Relative Risks for Stroke by Age, Sex, and Population Based on Follow-Up of 18 European Populations in the MORGAM Project

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Background and Purpose—Within the framework of the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project, the variations in impact of classical risk factors of stroke by population, sex, and age were analyzed.

Methods—Follow-up data were collected in 43 cohorts in 18 populations in 8 European countries surveyed for cardiovascular risk factors. In 93,695 persons aged 19 to 77 years and free of major cardiovascular disease at baseline, total observation years were 1,234,252 and the number of stroke events analyzed was 3,142. Hazard ratios were calculated by Cox regression analyses.

Results—Each year of age increased the risk of stroke (fatal and nonfatal together) by 9% (95% CI, 9% to 10%) in men and by 10% (9% to 10%) in women. A 10-mm Hg increase in systolic blood pressure involved a similar increase in risk in men (28%; 24% to 32%) and women (25%; 20% to 29%). Smoking conferred a similar excess risk in women (104%; 78% to 133%) and in men (82%; 66% to 100%). The effect of increasing body mass index was very modest. Higher high-density lipoprotein cholesterol levels decreased the risk of stroke more in women (hazard ratio per mmol/L 0.58; 0.49 to 0.68) than in men (0.80; 0.69 to 0.92). The impact of the individual risk factors differed somewhat between countries/regions with high blood pressure being particularly important in central Europe (Poland and Lithuania).

Conclusions—Age, sex, and region-specific estimates of relative risks for stroke conferred by classical risk factors in various regions of Europe are provided. From a public health perspective, an important lesson is that smoking confers a high risk for stroke across Europe. (Stroke. 2009;40:2319-2326.)

Key Words: blood pressure ■ cholesterol ■ cohort studies ■ smoking ■ stroke risk factors

The appraisal of stroke risk in populations or individuals is based on the recognition that all cardiovascular disorders are multifactorial in nature. The most widely used risk score for stroke was developed within the framework of The Framingham Heart Study, the original version being published in 1971 with later refinements based on longer follow-up, addition of more predictors, and using more sophisticated statistical techniques. The Framingham stroke risk score has been used extensively when international and national guidelines for cardiovascular prevention have been developed.

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Evaluation (SCORE) Project,3 the Prospective Cardiovascular Münster (PROCAM) cohort in Germany,4 a Chinese cohort of male steelworkers,5 and the Italian Progetto Epidemiologia e prevenzione delle malattie cerebro e cardiovascolari (CUORE) study.6 It seems that these stroke risk scores capture a substantial amount of variation of stroke risk.2 However, the risk equations available have been based on fatal strokes only,3 limited to one population,2,4,5 or not large enough to permit detailed analyses by age and sex. It has become obvious that stroke or cardiovascular risk equations developed in one population may not be very accurate to predict stroke risk in other populations.7–10

Table 1. Characteristics of Cohorts Included in the Analyses

<table>
<thead>
<tr>
<th>Region, Country</th>
<th>Population</th>
<th>No. of Cohorts</th>
<th>Type of Cohort (Reference)*</th>
<th>Age Range at Baseline (Survey Period)</th>
<th>Years of Follow-Up</th>
<th>Total Years of Observation†</th>
<th>No. of Fatal Strokes‡</th>
<th>No. of All Strokes, Fatal and Nonfatal‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Europe</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lithuania</td>
<td></td>
<td>3</td>
<td>MONICA center</td>
<td>33–65 (1986–1993)</td>
<td>5–13</td>
<td>35 520/40 351</td>
<td>13/17</td>
<td>15/17 28/34 44/54 32/40 76/84</td>
</tr>
<tr>
<td>France</td>
<td></td>
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<tr>
<td>France</td>
<td></td>
<td>1</td>
<td>PRIME (MONICA procedures), men only</td>
<td>49–64 (1991–1993)</td>
<td>10</td>
<td>24 249/25 139</td>
<td>5/6 0/0 5/6</td>
<td>42/57 0/0 42/57</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td>1</td>
<td>PRIME (MONICA procedures), men only</td>
<td>49–60 (1991–1993)</td>
<td>10</td>
<td>23 672/24 892</td>
<td>4/5 0/0 4/5</td>
<td>26/27 0/0 26/27</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
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</tr>
<tr>
<td>Italy</td>
<td></td>
<td>4</td>
<td>MONICA center (3 cohorts) and MONICA procedures (1 cohort)</td>
<td>24–65 (1986–1994)</td>
<td>3–12</td>
<td>45 829/47 865</td>
<td>4/7 7/7 11/14</td>
<td>21/26 17/20 38/46</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td>1</td>
<td>PRIME (MONICA procedures), men only</td>
<td>49–60 (1991–1993)</td>
<td>10</td>
<td>24 438/24 933</td>
<td>2/2 0/0 2/2</td>
<td>22/24 0/0 22/24</td>
</tr>
<tr>
<td>Nordic countries</td>
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<tr>
<td>United Kingdom</td>
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<td></td>
</tr>
<tr>
<td>Northern Ireland</td>
<td></td>
<td>1</td>
<td>PRIME (MONICA procedures), men only</td>
<td>50–60 (1991–1994)</td>
<td>5</td>
<td>12 515/13 500</td>
<td>4/5 0/0 4/5</td>
<td>14/16 0/0 14/16</td>
</tr>
<tr>
<td>All MORGAM cohorts</td>
<td></td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td>1 234 252/1 346 069 545/714 418/495</td>
<td>963/1209 1851/2357 1291/1499 3142/3856</td>
<td>96/181 0/0 96/181</td>
</tr>
</tbody>
</table>

*Reference(s) to detailed information on the cohort and methods used for obtaining baseline information.
†Analysis data set/subjects on whom data were transferred to the MORGAM data center (including subjects with missing data).
‡In some populations, follow-up for stroke deaths covered a wider age group than follow-up for nonfatal strokes as described in “Methods.” The “No. of All Strokes” covers the follow-up period of nonfatal strokes only. Therefore, the no. of fatal strokes is occasionally as high as no. of fatal and nonfatal events together.
Table 2. Comparisons of HRs and their 95% Confidence Limits Between Calculations Based on All Strokes (Fatal+Nonfatal) and Fatal Strokes Only*

<table>
<thead>
<tr>
<th></th>
<th>Fatal and Nonfatal Strokes</th>
<th>Fatal Strokes Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (N=51 703)</td>
<td>1851 545</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>1.09 (1.09–1.10) 1.12 (1.10–1.13)</td>
<td>1.28 (1.24–1.32) 1.38 (1.31–1.45)</td>
</tr>
<tr>
<td>Age per year</td>
<td>BMI per unit</td>
<td>Smoking, yes/no</td>
</tr>
<tr>
<td>Blood pressure† per 10 mm Hg</td>
<td>0.92 (1.01–1.03) 1.03 (1.00–1.05)</td>
<td>1.82 (1.66–2.00) 2.00 (1.68–2.38)</td>
</tr>
<tr>
<td>HDL cholesterol per mmol/L</td>
<td>0.80 (0.69–0.92) 1.01 (0.78–1.31)</td>
<td></td>
</tr>
<tr>
<td>Women (N=41 992)</td>
<td>1291 418</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>1.10 (1.09–1.10) 1.13 (1.11–1.14)</td>
<td></td>
</tr>
<tr>
<td>Age per year</td>
<td>BMI per unit</td>
<td>Smoking, yes/no</td>
</tr>
<tr>
<td>Blood pressure† per 10 mm Hg</td>
<td>1.25 (1.20–1.29) 1.26 (1.19–1.34)</td>
<td>2.04 (1.78–2.33) 2.56 (2.01–3.24)</td>
</tr>
<tr>
<td>HDL cholesterol per mmol/L</td>
<td>0.58 (0.49–0.68) 0.48 (0.36–0.65)</td>
<td></td>
</tr>
</tbody>
</table>

*Risk factor data missing in <2.4% of each population except HDL cholesterol in LTU-KAU (9.2% missing), UNK-CAE (24.0%), and UNK-GLA (7.8%).
†Mean of systolic and diastolic blood pressure.

The same was applied to age groups when differences between age groups were analyzed. Populations within one country were merged and, to reduce statistical variation, some countries were also aggregated. Testing several model specifications showed the most reasonable model to use was the proportional hazards model and assuming linear effects of age at baseline, mean of systolic and diastolic blood pressure, HDL cholesterol, and BMI without interactions between these risk factors. In the initial analyses, non-HDL cholesterol (including low-density lipoprotein cholesterol) was not a statistical predictor of stroke in any of the subgroups and it was therefore not included in the final models. Population and sex were considered as stratifying variables in the analyses, ie, the baseline hazard was allowed to vary between populations and between men and women. The same was applied to age groups when differences between age groups were analyzed. Populations within one country were merged and, to reduce statistical variation, some countries were also aggregated. Thus, Lithuania and Poland were analyzed together as “central Europe” and data from Finland, Sweden, and Denmark were pooled as “Nordic countries.” The 5 regions compared in the analyses were Nordic countries, central Europe, the United Kingdom, France, and Italy.
The following 3 hypotheses were tested using likelihood ratio tests: (1) the risk factors have similar effects in all 5 regions; (2) the risk factors have similar effects for men and women; and (3) the risk factors have similar effects for age groups 45 years, 45 to 54 years, 55 to 65 years, and ≥65 years at baseline. Details of the statistical models are given on the MORGAM web site (www.ktl.fi/publications/morgam/stroke). The analyses were performed using R.17

Results

Characteristics of the MORGAM Populations

In the stroke component of the MORGAM Project, 51,703 men and 41,992 women who were free of cardiovascular disease at baseline were followed for an average of 13.2 years (total of 1,234,252 observation years), during which 1,851 strokes occurred in men and 1,291 in women. As shown in Table 1, the study covered 43 cohorts in 18 populations in 8 European countries. After aggregation, 5 European regions were used in the analyses: central Europe (Lithuania and Poland), France, Italy, Nordic countries (Finland, Sweden, and Denmark), and the United Kingdom (Scotland, Northern Ireland, and Wales). In the populations from Northern Ireland, Wales, and France, only men were studied.

Hazard Ratios for All Populations Together

Table 2 shows the hazards ratios for age, blood pressure, smoking, BMI, and HDL cholesterol as predictors of stroke during follow-up of people free of serious cardiovascular disease (as defined in “Methods”) at baseline. Total serum
cholesterol was not a significant independent predictor of stroke and is therefore not reported.

For each 10-mm Hg increase in blood pressure, the risk of stroke increased by 23% to 29%. Smoking conferred almost a doubling of the risk of stroke (hazard ratio [HR], 1.8 in men and 2.0 in women). One BMI unit increased the risk by 2% in men but not in women. Higher HDL serum cholesterol levels decreased the risk of stroke during follow-up (HR per mmol/L, 0.80; 95% CI, 0.69 to 0.92 in men and 0.58; 95% CI, 0.49 to 0.68 in women).

HRs by Region, Sex, and Age
As indicated by Figure 1, the coefficients showed some heterogeneity across the regions. The heterogeneity was statistically significant in men but not in women. For men, age was less important as a risk factor in central Europe and more important in Italy than in the other regions. On the other hand, blood pressure levels at baseline predicted future stroke more strongly in central Europe than in other regions; the difference was statistically significant in men. There were no significant differences between regions in the impact of smoking on stroke risk. Increasing BMI or decreasing HDL conferred a similar excess risk of stroke in all regions. It was also checked whether the exclusion of Wales and Northern Ireland changes the results for the United Kingdom, but no major changes in the point estimates were observed.

When all populations were analyzed together, there were significant differences between men and women in hazard ratios for HDL cholesterol. The other 4 variables all had similar HRs in men and women (Figure 2).

On average, one additional year at baseline increased the risk of stroke by 9% to 10% (Table 2). However, there was a general pattern of greater impact of risk factors at younger ages (Figure 3). For high blood pressure, the differences by age group were statistically significant.

Discussion
There are many reasons why stroke risk factors would have varying impact in different populations, whether they are defined by sex, age, or geography. In addition to genetic variations, the burden of socioeconomic risk factors in whole populations or subsets may well interact with classical cardiovascular risk factors to modify the risk of stroke.

Several scores based on data collected during clinical trials for predicting risk of death from stroke have been developed. This includes scores based on follow-up of participants in randomized trials of antihypertensive treatment and stroke risk estimates of participants in the Multiple Risk Factor Intervention Trial (MRFIT). The risk coefficients differ markedly among the scores presented, illustrating the problems involved in analyzing highly selected cohorts such as people fulfilling all entry criteria of a clinical trial. Therefore, risk equations or risk charts based on follow-up of whole populations and with a sufficiently large number of stroke events are preferred. Such strictly population-derived risk estimates based on at least 300 stroke events have been presented within the frameworks of the Framingham study, the US Cardiovascular Health Study, the Honolulu Heart Programme, the Copenhagen City Heart Study, the Seven Countries Study, the Scottish Renfrew/Paisley study, and the Dijon stroke study. The widely used SCORE risk equations are based on follow-up of a large number of European populations, but only fatal stroke events as diagnosed in routine cause-of-death registers have been recorded.

The strengths of this study are that it includes a very large number of population-based cohorts of both men and women across Europe and that it includes both fatal and nonfatal strokes with individual validation of the diagnosis in the majority of stroke events. With more than 3100 stroke events, MORGAM is, by far, the largest prospective stroke study performed. In 15 of the 16 populations, baseline data collec-
tion was performed by the standardized MONICA criteria or by procedures similar to those used by MONICA (the 3 French cohorts used only one blood pressure measurement by an automatic device). An obvious limitation of a very large study like this is that only a very limited set of risk factors were available for analysis. For instance, data on diabetes, atrial fibrillation, physical inactivity, excess alcohol consumption, or left ventricular hypertrophy, all well established risks for stroke, were not available from all cohorts.

Because relative risks conferred by amenable stroke risk factors usually decline with increasing age, a relatively low upper age limit at baseline (60 years) and short follow-up (5 to 10 years) could possibly have led to slightly inflated hazard ratios in the PRIME cohorts in France and Northern Ireland when compared with the other MORGAM populations.

For several reasons, HRs for ischemic and hemorrhagic strokes together were calculated. First, in some of the populations, CT scanners were not widely available for patients with stroke (particularly so in Lithuania but during the initial years of the MONICA Project; also in several other populations) or autopsy rates were low in patients dying out of the hospital (several west European populations) so that accurate stroke subtyping was not always possible. Second, the statistical power to determine risk for hemorrhagic stroke was low. Third, previous risk appraisals have identified the same risk factors for ischemic and hemorrhagic stroke. The risk estimates have been reported to differ between the stroke subtypes, but the CIs have been very wide for intracerebral hemorrhages and overlapping with those of ischemic stroke.

The extent to which elevated blood pressure increased the risk of stroke varied between populations and regions. For each 10-mm Hg increase in blood pressure, the stroke risk increased, on average, by \( \frac{1}{5} \) in men and \( \frac{1}{4} \) in central European women, whereas the excess risk was as low as 25% in Nordic men and women. A weakness of cohort studies is that exposure may change during the observation time. It is conceivable that, in some MORGAM populations, better blood pressure control during follow-up in those identified as being hypertensive could contribute to an apparent lower stroke risk. The geographic variation in risk was less for cigarette smoking than for blood pressure levels. An important message from MORGAM is that smoking confers a high risk for stroke across Europe.

When the present risk estimates for all 18 European populations together are compared with those based on other cohorts, some similarities and some differences are noted.

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Figure 3. HRs for stroke during follow-up of men and women free of cardiovascular disease at baseline by age at baseline, all MORGAM populations together. The horizontal lines represent 95% CIs of the estimates. The data are adjusted for other factors in a multivariate model with no other explanatory variables than those shown in the figure included in the model.
Although relative risks differ, high blood pressure has generally been the strongest predictor of stroke. Total cholesterol levels were not a predictor of stroke either in the Framingham study or in the present study. Higher HDL cholesterol levels were associated with a lower risk of stroke. The same was observed in the male, but not in the female, cohorts followed in EUROSTROKE (Prediction of Stroke in the General Population in Europe).27 The excess risk increase conveyed by increasing BMI was much greater in previous studies than in the MORGAM cohorts. Thus, the excess risk was approximately 30% per BMI unit in Framingham men,26 10% in Japanese–American men in Honolulu,26 and only 3% per BMI unit in the present study. On the other hand, daily smoking involved about the same excess risk (doubling) in the present European male populations as in Honolulu and China,2,21,26 but it was much higher than reported from Framingham (+30% at 20 cigarettes per day),1 in Danes aged of >55 years (+18%),28 and in Americans >65 years (no apparent excess risk).2 Among smoking women, the relative risk reported in previous studies ranged from no excess risk (elderly Americans2) to 1.54 (Framingham1) to be compared.

HDL cholesterol levels, nonlow-density lipoprotein cholesterol were poor predictors of stroke trends.29 These results from the multivariate models may also contribute to the discrepancies. For instance, when we in the MORGAM study adjusted for conventional risk factors on stroke. Different factors included in the multivariate models may also contribute to the discrepancies. It should be emphasized that the present results refer only to relative risks for stroke. These relative risks do not necessarily translate into risks of stroke in absolute terms. In the stroke component of the World Health Organization MONICA Project, which included a large number of populations from high-income, middle-income, and low-income countries, differences in population levels of conventional risk factors have explained only a modest part of the variation in stroke incidence rates in cross-sectional comparisons.28 Furthermore, secular risk factor trends in the populations were poor predictors of stroke trends.29 These results from ecological analyses indicate that there are population-specific factors that explain much of the absolute levels of stroke incidence and/or mortality in a population. Forthcoming analyses within the MORGAM Project will attempt to address deterrents of variations in absolute risks for stroke between populations.

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Disclosures
None.

References


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