Global Variation in the Relative Burden of Stroke and Ischemic Heart Disease

Anthony S. Kim, MD; S. Claiborne Johnston, MD, PhD

Background—Although stroke and ischemic heart disease (IHD) have several well-established risk factors in common, the extent of global variation in the relative burdens of these forms of vascular disease and reasons for any observed variation are poorly understood.

Methods and Results—We analyzed mortality and disability-adjusted life-year loss rates from stroke and IHD, as well as national estimates of vascular risk factors that have been developed by the World Health Organization Burden of Disease Program. National income data were derived from World Bank estimates. We used linear regression for univariable analysis and the Cuzick test for trends. Among 192 World Health Organization member countries, stroke mortality rates exceeded IHD rates in 74 countries (39%), and stroke disability-adjusted life-year loss rates exceeded IHD rates in 62 countries (32%). Stroke mortality ranged from 12.7% higher to 27.2% lower than IHD, and stroke disability-adjusted life-year loss rates ranged from 6.2% higher to 10.2% lower than IHD. Stroke burden was disproportionately higher in China, Africa, and South America, whereas IHD burden was higher in the Middle East, North America, Australia, and much of Europe. Lower national income was associated with higher relative mortality ($P<$0.001) and burden of disease ($P=0.001$) from stroke. Diabetes mellitus prevalence and mean serum cholesterol were each associated with greater relative burdens from IHD even after adjustment for national income.

Conclusions—There is substantial global variation in the relative burden of stroke compared with IHD. The disproportionate burden from stroke for many lower-income countries suggests that distinct interventions may be required. (Circulation. 2011;124:314-323.)

Key Words: stroke ■ ischemic heart disease ■ international health problems ■ cardiovascular diseases ■ mortality rates

According to World Health Organization (WHO) estimates, ischemic heart disease (also known as coronary artery disease) and cerebrovascular disease are the 2 leading causes of mortality worldwide and account for well over 20% of all deaths. Ischemic heart disease and cerebrovascular disease also result in substantial long-term morbidity and are leading causes of overall disease burden (as measured in disability-adjusted life-years [DALYs] lost).1

Ischemic heart disease and stroke involve overlapping atherosclerotic disease mechanisms and share major modifiable risk factors, including physical inactivity, hypertension, diabetes mellitus, tobacco use, alcohol use, and dyslipidemia. Although the particular impacts of vascular risk factors on the development of these subtypes of vascular disease vary on an individual level, ischemic heart disease has consistently accounted for a greater proportion of overall mortality and disease burden than stroke from a global standpoint.1 In contrast, on the national level, where public health priorities are often set, there may be substantial heterogeneity in the relative burdens of these 2 forms of vascular disease; however, the extent of variation in the composition and burden of vascular disease across countries and the precise reasons for any heterogeneity in the relative burdens of stroke and cardiovascular disease are less well understood. Better information on these relative burdens of vascular disease would help to inform efforts to prioritize and target specific interventions for stroke and ischemic heart disease, respectively, and would have particular application in the developing world, which already bears a disproportionate and growing burden from vascular disease.2

We sought to further characterize the relative burdens of these forms of vascular disease by detailing the geographic distribution of countries with disproportionately higher or lower stroke burden compared with ischemic heart disease burden. Then, as a first step toward understanding the reasons for any observed variation, we evaluated the relationship of the national prevalence of vascular risk factors and sociodemographic characteristics to the composition of vascular disease burden by country.
Methods
We conducted an ecological study examining the relative mortality and DALY loss rates from ischemic heart disease and stroke using individual countries as the units of analysis. All analyses were based on publicly available data from the WHO Global InfoBase, WHO Global Burden of Disease Program (GBD), and World Bank.3–6

Case Definitions
The WHO GBD classification system is based on the International Statistical Classification of Diseases and Related Health Problems (ICD) 9th and 10th revisions (ICD-9 and ICD-10, respectively), with some modifications.3 GBD Cause Category G defines a cardiovascular disease grouping that includes rheumatic heart disease, hypertensive heart disease, ischemic heart disease, cerebrovascular disease, and inflammatory heart diseases. For our analysis, we used 2 subcategories, G3 and G4. For ischemic heart disease, we used GBD Cause Category G3, which includes ICD-9 codes 410 to 414 or ICD-10 codes I20 to I25, as well as additional cases redistributed from so-called garbage ICD-9 codes 427.1, 427.4, 427.5, 428, 429.0, 429.1, 429.2, 429.9, and 440.9 or ICD-10 codes I47.2, I49.0, I46, I50, I51.4, I51.5, I51.6, I51.9, and I70.9. For cerebrovascular disease, we used GBD Cause Category G4, which includes ICD-9 codes 430 to 438 or ICD-10 codes I60 to I69. The GBD classification for cerebrovascular disease does not distinguish between ischemic and hemorrhagic stroke, in part because subclassification is prone to error, particularly in resource-poor environments with limited access to neuroimaging studies.3

Cause-Specific Mortality Rates
Estimates of cause-specific mortality rates due to ischemic heart disease and stroke for each of the 192 WHO member countries were compiled from WHO GBD estimates from the most recent update available (2004), and were age and sex standardized to the WHO global standard population. The cause-specific mortality estimates were generated by previously documented methods and data from more than 2700 data sources that were internally consistent estimates. Data sources included national death registries where available, census and survey data, disease surveillance data, and outputs from well-validated disease models that used age-, sex-, and sociodemographic-adjusted rates from similar countries. Relative uncertainty ranges varied from less than 1% in countries with good death registration systems up to +/-25% in countries with limited information on mortality.7

Cause-Specific Disease Burden
Estimates of disease burden from ischemic heart disease and stroke as measured by DALY loss rates were compiled from WHO GBD estimates from the most recent update available (2004) for each country, and were age and sex standardized to the WHO global standard population.4 A DALY is a summary metric that takes into account the impact of premature deaths and nonfatal events that cause long-term disability, multiplied by a disability weight from 0 (no disability) to 1 (death) to account for the disutility of an additional year of survival with disability. A DALY loss of 1 is equivalent to 1 year of perfect health.8 These estimates were based on more than 8700 sources, including disease registries, population surveys, epidemiological studies, and health facility data, as well as disease modeling from similar countries.7,9

Vascular Risk Factors
The national prevalence of selected modifiable vascular risk factors was compiled from the WHO Global InfoBase.4 These estimates are based on national and subnational studies that are adjusted for differences in study methodology or by modeling from sociodemographically similar countries. Predictors include mean systolic blood pressure (in millimeters of mercury) from 2002,6 diabetes prevalence (as a percentage of the population) from 2002,10 mean serum total cholesterol (in millimoles per liter) from 2005,6 smoking prevalence (as a percentage of the population) from 2005,4 per capita alcohol consumption (in liters per years) from 2003,11,12 alcohol drinking score (from 1 [least risky drinking pattern] to 5 [most risky drinking pattern]) from 2005,13 mean body mass index (in kilograms per meter squared) from 2005,6 and prevalence of obesity (body mass index $\geq 30$ kg/m²) from 2005.6 Risk factors were age and sex standardized to the WHO standard population distribution as well, with the exception of diabetes mellitus prevalence and alcohol drinking pattern score.

Income Categories and National Income
We compiled national income information using World Bank income estimates of gross national income per capita in 2004 dollars4 and World Bank Income Categories (low income < $825; lower middle income $826 to 3255; upper middle income $3256 to $10 066, and upper income > $10 066).10

Outcomes
The primary outcome measure was a calculated index that was designed to capture the relative burden of stroke compared with ischemic heart disease for each country. To generate this index, we subtracted the age- and sex-standardized stroke mortality rate for stroke and the corresponding ischemic heart disease mortality rate from each country to generate a rate difference. Then, we standardized this rate difference to the total mortality rate for each country to account for differences in the total mortality rate for each country. A similar index for relative DALY losses from stroke compared with ischemic heart disease was generated for each country by this same method. We chose this measure because a ratio of rates would magnify small differences in rates in countries with very low rates of both stroke and ischemic heart disease, with the straightforward interpretation notwithstanding. Similarly, a simple rate difference would not distinguish between countries with a 1% versus 6% rate difference compared with a 30% versus 36% rate difference. This standardized rate difference takes into account total disease burdens, and is used here primarily as a relative measure for comparisons between countries, at the expense of a measure that is not as directly interpretable as the pure additive and multiplicative alternatives described above.

Data Analysis
We generated a rank-ordered list of countries from those with a disproportionately high stroke mortality compared to ischemic heart disease mortality to those with a disproportionately low stroke mortality compared to ischemic heart disease mortality. These tables were combined with geographic data to generate choropleth maps using the sphmap module for Stata (StataCorp LP, College Station, TX).14 These maps use color and saturation to indicate the relative value of the variable by geographic unit. Separate maps for absolute stroke mortality rates, absolute ischemic heart disease mortality rates, and the relative stroke to ischemic heart disease mortality index were generated. Similar methods were used to generate maps for corresponding DALY loss rates.

To examine unvariable relationships between vascular risk factors and national income and the stroke to ischemic heart disease relative mortality index, we used linear regression and the Cuzick nonparametric test of trend for categorical predictors (drinking pattern score and World Bank income category). To enhance the linearity of the association between cardiovascular risk factor and income predictors and the stroke to IHD mortality index outcome (which was approximately normally distributed), the variables for the prevalence of diabetes mellitus, the quantity of alcohol consumed per year, and the national income per capita were log transformed. Similar techniques were used to evaluate the association between vascular risk factors and income and the relative stroke to ischemic heart disease DALY loss index.

Stata (MP version 11.2, StataCorp LP) was used for all analysis and data visualization. Ethics approval for the present study was not required, because all data were collected and analyzed in aggregate form at the country level.

Results
There was substantial variation in estimates of standardized mortality rates due to stroke and ischemic heart disease across countries. Stroke mortality rates ranged from 25 per 100 000 in Seychelles to 249 per 100 000 in Kyrgyzstan, and ischemic heart disease mortality rates ranged from 13 per 100 000 in Kiribati to 456 per 100 000 in Turkmenistan (Table 1; online-only Data Supplement).
On a worldwide basis, mortality rates from ischemic heart disease exceeded mortality rates from stroke, but stroke mortality rates were higher than ischemic heart disease mortality rates in 74 countries (39%; Table 1). Kiribati had a standardized mortality rate due to stroke that was 11 times higher than that for ischemic heart disease, with a stroke mortality rate of 143 per 100 000, which represents 14.0% of total mortality, compared with an ischemic heart disease mortality rate of 13 per 100 000, which represents 1.2% of total mortality. In contrast, Azerbaijan had a mortality rate due to ischemic heart disease that was more than 3 times higher than that due to stroke, with a stroke mortality rate of 116 per 100 000, which represents 11.0% of total mortality, compared with an ischemic heart disease mortality rate of 403 per 100 000, which represents 38.2% of total mortality (Table 1).

Similar variation in national estimates of disease burden, as measured in standardized DALY loss rates, was seen for both stroke and ischemic heart disease (Table 2; online-only Data Supplement). Disease burden from stroke ranged from 175 DALYs lost per 100 000 in Seychelles to 2078 DALYs lost per 100 000 in Kyrgyzstan. Disease burden from ischemic heart disease ranged from 145 DALYs lost per 100 000 in Kiribati to 4259 DALYs lost per 100 000 in Afghanistan.

On a worldwide basis, disease burdens from ischemic heart disease exceeded disease burdens from stroke, but standardized disease burdens from stroke were greater than for ischemic heart disease in 62 countries (32%). Kiribati had a standardized disease burden from stroke that was more than 11 times higher than that for ischemic heart disease, with 1673 DALYs lost per 100 000

Table 1. Top 15 and Bottom 15 Ranked Countries for Age and Sex Standardized Stroke Mortality in Excess of Ischemic Heart Disease Mortality (as % of Total Mortality) Among 192 WHO Member Countries (WHO Global Burden of Disease Program, 2004)

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Country</th>
<th>Stroke Mortality Rate per 100 000 (as % of Total Mortality Rate)</th>
<th>Ischemic Heart Disease Mortality Rate per 100 000 (as % of Total Mortality Rate)</th>
<th>Total All-Cause Mortality Rate per 100 000</th>
<th>Stroke Mortality in Excess of Ischemic Heart Disease Mortality (as % of Total Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kiribati</td>
<td>143 (14.0)</td>
<td>13 (1.2)</td>
<td>1027</td>
<td>12.7</td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>157 (19.9)</td>
<td>63 (8.0)</td>
<td>786</td>
<td>11.9</td>
</tr>
<tr>
<td>3</td>
<td>Maldives*</td>
<td>207 (16.2)</td>
<td>66 (5.2)</td>
<td>1278</td>
<td>11.0</td>
</tr>
<tr>
<td>4</td>
<td>Saint Kitts and Nevis</td>
<td>218 (23.9)</td>
<td>124 (13.5)</td>
<td>913</td>
<td>10.4</td>
</tr>
<tr>
<td>5</td>
<td>Republic of Korea</td>
<td>97 (17.0)</td>
<td>40 (7.1)</td>
<td>569</td>
<td>9.9</td>
</tr>
<tr>
<td>6</td>
<td>Mongolia</td>
<td>186 (16.0)</td>
<td>93 (8.0)</td>
<td>1162</td>
<td>8.0</td>
</tr>
<tr>
<td>7</td>
<td>Macedonia</td>
<td>164 (19.4)</td>
<td>108 (12.8)</td>
<td>846</td>
<td>6.7</td>
</tr>
<tr>
<td>8</td>
<td>Thailand</td>
<td>99 (11.9)</td>
<td>44 (5.3)</td>
<td>832</td>
<td>6.6</td>
</tr>
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<td>9</td>
<td>Haiti</td>
<td>158 (8.8)</td>
<td>58 (3.6)</td>
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<td>6.2</td>
</tr>
<tr>
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<td>Portugal</td>
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<td>61 (11.4)</td>
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<td>5.5</td>
</tr>
<tr>
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<td>48 (7.3)</td>
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<td>4.9</td>
</tr>
<tr>
<td>12</td>
<td>Suriname</td>
<td>150 (15.2)</td>
<td>119 (12.1)</td>
<td>990</td>
<td>3.1</td>
</tr>
<tr>
<td>13</td>
<td>Japan</td>
<td>42 (11.7)</td>
<td>32 (8.9)</td>
<td>362</td>
<td>2.8</td>
</tr>
<tr>
<td>14</td>
<td>Bosnia and Herzegovina</td>
<td>135 (18.2)</td>
<td>114 (15.5)</td>
<td>738</td>
<td>2.7</td>
</tr>
<tr>
<td>15</td>
<td>Sao Tome and Principe*</td>
<td>141 (10.1)</td>
<td>107 (7.6)</td>
<td>1394</td>
<td>2.5</td>
</tr>
<tr>
<td>16</td>
<td>Georgia</td>
<td>145 (21.6)</td>
<td>246 (36.6)</td>
<td>671</td>
<td>−15.1</td>
</tr>
<tr>
<td>17</td>
<td>Estonia</td>
<td>100 (12.3)</td>
<td>222 (27.4)</td>
<td>810</td>
<td>−15.1</td>
</tr>
<tr>
<td>18</td>
<td>Saudi Arabia*</td>
<td>50 (5.8)</td>
<td>179 (21.0)</td>
<td>852</td>
<td>−15.2</td>
</tr>
<tr>
<td>19</td>
<td>Lebanon*</td>
<td>83 (9.3)</td>
<td>219 (24.7)</td>
<td>886</td>
<td>−15.3</td>
</tr>
<tr>
<td>20</td>
<td>Egypt</td>
<td>85 (8.1)</td>
<td>252 (23.9)</td>
<td>1057</td>
<td>−15.8</td>
</tr>
<tr>
<td>21</td>
<td>Libyan Arab Jamahiriya*</td>
<td>74 (9.3)</td>
<td>207 (26.0)</td>
<td>799</td>
<td>−16.7</td>
</tr>
<tr>
<td>22</td>
<td>Oman*</td>
<td>52 (7.1)</td>
<td>177 (24.3)</td>
<td>729</td>
<td>−17.2</td>
</tr>
<tr>
<td>23</td>
<td>Armenia</td>
<td>193 (16.3)</td>
<td>420 (35.5)</td>
<td>1183</td>
<td>−19.2</td>
</tr>
<tr>
<td>24</td>
<td>Slovakia</td>
<td>62 (8.7)</td>
<td>205 (28.9)</td>
<td>710</td>
<td>−20.2</td>
</tr>
<tr>
<td>25</td>
<td>Uzbekistan</td>
<td>152 (13.9)</td>
<td>376 (34.4)</td>
<td>1094</td>
<td>−20.4</td>
</tr>
<tr>
<td>26</td>
<td>Lithuania</td>
<td>88 (11.1)</td>
<td>251 (31.6)</td>
<td>793</td>
<td>−20.5</td>
</tr>
<tr>
<td>27</td>
<td>Republic of Moldova</td>
<td>179 (15.9)</td>
<td>428 (38.0)</td>
<td>1124</td>
<td>−22.1</td>
</tr>
<tr>
<td>28</td>
<td>Belarus</td>
<td>154 (14.9)</td>
<td>415 (40.0)</td>
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<td>−25.2</td>
</tr>
<tr>
<td>29</td>
<td>Turkmenistan</td>
<td>85 (6.0)</td>
<td>456 (32.0)</td>
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<td>−26.1</td>
</tr>
<tr>
<td>30</td>
<td>Ukraine</td>
<td>138 (12.9)</td>
<td>424 (39.6)</td>
<td>1072</td>
<td>−26.7</td>
</tr>
<tr>
<td>31</td>
<td>Azerbaijan</td>
<td>116 (11.0)</td>
<td>403 (38.2)</td>
<td>1055</td>
<td>−27.2</td>
</tr>
</tbody>
</table>

WHO indicates World Health Organization.
*Estimates generated from modeling.
Data for all 192 WHO member countries are available in the online-only Data Supplement.
from stroke (6.7% of total disease burden) compared with 145 DALYs lost per 100 000 for ischemic heart disease (0.6% of the total disease burden). In contrast, Turkmenistan had an ischemic heart disease burden more than 5 times higher than for stroke, with 677 DALYs lost per 100 000 (2.4% of total disease burden) from stroke compared with 3579 DALYs lost per 100 000 (12.6% of total disease burden) from ischemic heart disease (Table 2).

**Geographic Distribution**

The geographic distribution of age-standardized stroke and ischemic heart disease mortality rates is shown in Figures 1A and 1B. Stroke mortality rates appeared to be higher in much of Africa and Asia and lower in North America, Western and Northern Europe, and Australia, whereas ischemic heart disease mortality rates appeared to be higher in the Middle East and Eastern Europe.

The relative mortality from stroke compared with ischemic heart disease is shown in Figure 1C. China had considerably higher relative stroke mortality, and much of Africa and South America also had high stroke mortality. In contrast, ischemic heart disease mortality figured more prominently in the Middle East, North America, Australia, and Western Europe. Russia had high rates of both stroke and ischemic heart disease, but not disproportionately higher rates of one over the other.

### Table 2. Top 15 and Bottom 15 Ranking Countries for Age and Sex Standardized DALY Losses From Stroke in Excess of DALY Losses From Ischemic Heart Disease (as % of Total DALY Lost) Among 192 WHO Member Countries (WHO Global Burden of Disease Program, 2004)

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Country</th>
<th>Stroke DALY Loss Rate per 100 000 (as % of Total DALY Loss Rate)</th>
<th>Ischemic Heart Disease DALY Loss Rate per 100 000 (as % of Total DALY Loss Rate)</th>
<th>Total All-Cause DALY Loss Rate per 100 000</th>
<th>Stroke DALY Losses in Excess of Ischemic Heart Disease DALY Losses (as % of Total DALY Losses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kiribati</td>
<td>1673 (6.7)</td>
<td>145 (0.6)</td>
<td>24 819</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>Mongolia</td>
<td>1936 (8.2)</td>
<td>800 (3.4)</td>
<td>23 523</td>
<td>4.8</td>
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<tr>
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<td>China</td>
<td>1072 (6.8)</td>
<td>416 (2.6)</td>
<td>15 750</td>
<td>4.2</td>
</tr>
<tr>
<td>4</td>
<td>Maldives*</td>
<td>1346 (5.7)</td>
<td>475 (2.0)</td>
<td>23 507</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>Saint Kitts and Nevis</td>
<td>1737 (9.5)</td>
<td>1104 (6.1)</td>
<td>18 234</td>
<td>3.5</td>
</tr>
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<td>6</td>
<td>Republic of Korea</td>
<td>625 (5.1)</td>
<td>295 (2.4)</td>
<td>12 248</td>
<td>2.7</td>
</tr>
<tr>
<td>7</td>
<td>Haiti</td>
<td>1377 (3.8)</td>
<td>509 (1.4)</td>
<td>36 012</td>
<td>2.4</td>
</tr>
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<td>Thailand</td>
<td>740 (3.7)</td>
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</tr>
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<td>Japan</td>
<td>425 (5.3)</td>
<td>274 (3.4)</td>
<td>8013</td>
<td>1.9</td>
</tr>
<tr>
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<td>Portugal</td>
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<td>507 (4.4)</td>
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<td>Saint Lucia</td>
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<tr>
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<td>Grenada</td>
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</tr>
<tr>
<td>14</td>
<td>Sao Tome and Principe*</td>
<td>1112 (3.5)</td>
<td>822 (2.6)</td>
<td>31 628</td>
<td>0.9</td>
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<tr>
<td>15</td>
<td>Bosnia and Herzegovina</td>
<td>1234 (8.5)</td>
<td>1109 (7.6)</td>
<td>14 505</td>
<td>0.9</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>177</td>
<td>Morocco*</td>
<td>502 (2.8)</td>
<td>1437 (8.1)</td>
<td>17 780</td>
<td>–5.3</td>
</tr>
<tr>
<td>178</td>
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<td>2617 (13.0)</td>
<td>20 105</td>
<td>–5.7</td>
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<tr>
<td>179</td>
<td>Kuwait</td>
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<td>931 (8.0)</td>
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<td>–6.0</td>
</tr>
<tr>
<td>180</td>
<td>Lebanon*</td>
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<td>1819 (9.6)</td>
<td>18 881</td>
<td>–6.2</td>
</tr>
<tr>
<td>181</td>
<td>Lithuania</td>
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<td>1682 (10.2)</td>
<td>16 454</td>
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</tr>
<tr>
<td>182</td>
<td>Slovakik</td>
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<td>1332 (8.6)</td>
<td>13 844</td>
<td>–6.4</td>
</tr>
<tr>
<td>183</td>
<td>Egypt</td>
<td>757 (3.7)</td>
<td>2175 (10.7)</td>
<td>20 261</td>
<td>–7.0</td>
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<tr>
<td>184</td>
<td>Uzbekistan</td>
<td>1033 (4.9)</td>
<td>2629 (12.4)</td>
<td>21 277</td>
<td>–7.5</td>
</tr>
<tr>
<td>185</td>
<td>Libyan Arab Jamahiriya*</td>
<td>532 (3.3)</td>
<td>1755 (10.9)</td>
<td>16 177</td>
<td>–7.6</td>
</tr>
<tr>
<td>186</td>
<td>Armenia</td>
<td>1198 (6.5)</td>
<td>2618 (14.2)</td>
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</tr>
<tr>
<td>187</td>
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<td>360 (2.0)</td>
<td>1892 (10.7)</td>
<td>17 639</td>
<td>–8.7</td>
</tr>
<tr>
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<td>Belarus</td>
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DALY indicates disability-adjusted life-year; WHO, World Health Organization.

*Estimates generated from modeling. Data for all 192 WHO member countries are available in the online-only Data Supplement.
The geographic distribution of disease burden from stroke (Figure 2A) and ischemic heart disease (Figure 2B), as measured in DALY loss rates, appeared similar to the patterns seen for mortality (Figures 1A and 1B). Relative disease burdens from stroke compared with ischemic heart disease (Figure 2C) also closely mirrored the patterns seen for mortality.

**Vascular Risk Factors and National Income**

In an exploratory univariable analysis, lower World Bank income category \(P<0.001\) for trend; Figure 3) and lower gross national income per capita \(P<0.001\) were strongly associated with a lower relative mortality rate from stroke compared with ischemic heart disease (Table 3). A higher national prevalence of
diabetes mellitus ($P<0.001$) and smoking ($P=0.018$), as well as a higher mean serum cholesterol ($P<0.001$) and body mass index ($P=0.024$), were also associated with a lower relative mortality due to stroke compared with ischemic heart disease (Table 3). Similar associations were observed for the relative disease burden from stroke compared with heart disease (Table 3). These findings were replicated in a sensitivity analysis using crude mortality and DALY loss rates instead of age- and sex-standardized outcomes (not shown).

After controlling for national income, both higher diabetes mellitus prevalence ($\beta=-0.032, P=0.001$) and higher mean serum cholesterol ($\beta=-0.034, P=0.01$) remained significantly
associated with lower mortality due to stroke compared with ischemic heart disease, whereas higher smoking prevalence (\(P=0.440\)) and higher body mass index (0.450) were no longer associated with lower mortality due to stroke compared with ischemic heart disease. Similar results were seen with burden of disease, as measured in DALY loss rates for diabetes (\(P=0.014\), \(P<0.001\)) and mean serum cholesterol (\(P=0.012\), \(P=0.021\)).

**Discussion**

The present analysis provides a comprehensive overview of global variation in the relative mortality and burden of disease attributable to 2 major forms of vascular disease: ischemic heart disease and stroke. Our study draws specific attention to countries and regions with vascular disease burdens that are disproportionately due to cerebrovascular disease or to ischemic heart disease. We propose that by highlighting the global variation in these forms of vascular disease, and by exploring and understanding the factors that may explain this variation, we can better inform current efforts to reduce the burden of stroke and ischemic heart disease worldwide.

Previous reports have highlighted high stroke or ischemic heart disease burdens in specific geographic regions\(^{15,16}\) or specific countries,\(^2\) but without a comprehensive focus on the comparative burden of stroke versus ischemic heart disease. Other reports have focused on the overall cardiovascular disease burden on a worldwide basis, in which ischemic heart disease predominates,\(^3\) or have focused specifically on the disproportionate impact of stroke in the developing world, but without a specific comparison to ischemic heart disease burdens,\(^7\) or have combined the burdens due to stroke and ischemic heart disease together under the general category of cardiovascular disease.\(^8\) The distinctive focus of the present study was on providing a comprehensive view of the comparative burdens of these forms of vascular disease globally.

**Geographic Distribution**

The geographic distribution of countries with disproportionate burdens from stroke or ischemic heart disease allows for several noteworthy observations and avenues for future investigation. First, several countries in Asia demonstrated some of the highest relative mortality and burden of disease from stroke. In particular, the disease burden from
stroke in China was among the highest outliers for stroke in our analysis. This finding is particularly relevant given the current demographic shifts and changes in the prevalence of vascular risk factors in China's large population and the projected large surge in mortality due to cardiovascular disease overall, including stroke, in coming decades.19

Relatively higher stroke burdens were also seen in parts of Africa and, to a lesser extent, in South America, particularly among low- and middle-income countries, where communicable diseases are often the leading focus of public health efforts. Given the strong associations between morbidity and mortality due to stroke and national income,17 this finding focuses attention on the role of economic conditions and available resources on disease burden from cardiovascular disease in general and cerebrovascular disease in particular, especially because the burden of disease from noncommunicable diseases, such as stroke and ischemic heart disease, is projected to surpass the burden of disease from infectious disease in low- to middle-income countries over the next few decades.1,20

Several countries in the Middle East also reported much higher disease burdens from ischemic heart disease than from stroke. Although these findings are concordant with the predominant patterns in much of northern Europe, the United States, Canada, and Australia, the magnitude of differences between the relative burdens from ischemic heart disease and stroke was greater, and largely driven by very high absolute ischemic heart disease mortality and DALY losses. Here again, little is known about the precise reasons for the relatively high burdens of ischemic heart disease over stroke.
Vascular Risk Factors
In our exploratory analysis, we evaluated whether epidemiological factors, such as vascular risk factors, or economic factors, such as national income, could play a role in this variation. For vascular risk factors, because high blood pressure, heavy alcohol use, and advanced age are stronger predictors for stroke than for ischemic heart disease, whereas dyslipidemia, diabetes mellitus, and smoking are more strongly linked to ischemic heart disease, we hypothesized that higher relative burdens of stroke or ischemic heart disease could result from differences in the pattern of these risk factors. For example, the high relative burden of cerebrovascular disease in China might reflect high rates of very high blood pressure, as well as the higher case-fatality rates from the greater incidence of hemorrhagic strokes caused by hypertension. In contrast, some have suggested that the particularly high burden of cardiovascular disease in India may reflect the increasing incidence of diabetes mellitus over time. We did find that national measures of diabetes mellitus, dyslipidemia, and obesity—precisely the vascular risk factors that are operative in high-income countries—were associated with higher relative ischemic heart disease in the present univariable analysis. This was in keeping with the predominant pattern of vascular disease in high-income countries and worldwide, in which ischemic heart disease burden is greater than stroke burden.

Economic Factors
Previous studies have also emphasized the importance of economic factors as predictors of stroke mortality and burden. The availability of adequate resources may impact case fatality and long-term morbidity for countries at various stages along the epidemiological transition and access to prevention, treatment, and follow-up care may more directly affect stroke mortality and the impact of ongoing disability from stroke in resource-constrained environments. For example, aspirin for acute myocardial infarction has an estimated incremental cost-effectiveness ratio of $9 to $20 per DALY averted, whereas the incremental cost-effectiveness ratio of aspirin for acute stroke is $100 to $700 per DALY averted. Therefore, in resource-constrained environments, a given expenditure on aspirin therapy for secondary prevention may have differential impact on the burdens of disease from stroke and ischemic heart disease. Here again, we found that lower national income was more strongly associated with higher relative stroke mortality than with higher ischemic heart disease mortality in univariable analysis.

Other Factors
We also speculated that other factors related to both national income and region, such as genetic/ethnic variation in local population, could play a role in determining the composition of vascular disease burden. For example, the prevalence of intracranial compared with extracranial carotid disease varies among ethnic groups, with intracranial atherosclerosis more common in Asian and African populations and extracranial carotid and aortic arch atherosclerotic disease more common in white populations. Therefore, a given pattern of atherosclerotic risk factors present in a population could result in different patterns of ischemic heart disease and stroke based on host factors alone.

Study Limitations
The present study has several limitations. First, because vascular risk factors were measured on a national level, we were unable to account for the population distribution of risk factors or for joint effects of risk factors within specific subpopulations in this ecological analysis. Second, although the data sources used for the present study represent best-available estimates, we did use modeling to develop estimates for some countries, particularly developing countries, where there may be a greater risk of inaccurate estimates even after careful systematic review or rigorous modeling given the heterogeneity in data collection methods and the limited availability of primary source data. In particular, reliable and comprehensive country-specific breakdowns on ischemic and hemorrhagic stroke incidence and case-fatality rates were not available, particularly because the distinction between these 2 forms of stroke often rests on costly neuroimaging or autopsy studies. Our analysis would be impacted to the extent that there may be country-specific differences in the ascertainment and assignment of the cause of disease. Our ability to explain the observed variation in relative stroke and ischemic heart disease burdens was also limited by the cross-sectional nature of the analysis. Finally, heterogeneity in acute care and severity of disease vary substantially between countries and may contribute to national differences in ways that were not captured in our analysis.

We were unable to assess for secular trends in both vascular disease patterns and vascular risk factors given that our analysis was cross-sectional; however, a follow-up study using data from the anticipated update from the GBD program may provide additional insight into the factors that explain the observed variation in the burdens from these forms of vascular disease. The example in Japan might be illustrative here, where, despite an increase in the prevalence of metabolic disorders such as hypercholesterolemia, obesity, and glucose intolerance in recent years, there has been a dramatic reduction in stroke incidence and mortality over the last decade, possibly attributable to better control of extremely high blood pressure; there was little change in corresponding myocardial infarction incidence or mortality over the same period.

The present analysis does paint a global picture of relative stroke and ischemic heart disease burdens with implications for national priorities for the treatment and prevention of cardiovascular disease in general and for stroke in particular. Ischemic heart disease and stroke are already the 2 leading causes of death in many developing countries, and vascular disease is expected to overtake infectious diseases as the leading cause of disease burden worldwide. Targeting outlier countries and regions with particularly high relative stroke burdens for stroke-specific surveillance, particularly in low- and middle-income countries and in Asian countries, may help us better understand the biological, economic, and systemic factors responsible for disproportionate stroke burden and mortality and develop interventions designed to address these specific burdens.

Conclusions
There is substantial global variation in the relative burden of stroke compared with ischemic heart disease; mortality and disease burdens from stroke and ischemic heart disease do not track uniformly with each other. Lower-income countries have a higher relative stroke burden overall, which may be related in part to associations with income and with vascular risk factor profiles. Further investi-
Stroke and ischemic heart disease account for a substantial and growing share of overall mortality and disease burden worldwide. However, despite having overlapping risk factors and disease mechanisms, they may be significant variation in the relative burden of disease from stroke compared with ischemic heart disease worldwide. In the present study, we used data from the World Health Organization Burden of Disease Program to develop a comprehensive overview of the geographic patterns of variation in burden of stroke and heart disease. We found that there is substantial global variation in the relative burden of stroke versus ischemic heart disease; mortality and disease burdens from stroke and ischemic heart disease do not track uniformly with each other. There was disproportionately greater stroke burden in China, Africa, and South America, whereas ischemic heart disease burden was greater in the Middle East, North America, Australia, and much of Europe. Lower-income countries have a higher relative stroke burden overall, which may be related in part to associations with vascular risk factor profiles. These data suggest that a better understanding of the reasons for this variation may be helpful to develop targeted national interventions.
Global Variation in the Relative Burden of Stroke and Ischemic Heart Disease
Anthony S. Kim and S. Claiborne Johnston

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Supplemental Table 1.

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## Supplemental Table 1.

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<td>25305</td>
<td>-5.0</td>
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<td>1538 (9.5)</td>
<td>16212</td>
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<td>Iran (Islamic Republic of)</td>
<td>764 (3.9)</td>
<td>1769 (9.1)</td>
<td>19432</td>
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<td>Morocco*</td>
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<td>17780</td>
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<td>Kuwait</td>
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<td>Lebanon*</td>
<td>642 (3.4)</td>
<td>1819 (9.6)</td>
<td>18881</td>
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<tr>
<td>Ranking</td>
<td>Country</td>
<td>Stroke DALY Loss Rate per 100,000 (as % of Total DALY Loss Rate)</td>
<td>Ischemic Heart Disease DALY Loss Rate per 100,000 (as % of Total DALY Loss Rate)</td>
<td>Total All-Cause DALY Loss Rate per 100,000 (as % of Total DALY Loss Rate)</td>
<td>Stroke DALY Losses in Excess of Ischemic Heart Disease DALY Losses (as % of Total DALY Losses)</td>
</tr>
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<td>3579 (12.6)</td>
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