Objective: To examine body composition in individuals with early AD and without dementia and its relation to cognition and brain volume.

Design: Cross-sectional case-control study.

Participants: Individuals without dementia (Clinical Dementia Rating, 0; n=70) and with early-stage AD (Clinical Dementia Rating, 0.5 or 1; n=70) in the Alzheimer and Memory Program at the University of Kansas School of Medicine.

Main Outcome Measures: Participants were evaluated with brain magnetic resonance imaging (MRI), neuropsychological testing, and dual-energy x-ray absorptiometry to determine whole-body fat and lean masses. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Results: Lean mass was reduced in persons with early AD compared with controls without dementia ($F=7.73$; $P=.006$) after controlling for sex. Whole-brain volume ($\beta=.20$; $P<.001$), white matter volume ($\beta=.19$; $P<.001$), and global cognitive performance ($\beta=.12$; $P=.007$) were associated with lean mass (dependent variable) when controlling for age and sex. The total body fat and percentage of body fat values were not different across groups or related to cognition and brain volume.

Conclusion: Loss of lean mass is accelerated in AD and is associated with brain atrophy and cognitive performance, perhaps as a direct or indirect consequence of AD pathophysiology or through shared mechanisms common to both AD and sarcopenia.

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SAMPLE AND RECRUITMENT

Participants were aged 60 years and older and either did not have dementia (Clinical Dementia Rating [CDR], 0; n = 70) or were diagnosed with early-stage AD (CDR, 0.5; n = 56 and CDR, 1; n = 14) as detailed below. Participants without dementia and 63% of the participants with AD were self-referred from the community (primarily through media coverage and word of mouth), while 37% of the participants with AD were recruited from a referral-based memory clinic. Study exclusions included neurologic disease other than AD, diabetes mellitus, recent (<2 years) history of ischemic heart disease, clinically significant depressive symptoms, use of antipsychotic and investigational medications, and significant sensory impairment or systemic illness that could impair completion of the study. All participants were required to be accompanied by a study partner who was knowledgeable about the participant’s daily activities. We have previously reported results from subsamples of this cohort.12-14

CLINICAL ASSESSMENT

All participants were evaluated using a semistructured interview of the participant and a study partner to determine the presence or absence of dementia and its severity, if present, using the CDR.13 Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and at least 1 other cognitive and functional domain.16 These diagnostic methods have an accuracy of 93% for AD17 and sensitively detect the earliest stages of AD by focusing on intradividual change rather than comparison with group reference values.18 Additionally, they accurately identify the subset of individuals who meet criteria for mild cognitive impairment and have early-stage AD.19 A global neurological examination. Functional activity level was estimated using the Physical Activity Scale in the Elderly; a reliable and valid measure of physical activity developed specifically for older individuals.20 The Physical Activity Scale in the Elderly estimates an individual’s level of physical activity in the last 7 days by assessing the frequency and duration of participation in a variety of activities. The Physical Activity Scale in the Elderly was given to both the subject and the study partner and, for individuals with AD, data collected from the study partner were used in the analyses. We assessed peripheral insulin levels by radioimmunooassay using a fasting, 14-sample, 3-hour intravenous glucose tolerance test as previously described.21 Total 3-hour area under the curve (AUC) values for glucose and insulin served as overall indices of glucose and insulin levels. The Physical Performance Test was used as a measure of physical performance and frailty.22 Fasting venous blood samples were assessed using commercial enzymatic assays for total cholesterol (Diagnostic Chemicals, Ltd, Oxford, Connecticut). High-sensitive C-reactive protein was determined in fasting blood by turbidimetric assay (Roche Diagnostics Systems, Basel, Switzerland).

OTHER CLINICAL MEASURES

We also examined potential covariates that may mediate brain and body composition relationships including habitual level of physical activity, frailty, and laboratory assessments of insulin, lipids, inflammation, and apolipoprotein E4 allele status, as previously described.12-14 Briefly, level of habitual physical activity was estimated using the Physical Activity Scale in the Elderly, a reliable and valid measure of physical activity developed specifically for older individuals.20 The Physical Activity Scale in the Elderly estimates an individual’s level of physical activity in the last 7 days by assessing the frequency and duration of participation in a variety of activities. The Physical Activity Scale in the Elderly was given to both the subject and the study partner and, for individuals with AD, data collected from the study partner were used in the analyses. We assessed peripheral insulin levels by radioimmunooassay using a fasting, 14-sample, 3-hour intravenous glucose tolerance test as previously described.21 Total 3-hour area under the curve (AUC) values for glucose and insulin served as overall indices of glucose and insulin levels. The Physical Performance Test was used as a measure of physical performance and frailty.22 Fasting venous blood samples were assessed using commercial enzymatic assays for total cholesterol (Diagnostic Chemicals, Ltd, Oxford, Connecticut). High-sensitive C-reactive protein was determined in fasting blood by turbidimetric assay (Roche Diagnostics Systems, Basel, Switzerland).

NEUROIMAGING

Structural magnetic resonance imaging was obtained for all participants using a Siemens 3.0 Tesla Allegra MRI scanner (Siemens Medical Solutions, Erlangen, Germany). High-resolution T1-weighted anatomic images were acquired to provide detailed gross anatomy with high gray/white matter contrast (magnetization-prepared 180° radiofrequency pulses and rapid gradient-echo; 1 × 1 × 1 mm³ voxels; time to repetition, 2500 milliseconds; echo time, 4.38 milliseconds; time following inversion pulse, 1100 milliseconds; field of view, 256 × 256 mm² with 18% oversample; flip angle, 8 degrees). Normalized whole-brain volume (WBV) was computed for each imaging session using validated imaging tools from the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl), as previously described,14 using the Laboratory of Neuro Imaging Pipeline (University of California Los Angeles; http://pipeline.loni.ucla.edu). Briefly, the images were preprocessed and skull-stripped using the Brain Extraction Tool. Skull-stripped images were then segmented into white matter, gray matter, and cerebrospinal fluid using FMRIB’s Automated Segmentation Tool by registering them to the Montreal Neuroimaging Institute avg152 template. Normalized volumes for white matter (WMV), gray matter (GMV), and the whole brain (WBV; sum of white and gray matter) were calculated by dividing each by the total intracranial volume (the sum of white, gray, and cerebrospinal fluid volumes) and expressed as the percentage of the total intracranial volume. Normalized brain volumes minimize sex differences and produce an estimate of brain atrophy. Imaging data was unavailable for 3 participants without dementia and 1 with early AD.

BODY COMPOSITION

Dual-energy x-ray absorptiometry (GE Lunar Corp, Madison, Wisconsin) was used to determine total body measures of lean and fat mass. Percentage of body fat represents the percentage of total body mass (determined by DEXA) composed of fat (ie, total fat × 100/total body mass). We used total body mass determined by DEXA. Mass determined by DEXA was highly correlated with our manually measured (by scale) body weight (r=0.99; P<.001) and also minimized the influence of clothing. Height was measured using a standard stadiometer.
A multistep hierarchical linear regression was conducted to examine the relationship between clinical predictors (ie, brain volume, cognition) with body composition (ie, BMI, lean mass, and fat mass as dependent variables). All analyses controlled for age and sex. Variables correlating with body composition (ie, dementia status, physical activity, and insulin [3-hour AUC]) were used as covariates, and the increment in variance predicted from each new variable entered was calculated than controls (15.2 years vs 16.5 years; t = 2.60; P = .01). As expected, they also demonstrated mild global cognitive dysfunction. On average, they scored 3.4 points lower on the MMSE (of 30 points) and 1.7 SD (z scored) lower on the global cognitive composite index than controls without dementia. More participants with early AD were carriers of the apolipoprotein E4 allele. The groups did not differ on clinical indices of metabolic function (total cholesterol, C-reactive protein, insulin AUC, and glucose AUC).

Brain volumetrics demonstrated evidence of whole-brain and gray matter atrophy in early AD, with no difference in WMV across groups, suggesting that differences in WBV were driven by reduced GMV in the participants with AD.

Indices of physical function were significantly lower in early AD. Individuals with early AD had impairments in activities of daily living (Mild Cognitive Impairment Activities of Daily Living Scale) and physical function (Physical Performance Test) and lower levels of habitual physical activity (Physical Activity Scale in the Elderly).

## BODY COMPOSITION IN PARTICIPANTS WITH AD AND WITHOUT DEMENTIA

Body mass index, body weight, and body fat measures were not different across the control and early-AD groups (Table 2). Total lean mass was reduced in individuals with early AD compared with controls after controlling for known sex differences in lean mass (F = 7.73; P = .006). There were no dementia group × sex interactions, suggesting that AD-related differences in lean mass were not different in men and women.

To identify potential mediators of reduced lean mass in AD, we performed a series of linear regressions that examined the relationship of individual covariates with lean mass (dependent variable). Because age and sex influence lean mass and all of the clinical covariates tested (all β > .10; P < .01), we included age and sex as the first step in all regression analyses and report resultant partial correlations as standardized β values (Table 3).

The strongest predictor of lean mass was WBV (Figure), largely driven by a relationship between WMV and lean mass. Gray-matter volume was not related to lean mass. Additional significant correlates related to lean mass included cognitive indices (global cognitive performance and MMSE), insulin levels (3-hour AUC), and habitual physical activity levels. Glucose, C-reactive pro-

### Table 1. Characteristics of Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=70)</th>
<th>Early AD (n=70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.2 (7.3)</td>
<td>74.9 (6.7)</td>
<td>.17</td>
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<td>Education, y</td>
<td>16.5 (2.7)</td>
<td>15.2 (3.3)</td>
<td>.01</td>
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<tr>
<td>Sex, male/female</td>
<td>30/40</td>
<td>29/41</td>
<td>.86</td>
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<tr>
<td>Apolipoprotein E4 carrier, No. (%)</td>
<td>19 (27.9)</td>
<td>59.1 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mini-Mental State Examination score</td>
<td>29.4 (0.8)</td>
<td>26.0 (3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Global cognitive performance, z score</td>
<td>0.0 (1.0)</td>
<td>−1.7 (1.8)</td>
<td>&lt;.001</td>
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<tr>
<td>Whole-brain volume, % ICV</td>
<td>78.0 (2.9)</td>
<td>75.3 (3.3)</td>
<td>&lt;.001</td>
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<td>White matter volume, % ICV</td>
<td>35.0 (1.9)</td>
<td>34.6 (2.4)</td>
<td>.32</td>
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<td>Gray matter volume, % ICV</td>
<td>43.0 (2.5)</td>
<td>40.6 (2.4)</td>
<td>&lt;.001</td>
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<td>Activities of daily living</td>
<td>48.5 (3.3)</td>
<td>40.2 (7.8)</td>
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<td>Physical performance test</td>
<td>30.5 (3.4)</td>
<td>27.6 (3.9)</td>
<td>&lt;.001</td>
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<td>Physical activity level, PASE score</td>
<td>130.4 (51.8)</td>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
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</thead>
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<tr>
<td>Body mass index</td>
<td>25.7 (3.6)</td>
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<td>.38</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.2 (14.0)</td>
<td>69.1 (12.9)</td>
<td>.10</td>
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<tr>
<td>Height, cm</td>
<td>169.6 (11.2)</td>
<td>166.2 (9.1)</td>
<td>.14</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>25.8 (8.3)</td>
<td>24.7 (8.7)</td>
<td>.41</td>
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<tr>
<td>Body fat, %</td>
<td>35.3 (8.7)</td>
<td>35.4 (9.7)</td>
<td>.93</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>44.6 (10.4)</td>
<td>41.9 (9.3)</td>
<td>.02</td>
</tr>
</tbody>
</table>

| Abbreviations: AD, Alzheimer disease; % ICV, percentage of intracranial volume; PASE, Physical Activity Scale in the Elderly. SI conversion factors: to convert total cholesterol to millimoles per liter, multiply by 0.0259; C-reactive Protein to nanomoles per liter, 9.524. | |

### Table 2. Body Composition in Participants With Early AD and Controls

<table>
<thead>
<tr>
<th>Variable</th>
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</thead>
<tbody>
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<td>.02</td>
</tr>
</tbody>
</table>

a Group comparison by general linear model, controlling for age and sex. b Calculated as weight in kilograms divided by height in meters squared.
Regression analyses identified a relationship between WBV and lean mass (Figure). This relationship was driven primarily by a relationship between WMV and lean mass ($\beta = 0.19; P < .001$). In contrast, GMV was unrelated to lean mass. The association of WBV and WMV with lean mass was unchanged after controlling for additional covariates of dementia status, physical activity, global cognition, and insulin AUC. There were no dementia status × WBV or sex × WBV interactions, suggesting that the positive relationship between WBV and body composition was similar in participants with AD vs controls and men vs women.

Whole-brain volume was not related to total body fat ($\beta = 0.14; P = .21$) or percentage of body fat ($\beta = 0.01; P = .89$) but was modestly associated with BMI ($\beta = 0.20; P = .05$), with higher BMI associated with higher brain volume (ie, less brain atrophy). Although BMI is a proxy measure for adiposity ($r = 0.55; P < .001$), it also reflects lean mass ($r = 0.28; P = .001$), and thus the modest relationship between BMI and WBV appears to be largely driven by the observed lean mass–WBV relationship.

**OVERALL MODEL.**

We next examined an overall model that included all variables of interest (WBV, global cognition) and covariates (age, sex, dementia status, physical activity, and insulin levels) to assess which variables were most strongly related to lean mass. Age, sex, and dementia status (AD vs control) were forced into the model (step 1), with all covariates assessed in step 2 using a stepwise model of inclusion ($F = 3.94; P < .05$ to retain). In this model, WBV ($\beta = 0.12; P = 0.04$), insulin (3-hour AUC; $\beta = 0.10; P = .02$), and physical activity level ($\beta = 0.11; P = 0.02$) were each independently associated with lean mass. When WMV and GMV were used rather than WBV, WMV, but not GMV, was retained ($\beta = 0.17; P < .001$) with insulin ($\beta = 0.09; P = .05$) and physical activity ($\beta = 0.12; P = .009$).

**COMMENT.**

Our findings are consistent with prior studies indicating that alterations in body composition are apparent in
the earliest clinical stages of AD and extends these findings by suggesting that AD-related alterations in body composition may be predominantly related to loss of lean mass (ie, sarcopenia). This is consistent with at least one large epidemiological study that found an association between cognitive impairment and reduced muscle mass in women without dementia. Although the cross-sectional, case-control study design limits our ability to infer causal relationships, our data suggest that sarcopenia may be accelerated in the earliest stages of AD.

Our findings also suggest that lean mass may be a more sensitive measure to relate body composition to cognitive outcomes and dementia than measures of adiposity. Lean mass was reduced in individuals with AD compared with controls and was associated with brain volume and cognition; total body fat, however, was not related to dementia status, brain volume, or cognition. Although we observed a modest relationship between the nonspecific adiposity measure BMI and brain volume, this relationship was primarily driven by lean mass, as only lean mass, and not fat mass, was associated with WBV. Thus, our data highlight the importance of assessing specific measures of body composition and suggest the hypothesis that loss of lean mass may underlie previously described relationships of nonspecific measures of body composition (ie, BMI) with cognitive decline and dementia. We observed a direct correlation between WBV (an estimate of brain atrophy) and lean mass, suggesting that brain atrophy and loss of muscle mass may co-occur. Brain atrophy is considered a neuroimaging measure reflective of AD pathology. Thus, our data are consistent with other studies suggesting that brain pathology may contribute to decline in body composition, perhaps by disrupting central nervous system regulation of energy metabolism and food intake. While AD and neurodegeneration predominantly affect gray matter, we find it particularly interesting that we observed a strong relationship between lean mass and WMV rather than GMV, and this relationship was similar in participants without dementia and those with AD, suggesting that mechanisms other than AD processes may underline these relationships.

Sarcopenia in normal aging is most strongly associated with age-related reductions in physical activity. In our cohort, individuals with early AD had reduced physical activity levels compared with the cohort without dementia. Additionally, lower physical activity was associated with less lean mass, suggesting that behavioral changes associated with AD may result in loss of lean mass. Alternatively, physical activity itself may attenuate the structural and functional brain and body changes associated with AD and aging. This is biologically plausible given accumulating animal and human evidence linking exercise and physical fitness with brain health. Even after controlling for physical activity levels, however, lean mass remained independently associated with brain volume, suggesting that the decline in physical activity observed in aging and AD is unlikely to fully explain our results.

An alternative explanation for our observations is that AD and sarcopenia share common underlying mechanisms. Alzheimer disease is associated with systemic anabolic and inflammatory abnormalities that are also implicated in sarcopenia. Although our measures of anabolic and inflammatory processes are limited in this study, we observed an independent relationship between lean mass and insulin, a well-known anabolic hormone that may have neurotrophic and neuroprotective properties. We previously reported that insulin levels are associated with cognition and brain volume in early AD and, as in this study, the association was stronger for white matter than gray. Interestingly, insulin signaling preferentially affects the development of white matter structures, which, taken with our prior results, suggests that insulin signaling may play a role in maintaining cerebral white matter. Thus, our observation that WMV, lean mass, and insulin levels are interrelated suggests that reduced anabolic support to both the muscle and brain may be a potential mechanism underlying the observed relationships.

The current study is limited by its cross-sectional design, and further longitudinal and interventional studies will be necessary to more precisely define the nature and mechanisms of body composition changes in AD. Although clinical methods are imperfect in predicting AD pathology, we used sensitive and validated methods for diagnosing the earliest stages of AD. Additionally, participants were a convenience sample, which limits generalizability and may have introduced sampling bias that could affect the results. The relatively small sample size (n = 140) could limit the power to resolve group differences or important interactions for marginal effects and thus increase the chance of type II error. Additionally, potentially important dietary factors were not measured. Nevertheless, our data suggest that loss of lean mass may be accelerated in AD, perhaps as a direct or indirect consequence of AD pathophysiology or through shared mechanisms common to both AD and sarcopenia.

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Author Contributions: Study concept and design: Burns and Brooks. Acquisition of data: Burns and Brooks. Analysis and interpretation of data: Burns, Johnson, Watts, Swerdlow, and Brooks. Drafting of the manuscript: Burns, Johnson, Watts, and Swerdlow. Critical revision of the manuscript for important intellectual content: Burns, Johnson, Watts, and Swerdlow. Obtained funding: Burns and Brooks. Administrative, technical, and material support: Burns and Brooks. Study supervision: Burns and Brooks.

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