An 18-Year Follow-up of Overweight and Risk of Alzheimer Disease

Deborah Gustafson, PhD; Elisabet Rothenberg, PhD; Kaj Blennow, PhD; Bertil Steen, MD, PhD; Ingmar Skoog, MD, PhD

Background: Overweight and obesity are epidemic in Western societies and constitute a major public health problem because of adverse effects on vascular health. Vascular factors may play a role in the development of a rapidly growing disease of late life, Alzheimer disease (AD). Using body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), we examined whether overweight is a risk factor for dementia and AD.

Methods: The relationship between BMI and dementia risk was investigated in a representative cohort of 392 nondemented Swedish adults who were followed up from age 70 to 88 years, with the use of neuropsychiatric, anthropometric, and other measurements. Multivariate Cox proportional hazards regression analyses included BMI, blood pressure, cardiovascular disease, cigarette smoking, socioeconomic status, and treatment for hypertension.

Results: During the 18-year follow-up (4184.8 risk-years), 93 participants were diagnosed as having dementia. Women who developed dementia between ages 79 and 88 years were overweight, with a higher average BMI at age 70 years (27.7 vs 25.7; P = .007), 75 years (27.9 vs 25.0; P < .001), and 79 years (26.9 vs 25.1; P = .02) compared with nondemented women. A higher degree of overweight was observed in women who developed AD at 70 years (29.3; P = .009), 75 years (29.6; P < .001), and 79 years (28.2; P = .003) compared with nondemented women. For every 1.0 increase in BMI at age 70 years, AD risk increased by 36%. These associations were not found in men.

Conclusions: Overweight is epidemic in Western societies. Our data suggest that overweight at high ages is a risk factor for dementia, particularly AD, in women. This may have profound implications for dementia prevention.

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METHODS

PARTICIPANTS

In 1971 to 1972, the 70-year-old residents of Go¨teborg were systematically sampled from the Population Register by selecting individuals born on dates (days) ending with 2, 5, and 8 (N = 1148).13,14 The response rate was 85%; therefore, 973 took part in a comprehensive examination of aging.13,14 All participants were consecutively given proband number 1 to 5. A subsample comprising those with numbers 1 and 2 were selected for a psychiatric examination; thus, 392 individuals, 166 men and 226 women, took part in the psychiatric examination.15 The main sample and subsample were found to be representative of their population base with regard to sex; marital status; income; community rent allowance; rate of inpatient and outpatient care in psychiatric hospitals, clinics, and municipal outpatient departments; and rates of registration with the Temperance Board.16 In the present study, individuals with dementia already at age 70 years (n=10) were excluded, leaving 382 nondemented participants with anthropometric measurements. Participants were invited for new examinations at 75, 79, 81, 83, 85, and 88 years of age. Those who died or refused to take part were traced in records from hospitals and homes for the aged, inpatient and outpatient departments in psychiatric hospitals and clinics, municipal psychiatric outpatient departments in Go¨teborg, the hospital-linkage system, and death certificates.13 Thus, information regarding a dementia diagnosis was obtained for all study participants, since almost all people in Sweden receive their health care from the community and all participants have an equal chance of having a case record.

All participants (or their nearest relatives) gave their informed consent to participate in the study. The study was approved by the Ethics Committee for Medical Research at Go¨teborg University.

METHODS

The detailed, longitudinal examinations of manifestations of aging and somatic and psychiatric disorders included a physical examination performed by a geriatrcian, an electrocardiogram, a chest x-ray, a battery of blood tests, and a neuropsychiatric examination performed by a psychiatrist.13,14,15 The examination at 85 and 88 years included a key informant interview and computed tomographic scan. Participants were surveyed about a variety of potential risk factors for age-related diseases, such as education, smoking habits, socioeconomic status, alcohol intake, medication use, and medical history.

The diagnosis of dementia at 70, 75, 79, 81, and 83 years required the presence of severe disorientation for time and place and/or a long-standing severe memory impairment as measured by rating scales and information from case records or relatives.13 The diagnosis of dementia at ages 85 and 88 years was based on the psychiatric examination and a close informant interview with the use of criteria from the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition,17 as described previously.2 Diagnoses from collateral sources required information on symptoms of dementia in case records, death certificates, and the hospital linkage system. Dementia onset was defined as the point at which there was loss of cognitive abilities sufficient to produce obvious impairment in psychosocial functioning.

Type of dementia was determined for dementia cases between 79 and 88 years old. Alzheimer disease was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations criteria18 and VaD according to National Institute of Neurological and Communicative Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria.19 Vascular dementia was diagnosed when an individual had 1 or more infarcts detected by computed tomographic scanning, and/or a history of acute focal neurologic symptoms and signs (restricted to definite symptoms or signs, such as acute hemiparesis or acute motor aphasia). Case records were consulted for participants lost to follow-up by means of compatible diagnostic criteria. Information gathered during examinations at 70, 75, and 79 years did not permit classification of type of dementia.

Anthropometric measurements were standardized during all follow-up years and were conducted in the morning with participants wearing light clothing. Body weight was recorded to the nearest 0.1 kg, and body height was measured to the nearest centimeter. Body mass index is a weight-per-height measurement and was calculated as kilograms per meter squared.

Casual blood pressure was measured in the right arm in the seated position with a mercury manometer after 5 minutes' rest. Systolic and diastolic blood pressures were registered to the nearest 3 mm Hg. Diastolic blood pressure (DBP) was defined as Korotkoff phase 5. Apolipoprotein E isoforms 2, 3, and 4 were identified by means of a monoclonal antibody to apolipoprotein E after protein purification, protein separation via isoelectric focusing, and Western blotting.19

STATISTICAL ANALYSIS

We used t tests to assess differences in mean BMI at ages 70, 75, 79, and 85 years among those who became demented at 70 to 75, 75 to 79, and 79 to 88 years of age, and those who did not develop dementia. Total dementia, as well as AD and VaD subtypes, were evaluated at 79 to 88 years. Change in BMI during the follow-up period, with BMI at age 70 years used as the referent year, was also evaluated in relationship to dementia risk.

Cox proportional hazards regression analyses were used to calculate the hazard ratios for factors related to incident dementia, AD, and VaD among women at age 70 to 79 years and 79 to 88 years of age. Time at risk was calculated to age 88 years, death, or diagnosis of dementia. Men were not included in regression analyses because of low participant numbers in our sample. Univariate regression analyses were used to evaluate the following potential confounders of the BMI-dementia relationship: apolipoprotein E4 phenotype, DBP, cardiovascular disease, stroke, diabetes mellitus, cancer, late-life depression, education, socioeconomic status, cigarette smoking, alcohol intake, and use of antihypertensive medications. The relationship between these factors and BMI was also assessed by means of analysis of variance and ch² analysis, and the interaction between DBP and BMI was tested in regression models. Variables were included in multivariate regression models if they met the criterion of P<.05 in univariate analyses. Thus, final regression models included measurements of BMI and DBP at ages 70, 75, and 79 years; cardiovascular disease; cigarette smoking; socioeconomic status; and treatment for hypertension. The BMI and DBP were modeled as continuous variables. Two levels of socioeconomic status, middle or upper vs working class (working class was the referent group), were entered into each model. Cardiovascular disease and treatment for hypertension were considered as dichotomous variables.

Covariates were entered into Cox proportional hazards regression models by a single-step approach. In all analyses, concurrent (during 1 examination year) measures of BMI, DBP, smoking, and cardiovascular disease were included in individual models. Risk of dementia was calculated per 1.0 increment of BMI, as well as per 1-SD increment of BMI. Two-tailed tests were used in all analyses at a significance level of P<.05.
RESULTS

Among women, the mean±SD BMI was 26.1±4.2 at age 70 years, 25.6±3.9 at age 75 years, 23.5±4.0 at age 79 years, and 25.2±3.1 at age 85 years. Overweight (BMI ≥25) was prevalent in 57.9% of women at age 70 years, 42.0% at age 75 years, and 32.3% at age 79 years. Among men, the mean BMI was 25.5±3.4 at age 70 years, 24.8±3.7 at age 75 years, 24.3±3.6 at age 79 years, and 24.4±3.4 at age 85 years. Overweight was prevalent in 58.1% of men at age 70 years, 44.3% at age 75 years, and 32.3% at age 79 years. Dementia occurred in 93 participants (6 women and 13 men between 70 and 75 years of age; 17 women and 12 men between 75 and 79 years of age; and 36 women and 9 men between 79 and 88 years of age). Between the ages of 79 and 88 years, 24 AD, 18 VaD, and 3 “other” dementia cases were diagnosed. Total risk time evaluated between ages 70 and 88 years was 4194.8 risk-years (2705.6 in women and 1489.2 in men).

There was no association between apolipoprotein E4 phenotype and BMI, and no interaction between BMI and DBP, and there was no significant change in BMI during the 18-year follow-up period in demented or non-demented women and men (data not shown).

Women who developed dementia at age 79 to 88 years had a higher BMI at age 70 years (P = .007), 75 years (P < .001), and 79 years (P = .02) than those who did not develop dementia (Table 1 and Figure). Notably, women who developed AD at 79 to 88 years also had a higher BMI at ages 70 years (P = .009), 75 years (P < .001), and 79 years (P = .003) than women who did not develop dementia. The BMI was not related to the incidence of VaD.

In contrast, there were no BMI differences between men who became demented at 79 to 88 years and those who did not at age 70 years (24.2 vs 25.4; P = .29), 75 years (23.2 vs 25.2; P = .11), and 79 years (23.1 vs 25.0; P = .17). There were no BMI differences based on AD or VaD subtype, as well.

Table 1. Mean BMI at Examination Ages 70, 75, and 79 Years by Dementia Status During the Age Interval 79 to 88 Years Among Women

<table>
<thead>
<tr>
<th>Age at Examination</th>
<th>No Dementia</th>
<th>Total Dementia at 79-88 y</th>
<th>AD at 79-88 y</th>
<th>VaD at 79-88 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI at 70 y</td>
<td>Mean (SD)</td>
<td>25.7 (4.1)</td>
<td>29.3 (3.3)</td>
<td>26.0 (3.9)</td>
</tr>
<tr>
<td></td>
<td>No. of subjects</td>
<td>162</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>P value</td>
<td>.007</td>
<td>.009</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>BMI at 75 y</td>
<td>Mean (SD)</td>
<td>25.0 (3.7)</td>
<td>29.6 (3.4)</td>
<td>26.1 (3.7)</td>
</tr>
<tr>
<td></td>
<td>No. of subjects</td>
<td>129</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>BMI at 79 y</td>
<td>Mean (SD)</td>
<td>25.1 (3.9)</td>
<td>28.2 (3.8)</td>
<td>25.3 (2.8)</td>
</tr>
<tr>
<td></td>
<td>No. of subjects</td>
<td>98</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>P value</td>
<td>.02</td>
<td>.003</td>
<td>.86</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); VaD, vascular dementia. *P values compare total dementia, AD, or VaD vs no dementia.

Table 2. Hazard Ratios for Total Dementia, AD, and VaD per 1.0 Increase in BMI Among Women aged 79 to 88 Years

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dementia</td>
<td>BMI at age 70 y</td>
<td>1.13 (1.04-1.24)</td>
</tr>
<tr>
<td></td>
<td>BMI at age 75 y</td>
<td>1.13 (1.04-1.24)</td>
</tr>
<tr>
<td></td>
<td>BMI at age 79 y</td>
<td>1.15 (1.05-1.26)</td>
</tr>
<tr>
<td>AD</td>
<td>BMI at age 70 y</td>
<td>1.36 (1.16-1.59)</td>
</tr>
<tr>
<td></td>
<td>BMI at age 75 y</td>
<td>1.35 (1.19-1.53)</td>
</tr>
<tr>
<td></td>
<td>BMI at age 79 y</td>
<td>1.23 (1.10-1.37)</td>
</tr>
<tr>
<td>VaD</td>
<td>BMI at age 70 y</td>
<td>1.01 (0.88-1.15)</td>
</tr>
<tr>
<td></td>
<td>BMI at age 75 y</td>
<td>1.07 (1.02-1.12)</td>
</tr>
<tr>
<td></td>
<td>BMI at age 79 y</td>
<td>1.00 (0.89-1.13)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; VaD, vascular dementia. *Hazard ratios and 95% CIs were calculated by Cox proportional hazards regression analyses and adjusted for diastolic blood pressure, cardiovascular disease, cigarette smoking, socioeconomic status, and treatment for hypertension. The hazard ratios reflect a 1.0 increase in BMI. BMI was the only significant predictor in the multivariate models for total dementia and AD.

The mean±SD BMI at age 70 years in women who developed dementia at 70 to 75 years (25.8±4.7) or 75 to 79 years (26.7±4.4) did not differ from that of women who did not develop dementia between 70 and 79 years (26.1±4.1). Similarly, the mean BMI at age 70 years in men who had not developed any type of dementia by age 79 years (25.7±3.2) did not differ from the mean BMI at age 70 years of men who developed dementia at age 70 to 75 years (26.4±3.2) or 75 to 79 years (25.8±4.9).

Multivariate Cox proportional hazards regression models for the prediction of total dementia, AD, and VaD among women at 79 to 88 years of age are shown in Table 2. Time at risk for evaluating dementia outcomes during ages 79 to 88 years was 962.2 risk-years for women and 397.1 for men. The BMI measures at 70, 75, and 79 years were the sole independent predictors of total dementia and AD risk at ages 79 to 88 years in women. The BMI was not a significant predictor of VaD.
We found a striking relationship between overweight at age 70 years and the development of AD 10 to 18 years later in elderly white women. Dementia risk was associated with a BMI that was clearly overweight (≥25.0). The BMI was, on average, 3.6 higher among those who developed AD than those who never became demented. This relationship remained after a number of potential confounders were considered.

The role of overweight as a risk factor for dementia is largely unexplored despite recent interest in dementia and vascular factors related to overweight. A recent longitudinal Finnish study suggested that high BMI is a risk factor for AD; however, instead of considering BMI as an independent risk factor for AD, BMI was included as a covariate in analyses focusing on blood pressure and blood cholesterol levels. In addition, one cross-sectional study20 has reported a higher BMI among men and women with probable AD. Other cross-sectional or short-term follow-up studies have reported a lower body weight or BMI in individuals with manifest AD, possibly because of weight loss occurring during the course of the disorder.9-12 The weight loss accompanying dementia may be caused by a number of factors, including the dementia disorder itself, decreased lean body mass, decreased food intake, and comorbid conditions.21

Our findings support recent reports that vascular factors, such as atherosclerosis,2 hypertension, coronary heart disease, dyslipoproteinemia, and diabetes mellitus, may play a role in the etiology of AD.1 An overweight or obese phenotype underlies each of these disorders, and thus may aggravate or independently contribute to dementia processes. Perhaps the strongest of these vascular risk factors to date is high blood pressure.22-24; however, the interrelationship between BMI and blood pressure remains controversial. A high BMI may lead to high blood pressure25 and may thus increase dementia risk. Alternatively, the Framingham Heart Study and Tecumseh study have both shown a longitudinal relationship between baseline hypertension and increased risk of overweight or obesity, pointing to a general increase in sympathetic activity.26 Irrespective of the temporal relationship between these 2 factors, our findings suggest that BMI is a driving force, as BMI at 70, 75, and 79 years of age was a consistent, independent predictor of AD and total dementia at 79 to 88 years.

The association between large body size and dementia was found only in women. This may be due to selective survival, a true metabolic phenomenon in women (eg, estrogen), sex differences in body fat distribution, or the low number of men in our sample. A recent summary that included data from our Gerontological and Geriatric Population Studies population reported that women with a high BMI are more likely to survive past the age of 70 years than men, and that a higher mean BMI may be protective against death, especially in women.27 Support for sex differences in the etiology of dementia comes from recent EURODEM reports28 showing that incidence rates of AD, and not VaD, are truly higher in women after age 85 years. This may be related to age- and sex-related interactions among vascular factors in relationship to dementia risk. In addition, Kalmijn et al29 recently reported that a unique combination of cardiovascular risk factors, including BMI, played a role in the development of dementia, particularly VaD, in Japanese American men aged 71 to 93 years. A 1-SD increase (2.9) in BMI was associated with a 21% increase in dementia risk. In our study, a 1-SD increase (approximately 4) in the BMI of women aged 70 and 75 years resulted in an approximate 60% increase in risk for dementia at 79 to 88 years, after multivariate adjustment.

Among the strengths of this study are the lengthy follow-up, the high age and representativeness of the sample, the comprehensive examinations, and a clinical anthropometric assessment. However, there are also some limitations and methodologic factors that need to be addressed. First, the number of dementia cases was small. Therefore, the results for men and some subgroups should be interpreted cautiously. However, our study population is representative of persons surviving to age 88 years, and the differences we observed are highly significant. Second, it is often difficult to discriminate between AD and VaD. However, our criteria for AD are strict, since all cases with stroke or infarcts on computed tomography were given a diagnosis of VaD. The possibility that a high BMI among AD cases is due to an underdiagnosis of VaD is not likely in this population, from which we have reported some of the highest rates of VaD in the world. Third, selective survival may have influenced the results in the oldest age groups and may have contributed to the sex differences we found in the Gerontological and Geriatric Population Studies that were discussed in the previous paragraph. We tried to eliminate this bias by collecting information from case records in those who died. Fourth, physical activity was not assessed in this study. We therefore cannot comment on its potential influence on BMI and dementia risk in this population. Finally, the diagnosis of dementia in those who were lost to follow-up was based on case records, the hospital linkage system, and death certificates. These sources of information are known to underrate dementia. Thus, undiagnosed cases of dementia may be included in the control group, which would most likely diminish differences between the 2 groups.

Our findings have important public health implications. The prevention of overweight and obesity, even at greater ages, might be important for the prevention of dementia, the fastest growing disease of late life. The fastest growing age group in Western societies, women older than 50 years, experiences the highest prevalence of overweight and obesity.2 Thus, the increasing prevalence of overweight and obesity in Western populations may have consequences for the future occurrence of dementia in elderly populations. These data support the use of current population-based BMI standards to ensure optimal health throughout the course of the adult life span.

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Corresponding author and reprints: Deborah Gustafson, PhD, Department of Psychiatry, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden (e-mail: deb.gustafson@neuro.gu.se).

REFERENCES