

## Body Size and Fat Distribution as Predictors of Stroke among US Men

Susan P. Walker,<sup>1</sup> Eric B. Rimm,<sup>1,2</sup> Alberto Ascherio,<sup>1,2</sup> Ichiro Kawachi,<sup>3,4</sup> Meir J. Stampfer,<sup>1,2,4</sup> and Walter C. Willett<sup>1,2,4</sup>

Evidence for an association between general obesity and risk of stroke is weak. However, abdominal obesity may be more closely related to stroke risk. The association of body mass index and abdominal obesity (waist/hip ratio) with stroke incidence was examined in 28,643 US male health professionals, aged 40–75 years in 1986, who had no history of cardiovascular disease or stroke. In 5 years of follow-up, there were 118 cases of stroke, of which 80 were ischemic. Compared with men in the lowest quintile of body mass index, men in the highest quintile had an age-adjusted relative risk of stroke of 1.29 (95% confidence interval 0.73–2.27). In contrast, the age-adjusted relative risk for extreme quintiles of waist/hip ratio was 2.33 (95% confidence interval 1.25–4.37). This relative risk was not substantially altered in a multivariate model including body mass index, height, and other potential risk factors. There was a weaker relation with waist circumference alone, with men in the highest quintile (>40.2 inches) having a relative risk of 1.52 (95% confidence interval 0.82–2.82) compared with men in the lowest quintile ( $\leq$ 34.5 inches) (1 inch = 2.54 cm). The results suggest that abdominal obesity, but not elevated body mass index, predicts risk of stroke in men. *Am J Epidemiol* 1996; 144:1143–50.

body mass index; cerebrovascular disorders; obesity

Obesity is associated with an increased risk of all-cause mortality (1–3) and many specific health consequences, including hypertension (4–6), diabetes (7–9), coronary heart disease (10–12), and some cancers (13). In contrast, the relation between obesity and cerebrovascular disease remains unclear. Although an association between body mass index or relative weight and stroke incidence or mortality has been reported in some studies (14, 15), in other studies associations were found only for thromboembolic strokes (16), in women but not men (17), or only in diabetics (18). In several other studies no association was found between body mass index or relative weight and risk of stroke (19–25).

Although small numbers of cases (21, 22) or the inclusion of transient ischemic attacks among the cases (23) may have contributed to the lack of asso-

ciation in some studies, it is possible that body mass index may not be the most informative measure of obesity with respect to risk of stroke. Strokes are most common in the elderly among whom loss of lean body mass may be substantial (26, 27), so that weight may remain stable or even decrease though the percentage of body fat increases. The relation between the body mass index and the degree of adiposity may thus be weaker in older persons, and other measures such as the waist circumference and waist/hip ratio may provide a better measure of risk associated with obesity.

Abdominal obesity is related to known risk factors for stroke, such as hypertension (28–30) and diabetes (7, 31–33); however, the relation between abdominal obesity and stroke has been evaluated in only a few studies. Significant associations between the waist/hip ratio and stroke incidence were reported in two small Swedish studies (21, 22) and in a follow-up of US Army veterans (34), and in the Framingham cohort the ratio of waist to height predicted stroke risk (17).

We therefore assessed both body mass index and waist/hip ratio as predictors of stroke in a cohort of 28,643 US male health professionals who were followed prospectively for 5 years.

### MATERIALS AND METHODS

The Health Professionals Follow-up Study is a prospective study of 51,529 male health professionals

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<sup>1</sup> Department of Nutrition, Harvard School of Public Health and the Channing Laboratory, Boston, MA.

<sup>2</sup> Department of Epidemiology, Harvard School of Public Health and the Channing Laboratory, Boston, MA.

<sup>3</sup> Department of Health and Social Behavior, Harvard School of Public Health and the Channing Laboratory, Boston, MA.

<sup>4</sup> Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA.

Reprint requests to Dr. Eric Rimm, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115

who were 40–75 years of age when the study began in 1986. The cohort includes dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists. Participants completed in 1986 a detailed dietary and medical history questionnaire that included information on weight and height. Follow-up questionnaires were completed every 2 years in 1988, 1990, and 1992 to update exposure information and record newly diagnosed diseases. After repeated mailings, follow-up questionnaires were received or deaths confirmed for over 94 percent of eligible participants (35). A brief supplementary questionnaire was sent in 1987 to obtain self-reported waist and hip circumferences. The response rate to this questionnaire (65 percent) was lower than for the usual biennial mailings, as fewer follow-up mailings were conducted for this off-year questionnaire.

Men with cerebrovascular or cardiovascular disease or related conditions prior to 1987 were excluded from the present analyses. A total of 5,050 men who reported stroke, transient ischemic attack, myocardial infarction, coronary artery bypass graft or coronary angioplasty, angina, intermittent claudication, and peripheral venous thrombosis were excluded. We excluded men who had missing information for body mass index in 1986 ( $n = 573$ ), who did not complete the supplementary questionnaire ( $n = 15,668$ ), or who had missing dietary information ( $n = 1,595$ ). This left 28,643 men who were followed for a 5-year period from 1987 to 1992.

### Anthropometric assessment

Height (in inches) and current weight (in pounds) were self-reported on the 1986 questionnaire and used to calculate body mass index (weight (kg)/height (m)<sup>2</sup>). A paper tape measure and pictorial instructions were provided with the 1987 questionnaire to assist the participants in reporting their waist and hip circumferences. Waist was defined as the circumference at the umbilicus, and hip circumference, as the largest circumference between the waist and thighs. The ratio of the circumferences was calculated and used as a measure of abdominal obesity.

The validity of the anthropometric measurements was assessed in a random sample of 123 men. The Pearson correlation coefficients between self-reported and technician measurements were 0.97 for the weight, 0.95 for the waist, 0.88 for the hips, and 0.68 for the waist/hip ratio (36).

Information on potential confounding variables including diet, physical activity, and smoking status was obtained from the 1986 questionnaire (37).

### Cases

Fatal and nonfatal strokes were included in the study. If a nonfatal stroke was reported on a follow-up questionnaire, permission was sought to review the subject's medical records. Strokes were confirmed if characterized by a typical neurologic deficit of sudden or rapid onset, lasting at least 24 hours and attributable to a cerebrovascular event. Strokes caused by infection or neoplasia were excluded. Reviews were conducted by physicians with no knowledge of the subjects' risk factor status. Strokes were subclassified according to the criteria of the National Survey of Stroke, as due to ischemia (embolism or thrombosis), subarachnoid hemorrhage, intracerebral hemorrhage, or unknown cause (38). If no records could be obtained, strokes were considered probable if they required hospitalization and were corroborated by additional information provided by letter or interview.

Most deaths in the cohort are reported by relatives or the postal authorities. A search of the National Death Index for nonrespondents is conducted after each questionnaire cycle. Fatal strokes were confirmed by medical records (or considered probable if these were not obtainable) and if this was the cause listed on the death certificate.

### Analysis

Participants contributed follow-up time from the date of return of the 1987 questionnaire until occurrence of a stroke, death from other causes, or January 31, 1992. The body mass index and waist/hip ratio were divided into quintiles, and relative risks were calculated as the incidence rate among men in each quintile divided by the rate among men in the lowest quintile of each index. Relative risks were adjusted for age (in 5-year categories) using the Mantel-Haenszel method (39), and the Mantel extension test (40) was used to test for linear trends. Multiple logistic regression analysis was used to adjust for other potential risk factors. Each multivariate model comprised the anthropometric index or indices, age, activity, and intakes of antioxidant vitamins (all in quintiles). Reported blood pressure, diabetes, and hypercholesterolemia were not included because they are likely to be in the causal pathway between obesity and stroke. We were interested in the overall effect of obesity so that control for these variables would be inappropriate. Tests for trends across increasing levels of obesity were calculated by creating a new variable from the median values for each quintile. This was then used in place of the quintiles as a single continuous variable.

## RESULTS

During 130,675 person-years of follow-up, 118 strokes including 17 fatal strokes were recorded. Of these, 80 strokes were classified as ischemic and 25 as hemorrhagic, with 13 of unknown cause.

The age-adjusted prevalence of other potential risk factors according to body mass index quintile is shown in table 1. Intakes of the antioxidant vitamins (vitamin E, vitamin C, and carotene) decreased with increasing category of body mass index. Since these may be related to stroke risk (41), they were included (as quintiles of intake) in the multivariate analysis. Energy intake did not vary across quintiles, but leisure-time physical activity decreased with increasing body mass index, and this was also included in the multivariate analysis. Activity and intakes of vitamin E, vitamin C, and carotene also decreased across increasing quintiles of waist/hip ratio (table 2). The percentage of smokers was slightly higher in the leanest men and in men with higher waist/hip ratios; however, the prevalence of smoking was low in this cohort.

Body mass index was not significantly associated with the risk of stroke (table 3). Men in the top quintile of body mass index had an age-adjusted relative risk of 1.29 (95 percent confidence interval 0.73–2.27) compared with men in the lowest quintile. This risk was not materially changed when dietary and lifestyle factors were included in a multiple logistic model but was reduced to 0.87 (95 percent confidence interval 0.48–1.58) when the waist/hip ratio was included.

Men in the second quintile of the body mass index tended to have a lower risk of stroke compared with men in the lowest quintile (multivariate relative risk = 0.55, 95 percent confidence interval 0.29–1.04). In a further analysis, we included body mass index as a continuous (linear) and a quadratic (squared) variable. There was no indication of a significant nonlinear relation between the body mass index and the risk of stroke. Further control for smoking and alcohol did not appreciably alter the results presented in table 3.

The association between body mass index and stroke was also estimated in an analysis including the 15,668 men who did not report their waist and hip circumferences (table 4). The association between body mass index and stroke was slightly weaker in the full cohort; comparing extreme quintiles, the age-adjusted relative risk was 1.12 (95 percent confidence interval 0.74–1.72).

Compared with men in the lowest quintile of the waist/hip ratio, men in the highest quintile had an age-adjusted relative risk of 2.33 (95 percent confidence interval 1.25–4.37). This was only slightly changed after controlling for body mass index and height and other potential risk factors (table 3). The

TABLE 1. Baseline characteristics of 28,643 men in the Health Professionals Follow-up Study (mean, range, or %), adjusted for age, according to quintile of body mass index in 1986

BMI* by quintile (kg/m <sup>2</sup> )	No	Age (years)	BMI (kg/m <sup>2</sup> )	WHR*	Waist circumference (inches)†	Height (inches)	Current smoker (%)	Hypertensive (%)	Diabetic (%)	Leisure time physical activity (METs/week)‡	Energy intake (kcal/day)	Alcohol (g/day)	Vitamin C (mg/day)	Vitamin E (IU/day)	Carotene (IU/day)
≤23.0	6,280	53.4	21.8	0.91	34.2	70.2	9.6	13.4	2.0	23.2	2,025	11.4	462	99.6	10,718
23.1–24.4	6,006	53.9	23.8	0.92	35.9	70.2	8.1	16.0	2.0	21.8	2,009	12.3	436	95.2	10,243
24.5–25.8	5,950	54.3	25.1	0.93	37.2	70.4	8.9	18.5	2.2	19.9	1,999	12.7	411	87.3	9,773
25.9–27.6	5,371	54.7	26.6	0.94	38.5	70.0	8.7	20.9	2.2	18.3	1,999	12.1	389	83.0	9,423
≥27.7	5,036	54.3	30.1	0.96	41.9	70.2	9.0	31.2	3.8	14.5	2,032	12.1	380	82.9	9,453

\* BMI, body mass index; WHR, waist/hip ratio.

† One inch = 2.54 cm.

‡ METs are defined for each type of physical activity as a multiple of metabolic equivalent of sitting quietly for 1 hour. For example, a participant who runs (7 METs/hour) 1 hour a day three times a week would have a MET score of 21.

TABLE 2. Baseline characteristics of 28,643 men in the Health Professionals Follow-up Study (mean, range, or %), adjusted for age, according to quintile of waist/hip ratio in 1986

WHR* by quintile	No	Age (years)	BMI* (kg/m <sup>2</sup> )	WHR	Waist circumference (inches)†	Height (inches)	Current smoker (%)	Hypertensive (%)	Diabetic (%)	Leisure time physical activity (METs/week)‡	Energy intake (kcal/day)	Alcohol (g/day)	Vitamin C (mg/day)	Vitamin E (IU/day)	Carotene (IU/day)
<0.89	6,035	50.6	23.8	0.87	34.4	70.0	7.6	13.8	2.0	25.1	1,998	10.7	445	93.9	10,617
0.89-0.91	6,100	53.0	24.5	0.91	36.0	70.2	8.0	15.8	1.7	21.5	2,006	11.8	426	92.2	10,226
0.92-0.94	5,466	54.3	25.1	0.94	37.2	70.2	8.6	19.2	2.0	19.3	2,010	12.0	425	90.8	9,907
0.95-0.97	5,582	55.9	26.0	0.96	38.7	70.3	9.7	22.3	2.7	16.7	2,011	12.5	398	84.9	9,432
≥0.98	5,450	57.0	27.1	1.02	41.0	70.3	10.8	27.1	3.5	14.3	2,036	13.4	386	81.9	9,512

\* WHR, waist/hip ratio; BMI, body mass index

† One inch = 2.54 cm.

‡ METs are defined for each type of physical activity as a multiple of metabolic equivalent of sitting quietly for 1 hour. For example, a participant who runs (7 METs/hour) 1 hour a day three times a week would have a MET score of 21.

risk of stroke increased significantly across quintiles of waist/hip ratio (significance level of test for trend,  $p < 0.001$ ). In analyses using the waist/hip ratio as a continuous variable and the square of the waist/hip ratio, there was no evidence of a nonlinear relation. The analyses were repeated using as cases only those strokes that were classified as ischemic. The results were similar, although the risk associated with a high waist/hip ratio slightly increased.

Loss of lean body mass with aging can result in overall weight loss and a change in the relative proportions of fat mass to lean body mass in older individuals. The body mass index tends to decline among men in this cohort after the age of 65 years (42). We therefore divided the cohort into younger (aged <65 years,  $n = 23,746$ ) and older (aged  $\geq 65$  years,  $n = 4,897$ ) groups and examined the associations of body mass index and waist/hip ratio with stroke within these strata. There were 64 cases in the younger group and 51 cases in the older group; relations with the body mass index and the waist/hip ratio were not substantially altered in either group.

Taller men (height = 73 inches (183 cm) or greater) had an age-adjusted relative risk of 0.57 (95 percent confidence interval 0.31-1.05) compared with men whose height was  $\leq 68$  inches (173 cm) (table 5). This was not altered after adjustment for other risk factors including body mass index and the waist/hip ratio.

The measurement error associated with the waist/hip ratio is greater than that associated with individual circumferences. If most of the risk related to the waist/hip ratio is due to the waist circumference, then this might be a more predictive measure. However, the age-adjusted relative risk comparing men in the highest quintile of waist circumference with men in the lowest was 1.52 (95 percent confidence interval 0.82-2.82).

Although the prevalence of smoking is low in this cohort, smoking is associated with a lower body mass index and a higher waist/hip ratio. We therefore repeated the analyses in 13,395 men who reported never having smoked. The multivariate relative risk comparing extreme quintiles was 0.96 (95 percent confidence interval 0.40-2.34) for the body mass index and 3.19 (95 percent confidence interval 1.16-8.77) for the waist/hip ratio.

## DISCUSSION

In this prospective study of US health professionals, we found that men with a waist/hip ratio of  $>0.98$  had 2.3 times the risk of a stroke than did men whose waist/hip ratio was  $\leq 0.89$ . In contrast, body mass index was much more weakly associated with increased risk of stroke. Our results support the lack of

**TABLE 3. Body mass index, waist/hip ratio, and risk of stroke among 28,643 men in the Health Professionals Follow-up Study, 1987–1992**

	No of cases	No of person-years	Age-adjusted RR*	Multivariate† RR	Multivariate‡ RR
<b>BMI* by quintile (kg/m<sup>2</sup>)</b>					
≤23.0	25	28,661	1.0	1.0	1.0
23.1–24.4	15	27,486	0.61 (0.32–1.15)§	0.61 (0.32–1.16)	0.55 (0.29–1.04)
24.5–25.8	25	27,162	1.03 (0.59–1.80)	1.00 (0.57–1.75)	0.83 (0.47–1.46)
25.9–27.6	27	24,468	1.24 (0.72–2.14)	1.16 (0.67–2.02)	0.91 (0.51–1.61)
≥27.7	26	22,987	1.29 (0.73–2.27)	1.25 (0.72–2.19)	0.87 (0.48–1.58)
<i>p</i> , trend			0.09	0.25	0.90
<b>Waist/hip ratio by quintile</b>					
<0.89	13	27,625	1.0	1.0	1.0
0.89–0.91	12	27,966	0.76 (0.35–1.68)	0.77 (0.35–1.68)	0.79 (0.36–1.74)
0.92–0.94	21	24,986	1.33 (0.66–2.68)	1.32 (0.66–2.66)	1.37 (0.68–2.77)
0.95–0.97	28	25,440	1.60 (0.82–3.13)	1.54 (0.79–3.01)	1.58 (0.79–3.14)
≥0.98	44	24,658	2.33 (1.25–4.37)	2.33 (1.23–4.40)	2.36 (1.21–4.64)
<i>p</i> , trend			<0.001	<0.001	<0.001

\* RR, relative risk; BMI, body mass index.

† Multivariate models include age, activity, vitamin E, vitamin C, and carotene.

‡ Multivariate models include age, activity, vitamin E, vitamin C, carotene, BMI, and waist/hip ratio.

§ Numbers in parentheses, 95% confidence interval.

**TABLE 4. Body mass index (BMI) and risk of stroke among 43,830 men in the Health Professionals Follow-up Study,\* 1987–1992**

BMI by quintile (kg/m <sup>2</sup> )	No. of cases	No of person-years	Age-adjusted RR†
≤23.0	43	41,736	1.0
23.1–24.4	26	41,541	0.60 (0.37–0.97)‡
24.5–25.8	34	42,057	0.76 (0.49–1.20)
25.9–27.6	44	40,659	1.03 (0.67–1.56)
≥27.7	47	40,180	1.12 (0.74–1.72)
<i>p</i> , trend			0.13

\* Analysis includes men who did not report their waist and hip circumferences.

† RR, relative risk.

‡ Numbers in parentheses, 95% confidence interval.

association between general obesity and stroke reported in previous studies (19–25) and suggest that fat distribution or abdominal obesity may be more important for identifying men at higher risk of stroke.

Because this was a prospective study, it is unlikely that the self-reported measurements were biased by subsequent risk of disease. The distribution of adiposity measures may be somewhat nonrepresentative because the analyses were restricted to the 28,643 men who reported their waist and hip circumferences. However, the association of body mass index and stroke was not materially altered in analyses of the entire cohort, including the men who did not report their circumferences. We have demonstrated the va-

lidity, in this cohort, of self-reported measurements of body weight and of waist and hip circumferences (36). The validity of the waist/hip ratio calculated using self-reported circumferences is comparable to that of a single measure of blood pressure (43).

Body mass index may be a poor measure of obesity in older men as adiposity may increase, even though the weight or body mass index remains stable or may even decrease because of the loss of lean body mass (27, 44). Because most strokes occur in older men (in the study cohort, men aged 65 years or more were 7.5 times as likely to have a stroke as were men aged 40–45 years), this may contribute to the weak association between body mass index and stroke. In an earlier report from this cohort, we found only a modest association between body mass index and coronary heart disease among men aged 65 years or older, although a strong association was seen in younger men (45). Similarly, the association between body mass index and the risk of diabetes was weaker in older men (7). Shinton et al. (15) observed increased mortality from stroke with increasing body mass index among men aged 40–54 years but not among men aged 55–64 years. In the present study, even among men below the age of 65 years, we found no clear association between body mass index and stroke incidence.

Men in the second quintile of body mass index had a somewhat lower risk of stroke than did the leanest men. The reasons for this are not clear and may be due

**TABLE 5. Height and risk of stroke among 28,643 men in the Health Professionals Follow-up Study, 1987-1992**

Height category (inches)*	No of cases	No. of person-years	Age-adjusted RR†	Multivariate‡ RR
≤68	46	33,841	1.0	1.0
69	11	15,018	0.58 (0.31-1.10)§	0.59 (0.30-1.14)
70-71	33	40,773	0.70 (0.45-1.08)	0.69 (0.44-1.08)
72	15	17,965	0.79 (0.45-1.39)	0.79 (0.44-1.42)
≥73	13	23,058	0.57 (0.31-1.05)	0.59 (0.31-1.10)
<i>p</i> , trend			0.13	0.31

\* One inch = 2.54 cm.

† RR, relative risk.

‡ Multivariate model includes age, activity, vitamin E, vitamin C, carotene, body mass index, and waist/hip ratio.

§ Numbers in parentheses, 95% confidence interval.

to chance. The percentage of smokers was slightly lower in the second quintile of body mass index than in the lowest, but the results were similar among men who reported never having smoked (the age-adjusted relative risk for men in the second quintile was 0.29 (95 percent confidence interval 0.11-0.79)).

The lowest body mass index quintile may include men who have lost weight as a result of subclinical disease. Because information on the waist/hip ratio was obtained in 1987, follow-up began 1 year after the baseline date for body mass index. This may reduce bias due to subclinical disease. Ideally, a longer lag period would be desirable (3), but we had insufficient cases to test this hypothesis.

A strong association between the waist/hip ratio and stroke incidence remained after controlling for body mass index and other covariates. These results confirm and extend previous reports based on fewer cases (21, 22, 34). The waist/hip ratio is an indicator of absolute and, to a lesser degree, relative amounts of abdominal visceral fat (46). Intraabdominal fat has a high lipolytic activity and is less sensitive than subcutaneous adipose tissue to the inhibitory effects of insulin on lipolysis (47). An increase in intraabdominal adipose tissue is therefore associated with an increased supply of free fatty acids to the liver (48). This may increase hepatic production of very low density lipoprotein cholesterol and lead to elevated circulating concentrations of very low density and low density lipoprotein cholesterol. The waist/hip ratio is positively correlated with plasma concentrations of triglycerides and of very low density and low density lipoprotein cholesterol and inversely associated with high density lipoprotein cholesterol (49). High levels of free fatty acids may also interfere with the hepatic clearance of insulin, resulting in hyperinsulinemia and increased risk of hypertension (47, 50).

The use of the waist circumference as an indicator

of abdominal obesity would be simpler and more practical in clinical settings. Furthermore, waist circumference has less measurement error than the ratio of waist to hip circumference (36). However, in this cohort, the relation between waist circumference and the risk of stroke was weaker than that between the waist/hip ratio and stroke. More information is needed on the relation between waist circumference and the risk of chronic diseases before the use of this measure instead of the use of the waist/hip ratio can be recommended.

Taller men tended to have a lower risk of stroke than did men with heights of 68 inches (173 cm) or less. This suggests that the relation between height and stroke may be similar to that seen with coronary heart disease (45, 51, 52). There are few other reports of the relation between stature and stroke incidence. In contrast to our findings, Hebert et al. (51) observed no association between height and the risk of stroke among US physicians. Although height is not a modifiable risk factor, it may still be useful as part of overall risk assessment, but further data are needed to confirm this association.

In conclusion, our results suggest that a strong association exists between abdominal obesity and stroke incidence. The waist/hip ratio and, to a lesser extent, waist circumference predicted risk of stroke, although it remains uncertain whether this represents a causal relation. Our data do not exclude a modest association between body mass index and stroke but do provide further evidence of the importance of considering fat distribution when evaluating associations between obesity and chronic diseases. The relation between obesity and stroke differed from the pattern observed with coronary heart disease and diabetes in the same group of men. This difference may be related to differences in etiology and suggests that the most useful measure of obesity may vary by disease.

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