Alzheimer disease biomarkers are associated with body mass index

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ABSTRACT

Objective: Both low and high body mass index (BMI) has been associated with cognitive impairment and dementia risk, including Alzheimer disease (AD). We examined the relationship of BMI with potential underlying biological substrates for cognitive impairment.

Methods: We analyzed cross-sectional data from participants enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with PET imaging using Pittsburgh Compound B (PiB, n = 101) or CSF analyses (n = 405) for β-amyloid peptide (Aβ) and total tau. We assessed the relationship of CSF biomarkers and global PiB uptake with BMI using linear regression controlling for age and sex. We also assessed BMI differences between those who were and were not considered biomarker positive. Finally, we assessed BMI change over 2 years in relationship to AD biomarkers.

Results: No dementia, mild cognitive impairment (MCI), and AD groups were not different in age, education, or BMI. In the overall sample, CSF Aβ ($\beta = 0.181$, $p < 0.001$), tau ($\beta = -0.179$, $p < 0.001$), tau/Aβ ratio ($\beta = -0.180$, $p < 0.001$), and global PiB uptake ($\beta = -0.272$, $p = 0.005$) were associated with BMI, with markers of increased AD burden associated with lower BMI. Fewer overweight individuals had biomarker levels indicative of pathophysiology ($p < 0.01$). These relationships were strongest in the MCI and no dementia groups.

Conclusions: The presence and burden of in vivo biomarkers of cerebral amyloid and tau are associated with lower BMI in cognitively normal and MCI individuals. This supports previous findings of systemic change in the earliest phases of the disease. Further, MCI in those who are overweight may be more likely to result from heterogeneous pathophysiology. *Neurology*® 2011;77:1913–1920

GLOSSARY

Aβ = β-amyloid peptide; **AD** = Alzheimer disease; **ADAS-cog** = Alzheimer's Disease Assessment Scale–cognitive subscale; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **BMI** = body mass index; **CDR** = Clinical Dementia Rating; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **ND** = participants without dementia; **PiB** = Pittsburgh Compound B; **SUVR** = standardized uptake value ratio.

Many studies have demonstrated that individuals who are overweight or obese are at an increased risk of developing cognitive decline, dementia, and Alzheimer disease (AD) up to 3 decades later.[1–5] The relationship of body composition and cognitive outcomes, however, is complex and appears to attenuate with age. For example, several studies have demonstrated that being overweight in later life is associated with a lower risk of developing dementia and AD.[3,6–8] This interaction of age and body composition on cognitive risk has been called the "obesity paradox"[3] where increased body mass index (BMI; a measure of adiposity) in midlife appears to be a risk factor for dementia but increased BMI in late life appears protective.

One explanation of the apparent obesity paradox is a long preclinical phase, that can include accelerated weight loss, in which neuropathologic changes are present in the brain for up to a decade

Supplemental data at www.neurology.org

Supplemental Data

From the Department of Neurology (E.D.V., R.A.H., J.M.B.) and School of Medicine (R.T.), University of Kansas Medical Center, Kansas City.

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete list of ADNI investigators is included on the *Neurology*® Web site at www.neurology.org.

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without recognizable clinical signs. The preclinical and earliest stages of AD are associated with lower body mass, accelerating sarcopenia, and fat mass reduction.[9–14] Additionally, autopsy evidence links AD neuropathologic changes with low and declining BMI, even in individuals with normal cognition, suggesting AD-related neurodegenerative brain changes may influence body composition.[15]

We sought to extend our prior observations of accelerated cognitive decline in MCI participants with lower BMI[16] by examining the relationship of BMI with potential underlying biological markers of disease. We hypothesized that markers of AD pathophysiology would be related to lower BMI and greater decline in BMI.

METHODS

Sample. All participant data were obtained from the ADNI database (www.loni.ucla.edu/ADNI) in November 2010. ADNI is an ongoing, 58-site, public-private cooperative partnership conducted by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations (PI: Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco). Its primary goal is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. Biomarker measures include in vivo assessments that reflect cerebral amyloid burden (CSF amyloid-β 1–42 [Aβ] and PET imaging with Pittsburgh Compound B [PiB]) and neurofibrillary tangles (CSF tau). For additional information, see www.adni-info.org.

Clinical assessment. Standard clinical and neuropsychological evaluations were conducted at regular intervals. The evaluations included a Clinical Dementia Rating,[17] physical examination, laboratory procedures, and neuropsychological tests. Evaluating clinicians rendered diagnoses using standardized criteria for participants without dementia (ND), MCI, and AD (ADNI protocol available at http://www.adni-info.org). Baseline height and weight measures were used to calculate BMI (kg body weight/m^2 height). The Mini-Mental State Examination[18] score and 11-item Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog)[19] were used as cognitive measures.

ND had Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a Clinical Dementia Rating (CDR) score of 0, and did not have significant depression. Visits were scheduled at baseline, 6, 12, 24, 36, and 48 months postenrollment for those with cognitive impairment. Participants diagnosed with MCI had MMSE scores between 24 and 30 (inclusive), a memory complaint and objective memory loss measured by education-adjusted scores on Wechsler Memory Scale–Revised Logical Memory II, a CDR of 0.5, largely preserved activities of daily living, and an absence of dementia. Visits occurred at baseline, 6, 12, 18, 24, 36, and 48 months postenrollment for those diagnosed with MCI. Participants diagnosed with AD had MMSE scores between 20 and 26 (inclusive), CDR of 0.5 or 1.0, and met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD. Visits occurred at baseline, 6, 12, and 24 months postenrollment.

CSF biomarkers. The ADNI Biomarker Core has previously described the procedures for acquiring and processing CSF for biomarker analysis.[20] Briefly, individuals with MCI provided CSF samples after overnight fasting. Aβ and tau were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with immunoassay kit–based, research use–only reagents (INNO-BIA AlzBio3; Innogenetics, Ghent, Belgium). Analyses of the ADNI cohort[20] have demonstrated that CSF Aβ values below 192 pg/mL and a tau/Aβ ratio >0.39 are sensitive and specific to discriminating participants with AD from controls without dementia. Using these cutpoints, we classified participants as CSF Aβ-positive and as having an elevated tau/Aβ ratio.

PiB PET imaging. PiB PET imaging was performed on a subset of ADNI participants at 14 sites. Procedures for acquisition (adni.loni.ucla.edu/research/protocols/pet-protocols/) and processing (www.loni.ucla.edu/twiki/pub/ADNI/ADNIPostProc/UPitt_PIBPET_Analysis.doc) are available online. PiB standardized uptake value ratios (SUVR) normalized to the cerebellum were averaged within 14 a priori regions of interest. Only PiB values from the first PiB imaging timepoint were used in the present analysis. Global PiB uptake was calculated as the average of PiB SUVR from gray matter regions that demonstrated AD vs ND control differences (data not shown) and included the anterior cingulate, anterior ventral striatum, frontal cortex, lateral temporal cortex, occipital cortex, parietal cortex, precuneus, and sensorimotor cortex regions of interest. We classified individuals as "PiB-positive" using a previously reported cutpoint of 1.5 or greater for the global PiB index, which is considered to reflect abnormally high cerebral amyloid levels.[21]

Statistical analyses. Differences between groups were tested using parametric analyses (analysis of variance) or nonparametric analyses (χ^2, Kruskal-Wallis) when appropriate. Post hoc testing (Fisher least significant difference or Mann-Whitney *U*) was performed on measures with significant main effects to identify specific differences between groups. We also assessed the relationship of amyloid (CSF Aβ and global PiB uptake) and tau biomarkers (CSF tau and tau/Aβ) with BMI using multiple linear regression controlling for age and sex. We did not include *APOE*4 as a covariate in the primary model to avoid variance inflation given its high correlation with CSF Aβ.[22] Repeated-measures analysis of variance was used to examine the relationship of AD biomarkers with change in BMI over time.

RESULTS

Descriptive information for the CSF and PiB subsamples is provided in tables 1 and 2. We analyzed 405 individuals who underwent lumbar puncture at baseline (n = 112 ND; 193 MCI, 100 AD) and 101 individuals with at least one PiB-PET scan (n = 20 ND; 56 MCI, 25 AD). There were no differences in age, education, BMI, or prevalence of overweight (BMI >25) across diagnosis groups, although fewer women (p = 0.01) were present in MCI. CSF and PiB-PET measures of AD biomarkers

Table 1 Demographic and biomarker measures of ADNI participants with CSF data[a]

CSF subsample	ND (n = 112)	MCI (n = 193)	AD (n = 100)	*p* Value	Post hoc results
Age, y	75.7 (5.2)	74.5 (7.6)	75.0 (7.9)	0.637	—
% Female	50.0	32.6	42.0	0.010	ND > MCI
Education, y	15.7 (2.8)	15.8 (3.0)	15.1 (3.3)	0.155	—
APOE ε4 carrier, %	23.2	53.4	69.0	<0.001	ND < MCI < AD
MMSE	29.1 (1.0)	26.9 (1.8)	23.5 (1.9)	<0.001	ND > MCI > AD
ADAS-Cog	6.4 (2.9)	11.6 (4.5)	18.2 (6.2)	<0.001	ND < MCI < AD
BMI, kg/m^2	26.5 (4.2)	25.83 (3.8)	25.6 (3.7)	0.174	—
Overweight and obese (% BMI ≥25 kg/m^2), %	59.8	55.4	54.0	0.658	—
BMI <20, n (%)	3 (2.6)	7 (3.6)	5 (5.0)	0.742	—
BMI >30, n (%)	25 (22.3)	31 (16.1)	11 (11.0)	0.114	—
Total tau, pg/mL	70.0 (30.5)	103.7 (61.2)	121.6 (57.6)	<0.001	ND < MCI < AD
β-Amyloid, pg/mL	204.7 (55.1)	163.7 (55.0)	143.5 (41.0)	<0.001	ND > MCI > AD
β-Amyloid positivity (<192 pg/mL), %	38.4	74.1	91.0	<0.001	ND < MCI < AD
Tau/Aβ ratio	0.39 (0.27)	0.76 (0.62)	0.92 (0.48)	<0.001	ND < MCI < AD
Elevated tau/Aβ ratio (>0.39), %	35	69.4	88.0	<0.001	ND < MCI < AD

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADNI = Alzheimer's Disease Neuroimaging Initiative; BMI = body mass index; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; ND = no dementia.

[a] All values are means (SD). *p* Values <0.05 represent a significant difference is present among the 3 groups (ND, MCI, AD). When group differences were present, we identified specific group differences using post hoc contrasts described in the column post hoc results. For example, CSF Aβ is greater in the no dementia than the MCI group, which is in turn greater than the AD group (ND > MCI > AD).

were different across groups, with measures reflecting higher AD pathophysiology highest in AD, intermediate in MCI, and lowest in ND. BMI was not correlated with MMSE or ADAS-cog within diagnosis groups, even after controlling for age and sex ($p > 0.19$). In the subset of individuals with both CSF Aβ and global PiB

Table 2 Demographic and biomarker measures of ADNI participants with PiB-PET data[a]

PiB subsample	ND (n = 20)	MCI (n = 56)	AD (n = 25)	*p* Value	Post hoc results
Age, y	77.2 (6.3)	75.3 (7.7)	75.1 (9.0)	0.617	—
% Female	40.0	35.7	32.0	0.856	—
Education, y	15.8 (3.4)	16.2 (2.6)	15.4 (3.0)	0.495	—
APOE ε4 carrier, %	30.0	53.6	64.0	0.069	—
MMSE	28.8 (1.4)	27.3 (1.95)	22.8 (2.9)	<0.001	ND > MCI > AD
ADAS-Cog	4.9 (3.0)	10.9 (5.0)	18.6 (6.5)	<0.001	ND < MCI < AD
BMI, kg/m^2	27.4 (3.6)	25.8 (4.1)	26.2 (4.5)	0.332	—
Overweight and obese (% BMI ≥25 kg/m^2), %	70.0	51.8	52.0	0.343	—
BMI <20, n (%)	0	1 (1.8)	2 (8.0)	0.214	—
BMI >30, n (%)	5 (20.0)	9 (16.1)	5 (20.0)	0.670	—
Global PiB uptake	1.51 (0.27)	1.68 (0.35)	1.80 (0.3)	0.009	ND < MCI and AD
PiB positivity (global PiB >1.5), %	50.0	66.1	88.0	0.021	ND and MCI < AD

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADNI = Alzheimer's Disease Neuroimaging Initiative; BMI = body mass index; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; ND = no dementia; PiB = Pittsburgh Compound B.

[a] All values are means (SD). Values of *p* <0.05 represent a significant difference among the 3 groups (ND, MCI, AD). When group differences were present, we identified specific group differences using post hoc contrasts described in the column post hoc results. For example, global PiB uptake is lower in the no dementia than the MCI and AD groups (ND < MCI and AD).

Table 3 Relationship of AD biomarkers with BMI[a]

	Aβ	Tau	Tau/Aβ	PiB
Overall	0.18[b]	−0.18[b]	−0.18[b]	−0.27[c]
ND	0.19[d]	−0.20[d]	−0.24[d]	−0.43 ($p = 0.083$)
MCI	0.14 ($p = 0.053$)	−0.17[d]	−0.16[d]	−0.32[d]
AD	0.14	−0.12	−0.11	0.017

Abbreviations: AD = Alzheimer disease; BMI = body mass index; MCI = mild cognitive impairment; ND = no dementia; PiB = Pittsburgh Compound B.
[a] Values presented are standardized linear regression coefficients (β) representing the correlation of AD biomarkers with BMI after controlling for age and sex in the overall sample and in each diagnosis group.
[b] $p < 0.001$.
[c] $p < 0.01$.
[d] $p < 0.05$.

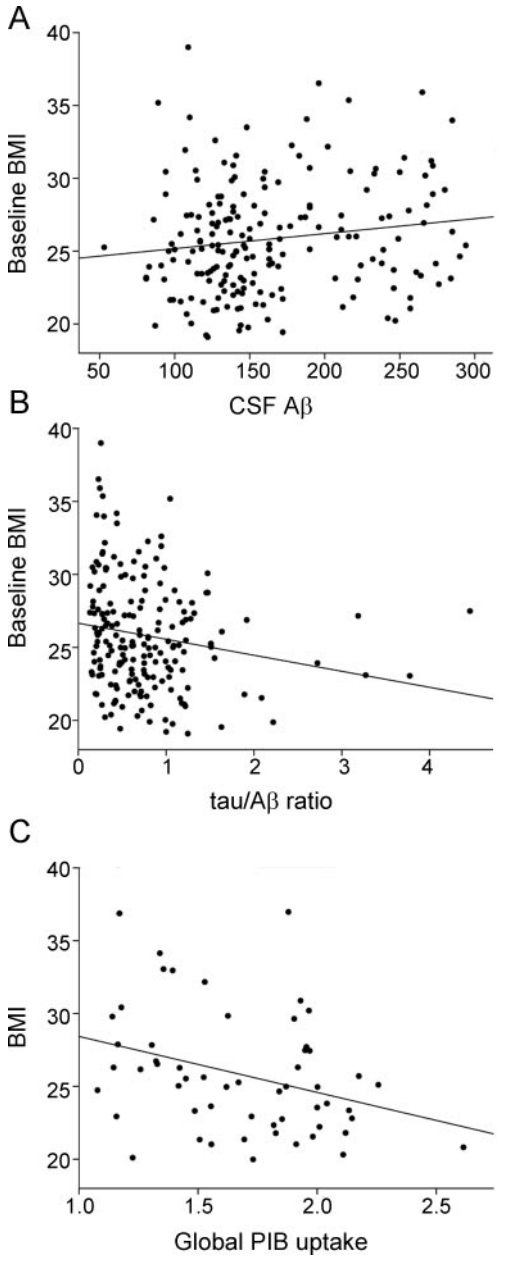
measures, the 2 indices were correlated (n = 50, Pearson $r = -0.617$, $p \leq 0.001$).

AD biomarkers and BMI. All analyses were controlled for age and sex. In the overall sample (AD, MCI, and ND participants combined), CSF Aβ, tau, tau/AB ratio, and global PiB uptake were associated with BMI, with measures reflective of higher AD neuropathologic burden associated with lower BMI ($p \leq 0.005$). Table 3 provides the standardized coefficients (β) representing the relationship between each biomarker (predictor variable) and BMI (outcome variable) after controlling for age and sex. There were no AD biomarker × sex interactions in predicting BMI to suggest a prominent sex effect. Additionally, adding *APOE4* to the model did not alter the results.

For within-group analyses, lower CSF Aβ was associated with lower BMI in the ND and MCI (figure, A) groups but not in AD ($p = 0.19$). Higher CSF tau and tau/Aβ ratio were associated with lower BMI in the ND and MCI (figure, B) groups but not in AD ($p = 0.24$). Higher global PiB uptake was associated with lower BMI in MCI participants (figure, C) and a trend was observed in the ND group ($p = 0.08$), but no relationship was evident in the AD group ($p = 0.94$).

We also assessed biomarkers as binary variables (i.e., positive or negative) corresponding to cutpoints indicative of AD pathophysiology. Individuals who were CSF Aβ-positive, PiB-positive, or had an elevated tau/Aβ ratio had lower mean BMI than Aβ-negative individuals in the overall sample ($p \leq 0.02$; table 4). In the ND group specifically, BMI was lower in those who were Aβ-positive or had an elevated tau/Aβ ratio ($p \leq 0.010$). BMI was lower in MCI participants who were Aβ-positive, PiB-positive, or had an elevated tau/Aβ compared to those who were not considered positive for these biomarkers ($p \leq 0.05$). In AD, BMI was lower in those who had elevated tau/Aβ ($p = 0.001$) but was not different for Aβ-positive or PiB-positive groups ($p > 0.37$).

Figure Alzheimer disease biomarkers are associated with body mass index (BMI) in participants with mild cognitive impairment



(A) Lower CSF Aβ was associated with lower BMI and (B) higher CSF tau/Aβ ratio was associated with lower BMI. (C) Higher global Pittsburgh compound B (PiB) uptake was also associated with lower BMI. Scatterplots depict raw values for ease of interpretation and are not corrected for age and sex as presented in table 3.

AD pathophysiology and overweight. We also assessed the frequency of biomarker positivity in normal weight vs overweight (BMI >25 kg/m^2) individuals. Overall, the prevalence of biomarker "positivity" was higher in normal weight compared to overweight individuals (table e-1 on the *Neurology*® Web site at www.neurology.org). In the ND group specifically,

Table 4 BMI in biomarker-positive vs biomarker-negative participants[a]

	Aβ-negative	Aβ-positive	p Value
Overall (n = 405)	27.0 (4.1)	25.5 (3.7)	<0.001
ND (n = 112)	27.3 (4.3)	25.2 (3.9)	0.01
MCI (n = 193)	26.8 (4.1)	25.5 (3.7)	0.05
AD (n = 100)	26.2 (3.4)	25.5 (3.8)	0.37
	PiB-negative	PiB-positive	
Overall (n = 101)	27.7 (4.1)	25.5 (4.0)	0.02
ND (n = 20)	28.4 (3.6)	26.5 (3.6)	0.17
MCI (n = 56)	27.7 (4.2)	24.8 (3.8)	0.02
AD (n = 25)	25.2 (6.1)	26.3 (4.4)	0.74
	Normal tau/Aβ	Elevated tau/Aβ	
Overall (n = 405)	27.6 (4.2)	25.1 (3.5)	<0.001
ND (n = 112)	27.6 (4.4)	24.7 (3.2)	<0.001
MCI (n = 193)	27.3 (4.1)	25.2 (3.5)	<0.001
AD (n = 100)	28.7 (3.1)	25.2 (3.6)	0.001

Abbreviations: AD = Alzheimer disease; BMI = body mass index; MCI = mild cognitive impairment; ND = participants without dementia; PiB = Pittsburgh Compound B.
[a] All values are mean BMI in kg/m^2 (SD). Standard cutpoints were used to classify individuals as positive for global PiB index (≥1.5) and CSF Aβ (≤192 pg/mL) and as having an elevated tau/Aβ ratio (>0.39). *p* Values represent significance of a test comparing BMI in biomarker-positive vs negative individuals controlled for age and sex.

normal weight individuals had higher prevalence of biomarker positivity for CSF Aβ, tau/Aβ ratio, and global PiB uptake ($p < 0.01$). In MCI, this was true for global PiB uptake and tau/Aβ ratio ($p < 0.01$), but not CSF Aβ. In AD participants, no clear pattern was evident with respect to overweight vs normal weight categories: the prevalence of an elevated tau/Aβ ratio was higher in the normal weight group ($p < 0.05$) whereas PiB positivity was higher in those who were overweight ($p < 0.01$).

Biomarker positivity and BMI change. We also assessed whether biomarker-positive participants had subsequent changes in BMI over 2 years using data from the participants in the CSF subsample who had BMI data at baseline, 1 year, and 2 years (100 ND, 153 MCI, and 78 AD participants). In the overall sample, there was no main effect of time on BMI and no interaction of time on biomarker positivity or diagnosis ($p > 0.1$). This indicates there was no consistent change in BMI over 2 years related to diagnosis or an individual's biomarker positivity status. Similar results were found when we assessed diagnosis groups separately.

DISCUSSION Over 50% of adults are obese or overweight and current trends suggest these numbers will increase in the coming decades.[23] The rising prevalence of overweight and obesity is likely to have important public health implications on the cognitive health of the aging population. We found that biomarker levels reflective of AD pathophysiology were associated with lower BMI in a sample of cognitively normal, MCI, and AD participants enrolled in ADNI. This relationship was most strongly evident in individuals with MCI, a heterogeneous pathologic state, suggesting that individuals with MCI who are normal or low weight (BMI 18.5–25 kg/m^2) are more likely to have amyloid-based cognitive impairment compared to those who are overweight (BMI >25 kg/m^2). This relationship was also evident in cognitively normal adults, of which a portion (>38%) had significant cerebral amyloid burden without associated functional and clinical symptoms.

Conflicting findings have obscured a precise definition of the relationship between body mass and late-life cognitive decline. Being overweight (BMI >25) in midlife is associated with an increased risk of cognitive impairment and dementia[1,5] while being overweight in late life is associated with reduced cognitive risk.[6–8] Mortality studies suggest the chronic disease associated with obesity drives mortality risk while the association of low BMI (<20) with mortality may be an artifact of preexisting disease.[24,25] Our data in cognitively healthy participants demonstrate that low BMI is associated with AD pathophysiologic markers. Interestingly, the vast majority of our cohort was not at the extremes of BMI, with less than 17% of the overweight group classified as obese (BMI >30) and few participants (3.6%) with a BMI <20. Nevertheless, we observed robust relationships between BMI and the presence and burden of AD biomarkers.

We observed that lower BMI (<25 kg/m^2) was associated with a higher burden of AD biomarkers and greater prevalence of AD biomarker "positivity" in both the cognitively normal and MCI groups. Surprisingly, we found no evidence of change in BMI or weight over 2 years in biomarker "positive" vs "negative" groups although multiple studies have demonstrated that weight loss is a nonspecific preclinical marker of AD that may be present 6–10 years prior to the onset of clinically recognizable cognitive and functional symptoms.[11,26] Both autopsy and imaging data suggest that weight loss may in part be related to brain pathology. An autopsy study of individuals with and without dementia found that AD plaque and tangle pathology was associated with both low BMI and declining BMI in the years preceding death.[15] Imaging data also suggest that structural brain changes, including whole brain and hippocampal atrophy, are associated with alterations in body composition, including reductions in more specific measures of lean mass and bone density.[9,27] As BMI is also a marker of systemic energy metabolism, our findings are consistent with others that suggest that

systemic metabolic changes are present early in the disease process.[28]

Potential mechanisms underlying the relationship of BMI and AD pathophysiology include neuropathologic changes known to occur in areas such as the hypothalamus that play a role in regulating energy metabolism and food intake.[29] It is also important to consider mechanisms that influence both weight loss and cognitive impairment, including systemic anabolic and inflammatory abnormalities that are common to both AD and wasting states such as sarcopenia.[30,31] Behavioral and cognitive changes associated with dementia can also influence body composition by interfering with nutrition (i.e., forgetting to eat) or through reductions in physical activity, a strong predictive factor of sarcopenia.[32] Our observations were strongest in those without significant cognitive and functional limitations and we found no evidence of weight loss in any group, reducing this likelihood.

The substrate for cognitive impairment across selected populations of individuals with MCI is heterogeneous and includes both AD and vascular changes. Our data suggest that the underlying etiology of cognitive impairment in MCI participants with higher BMI is less likely to be related to amyloid pathophysiology than those with normal or low BMI. For example, more individuals with MCI who had a BMI below 25 kg/m^2 were PiB-positive than individuals who were overweight (85.2% vs 48.3%). The same was true with regard to elevated tau/Aβ (80.2% vs 60.7%). Prior studies in healthy older adults have found that high BMI is associated with structural and metabolic brain changes. Higher BMI in participants in the ADNI cohort has previously been associated with brain atrophy, although this association was observed predominantly in the cerebellum, brainstem, frontal, temporal, and occipital lobes and spared those areas most commonly affected by AD pathophysiology such as the medial temporal lobe or default mode network.[33] It is possible that being overweight may contribute to cognitive impairment through comorbidities such as cerebrovascular disease. Additionally, cerebrovascular burden influences the expression of clinical symptoms at lower levels of AD pathophysiology in an additive fashion.[34,35] High BMI in individuals with cognitive impairment similar to that of normal weight individuals such as in the present study may thus be associated with an increased likelihood of underlying mixed or nonamyloid pathologies.

This study has several important limitations. Given that multiple secondary analyses were performed there is an increased chance of type I error and spurious observations. BMI is a nonspecific measure of body composition that does not adequately reflect distribution of body fat and important components of body composition. This is an increasingly important limitation given variable risks associated with the location of adipose tissue,[7] weight stability despite sarcopenia in older age,[36] and the possibility that AD may be specifically associated with sarcopenia.[9] However, BMI continues to be a useful heuristic associated with adverse health outcomes including coronary artery disease, diabetes, and hypertension.[37] Additionally, our findings were confined to associations between AD biomarkers and BMI at baseline and we did not observe an association with change in BMI over time. These data were collected from a selected group of research participants which may affect the study's generalizability. These data should not be interpreted as establishing evidence of a causal or temporal relationship between body composition and AD pathology.

Our in vivo results extend previous autopsy findings to demonstrate a relationship between BMI and AD pathophysiology in the earliest stages of AD. Importantly, this relationship of higher AD pathophysiology with lower BMI was most strongly evident in those without major cognitive or functional change. These results provide further support that AD has systemic manifestations that may be the result of longstanding neuropathologic change or lifestyle patterns. Further, cognitive impairment in those who are overweight may be more likely to be the result of heterogenous pathophysiology. Future investigations should investigate if the association between BMI and AD reflects a systemic response to unrecognized disease or a longstanding trait that predisposes one to developing the disease.

AUTHOR CONTRIBUTIONS

All authors (E.D.V., R.T., R.H., J.M.B.) contributed to analysis design, results interpretation, and manuscript preparation. J.M.B. and E.D.V. additionally performed the statistical analysis.

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DISCLOSURE

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