Body Mass Index and the Risk of Stroke in Men

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Background: Although obesity is an established risk factor for coronary heart disease, its role as a risk factor for stroke remains controversial.

Methods: Prospective cohort study among 21,414 US male physicians participating in the Physicians’ Health Study. Incidence of total, ischemic, and hemorrhagic stroke was measured by self-report and confirmed by medical record review. We used Cox proportional hazards models to evaluate the association of body mass index (BMI), calculated as self-reported weight in kilograms divided by the square of the height in meters, with risk of total, ischemic, and hemorrhagic stroke.

Results: During 12.5 years of follow-up, 747 strokes (631 ischemic, 104 hemorrhagic, and 12 undefined) occurred. Compared with participants with BMIs less than 23, those with BMIs of 30 or greater had an adjusted relative risk of 2.00 (95% confidence interval [CI], 1.48-2.32) for total stroke, 2.25 (95% CI, 1.01-5.01) for hemorrhagic stroke. When BMI was evaluated as a continuous variable, each unit increase of BMI was associated with a significant 6% increase in the adjusted relative risks of total (95% CI, 4%-8%), ischemic (95% CI, 3%-8%), and hemorrhagic stroke (95% CI, 1%-12%). Additional adjustment for hypertension, diabetes mellitus, and hypercholesterolemia slightly attenuated the risks for total and ischemic (relative risk, 4%; 95% CI, 2%-7%), but not hemorrhagic, stroke.

Conclusions: These prospective data indicate a significant increase in the relative risk of total stroke and its 2 major subtypes with each unit increase of BMI that is independent of the effects of hypertension, diabetes, and cholesterol. Because BMI is a modifiable risk factor, the prevention of stroke may be another benefit associated with preventing obesity in adults.

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We used Cox proportional hazards models to analyze the association between BMI and stroke. Person-time was calculated from return of the baseline questionnaire until the date of stroke, death, or the study's end, whichever occurred first. Body mass index was calculated as self-reported weight in kilograms divided by the square of the height in meters.

EVALUATION OF STROKE
Participants who self-reported stroke on a follow-up questionnaire were asked for permission to obtain their medical records. An end points committee confirmed a diagnosis of stroke after review of medical records and reports of brain imaging. Stroke was defined as a focal neurological deficit of vascular mechanism lasting more than 24 hours and was classified according to criteria established by the National Survey of Stroke into ischemic, hemorrhagic (including intraparenchymal and subarachnoid hemorrhage), and undefined subtypes. Fatal stroke was documented by evidence of a cerebrovascular mechanism from the hospital discharge summary. The MRS classifies stroke cases from 1 (no residual symptoms) to 6 (fatal stroke). We categorized stroke severity as mild (MRS score of 1-3), severe (MRS score of 4-5), or fatal (MRS score of 6).

An independent review by 2 neurologists of the diagnostic coding of stroke from the start of randomization of the PHS until 1988 yielded excellent interobserver agreement. Similar analysis of data from 1988 until the trial's end also yielded strong intrarater reliability, with agreement for ischemic stroke of 96.4% (κ=0.84) and for hemorrhagic stroke of 97.1% (κ=0.87). The overall agreement for stroke severity, calculated with quadratic weighted κ statistics, was excellent, with concordance of 94.3% (κ=0.71) for the period until 1988 and 97.2% (κ=0.86) for the remainder of the study.

STATISTICAL ANALYSES
We used Cox proportional hazards models to analyze the association between BMI and stroke. Person-time was calculated from return of the baseline questionnaire until the date of stroke, death, or the study's end, whichever occurred first. Body mass index was calculated as self-reported weight in kilograms divided by the square of the height in meters.

CONTROLLED FOR AGE (continuous); smoking (never, past, or current); alcohol consumption (≥1 drinks per day, 2-6 drinks per week, ≤1 drink per week); exercise (≥1 week or <1 week); history of angina (yes or no); parental history of myocardial infarction prior to 60 years (yes or no); and randomized treatment assignment. The use of finer categories of both alcohol consumption and exercise did not appreciably change the estimates of the association between BMI and stroke. We considered hypertension, diabetes, and high cholesterol levels as possible biological mediators of the effect of BMI on stroke and therefore did not control for these factors in the primary analysis. However, hypertension (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or taking antihypertensive medication regardless of blood pressure), history of self-reported diabetes, and history of self-reported high cholesterol levels were added sequentially to multiple regression models in a secondary analysis. The use of different categorization of blood pressure did not appreciably change the estimates of the association between BMI and stroke. We evaluated effect modification of BMI by smoking, hypertension, alcohol consumption, and age.

We calculated the proportion of total stroke and stroke types directly standardized for age to evaluate the association of BMI and stroke severity. We used the Mantel-Haenszel extension test to test for trend in risk across BMI categories. To compare BMI measurements over the study period, we calculated a Spearman correlation coefficient comparing baseline BMI to BMIs from the 8-year follow-up and study-end questionnaires after excluding subjects with severe illnesses.

RESULTS
During 12.5 years (268,269 person-years) of follow-up, 747 incident strokes occurred, including 631 ischemic, 104 hemorrhagic (83 intraparenchymal and 21 subarachnoid hemorrhages), and 12 undefined strokes. The mean BMI was 24.9, ranging from 14.4 to 56.0. Based on WHO criteria, 12125 (56.6%) of the 21414 men were in the normal weight category, 8105 (37.9%) were overweight, and 1184 (5.5%) were obese.

Table 1 gives the age-adjusted baseline characteristics of the participants according to BMI categories. Mean systolic and diastolic blood pressures as well as prevalence of hypertension increased with increasing BMI. The percentage of men who had never smoked decreased with increasing BMI, whereas the percentage of men who reported current smoking was highest in the obese category. The proportion of men who reported exercising regularly decreased with increasing BMI. The leanest men were more likely to have reported alcohol consumption of 1 drink or more per day and less likely to have reported consumption of less than 2 drinks per week compared with obese men.

The age- and multiple-adjusted relative risks of total, ischemic, and hemorrhagic stroke according to BMI categories are summarized in Table 2. The age-adjusted relative risks of total stroke as well as stroke types increased steadily across BMI categories compared with the referent (BMI <23). Multiple adjustments for various risk factors attenuated the relative risks only slightly.

Using the WHO categories, overweight men had multiple-adjusted relative risks for total stroke of 1.32 (95% confidence interval [CI], 1.14-1.54), for ischemic stroke of 1.35 (95% CI, 1.15-1.59), and for hemorrhagic stroke of 1.25 (95% CI, 0.84-1.88) compared with men with BMIs...
less than 25. Obese men had multiple-adjusted relative risks of 1.91 (95% CI, 1.45-2.52) for total stroke, 1.87 (95% CI, 1.38-2.54) for ischemic stroke, and 1.92 (95% CI, 0.94-3.93) for hemorrhagic stroke compared with men with BMIs less than 25.

When BMI was examined as a continuous variable, each 1-unit increase in BMI was associated with a multiple-adjusted increase of 6% (95% CI, 4%-8%) in the risk of total and ischemic stroke and 6% (95% CI, 1%-12%) for hemorrhagic stroke.

The influence of hypertension, diabetes, and hypercholesterolemia on the association between BMI and stroke risk was evaluated in a stepwise fashion using the continuous measurement of BMI. For both total and ischemic stroke, the increased risk was reduced to 4% (95% CI, 2%-7%) per unit increase in BMI when hypertension was included in the model. Additional adjustment for diabetes did not further reduce the relative risks. Hemorrhagic stroke was only marginally mediated by hypertension and diabetes, and the effect estimate of 6% was unchanged. After controlling for hypertension and diabetes, the inclusion of cholesterol levels of 240 mg/dL or greater (≥6.22 mmol/L) did not further attenuate the association between BMI and any stroke type.

Smoking, alcohol consumption, and age did not substantially modify the effect for total, ischemic, and hemorrhagic stroke. The risk of both ischemic and hemorrhagic stroke was highest among individuals with hypertension, but no substantial effect modification was observed between hypertension status and BMI (Figure 1 and Figure 2).

Although the overall stroke 30-day fatality was 6.3%, large differences were seen between the fatality among stroke types. Among the hemorrhagic stroke cases, 27.9% were fatal (25.3% of intraparenchymal hemorrhages and 38.1% of subarachnoid hemorrhages) compared with only 2.4% of ischemic strokes. Table 3 summarizes the age-adjusted proportion of stroke severity in each BMI category. Stroke severity for total and ischemic stroke was not associated with BMI. For hemorrhagic stroke, mild strokes occurred more often in men with BMIs of 30 or greater, while fatal strokes occurred more often in men with BMIs lower than 23. Further analysis of hemorrhagic stroke subtypes showed that the age-adjusted inverse association between fatal hemorrhagic stroke and BMI was primarily owing to an increased incidence of subarachnoid hemorrhage. Of the 29 fatal hemorrhagic stroke cases, 8 had subarachnoid hemorrhages, of which 3 (age-adjusted percentage, 45.2%) occurred in men with BMIs lower than 23 and 4 (age-adjusted percentage, 39.3%) with BMIs between 23 and 24.9, while only 1 (age-adjusted percentage, 14.3%) occurred in those with BMIs between 25 and 26.9, with no cases in the heavier categories. However, the age-adjusted percentage of fatal intraparenchymal hemorrhages among obese men (8.4%) was also lower than that among men in BMI categories of less than 23 or 23 to 24.9 (30.1% each). These findings were not changed with additional adjusted-for-hypertension.

The correlation between baseline BMI, BMI at 8 years of follow-up (r = 0.86), and BMI at the study’s end (r = 0.80) was high. Body mass index was relatively stable throughout the study, with 42% of participants with baseline BMIs

### Table 1. Age-Adjusted Baseline Characteristics of the Study Participants According to Their BMI Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI&lt;25 (n = 12126)</th>
<th>BMI 25-29.9 (n = 8182)</th>
<th>BMI≥30 (n = 1182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>52.9 ± 9.8</td>
<td>53.6 ± 9.1</td>
<td>52.4 ± 8.7</td>
</tr>
<tr>
<td>Blood pressure, mean ± SD, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.4 ± 10.7</td>
<td>127.9 ± 11.2</td>
<td>130.8 ± 12.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.8 ± 7.3</td>
<td>79.9 ± 7.3</td>
<td>81.8 ± 7.8</td>
</tr>
<tr>
<td>Hypertension, %†</td>
<td>19.1</td>
<td>28.3</td>
<td>38.1</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>51.4</td>
<td>47.4</td>
<td>45.6</td>
</tr>
<tr>
<td>Past</td>
<td>38.2</td>
<td>40.7</td>
<td>41.5</td>
</tr>
<tr>
<td>Current</td>
<td>10.4</td>
<td>11.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Exercise ≥1/wk, %</td>
<td>75.2</td>
<td>69.3</td>
<td>63.2</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1/wk</td>
<td>37.9</td>
<td>41.5</td>
<td>50.6</td>
</tr>
<tr>
<td>2-6/wk</td>
<td>35.9</td>
<td>34.7</td>
<td>30.2</td>
</tr>
<tr>
<td>≥1/d</td>
<td>26.2</td>
<td>23.8</td>
<td>19.2</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>2.0</td>
<td>2.5</td>
<td>5.0</td>
</tr>
<tr>
<td>History of angina, %</td>
<td>1.1</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Parental history of MI, %‡</td>
<td>12.7</td>
<td>13.8</td>
<td>13.4</td>
</tr>
<tr>
<td>History of high cholesterol level, %§</td>
<td>11.1</td>
<td>12.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Random assignment to aspirin group, %</td>
<td>50.4</td>
<td>49.3</td>
<td>51.0</td>
</tr>
</tbody>
</table>

*Adjusted for age in 5-year categories. BMI indicates body mass index (calculated as self-reported weight in kilograms divided by the square of the height in meters; MI, myocardial infarction. †Hypertension was defined as self-reported systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher or current use of antihypertensive medication (regardless of blood pressure). ‡Parental history of MI at an age younger than 60 years. §History of elevated total cholesterol level of 240 mg/dL (≥6.22 mmol/L).

In this prospective cohort, increasing BMI was associated with a steady increase in the risks of total, ischemic, and hemorrhagic stroke. Although concomitant hypertension and diabetes accounted for much of the increase in total and ischemic stroke, a significant increase remained after adjustment for these potential biological mediators. Although the risk of ischemic stroke was highest among smokers and individuals with hypertension, these factors did not substantially modify the relationship between BMI and stroke. Body mass index was not associated with the severity of total and ischemic stroke, but the data suggest that it might be inversely associated with severity of fatal hemorrhagic stroke, particularly subarachnoid hemorrhage.

The association between excess weight and stroke risk has been controversial. Among men, few prospective studies have investigated this relationship. Some of these had small sample sizes and others did not classify stroke subtypes. To our knowledge, the association between BMI and stroke severity has not been examined prospectively before.
Table 2. Age-Adjusted and Multiple-Adjusted Relative Risks and 95% Confidence Intervals of Total, Ischemic, and Hemorrhagic Stroke by BMI Category

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Total stroke†</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Age adjusted</td>
<td>Multiple adjusted‡</td>
</tr>
<tr>
<td>&lt;23 (Reference)</td>
<td>(66 638 Person-Years)</td>
<td>151</td>
<td>1.00</td>
</tr>
<tr>
<td>23-24.9</td>
<td>(85 517 Person-Years)</td>
<td>212</td>
<td>1.09 (0.88-1.34)</td>
</tr>
<tr>
<td>25-26.9</td>
<td>(65 432 Person-Years)</td>
<td>201</td>
<td>1.09 (0.88-1.34)</td>
</tr>
<tr>
<td>27-29.9</td>
<td>(35 958 Person-Years)</td>
<td>124</td>
<td>1.09 (0.88-1.34)</td>
</tr>
<tr>
<td>≥30</td>
<td>(14 734 Person-Years)</td>
<td>59</td>
<td>1.09 (0.88-1.34)</td>
</tr>
</tbody>
</table>

*Data are relative risk (95% confidence interval) unless otherwise specified. BMI indicates body mass index (see footnote to Table 1 for BMI calculation).
†Total stroke included strokes of unknown subtype in addition to ischemic and hemorrhagic strokes.
‡Multiple regression models adjusted for age (continuous); smoking (never, past, current); alcohol consumption (1 drink per day, 2-6 drinks per week, ≥1 drink per week); exercise (≥1 time per week, <1 time per week); history of angina; parental history of myocardial infarction at an age younger than 60 years; and randomized treatment assignment.
§Hemorrhagic strokes included both intraparenchymal and subarachnoid hemorrhages.

In the Honolulu Heart Program, nonsmoking men in the highest tertile of BMI at age 25 years had a 2-fold increased risk of ischemic stroke over 22 years of follow-up. In the Whitehall Study, a 2-fold increase in risk of stroke mortality was observed among men with BMIs of 24 or greater compared with those with BMIs less than 24. Obesity was also a risk factor for nonfatal stroke in a long-term follow-up study of male college alumni. The modest to small associations observed in some studies, such as among 2773 elderly men and women in Chicago, Ill, may be a result of controlling for hypertension and diabetes, which may directly mediate the association between excess weight and stroke. Other studies, however, failed to find a strong association between obesity and stroke in men. Among women, the data are also inconsistent, with some studies showing a positive association and others showing no association.

In the Nurses’ Health Study, a nonsignificant inverse association was observed between BMI and hemorrhagic stroke. In contrast, we found a 6% increase in risk of hemorrhagic stroke per unit increase of BMI. On examination by subtype, a direct association was observed between BMI and intraparenchymal hemorrhage, while an inverse association was observed for subarachnoid hemorrhage. A similar inverse association was observed in a community-based Finnish cohort of 187 subjects with subarachnoid hemorrhage. Low BMI (≤23.5) was associated with a markedly increased risk of subarachnoid hemorrhage among current smokers and those who have hypertension. If the same divergent associations between BMI and subarachnoid and intraparenchymal hemorrhages.

Figure 1. Age-adjusted relative risk for ischemic stroke according to body mass index (BMI) categories (calculated as self-reported weight in kilograms divided by the square of the height in meters), and hypertension status. Reference (relative risk=1.0): normotensive with a BMI less than 23 (P for trend: hypertension, P=.02; normotension, P=.001).

Figure 2. Age-adjusted relative risk for hemorrhagic stroke according to body mass index (BMI) (for calculation of BMI, see legend to Figure 1) categories and hypertension status. Reference (relative risk=1.0): normotensive with a BMI less than 23 (P for trend: hypertension, P=.34; normotension, P=.20).
women,\textsuperscript{13} since subarachnoid hemorrhage is more frequent in women than men.\textsuperscript{40}

The severity of ischemic and total stroke did not appear to be influenced by BMI in our study, while fatal hemorrhagic stroke occurred more often in lean men than in overweight or obese men. These findings were mainly owing to subarachnoid hemorrhage, which has a higher 28-day case fatality rate than intraparenchymal hemorrhage.\textsuperscript{41,42} However, because few fatal hemorrhagic strokes occurred in our study, we were unable to estimate more precisely the association between hemorrhagic subtypes and categories of BMI.

The mechanism by which BMI affects stroke risk independent of established risk factors such as hypertension and diabetes is not fully understood. Some investigators have proposed that an increase in prothrombic factors observed among overweight and obese individuals may contribute to their increased risk for ischemic events.\textsuperscript{13-45} Higher levels of prothrombic factors, such as plasminogen activator inhibitor-1 (PAI-1) antigen and activity, fibrinogen, von Willebrand factor, and factor VII, have been found in obese women compared with normal-weight women.\textsuperscript{43} Adipose tissue seems to play a role in determining elevated plasma levels of PAI-1,\textsuperscript{44} which are also linked to the development of atherothrombosis.\textsuperscript{45} Increased levels of C-reactive protein in overweight and obese individuals\textsuperscript{46,47} may also play a role in their increased risk of ischemic cardiovascular events\textsuperscript{48} since an association between increased levels of inflammatory markers and risk of cardiovascular disease,\textsuperscript{49-51} including ischemic stroke,\textsuperscript{12,33} has been documented.

Our study has several strengths, including its large size, prospective design, and the relatively homogeneous nature of the cohort, which reduces confounding by several variables, including access to medical care, educational attainment, and socioeconomic status. Misclassification of stroke was reduced by detailed review of medical records, and interobserver agreement in classifying stroke, stroke subtypes, and stroke severity was high. The study also has several potential limitations. Body mass index was calculated using self-reported data, which can lead to misclassification. In several validation studies of other cohorts of health professionals, however, self-reports of height, weight, and other cardiovascular risk factors were reliable.\textsuperscript{54-57} In the Health Professionals Follow-up Study, the correlation coefficient for self-reported and measured weight in men was \( r = 0.97.\textsuperscript{50} \) Body mass index is not a perfect measurement of adiposity,\textsuperscript{56} and abnormal regional adiposity may further increase risk for stroke.\textsuperscript{15,37} To the extent that our single measure of BMI imperfectly reflects adiposity, our results would tend to underestimate the deleterious effects of obesity. Moreover, because our study population contains solely physicians who were mostly white and somewhat leaner than the average US population,\textsuperscript{59,60} the results may not be generalizable to a less-selective population. However, since the pathomechanism that leads to stroke is likely to be similar across populations, our results may underestimate the contribution of obesity to stroke risk. In conclusion, this study demonstrates that overweight and obese men are at increased risk of total, ischemic, and hemorrhagic stroke. These risks appeared to be independent of the potential biological mediators of hypertension, diabetes, and cholesterol level. These results suggest that individuals and their physicians should consider increased risk of stroke another hazard of obesity. Prevention of obesity should help prevent risk of stroke in men.

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<table>
<thead>
<tr>
<th>Table 3. Age-Adjusted Severity of Total, Ischemic, and Hemorrhagic Stroke According to BMI Categories*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI Category</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>&lt; 23 (Reference)</td>
</tr>
<tr>
<td>23-24.9</td>
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<tr>
<td>25-26.9</td>
</tr>
<tr>
<td>27-29.9</td>
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<tr>
<td>≥30</td>
</tr>
<tr>
<td>Trend Test</td>
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<td>P Value</td>
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</tbody>
</table>

*Data are percentage of patients unless otherwise specified. BMI indicates body mass index (see footnote to Table 1 for BMI calculation).†Total stroke included strokes of unknown subtype in addition to ischemic and hemorrhagic strokes.‡Hemorrhagic strokes included both intraparenchymal and subarachnoid hemorrhages.
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43. 1995;32:917-924.
44. 1991;338:774-778.
47. 1994;13:2370-2376.
50. 1994;151:973-976.
52. 1992;1:466-473.
55. 1993;276:290-299.
57. 1991;341:227-327.
58. 1993;141:1117-1127.
59. 1991;301:38-44.
60. 1994;31:129-135.
65. 1991;301:1027-1032.
68. 1999;341:462-466.
69. 1993;276:290-299.
73. 1994;338:774-778.
74. 1991;301:38-44.
77. 1990;322:882-889.