Original Contributions

Risk Factors for Stroke in Middle-Aged Men in Göteborg, Sweden

Per Harmsen, MD, Annika Rosengren, MD, Alecka Tsipogianni, BSc, and Lars Wilhelmsen, MD, PhD

To evaluate stroke risk factors in Göteborg, Sweden, during 1970–1973 a cohort of 7,495 participating men from a general population sample of 9,998 men aged 47–55 years were examined with respect to cardiovascular risk factors. Men with hypertension and hypercholesterolemia and men who were heavy smokers were treated. We assessed stroke end points and cause-specific mortality using a stroke register and death certificates. During a mean follow-up of 11.8 years, 230 strokes occurred in the entire population sample (participants and nonparticipants) (7% subarachnoid hemorrhages, 13% intracerebral hemorrhages, 42% cerebral infarctions, and 38% unspecified strokes). Using univariate analysis, we found measured high blood pressure (systolic and diastolic), smoking, known hypertension, diabetes mellitus, stroke in either parent, severe psychological stress, marital status, atrial fibrillation, previous transient ischemic attacks, previous myocardial infarction, effort-induced chest pain, and intermittent claudication to be significantly related to all stroke. Of the stroke types, subarachnoid hemorrhage was not related to any of these indicators, and intracerebral hemorrhage was related only to measured high blood pressure. Using multivariate analyses, we found measured high blood pressure, smoking, and severe psychological stress as well as atrial fibrillation, previous transient ischemic attacks, and intermittent claudication to be independent risk factors for nonhemorrhagic stroke. Serum cholesterol concentration, occupational and leisure-time physical activity, body mass index, alcohol abuse, and low occupational class were not risk factors for stroke. (Stroke 1990;21:223–229)

Still a major cause of ill health, stroke is the third most common cause of death in most industrialized countries and the leading cause of neurologic handicap, particularly among the elderly. Huge costs are involved in the care of persons afflicted with stroke. It has long been recognized that preventive measures are of the utmost importance in attempts to reduce the incidence of stroke since no effective cures are available.

The best-documented risk factor for stroke, hypertension, is essentially treatable, and part of the decline in stroke morbidity and mortality during the past decades is presumably due to its better management. However, apart from hypertension, risk factors for stroke are less well defined and documented than risk factors for coronary heart disease.

Recently, a longitudinal cohort study from Göteborg, Sweden, showed fibrinogen level and family history of stroke also to be risk factors for stroke. We report another prospective, larger study from the same city.

Subjects and Methods

The study population comprised the intervention group of the Multifactor Primary Prevention Study, the main results of which have been published. The Multifactor Primary Prevention Study started in Göteborg in 1970 and included all men in the city born between 1915 and 1925, with the exception of men born in 1923 (N=30,000). The intervention group of 9,998 men represents a random third of the men; the remaining two thirds were control groups. All men in the intervention group were invited to a screening examination performed between January 1970 and March 1973. Altogether, 7,495 men (75% of those invited) participated. Their mean age at the screening examination was 51 (range 47–55) years.

All participants completed a postal questionnaire before the screening examination. The questionnaire...
we used similar principles in persons older than age 65 years of age as nonparticipants) were followed until March 1983 (mean follow-up period 11.8 years), and all end points of myocardial infarction, stroke, and death were recorded. Since 1970, all fatal and nonfatal strokes in persons up to 65 years of age who resided in Göteborg have been recorded in a stroke register; we used similar principles in persons older than age 65. This stroke register includes all cases of subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and unspecified stroke according to criteria for stroke specified by the World Health Organization; stroke type was diagnosed as described previously, with the addition of information from computed tomography (CT scans), routinely available since 1976.

Death certificates were collected throughout the follow-up period, and the Swedish National Cause-Specific Death Register was matched against the computer file for all the men in the study. Cause-specific mortality was coded by two physicians according to the eighth revision of the International Classification of Diseases. The overall autopsy rate was 71%.

We used conventional statistical methods to calculate the means and standard deviations. Possible associations between continuous and/or graded variables were tested using Pitman’s nonparametric permutation test after adjustment for age. Two-sided tests were used, and \( p < 0.05 \) was considered to indicate significance. Relative risks were calculated as odds ratios, and 95% confidence intervals are given. Adjusted odds ratios were obtained by way of logistic regression.

### Results

During a mean 11.8 years of follow-up, among the 7,495 participants 141 had a first stroke. In addition, seven strokes occurred among men who reported a previous stroke at the screening examination. Among the 2,503 nonparticipants, 82 experienced a stroke during follow-up, for a total of 230 strokes in the entire group of 9,998 men. The rate of each stroke type among participants and nonparticipants is shown in Table 1. The relatively large proportion of subarachnoid hemorrhages corresponds to the comparatively young population. During the first few years of follow-up CT was not available, and therefore the number of unspecified strokes was fairly large. Later, most of these strokes would have been diagnosed as small cerebral infarcts or hemorrhages. The frequency of CT scans increased from 0% in 1976 to 90% of all stroke cases in 1983. Subarachnoid hemorrhage and intracerebral hemorrhage had high case-fatality rates, whereas the case-fatality rates of cerebral infarction and particularly of unspecified stroke were much lower. Of the 185 stroke survivors, 16 died of a new stroke, 27 of coronary heart disease, and 21 of other causes. Among the men with nonhemorrhagic stroke, particularly those with unspeci-
fied stroke, coronary heart disease was an important cause of death. All-cause mortality during follow-up for the men who sustained a stroke was high, almost four times that in men who had no stroke during follow-up.

Table 2 shows the mean values for quantitative variables recorded at the screening examination among the 7,450 participants, who were stroke-free at screening. The results are age-standardized because those who developed stroke were on average 0.7 years older at the screening examination than those who did not. Systolic as well as diastolic BP were significantly higher in men who subsequently suffered a first intracerebral hemorrhage or cerebral infarction than in men who did not develop stroke. First subarachnoid hemorrhage and unspecified stroke were not related to BP. There were no significant differences in cholesterol concentrations (Table 2), heart rate (data not shown), or BMI (data not shown).

Figure 1 shows the increasing incidence of first stroke by quintiles of measured systolic BP, with a marked increase in risk for men in the fifth quintile. Similarly, the greatest increase in risk occurred for men in the fifth quintile of measured diastolic BP (>104 mm Hg) (data not shown). This relation applies to first cerebral infarction and first unspecified stroke, but no significant correlation between measured BP and first subarachnoid hemorrhage could be found. For first intracerebral hemorrhage, a very marked increase in risk was found in the two highest quintiles of measured diastolic BP (data not shown), with only one in 14 cases occurring in men with a diastolic BP of <97 mm Hg at the screening examination. In addition, known hypertension carried an increased risk of cerebral infarction and unspecified stroke (Table 3).

Stroke end points in relation to the cardiovascular risk factors smoking, known hypertension, diabetes mellitus, family history of stroke, psychological stress, and other personal characteristics are shown in Table 3. The only factor significantly associated with subarachnoid hemorrhage was marital status, with an increase in risk among unmarried men. Intracerebral hemorrhage was not significantly associated with any factor, but the numbers were small. Smoking was significantly associated with both cerebral infarction and unspecified stroke. Men with diabetes had an increased incidence of unspecified stroke, but not of cerebral infarction. Family history of stroke was significantly associated with stroke only when all types of stroke were considered together. Severe

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**TABLE 2.** Age-Adjusted Mean Systolic and Diastolic Blood Pressures and Serum Cholesterol Concentrations for 7,450 Participants at Screening Examination by Type of First Stroke, Multifactor Primary Prevention Study, 1970–1983

<table>
<thead>
<tr>
<th>Stroke type</th>
<th>Blood pressure (mm Hg)</th>
<th>Cholesterol (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>No stroke (n=7,309)</td>
<td>149*</td>
<td>94</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage (n=13)</td>
<td>143</td>
<td>90</td>
</tr>
<tr>
<td>Intracerebral hemorrhage (n=14)</td>
<td>170†</td>
<td>109†</td>
</tr>
<tr>
<td>Cerebral infarction (n=68)</td>
<td>144</td>
<td>92</td>
</tr>
<tr>
<td>Unspecified stroke (n=46)</td>
<td>161‡</td>
<td>103‡</td>
</tr>
<tr>
<td>All stroke (n=141)</td>
<td>161*</td>
<td>103*</td>
</tr>
</tbody>
</table>

*Missing data for 10 men.
†‡p<0.01, 0.001, respectively, by Pitman's nonparametric permutation test.

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**FIGURE 1.** Graph of incidence of stroke end points according to quintiles of systolic blood pressure at screening examination, Multifactor Primary Prevention Study, 1970–1983. Unspecif., unspecified; Intracerebr., intracerebral; hem., hemorrhage; Subarachn., subarachnoid. Missing data for 10 men.
TABLE 4. Odds Ratios and 95% Confidence Intervals for First Stroke End Points During 11.8 Years of Follow-up by Previous History of Myocardial Infarction

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Stroke type</th>
<th>Subarachnoid hemorrhage</th>
<th>Intracerebral hemorrhage</th>
<th>Cerebral infarction</th>
<th>Unspecified stroke</th>
<th>All stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (yes/no)</td>
<td>OR 95% CI</td>
<td>2.0 0.6-6.6</td>
<td>0.4 0.1-1.3</td>
<td>1.7 1.0-2.8</td>
<td>1.9 1.0-2.4</td>
<td>1.5 1.1-2.1</td>
</tr>
<tr>
<td>Known hypertension (yes/no)</td>
<td></td>
<td>1.3 0.3-6.1</td>
<td>2.0 0.6-7.2</td>
<td>2.5 1.4-4.3</td>
<td>2.1 1.0-4.2</td>
<td>2.2 1.5-3.3</td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td></td>
<td></td>
<td></td>
<td>0.8 0.1-5.5</td>
<td>6.5 2.5-16.8</td>
<td>2.3 1.01-5.4</td>
</tr>
<tr>
<td>Stroke in mother, father, or both (yes/no)</td>
<td></td>
<td>1.7 0.6-5.3</td>
<td>2.1 0.7-6.0</td>
<td>1.4 0.9-2.5</td>
<td>1.3 0.7-2.5</td>
<td>1.5 1.05-2.1</td>
</tr>
<tr>
<td>Severe psychological stress (score 6/score 1-5)</td>
<td></td>
<td>0.8 0.1-6.0</td>
<td>1.4 0.3-6.3</td>
<td>1.9 0.99-3.5</td>
<td>3.0 1.5-6.1</td>
<td>2.1 1.3-3.2</td>
</tr>
<tr>
<td>Physical inactivity (score 1/score 2-4)</td>
<td></td>
<td>1.8 0.6-5.5</td>
<td>1.1 0.4-3.7</td>
<td>1.2 0.7-2.0</td>
<td>1.2 0.6-2.2</td>
<td>1.2 0.8-1.8</td>
</tr>
<tr>
<td>Marital status (unmarried/married)</td>
<td></td>
<td>3.4 1.1-10.5</td>
<td>0.9 0.2-4.1</td>
<td>1.2 0.6-2.2</td>
<td>1.9 1.002-3.8</td>
<td>1.6 1.04-2.3</td>
</tr>
<tr>
<td>Registered alcohol abuse (yes/no)</td>
<td></td>
<td>1.1 0.1-8.5</td>
<td>1.0 0.1-7.8</td>
<td>0.8 0.3-2.3</td>
<td>1.6 0.6-4.1</td>
<td>1.1 0.6-2.1</td>
</tr>
<tr>
<td>Low occupational class (1,2/3-5)</td>
<td></td>
<td>1.3 0.4-4.3</td>
<td>1.3 0.4-4.3</td>
<td>0.9 0.6-1.5</td>
<td>1.1 0.6-2.0</td>
<td>1.1 0.7-1.5</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

psychological stress (score 6) significantly increased the risk of unspecified stroke and total stroke; no increase in risk could be seen with any lower psychological stress score. Leisure-time physical activity, alcohol abuse, and occupational class were not associated with any stroke end point. A moderate increase in the incidence of unspecified stroke as well as total stroke could be seen in unmarried men.

Table 4 shows stroke end points by manifestations of cardiovascular disease. No significant associations could be found between previous cardiovascular disease and either subarachnoid hemorrhage or intracerebral hemorrhage, but as the number of cases was low, the confidence intervals were wide. Presence of atrial fibrillation at the screening examination greatly increased the risk of cerebral infarction and unspecified stroke. Previous TIAs and history of myocardial infarction were strongly associated with unspecified stroke and total stroke but not with cerebral infarction. Men with effort-induced chest pain and intermittent claudication had a significantly increased incidence of cerebral infarction and total stroke. Dyspnea did not significantly predict an increased risk of stroke, though the lower limit of its confidence interval was close to 1.0.

We excluded all cases of hemorrhagic stroke from the multivariate analyses (Table 5), leaving only strokes of presumably nonhemorrhagic origin. As measured systolic and diastolic BP were strongly related to each other, only diastolic BP was entered since it was found to predict stroke somewhat better than systolic BP. We performed two multivariate analyses, one including all risk factor variables but excluding manifestations of cardiovascular disease, and the other analysis including manifestations of cardiovascular disease. We give only the significant risk indicators and we dichotomized them, with cutoff points listed in Table 5. In the first analysis, mea-
TABLE 5. Age-Adjusted Odds Ratios for First Nonhemorrhagic Stroke End Points During 11.8 Years of Follow-up by Significant (Dichotomized) Risk Indicators at Screening Examination, Multifactor Primary Prevention Study, 1970-1983

<table>
<thead>
<tr>
<th>Risk indicator</th>
<th>Adjusted for significant risk factors only *</th>
<th>Adjusted for significant risk factors and manifestations of cardiovascular disease†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Diastolic blood pressure (&gt;96 mm Hg ≤96 mm Hg)</td>
<td>2.4</td>
<td>1.7-3.6</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>1.8</td>
<td>1.2-2.6</td>
</tr>
<tr>
<td>Severe psychological stress (score 6/score 1-5)</td>
<td>2.0</td>
<td>1.3-3.2</td>
</tr>
<tr>
<td>Atrial fibrillation (yes/no)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Previous transient ischemic attacks (yes/no)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intermittent claudication (yes/no)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
*Adjusted for serum cholesterol concentration, body mass index, diastolic blood pressure, smoking, diabetes, family history of stroke, stress, leisure-time physical activity, marital status, and alcohol abuse.
†Adjusted for all variables above in addition to atrial fibrillation, previous transient ischemic attacks, history of myocardial infarction, chest pain, dyspnea, and intermittent claudication.

sured diastolic BP, smoking, and severe psychological stress remained significantly and independently associated with nonhemorrhagic stroke. In the second analysis, the odds ratios for measured diastolic BP, smoking, and severe psychological stress changed very little, and atrial fibrillation, previous TIAs, and intermittent claudication were also significant predictors of stroke.

Discussion

The distribution of stroke types in our study population is similar to those in Copenhagen, Denmark,11 Framingham, Massachusetts,12,13 and Rochester, Minnesota,14 and to that of a previous study in Göteborg.4 Our case-fatality rates at 1 month were almost identical to those in Copenhagen11 for all stroke (19%).

Results from a number of recent cohort studies of risk factors for stroke3-4-11-24 are summarized in Table 6. Hypertension is the dominating risk factor. We found a small increase in the risk of stroke among men in the lowest three quintiles of the measured BP distribution and a marked increase in the risk of stroke among men in the two highest quintiles, as in

Table 6. Variables Examined in Some Recent Cohort Studies of Risk Factors for Stroke

<table>
<thead>
<tr>
<th>Copenhagen, Denmark11</th>
<th>North Karelia, Finland15</th>
<th>Framingham, Massachusetts12,13,25,26</th>
<th>Rochester, Minnesota14</th>
<th>Göteborg, Sweden14</th>
<th>Taisho, Japan16</th>
<th>Akita, Japan17</th>
<th>Shibata, Japan18</th>
<th>Hisayama, Japan19,20</th>
<th>Honolulu, Hawaii21-23</th>
<th>Multiple Risk Factor Intervention Trial, USA24</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>Smoking</td>
<td>Stress</td>
<td>Obesity</td>
<td>Chol</td>
<td>Activity</td>
<td>Alcohol</td>
<td>Father</td>
<td>Mother</td>
<td>Stroke TIsas</td>
<td>CHD</td>
<td>LVH</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

BP, blood pressure; Chol, serum cholesterol concentration; TIAs, transient ischemic attacks; CHD, coronary heart disease; LVH, left ventricular hypertrophy on electrocardiogram; AF, atrial fibrillation; Claud, intermittent claudication; DM, diabetes mellitus. +, examined, positive correlation with stroke risk; -, examined, no correlation with stroke risk; no sign, not examined.
Copenhagen.\textsuperscript{11} Findings from Framingham with a broader age range and generally older people indicated a gradually increasing risk of stroke from the very lowest BP levels.\textsuperscript{22} It should be noted that all men in the intervention group with hypertension at the screening examination of the Multifactor Primary Prevention Study were treated at a special hypertension unit and that by the end of the study 26\% of the participants had received antihypertensive treatment.\textsuperscript{5} Other predictors of stroke frequently found in cohort studies include diabetes mellitus and the presence of signs or symptoms of coronary heart disease. Obviously, variables identified as risk indicators in some studies are not recognized in others for the simple reason that they were not investigated.

Our finding of smoking to increase the risk of stroke was also found in Copenhagen,\textsuperscript{11} in North Karelia, Finland,\textsuperscript{15} in Framingham,\textsuperscript{25,26} and in the Honolulu Heart Program.\textsuperscript{22,27}

In our study severe psychological stress indicated a significant risk, even after adjustment for other significant risk factors. This has not previously been reported.

A family history of stroke was recently reported as a risk factor for stroke,\textsuperscript{4,28} with puzzling sex differences. In our study, stroke in either parent predicted stroke, though this was not an independent risk factor in the multivariate analysis.

Diabetes mellitus has been shown to increase the risk of stroke in many studies.\textsuperscript{11,12,14,15,25,29,30} In the first series of strokes registered in Göteborg,\textsuperscript{6} diabetes was 10 times more prevalent among stroke cases than in the background population. Diabetes was associated with stroke in our study, though only in the univariate analysis. In Framingham,\textsuperscript{25} diabetes was strongly related to hypertension, and this association between diabetes and hypertension, which we also found, may explain why diabetes was not an independent risk factor.

Total serum cholesterol concentration has been shown to be unrelated or inversely related to stroke risk.\textsuperscript{16-19,21,22} An exception is the recent finding in Copenhagen\textsuperscript{11} of increased stroke risk at the very highest levels of the serum cholesterol concentration distribution, and very recently the American Multiple Risk Factor Intervention Trial\textsuperscript{24} found a positive association between serum cholesterol level and death from nonhemorrhagic stroke but an inverse association with the risk of death from intracranial hemorrhage in men with a diastolic BP of >89 mm Hg.

The presence of signs or symptoms of coexistent cardiovascular disease have been shown to increase stroke risk in many studies\textsuperscript{11,12,14,16,17,21-23,25} although not in the study of men born in 1913 in Göteborg, Sweden.\textsuperscript{4} In our study atrial fibrillation in particular indicated a high risk of nonhemorrhagic stroke, similar to the findings in Framingham\textsuperscript{31} and in Reykjavik, Iceland\textsuperscript{32} but contrasting with the report from Rochester\textsuperscript{44} of stroke risk in patients with nonrheumatic chronic atrial fibrillation being so low that "routine anticoagulation may not be warranted."\textsuperscript{33} Previous TIAs in our study indicated a significant increase in stroke risk, similar to the results of others.\textsuperscript{14,34} The few men with atrial fibrillation and/or a history of TIAs at the screening examination (38 and 128, respectively, in this study) make these causes of stroke numerically marginal in this age group.

In our study alcohol consumption was defined as abuse carrying legal consequences, and we found no correlation with stroke risk. Measured in this way, alcohol abuse is more an estimate of the life-long prevalence of alcohol problems than an indicator of current heavy drinking; consequently, an association between heavy drinking and stroke may have been obscured. Our findings are in keeping with the report from Copenhagen\textsuperscript{11} but are in contrast with the findings of the Honolulu Heart Program.\textsuperscript{35}

Some studies have examined the risk of obesity for stroke and most have found no correlation,\textsuperscript{11,16-18} whereas the Göteborg study of men born in 1913 found that the waist:hip circumference ratio predicted both stroke and heart disease, though not independently of other stroke risk factors.\textsuperscript{36} In our study BMI was not found to predict stroke.

Only one study\textsuperscript{23} has reported low physical activity at work to be related to stroke. We did not find any such association; neither was there any relation between stroke and physical activity at leisure.

There may be differences in risk profiles among the types of stroke. The few cases of subarachnoid hemorrhage and intracerebral hemorrhage in our study preclude any conclusions regarding their risk factor patterns. The differences that we found in risk factors between cerebral infarction and unspecified stroke may partly be due to differences in diagnostic procedures. However, measured high BP at the screening examination was not associated with subarachnoid hemorrhage in our study, in contrast to the other types of stroke. Atrial fibrillation was related only to cerebral infarction and unspecified strokes. A number of studies reported smoking and hypertension in particular to be related to subarachnoid hemorrhage.\textsuperscript{13,38,39}

Acknowledgments

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KEY WORDS: cerebrovascular disorders • epidemiology • risk factors • Sweden

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