Body Mass Index, Other Cardiovascular Risk Factors, and Hospitalization for Dementia

Annika Rosengren, MD, PhD; Ingmar Skoog, MD, PhD; Deborah Gustafson, PhD; Lars Wilhelmsen, MD, PhD

Background: Previous studies have shown that risk factors commonly associated with coronary disease, stroke, and other vascular disorders also predict dementia. We investigated the longitudinal relationship between body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) and risk of hospital discharge or death certificate diagnosis of dementia.

Methods: A total of 7402 men who were 47 to 55 years old in 1970 to 1973, without prior stroke or myocardial infarction, derived from a population sample of 9998 men were prospectively followed up until 1998. Two hundred fifty-four men (3.4%) had a hospital discharge diagnosis or a death certificate diagnosis of dementia: 176 with a primary diagnosis or cause of death and 78 with a secondary diagnosis.

Results: The relationship between BMI and dementia as a primary diagnosis was J-shaped, and men with a BMI between 20.00 and 22.49 had the lowest risk. Subsequently, after adjustment for smoking, blood pressure, serum cholesterol level, diabetes mellitus, and social class, the risk increased linearly in men who had a BMI of 22.50 to 24.99 (multiple-adjusted hazard ratio [HR], 1.73; 95% confidence interval [CI], 0.92-3.25), 25.00 to 27.49 (HR, 1.93; 95% CI, 1.03-3.63), 27.50 to 29.99 (HR, 2.30; 95% CI, 1.18-4.47), and 30.00 or greater (HR, 2.45; 95% CI, 1.20-5.36) (P for linear trend = .03). Men with a BMI less than 20.00 had a nonsignificantly elevated risk (HR, 2.4; 95% CI, 0.77-6.25).

Conclusions: A J-shaped relationship was observed between BMI and dementia, such that a BMI less than 20 and an increasing BMI of 22.5 or greater were associated with increased risk from midlife to old age of a primary hospital diagnosis of dementia. Overweight and obesity could be major preventable factors in the development of dementia.

Arch Intern Med. 2005;165:321-326

Risk of dementia affects approximately 1 in 3 people who survive to the age of 85 years. Still, the development of dementia is not necessarily a natural phenomenon in old people. Several studies have shown that risk factors commonly associated with coronary disease, stroke, and other vascular disorders also predict dementia, and accordingly some dementia processes may be preventable.

The 2 major dementia disorders are Alzheimer disease and vascular dementia. Discriminating between the two may not always be possible, which is illustrated by the findings that different criteria may result in substantial differences in the proportion of patients diagnosed as having one or the other disorder. Vascular dementia, obviously, shares risk factors with stroke, such as hypertension, but lately the risk of developing Alzheimer disease has been associated with vascular risk factors as well. Both disorders, however, are common in elderly people and often coincide.

Obesity is a common denominator for many cardiovascular risk factors, such as hypertension, dyslipidemia, insulin resistance, and diabetes mellitus, factors that have been linked to the development of vascular dementia and Alzheimer disease. Some studies have indicated that the optimal body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) with respect to coronary disease and stroke is probably in the lower reference range. Few studies have prospectively evaluated the role of overweight and obesity in the development of dementia. However, in a recently published cohort study, Gustafson et al showed that BMI was, on average, 3.6 higher at the age of 70 years among women who developed Alzheimer disease 10 to 18 years later compared with those who did not develop de-
mentia. In addition, in an analysis that focused on the role of serum cholesterol and blood pressure related to dementia, Kivipelto et al.\textsuperscript{10} found that persons diagnosed as having dementia had significantly higher midlife BMI than those who maintained normal cognitive function, but the study design did not permit an analysis of people who had died or who did not take part in the examination. The purpose of the present investigation was to study the association between BMI in midlife and all hospitalizations or deaths with a diagnosis of dementia in men during a 28-year period.

### Methods

Data were derived from 7404 male participants from the intervention group in the multifactor Primary Prevention Study that began in Göteborg, Sweden, in 1970.\textsuperscript{16} All men in the city who were born between 1915 and 1925 (N=30000), except those born in 1923, were randomized into 3 groups of 10000 men each. The men in one of the groups (intervention group; n=9998) were offered a medical examination to identify and treat risk factors. The intervention was essentially a high-risk strategy directed toward men with pronounced hypercholesterolemia, severe hypertension, or heavy smoking habits, according to predefined criteria. All participants gave their informed consent to participate in the study. The study was approved by the Ethics Committee for Medical Research at Göteborg University.

The first screening examination included 7495 men (75% of those invited) in the intervention group and took place between January 1970 and March 1973. Of those 7495, 7404 men (98.8%) without prior history of myocardial infarction or stroke form the basis for the present study. Two men had missing data for BMI and were excluded, leaving a total of 7402 men. During the first 12-year follow-up, there were no significant differences in outcomes with respect to cardiovascular disease, cancer, or all-cause mortality between the intervention and control groups.\textsuperscript{15} Thus, we consider the study group to be representative of the general Göteborg male population.

Information on smoking habits, physical activity during leisure time, occupation, and diabetes mellitus was collected via a questionnaire mailed to all men in the intervention group. Men who returned the questionnaire were invited to the study center. Examinations were performed in the afternoon. Weight was measured in kilograms to the nearest 0.10 kg, height was measured in meters to the nearest 0.01 m, and blood pressure was measured to the nearest mm Hg after 5 minutes of rest with the participant seated. Serum cholesterol concentration (from a sample taken after fasting for $\geq$2 hours) was determined according to standard laboratory procedures.

Smoking habits were defined using 5 categories: never smoker, former smoker of more than 1 month’s duration, and current daily smoking of 1 to 14 g, 15 to 24 g, and 25 g or more of tobacco. One cigarette was considered to contain 1 g of tobacco; one cigarillo, 2 g; and one cigar, 5 g. Occupation was coded according to the Swedish socioeconomic classification system (Socio-Economic Index), with 5 occupational classes: (1) unskilled and semiskilled workers, (2) skilled workers, (3) foremen in industrial production and assistant nonmanual employees, (4) intermediate nonmanual employees, and (5) employed and self-employed professionals, higher civil servants, and executives. Physical activity during leisure time was categorized into 3 levels: sedentary, moderate activity such as walking or light gardening for at least 4 hours per week, and regular, strenuous, or very strenuous activity for at least 2 to 3 hours per week.

### Follow-Up

All participants in the multifactor Primary Prevention Study were followed up from the date of their baseline examination until December 31, 1998, with the use of their unique personal identification number. A computer file of the men in the study was run against the Swedish national register on cause of death and the Swedish Hospital Discharge Register. This process was approved by the review board of the Göteborg University Ethics Committee. The Hospital Discharge Register has operated on a nationwide basis since 1987, but all discharges from Göteborg hospitals have been entered in the national register since 1970 (except 1976 owing to a legislative change for that single year). A manual checking of selected diagnoses (myocardial infarction, heart failure, and atrial fibrillation) showed that less than 3% of these diagnoses were missed by the Hospital Discharge Register. For ethical, legislative, and technical reasons, the dementia cases in the present study could not be validated or classified further by examining the medical records.

For the purpose of these analyses, follow-up of dementia, myocardial infarction, stroke, and diabetes was completed. Dementia was defined as a discharge or death with a primary or secondary diagnosis code of 290 (International Classification of Diseases, Eighth Revision [ICD-8]) and 431, 432, 433, 434, or 436 (International Classification of Diseases, Ninth Revision [ICD-9]) for F00.0, F00.1, F00.2, F00.9, F01, F02, or F03 (International Classification of Diseases, 10th Revision [ICD-10]). Among the patients with dementia, a subgroup with Alzheimer disease was created that included those who at any time had a diagnosis of 290.10 (ICD-8), 290B or 331A (ICD-9), or F00.0, F00.1, F00.2, or F00.9 (ICD-10). Diabetes mellitus was defined as any discharge using 250 (ICD-8 and ICD-9) or E10 or E11 (ICD-10) as primary or secondary diagnoses. Stroke was defined as any primary diagnosis with 431, 432, 433, 434, or 436 (ICD-8 and ICD-9) or 161, 162, 163, or 164 (ICD-10).

### Statistical Analysis

We formed 4 groups: (1) 22 men who had been diagnosed as having Alzheimer disease at any time, (2) 78 men who had been diagnosed as having dementia as a secondary diagnosis only, (3) 154 men diagnosed as having dementia as a primary diagnosis or cause of death, and (4) 7148 men who had never been hospitalized with a dementia diagnosis. Only 4 of 27 deaths due to dementia occurred in men who had not already been discharged with a dementia diagnosis.

We used unpaired t tests for the comparison of continuous variables between the separate dementia groups and the non-dementia group, whereas the Fisher exact test was used for categorical variables. All tests were 2-tailed. Prospective analyses were accomplished using Cox proportional hazards regression models to identify factors related to a hospital discharge diagnosis of dementia. In this analysis, the small group of 22 men diagnosed at any time as having Alzheimer disease (all primary diagnoses) was merged with the 154 men with a primary, non-Alzheimer dementia diagnosis. We also present data for the entire group of men diagnosed as having dementia (n=254). Time at risk was calculated to first hospitalization with a dementia diagnosis, to death, or to December 31, 1998. To measure the relationship between BMI and dementia, BMI was entered in regression models as a continuous and a categorical variable. Increasing levels of BMI were created using 6 BMI categories: less than 20.00, 20.00 to 22.49, 22.50 to 24.99, 25.00 to 27.49, 27.50 to 29.99, and 30.00 or greater.

Univariate regression analyses were used to evaluate potential confounders of the BMI-dementia relationship. These potential confounders included systolic and diastolic blood press-
Table 1. Baseline Risk Factors According to Diagnosis at Follow-up

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Diagnosis of Alzheimer Disease at Any Time (n = 22)</th>
<th>Dementia as a Secondary Diagnosis Only (n = 78)</th>
<th>Dementia as a Primary Diagnosis or Cause of Death (n = 154)</th>
<th>No Dementia (n = 7148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, mean (SD), y</td>
<td>51.2 (2.0)</td>
<td>52.6 (1.8)‡</td>
<td>52.6 (2.1)‡</td>
<td>51.5 (2.3)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD), y</td>
<td>74.1 (5.2)</td>
<td>77.5 (3.6)</td>
<td>77.2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD)*</td>
<td>25.8 (3.2)</td>
<td>25.3 (3.5)</td>
<td>26.0 (3.1)‡</td>
<td>25.5 (3.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>141 (23)</td>
<td>153 (23)</td>
<td>148 (23)</td>
<td>149 (22)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>92 (15)</td>
<td>96 (14)</td>
<td>95 (12)</td>
<td>95 (13)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), per minute</td>
<td>67 (12)‡</td>
<td>75 (13)‡</td>
<td>71 (12)‡</td>
<td>73 (14)</td>
</tr>
<tr>
<td>Treatment for hypertension, No. (%)</td>
<td>5 (1)</td>
<td>4 (3)</td>
<td>6 (9)</td>
<td>5 (385)</td>
</tr>
<tr>
<td>Serum cholesterol, mean (SD), mg/dL</td>
<td>247 (39)</td>
<td>256 (53)</td>
<td>254 (40)</td>
<td>249 (45)</td>
</tr>
<tr>
<td>Current smoking, No. (%)</td>
<td>41 (9)</td>
<td>51 (40)</td>
<td>51 (78)</td>
<td>50 (3588)</td>
</tr>
<tr>
<td>Sedentary leisure time, No. (%)</td>
<td>18 (4)</td>
<td>31 (24)</td>
<td>28 (43)</td>
<td>25 (1820)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>0 (0)</td>
<td>5 (4)‡</td>
<td>3 (4)</td>
<td>2 (137)</td>
</tr>
<tr>
<td>Nonmanual occupational class, No. (%)</td>
<td>36 (8)</td>
<td>22 (17)</td>
<td>27 (42)</td>
<td>28 (1992)</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert serum cholesterol to millimoles per liter, multiply by 0.0259.
*Calculated as weight in kilograms divided by the square of height in meters.
‡P<.001 for comparison with no dementia.
†P<.05 for comparison with no dementia.

Risk factors at baseline by dementia categories during follow-up are shown in Table 1. In longitudinal analyses, a J-shaped relationship was observed between BMI and dementia as a primary diagnosis (Table 2). Men with a BMI between 20.00 and 22.49 had the lowest risk. Using these men as the reference group, men with a BMI less than 20.00 had a higher yet nonsignificant risk of 2.38 (95% CI, 0.84-6.75). At BMIs greater than 22.49, risk increased linearly (P for linear trend=.03) to 2.45 (95% CI, 1.17-5.12) in men with BMIs of 30.00 or above.

Considering all dementia diagnoses, men with BMIs of 30.00 or greater, risk was increased to 1.98 (95% CI, 1.10-3.56) compared with the reference group.

Regarding other cardiovascular risk factors, an increased risk for dementia as a primary or secondary diagnosis was found in men with a baseline serum cholesterol level of 290 mg/dL (7.5 mmol/L) or greater (HR, 1.78; 95% CI, 1.04-3.05), with a positive linear trend between serum cholesterol and dementia risk (P=.03). There was no significant relationship between serum cholesterol and dementia as a primary diagnosis (P=.11). Self-reported diabetes at baseline was significantly associated with all dementia (P<.001). Systolic blood pressure was not related to dementia. Other factors that were not significantly related to dementia, either as a primary diagnosis or as all dementia, include diastolic blood pressure, treatment for hypertension at baseline, low physical activity, and low occupational class (data not shown).

Consideration of potential confounders of the dementia and BMI relationship only marginally altered risks (Table 3). Occurrence of stroke and diabetes mellitus during the interval between the baseline investigation and the first diagnosis of dementia did not alter our conclusions (data not shown). Of all variables entered into the full model, BMI was the only factor that was independently associated with dementia as a principal diagnosis (P for trend=.03). In addition, diabetes at baseline was independently associated with increased risk of all dementia (HR, 3.10; 95% CI, 1.52-6.34; data not shown).

We observed a J-shaped relationship between BMI in midlife and risk for dementia. The lowest risk was observed in men who had a low yet healthy BMI. Contrary to other studies, we found no increased dementia risk with hypertension and only a comparatively weak relation with serum cholesterol. Thus, there was no indication that a higher demen-
The association between body weight or BMI and dementia has been long obscured by observations that dementia onset and progress is associated with weight loss. However, several prospective studies have reported that patients with dementia have higher BMIs at baseline. The present study confirms these findings but also indicates that risk may increase even within normal BMIs.

There is evidence from cross-sectional studies that diabetes and impaired glucose tolerance may adversely influence cognitive function and that dementia is more prevalent in persons with diabetes. In prospective studies, diabetes has been found to increase risk of dementia by a factor of 1.5 to 2.5. Diabetes mellitus, impaired glucose tolerance, and dyslipidemia are aspects of the metabolic syndrome, which also includes hypertension and obesity. In the Honolulu-Asia Aging Study, a higher cardiovascular risk factor burden in middle age increased the risk of vascular dementia 25 years later. Given the central role of obesity in the development of hypertension, dyslipidemia, diabetes, and the metabolic syndrome, a potential association between obesity and dementia is hardly surprising.

**BLOOD PRESSURE, CIGARETTE SMOKING, AND SERUM CHOLESTEROL LEVELS**

In the present study, we found no association between blood pressure in midlife and subsequent hospitalization related to dementia. However, other prospective studies have shown that high blood pressure may increase the risk for dementia by inducing small vessel disease and other vascular complications.
white matter lesions and that antihypertensive medication may help lower that risk. In a longitudinal study of elderly persons in Göteborg, Sweden, participants who developed dementia at the age of 79 to 85 years or who had white matter lesions on computed tomography at the age of 85 years had higher blood pressure at the age of 70 years than those who did not develop dementia. Among Japanese American men, the risk for late-life Alzheimer disease increased with increasing blood pressure 25 years before onset. The lack of an association between blood pressure and dementia in this population is unexpected, particularly because systolic blood pressure was an excellent predictor of cardiovascular death. After 10 years, 26% of the men were taking antihypertensive medication. Possibly, this could have obscured an association, but the increased risk in hypertensive men was even more pronounced in the latter part of the follow-up.

Dementia and cognitive disturbances have also been associated with smoking and the role of elevated serum total cholesterol levels in Alzheimer disease has also been documented. Why the present study failed to confirm these established cardiovascular risk factors in the development of dementia is unclear. However, the CIs were fairly wide, and positive associations between dementia and smoking or elevated serum cholesterol levels cannot be ruled out from our results.

OTHER MORBIDITY

The strongest association was found for those with a primary diagnosis of dementia. The primary diagnoses among those with dementia as a secondary diagnosis were varied and included infections, fractures, and malignancy, as well as vascular disease, and did not suggest any particular pattern of comorbidity. For some of these diagnoses, poor nutrition could play a role and obscure the observed association between overweight and dementia. Among the vascular diagnoses, stroke was nonsignificantly more prevalent among men diagnosed as having dementia. Dementia is common after stroke, and even if adjustment for stroke did not alter the observed associations, it is still possible that some of the association between high BMI and dementia was mediated through unrecognized stroke episodes.

LIMITATIONS

Although our study points to a strong relationship between BMI and dementia risk, there are potential limitations. First, our case ascertainment depended entirely on hospital diagnoses and, in rare cases, on dementia as a cause of death. Milder cases that were managed at home were not identified. However, this approach may result in a more complete follow-up of severe cases than through follow-up with clinical examination. In the present study, we identified dementia in 3.4% of men during a mean follow-up of 23 years. In the study reported by Kivipelto et al from a similar-aged longitudinal sample, there was an overall incidence of 2.9% among participants. After a 20- to 26-year follow-up in the Honolulu-Asia Aging Study, 197 participants with dementia were identified among 3734 survivors of an original sample of 8006 Japanese American men. This is 5.3% of the survivors but only 2.5% of the original sample. Other studies have found considerably higher incidence rates both because they studied older populations and because milder cases were diagnosed by clinical examination. Our results are most likely conservative, because mild dementia cases will not have been identified.

Second, we were unable to distinguish type of dementia with certainty. Only 22 of 176 patients with dementia were at any time diagnosed as having Alzheimer disease, which is clearly a much lower proportion than would have been expected. Any subdiagnosis of dementia based}

<table>
<thead>
<tr>
<th>Body Mass Index Categories</th>
<th>No. of Cases per 100000 Observation Years (Actual No.)</th>
<th>HR (95% CI) for Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age Adjusted</td>
<td>Adjusted for Age, Smoking, Social Class, Systolic Blood Pressure, Diabetes Mellitus, and Cholesterol</td>
</tr>
<tr>
<td></td>
<td>All Dementia (254 Cases)</td>
<td></td>
</tr>
<tr>
<td>&lt;20.00</td>
<td>2.43 (1.11-5.29)</td>
<td>2.24 (1.02-4.90)</td>
</tr>
<tr>
<td>20.00-22.49</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>22.50-24.99</td>
<td>1.49 (0.92-2.41)</td>
<td>1.49 (0.92-2.42)</td>
</tr>
<tr>
<td>25.00-27.49</td>
<td>1.49 (0.92-2.41)</td>
<td>1.51 (0.93-2.46)</td>
</tr>
<tr>
<td>27.50-29.99</td>
<td>1.72 (1.03-2.88)</td>
<td>1.69 (1.00-2.85)</td>
</tr>
<tr>
<td>&gt;=30.00</td>
<td>1.98 (1.10-3.56)</td>
<td>1.84 (1.01-3.34)</td>
</tr>
<tr>
<td>P for trend</td>
<td>.12</td>
<td>.22</td>
</tr>
<tr>
<td>Dementia as a Principal Diagnosis (176 Cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.00</td>
<td>2.38 (0.84-6.75)</td>
<td>2.19 (0.77-6.25)</td>
</tr>
<tr>
<td>20.00-22.49</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>22.50-24.99</td>
<td>1.74 (0.93-3.26)</td>
<td>1.73 (0.92-3.25)</td>
</tr>
<tr>
<td>25.00-27.49</td>
<td>1.88 (1.01-3.51)</td>
<td>1.93 (1.03-3.63)</td>
</tr>
<tr>
<td>27.50-29.99</td>
<td>2.29 (1.19-4.42)</td>
<td>2.30 (1.18-4.47)</td>
</tr>
<tr>
<td>&gt;=30.00</td>
<td>2.45 (1.17-5.12)</td>
<td>2.54 (1.20-5.36)</td>
</tr>
<tr>
<td>P for trend</td>
<td>.03</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Calculated as weight in kilograms divided by the square of height in meters.
solely on hospital discharge diagnoses is bound to be inaccurate. The dementia cases in the present study could not be validated or classified further by examining the medical records.

Third, we used BMI as a measurement of overweight and obesity. More sophisticated methods of determining body fatness were not feasible in an epidemiologic study at the time. Measures of central obesity such as waist circumference were not available. However, ultimately, BMI and other markers of obesity are secondary to lifestyle factors, such as diet and physical activity, factors that are amenable to intervention.

A fourth limitation is that we were unable to measure with accuracy the onset of dementia. This means that the use of HRs as an estimate of risk will lack in precision, because dementia usually has an insidious onset and hospitalization and death will in most instances occur only at an advanced stage.

CONCLUSIONS

The central finding of the present study was that low yet healthy BMI in midlife is associated with the least risk of dementia. Among the strengths of this study are the extended follow-up that was virtually complete for the end point under study, the high participation rate, and a clinical anthropometric assessment. The methods that we used will have underestimated the true prevalence of dementia to an unknown degree, although it is probable that most cases with severe dementia were identified. Bearing these limitations in mind, the results of the present study indicate that prevention of dementia in old age should probably focus more on the maintenance of a healthy body weight in midlife. Overweight and obesity could be major preventable factors in the development of dementia.

Accepted for Publication: July 31, 2004.

Correspondence: Annika Rosengren, MD, PhD, Department of Medicine, Sahlgrenska University Hospital/Ostra, SE-416 85 Goteborg, Sweden (Annika.Rosengren@hjl.gu.se).

Funding/SUPPORT: This study was funded by the Swedish Research Council, Stockholm, and the Swedish Heart and Lung Foundation, Stockholm.

Acknowledgment: The statistical help and expertise of George Lappas, Cardiovascular Institute, Sahlgrenska University Hospital/Ostra, is gratefully acknowledged.

REFERENCES