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Higher Body Mass Index Is Associated with Lower Cortical Amyloid-β Burden in Cognitively Normal Individuals in Late-Life

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Abstract

Background—Both low and high body mass index (BMI) have been associated with an increased risk of dementia, including that caused by Alzheimer's disease (AD). Specifically, high middle-age BMI or a low late-age BMI has been considered a predictor for the development of AD dementia. Less studied is the relationship between BMI and AD pathology.

Objective—We explored the association between BMI and cortical amyloid-β (Aβ) burden in cognitively normal participants that were either in mid-life (45–60 years) or late-life (>60).

Methods—We analyzed cross-sectional baseline data from the Knight Alzheimer Disease Research Center (ADRC) at Washington University. Aβ pathology was measured in 373 individuals with Aβ PET imaging and was quantified using Centiloid units. We split the cohort into mid- and late-life groups for analyses ($n = 96$ and $n = 277$, respectively). We ran general linear regression models to predict Aβ levels from BMI while controlling for age, sex, years of education, and *APOE4* status. Analyses were also conducted to test the interaction between BMI and *APOE4* genotype and between BMI and sex.

Results—Higher BMI was associated with lower cortical Aβ burden in late-life ($\beta = -0.81$, $p = 0.0066$), but no relationship was found in mid-life ($\beta = 0.04$, $p > 0.5$). The BMI × *APOE4+* and BMI × male interaction terms were not significant in the mid-life ($\beta = 0.28$, $p = 0.41$; $\beta = 0.64$, $p = 0.13$) or the late-life ($\beta = 0.17$, $p > 0.5$; $\beta = 0.50$, $p = 0.43$) groups.

Conclusion—Higher late-life BMI is associated with lower cortical Aβ burden in cognitively normal individuals.

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Keywords

Alzheimer disease; amyloid-β; apolipoproteins E; body mass index; obesity; positron emission tomography

INTRODUCTION

Alzheimer's disease (AD) is a debilitating, progressive neurodegenerative disease that is the leading cause of dementia in the United States [1, 2]. The disease disproportionately affects the population aged 65 and older. Roughly 96% of total AD cases in the U.S. fall within this age group [3]. As the number of 65+ individuals in the U.S. is projected to increase from 53 million to 88 million by 2050, the number of Americans with AD will rapidly escalate [4]. Given that $277 billion was spent on AD in 2017 [5], it is imperative that risk factors are identified in cognitively normal populations to better understand how disease progression might be controlled and to minimize future AD-related healthcare expenditures. Obesity, like AD, also poses a significant public health problem in the U.S. One in five Americans are morbidly obese, and obesity itself has been linked with an increased risk of diabetes, coronary heart disease, and cancer [6]. Although higher body mass index (BMI) is generally associated with adverse health outcomes [7, 8], there is evidence that large body size is actually beneficial for those with certain chronic cardiovascular, pulmonary, and renal diseases [9]. These counterintuitive findings also appear in studies examining the relationship between obesity and dementia [10–15].

Generally, epidemiological studies show that being overweight increases the risk [10, 11] of developing a dementing disorder (vascular, AD, etc.). However, there has also been research showing no increased risk of dementia [12–14] or even a reduced risk of dementia [15]. When examining AD specifically, epidemiological work has shown being overweight is both associated with an increased risk [16, 17] and a decreased risk [9, 18–20]. These inconsistent findings relating obesity to an increased risk of dementia may arise from the heterogeneous nature of the populations being studied. Specifically, the obesity-dementia relationship seems to differ for those in mid-life versus late-life [10, 21–26], and this difference may be attributed to weight loss occurring near the onset of dementia [25, 26] or a long preclinical phase that is associated with weight loss, sarcopenia, and fat mass reduction [27–32]. Due to these findings, it is imperative to study the obesity-dementia relationship separately for each age group within a cognitively normal cohort.

Prior work has primarily focused on how obesity impacts the risk of developing dementia. As a result, it is unclear if changes in obesity directly impact AD pathology, or instead just represent co-morbid processes that impact cognition directly. Animal work suggests that obesity and diabetes can directly influence the accumulation of AD pathology [33–38]. In humans, only a modest number of studies have directly examined the relationship between obesity measured with BMI and AD pathology [25, 39–44] using biomarkers such as cerebrospinal fluid (CSF) amyloid-β (Aβ) 1–42 [43], CSF total tau [40], and cortical Aβ as measured by positron emission tomography [39, 44]. These studies have found an association between a greater weight and lower AD pathology. While this prior work has

been informative, these studies typically have small sample sizes or do not take into the account both how the relationship of BMI on AD pathology may vary as a function of both age group and *APOE4* genotype, the latter of which has been shown to modify the AD-body composition relationship [39, 40].

We sought to further characterize the relationships between obesity and AD by examining the cross-sectional relationship between BMI and cortical Aβ burden as measured by PET in cognitively normal (CN) participants. We examined the relationship between weight and AD pathology in both those in mid-life (45–60 years) and late life (>60) in a cross-sectional cohort. Based upon prior work, we hypothesized that in CN mid-life individuals, higher BMI will be associated with elevated cortical Aβ burden. In CN late-life individuals, we hypothesized that higher BMI will be associated with lower cortical Aβ burden. Additionally, we were interested in whether the BMI-Aβ relationship is modified by the presence of an *APOE ε*4 allele or by sex.

METHODS

Participants

Participants were selected from ongoing longitudinal studies of aging and dementia from the Knight Alzheimer Disease Research Center (ADRC) at Washington University in St. Louis. Cognitive status in these participants was assessed using the clinical dementia rating (CDR) [45]. Participants were required to be clinically normal (CDR = 0), have an Aβ PET scan, have information on demographic variables (age, sex, and education), have information on *APOE* genotype, and have a recorded height and weight (to calculate BMI) from the day of their scan. Participants were classified as being mid-life (45–60 years) and late-life (>60 years).

Imaging acquisition and processing

Magnetic resonance imaging (MRI) scans were obtained using 3 Tesla volumetric T1-weighted MRI scanners following the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/) and processed through FreeSurfer, version 5.3 [46] (Martinos Center, Boston, MA), as previously described [47]. The T1-weighted images were used for measurements of hippocampal volumes adjusted for total intracranial volumes using a regression approach, and for measurements of cortical volumes and ventricular volumes.

Aβ PET imaging was completed using two tracers: [^{18}F] florbetapir (AV-45, n = 18) and [^{11}C]- Pittsburgh Compound B (PiB, n = 355). Data were analyzed with an in-house pipeline using regions of interest (ROIs) derived from FreeSurfer 5.3 segmentations [47]. Standardized Uptake Value ratios (SUVRs) were calculated for the time windows between 50–70 min post-injection for AV45 and 30–60 min post-injection for PiB using cerebellar cortex as a reference region. Partial volume effects were corrected for using a regional spread function (RSF) technique [48, 49].

To assess global Aβ burden, the arithmetic mean of SUVRs from the Freesurfer ROIs in the prefrontal cortex, precuneus, gyrus rectus, and lateral temporal regions were calculated as the mean cortical SUVR (MCSUVR), as previously published [47]. To combine the data

from both tracers, partial volume corrected SUVRs were converted into Centiloid units [50, 51]. Aβ value of 0 on the scale represents the mean Aβ burden of a young control group with no Aβ pathology. A value of 100 represents the mean Aβ burden of an AD group [51].

The equations to convert AV45 and PiB MCSU-VRRSF to Centiloid Units derived at our center are:

$$53.6 * AV45\ MCSUVRRSF - 43.2 = Centiloid\ Units$$
$$45 * PiB\ MCSUVRRSF - 47.5 = Centiloid\ Units$$

Body mass index

Each participant had a height and weight measurement taken the day of their PET scan. The standard formula for calculating BMI as defined by the NIH was used to transform height and weight into participant BMI [52]. As it is common to examine categorical groupings for additional analyses, we investigated the BMI-Aβ relationship using BMI subdivisions rather than a continuous value of BMI. The subdivisions were defined using current NIH guidelines: underweight (BMI <18.5), normal (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI >30). The underweight subdivision was not used for additional analyses as there were too few individuals in this group ($n = 5$).

APOE genotype

DNA was extracted from peripheral blood samples using standard procedures, as previously described [53]. *APOE4* carrier status was determined by having at least one *APOE4* allele.

Statistical analyses

Statistical analyses were performed in R, version 3.5.1. Separate general linear regression models (GLMs) incorporated continuous measures of BMI and cortical Aβ burden (measured in Centiloid units). Primary models included the main effect of BMI, age group (mid-life/late-life), an interaction term of BMI and age group as well as covariates for *APOE4* carrier status, sex, age, and education. Additional linear regressions were run separately for each age group while including a main effect of BMI and all covariates. Partial regression plots were used to take into account the effect of multiple independent variables.

Although BMI is continuous, it is often conceptualized as an ordinal measure. For additional analyses, we investigated the differences in mean cortical Aβ burden between BMI groups (normal, overweight, obese) by computing a one-way analysis of variance (ANOVA) testing whether there was a main effect of BMI group on Aβ level followed by a multiple pairwise-comparison *t*-test between the means of the BMI groups.

As prior work suggests an interaction between BMI and *APOE* genotype, we also investigated the association of continuous measures of BMI and cortical Aβ burden by including an interaction term for continuous BMI and *APOE4* status within each age group.

Finally, we also investigated the interaction between BMI and sex by including an interaction term for continuous BMI and sex within each age group.

RESULTS

Baseline characteristics

Based upon the selection criteria, all participants were CN (global CDR = 0). Those in mid-life (n = 96) were on average 53.5 years of age (range: 45–60), college educated (mean: 16.3 years of education), 72.9% female, 35.4% had at least one *APOE4* allele (E4+). Those in mid-life had a mean Mini-Mental State Examination score of 28.9 and a mean CDR sum of boxes (CDR-SOB) of 0.0053. Those in late-life (n = 277) were on average 71.4 years of age (range: 61–100), college educated (mean: 15.8 years of education), 59.9% female, and 28.5% E4+. Those in late-life had a mean MMSE score of 28.8 and a mean CDR-SOB of 0.033 (see Table 1 for demographics).

In both the mid- and late-life groups, the majority of participants were overweight or obese (64.6% and 59.6%, respectively). Due to the small number of underweight participants in both groups, underweight participants were excluded in analyses investigating BMI subdivisions given the lack of power. *APOE4* carrier status, education, age, and other baseline characteristics were not significantly different between BMI subdivisions in either the mid- or late-life groups as assessed by t-tests.

Continuous BMI and cortical Aβ burden in mid- and late-life

The relationship between a continuous measure of BMI and cortical Aβ burden is presented in Fig. 1. When modeling an interaction between BMI and age group for the whole cohort, the BMI × age-group interaction term was significant (p = 0.0309). Thus, there is a differential effect of BMI in mid-life versus late-life. In the late-life cohort, higher BMI was associated with a lower cortical Aβ burden (β = −0.82, p = 0.0074) in the linear regression model after including age, sex, years of education, and *APOE4* carrier status. BMI in the mid-life cohort did not show any significant association with cortical Aβ burden (β = 0.03, p > 0.5) after adjusting for the same variables (Fig. 2). These results remained the same after excluding the four individuals with highest BMI.

The main effect of *APOE4* carrier status was significant in both the mid- and late-life models, (β = 6.1, p = 0.0012 and β = 18.1, p < 0.001, respectively), with *APOE4* carriers having elevated cortical Aβ burden compared to non-carriers. Age was also significant in both the mid- and late-life models (β = 0.51, p = 0.0283 and β = 0.90, p < 0.001, respectively), with higher age being associated with elevated cortical Aβ burden.

Differences in cortical Aβ burden by BMI group in mid- and late-life

To test group differences in mean cortical Aβ burden between the three BMI groups (normal, overweight, and obese) in mid- or late-life, we computed a one-way ANOVA test examining the main effect of BMI group separately for the late-life and mid-life cohorts. The ANOVAs showed that there was a significant difference in the mean cortical Aβ burden between BMI groups in late-life ($F_{2,269}$ = 5.60, p = 0.0042). Pairwise-comparison t-tests show a significant difference in mean cortical Aβ burden between the normal and obese groups in late-life (p < 0.001) (Fig. 3A). The mean cortical Aβ burden of the overweight

group was not significantly different from that of the normal group ($p = 0.0763$) or the obese group ($p = 0.0616$) in late-life (Fig. 3A).

There was no significant main effect of BMI group on Aβ burden in mid-life ($F_{2,93} = 0.069$, $p > 0.5$). Even in the pair-wise contrasts, there were no significant differences between any BMI groups in mid-life (Fig. 3B), with $p > 0.5$ for all three comparisons.

We then utilized a general linear regression model for late-life participants with categorical BMI and controlled for age, sex, years of education, and *APOE4* status. Compared to a normal BMI, being classified as overweight or obese was significantly associated with a lower cortical Aβ burden (β = −7.7, $p = 0.0499$ and β = −12.4, $p = 0.0033$, respectively). E4+ and age both remained significant in the model with categorical BMI for late-life (β = 17.8, $p < 0.001$ & β = 0.87, $p < 0.001$, respectively).

Although by definition sorting individuals into BMI groups limits the ranges values can take, prior work [39] examined whether there was a significant effect of continuous BMI levels *within* the different BMI categories. Therefore, we also tested the association between continuous BMI and cortical Aβ burden within the three BMI categories in late-life individuals while controlling for age, sex, years of education, and *APOE4* status. We found no significant association between continuous BMI and cortical Aβ burden in any of these groups (normal: β = −0.42, $p > 0.5$; overweight: β = −0.19, $p > 0.5$; obese: β = −0.03, $p > 0.5$).

Differences in cortical Aβ burden by APOE4 group in mid- and late-life

Additional models for the mid-life and late-life participants added a continuous BMI × *APOE4+* interaction term to the primary model (from Fig. 1) in order to evaluate if there is a differential effect of BMI in *APOE4* carriers versus non-carriers. This interaction term was not significant in the mid-life (β = 0.33, $p = 0.296$) or the late-life (β = 0.29, $p > 0.5$) groups (Fig. 4). As expected, age remained significant in both the mid-life (β = 0.50, $p = 0.035$) and late-life (β = 0.89, $p < 0.001$) models with the interaction term.

Differences in cortical Aβ burden by sex in mid- and late-life

Additional models for the mid-life and late-life participants added a continuous BMI × male interaction term to the primary model (from Fig. 1) in order to evaluate if there is a differential effect of BMI in males versus females. This interaction term was not significant in the mid-life (β = 0.64, $p = 0.13$) or the late-life (β = 0.50, $p = 0.43$) groups.

A summary of the additional analyses can be seen in Table 2.

Total hippocampal volume

We also ran a general linear regression model assessing the relationship between continuous BMI and total hippocampal volume. The models were adjusted for the same covariates as in the Aβ analysis. We found no relationship between continuous BMI and total hippocampal volume in either the mid-life (β = −11.99, $p = 0.46$). or late-life (β = 4.0, $p > 0.5$) groups.

DISCUSSION

A high percentage of adults in Western countries are overweight or obese, just as 61% of the total cohort in this study was overweight or obese. Trends indicate that the percentages of adults in these categories will only increase in coming years [54]. The rising prevalence of obesity has the potential to have important implications for the cognitive health of adults in different stages of life. Prior work suggested there might be a relationship between obesity and the risk for developing dementia. In our analyses, we examined whether a cross-sectional relationship existed between cortical Aβ burden, a biomarker reflective of AD pathophysiology, and BMI in both mid- and late-life cognitively normal individuals. We found that higher BMI was associated with lower cortical Aβ burden in late-life participants. Although prior epidemiological work suggests obesity increases the risk of AD [10, 11, 16], the current finding showing a *negative* relationship between BMI and Aβ burden is consistent with similar relationships found using similar cohorts [39, 40].

When examining BMI as a continuous variable we found that greater levels of BMI were associated with lower levels of Aβ burden. This pattern was present in the late-life, but not the mid-life cohort. Although some previous studies included individuals with mild cognitive impairment and mild AD dementia, we found that this relationship persists even in a large cohort that was limited to participants who were cognitively normal at baseline. This finding shows that BMI and cortical amyloid burden can be directly related, and it gives a platform for future work to elucidate whether the BMI-amyloid relationship is reflected by comorbid process or some causal mechanism. If an aspect of body composition can become a biomarker for AD, then identification of AD may be easier and expenditures may be minimized.

When examining BMI as a categorical variable (normal, overweight, and obese), we found that there was a significant difference in the mean cortical Aβ burden between BMI groups in late-life but not in mid-life. As seen with our analyses of BMI as a continuous variable, the relationship was such that the categories representing greater levels of obesity on average had less Aβ burden measured with PET. Prior work using a cognitively normal cohort or a mixed cognitively normal and impaired cohort has found effects of continuous levels of BMI within categories [39, 40]. We found that when dividing the late-life group into three distinct BMI categories (normal, overweight, and obese), the association between BMI and cortical Aβ burden was non-significant in each of these three groups. Thus, our results show that the differences in BMI within a restricted BMI range have less predictive power of cortical Aβ burden than the BMI range an individual falls within. This is unsurprising as classifying individuals into BMI groups constrains the range of BMI values, limiting the sensitivity as well as the interpretability of such analyses.

The results of this study support some of the findings from previous literature. Specifically, higher BMI in late-life is associated with lower pathology [40–44]. However, our study does not find evidence that higher BMI is associated with an increased risk of AD in mid-life participants. As evidenced by our BMI x age-group model, the effect of BMI on cortical amyloid burden differs by age group. One possible explanation for the non-significant finding in the mid-life group, as opposed to the significant finding in the late-life group, is

that the range of Centiloid values is much narrower for the mid-life group. With greater longitudinal data it may also be possible that mid-life obesity would later predict biomarkers in late-life.

We were also interested in whether the BMI-Aβ relationship is modified by the presence of an *APOE ε*4 allele or by sex. *APOE4* largely enhances Aβ pathology [55, 56] and is associated with greater rates of cognitive decline [57–60], so it is possible that being E4+ obscures any relationship between BMI and Aβ. Alternatively, secondary health factors may only exacerbate AD pathology in those with a predisposition toward elevated Aβ burden. There is also a suggestion that Aβ accumulation in E4+ individuals is moderated by leptin signaling in the hypothalamus and may in itself promote weight loss [61], such that the inverse relationship between BMI and Aβ may be stronger in E4+ individuals. However, we found no significant BMI by *APOE4* interactions in either mid-life or late-life, unlike a few previous studies [39, 61]. Additionally, we were interested in sex as a modifier of the BMI-Aβ relationship, as many studies have found sex differences in AD [62–64]. We did not find any significant BMI by sex interactions in either mid-life or late-life. Previous studies have shown differences in brain atrophy rates [62], cognitive decline [62, 63, 65], mortality [66], and CSF $A\beta_{1\text{-}42}$ [64] but not Aβ measured with PET [62], so our finding is unsurprising.

The inverse relationship of BMI-Aβ in late-life is counterintuitive to studies that have shown BMI is associated with adverse health outcomes [7, 8]. However, this “obesity paradox” also appears in AD and dementia. In 40–45 year olds, obesity has been shown to increase the risk of dementia later in life [21]. However, lower BMI in those aged over 65 is related to an increased risk of dementia, AD, and vascular dementia [10]. Higher late-life BMI is also indicative of good health status [18], reduced risk of dementia [19], and better cognitive performance [20]. The results of our study support one component of the “obesity paradox” in AD. Specifically, that higher BMI in late-life is associated with lower pathology, as other studies have shown [40–44]. However, our study does not support the other component of the “obesity paradox” because we did not find that higher BMI is associated with an increased risk of AD in mid-life participants. This relationship should be explored in a larger sample of mid-life participants with longitudinal AD pathology data to show the effects of an increasing BMI or sustained high BMI over time. This may shed light on the relationship between a higher BMI and an increased risk of AD in mid-life as reported by various studies [21, 67, 68] and the possibility that the predictive ability of BMI changes over time.

This study has several limitations. Firstly, BMI is a nonspecific measure of body composition and may not accurately reflect the amount and distribution of body fat [27, 69, 70]. Because the location of adipose tissue has been shown to be important in predicting dementia risk [70], a more specific measure of adiposity (e.g., waist circumference, percent body fat, and skinfold thickness) may have better predictive ability of AD risk. In addition, there is a greater misclassification inherent in BMI at mid-life in comparison to late-life [11]. The variation of adiposity in an individual throughout life stages warrants a more accurate measurement of adiposity that can be used in future studies relating BMI and AD pathology.

Our study did not assess the relationship between BMI and Aβ over time. As obesity represents a chronic condition, it may be necessary to examine the relationship between obesity and AD pathology over the course of decades. Such analyses would also be able to take into account common weight declines that occur before clinical AD onset [71]. Additionally, a longitudinal analysis could shed light on the association between BMI and rate of Aβ accumulation. We would also be able to assess if mid-life obesity predicts AD or dementia in late-life, as indicated by other studies [21, 67, 68]. The limitations of our data indicate that our results should not be interpreted as evidence for a temporal or causal relationship between BMI and Aβ.

It is also possible that BMI is related to other biomarkers (e.g., CSF Aβ, total tau, p-tau, tau PET, [^{18}F]-fluorodeoxyglucose PET, and structural MR). It would be worthwhile to see if lower late-life BMI is associated not only with an elevated Aβ burden but also a greater rate of tau accumulation or neurodegeneration after AD onset. Future studies should investigate the relationship between BMI and these other biomarkers in an effort to isolate the associations between BMI, AD risk, and pathology after AD onset. Finally, any group of individuals who agree to participate in longitudinal studies in which molecular biomarkers of AD are obtained are not representative of the population from which they are recruited, so our results may not be generalizable.

Our study also had a number of strengths. Our sample of CN adults at baseline was large, especially for the late-life group. The primary models accounted for multiple demographic variables and the primary genetic risk factor for sporadic AD—*APOE* genotype. Additionally, we were able to investigate the relationship of continuous BMI and cortical Aβ in BMI and *APOE4* subdivisions. Furthermore, we were to directly relate a high Aβ burden, a marker of increased dementia risk, directly with BMI in cognitively normal elderly. Future studies will be able to use this baseline data and harmonize with other databases that have been successfully enrolling cognitively normal participants at baseline and tracking multiple AD biomarkers in these same participants over time.

Ultimately, exploring the relationship between BMI and AD biomarkers is important to better quantify risk of progressing to symptomatic stages of AD. The results from our study reinforce the need to monitor unintentional weight loss closely in older adults. Future studies should investigate the longitudinal association between adiposity and Aβ and examine whether the association between BMI and AD is mediated by possible confounding factors, like cardiovascular health, diabetes, and other disease conditions.

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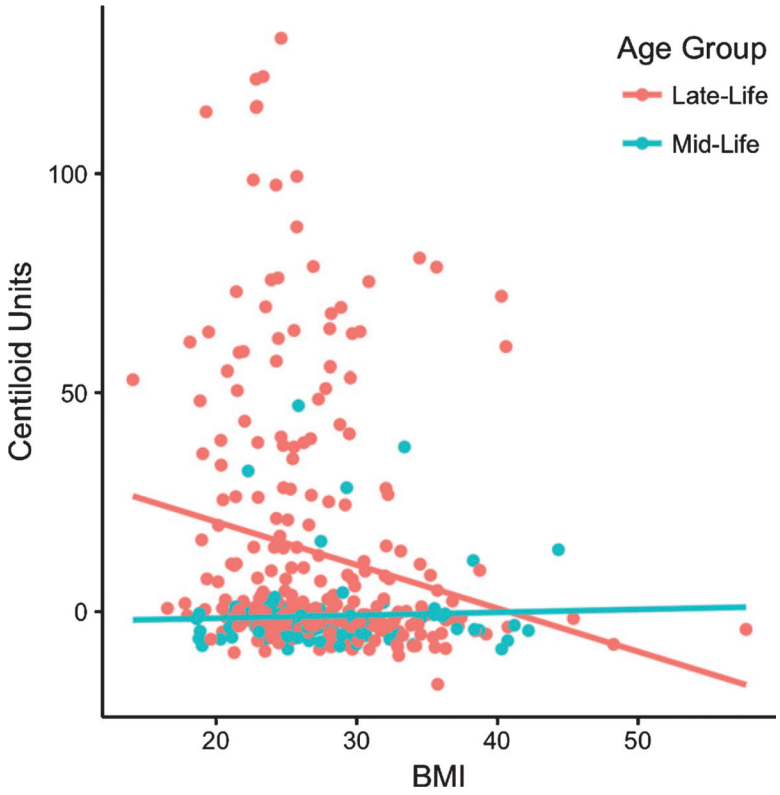

Fig. 1.

Scatter plot of BMI and cortical Aβ burden by age group. The scatter plot reflects raw values for ease of interpretation. Late-life participants are dark circles, and mid-life participants are grey triangles. Lines of best fit are also shown.

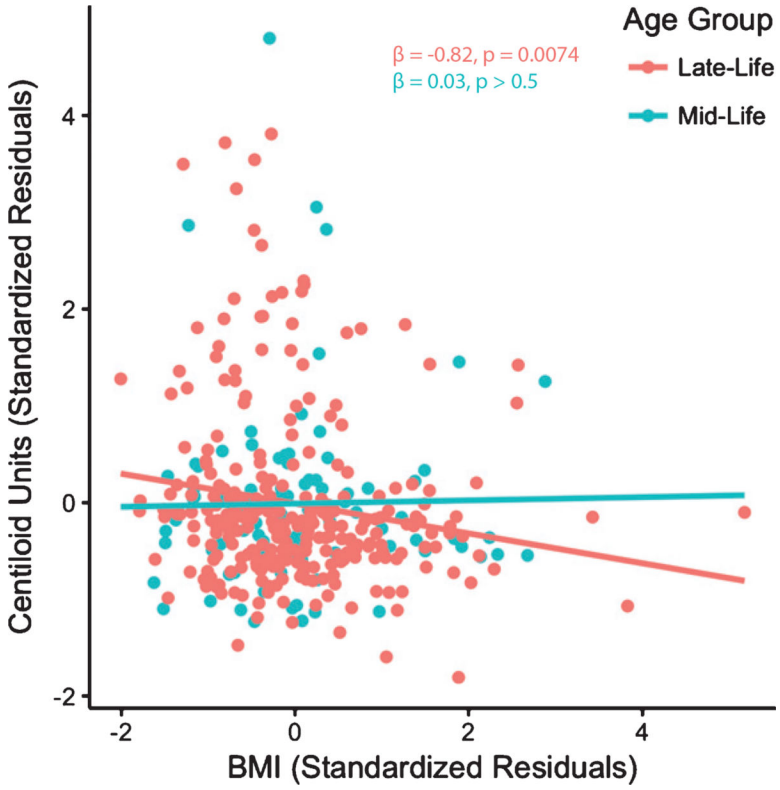

Fig. 2.

Partial regression plot from primary analysis of BMI and cortical Aβ burden (as measured in Centiloid units) in mid- and late-life individuals. The model was adjusted for age, sex, years of education, and APOE4 carrier status. Standardized residuals for Centiloid units were calculated after regressing cortical Aβ burden against all the independent variables except BMI while standardized residuals for BMI were calculated after regressing BMI against the remaining independent variables. BMI was significant in the late-life model but not the mid-life model. These results remained the same even after exclusion of the four individuals with highest BMI.

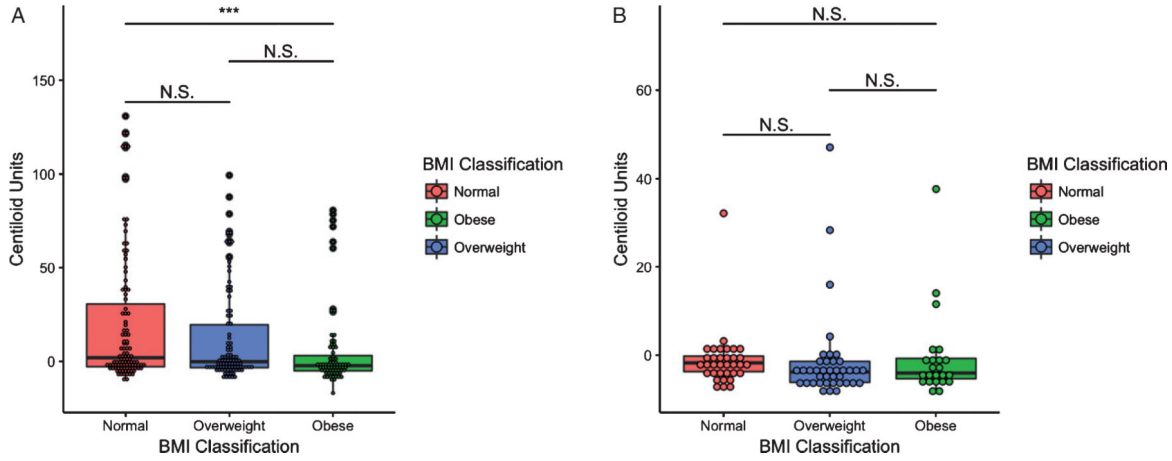

Fig. 3.

Boxplots of the distributions of cortical Aβ burden in each of the three BMI groups in late-life (A) and mid-life (B) individuals. Pairwise comparisons are denoted as N.S. $p > 0.05$ and ***$p < 0.001$.

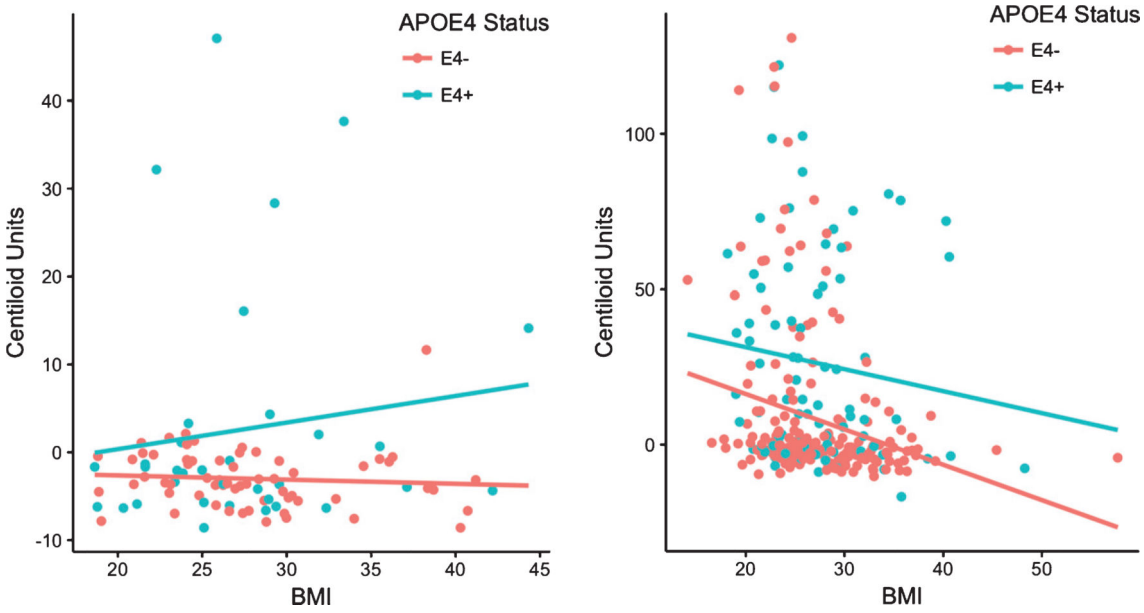

Fig. 4.

Scatterplot of BMI and cortical Aβ burden within APOE4 subdivisions in mid-life (A) and late-life (B). The scatter plots reflect raw values for ease of interpretation. E4 non-carriers are black circles, and E4 carriers are grey triangles. Lines of best fit are also shown. The BMI × APOE4 interaction term was not significant in the mid-life (β = 0.33, $p = 0.296$) or the late-life (β = 0.29, $p > 0.5$) groups.

Table 1

Demographics of Mid-Life and Late-life Knight ADRC cohorts with Aβ PET

Characteristic	Mid-Life	Late-life
N	96	277
Age: mean (range)	53.5 (45–60)	71.4 (61–100)
Sex (% female)	72.9%	59.9%
Years of Education: mean (range)	16.3 (6–24)	15.8 (8–24)
APOE4 Status (% carriers)	35.4%	28.5%
Body Mass Index	27.7 (18.6–44.3)	27.5 (14.1–58.7)
Underweight (BMI <18.5)	0.0 % (*n* = 0)	1.8% (*n* = 5)
Normal (BMI 18.5 – 24.9)	35.5% (*n* = 34)	38.6% (*n* = 107)
Overweight (BMI 25 – 29.9)	40.6% (*n* = 39)	33.6% (*n* = 93)
Obese (BMI >30)	24.0% (*n* = 23)	26.0% (*n* = 72)
Centiloid value: mean(range)	−0.96 (−8.5 – 47.1)	13.5 (−16.6 – 131.05)
MMSE score: mean (standard deviation)	28.9 (4.3)	28 (2.2)
CDR-SOB: mean (standard deviation)	0.0053 (0.052)	0.033 (0.15)

MMSE, Mini-Mental State Examination; CDR-SOB, Clinical Dementia Rating Sum of Boxes.

Table 2

Summary of additional analyses. All models adjusted for age (or age-group), sex, years of education, and APOE4 status

Model	Term	β	*p*
BMI × Age-Group Model	BMI × Age-Group	–	**0.0309**
BMI Subdivision Model (Late-life)	Normal BMI	–	–
	Overweight BMI	−7.7	**0.0499**
	Obese BMI	−12.4	**0.0033**
BMI × *APOE4* Models	BMI × *APOE4+* (late-life)	0.29	>0.5
	BMI × *APOE4+* (mid-life)	0.33	0.296
BMI × Sex Models	BMI × male (late-life)	0.50	0.43
	BMI × male (mid-life)	0.64	0.13