Body Mass Index in Mid-Life Is Associated With a First Stroke in Men
A Prospective Population Study Over 28 Years

Katarina Jood, MD; Christina Jern, MD, PhD; Lars Wilhelmsen, MD, PhD; Annika Rosengren, MD, PhD

Background and Purpose—Data on the association between obesity and stroke are still limited. We examined the possible association between mid-life body mass index (BMI) and risk of stroke in the prospective Multifactor Primary Prevention Study in Göteborg, Sweden.

Methods—7402 apparently healthy men aged 47 to 55 at baseline were followed-up over a 28-year period. Incidence of fatal and nonfatal stroke was recorded in a local stroke registry through the Swedish National Register on Cause of Death and the Swedish Hospital Discharge Registry.

Results—A total of 873 first strokes were recorded, including 495 ischemic, 144 hemorrhagic, and 234 unspecified strokes. Compared with men with low normal weight (BMI, 20.0 to 22.49 kg/m²), men with BMI ≥30.0 kg/m² had a multiple adjusted hazard ratio of 1.93 (95% CI, 1.44 to 2.58) for total stroke, 1.78 (95% CI, 1.22 to 2.60) for ischemic stroke, and 3.91 (95% CI, 2.10 to 7.27) for unspecified stroke. There was no significant association between BMI and hemorrhagic stroke. Adjustment for potential mediators, eg, hypertension, diabetes and serum cholesterol levels, attenuated but did not eliminate the risk.

Conclusion—In this prospective population-based study of men, increased BMI in mid-life was associated with an increased risk for total, ischemic, and unspecified stroke, but not with hemorrhagic stroke. The result supports the role of mid-life BMI as a risk factor for stroke later in life and suggests a differentiated effect on stroke subtypes. (Stroke. 2004;35:2764-2769.)

Key Words: prospective studies ■ obesity ■ risk factors ■ stroke

Stroke is one of the leading causes of disability and death in Western countries. Because there are few efficient therapies, the best approach to reduce the burden of stroke remains prevention. Identifying potential risk factors leading to stroke is therefore of great importance.

Obesity is increasingly being recognized as a modifiable risk factor for cardiovascular disease, particularly ischemic heart disease.1,3 The association between obesity and stroke is less clear, and in the most recent guideline statement for health professionals from the Stroke Council of the American Heart Association,4 obesity was categorized as a “less well-documented or potentially modifiable risk factor.” Several prospective studies have shown an increased risk for stroke with increasing body mass index (BMI),5-13 whereas others found no association.14-17 In some studies there was an association with waist-to-hip ratio, but not BMI, suggesting that abdominal obesity rather than general obesity is associated to an increased risk for stroke.18,19 Few prospective studies have investigated the effect of obesity on the major subtypes of stroke. These studies show an increased risk for ischemic stroke with increasing BMI,5,10,13 but with divergent results regarding hemorrhagic stroke with a linear positive association in one,5 a nonsignificant inverse association in the other,9 and a J-shaped association in the third.13 Variations in study design, population characteristics, and in the endpoints undergoing study (stroke mortality, stroke incidence, atherothrombotic stroke, and subarachnoid hemorrhage) may contribute to the divergent findings.

Although stroke is more common in the elderly, measures for prevention needs to be undertaken earlier in life. Because data from large studies with long-term follow-up of middle aged populations are sparse, information about the risk of overweight or obesity in mid-life is limited.

In the present study we investigated the association between BMI and total, ischemic, and hemorrhagic stroke in a large random population sample of urban Swedish middle-aged men followed-up for 28 years.

Materials and Methods

Study Population
Data were derived from 7402 male participants from the intervention group in the Multifactor Primary Prevention Study20 that began in
Göteborg, Sweden in 1970. All men in the city who were born between 1915 and 1925 (n=30 000), except those born in 1923, were randomized into 3 groups of 10 000 men each. The men in one of the groups (the intervention group) were offered a medical examination to identify and treat risk factors. The intervention was essentially a high-risk strategy directed toward men with pronounced hypercholesterolemia, severe hypertension, or heavy smoking habits, according to predefined criteria with treatment offered at specialist clinics. There was no specific intervention directed toward obesity. All participants gave their informed consent to participate in the study. The study was approved by the Ethics Committee for Medical Research at Göteborg University. After a first 10-year follow-up, there were no significant differences in smoking, cholesterol levels, blood pressure, or outcomes with respect to cardiovascular disease, cancer, or all-cause mortality between the intervention and control groups.20 Thus, we consider the study group to be representative of the general male population in the city.

Screening
A baseline screening examination took place between January 1970 and March 1973. Altogether, 7495 men (75% of those invited) participated. Ninety-one men reported a previous stroke and/or myocardial infarction and were excluded, as were 2 men with missing data for BMI. Data on smoking habits, diabetes, treatment for hypertension, leisure time physical activity, psychological stress, occupation, and parental history of stroke were collected by a postal questionnaire sent to all subjects, along with an invitation to the study.17 Screening examinations were performed in the afternoon. Blood pressure was measured after 5 minutes of rest with the subject seated. Serum cholesterol concentration after fasting for at least 2 hours was determined according to standard laboratory procedures. Weight and height were measured. BMI was calculated as weight in kilograms divided by the square of the height in meters.

Follow-up
All participants were followed-up from the date of their baseline examination until December 31, 1998 using the Swedish National Register on Cause of Death and the Swedish Hospital Discharge Register. This process was approved by the Ethics Committee for Medical Research at Göteborg University. The Cause of Death register includes all fatalities in the country, including those occurring outside hospitals, and was operating throughout the study period. All discharges from the 2 hospitals in the city have been entered in the Hospital Discharge Register since 1970 for all years and includes rehospitalization and the diagnosis of disease. The Swedish socioeconomic classification system.24 The second model added diabetes, systolic blood pressure, treatment for hypertension, and serum cholesterol. We checked the assumption of proportional hazards through entering in the Cox regression model time-dependent variables related to the factors we studied. The impact of these variables was not significant on the model fit, which indicates that the assumption holds.

Results
During 28 years (168 585 person-years) of follow-up, 873 of the participants had a primary cause of death or a primary hospital discharge diagnosis of stroke, of which 495 had a first ischemic stroke diagnosed. A first hemorrhagic stroke was diagnosed in 144, whereas a first stroke that was not specified as hemorrhagic or ischemic was diagnosed in 234. During the first years of this study, computed tomography (CT) scan was not available, but during the follow-up it came into common use, and after 1983 CT scan of the brain was performed in >90% of the cases. The majority (83%) of the cases occurred after 1983. The proportion of unspecified strokes decreased during follow-up, but continued to be diagnosed throughout the study period (Table 1). The mean age at first stroke diagnosis was 75.5 years for ischemic stroke, 73.8 years for hemorrhagic stroke, and 74.0 years for unspecified stroke.

The mean BMI at screening was 25.5 kg/m², ranging from 14.9 to 47.9 kg/m². Table 2 describes baseline characteristics of the subjects according to BMI categories. Age-adjusted hazard ratios of stroke and the major subtypes for vascular risk factors are presented in Table 3. Systolic blood pressure, diastolic blood pressure, and severe psychological stress were significantly associated with increased risk and regular strenuous activity with a protective effect for total stroke and all subtypes. Smoking, diabetes mellitus, and treatment for hypertension were associated with a significantly increased risk for total, ischemic, and unspecified stroke, but not for hemorrhagic stroke. Parental history of stroke was associated with a significantly increased risk for total, hemorrhagic, and unspecified, but not ischemic, stroke. There was no significant association between cholesterol levels or occupational class and stroke.
The age and multiple-adjusted hazard ratios of total, ischemic, hemorrhagic, and unspecified stroke according to BMI category are summarized in Table 4. Increased BMI in mid-life was associated with an increased risk for total, ischemic, and unspecified stroke, but not with hemorrhagic stroke. The association was strongest for unspecified stroke in which the risk was significantly increased for all BMI categories >22.49 kg/m². Multivariate adjustment for other risk factors including smoking, exercise, psychological stress, occupational class, and parental history of stroke had little effect on this relation. Compared with men with BMI 20 to 22.49 kg/m², men with BMI >30.0 kg/m² had a multiple adjusted hazard ratio of 1.93 (95% CI, 1.44 to 2.58) for total stroke, 1.78 (95% CI, 1.22 to 2.60) for ischemic stroke, and 3.91 (95% CI, 2.10 to 7.27) for unspecified stroke. When BMI was examined as a continuous variable, each 1-unit increase in BMI was associated with a multiple-adjusted increase of 5.0% (95% CI, 2.9 to 7.1%) for total stroke, 5.3% (95% CI, 2.5 to 8.2%) for ischemic stroke, and 7.0% (95% CI, 3.1 to 11.0%) for unspecified stroke. For total, ischemic, and unspecified stroke, a tendency for a J-shaped relation was observed with a nonsignificant risk increase at the lowest end.

When potential mediators, eg, hypertension, diabetes, and cholesterol levels were entered into the model, the associations between BMI and total, ischemic, and unspecified stroke were attenuated. However, the risk for total and unspecified stroke remained significantly increased for the highest BMI category. When adjusting BMI as a continuous variable in the same way as mentioned, each 1-unit increase in BMI was associated with a significant increased risk of 2.7% (95% CI, 0.6 to 4.9%) for total stroke, 3.3% (95% CI, 0.5 to 6.2%) for ischemic stroke, and 4.2% (95% CI, 0.2 to 8.3%) for unspecified stroke.

**Discussion**

In this large prospective study of middle-aged men randomly selected from a Swedish population, we found an association between BMI in mid-life and total stroke after 28 years of follow-up. This finding supports the role of mid-life BMI as a risk factor for stroke later in life. We also found that the association between BMI and stroke differs between stroke subtypes. Compared with men with BMI 20 to 22.49, the most obese men (BMI >30.0) had a nearly 2-fold increased risk of both total and ischemic stroke, whereas there was no significant association between BMI and hemorrhagic stroke. The association between BMI and stroke was J-shaped, but the increased risk for the leanest was nonsignificant, which may indicate no further risk reduction rather than an increased risk among the very lean men.

Our finding of an increased risk for ischemic stroke with increasing BMI is in line with results from other studies.5–13 Regarding hemorrhagic stroke, only a few studies have previously been published. In contrast to our results, a large prospective study of male public servants in Korea13 recently reported a significantly increased risk for hemorrhagic stroke with increasing BMI. However, Asian and Western populations differ regarding prevalence of cardiovascular risk factors and incidence of cardiovascular diseases, which can contribute to the conflicting results. The investigators of the Physicians’ Health Study5 also reported a significant risk for hemorrhagic stroke with increasing BMI. The fact that a similar association was not seen in the present study may be because of the fact that the number of hemorrhagic strokes was small and/or that some of the hemorrhagic stroke cases may have been included among the unspecified strokes. In the Nurses Health study, there was a nonsignificant inverse relation between BMI and hemorrhagic stroke.9 An inverse relation has been reported between BMI and subarachnoid hemorrhage.25,26 Hence, the fact that subarachnoid hemorrhage was included in the Nurses Health study, but not the present study, could contribute to the different results. A gender-specific effect of BMI on hemorrhagic stroke cannot, however, be excluded.

Among stroke subtypes, unspecified stroke showed the strongest association with BMI, with a doubled risk already at high-normal weight (BMI 22.5 to 24.99 kg/m²). The explanation for this is not obvious and it deserves a few comments. First, there was no age difference between stroke subtypes that could explain the strong association between BMI and unspecified stroke. Second, because there was an increased

**TABLE 2. Baseline Characteristics According to Body Mass Index Category**

<table>
<thead>
<tr>
<th>BMI kg/m²</th>
<th>All, n=7,402</th>
<th>&lt;20, n=214</th>
<th>20–22.49, n=951</th>
<th>22.5–24.99, n=2,249</th>
<th>25–27.49, n=2,194</th>
<th>27.5–30.0, n=1,186</th>
<th>&gt;30, n=608</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.6</td>
<td>51.3</td>
<td>51.5</td>
<td>51.5</td>
<td>51.6</td>
<td>51.7</td>
<td>51.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148.7</td>
<td>138.1</td>
<td>143.6</td>
<td>145.8</td>
<td>149.4</td>
<td>153.5</td>
<td>158.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>94.6</td>
<td>87.4</td>
<td>90.5</td>
<td>92.2</td>
<td>95.2</td>
<td>98.5</td>
<td>102.8</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>1.9</td>
<td>4.2</td>
<td>2.4</td>
<td>1.6</td>
<td>1.6</td>
<td>1.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>50.0</td>
<td>78.4</td>
<td>61.7</td>
<td>52.7</td>
<td>45.1</td>
<td>43.5</td>
<td>41.9</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L.</td>
<td>6.46</td>
<td>6.02</td>
<td>6.23</td>
<td>6.37</td>
<td>6.53</td>
<td>6.67</td>
<td>6.65</td>
</tr>
<tr>
<td>Sedentary leisure time, %</td>
<td>25.9</td>
<td>33.7</td>
<td>25.8</td>
<td>22.4</td>
<td>24.0</td>
<td>29.8</td>
<td>35.5</td>
</tr>
<tr>
<td>Severe psychological stress, %</td>
<td>20.6</td>
<td>21.5</td>
<td>20.8</td>
<td>18.4</td>
<td>19.8</td>
<td>23.4</td>
<td>23.4</td>
</tr>
<tr>
<td>Parental history of stroke, %</td>
<td>26.5</td>
<td>26.2</td>
<td>27.4</td>
<td>27.5</td>
<td>26.3</td>
<td>23.8</td>
<td>27.6</td>
</tr>
<tr>
<td>Employed and self-employed professionals, intermediate and higher civil servants, executives, %</td>
<td>27.8</td>
<td>18.2</td>
<td>29.1</td>
<td>29.9</td>
<td>28.8</td>
<td>24.7</td>
<td>23.8</td>
</tr>
</tbody>
</table>
risk for unspecified stroke already at high-normal weight, a contribution of discrimination with a lower CT frequency in obese individuals to this association is unlikely. Third, when the analysis was restricted to nonfatal cases, the association between BMI and unspecified stroke was attenuated, indicating that the relation may have been influenced by the larger proportion of fatal cases in this group (19% fatal cases for unspecified stroke versus 18% and 13% for total and ischemic stroke, respectively). Fourth, results from previous studies indicate that subtypes of ischemic stroke differ regarding risk factor profile, and some studies indicate that obesity is more common in small-vessel cause compared with other subtypes. Apart from being an important causative factor for stroke, small-vessel disease also contributes to development of dementia. It is therefore of interest that in the same population, Rosengren et al recently found an association between mid-life BMI and hospitalization for dementia, with an increasing risk already at high-normal weight.

Unspecified stroke, ICD codes 436 and I64, is diagnosed in a stroke-patient when CT scan or lumbar puncture is not performed. It is, however, worth noting that a considerable proportion of stroke cases were classified as unspecified after CT scan came into common use. Because medical records were not reviewed in the present study, the explanation for the strong association between BMI and unspecified stroke remains unclear.

When the association between BMI and total, ischemic, and unspecified stroke was adjusted for potential mediators,
the association was attenuated, but not eliminated. This finding supports the role of hypertension, diabetes, and cholesterol levels as mediators in the link between obesity and stroke, but also suggests that there is an association independent of established risk factors. A similar independent association has been found in other studies of stroke\(^5\),\(^8\),\(^12\) and the association was attenuated, but not eliminated. This finding supports the role of mid-life BMI as a risk factor for stroke later in life. The risk was partly independent of established risk factors, which underlines the importance of reducing obesity for stroke prevention.

### Acknowledgments

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### References


### TABLE 4. Adjusted Hazard Ratios and 95% Confidence Intervals for Total, Ischemic, Hemorrhagic, and Unspecified Stroke by Body Mass Index Category

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>&lt;20 (reference)</th>
<th>20–22.49</th>
<th>22.5–24.99</th>
<th>25–27.49</th>
<th>27.5–30.0</th>
<th>&gt;30</th>
<th>Trend test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke, n=875</td>
<td></td>
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<tr>
<td>Age-adjusted</td>
<td>1.12 (0.88–1.44)</td>
<td>1.00</td>
<td>1.12 (0.88–1.43)</td>
<td>1.22 (0.96–1.55)</td>
<td>1.42 (1.10–1.84)</td>
<td>1.91 (1.44–2.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple-adjusted*</td>
<td>1.10 (0.67–1.81)</td>
<td>1.00</td>
<td>1.13 (0.89–1.45)</td>
<td>1.24 (0.97–1.58)</td>
<td>1.44 (1.11–1.87)</td>
<td>1.93 (1.44–2.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>1.11 (0.67–1.82)</td>
<td>1.00</td>
<td>1.14 (0.89–1.45)</td>
<td>1.19 (0.93–1.52)</td>
<td>1.31 (1.00–1.71)</td>
<td>1.52 (1.13–2.06)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ischemic stroke, n=495</td>
<td></td>
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<tr>
<td>Age-adjusted</td>
<td>1.24 (0.88–2.63)</td>
<td>1.00</td>
<td>0.91 (0.67–1.26)</td>
<td>1.12 (0.83–1.53)</td>
<td>1.35 (0.97–1.89)</td>
<td>1.79 (1.24–2.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple-adjusted*</td>
<td>1.23 (0.67–2.24)</td>
<td>1.00</td>
<td>0.92 (0.67–1.27)</td>
<td>1.14 (0.84–1.55)</td>
<td>1.36 (0.97–1.90)</td>
<td>1.78 (1.22–2.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>1.23 (0.67–2.26)</td>
<td>1.00</td>
<td>0.94 (0.69–1.30)</td>
<td>1.10 (0.81–1.51)</td>
<td>1.26 (0.90–1.77)</td>
<td>1.45 (0.98–2.14)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n=144</td>
<td></td>
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<tr>
<td>Age-adjusted</td>
<td>0.58 (0.14–2.52)</td>
<td>1.00</td>
<td>1.08 (0.63–1.87)</td>
<td>0.99 (0.57–1.73)</td>
<td>1.04 (0.56–1.94)</td>
<td>1.11 (0.52–2.34)</td>
<td>0.39</td>
</tr>
<tr>
<td>Multiple-adjusted*</td>
<td>0.59 (0.14–2.56)</td>
<td>1.00</td>
<td>1.10 (0.64–1.90)</td>
<td>0.94 (0.53–1.64)</td>
<td>1.02 (0.54–1.89)</td>
<td>1.05 (0.49–2.24)</td>
<td>0.58</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>0.62 (0.14–2.70)</td>
<td>1.00</td>
<td>1.09 (0.63–1.88)</td>
<td>0.88 (0.50–1.63)</td>
<td>0.87 (0.40–1.89)</td>
<td>0.87 (0.40–1.89)</td>
<td>0.85</td>
</tr>
<tr>
<td>Unspecified stroke, n=234</td>
<td></td>
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</tr>
<tr>
<td>Age-adjusted</td>
<td>1.34 (0.45–4.05)</td>
<td>1.00</td>
<td>1.98 (1.14–3.46)</td>
<td>1.94 (1.11–3.40)</td>
<td>2.23 (1.24–4.02)</td>
<td>3.63 (1.96–6.72)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multiple-adjusted*</td>
<td>1.30 (0.43–3.91)</td>
<td>1.00</td>
<td>2.02 (1.16–3.53)</td>
<td>2.09 (1.19–3.66)</td>
<td>2.37 (1.31–4.28)</td>
<td>3.91 (2.10–7.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>1.24 (0.41–3.75)</td>
<td>1.00</td>
<td>1.96 (1.12–3.42)</td>
<td>1.97 (1.12–3.45)</td>
<td>2.11 (1.16–3.82)</td>
<td>2.88 (1.53–5.41)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking, physical activity, parental history of stroke, occupational class, and psychological stress.
†Adjusted for age, smoking, physical activity, parental history of stroke, occupational class, psychological stress, systolic blood pressure, hypertension treatment, diabetes mellitus, and serum cholesterol levels.


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