Gross Domestic Product and Health Expenditure Associated With Incidence, 30-Day Fatality, and Age at Stroke Onset

A Systematic Review

Luciano A. Sposato, MD, MBA; Gustavo Saposnik, MD, MSc, FAHA

Background and Purpose—Differences in definitions of socioeconomic status and between study designs hinder their comparability across countries. We aimed to analyze the correlation between 3 widely used macrosocioeconomic status indicators and clinical outcomes.

Methods—We selected population-based studies reporting incident stroke risk and/or 30-day case-fatality according to prespecified criteria. We used 3 macrosocioeconomic status indicators that are consistently defined by international agencies: per capita gross domestic product adjusted for purchasing power parity, total health expenditures per capita at purchasing power parity, and unemployment rate. We examined the correlation of each macrosocioeconomic status indicator with incident risk of stroke, 30-day case-fatality, proportion of hemorrhagic strokes, and age at stroke onset.

Results—Twenty-three articles comprising 30 population-based studies fulfilled the eligibility criteria. Age-adjusted incident risk of stroke using the standardized World Health Organization World population was associated to lower per capita gross domestic product adjusted for purchasing power parity ($\rho=-0.661$, $P=0.027$, $R^2=0.32$) and total health expenditures per capita at purchasing power parity ($\rho=-0.623$, $P=0.040$, $R^2=0.26$). Thirty-day case-fatality rates and proportion of hemorrhagic strokes were also related to lower per capita gross domestic product adjusted for purchasing power parity and total health expenditures per capita at purchasing power parity. Moreover, stroke occurred at a younger age in populations with low per capita gross domestic product adjusted for purchasing power parity and total health expenditures per capita at purchasing power parity. There was no correlation between unemployment rates and outcome measures.

Conclusions—Lower per capita gross domestic product adjusted for purchasing power parity and total health expenditures per capita at purchasing power parity were associated with higher incident risk of stroke, higher case-fatality, a greater proportion of hemorrhagic strokes, and lower age at stroke onset. As a result, these macrosocioeconomic status indicators may be used as proxy measures of quality of primary prevention and acute care and considered as important factors for developing strategies aimed at improving worldwide stroke care. (Stroke. 2012;43:00-00.)

Key Words: employment ■ gross domestic product ■ health expenditure ■ mortality ■ socioeconomic status ■ stroke incidence

At the population level, the incident risk of stroke and its consequences (eg, mortality) are considered the interactive result of ethnic, genetic, environmental, socioeconomic, and quality of care-related factors. Low socioeconomic status (SES) is associated with health inequalities in terms of access to care, increased incident risk of cardiovascular diseases, and early death. Relatively few studies have investigated the relation between SES and stroke at the population level.¹⁻³ SES is a multidimensional concept comprising various indicators interacting over a lifespan. Commonly used SES measurements are educational level, employment, income, and possessions. However, each individual factor measures different components and provides dissimilar information about SES; thus, they are not transferable by having distinct associations and implications. The selection of SES indicators is frequently influenced by availability of data, which may constitute a limitation for comparing their impact on stroke incidence and outcome across different countries.¹ If associated with stroke incidence and outcomes, the identification of widely used and consistently measured macroindicators of SES would be useful for defining health policies and targeting public health interventions worldwide.
The aim of our study was to analyze the association of per-capita gross domestic product (GDP), total health expenditures, and unemployment rate with incident risk of stroke, 30-day case-fatality, proportion of primary intracerebral hemorrhages, and age at stroke onset in population-based studies.

Methods

Search Strategy
We conducted a systematic review of the literature to identify population-based studies reporting the incident risk of first-ever stroke (any type) and/or 30-day case-fatality. We searched Medline, Scopus, EMBASE, and PubMed for articles published between 2000 and 2011 using similar terms as proposed by Feigin et al: “stroke,” “cerebrovascular,” “population-based,” “community-based,” “community,” “epidemiology,” “epidemiological,” “incidence,” “attack rates,” “survey,” “surveillance,” “registry,” “register,” “mortality,” “morbidity,” “fatality,” “case fatality,” or “trends.” Two investigators (L.A.S. and G.S.) independently screened all titles and abstracts to identify potentially relevant articles. Discrepancies were resolved by consensus. For those articles reporting studies performed in ≥1 population, we considered each population individually. Similarly, for studies reporting data on the same population but from different recruitment periods, we considered each period independently, because macroindicators of SES may have changed over time.

Eligibility Criteria
For all potentially relevant articles, full-text articles were retrieved, and data were extracted if they met the following criteria: (1) articles published in English; (2) reporting first-ever stroke incidence or 30-day case fatality; (3) age-standardized using either the World Health Organization (WHO) World population or the European population; (4) recruitment period between 2000 and 2010; (5) prospective data collection over whole years; and (6) population-based studies including participants aged ≥18 years (with no upper age limit). We decided not to include studies reported before the Year 2000 because of the significant improvements in cardiovascular prevention and treatment interventions experienced during the last decade. Population-based studies reporting only 1 pathological type of stroke (eg, ischemic stroke) were excluded from the analysis. Our analyses of stroke incidence and 30-day case-fatality rates were restricted to incident stroke cases.

Data Elements
We recorded age, percentage of males, proportion of different stroke types, rate of hospitalizations, and proportion of cases undergoing neuroimaging studies, when available. On the basis of neuroimaging and autopsy findings, strokes were classified into 4 types: ischemic stroke, primary intracerebral hemorrhage, subarachnoid hemorrhage, and undefined.

Macroindicators of SES: Definitions
We used per-capita GDP adjusted for purchasing power parity expressed in 2005 constant international dollars (PPP-aGDP), total health expenditures per capita at purchasing power parity expressed in National Current Unit per US dollars (PPP-aTHE), and unemployment rate as macroindicators of SES. PPP-aGDP is the most commonly used indicator of economic wealth. An international dollar has the same purchasing power over GDP as the US dollar has in the United States. We used this indicator with the intention of avoiding the potential bias of monetary exchange rates between countries. PPP-aGDP, obtained from the World Bank Web site, was expressed in 2005 constant international dollars with the aim of neutralizing the effect of inflation when comparing studies from different years.

PPP-aTHE is the sum of general government health expenditure and private health expenditure in a given year. This indicator reflects a country’s true investment in health irrespective of its PPP-aGDP. The source for the PPP-aTHE was the WHO Web site.

Outcome Measures
The primary outcome was incident risk of stroke. For this purpose, we used first-ever stroke incidence rates per 100 000 individuals age-standardized for the WHO World population with corresponding 95% CIs. Similarly, we used first-ever stroke incidence age-standardized for the World population for a sensitivity analysis. Secondary outcome measures included 30-day case-fatality, the proportion of primary intracerebral hemorrhages, and age at stroke onset.

Statistical Analysis
Two-tailed Spearman test and scatterplots were used to examine the correlation of each macroindicator of SES with outcome measures. The level of significance was set at P<0.05.

We also analyzed the correlation between the proportion of PPP-aGDP allocated to total health expenditures and the annual average PPP-aGDP during the study period for the 22 countries participating in the study. The purpose of this analysis was to determine if the investment on health among less developed countries was lower in both absolute and relative terms. Analyses were performed with SPSS 13.0 (SPSS Inc, Chicago, IL).

Results
We identified 48 potentially relevant manuscripts reporting stroke incidence and/or 30-day case-fatality rates in 58 populations (Figure 1). We excluded 25 articles reporting data on 28 cities/regions for not meeting the eligibility criteria (Supplemental Table I; http://stroke.ahajournals.org). Finally, 23 articles comprising population-based studies done in 30 populations were available for the analysis (Table 1).

Data on age-standardized incident stroke risk for the WHO World and European populations, 30-day case-fatality rates, proportion of primary intracerebral hemorrhages, and age at stroke onset was available from 11, 13, 26, 28, and 30 populations, respectively (Tables 2 and 3).
Table 1. Summary of Included Population-Based Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Country</th>
<th>Persons-Years</th>
<th>Recruitment Period</th>
<th>Incident Strokes, No.</th>
<th>Age at Stroke Onset, Mean (SD)</th>
<th>Males, %</th>
<th>Hospitalization Rate, %</th>
<th>Documentation With Neuroimaging, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corbin</td>
<td>Barbados</td>
<td>Barbados</td>
<td>239 068</td>
<td>2001–2002</td>
<td>335</td>
<td>72.5 (14.8)</td>
<td>39.4</td>
<td>68.8</td>
<td>96.0</td>
</tr>
<tr>
<td>Kulesh</td>
<td>Grodno</td>
<td>Belarus</td>
<td>933 402</td>
<td>2001–2003</td>
<td>2069</td>
<td>65.8 (11.6)</td>
<td>49.1</td>
<td>89.7</td>
<td>30.3</td>
</tr>
<tr>
<td>Palm</td>
<td>Ludwigshafen</td>
<td>Germany</td>
<td>335 812</td>
<td>2006–2007</td>
<td>1231</td>
<td>71.6 (12.9)</td>
<td>48.9</td>
<td>95.3</td>
<td>97.7</td>
</tr>
<tr>
<td>Azarpazhooh</td>
<td>Mashad</td>
<td>Iran</td>
<td>450 229</td>
<td>2006–2007</td>
<td>624</td>
<td>64.7 (14.8)</td>
<td>52.4</td>
<td>71.8</td>
<td>30.3</td>
</tr>
<tr>
<td>Minelli</td>
<td>Matoa</td>
<td>Brazil</td>
<td>75 053</td>
<td>2003–2004</td>
<td>81</td>
<td>65.3 (12.1)</td>
<td>62.9</td>
<td>92.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Lavados</td>
<td>Iquique</td>
<td>Chile</td>
<td>429 052</td>
<td>2000–2002</td>
<td>292</td>
<td>68.5 (14.6)</td>
<td>56.2</td>
<td>70.9</td>
<td>91.4</td>
</tr>
<tr>
<td>Manobianca</td>
<td>Puglia</td>
<td>Italy</td>
<td>77 470</td>
<td>2001–2002</td>
<td>127</td>
<td>74.5</td>
<td>60.6</td>
<td>95.2</td>
<td>93.7</td>
</tr>
<tr>
<td>Tsiskaridze</td>
<td>Tbilisi</td>
<td>Georgia</td>
<td>128 115</td>
<td>2000–2003</td>
<td>233</td>
<td>67.3 (10.2)</td>
<td>44.6</td>
<td>66.1</td>
<td>66.7</td>
</tr>
<tr>
<td>Hallström</td>
<td>Lund-Orup</td>
<td>Sweden</td>
<td>234 505</td>
<td>2001–2002</td>
<td>456</td>
<td>NA</td>
<td>56.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Correia</td>
<td>Northern Portugal</td>
<td>Portugal</td>
<td>246 224</td>
<td>1998–2000</td>
<td>688</td>
<td>73.0</td>
<td>41.3</td>
<td>58.0</td>
<td>96.9</td>
</tr>
<tr>
<td>Corso</td>
<td>Aosta</td>
<td>Italy</td>
<td>247 496</td>
<td>2004–2005</td>
<td>553</td>
<td>75.6 (13.8)</td>
<td>49.2</td>
<td>88.1</td>
<td>94.2</td>
</tr>
<tr>
<td>Vibo</td>
<td>Tartu</td>
<td>Estonia</td>
<td>202 244</td>
<td>2002–2003</td>
<td>451</td>
<td>71.6 (12.3)</td>
<td>40.8</td>
<td>87.6</td>
<td>89.8</td>
</tr>
<tr>
<td>Benatru</td>
<td>Dijon1</td>
<td>France</td>
<td>750 690</td>
<td>2000–2004</td>
<td>NA</td>
<td>73.4</td>
<td>NA</td>
<td>70.7</td>
<td>NA</td>
</tr>
<tr>
<td>EROS Investigators</td>
<td>Dijon2</td>
<td>France</td>
<td>304 830</td>
<td>2004–2006</td>
<td>386</td>
<td>70.7 (13.8)</td>
<td>49.0</td>
<td>94.6</td>
<td>NA</td>
</tr>
<tr>
<td>EROS Investigators</td>
<td>Sesto Fiorentino</td>
<td>Italy</td>
<td>94 472</td>
<td>2004–2006</td>
<td>161</td>
<td>75.9 (11.9)</td>
<td>49.7</td>
<td>92.6</td>
<td>NA</td>
</tr>
<tr>
<td>EROS Investigators</td>
<td>Kaunas</td>
<td>Lithuania</td>
<td>365 191</td>
<td>2004–2005</td>
<td>816</td>
<td>69.9 (12.8)</td>
<td>43.5</td>
<td>96.7</td>
<td>NA</td>
</tr>
<tr>
<td>EROS Investigators</td>
<td>London</td>
<td>United Kingdom</td>
<td>653 770</td>
<td>2004–2006</td>
<td>459</td>
<td>68.2 (15.3)</td>
<td>55.0</td>
<td>93.3</td>
<td>NA</td>
</tr>
<tr>
<td>EROS Investigators</td>
<td>Menorca</td>
<td>Spain</td>
<td>150 270</td>
<td>2004–2006</td>
<td>77</td>
<td>72.2 (14.1)</td>
<td>56.7</td>
<td>87.7</td>
<td>NA</td>
</tr>
<tr>
<td>EROS Investigators</td>
<td>Warsaw</td>
<td>Poland</td>
<td>120 186</td>
<td>2005</td>
<td>135</td>
<td>69.0 (13.9)</td>
<td>49.6</td>
<td>97.0</td>
<td>NA</td>
</tr>
<tr>
<td>Musolinò</td>
<td>Aeolian Island</td>
<td>Italy</td>
<td>13 431</td>
<td>1999–2000</td>
<td>62</td>
<td>72.5 (9.9)</td>
<td>41.9</td>
<td>82.2</td>
<td>82.2</td>
</tr>
<tr>
<td>Syme</td>
<td>Scottish Borders</td>
<td>United Kingdom</td>
<td>212 704</td>
<td>1998–2000</td>
<td>596</td>
<td>76.6 (12.0)*</td>
<td>46.0</td>
<td>91.0</td>
<td>90.6</td>
</tr>
<tr>
<td>Islam</td>
<td>Perth</td>
<td>Australia</td>
<td>143 417</td>
<td>2000–2001</td>
<td>183</td>
<td>77.0 (32–98)*</td>
<td>48.1</td>
<td>92.3</td>
<td>89.1</td>
</tr>
<tr>
<td>Anderson</td>
<td>Auckland</td>
<td>New Zealand</td>
<td>1 000 000</td>
<td>2002–2003</td>
<td>1938</td>
<td>73.0 (13.8)</td>
<td>46.0</td>
<td>70.2</td>
<td>87.6</td>
</tr>
<tr>
<td>Dalal</td>
<td>Mumbai</td>
<td>India</td>
<td>313 722</td>
<td>2005–2006</td>
<td>456</td>
<td>66.0 (13.6)</td>
<td>52.2</td>
<td>67.2</td>
<td>89.2</td>
</tr>
<tr>
<td>Damasceno</td>
<td>Maputo</td>
<td>Mozambique</td>
<td>1 094 628</td>
<td>2005–2006</td>
<td>531</td>
<td>59.1 (13.2)</td>
<td>52.5</td>
<td>NA</td>
<td>83.4</td>
</tr>
<tr>
<td>Cabral</td>
<td>Joinville</td>
<td>Brazil</td>
<td>974 094</td>
<td>2005–2006</td>
<td>759</td>
<td>64.9 (13.9)</td>
<td>50.7</td>
<td>84.2</td>
<td>93.1</td>
</tr>
<tr>
<td>Wang</td>
<td>Beijing</td>
<td>China</td>
<td>50 581</td>
<td>2000</td>
<td>90</td>
<td>69.5 (9.6)</td>
<td>NA</td>
<td>NA</td>
<td>91.3</td>
</tr>
<tr>
<td>Wang</td>
<td>Shanghai</td>
<td>China</td>
<td>45 680</td>
<td>2000</td>
<td>73</td>
<td>73.5 (9.5)</td>
<td>NA</td>
<td>NA</td>
<td>79.9</td>
</tr>
<tr>
<td>Wang</td>
<td>Changsha</td>
<td>China</td>
<td>51 165</td>
<td>2000</td>
<td>103</td>
<td>68.8 (10.0)</td>
<td>NA</td>
<td>NA</td>
<td>74.1</td>
</tr>
<tr>
<td>Cantu-Brito</td>
<td>Durango</td>
<td>Mexico</td>
<td>247 665</td>
<td>2007–2008</td>
<td>238</td>
<td>51.0 (58–82)*</td>
<td>50.5</td>
<td>100.0</td>
<td>89.5</td>
</tr>
</tbody>
</table>

EROS indicates European Registers of Stroke; NA, not available.

*Expressed as median (range).

Populations with lower PPP-aGDP showed a higher incident risk of stroke, standardized for the WHO World population ($\rho = -0.661$, $P = 0.027$, $R^2 = 0.32$; Table 3; Figure 2A); higher 30-day case-fatality rates ($\rho = -0.713$, $P < 0.001$, $R^2 = 0.43$; Table 3; Figure 2B); a greater proportion of intracerebral hemorrhages ($\rho = -0.689$, $P < 0.001$, $R^2 = 0.43$; Table 3; Figure 2C); and lower age at stroke onset ($\rho = 0.622$, $P < 0.001$, $R^2 = 0.47$; Table 3; Figure 2D). Similarly, populations with lower PPP-aTHE had a higher incident risk of stroke standardized for the WHO World population ($\rho = -0.623$, $P = 0.040$, $R^2 = 0.26$; Table 3; Figure 3A); higher 30-day case-fatality rates ($\rho = -0.701$, $P < 0.001$, $R^2 = 0.45$; Table 3; Figure 3B); a greater proportion of intracerebral hemorrhages ($\rho = -0.643$, $P < 0.001$, $R^2 = 0.32$; Table 3; Figure 3C); and a lower age at stroke onset ($\rho = 0.606$, $P < 0.001$, $R^2 = 0.36$; Table 3; Figure 3D). The sensitivity analysis of incident stroke risk standardized for the European population also showed a significant correlation with PPP-aGDP ($\rho = -0.553$, $P = 0.050$, $R^2 = 0.33$) and PPP-aTHE ($\rho = -0.587$, $P = 0.035$, $R^2 = 0.29$). Similar results were obtained by only including studies of European populations (Supplemental Data). We found no correlations between unemployment rate and outcome measures (Table 3).

Finally, we found a significant correlation between the proportion of PPP-aGDP allocated to total health expenditures and the average annual PPP-aGDP ($\rho = 0.651$, $P = 0.001$, $R^2 = 0.50$; Supplemental Figure 1) for the 22 countries participating in the study, suggesting that the investment on health among less developed countries was lower both in absolute and relative terms.

**Discussion**

PPP-aGDP, PPP-aTHE, and unemployment rate are the most common macroeconomic indicators of a country’s standard...
of living and public health policies. Despite the worldwide use of these indicators, to the best of our knowledge, there are no studies particularly assessing their association with the incident risk of stroke and outcomes at the population level. In a systematic review, Feigin et al analyzed population studies reporting on the incidence/prevalence of stroke in different countries. The results were then divided according to the country’s socioeconomic level (low to middle to high income). However, no economic indicators were included.

In the present systematic review of population-based studies, we analyzed the correlation of PPP-aGDP, PPP-aTHE, and unemployment rate with standardized risk of incident stroke, 30-day case-fatality rates, proportion of primary intracerebral hemorrhages, and age at stroke onset. PPP-aGDP was associated with incident risk of stroke, 30-day case-fatality, and proportion of primary intracerebral hemorrhages. These results were consistent when the analysis was standardized for the European population (sensitivity analysis). Interestingly, stroke onset occurred at younger ages in countries with lower per-capita PPP-aGDP. Similarly, the study of Feigin et al found higher first-ever stroke incidence, greater early mortality rates, and a larger proportion of hemorrhagic strokes among lower to middle-income countries when compared with higher income nations. A recent study also showed a higher burden of stroke in lower income countries.

Table 2. Macroindicators of Socioeconomic Status, Incident Stroke Risk, Proportion of Intracerebral Hemorrhages, and 30-Day Case-Fatality Rates

<table>
<thead>
<tr>
<th>Author</th>
<th>PPP-aGDP International $</th>
<th>PPP-aTHE NCU per US $</th>
<th>Unemployment Rate, %</th>
<th>First-Ever Stroke Incidence (WHO World) × 100 000 Population (95% CI)</th>
<th>First-Ever Stroke Incidence (EUR) × 100 000 Population (95% CI)</th>
<th>Intracerebral Hemorrhage, %</th>
<th>30-D Case-Fatality Rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corbin10</td>
<td>19 189</td>
<td>989</td>
<td>10.1</td>
<td>88 (70–106)</td>
<td>135 (112–158)</td>
<td>11.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Kulesh11</td>
<td>6 592</td>
<td>434</td>
<td>2.1</td>
<td>220 (210–231)</td>
<td>287 (274–301)</td>
<td>NA</td>
<td>26.1</td>
</tr>
<tr>
<td>Palm12</td>
<td>32 910</td>
<td>3557</td>
<td>9.5</td>
<td>NA</td>
<td>146 (135–157)</td>
<td>9.1</td>
<td>13.6</td>
</tr>
<tr>
<td>Azarpazhooh13</td>
<td>10 033</td>
<td>592</td>
<td>10.6</td>
<td>NA</td>
<td>309 (274–343)</td>
<td>12.7</td>
<td>NA</td>
</tr>
<tr>
<td>Minelli14</td>
<td>8 169</td>
<td>520</td>
<td>9.3</td>
<td>137 (112–166)</td>
<td>NA</td>
<td>13.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Lavados15</td>
<td>10 658</td>
<td>613</td>
<td>9.1</td>
<td>108 (96–121)</td>
<td>140 (124–156)</td>
<td>23.6</td>
<td>23.3</td>
</tr>
<tr>
<td>Manobianca16</td>
<td>28 222</td>
<td>2229</td>
<td>7.8</td>
<td>76 (62–90)</td>
<td>150 (130–180)</td>
<td>18.9</td>
<td>18.1</td>
</tr>
<tr>
<td>Tsiskaridze17</td>
<td>2 743</td>
<td>141</td>
<td>12.0</td>
<td>NA</td>
<td>150 (130–170)</td>
<td>26.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Hallström18</td>
<td>29 756</td>
<td>2 506</td>
<td>5.2</td>
<td>NA</td>
<td>140 (130–158)</td>
<td>10.2</td>
<td>14.3</td>
</tr>
<tr>
<td>Correia19</td>
<td>20 756</td>
<td>1507</td>
<td>4.2</td>
<td>NA</td>
<td>181 (164–197)</td>
<td>16.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Corso20</td>
<td>28 222</td>
<td>2 412</td>
<td>7.8</td>
<td>97 (80–114)</td>
<td>126 (106–146)</td>
<td>10.5</td>
<td>19.0</td>
</tr>
<tr>
<td>Vibo21</td>
<td>12 814</td>
<td>670</td>
<td>10.9</td>
<td>NA</td>
<td>188 (171–207)</td>
<td>12.6</td>
<td>26.2</td>
</tr>
<tr>
<td>Benatri22</td>
<td>28 876</td>
<td>2 844</td>
<td>9.1</td>
<td>NA</td>
<td>99 (92–106)</td>
<td>9.0</td>
<td>10.0</td>
</tr>
<tr>
<td>EROS Investigators23</td>
<td>29 822</td>
<td>3 292</td>
<td>8.9</td>
<td>NA</td>
<td>NA</td>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>EROS Investigators23</td>
<td>28 289</td>
<td>2 361</td>
<td>7.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>16.8</td>
</tr>
<tr>
<td>EROS Investigators23</td>
<td>14 226</td>
<td>742</td>
<td>9.9</td>
<td>NA</td>
<td>NA</td>
<td>11.3</td>
<td>23.6</td>
</tr>
<tr>
<td>EROS Investigators23</td>
<td>32 802</td>
<td>2 945</td>
<td>4.8</td>
<td>NA</td>
<td>NA</td>
<td>14.1</td>
<td>15.0</td>
</tr>
<tr>
<td>EROS Investigators23</td>
<td>27 377</td>
<td>2 109</td>
<td>9.6</td>
<td>NA</td>
<td>NA</td>
<td>25.2</td>
<td>33.3</td>
</tr>
<tr>
<td>EROS Investigators23</td>
<td>27 416</td>
<td>857</td>
<td>17.7</td>
<td>NA</td>
<td>NA</td>
<td>6.7</td>
<td>17.0</td>
</tr>
<tr>
<td>Musolino24</td>
<td>27 226</td>
<td>2 063</td>
<td>11.3</td>
<td>NA</td>
<td>154 (103–180)</td>
<td>12.9</td>
<td>24.2</td>
</tr>
<tr>
<td>Syme25</td>
<td>28 232</td>
<td>1 883</td>
<td>5.7</td>
<td>NA</td>
<td>NA</td>
<td>8.4</td>
<td>18.6</td>
</tr>
<tr>
<td>Islam26</td>
<td>29 855</td>
<td>2 266</td>
<td>6.6</td>
<td>74 (63–86)</td>
<td>NA</td>
<td>10.4</td>
<td>20.2</td>
</tr>
<tr>
<td>Anderson27</td>
<td>24 042</td>
<td>1 847</td>
<td>5.1</td>
<td>139 (132–147)</td>
<td>NA</td>
<td>NA</td>
<td>21.0</td>
</tr>
<tr>
<td>Dalal28</td>
<td>2389</td>
<td>90</td>
<td>4.4</td>
<td>NA</td>
<td>NA</td>
<td>17.7</td>
<td>29.8</td>
</tr>
<tr>
<td>Damasceno29</td>
<td>688</td>
<td>40</td>
<td>16.0</td>
<td>NA</td>
<td>NA</td>
<td>40.3</td>
<td>47.6</td>
</tr>
<tr>
<td>Cabral30</td>
<td>8625</td>
<td>766</td>
<td>8.9</td>
<td>NA</td>
<td>NA</td>
<td>12.4</td>
<td>19.1</td>
</tr>
<tr>
<td>Wang31</td>
<td>2 667</td>
<td>107</td>
<td>3.1</td>
<td>120</td>
<td>NA</td>
<td>26.7</td>
<td>NA</td>
</tr>
<tr>
<td>Wang31</td>
<td>2 667</td>
<td>107</td>
<td>3.1</td>
<td>64</td>
<td>NA</td>
<td>34.6</td>
<td>NA</td>
</tr>
<tr>
<td>Wang31</td>
<td>2 667</td>
<td>107</td>
<td>3.1</td>
<td>118</td>
<td>NA</td>
<td>51.5</td>
<td>NA</td>
</tr>
<tr>
<td>Cantu-Brito32</td>
<td>13 402</td>
<td>852</td>
<td>3.5</td>
<td>118 (103–133)</td>
<td>NA</td>
<td>20.7</td>
<td>39.0</td>
</tr>
</tbody>
</table>

PPP-aGDP indicates per-capita gross domestic product adjusted for purchasing power parity in 2005 constant international dollars; PPP-aTHE, total health expenditures per capita at purchasing power parity expressed in National Current Unit per US dollars; WHO World, age-standardized for World Health Organization World Population; EUR, age-standardized for European Population; NCU, National Current Unit; EROS, European Registers of Stroke; NA, not available.
primary intracerebral hemorrhages, and lower age at stroke onset. These findings expose the potential consequences of low investment on health on the burden of cerebrovascular disease irrespective of PPP-aGDP. Moreover, we found that the investment on health in less developed countries was lower not only in absolute, but also in relative terms. This means that poorer countries allocate a lower proportion of their economic resources to health when compared with more developed nations. Together, these results (stroke onset at younger age with a higher incident risk of hemorrhagic

Table 3. Correlation Analyses of Macroindicators of Socioeconomic Status

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Unemployment</th>
<th>PPP-aGDP</th>
<th>PPP-aTHE</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployment</td>
<td>Spearman ρ</td>
<td>P Value</td>
<td>R²</td>
<td>Spearman ρ</td>
</tr>
<tr>
<td>Incident risk of stroke, WHO*</td>
<td>-0.492</td>
<td>0.12</td>
<td>0.31</td>
<td>-0.661</td>
</tr>
<tr>
<td>Incident risk of stroke, European†</td>
<td>0.102</td>
<td>0.74</td>
<td>0.07</td>
<td>-0.553</td>
</tr>
</tbody>
</table>

PPP-aGDP indicates per-capita gross domestic product adjusted for purchasing power parity in 2005 constant international dollars; PPP-aTHE, total health expenditures per capita at purchasing power parity expressed in National Current Unit per US dollars; R², effect size; Spearman ρ, Spearman rank correlation coefficient.

*A standardized for the World Health Organization World Population (Shanghai city was excluded from the analysis for being an outlier).

†Standardized for the European population.

Figure 2. Scatterplots for PPP-aGDP: PPP-aGDP vs incident stroke risk age-standardized for the WHO World Population (A), PPP-aGDP vs 30-day case-fatality rates (B) PPP-aGDP vs proportion of patients with primary intracerebral hemorrhage (C), and PPP-aGDP vs age at stroke onset (D). PPP-aGDP indicates per-capita gross domestic product adjusted for purchasing power parity in 2005 constant international dollars; WHO, World Health Organization.
stroke) may suggest poorer control of vascular risk factors, especially arterial hypertension, in populations with a low GDP.34

Finally, we found no association between unemployment rate and any of the outcome measures. This finding is not surprising, because the information on the association between unemployment and stroke is scarce and perhaps has marginal impact.35 There are several possible explanations for the association of PPP-aGDP and PPP-aTHE with higher stroke incidence and case-fatality. GDP is used to analyze how economies evolve worldwide, because its variations are rapidly identified. PPP-aGDP is a better indicator of wealth, because it compensates for differences of local currencies. The burden of cardiovascular diseases is higher in lower-income countries4 where health expenditures are smaller in absolute (lower PPP-aGDP) and relative terms (lower proportion of PPP-aGDP allocated to total health expenditures) as shown in our analysis. Concurrently, vascular diseases cause significant reductions in GDP,36 suggesting a reciprocal relationship. For example, vascular risk factors are more prevalent and access to medical care is more limited in poorer economies.37 As a consequence and according to WHO estimates, China will lose $558 billion between 2006 and 2015 in its expected national income due to the combination of heart disease, stroke, and diabetes.36

Some limitations and strengths should be considered. First, we acknowledge the ecological nature of our study. However, ecological studies can answer important questions that cannot be addressed by other study designs (eg, randomized clinical trials).38 Second, the PPP-aGDP for a given country may not be representative of the particular population or the city where a study was done. Moreover, significant differences in PPP-aGDP can be found within a country. However, we attempted to use PPP-aGDP, PPP-aTHE, and unemployment rates for the studied populations. Third, because PPP-aGDP does not consider the “black market” and ignores unpaid work, it might be subject to inaccurate estimations, especially in lower-income countries. Nevertheless, our results would have underestimated the true relationship between PPP-aGDP.
and the incident risk of stroke and case-fatality. Fourth, our study did not include unpublished data or studies that we might have involuntarily omitted.

Despite the aforementioned limitations, our study is novel in the sense that it assessed the relationship among 3 widely used macroindicators of SES (ie, adjusted GDP, total health expenditures, and unemployment) and several outcome measures, including the proportion of hemorrhagic strokes and age at stroke onset. Moreover, the results of our study are consistent not only with respect to the association between these macroindicators of SES and the outcome measures, but also with the results of other recent studies. Together, these findings provide evidence for a better understanding of the relationship between macroindicators of SES and stroke burden at the population level. These results may also serve to generate hypotheses for identifying and answering relevant questions in health policy that otherwise would not be identified due to the impracticality of using alternative study designs (eg, randomized controlled trials).

In conclusion, lower PPP-aGDP and PPP-aTHE were associated with onset of cerebrovascular disease at younger age, a higher proportion of intracerebral hemorrhages, and a higher incident risk of stroke and mortality. These macroindicators of SES could be used for estimating measures of quality of care in primary prevention (eg, incidence) and access to acute stroke care (eg, 30-day mortality) among different countries. Furthermore, PPP-aGDP and PPP-aTHE should be taken into account when implementing strategies aimed at improving worldwide stroke care, particularly in developing or low- to middle-income countries.

Acknowledgments

We thank Rosane Nisenbaum (senior statistician at The Keenan Research Centre in the Li Ka Shing Knowledge Institute, St Michael’s Hospital) for her critical comments and suggestions regarding the analytic approach.

Sources of Funding

L.A.S. was supported by an unrestricted grant of INECO Foundation.

Disclosures

None.

References


SUPPLEMENTAL MATERIAL

Gross Domestic Product and Health Expenditure Associated with Incidence, 30-Day Fatality and Age at Stroke Onset: A Systematic Review

This supplemental file includes:

1. Results of a sensitivity analysis done for the 17 European populations included in the study.
2. Table 1. Excluded studies and reasons for exclusion.
3. Results of a sensitivity analysis incorporating a Study from Japan (includes Table 2).
4. Figure 1. Correlation between Proportion of PPP-aGDP Allocated to Total Health Expenditures and the Average Annual PPP-aGDP during the Study Period for the 22 Countries Participating in the Study.
5. References

Sensitivity Analyses

A sensitivity analysis restricted to the 17 European populations included in the study showed the following correlations between PPP-aGDP and incidence risk of stroke adjusted for the European population (Spearman's $\rho=-0.723$, $P=0.018$, $R^2=0.04$), 30-day case fatality (Spearman's $\rho=-0.817$, $P<0.001$, $R^2=0.44$), and proportion of intracerebral hemorrhages (Spearman's $\rho=-0.449$, $P=0.081$, $R^2=0.22$).

Results of a sensitivity analysis incorporating Takashima Study

As there were no studies from Japan meeting the eligibility criteria (e.g. age-standardized stroke incidence for WHO or European populations), we elected to complete a sensitivity analysis by including the Takashima Study. For this purpose, we incorporated the stroke incidence rates standardized for the Japanese population reported by the authors in the group of studies standardized for the European Population. As shown in Table 2, the sensitivity analysis did not significantly change the results, thus confirming our previous findings.
<table>
<thead>
<tr>
<th>Author</th>
<th>City/Region</th>
<th>Country</th>
<th>Recruitment Years</th>
<th>Main Reasons for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzamora</td>
<td>Barcelona</td>
<td>Spain</td>
<td>2003</td>
<td>J</td>
</tr>
<tr>
<td>Carandang</td>
<td>Framingham</td>
<td>United States</td>
<td>1990-2004</td>
<td>K</td>
</tr>
<tr>
<td>Cesaroni</td>
<td>Rome</td>
<td>Italy</td>
<td>2001-2004</td>
<td>E, G</td>
</tr>
<tr>
<td>Chau</td>
<td>Hong Kong</td>
<td>China</td>
<td>1999-2007</td>
<td>E, F</td>
</tr>
<tr>
<td>Das</td>
<td>Kolkata</td>
<td>India</td>
<td>2003-2005</td>
<td>I</td>
</tr>
<tr>
<td>Delbari</td>
<td>Qom</td>
<td>Iran</td>
<td>2001</td>
<td>F</td>
</tr>
<tr>
<td>Gostynski</td>
<td>Canton Basle</td>
<td>Switzerland</td>
<td>2002-2003</td>
<td>J</td>
</tr>
<tr>
<td>Harmsen</td>
<td>Gothenburg</td>
<td>Sweden</td>
<td>1997-2006</td>
<td>F</td>
</tr>
<tr>
<td>Heuschmann</td>
<td>South London</td>
<td>UK</td>
<td>2003-2004</td>
<td>H</td>
</tr>
<tr>
<td>Goulart</td>
<td>Sao Paulo</td>
<td>Brazil</td>
<td>2006-2009</td>
<td>B, F</td>
</tr>
<tr>
<td>Johnson</td>
<td>Edmonton</td>
<td>Canada</td>
<td>2003-2007</td>
<td>E</td>
</tr>
<tr>
<td>Kita</td>
<td>Takashima County</td>
<td>Japan</td>
<td>1999-2001</td>
<td>B</td>
</tr>
<tr>
<td>Kleindorfer</td>
<td>Cincinnati</td>
<td>United States</td>
<td>2005</td>
<td>F</td>
</tr>
<tr>
<td>Kubo</td>
<td>Hisayama</td>
<td>Japan</td>
<td>1961, 1974, 1988</td>
<td>D, G</td>
</tr>
<tr>
<td>Lewsey</td>
<td>-</td>
<td>Scotland</td>
<td>1986-2005</td>
<td>E, F</td>
</tr>
<tr>
<td>Marsden</td>
<td>Hunter Area</td>
<td>Australia</td>
<td>1996-2008</td>
<td>E, F</td>
</tr>
<tr>
<td>Mihálka</td>
<td>Uzhgorod</td>
<td>Ukraine</td>
<td>1999-2000</td>
<td>C</td>
</tr>
<tr>
<td>Ni Chrónin</td>
<td>Dublin</td>
<td>Ireland</td>
<td>2005-2006</td>
<td>J</td>
</tr>
<tr>
<td>Powles</td>
<td>Varna &amp; Two rural cities</td>
<td>Bulgaria</td>
<td>2000-2001</td>
<td>G</td>
</tr>
<tr>
<td>Rothwell</td>
<td>Oxfordshire</td>
<td>UK</td>
<td>2002-4 &amp; 2004-5</td>
<td>B</td>
</tr>
<tr>
<td>Sridharan</td>
<td>Trivandrum</td>
<td>India</td>
<td>2005</td>
<td>E</td>
</tr>
<tr>
<td>Sturgeon</td>
<td>Minneapolis-St. Paul</td>
<td>United States</td>
<td>1980-2002</td>
<td>E, F</td>
</tr>
<tr>
<td>Vaartjes</td>
<td>-</td>
<td>Netherlands</td>
<td>2000</td>
<td>E</td>
</tr>
<tr>
<td>Walker</td>
<td>Hai &amp; Dar-es-Salaam</td>
<td>Tanzania</td>
<td>2003-2006</td>
<td>A</td>
</tr>
<tr>
<td>Zhao</td>
<td>Lhasa</td>
<td>China</td>
<td>2006-2008</td>
<td>E</td>
</tr>
</tbody>
</table>

A: not reporting first-ever stroke incidence or 30-day case fatality rates. B: not age-standardized using either the World Health Organization (WHO) World population or the European population. C: not distinguishing between first-ever and recurrent events. D: recruitment before 2000 or after 2010. E: retrospective data collection or not recorded over whole years. F: not population-based or limited to hospital admissions. G: limits for the age of the population studied (other than ≥18 years). H: not reporting overall stroke data (e.g. reporting adjusted stroke incidence rates but stratified by sex, stroke subtypes or ethnic groups). I: door-to-door capture. J: limited to only one stroke type (e.g. ischemic or...
hemorrhagic). K: studies predominantly taking place before year 2000 and not reporting significant or exclusive data for the 2000-2010 decade.
Table 2. Sensitivity Analysis Incorporating a Study from Japan

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Unemployment</th>
<th>PPP-aGDP</th>
<th>PPP-aTHE</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s ( \rho )</td>
<td>P</td>
<td>R(^2)</td>
<td>Spearman’s ( \rho )</td>
</tr>
<tr>
<td>Incident Risk of Stroke, European *</td>
<td>0.166</td>
<td>0.57</td>
<td>0.03</td>
<td>-0.596</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-Day Case Fatality</td>
<td>0.204</td>
<td>0.32</td>
<td>0.04</td>
<td>-0.713</td>
</tr>
<tr>
<td>Proportion of Intracerebral</td>
<td>-0.287</td>
<td>0.13</td>
<td>0.04</td>
<td>-0.643</td>
</tr>
<tr>
<td>Hemorrhages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at stroke Onset</td>
<td>-0.225</td>
<td>0.22</td>
<td>0.10</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Spearman’s \( \rho \):** Spearman’s rank correlation coefficient. **PPP-aGDP:** per capita gross domestic product adjusted for purchasing power parity in 2005 constant international dollars. **R\(^2\):** effect size. *Standardized for the European Population. **PPP-aTHE:** total health expenditures per capita at purchasing power parity (National Current Unit per US dollars).
Figure 1. Correlation Between Proportion of PPP-aGDP Allocated to Total Health Expenditures and the Average Annual PPP-aGDP during the Study Period for the 22 Countries Participating in the Study.
References


