have been very different, suggesting important differences in causal factors in these 2 stroke subtypes [9].

GBD 2010 included only studies that had computed tomography of the head and magnetic resonance imaging within 2 weeks of stroke onset as crucial inclusion criteria for confirming the validity of stroke diagnosis; yet, it represents an important limitation for studies from LMIC where access to medical imaging is limited. However, this potential bias was minimized by approximating estimates of HS burden from studies reporting neuroimaging in ≥70% of cases for pathological subtype verification. The analysis of HS burden grouped together data for intracerebral hemorrhage and subarachnoid hemorrhage. The proportion of incident cases and etiology of the 2 subtypes of HS differs; therefore, results need to be interpreted in consideration of this limitation. Sex differences in stroke outcome, by pathological subtypes, are also an important consideration given differences in both incidence and outcomes for male and female patients [32]. The incidence and prevalence of intracerebral hemorrhage is higher in men, whereas the incidence of subarachnoid hemorrhage is higher in women, and women also have more severe strokes than men do. Although the current report does not present analyses for sex differences in HS incidence and outcomes, this would be an important consideration for future reports.

The GBD 2010 study is a globally representative and reliable resource for information on stroke burden by pathological subtypes. This valuable resource provides detailed data on stroke burden for each subtype by age and country income level; hence, it can be used for the planning of preventive strategies and future healthcare policies.

CONTRIBUTORS

R.K. wrote the first draft of the report. All members of the writing committee contributed to the critical revision of the manuscript for important intellectual content.

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