Prospective Study of Body Mass Index and Risk of Stroke in Apparently Healthy Women

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Background—Obesity is an escalating pandemic in the United States, and its association with coronary heart disease is well understood. Several studies have found positive associations between body mass index (BMI) and stroke in men, but the association with stroke and its subtypes is less clear in women.

Methods and Results—This was a prospective cohort study among 39,053 women participating in the Women’s Health Study. BMI was measured as self-reported weight (in kilograms) divided by height (in meters) squared. Incident stroke was self-reported and confirmed by medical record review. We used the Cox proportional hazards model to evaluate the association between BMI and stroke. After a mean follow-up of 10 years, a total of 432 strokes (347 ischemic, 81 hemorrhagic, and 4 undefined) occurred. We found a statistically significant trend for increased risk of total and ischemic stroke across 7 BMI categories. With World Health Organization criteria, women who were obese (BMI ≥30 kg/m²) had hazard ratios of 1.50 (95% CI 1.16 to 1.94) for total stroke, 1.72 (95% CI 1.30 to 2.28) for ischemic stroke, and 0.82 (95% CI 0.43 to 1.58) for hemorrhagic stroke compared with women with BMI <25 kg/m². Additional control for history of hypertension, diabetes, and elevated cholesterol substantially attenuated the hazard ratios for total and ischemic stroke. There was no effect modification for age, exercise, or smoking.

Conclusions—In this large prospective cohort study among women, BMI was a strong risk factor for total and ischemic stroke but not for hemorrhagic stroke. The association was highly mediated by hypertension, diabetes, and elevated cholesterol. (Circulation. 2005;111:1992-1998.)

Key Words: obesity ■ stroke ■ epidemiology ■ women

Overweight and obesity represent an emerging threat to public health,1–3 affecting nearly 59 million adults in the United States alone.4 In addition, and perhaps more worrisome, the percentage of young people who are overweight has more than doubled over the last 20 years.4,5 Approximately 300,000 deaths each year in the United States are estimated to be attributable to obesity,6 and the economic burden is enormous.4 Overweight and obesity are well-documented risk factors for a variety of diseases,2 including coronary heart disease, hypertension, type 2 diabetes mellitus, osteoarthritis, and certain cancers.7,8 There is increasing evidence that obesity is a risk factor for ischemic stroke.9–14 Despite this, excess weight has not been recognized as an established risk factor for stroke15 and generally has not been included in the overall estimation of stroke risk.16–18 In addition, the association between body mass index (BMI) and hemorrhagic stroke is less clear.9,10,12,14,19–21 Stroke remains a leading cause of severe disability and premature death in the United States and other Western countries. Effective therapies for the treatment of acute ischemic stroke only are used in a small number of patients22 and do not help to completely reverse the impaired function of affected brain areas. Thus, the identification of modifiable lifestyle factors remains critical for stroke prevention. We aimed to evaluate the association between BMI and total stroke, ischemic stroke, and hemorrhagic stroke in more than 39,000 apparently healthy female health professionals participating in the Women’s Health Study (WHS).

Methods

Participants
Study individuals were all participants in the WHS, a recently completed randomized, double-blind, placebo-controlled trial that tested the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among apparently healthy women. The design and methods of the WHS have been described in detail previously.23,24 Briefly, a total of 39,876 US female health professionals aged 45 years or older at
Assessment of BMI

Participants reported their height and weight on the baseline questionnaire. On the 24-, 36-, 60-, 72-, and 108-month questionnaires, participants were asked again to report their weight, and on the 72- and 108-month questionnaires, they were asked to report their height again. BMI was calculated as self-reported weight in kilograms divided by height in meters squared (kg/m²). We used the baseline height information to calculate BMI for all but the 72- and 108-month time points. We categorized BMI into a priori categories of height information to calculate BMI for the 38 053 participants, including 347 ischemic, 81 hemorrhagic, and 4 undefined strokes. The mean BMI was 26.0 kg/m² (±5.1 SD), with 19 841 women (50.8%) reporting BMI values of <25.0 kg/m², 12 081 (30.9%) reporting values between 25.0 and 29.9 kg/m², and 7131 (18.3%) reporting BMI ≥30 kg/m². The association between BMI WHO categories and baseline characteristics is summarized in Table 1. Women who reported BMI values of 30 kg/m² or higher were more frequently reported a history of hypertension, elevated cholesterol, and diabetes. In addition, they smoked fewer cigarettes, drank less alcohol, exercised less, and reported less postmenopausal hormone use.

Ascertaining of Stroke

Participants who reported a stroke on a follow-up questionnaire were asked for permission to review their medical records. A diagnosis of stroke was confirmed only after review of the medical records by an End Points Committee of physicians that included a neurologist. A nonfatal stroke was defined as a focal neurological deficit of sudden onset and vascular mechanism that lasted >24 hours. Cases of fatal stroke were documented by evidence of a cerebrovascular mechanism obtained from all available sources, including death certificates and hospital records. Stroke was classified according to the criteria established by the National Survey of Stroke as ischemic stroke, hemorrhagic stroke, and unknown subtype. The interobserver agreement of the classification of stroke and its major subtypes in the WHS was excellent.

Statistical Analysis

Of the 39 876 randomized participants, we excluded 820 women with missing information on weight or height on the baseline questionnaire. We additionally excluded 3 participants who reported a stroke before the receipt of the baseline questionnaire, which left a total of 39 053 women for the present study.

We compared the characteristics of participants with respect to baseline BMI categories using direct standardization to adjust categorical variables for age in 5-year increments. We used the Cox proportional hazards model to analyze the association between BMI and the incidence of stroke. We calculated age- and multi-variable-adjusted hazard ratios (HRs) and their 95% CIs for total (including ischemic, hemorrhagic, and undefined stroke cases), ischemic, and hemorrhagic (including subarachnoid and intracerebral hemorrhage) strokes. We made a distinction in the multivariable models between variables that were considered potential confounders and those considered potential biological intermediate variables in the association between BMI and stroke risk. In the first multivariable model (model 1), we controlled for age (quadratic term), alcohol consumption (<1 drink per week, 1 to 6 drinks per week, ≥1 drink per day), smoking (never, past, current <15 cigarettes per day, current ≥15 cigarettes per day), physical activity (<1 time per week, 2 to 3 times per week, ≥4 times per week), and postmenopausal hormone use. We considered other potential confounding variables including ethnicity, oral contraceptive use, and education, which did not lead to substantially different results. We then considered 3 potential biological mediators: history of hypertension (defined as self-reported systolic blood pressure of ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or report of diagnosis of hypertension by a physician), history of diabetes, and history of elevated cholesterol (≥240 mg/dL). In the second multivariable model (model 2), we controlled for all variables in model 1 plus hypertension at baseline. In the third model, we then additionally controlled for history of diabetes and elevated cholesterol at baseline. We decided a priori not to control for randomized treatment assignment. Because randomization in this large trial was successful, randomized treatment assignment is not associated with BMI. Consequently, by definition, randomized treatment assignment cannot be a confounder of the association between BMI and stroke.

Our primary analysis was to evaluate the association between baseline BMI and risk of total, ischemic, and hemorrhagic stroke. As a secondary approach, we updated the information on BMI by incorporating weight change over time. We evaluated effect modification by age (<60 versus ≥60 years), exercise frequency (<1 times per week versus ≥1 times per week), and smoking status (current versus never/past). We used the likelihood ratio test to test for statistical significance. All probability values were 2 tailed, and we considered P<0.05 as statistically significant.

Results

After a mean of 10 years of follow-up (384 345 person-years), a total of 432 strokes occurred among the 39 053 participants, including 347 ischemic, 81 hemorrhagic, and 4 undefined strokes. The mean BMI was 26.0 kg/m² (±5.1 SD), with 19 841 women (50.8%) reporting BMI values of <25.0 kg/m², 12 081 (30.9%) reporting values between 25.0 and 29.9 kg/m², and 7131 (18.3%) reporting BMI ≥30 kg/m². The association between BMI WHO categories and baseline characteristics is summarized in Table 1.
This pattern was different from that seen for ischemic stroke. When we used WHO categories for BMI, women in the obese category (≥30 kg/m²) had multivariable-adjusted (model 1) HRs of 1.50 (95% CI 1.16 to 1.94) for total stroke, 1.72 (95% CI 1.30 to 2.28) for ischemic stroke, and 0.82 (95% CI 0.43 to 1.58) for hemorrhagic stroke compared with women with BMI <25 kg/m². After we additionally con-

### TABLE 1. Age-Adjusted Baseline Characteristics According to BMI Categories

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25.0 (n=19 841)</td>
<td>25.0–29.9 (n=12 081)</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>54.5 (7.2)</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>16.4</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>0.9</td>
</tr>
<tr>
<td>History of cholesterol ≥240 mg/dL, %</td>
<td>25.3</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>50.4</td>
</tr>
<tr>
<td>Past</td>
<td>35.4</td>
</tr>
<tr>
<td>Current &lt;15 cigarettes/d</td>
<td>5.4</td>
</tr>
<tr>
<td>Current ≥15 cigarettes/d</td>
<td>8.8</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td></td>
</tr>
<tr>
<td>&lt;1 drink/wk</td>
<td>51.6</td>
</tr>
<tr>
<td>1–6 drinks/wk</td>
<td>35.1</td>
</tr>
<tr>
<td>≥1 drink/d</td>
<td>13.3</td>
</tr>
<tr>
<td>Physical activity, %</td>
<td></td>
</tr>
<tr>
<td>1 time/wk</td>
<td>51.7</td>
</tr>
<tr>
<td>1–3 times/wk</td>
<td>34.4</td>
</tr>
<tr>
<td>≥4 times/wk</td>
<td>13.9</td>
</tr>
<tr>
<td>Postmenopausal hormone use, %</td>
<td>45.2</td>
</tr>
<tr>
<td>Randomized aspirin assignment, %</td>
<td>50.0</td>
</tr>
</tbody>
</table>

### TABLE 2. HRs for Total, Ischemic, and Hemorrhagic Stroke by BMI Categories

<table>
<thead>
<tr>
<th>BMI Categories, kg/m²</th>
<th>Total stroke</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases (n=432)</td>
<td>No. of cases (n=347)</td>
<td>No. of cases (n=81)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 1†</td>
<td>1.00 (0.64–1.65)</td>
<td>1.07 (0.66–1.74)</td>
<td>1.06 (0.65–1.75)</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>1.00 (0.62–1.59)</td>
<td>0.98 (0.61–1.59)</td>
<td>0.93 (0.56–1.53)</td>
</tr>
<tr>
<td>Model 3§</td>
<td>1.00 (0.62–1.60)</td>
<td>0.98 (0.61–1.59)</td>
<td>0.92 (0.56–1.51)</td>
</tr>
<tr>
<td>Model 1†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3§</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*P for trend across categories.  †Adjusted for age, smoking status, exercise, alcohol consumption, and postmenopausal hormone use.  ‡Adjusted for all variables in model 1 plus history of hypertension.  §Adjusted for all variables in model 2 plus history of diabetes and elevated cholesterol.
trolled for history of hypertension, diabetes, and elevated cholesterol, the risks of total and ischemic stroke were attenuated to 1.04 (95% CI 0.80 to 1.37) for total stroke and 1.15 (95% CI 0.85 to 1.55) for ischemic stroke.

When we evaluated BMI as a continuous variable, a 1-unit increase in BMI was associated with a 4% increase in total stroke (multivariable [model 1]-adjusted HR 1.04, 95% CI 1.02 to 1.06) and a 5% increase for ischemic stroke (HR 1.05, 95% CI 1.03 to 1.07) but had no association with hemorrhagic stroke (HR 0.99, 95% CI 0.94 to 1.04). These relative risks for total and ischemic stroke were also attenuated after we controlled for history of hypertension, diabetes, and elevated cholesterol: 1.01 (95% CI 0.99 to 1.03) for total stroke and 1.02 (95% CI 0.99 to 1.04) for ischemic stroke.

When we updated the information on BMI over the course of follow-up, the results were similar in direction compared with the association between baseline BMI and risk of stroke and stroke subtypes. After adjustment for potential confounders (model 1), women with BMI values $\geq$35 kg/m$^2$ had HRs of 1.66 (95% CI 1.01 to 2.71) for total stroke, 1.89 (95% CI 1.09 to 3.26) for ischemic stroke, and 0.79 (95% CI 0.23 to 2.65) for hemorrhagic stroke. As before, the HRs for total and ischemic stroke were attenuated when we additionally controlled for history of hypertension, diabetes, and elevated cholesterol, with HRs of 1.02 (95% CI 0.62 to 1.69) for total stroke and 1.10 (95% CI 0.63 to 1.94) for ischemic stroke.

The association between BMI and total, ischemic, or hemorrhagic stroke was not statistically significantly modified by age (<60 versus $\geq$60 years; $P$ for all stroke types $\geq$0.09). The association between BMI categories according to smoking status is summarized in Figure 2. There was a progressive increase in risk with higher BMI among never-smokers and past smokers. Women who were current cigarette smokers had increased risk irrespective of BMI. Overall, there was no statistically significant effect modification of the association between BMI and ischemic stroke by smoking status ($P$=0.62). There was also no significant effect modification by smoking status with regard to hemorrhagic stroke.

The association between BMI WHO categories according to exercise categories is presented in Table 3. Compared with women with BMI $<25$ kg/m$^2$, there was an excess risk of total and ischemic stroke for BMI 30 kg/m$^2$ or higher whether or not the women exercised. The HRs were somewhat stronger in those who exercised less, but there was no statistically significant effect modification ($P$=0.39 for all stroke types).
In men, a number of studies support an association between BMI and increased risk of stroke.\textsuperscript{9,10,21,34} A recent population-based study from Göteborg, Sweden, found a 2-fold increase in the risk for total, ischemic, and undetermined stroke for men with BMI $>30$ kg/m$^2$ compared with men with BMI of 20.0 to 22.5 kg/m$^2$.\textsuperscript{9} No association was observed between BMI and hemorrhagic stroke. Because that study showed a strong association between BMI and undetermined stroke, it is possible that some of these cases were in fact hemorrhagic strokes and that the association between BMI and hemorrhagic stroke was thus underestimated. Data from the Physicians’ Health Study showed a significant increase in the risk of total, ischemic, and hemorrhagic stroke with increasing BMI.\textsuperscript{10} Men with BMI $\geq 30$ kg/m$^2$ had a 2-fold risk increase for all stroke types. In both studies, the increased risk for total and ischemic stroke, although attenuated, remained statistically significant when additionally controlled for hypertension, diabetes, and elevated cholesterol.

The association between obesity and hemorrhagic stroke remains unclear. The present study is consistent with findings of others that showed an increased risk of hemorrhagic stroke among the lean.\textsuperscript{12,14,19} Other studies, however, found no association\textsuperscript{9,20,21} or an increased risk with increasing BMI.\textsuperscript{10} The fact that the incidence of hemorrhagic stroke is higher in Asian populations has led to the hypothesis that low cholesterol, in addition to lean body weight, may be associated with increased risk of hemorrhagic strokes.\textsuperscript{20,35} The low numbers of hemorrhagic strokes in most of the studies may explain in part the uncertainty with regard to the association between BMI and hemorrhagic stroke. Future studies are needed to determine whether lean BMI and/or low cholesterol or other factors are important contributors to hemorrhagic stroke.

There is an ongoing discussion about the best measure of obesity for stroke prediction.\textsuperscript{11,30,32,36} A report from the Northern Manhattan Stroke Study suggested that abdominal obesity, as measured by the waist-to-hip ratio, was a stronger predictor than BMI and had a greater effect among younger individuals.\textsuperscript{11} In that study, however, obesity was evaluated at the time of the stroke, which may indicate that abdominal obesity may be a better short-term predictor than BMI.

### TABLE 3. HRs of Ischemic Stroke by BMI and Exercise Categories

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Exercise $\geq 1$/wk</th>
<th>Exercise $&lt;1$/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Weight</td>
<td>Overweight</td>
<td>Obese</td>
</tr>
<tr>
<td>No. of cases (n=432)</td>
<td>114</td>
<td>98</td>
</tr>
<tr>
<td>Model 1*</td>
<td>1.00</td>
<td>1.00 (0.69–1.45)</td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking status, alcohol consumption, and postmenopausal hormone use. $P$ for interaction: 0.57 for total stroke; 0.39 for ischemic stroke, 0.92 for hemorrhagic stroke.
Nevertheless, obesity is a strong risk factor for total and ischemic stroke regardless of the measure used. Whether more detailed information on body fat distribution will lead to better prediction of stroke currently remains unclear.

Obesity is a strong risk factor for the development of hypertension, diabetes, and elevated cholesterol. In virtually all studies that have evaluated the association between obesity and ischemic stroke, hypertension, diabetes, and elevated cholesterol were biological mediators. This, however, should not downplay the importance of obesity as a primary risk factor for stroke. To the contrary, because obesity has such a strong influence on hypertension and diabetes, obesity may be the biggest overall contributor to stroke occurrence. In some studies, a statistically significant excess risk for stroke remained even after controlling for hypertension, diabetes, and elevated cholesterol.

In addition to the established mechanisms by which BMI affects stroke risk such as hypertension and diabetes, other mechanisms may be associated with the increased risk. Some investigators have proposed that an increase in prothrombotic factors observed among overweight and obese individuals may contribute to their increased risk for ischemic events. Increased levels of C-reactive protein in overweight and obese individuals may also play a role in their increased risk of stroke, because an association between increased levels of inflammatory markers and risk of ischemic stroke has been documented; however, the biological interrelationship between obesity, inflammatory markers, and ischemic stroke risk has yet to be determined.

The present study has several strengths, including the prospective method of data collection, the large size of the study population, the large number of incident strokes, the high rate and length of follow-up, and the homogeneous nature of WHS participants, which reduces potential confounding by access to medical care and other socioeconomic factors. On each of the follow-up questionnaires, WHS participants were asked specifically about stroke and transient ischemic attacks. Because stroke was a major end point of the WHS trial, all efforts were made to obtain the relevant medical records, and an experienced End Points Committee confirmed stroke cases only after review of these records. In addition, the interobserver agreement in the classification of stroke was excellent. We further ran several different models, including time-varying models, to update the most recent exposure information, used different cutpoints of BMI, and evaluated potential biological mediators and effect modifiers.

Several limitations should be considered when evaluating the present results. First, information on body weight and height, as well as on all potential confounders, was self-reported, and thus nondifferential misclassification is possible. Participants of the WHS, however, were all health professionals, who are known to accurately report information regarding lifestyle factors and health status. Specifically, self-reported and directed measured weight were highly correlated ($r$=0.96) in another comparable cohort of female health professionals. In addition, nondifferential misclassification in a prospective study most likely would lead to an underestimation of the association between BMI and stroke. We have no reason to believe that a significant number of participants did not report a stroke event and particularly no reasoning that such potential underreporting would be differential with regard to BMI status. Second, because participants in the WHS were all health professionals who participated in a randomized trial, and the vast majority (94.9%) of them were white, the present results may not necessarily be extrapolated to other populations; however, we have no a priori basis for believing that the biological mechanisms by which BMI may lead to stroke differ in the WHS cohort compared with other populations. In addition, the relative measures of effect for a wide variety of cardiovascular risk factors have been similar to those seen in other studies. Because women participating in the WHS were somewhat leaner than the general population, we may have underestimated the risk of heavier populations. Finally, as with all observational studies, residual and unmeasured confounding remains an alternative explanation for our findings, despite adjustment for many potential confounders.

In conclusion, our study indicates that obesity is associated with increased risk of total and ischemic stroke. This was not modified by age, smoking, or exercise and was strongly mediated by hypertension, diabetes, and elevated cholesterol, which may be biological intermediates of the obesity–stroke association. The association between BMI and hemorrhagic stroke remains less clear. Preventing obesity may lead to a substantial reduction of total and ischemic stroke occurrence.

Acknowledgments

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References


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