Measures of Adiposity and Dementia Risk in Elderly Persons

José A. Luchsinger, MD; Bindu Patel, MPH; Ming-Xin Tang, PhD; Nicole Schupf, PhD; Richard Mayeux, MD

Background: Studies relating adiposity to dementia are conflicting. We explored the associations of body mass index (BMI), (calculated as weight in kilograms divided by the square of height in meters) waist circumference, and weight change to dementia, probable Alzheimer disease, and dementia associated with stroke (DAS).

Design: Persons without dementia were followed up for 5 years; 893 persons had BMI data, 907 had waist circumference data, and 709 had a second weight measurement. Dementia was ascertained using standard methods. Cox proportional hazards regression was used for analyses using follow-up as time to event, adjusting for demographics and apolipoprotein E-ε4 status.

Results: Compared with persons in the first quartile of BMI, persons in the third quartile had a lower dementia and Alzheimer disease risk and persons in the second quartile had a lower DAS risk. The association between BMI and dementia resembled a U shape in those younger than 76 years, while dementia risk decreased with higher BMI in those 76 years and older. The fourth quartile of waist circumference was related to a higher DAS risk in the whole sample, and to dementia and Alzheimer disease in persons younger than 76 years. Weight loss was related to a higher dementia and DAS risk, and weight gain was related to a higher DAS risk only.

Conclusions: The prospective association between adiposity and dementia differs depending on the anthropometric measure used, and is modified by age. This may explain previous conflicting reports.

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tion to total body fat, and is an independent predictor of vascular risk factors and morbidity.16 The WC was measured at the level of the iliac crest at minimal inspiration to the closest 0.1 cm. The BMI and WC were used as continuous variables and categorized by quartiles. We did not use National Heart, Lung, and Blood Institute criteria for BMI because its value in elderly persons is questionable.20 We calculated the yearly rate of weight change between the first and second follow-up interval and classified persons into 3 groups: (1) weight loss (>1 kg), (2) stable weight (1 kg of loss to 1 kg of gain), and (3) weight gain (>1 kg).

DIAGNOSIS OF DEMENTIA

A dementia diagnosis was made by consensus of neurologists, psychiatrists, and neuropsychologists. The dementia diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria,21 and required evidence of cognitive deficit and evidence of impairment in social or occupational function (Clinical Dementia Rating Scale score of ≥1).22 An Alzheimer disease (AD) diagnosis was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association.23 A diagnosis of probable AD was made when dementia could not be explained by other disorders. A diagnosis of possible AD was made when the most likely cause of dementia was AD, but there were other disorders that could contribute, such as stroke and Parkinson disease. A diagnosis of vascular dementia was made when it started within 1 month of the stroke and its local effects were thought to be the primary cause. Brain imaging was available in 85% of stroke cases; in the remainder, World Health Organization stroke criteria were used.24 We conducted analyses with 3 outcomes: all-cause dementia, probable AD, and dementia associated with stroke (DAS), which included vascular dementia and probable AD with stroke. The rationale for these outcomes is that obesity is related to vascular disease and stroke,23 and we sought to distinguish the association of adiposity to dementias with and without a vascular component.

COVARIATES

Diabetes mellitus, hypertension, heart disease, and smoking were defined by self-report. Heart disease included a history of atrial fibrillation, other arrhythmias, congestive heart failure, myocardial infarction, and angina pectoris. Smoking was subclassified into current and past smoking. Fasting plasma cholesterol and triglyceride levels were determined at first follow-up using standard enzymatic techniques. High-density lipoprotein cholesterol levels were determined after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstic acid.26 The low-density lipoprotein cholesterol level was recalculated using the formula of Friedewald et al.27 The APOE (apolipoprotein E) genotypes were determined as described by Hixson and Vernier28 and Mayeux et al.29 We classified APOE-ε4 as present (homozygous or heterozygous) or absent.

STATISTICAL ANALYSES

Bivariate analyses compared variables among BMI quartiles. Continuous variables were compared using analysis of variance, and categorical variables were compared using χ² tests.30 First, global tests for all quartiles were made. If significant differences were found, further comparisons were made for continuous variables using the Scheffé multiple comparisons procedure; for categorical variables, pairwise comparisons with the reference category were conducted. An α value of .05 was used for all analyses.

Proportional hazards models31 were used in multivariate analyses. The time-to-event variable was time from BMI or WC measurement to incident dementia; individuals who did not develop dementia were censored at last follow-up. For analyses with weight change, the time-to-event variable was time from the second weight measurement to dementia onset. Individuals who developed dementia other than the one of interest were censored at diagnosis. We show the results of multivariate analyses for 2 models: one adjusted for age and sex and one further adjusted for years of education, ethnic group, and APOE-ε4 status. We adjusted for diabetes mellitus, hypertension, low-density lipoprotein level, heart disease, stroke, and current smoking in secondary analyses. Because stroke defines DAS, it was not used as a covariate in analyses by dementia subtype. These variables, with the exception of smoking, may be caused by higher adiposity,22 may be in the pathway between adiposity and dementia, and were not included in the main models. We conducted 3 main analyses, relating the following: (1) BMI to dementia, (2) WC to dementia, and (3) weight change to dementia. The reference in analyses with BMI and WC was the first quartile; in analyses with weight change, it was the stable weight group.

Current smoking is associated with higher dementia risk33 and lower BMI,40 and we conducted secondary analyses excluding smokers. A lower BMI may be associated with unidentified premorbid conditions, including preclinical dementia,35 and we conducted secondary analyses excluding individuals with less than 18 months of follow-up. All analyses were conducted using SAS statistical software, version 9.1, for Windows (SAS Institute Inc, Cary, NC).

RESULTS

There were 181 incident dementia cases (3.9/100 person-years), 112 AD cases, and 53 DAS cases in 4536 person-years of follow-up (mean±SD, 5.1±2.6 years). The mean±SD sample age was 77.0±5.7 years. Of the sample, 69.9% were women; 31.8% were African American, 45.2% were Caribbean-Hispanic, and 22.9% were white (percentages do not total 100 because of rounding). The mean±SD years of education were 8.8±4.6, and 27.9% had APOE-ε4 present; 18.5% reported diabetes mellitus, 59.6% reported hypertension, 25.9% reported heart disease, and 11.5% reported stroke. The mean±SD low-density lipoprotein level was 120.9±34.9 mg/dL (3.13±0.90 mmol/L).

We compared characteristics among quartiles of BMI (Table 1) using the first as the reference. Persons in the second quartile had a lower proportion of women, a higher diabetes mellitus prevalence, and lower prevalences of current smoking and stroke. Persons in the third quartile were younger, had higher hypertension and diabetes mellitus prevalences, and had a lower prevalence of current smoking. Persons in the fourth quartile were younger; had higher proportions of women and African Americans; had a lower proportion of whites; had higher hypertension, diabetes mellitus, and heart disease prevalences; and had a lower prevalence of current smoking.

RELATION OF BMI TO DEMENTIA

Body mass index as a continuous variable was not related to dementia (hazard ratio [HR], 0.9; 95% confidence interval [CI], 0.9-1.0), AD (HR, 0.9; 95% CI, 0.9-
Table 1. Comparison of Relevant Characteristics Between BMI Quartiles*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1: &lt; 23.4 (n = 220)</th>
<th>2: 23.4-26.2 (n = 222)</th>
<th>3: 26.3-29.6 (n = 228)</th>
<th>4: &gt; 29.6 (n = 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y‡</td>
<td>78.2 ± 6.1</td>
<td>77.2 ± 5.9</td>
<td>76.7 ± 5.4‡</td>
<td>76.0 ± 4.9‡</td>
</tr>
<tr>
<td>Female sex</td>
<td>150 (68.2)</td>
<td>126 (56.8)‡</td>
<td>159 (69.7)</td>
<td>182 (81.1)§</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>68 (30.9)</td>
<td>58 (26.1)</td>
<td>68 (29.8)</td>
<td>90 (40.4)†</td>
</tr>
<tr>
<td>Caribbean-Hispanic</td>
<td>91 (41.4)</td>
<td>105 (47.3)</td>
<td>111 (48.7)</td>
<td>97 (43.5)</td>
</tr>
<tr>
<td>White</td>
<td>61 (27.7)</td>
<td>59 (26.6)</td>
<td>49 (21.5)</td>
<td>36 (16.1)§</td>
</tr>
<tr>
<td>Education, y†</td>
<td>8.7 ± 4.7</td>
<td>9.0 ± 4.7</td>
<td>8.9 ± 4.4</td>
<td>8.6 ± 4.5</td>
</tr>
<tr>
<td>APOE-ε4 present</td>
<td>70 (31.8)</td>
<td>50 (22.5)</td>
<td>67 (29.4)</td>
<td>58 (26.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113 (51.4)</td>
<td>118 (53.2)</td>
<td>142 (62.3)§</td>
<td>159 (71.3)§</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (11.4)</td>
<td>39 (17.6)‡</td>
<td>48 (21.1)</td>
<td>53 (23.8)</td>
</tr>
<tr>
<td>LDL level, mg/dL†</td>
<td>120.0 ± 38.1</td>
<td>118.0 ± 32.2</td>
<td>122.7 ± 35.2</td>
<td>122.2 ± 34.2</td>
</tr>
<tr>
<td>Heart disease</td>
<td>43 (19.5)</td>
<td>20 (9.0)</td>
<td>19 (8.3)</td>
<td>19 (8.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>29 (13.2)</td>
<td>16 (7.2)‡</td>
<td>33 (14.5)</td>
<td>25 (11.2)</td>
</tr>
</tbody>
</table>

Table 2. Data Relating BMI Quartiles to Dementia Using the First Quartile as the Reference

<table>
<thead>
<tr>
<th>BMI Quartile</th>
<th>Persons at Risk</th>
<th>No. of Cases (Rate/100 Person-Years)</th>
<th>HR (95% CI)*</th>
<th>All Dementia</th>
<th>Alzheimer Disease</th>
<th>Dementia Associated With Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 1</td>
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</tr>
<tr>
<td>1: &lt; 23.4</td>
<td>220</td>
<td>53 (5.3)</td>
<td>1.0</td>
<td>1.0</td>
<td>30 (3.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>2: 23.4-26.2</td>
<td>222</td>
<td>48 (4.0)</td>
<td>0.8 (0.5-1.1)</td>
<td>0.7 (0.5-1.0)</td>
<td>35 (2.9)</td>
<td>0.9 (0.6-1.6)</td>
</tr>
<tr>
<td>3: 26.3-29.6</td>
<td>228</td>
<td>38 (3.1)</td>
<td>0.6 (0.4-0.9)</td>
<td>0.6 (0.4-0.9)</td>
<td>19 (1.6)</td>
<td>0.6 (0.3-1.0)</td>
</tr>
<tr>
<td>4: &gt; 29.6</td>
<td>223</td>
<td>42 (3.7)</td>
<td>0.9 (0.6-1.5)</td>
<td>0.8 (0.5-1.2)</td>
<td>28 (2.5)</td>
<td>1.2 (0.7-2.1)</td>
</tr>
</tbody>
</table>

Table 3. Persons at Risk

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<td>LDL level, mg/dL†</td>
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<tr>
<td>Stroke</td>
<td>29 (13.2)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); LDL, low-density lipoprotein.
SI conversion factor: To convert LDL to millimoles per liter, multiply by 0.0259.
*Data are given as number (percentage) of each group unless otherwise indicated, and are taken from the Washington Heights–Inwood Columbia Aging Project, 1992-2003.
†Data are given as mean ± SD.
‡P < .05.
§P < .001.
||P < .1.

1.0), or DAS (HR, 1.1; 95% CI, 0.9-1.3) in fully adjusted models.

The third quartile (Table 2) was associated with lower dementia risk compared with the first quartile after adjusting for age, sex, years of education, ethnic group, and APOE-ε4 status. The association between the second quartile and lower dementia risk was close to statistical significance (P=.06). For AD, the third quartile was associated with lower risk. For DAS, the association between the second quartile and lower risk was almost statistically significant (P=.06). The inclusion of vascular risk factors in the models did not change the results.

In persons younger than 76 years, the association between BMI quartiles and dementia resembled a U shape (Figure 1). The second (HR, 0.4; 95% CI, 0.2-0.9) and third (HR, 0.3; 95% CI, 0.1-0.8) quartiles were related to lower risk, while the fourth (HR, 1.0; 95% CI, 0.4-2.1; P=.91 for trend) was similar to the reference. In older people (≥76 years), dementia risk decreased with increasing BMI; this association was almost statistically significant (fourth quartile HR, 0.6; 95% CI, 0.4-1.1; P=.07 for trend). These associations were not modified by sex and did not change after exclusion of current smokers or persons with a short follow-up.

### RELATION OF WC TO DEMENTIA

The WC as a continuous variable was not associated with dementia (HR, 1.0; 95% CI, 0.9-1.0); the associations with AD and DAS were similar. The WC quartiles were not related to dementia or AD (Table 3), but DAS risk was increased for the fourth quartile (P=.02 for trend) after adjusting for age, sex, years of education, ethnic group, and APOE-ε4 status. The results were virtually unchanged after adjusting for vascular risk factors. In younger elderly persons, the fourth quartile was related...
RELOCATION OF WEIGHT CHANGE TO DEMENTIA

We had 1 follow-up weight measurement in 709 persons, of 713 persons without dementia eligible for follow-up. The mean±SD interval between weight measurements was 1.3±0.6 years. The mean±SD weight change was −0.5±3.4 kg. The mean±SD follow-up after the second weight measurement was 4.7±2.1 years. Weight change as a continuous variable was associated with decreased dementia risk (HR, 0.9; 95% CI, 0.8-0.9). In analyses categorizing with changes as loss, stable, or gain, persons with weight loss had a higher dementia risk (Figure 1) compared with persons with a stable weight after adjustment for baseline BMI, age, sex, years of education, ethnic group, and apolipoprotein E-ε4 status. The association was strongest for DAS. The DAS risk was also higher in persons who gained weight. The results were unchanged in models with vascular risk factors and after excluding current smokers and persons with a short follow-up. There was no effect modification by age or sex.

We conducted additional analyses exploring different cutoffs for weight change (tertiles, 25th and 75th percentiles, and 10th and 90th percentiles), and the results were similar.

The association between adiposity and incident dementia varied with the measure used and the outcome considered, and was modified by age. The only association that clearly resembled a linear pattern (higher risk with higher quartile) was that of WC and DAS. However, the fourth WC quartile was related to a higher dementia and AD risk in persons younger than 76 years, but not in the oldest old (those ≥76 years). The association of BMI with dementia resembled a U shape in those younger than 76 years. Weight loss was associated with a higher dementia risk. This association was stronger for DAS, and weight gain was also associated with DAS.

Alzheimer disease and vascular dementia are the most common forms of dementia. Alzheimer disease is probably caused by brain deposition of amyloid β, and peripheral hyperinsulinemia may have an important role in its clearance. Vascular risk factors and stroke cause vascular dementia, but they may also cause AD. There are conflicting data relating hyperinsulinemia, diabetes mellitus, and hyperinsulinemia features, such as hyperlipidemia and hypertension, to a higher risk of cognitive decline and AD. Higher adiposity is related to hyperinsulinemia, diabetes mellitus, hypertension, dyslipidemia, heart disease, and stroke. Thus, we hypothesized that a high BMI and WC are associated with a higher dementia, AD, and DAS risk.

A high BMI in middle age is associated with a higher dementia risk. A higher BMI at the ages of 70, 75, and 79 years also predicts a higher dementia risk. However, there have been reports of no association and of a lower BMI related to a higher AD risk. These paradoxical findings could be explained by different age groups in different studies; those conducted in middle age show...
a relation of high BMI to increased dementia risk, while those in older populations are conflicting. The association of high BMI with cardiovascular and general mortality is attenuated in older age groups, and high BMI becomes a predictor of decreased mortality in the oldest old.17 This is possibly because of survival bias and decreased value of BMI as an adiposity measure in the oldest old. Aging is characterized by lean body mass loss and adipose tissue increase without weight gain, which may not be captured by BMI, and traditional adiposity measures are less useful in elderly persons.60 Another potential explanation for paradoxical findings is the possibility of a U-shaped association between BMI and dementia, as has been reported for other outcomes.34 Low BMI related to worse outcomes is usually ascribed to conditions associated with weight loss. Higher BMI related to worse outcomes is usually interpreted as evidence of the consequences of high adiposity. The results of our study suggest a U-shaped association between BMI and dementia in younger elderly persons, while a higher BMI is related to lower dementia risk in the oldest old. It is possible that persons with the lowest BMI lost weight because of pre-

Persons may lose weight before dementia diagnosis.14,63 and this has been interpreted as a consequence rather than a direct cause of the disease.14 We did not have enough data to assess weight change up to dementia diagnosis. We had weights at 2 time points for a subsample and explored how weight change predicted dementia prospectively. We found that weight loss predicted higher dementia risk, in agreement with previous work. As mentioned previously, this could be a consequence of the dementia process, but could also be the consequence and a marker of hyperinsulinemia,63 an emerging dementia risk factor.7,8 We also found that weight gain predicted higher DAS risk, which, to our knowledge, has not been previously reported. This could reflect an increase in vascular risk factors with weight gain,32 but could also be a consequence of cardiovascular disease, such as heart failure causing edema and weight gain.54

We must consider the possibility that confounding, chance, or bias explains the results of this study. We conducted analyses excluding current smokers and persons with short follow-up, and the results were essentially unchanged. We adjusted for years of education and ethnic group as indexes of socioeconomic background without change in our findings, but we cannot rule out residual confounding. The ascertainment of covariates, such as smoking, was made by self-report, likely resulting in some misclassification that could have resulted in residual confounding. Another consideration is the fact that we conducted multiple comparisons, including those in stratified analyses. Invocation of multiple comparisons as an explanation of results is a controversial issue.60 but it is possible that our results could be explained by chance. The most striking results occurred in the stratified analyses. The find-

<table>
<thead>
<tr>
<th>WC Quartile</th>
<th>All Dementia</th>
<th>Alzheimer Disease</th>
<th>Dementia Associated With Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1.2</td>
<td>(Rate/100 Person-Years)</td>
<td>HR (95% CI)†</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>76 y</td>
<td>275</td>
<td>63 (5.4)</td>
<td>1.9 (1.3-3.0)</td>
</tr>
<tr>
<td>76 y</td>
<td>250</td>
<td>36 (2.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>76 y</td>
<td>184</td>
<td>34 (3.7)</td>
<td>1.2 (0.8-1.9)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 3.

*Weight loss was defined as loss of more than 1 kg/y; weight gain, gain of more than 1 kg/y; and stable weight, 1 kg/y of loss to 1 kg/y of gain.
†Model 1 is adjusted for age and sex, and model 2 is further adjusted for years of education, ethnic group, and apolipoprotein E-ε4 status.
ing of significant results for some quartiles by chance could lead to the identification of patterns that also occurred by chance. Despite the results not being unexpected, and consistent with previous publications in the aging literature, chance due to multiple comparisons is a possibility as an explanation for our findings, and our analyses should be replicated in other samples. The number of persons developing DAS was appreciably smaller than those developing AD, and this could have resulted in chance findings because of sparse data. When interpreting and generalizing the results, it is important to take into account that this study occurred in the context of a cohort study of elderly persons, with multiple ethnic groups, in an urban setting, with a high prevalence of vascular risk factors. It is a cohort with potential selection biases, particularly because high adiposity is related to increased morbidity and mortality that could have limited participation to persons who were less likely to have this risk factor.

Our study has several strengths. We had comprehensive research procedures for the diagnosis of dementia. We also had measures of BMI and WC, and weight at 2 time points, but did not have a weight history before inclusion in the cohort. To the best of our knowledge, this is the first study examining the relationship between WC and dementia in elderly persons.

Our results show that high adiposity may be associated with higher dementia risk, particularly in younger elderly persons. However, this association could be confounded by low weight and weight loss due to preclinical disease, and is attenuated in older age groups. This may explain conflicts in previous studies. Our results need to be replicated in other studies. Similar studies are needed with imaging or biomarkers of adipose tissue.

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Author Contributions: Study concept and design: Luchsinger and Mayeux. Acquisition of data: Schupf and Mayeux. Analysis and interpretation of data: Luchsinger, Patel, Tang, Schupf, and Mayeux. Drafting of the manuscript: Luchsinger, Patel, Tang, and Mayeux. Critical revision of the manuscript for important intellectual content: Schupf. Statistical analysis: Patel, Tang, and Schupf. Obtained funding: Luchsinger and Mayeux. Administrative, technical, and material support: Mayeux. Study supervision: Mayeux.

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REFERENCES


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