Body Fat Distribution and Long-Term Risk of Stroke Mortality

David Tanne, MD; Jack H. Medalie, MD; Uri Goldbourt, PhD

Background and Purpose—Excess weight is an important determinant of cardiovascular disease, but the relationship between excess weight, its distribution, and stroke is yet unclear. We examined in a large prospective cohort study the association between body fat distribution and stroke mortality among middle-aged men.

Methods—A cohort of male civil servants and municipal employees free of cardiovascular disease in Israel (n=9151) were followed up for mortality over 23 years. The subscapular skinfold (SSF) was used as a measure of trunk and overall obesity and the ratio of subscapular to triceps skinfold thickness (SFR) as an indicator of trunk versus peripheral distribution of body fat.

Results—During the follow-up period, 316 died of stroke, and 865 died of coronary heart disease. The estimated age-adjusted hazard ratios (HRs) for stroke mortality, associated with 1 SD increment of SSF, was 1.12 (95% CI, 1.01 to 1.25) and for body mass index, 1.17 (1.06 to 1.30), but these associations were markedly weakened when adjusting for blood pressure. SFR was associated with an age-adjusted HR for stroke mortality of 1.14 (1.03 to 1.26). Further adjusting for systolic blood pressure, diabetes mellitus, cigarette smoking, and socioeconomic status (HR, 1.11; 1.01 to 1.23) as well as body mass index (HR, 1.11; 1.00 to 1.23) only mildly attenuated this association. Subjects with SFR in the upper quartile exhibited a 1.5-fold higher adjusted HR (1.53; 1.10 to 2.12) compared with the lowest quartile.

Conclusion—Indices of body fat and body fat distribution predict long-term stroke and coronary heart disease mortality among middle-aged men. SFR, an indicator of trunk versus peripheral distribution of body fat, is associated with stroke mortality, independent of main mediators of the effect of obesity on health and of body mass index. (Stroke. 2005;36: 1021-1025.)

Key Words: body composition ■ coronary heart disease ■ obesity ■ stroke

Excess weight is an important determinant of cardiovascular disease. Several investigators have found that overweight men, defined on the basis of high body mass index (BMI), have a greater risk of developing stroke than subjects with normal levels of total body fatness, but other investigators did not find such an association. Indeed, some persons with increased BMI may have a normal amount of body fat and a large muscle mass, whereas others may have excess adiposity and reduced muscle mass. Therefore, it has become apparent that the relationship between obesity and cardiovascular disease depends not only on the amount of body fat but also on its distribution. Individuals with increased fat accumulation in the abdominal region, indicated by high waist-to-hip ratio, often have atherogenic lipid profiles and were found to be at an increased stroke risk.

The Israeli Ischemic Heart Disease (IIHD) project was a longitudinal investigation of cardiovascular disease among male civil servants and municipal employees in Israel. This cohort provided a wide range of occupations and socioeconomic levels in the male working population of Israel at the time of inclusion. Subjects underwent extensive appraisal of health and were followed for mortality over a long period of time. Skinfold thickness was measured at baseline and enabled estimation of body fat distribution. Thus, the subscapular skinfold (SSF) was used as a measure of trunk and overall obesity, whereas the ratio of subscapular to triceps skinfold thickness (SFR) as an indicator of trunk versus peripheral distribution of body fat. The present investigation deals with the prediction of stroke mortality over a long-term follow-up by body fat distribution among subjects free of known cardiovascular disease at baseline.

Subjects and Methods

Study Participants

Participants of the IIHD project were chosen by stratified sampling of male civil servants and municipal employees based on an age ≥40 years on inclusion, place of work confined to the 3 largest urban areas in Israel (Tel-Aviv, Jerusalem, and Haifa), and sampling
fractures aimed at obtaining numbers of study subjects from 6 areas of birth (central Europe, eastern Europe, the Balkan countries, the Middle East, northern Africa, and Israel), approximately proportional to the Israeli male population of this age. The percentage consenting to participate among eligible subjects and undergoing the baseline examination was 86%. Participants underwent clinical and blood biochemical evaluations in 1963, 1965, and 1968, as detailed previously. Subjects with either a history of myocardial infarction or those whose chest pain status was summarized as “definite” or “possible” angina pectoris according to the IIHD study protocol were excluded from this analysis.

Body Fat Assessments

For calculating BMI, height was measured (without shoes) to the nearest centimeter and weight to the nearest kilogram with subjects wearing trousers only. Skinfold thickness was measured in millimeter using a Lange skinfold caliper. SSF was measured at the inferior angle of the scapula, and the triceps skinfold was measured posteriorly at the halfway point between the outer edge of the acromium and the olecranon process of the ulna. SSF was used as a measure of trunk and overall obesity and SFR as an indicator of trunk versus peripheral distribution of body fat.

Cause of Death Determination

The underlying cause of death was documented on the basis of case-by-case determination by a review panel through mid-1970 and by the use of the International Classification of Diseases (ICD) codes 7, 8, and 9 thereafter. Deaths from cerebrovascular disease were based on ICD-9 codes 430 to 438 and those from coronary heart disease (CHD) by codes 410 to 414 and 798. For the earlier (pre-1971) deaths, comparison of death certificates with the analyses of hospital records by the panel yielded a 90% agreement. Information on mortality after 1970 was derived from the Israeli Mortality Registry.

Statistical Analysis

Analyses of the association between BMI and body fat distribution and the end points of stroke and CHD mortality were performed adjusted for traditional risk factors and potential confounders. Adjusted hazards were estimated using the proportional hazard model by Cox. The appropriateness of the proportional hazards assumption was examined by observing Schoenfield’s residuals. Adjusted hazard ratios (HRs) and 95% CIs are presented. Stata 7.0 software was used for the multivariate analysis of fatal stroke incidence over 23 years. 11

Results

Skinfold thickness was measured in 8638 of the 9151 participants free of cardiovascular disease at baseline (94%), of whom 316 died of stroke and 865 died of CHD during the 23-year follow-up. The mean BMI, SSF, and SFR in our cohort were $25.6 \pm 3.3 \text{ kg/m}^2$, $19.0 \pm 8.3 \text{ mm}$, and $1.62 \pm 0.74 \text{ mm}$, respectively. The distribution of these indicators by area of birth are shown in Table 1. Main risk factors for stroke by quartiles of BMI, SSF, and SFR are presented in Table 2. With increasing quartiles of BMI and central fat distribution, subjects tended to be somewhat older, to have higher blood pressure, more diabetes mellitus, and lower proportions of HDL cholesterol, and fewer of them smoked.

Mortality by BMI and Body Fat Distribution

The crude rates of death from stroke and CHD by BMI are summarized in Table 3. Rates of stroke mortality per 10 000 person years of follow-up rose by increasing quartiles of BMI from 15.7 to 17.5, 17.3, and 21.9. Four percent of our cohort was very lean (BMI <20 kg/m²), 37% had a BMI of 20 to 24.9 kg/m², 49% a BMI of 25 to 29.9 kg/m², and 9% were obese (BMI >30 kg/m²). Rates of stroke mortality by these categories ranged between 9.3 and 22.8 per 10 000 person years of follow-up.

The crude rates of death from stroke and CHD by indices of body fat distribution are summarized in Table 4. Rates of stroke mortality per 10 000 person years of follow-up range across quartiles of SSF between 15.1 to 15.4, 16.2 up to 20.6, and across quartiles of SFR from 13.4 to 15.8, 14.7, and up to 22.3, respectively.

Multivariate Analysis

Adjusted HRs for dying from stroke and for dying from CHD (per 1 SD change) are shown in Table 5. Results of hazards adjusted for age (model A), for age and systolic blood pressure (model B) and for age, systolic blood pressure, diabetes mellitus, smoking, and socioeconomic status (model C) are provided. The analysis of the association of SFR with incident fatal stroke is also shown incorporating adjustment for BMI (model D). Using proportional hazards, the age-adjusted HR associated with 1 SD increment of BMI was 1.17 (95% CI, 1.06 to 1.30) and for SSF, 1.12 (95% CI, 1.01 to 1.25). These associations were weakened when systolic or diastolic blood pressure, mediators of the effect of obesity on health, were also included in the model. A 1 SD increment of SFR was associated with an age-adjusted HR for stroke mortality of 1.14 (95% CI, 1.03 to 1.26). Further adjustment for systolic blood pressure, diabetes, cigarette smoking, and socioeconomic status (HR, 1.11; 95% CI, 1.01 to 1.23) only mildly attenuated this association. Further adjustment for baseline BMI did not change this association. Subjects with SFR in the upper quartile exhibited a ~1.5-fold higher HR.
compared with the lowest quartile (1.53; 95% CI, 1.10 to 2.12), adjusting for age, smoking, and socioeconomic status (Figure). Evidently, this ratio declines as weight-determined factors such as blood pressure and diabetes are also adjusted for (to 1.31).

**Discussion**

This article reports 1 of the few long-term longitudinal studies of central obesity and the subsequent development of stroke mortality, controlling for baseline BMI. In this cohort of middle-aged men free of cardiovascular disease at baseline, SFR, an indicator of trunk versus peripheral distribution of body fat, is an independent predictor of long-term stroke mortality.

Several studies have shown an association of obesity, as defined by BMI, with the risk of stroke. In the Physicians’ Health Study, increasing BMI was associated with a steady increase in the risks of total, ischemic, and hemorrhagic stroke. Although accounted for mostly by concomitant hypertension and diabetes, a significant increase remained after adjustment for these potential biological mediators. The Honolulu Heart Program reported that BMI was associated with increased risk of thromboembolic stroke among nonsmoking men in older middle age. In contrast, other studies have failed to find an independent relationship between obesity measured by BMI and increased risk of stroke in men.

Over the last 4 decades, the prevalence of obesity (BMI ≥30 kg/m2) has increased in the United States from 13% to 31%, and the prevalence of overweight (a BMI of 25 to 29.9 kg/m2) has increased from 31% to 34%. Increase in the prevalence of obesity was also observed over the years among middle-aged men in Israel. The working middle-aged men in our cohort, recruited in Israel in the mid-1960s, indeed included a low proportion of obese men.

The effects of obesity on cardiovascular health and disease are numerous, hypertension being one of the most profound. A weakening of associations between BMI with stroke

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**TABLE 3. BMI and 23-Year Fatal CHD and Stroke Rates***

<table>
<thead>
<tr>
<th>Person Years of Follow-Up</th>
<th>No. of Deaths</th>
<th>Crude Rates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD</td>
<td>Stroke</td>
</tr>
<tr>
<td>Quartiles of BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>45 986</td>
<td>156</td>
</tr>
<tr>
<td>II</td>
<td>47 096</td>
<td>214</td>
</tr>
<tr>
<td>III</td>
<td>46 807</td>
<td>227</td>
</tr>
<tr>
<td>IV</td>
<td>45 656</td>
<td>268</td>
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</table>

Categories of BMI, kg/m2

<table>
<thead>
<tr>
<th>Category</th>
<th>Person Years of Follow-Up</th>
<th>No. of Deaths</th>
<th>Crude Rates (95% CI)</th>
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<tr>
<td>&lt;20</td>
<td>8637</td>
<td>24</td>
<td>8</td>
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<td>20–24.9</td>
<td>70 933</td>
<td>286</td>
<td>116</td>
</tr>
<tr>
<td>25–26.9</td>
<td>44 950</td>
<td>203</td>
<td>67</td>
</tr>
<tr>
<td>27–29.9</td>
<td>44 359</td>
<td>240</td>
<td>87</td>
</tr>
<tr>
<td>≥30</td>
<td>10 666</td>
<td>112</td>
<td>38</td>
</tr>
</tbody>
</table>

* Rates per 10,000 person years of follow-up.
mortality and between SSF, an indicator of trunk obesity, and stroke mortality when blood pressure was adjusted for may indicate the role of the latter in mediating long-term health hazards among overweight men. If we regard blood pressure as well as diabetes as mediators rather than confounders of the association between obesity and clinical outcome, we consider adjustment to these weight-determined factors as potential overadjustment, and therefore present the HRs without these mediators as the findings of main significance.

Individuals with increased fat accumulation in the abdominal region often have atherogenic lipid profiles and are at increased cardiovascular risk. The Health Professionals Follow-Up Study showed that the highest quintile of waist-to-hip ratio was associated with an increased risk of stroke among men but did not ascertain the mediating effect of hypertension, diabetes, and hyperlipidemia. In a case-control study from the Northern Manhattan Stroke Study, abdominal obesity was an independent, potent risk factor for ischemic stroke and a stronger risk factor than BMI. In the National Health and Nutrition Examination Survey (NHANES) I Epidemiological Follow-up Study, higher SFR was associated with a mildly but significantly increased incidence of stroke but only in white male former smokers, with a 1.4-fold increased risk in those with SFR in the upper compared with the lower quartile. In middle-aged Finnish men, SSF was positively associated with stroke incidence (odds ratio, 1.6; 95% CI, 1.3 to 2.0, per 1 SD difference), independent of BMI and other variables, including plasma insulin.

There is a strong link between obesity and a generalized metabolic disorder of which insulin resistance is an indicator. Gavril et al found that in addition to overall obesity, central fat distribution is an independent negative predictor of serum adiponectin and suggest that adiponectin may represent a link between central obesity and insulin resistance. Abdominal adipose tissue accumulations are the critical correlates of elevated plasma C-reactive protein levels found in men with atherogenic dyslipidemia of the insulin resistance syndrome. There are different methods to assess body fat distribution. SFR likely measures a somewhat different aspect of relative body fat distribution than other measures such as waist circumference or waist-to-hip ratio. SSF measures subcutaneous trunk fat, a somewhat different aspect of absolute trunk body fat than indicators such as waist girth, which measures subcutaneous and intra-abdominal fat, or intra-abdominal fat on computerized tomographic scanning for visceral fat. Unlike the girth or radiographic measures, skinfolds do not directly reflect visceral fat. However, reported associations with incidence of hypertension have been similar. There should not be affected by changes in lean body mass with aging. Although not an optimal measure for clinical settings, the advantages of skinfold thickness are long-established standardized methods with wide availability in data sets from large population surveys, thus offering a useful opportunity to researchers and interested clinicians. Elevated SFR might be a marker for a state characterized by increased trunk and visceral fat, leading to insulin resistance and increased plasma insulin levels with resulting dyslipidemia, glucose intoler-

### TABLE 4. Indices of Body Fat and 23-Year Fatal CHD and Stroke Rates*

<table>
<thead>
<tr>
<th>Quartiles of SSF</th>
<th>Person Years of Follow-Up</th>
<th>No. of Deaths</th>
<th>Crude Rates (95% CI)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>CHD</td>
<td>Stroke</td>
</tr>
<tr>
<td>I</td>
<td>44 369</td>
<td>159</td>
<td>67</td>
</tr>
<tr>
<td>II</td>
<td>51 225</td>
<td>238</td>
<td>79</td>
</tr>
<tr>
<td>III</td>
<td>41 859</td>
<td>209</td>
<td>68</td>
</tr>
<tr>
<td>IV</td>
<td>43 170</td>
<td>232</td>
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</table>

<table>
<thead>
<tr>
<th>Quartiles of SFR</th>
<th>Person Years of Follow-Up</th>
<th>No. of Deaths</th>
<th>Crude Rates (95% CI)</th>
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<tbody>
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<td></td>
<td></td>
<td>CHD</td>
<td>Stroke</td>
</tr>
<tr>
<td>I</td>
<td>43 147</td>
<td>168</td>
<td>58</td>
</tr>
<tr>
<td>II</td>
<td>44 880</td>
<td>205</td>
<td>71</td>
</tr>
<tr>
<td>III</td>
<td>44 085</td>
<td>209</td>
<td>65</td>
</tr>
<tr>
<td>IV</td>
<td>43 136</td>
<td>234</td>
<td>96</td>
</tr>
</tbody>
</table>

*Rates per 10 000 person years of follow-up.

### TABLE 5. Adjusted HRs for Dying From CHD and Stroke by BMI, Trunk Obesity, and Body Fat Distribution*

<table>
<thead>
<tr>
<th>BMI</th>
<th>CHD (95% CI)</th>
<th>Stroke (95% CI)</th>
<th>SSF</th>
<th>CHD (95% CI)</th>
<th>Stroke (95% CI)</th>
<th>SFR</th>
<th>CHD (95% CI)</th>
<th>Stroke (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td>1.20 (1.13–1.27)</td>
<td>1.17 (1.06–1.30)</td>
<td>1.13 (1.06–1.20)</td>
<td>1.12 (1.01–1.25)</td>
<td>1.08 (1.02–1.16)</td>
<td>1.14 (1.03–1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model B</td>
<td>1.12 (1.05–1.20)</td>
<td>1.07 (0.96–1.20)</td>
<td>1.06 (1.00–1.13)</td>
<td>1.04 (0.93–1.16)</td>
<td>1.05 (0.99–1.12)</td>
<td>1.09 (0.99–1.22)</td>
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</tr>
<tr>
<td>Model C</td>
<td>1.11 (1.04–1.17)</td>
<td>1.05 (0.94–1.17)</td>
<td>1.06 (0.99–1.13)</td>
<td>1.04 (0.93–1.16)</td>
<td>1.05 (0.98–1.12)</td>
<td>1.11 (1.01–1.23)</td>
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<tr>
<td>Model D</td>
<td>…</td>
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<td>…</td>
<td>…</td>
<td>…</td>
<td>1.11 (1.00–1.23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Per 1 SD of change.

Model A adjusted for age; model B adjusted in addition for systolic blood pressure; model C adjusted in addition for diabetes mellitus, smoking, and socioeconomic status; model D adjusted in addition for BMI.
BMI. Although our results are consistent with an association of cardiovascular disease at baseline, independent of baseline long-term stroke mortality among middle-aged men free of distribution of body fat, was found to be a predictor of additional study, SBF, an indicator of trunk versus peripheral state of being overweight and diabetes and hypertension were although we have identified overweight as the best predictor for which nationwide information is virtually complete. Second, long-term mortality data were obtained from death examination of these relationships in women. However, the included subjects resemble the nationwide distribution of working middle-aged men in Israel at the time of inclusion. Second, long-term mortality data were obtained from death certificates, known for their potential inaccuracies, and the autopsy rate in Israel is extremely low. However, mortality data are available derived from the Israeli Mortality Registry, for which nationwide information is virtually complete. Third, no information was collected on stroke incidence, type, and underlying stroke mechanism. Fourth, analysis is based on a single assessment of skinfold thickness, known to be prone to interobserver and intraobserver variability, and other indices of abdominal obesity were not measured. Finally, as in many large observational studies, we do not have any data regarding changes occurring during follow-up. Specifically, although we have identified overweight as the best predictor of diabetes and hypertension that may contribute to development of arteriosclerosis and stroke.

Study limitations included the fact that only middle-aged male participants were recruited in this cohort, precluding examination of these relationships in women. However, the included subjects resemble the nationwide distribution of working middle-aged men in Israel at the time of inclusion. Bar graph of HRs and SE for stroke mortality by quartiles of SBF to SFR adjusted for age, smoking, socioeconomic status, and area of birth. Information is based on 8576 subjects and 286 stroke deaths. HR for the lower quartile is defined as 1. of SFR and incident fatal stroke that is little affected by confounders or mediators, support or disagreement of such a hypothesis would require examination of the association of SFR with long-term outcome in other prospective cohort studies.

References

14. Gillum RF, Mussolino ME, Madans JH. Body fat distribution, obesity, stroke, and area of birth. Information is based on 8576 subjects and 286 stroke deaths. HR for the lower quartile is defined as 1.
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