Midlife and Late-Life Obesity and the Risk of Dementia

Cardiovascular Health Study

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Background: While high adiposity in middle age appears to be related to greater dementia risk, studies exploring this association in the elderly are conflicting.

Objective: To evaluate associations between midlife and late-life obesity and risk of dementia.

Design: Prospective study with mean follow-up of 5.4 years (1992-1994 through 1999).

Setting: Community-dwelling sample in 4 US sites recruited from Medicare eligibility files.

Participants: A total of 2798 adults without dementia (mean age, 74.7 years; 59.1% women) participating in the Cardiovascular Health Study who underwent magnetic resonance imaging were measured for height and weight at baseline at age 65 years or older (late life), and self-reported weight at age 50 years (midlife). Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was calculated at both times.

Main Outcome Measures: Dementia, Alzheimer disease, and vascular dementia classified by a multidisciplinary committee using standardized criteria.

Results: Classification resulted in 480 persons with incident dementia, 245 with Alzheimer disease (no vascular dementia), and 213 with vascular dementia (with or without Alzheimer disease). In evaluations of midlife obesity, an increased risk of dementia was found for obese (BMI ≥30) vs normal-weight (BMI 20-25) persons, adjusted for demographics (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.03-1.87) and for cardiovascular risk factors (1.36; 0.94-1.95). The risk estimates were reversed in assessments of late-life BMI. Underweight persons (BMI <20) had an increased risk of dementia (1.62; 1.02-2.64), whereas being overweight (BMI 25-30) was not associated (0.92; 0.72-1.18) and being obese reduced the risk of dementia (0.63; 0.44-0.91) compared with those with normal BMI.

Conclusion: These results help explain the “obesity paradox” as differences in dementia risk across time are consistent with physical changes in the trajectory toward disability.

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Table 1. Selected Characteristics of 2798 Participants in the Cardiovascular Health Study by Categories of Baseline BMI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMI Category</th>
<th>Underweight (&lt;20) (n=117)</th>
<th>Normal (20-25) (n=920)</th>
<th>Overweight (&gt;25-30) (n=1207)</th>
<th>Obese (&gt;30) (n=554)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>76.1 (5.3)</td>
<td>75.0 (5.0)</td>
<td>74.4 (4.8)</td>
<td>73.6 (4.3)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>91 (5.5)</td>
<td>555 (33.6)</td>
<td>635 (38.4)</td>
<td>372 (22.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (2.3)</td>
<td>365 (18.8)</td>
<td>572 (30.3)</td>
<td>182 (15.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td>107 (4.3)</td>
<td>875 (35.0)</td>
<td>1056 (42.1)</td>
<td>465 (18.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (3.4)</td>
<td>45 (15.3)</td>
<td>151 (51.1)</td>
<td>89 (30.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>26 (4.3)</td>
<td>160 (26.8)</td>
<td>263 (44.6)</td>
<td>149 (24.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>33 (4.1)</td>
<td>258 (32.1)</td>
<td>353 (43.9)</td>
<td>160 (19.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>23 (3.3)</td>
<td>235 (33.5)</td>
<td>299 (42.6)</td>
<td>145 (20.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>34 (4.9)</td>
<td>267 (38.8)</td>
<td>292 (42.4)</td>
<td>96 (13.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>63 (5.0)</td>
<td>401 (31.7)</td>
<td>539 (42.7)</td>
<td>260 (20.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td>28 (2.2)</td>
<td>415 (32.2)</td>
<td>586 (45.5)</td>
<td>259 (20.1)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>26 (10.6)</td>
<td>103 (41.9)</td>
<td>82 (33.3)</td>
<td>35 (14.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>108 (5.1)</td>
<td>779 (36.5)</td>
<td>911 (42.7)</td>
<td>334 (15.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>History of diabetes mellitus, No. (%)</td>
<td>5 (1.7)</td>
<td>65 (21.6)</td>
<td>135 (44.8)</td>
<td>96 (31.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3 (0.8)</td>
<td>75 (21.3)</td>
<td>153 (43.3)</td>
<td>122 (34.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>History of hypertension, No. (%)</td>
<td>65 (5.3)</td>
<td>478 (38.9)</td>
<td>516 (42.0)</td>
<td>169 (13.8)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>16 (4.5)</td>
<td>123 (34.9)</td>
<td>149 (42.4)</td>
<td>64 (18.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>36 (3.0)</td>
<td>319 (26.2)</td>
<td>542 (44.4)</td>
<td>321 (26.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (3.8)</td>
<td>187 (34.2)</td>
<td>231 (42.2)</td>
<td>108 (19.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>History of coronary heart disease, No. (%)</td>
<td>&gt;1.0</td>
<td>80 (3.5)</td>
<td>723 (32.0)</td>
<td>1000 (44.3)</td>
<td>456 (20.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1.0-0.9</td>
<td>21 (8.2)</td>
<td>100 (39.1)</td>
<td>91 (35.5)</td>
<td>44 (17.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>&lt;0.9</td>
<td>15 (5.6)</td>
<td>96 (35.5)</td>
<td>109 (40.4)</td>
<td>50 (18.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>197.2 (38.4)</td>
<td>206.6 (36.8)</td>
<td>211.2 (38.6)</td>
<td>211.8 (37.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mean (SD), mg/L</td>
<td>4.49 (13.27)</td>
<td>4.08 (7.43)</td>
<td>4.68 (8.28)</td>
<td>6.79 (9.59)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6, mean (SD), pg/mL</td>
<td>1.72 (1.59)</td>
<td>1.72 (1.30)</td>
<td>2.01 (1.77)</td>
<td>2.43 (2.35)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>APOE genotype, No. (%)</td>
<td>33 (5.5)</td>
<td>204 (33.7)</td>
<td>259 (42.8)</td>
<td>109 (18.0)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>No e4 allele</td>
<td>79 (4.1)</td>
<td>626 (32.1)</td>
<td>851 (43.7)</td>
<td>391 (20.1)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; C-reactive protein to nanomoles per liter, multiply by 9.524.

aNumbers may not always add up to total because of missing variables.
bDetails and definitions of the characteristics are provided in the “Methods” section.
cRow percentages are shown across BMI.
dThe P values are based on χ² tests for categorical variables and on analysis of variance for continuous variables.

Pittsburgh, Pennsylvania. In 1992-1993, 687 African American individuals were recruited. From baseline (1989-1990) until 1998-1999, up to 10 annual clinic visits were completed. Data collected at these examinations each year included demographics, anthropometric measurements, vital signs, cognitive function, information from psychosocial interviews, depression level, medical history, and physical function. Phlebotomy was performed for laboratory analyses. Surveillance and collection of events data were ongoing. All the participants completed an informed consent form, and institutional review board approvals were received from all the sites. A separate, completed DNA informed consent form, and institutional review board approval were obtained for genetic studies. Surveillance and collection of events data were ongoing. All the participants completed an informed consent form, and institutional review board approvals were received from all the sites. A separate, completed DNA informed consent form, and institutional review board approval were obtained for genetic studies.

In 1998-1999, dementia was classified in 3602 CHS participants as a part of the CHS Cognition Study. Inclusion in the CHS-Cognition cohort required completion of cranial magnetic resonance imaging (MRI) and the modified Mini-Mental State Examination (MMSE) in 1992-1994. These participants were screened using data collected at the visit closest to MRI to identify those at higher risk who were asked to return to the clinic for additional cognitive testing. An individual was considered to be at high risk for dementia if he or she had previously scored less than 80 or had a decrease of 5 or more points on the modified MMSE administered at previous examinations, a previous Telephone Interview for Cognitive Status score of less than 28 or an Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score of greater than 3.6, incident stroke, or current residence in a nursing home. A battery of neuropsychiatric tests was administered to those agreeing to return to the clinic or to receive a home visit. The following examinations were used: the American version of the National Reading Test, Raven’s Colored Progressive Matrices, California Verbal Learning Test, Rey-Osterreith Figure, immediate and delayed recall, modified Boston Naming Test, verbal fluency test, block design (modified from the Wechsler Adult Intelligence Scale–Revised), Stroop Neuropsychological Screening Test, Trail Making Test, digit spans, and Baddeley and Papagno divided attention task. Methods to evaluate persons who declined the neuropsychiatric battery or who were no longer living included a medical record review of all hospitalizations, questionnaires sent to the personal physician, and standardized interviews by telephone with the participants (if living) or a designated informant (Telephone Interview for Cognitive Status, Neuropsychiatric Inventory, or IQCODE). In addition, all prospectively collected data from inception of the CHS were reviewed to provide additional information on cognitive decline during the 10 years of follow-up, includ-
was calculated as weight in kilograms divided by height in meters squared at age 50 years and height measured at study baseline. The BMI was estimated using this self-report of participants’ “usual” weight at age 50 years collected on the medical history form. Midlife BMI (Cognition). Midlife weight, however, relied on self-report of weight and hip circumference in 1992-1993 (baseline for the CHS-Cognition cohort, the participant was determined to have prevalent dementia at baseline.

Longitudinal data collected during the 10 years of study follow-up and by family input using the Neuropsychiatric Inventory criteria.32 Dementia onset was determined by review of the California Alzheimer’s Disease Diagnostic and Treatment Centers criteria (possible or probable). Alzheimer disease without VaD using the National Institute of Neurological and Communicative Disorders and Stroke criteria (possible or probable).

Vascular dementia with or without AD using the Alzheimer’s Disease Diagnostic and Treatment Centers criteria (possible or probable).

Abbreviations: AD, Alzheimer disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; VaD, vascular dementia.

a Adjusted for demographics (age, race, sex, and years of education).

b Adjusted for demographics (age, race, sex, and years of education) and cardiovascular and dementia risk factors (C-reactive protein level, interleukin 6 level, hypertension status, diabetes mellitus status, coronary heart disease, total cholesterol level, ankle-arm index, smoking status, kilocalories expended per week, and apolipoprotein E ε4 allele).

c Alzheimer disease without VaD using the National Institute of Neurological and Communicative Disorders and Stroke criteria (possible or probable).

d Vascular dementia with or without AD using the Alzheimer’s Disease Diagnostic and Treatment Centers criteria (possible or probable).

Table 2. Midlife BMI Estimated at Age 50 Years and Risk of Dementia, AD, and VaD in 2798 Participants From the Cardiovascular Health Study (1992-1999)

<table>
<thead>
<tr>
<th>Outcome and Risk Factor</th>
<th>Dementia/Normal, No.</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, overall</td>
<td>461/2245</td>
<td>1.02 (0.99-1.05)</td>
<td>.17</td>
<td>1.01 (0.98-1.04)</td>
<td>.58</td>
</tr>
<tr>
<td>BMI, categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>200/1063</td>
<td>1.09 (0.64-1.85)</td>
<td>.19</td>
<td>1.20 (0.66-2.17)</td>
<td>.55</td>
</tr>
<tr>
<td>Underweight</td>
<td>188/904</td>
<td>1.10 (0.90-1.35)</td>
<td>.74</td>
<td>1.01 (0.83-1.35)</td>
<td>.67</td>
</tr>
<tr>
<td>Obese</td>
<td>58/203</td>
<td>1.39 (1.03-1.87)</td>
<td>.35</td>
<td>1.36 (0.94-1.95)</td>
<td>.10</td>
</tr>
<tr>
<td>ADc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, overall</td>
<td>236/2245</td>
<td>0.99 (0.96-1.03)</td>
<td>.60</td>
<td>0.99 (0.95-1.04)</td>
<td>.84</td>
</tr>
<tr>
<td>BMI, categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>103/1160</td>
<td>1.46 (0.78-2.73)</td>
<td>.24</td>
<td>1.47 (0.70-3.09)</td>
<td>.30</td>
</tr>
<tr>
<td>Underweight</td>
<td>96/996</td>
<td>1.12 (0.84-1.48)</td>
<td>.44</td>
<td>1.04 (0.74-1.47)</td>
<td>.81</td>
</tr>
<tr>
<td>Obese</td>
<td>26/235</td>
<td>1.17 (0.75-1.81)</td>
<td>.48</td>
<td>1.25 (0.74-2.11)</td>
<td>.40</td>
</tr>
<tr>
<td>VaDd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, overall</td>
<td>206/2245</td>
<td>1.04 (1.00-1.08)</td>
<td>.06</td>
<td>1.02 (0.97-1.07)</td>
<td>.56</td>
</tr>
<tr>
<td>BMI, categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>89/1174</td>
<td>0.70 (0.26-2.19)</td>
<td>.48</td>
<td>0.87 (0.31-2.40)</td>
<td>.78</td>
</tr>
<tr>
<td>Underweight</td>
<td>85/1007</td>
<td>1.10 (0.82-1.49)</td>
<td>.52</td>
<td>1.00 (0.70-1.44)</td>
<td>.98</td>
</tr>
<tr>
<td>Obese</td>
<td>28/233</td>
<td>1.57 (1.02-2.42)</td>
<td>.04</td>
<td>1.33 (0.78-2.29)</td>
<td>.30</td>
</tr>
</tbody>
</table>

Underweight (<20), normal weight (20-25), overweight (>25-30), and obese (>30) based on recommendations for older adults.33 Time to dementia was calculated in days from entry into the CHS-Cognition cohort until dementia onset, death, or July 1, 1999 (end of dementia follow-up).

Covariates examined included self-reported age, race (white vs nonwhite), sex, and educational level; diabetes mellitus was ascertained using the American Diabetes Association definition. Hypertension was defined as systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. Coronary heart disease was based on a history of myocardial infarction, angina, coronary bypass surgery, or angioplasty. Total cholesterol, C-reactive protein, and interleukin 6 levels and apolipoprotein E genotype were assayed by the CHS central laboratory.34 Smoking status was self-reported (current, previous, or never). The ankle-arm index was calculated using blood pressure at the brachial artery and ankle.35

Of the 3602 participants in the CHS-Cognition, 227 with prevalent dementia on MRI and 577 with mild cognitive impairment were excluded. We calculated descriptive statistics for demographics and comorbidities by category of BMI. The χ² test and analysis of variance were used to determine bivariate differences. The sample size for these analyses included 2798 persons: 480 with dementia and 2318 without dementia throughout follow-up. Cox proportional hazards regression was used to estimate the risk of dementia associated with BMI at midlife and late life as continuous and categorical variables. We also examined WHR as an exposure. Models were adjusted for demographics (age, sex, race, and educational level) and cardiovascular and dementia risk factors (including history of hypertension, diabetes mellitus status, coronary heart disease, total cholesterol level, ankle-arm index, C-reactive protein level, interleukin 6 level, smoking status, kilocalories expended per week, and apolipoprotein E genotype). For dementia subtype, persons were cen-
sored at onset of VaD in models evaluating AD and for AD in models of VaD. All the analyses were performed using a software program (SPSS version 13.0; SPSS Inc, Chicago, Illinois).

RESULTS

Of the 2798 participants included in the analyses, 480 were classified with incident dementia during a mean of 5.4 years of follow-up. Of these, 245 were determined to have pure AD (AD without VaD), 62 with pure VaD (VaD without AD), and 151 with AD and VaD, or mixed dementia. Due to the low number of cases with pure VaD, these were combined with mixed dementia to provide 213 cases for VaD-specific models. The age of the participants ranged from 65 through 97 years (mean [SD], 74.7 [4.8] years); 59.1% were women, 10.1% were African American, and 10.5% were nonwhite. Less than one-third of the sample (n=920) had a normal BMI at baseline, whereas only 117 (4.2%) were underweight, 1207 (43.1%) were overweight, and 554 (19.8%) were obese. Table 1 provides characteristics of the study sample by BMI category. The BMI was related to primary demographics (age, sex, race, and educational level), other risk factors for cardiovascular disease (ankle-arm index, history of diabetes, history of hypertension, and smoking status), and measures of inflammation (C-reactive protein and interleukin 6). The BMI was not related to a history of coronary heart disease or the presence of the apolipoprotein E ε4 allele.

Higher midlife BMI was not associated with lower dementia risk using BMI as a continuous variable adjusted for demographics and cardiovascular risk factors (hazard ratio [HR] per BMI unit, 1.01; 95% confidence interval [CI], 0.98-1.04) (Table 2). However, in the categorical models, being obese was associated with a 40% increased risk of dementia adjusted for demographics (HR, 1.39; 95% CI, 1.03-1.87), as shown in Figure 1, although the association was attenuated in the fully adjusted model (1.36; 0.94-1.95). The relationships were similar for AD and VaD. Being underweight at midlife was not associated with dementia, AD, or VaD.

In contrast, an inverse relationship between late-life BMI as a continuous variable and incident dementia was found independent of demographics (HR per BMI unit, 0.97; 95% CI, 0.95-0.99) (Table 3). The association remained significant when adjusted for cardiovascular and dementia risk factors (HR, 0.95; 95% CI, 0.92-0.98). Adjusted for all covariates, being underweight (BMI <18.5) increased the risk of dementia by 60% (HR, 1.62; 95% CI, 1.02-2.64), whereas being overweight (BMI of 25-30) was not associated (0.92; 0.72-1.18) and being obese (BMI of >30) was associated with a reduced risk of dementia (0.63; 0.44-0.91) compared with being of normal weight (BMI of 18.5-24.9) (Figure 2). Results for the dementia subtypes were similar to those for total dementia. One difference was that higher estimates were produced in the models assessing VaD, suggesting that being underweight is a greater risk factor for VaD than for AD.

Figure 1. Risk of dementia by body mass index (BMI) at midlife (age 50 years).

Table 1 provides characteristics of the study sample by BMI category. The BMI was related to primary demographics (age, sex, race, and educational level), other risk factors for cardiovascular disease (ankle-arm index, history of diabetes, history of hypertension, and smoking status), and measures of inflammation (C-reactive protein and interleukin 6). The BMI was not related to a history of coronary heart disease or the presence of the apolipoprotein E ε4 allele.

Higher midlife BMI was not associated with lower dementia risk using BMI as a continuous variable adjusted for demographics and cardiovascular risk factors (hazard ratio [HR] per BMI unit, 1.01; 95% confidence interval [CI], 0.98-1.04) (Table 2). However, in the categorical models, being obese was associated with a 40% increased risk of dementia adjusted for demographics (HR, 1.39; 95% CI, 1.03-1.87), as shown in Figure 1, although the association was attenuated in the fully adjusted model (1.36; 0.94-1.95). The relationships were similar for AD and VaD. Being underweight at midlife was not associated with dementia, AD, or VaD.

In contrast, an inverse relationship between late-life BMI as a continuous variable and incident dementia was found independent of demographics (HR per BMI unit, 0.97; 95% CI, 0.95-0.99) (Table 3). The association remained significant when adjusted for cardiovascular and dementia risk factors (HR, 0.95; 95% CI, 0.92-0.98). Adjusted for all covariates, being underweight (BMI <18.5) increased the risk of dementia by 60% (HR, 1.62; 95% CI, 1.02-2.64), whereas being overweight (BMI of 25-30) was not associated (0.92; 0.72-1.18) and being obese (BMI of >30) was associated with a reduced risk of dementia (0.63; 0.44-0.91) compared with being of normal weight (BMI of 18.5-24.9) (Figure 2). Results for the dementia subtypes were similar to those for total dementia. One difference was that higher estimates were produced in the models assessing VaD, suggesting that being underweight is a greater risk factor for VaD than for AD.
The ability to evaluate BMI at 2 age categories in the CHS cohort provides insight into differences found in other studies and the obesity paradox. We found that whereas midlife obesity was related to higher dementia risk, BMI after age 65 years was inversely related. The greatest dementia risk was found in underweight individuals at older ages. These findings suggest that the predictive ability of BMI changes across time. High BMI in middle age has been found to be associated with higher dementia risk.\textsuperscript{13,14} Higher BMI at ages 70, 75, and 79 years has also been found to predict dementia,\textsuperscript{17} although there have been reports of no association,\textsuperscript{16} of lower BMI related to higher AD risk,\textsuperscript{13} and of a U-shaped relation between BMI and dementia at older ages.\textsuperscript{28} These conflicting findings could be explained by the different age groups observed in different studies; those conducted with middle-aged participants show a relation of high BMI to increased dementia risk, whereas those conducted with older populations differ. Whereas the association we found at midlife may be related to the emergence of conditions such as hypertension in middle age, the association of high BMI to cardiovascular and total mortality may be attenuated in older age groups, in which high BMI becomes a predictor of decreased mortality.\textsuperscript{20} However, the difference we found possibly may be due to the decreased value of BMI as a measure of adiposity in the oldest of the elderly. In addition, because associations we reported at midlife and late life involved the same individuals, these findings may also have been affected by changes in BMI with age, or they may reflect differences in the importance of exposure to high adiposity in middle age vs old age.

The curvilinear associations found in these results for late-life BMI are similar to those found by Sturman et al\textsuperscript{36} in a biracial cohort. This U-shaped association has been reported in other outcomes in older adults\textsuperscript{37} and helps explain the paradoxical findings between BMI and dementia. The relation of low BMI 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 obesity. The present study had the advantage of having had BMI measures at midlife and late life in the same persons; results are consistent with the body of literature showing that BMI in midlife is a predictor of dementia, whereas it is not at older ages. This study also supports the notion that important exposures related to a higher risk of dementia often occur in middle age, a period that is not assessed in most studies of aging. Thus, it is important to assess midlife exposures in studies of aging, either by enrolling participants at an earlier age, which has logistical and cost difficulties, or by including proxy measures of midlife exposures, such as subclinical markers or self-reported measures.

### Table 3. Late-Life BMI Measured at Age 65 Years or Older and Risk of Dementia, AD, and VaD in 2798 Participants of the Cardiovascular Health Study (1992-1999)

<table>
<thead>
<tr>
<th>Outcome and Risk Factor</th>
<th>Dementia/AD No.</th>
<th>Adjusted Hazard Ratio (95% CI)\textsuperscript{a}</th>
<th>P Value</th>
<th>Adjusted Hazard Ratio (95% CI)\textsuperscript{b}</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, overall</td>
<td>480/2311</td>
<td>0.97 (0.95-0.99)</td>
<td>.004</td>
<td>0.95 (0.92-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>31/85</td>
<td>1.62 (1.10-2.39)</td>
<td>.01</td>
<td>1.62 (1.02-2.64)</td>
<td>.04</td>
</tr>
<tr>
<td>Normal</td>
<td>168/752</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>203/1004</td>
<td>0.93 (0.76-1.15)</td>
<td>.51</td>
<td>0.92 (0.72-1.18)</td>
<td>.50</td>
</tr>
<tr>
<td>Obese</td>
<td>78/472</td>
<td>0.81 (0.61-1.07)</td>
<td>.13</td>
<td>0.63 (0.44-0.91)</td>
<td>.01</td>
</tr>
<tr>
<td>AD\textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, overall</td>
<td>245/2546</td>
<td>0.96 (0.93-0.99)</td>
<td>.009</td>
<td>0.95 (0.91-0.99)</td>
<td>.008</td>
</tr>
<tr>
<td>BMI, categorical</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>17/99</td>
<td>1.53 (0.91-2.58)</td>
<td>.11</td>
<td>1.42 (0.74-2.70)</td>
<td>.29</td>
</tr>
<tr>
<td>Normal</td>
<td>94/826</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>93/1114</td>
<td>0.76 (0.57-1.02)</td>
<td>.07</td>
<td>0.74 (0.52-1.05)</td>
<td>.10</td>
</tr>
<tr>
<td>Obese</td>
<td>41/509</td>
<td>0.70 (0.48-1.03)</td>
<td>.07</td>
<td>0.58 (0.36-0.96)</td>
<td>.03</td>
</tr>
<tr>
<td>VaD\textsuperscript{d}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, overall</td>
<td>213/2570</td>
<td>0.98 (0.94-1.01)</td>
<td>.17</td>
<td>0.95 (0.91-0.99)</td>
<td>.02</td>
</tr>
<tr>
<td>BMI, categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>14/102</td>
<td>1.89 (1.06-3.37)</td>
<td>.03</td>
<td>2.15 (1.11-4.19)</td>
<td>.02</td>
</tr>
<tr>
<td>Normal</td>
<td>67/853</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>98/1109</td>
<td>1.15 (0.84-1.57)</td>
<td>.39</td>
<td>1.20 (0.83-1.76)</td>
<td>.33</td>
</tr>
<tr>
<td>Obese</td>
<td>34/516</td>
<td>0.98 (0.64-1.50)</td>
<td>.92</td>
<td>0.72 (0.41-1.27)</td>
<td>.26</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; VaD, vascular dementia.

\textsuperscript{a}Adjusted for demographics (age, race, sex, and years of education).

\textsuperscript{b}Adjusted for demographics (age, race, sex, and years of education) and cardiovascular and dementia risk factors (C-reactive protein level, interleukin 6 level, hypertension status, diabetes mellitus status, coronary heart disease, total cholesterol level, ankle-arm index, smoking status, and apolipoprotein E ε4 allele).

\textsuperscript{c}Alzheimer disease without VaD using the National Institute of Neurological and Communicative Disorders and Stroke criteria (possible or probable).

\textsuperscript{d}Vascular dementia with or without AD using the Alzheimer’s Disease Diagnostic and Treatment Centers criteria (possible or probable).

Significant associations were not found between WHR in late life and dementia, AD, or VaD (data not shown). Although the HR was close to 1.0 for the association between WHR and dementia, adjusting for demographics, the point estimate fell below 1.0 when adjusted for cardiovascular risk factors (HR, 0.71; 95% CI, 0.15-3.27). However, the 95% CIs were wide, and the association was not significant. Results were similar by dementia subtype.

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Aging is characterized by lean body mass loss and adipose tissue increase without weight gain, a phenomenon that is not captured by BMI. Thus, traditional adiposity measures are less useful in elderly individuals. Because measurements such as BMI may be less accurate in assessing obesity in elderly individuals, alternative anthropometric tools could be used. The highest quintile of sagittal abdominal diameter measured in midlife was associated with a 3-fold increased risk of dementia. Waist circumference and WHR have been proposed as better adiposity measures in elderly people. One study in New York City found that elevated waist circumference was related to higher dementia risk in persons aged 65 to 76 years, but not in those older than 76 years, and to higher risk of VaD in all age groups. We found no associations for WHR in old age.

Weight loss occurs with comorbidities at older ages and is often reflective of poor health. Weight loss, along with psychological, behavioral, and mobility problems, is one of the principal manifestations of AD. Weight loss may predate dementia onset by as much as 10 years. We found that whereas higher BMI at midlife may increase the risk of dementia, when measured after age 65 years, increased BMI may actually be a marker for decreased dementia risk.

The large sample and well-characterized CHS data are strengths of this study, but there are several limitations. Although we have treated BMI at midlife and late life equally, midlife weight was collected by self-report, so recall bias may have occurred. We did not have height at age 50 years, and midlife BMI was calculated using height at the CHS-Cognition baseline. Because height may be lost with aging, the midlife BMI estimate may be biased. However, elevated weight is protective against bone and height loss. Thus, biases in this study would be most relevant to underweight participants. The greater misclassification inherent in BMI at midlife (vs late life) may also have affected results found in these models. Thus, it is possible that the relatively weak associations found for midlife BMI underestimate the true relationships that would be observed in a cohort recruited at middle age and followed up through late life. We should also note here that the methods for ascertaining dementia and date of onset used in the CHS-Cognition were nontraditional and may have resulted in misclassification. However, this type of error would have attenuated models toward the null and would not have changed the overall conclusions.

Finally, the results of this study are relevant only to those who live beyond age 65 years without dementia, and generalizations should be made only to this group. Similarly, because nutritional status is related to morbidity and mortality in elderly persons, competing risks must be taken into consideration.

The associations between midlife and late-life BMI and risk of dementia reported herein are consistent with physical changes in the trajectory toward disability and frailty. These results reinforce the necessity of monitoring weight loss closely in older adults. These data also suggest the value of modified classification of "overweight" in the elderly because being overweight (compared with obese) may con-
fer the same risk as being normal weight for some diseases, including dementia. Clarification of the consequences of intentional vs unintentional weight loss is also needed to help guide clinical recommendations for older adults.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fitzpatrick, Kuller, and Lopez. Acquisition of data: Kuller. Analysis and interpretation of data: Fitzpatrick, Diehr, O’Meara, Longstreth, and Luchsinger. Drafting of the manuscript: Fitzpatrick, Lopez, O’Meara, and Luchsinger. Critical revision of the manuscript for important intellectual content: Fitzpatrick, Kuller, Lopez, Diehr, and Longstreth. Statistical analysis: Fitzpatrick, Lopez, Diehr, and O’Meara. Obtained funding: Kuller and Lopez. Administrative, technical, and material support: Fitzpatrick and Kuller. Study supervision: Fitzpatrick, Longstreth, and Luchsinger.

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Additional Information: A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.

REFERENCES