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Body Mass Index Decrease Has a Distinct Association with Alzheimer's Disease Pathophysiology in *APOE* ε4 Carriers and Non-Carriers

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Abstract.
Background: Body mass index (BMI) changes may be related to Alzheimer's disease (AD) alterations, but it is unclear how the apolipoprotein E ε4 (*APOE* ε4) allele affects their association.
Objective: To explore the association of BMI changes with AD pathologies in *APOE* ε4 carriers and non-carriers.
Methods: In 862 non-demented ADNI participants with ≥ 2 BMI measurements, we investigated the relationships between BMI slopes and longitudinal changes in amyloid-β (Aβ) accumulation, neurodegeneration and cognition, and follow-up tau deposition in different Aβ and *APOE* ε4 statuses.
Results: In Aβ+ *APOE* ε4 non-carriers, faster BMI declines were associated with faster rates of Aβ accumulation (standardized β (β_{std}) = –0.29, $p = 0.001$), AD meta regions of interest (metaROI) hypometabolism ($\beta_{std} = 0.23$, $p = 0.026$), memory declines ($\beta_{std} = 0.17$, $p = 0.029$), executive function declines ($\beta_{std} = 0.19$, $p = 0.011$), and marginally faster Temporal-metaROI cortical thinning ($\beta_{std} = 0.15$, $p = 0.067$) and higher follow-up Temporal-metaROI tau deposition ($\beta_{std} = –0.17$, $p = 0.059$). Among Aβ- individuals, faster BMI decreases were related to faster Aβ accumulation ($\beta_{std} = –0.25$, $p = 0.023$) in *APOE* ε4 carriers, whereas predicted faster declines in memory and executive function in both *APOE* ε4 carriers ($\beta_{std} = 0.25$, $p = 0.008$; $\beta_{std} = 0.32$, $p = 0.001$) and *APOE* ε4 non-carriers ($\beta_{std} = 0.11$, $p = 0.030$; $\beta_{std} = 0.12$, $p = 0.026$).
Conclusions: This study highlights the significance of tracking BMI data in older adults by providing novel insights into how body weight fluctuations and *APOE* ε4 interact with AD pathology and cognitive decline.

Keywords: Alzheimer's disease, apolipoprotein E ε4, body mass index, cognitive decline, neurodegeneration

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). 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 listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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INTRODUCTION

More than 11% of individuals aged 65 and older have dementia, and Alzheimer's disease (AD) accounts for 60–80% of all dementia patients [1]. Amyloid-β (Aβ) deposition and neurofibrillary tau tangles are the key hallmarks of AD [2], which can be measured *in vivo* by positron emission tomography (PET) imaging [3, 4]. Low body mass index (BMI) in older adults may hasten the development of AD [5–7]. Previous studies have reported that older adults with lower BMI had more Aβ pathology [8–11], tau deposition [11], and neurodegeneration [11–14]. Body weight changes may be more helpful in studying weight-related AD alterations than cross-sectional body weight data [15], and recent studies [15–18] identified a significant association between BMI changes and abnormal alterations of Aβ, tau, and cognition, especially in the amyloid positive group.

ApoE is a major apolipoprotein with a primary function in mediating lipid/cholesterol transport in the periphery and brain. The ε4 allele is the strongest genetic risk factor for late-onset AD, dominantly driving amyloid pathology in a gene dose-dependent manner. The ε2 allele is protective only in the absence of an ε4 allele [19, 20]. Previous studies [9, 21–26] suggested that the *APOE* ε4 allele and obesity may be related to the pathological changes of AD in an interacting manner. However, it is still not fully understood how *APOE* ε4 allele modulates the relationships of BMI changes with longitudinal Aβ accumulation, tau, aggregation, neurodegeneration, and cognitive decline in Aβ negative (Aβ–) and Aβ positive (Aβ+) older adults. By analyzing how the *APOE* ε4 allele and BMI changes interact to influence the course of AD in older adults, we can better understand the clinical significance of body weight changes in *APOE* ε4 carriers and non-carriers with and without significant Aβ pathology.

In this study, we analyzed non-demented Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with longitudinal BMI, Aβ PET, ^{18}F-fluorodeoxyglucose (FDG) PET, structural magnetic resonance imaging (MRI), and cognitive assessments as well as follow-up tau PET to determine whether: 1) BMI changes are associated with aggregation of cortical Aβ and tau, cortical thickness decline, hypometabolism and cognitive decline in Aβ– and Aβ+ older adults; 2) BMI changes-induced abnormal increases of AD pathologies are modulated by *APOE* ε4 allele; 3) BMI changes have distinct effects on AD progression among individuals with normal weight, overweight, and obese BMI at baseline. The ultimate goal is to provide a significant reference for monitoring BMI data in older adults with and without the *APOE* ε4 allele.

METHODS

Participants

The data were obtained from the ADNI database (http://ida.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The diagnosis criteria of ADNI participants can be found on the ADNI website (http://ida.loni.usc.edu). The ADNI study was approved by institutional review boards of all participating centers, and written informed consent was obtained from all participants or their authorized representatives.

In this study, we focused on the association of BMI changes and *APOE* ε4 with AD progression in senior older adults and late-onset AD patients. Thus, we identified 417 cognitively unimpaired (CU) and 445 MCI participants whose ages were not less than 65 years and with *APOE* ε4 genotype, Aβ PET scan, and at least two BMI measurements. Part of them had longitudinal Aβ PET scans, FDG PET scans, MRI scans, cognitive assessments, and follow-up tau PET scans measured at around 5.5 years post-baseline Aβ PET scan.

PET imaging processing

Four × 5-min frames of ^{18}F-florbetapir (FBP) Aβ PET data, six × 5-min frames of ^{18}F-flortaucipir (FTP) Tau PET data, and six × 5-min frames of FDG PET data were acquired from 50–70 min, 75–105 min, 30–60 min post-injection, and more details are given elsewhere (http://adni-info.org). Aβ PET image was coregistered to their corresponding structural MRI scan that was closest in time to the Aβ PET scan. FreeSurfer (V7.1.0) was used to extract cortical florbetapir uptake in 68 FreeSurfer-defined ROIs defined by the Desikan-Killiany atlas [27]. Aβ PET standardized uptake value ratios (SUVRs) of 68 ROIs were calculated by referring regional florbetapir

to that found in the whole cerebellum. A cortical summary COMPOSITE FBP SUVR was created from a COMPOSITE cortical area (including frontal, cingulate, parietal, and temporal regions) [28]. Aβ+ was defined as COMPOSITE FBP SUVR ≥ 1.11, as we described previously [29]. Considering a composite reference region (made up of brainstem, whole cerebellum, and eroded white matter) showing less variance in longitudinal analyses [28], we calculated longitudinal Aβ PET slope by using SUVRs that referred to the composite reference region.

Tau PET image was coregistered to their corresponding structural MRI scan that was closest in time to the baseline tau PET scan. FTP SUVR was calculated by referring regional FTP uptake to that measured in inferior cerebellar gray matter uptake [30]. FTP SUVRs in 68 FreeSurfer-defined cortical ROIs were extracted from coregistered FTP PET images in MRI space. FTP SUVR in one composite Temporal-metaROI [31] (including the entorhinal, parahippocampal, fusiform, amygdala, inferior temporal, and middle temporal cortical regions) was calculated to represent cortical tau deposition.

FDG images were spatially normalized in SPM12 to the MNI PET template. FDG SUVR in a predefined MetaROIs (made up of left angular gyrus, right angular gyrus, bilateral posterior cingulate, left inferior temporal gyrus, and right inferior temporal gyrus) were calculated by normalizing averaging FDG counts in MetaROIs to that found in the upper 50% of voxels in a pons/vermis reference region [32].

MRI processing

Structural MRI images were acquired using Siemens, GE, or Philips MRI scanners according to a standard protocol [33], and more details can be found elsewhere (http://adni-info.org). The most fully pre-processed MRI images were downloaded from the LONI website (http://ida.loni.usc.edu). Cortical thicknesses of 68 FreeSurfer-defined ROIs were calculated from the structural MRI scan via FreeSurfer. Cortical thickness in one composite Temporal-metaROI [31] was calculated to represent cortical thickness.

Cognition

Previously validated memory and executive function composite scores derived from ADNI neuropsychological battery were used to represent cognition in this study [34, 35]. Specifically, the Rey Auditory Verbal Learning Test, the word list learning and recognition components of Alzheimer's Disease Assessment Scale–Cognitive Subscale, the word recall items from the Mini-Mental State Examination, and Logical Memory I from the Wechsler Memory Test–Revised were transferred to standard z scores and combined into one composite memory score. Similarly, the executive function composite score was calculated by combing the Category Fluency–animals, Category Fluency–vegetables, Trails A and B, Digit span backwards, WAIS-R Digit Symbol Substitution, and 5 Clock Drawing items (circle, symbol, numbers, hands, time) as described previously [36] and also in ADNI website (http://ida.loni.usc.edu).

Statistical analysis

Statistical analyses were performed in the statistical program R (v4.0.4, The R Foundation for Statistical Computing) unless otherwise noted. The normality of data distribution was assessed using the Shapiro-Wilk test. Data were presented as median (interquartile range [IQR]) or number (%) unless otherwise noted. The baseline characteristics of different groups were compared using a two-tailed Mann-Whitney or Fisher's exact test. Slopes of BMI (ΔBMI), Aβ PET (ΔAβ PET), FDG PET (ΔFDG PET), Cortical thickness (ΔCortical thickness), memory score (ΔMemory), and executive function score (ΔExecutive function) were estimated based on longitudinal data using linear mixed effects model (lme4 package) over time, including a random slope and intercept for each participant: Biomarker $\sim$ Time + (1 + Time|Subject). Notably, the biomarker in the equation above indicates those variables used for slope calculation.

To determine the associations of BMI changes (ΔBMI) with AD pathologies and cognitive decline in different Aβ PET and *APOE* ε4 statuses, we first used a generalized linear model (GLM) to study how ΔBMI relates to longitudinal changes of Aβ PET (ΔAβ PET). Second, we determined the association between ΔBMI and follow-up Temporal-metaROI Tau PET levels measured at around a median of 5.5 years follow-up post-baseline Aβ PET scan using the GLM model. Notably, to rectify the data's non-normal distribution, we used a "log" link function from the Gaussian family in GLM models for the Temporal-metaROI Tau PET. Third, we also explored the associations of ΔBMI with longitudinal changes of FDG SUVR (ΔFDG PET), cortical thick-

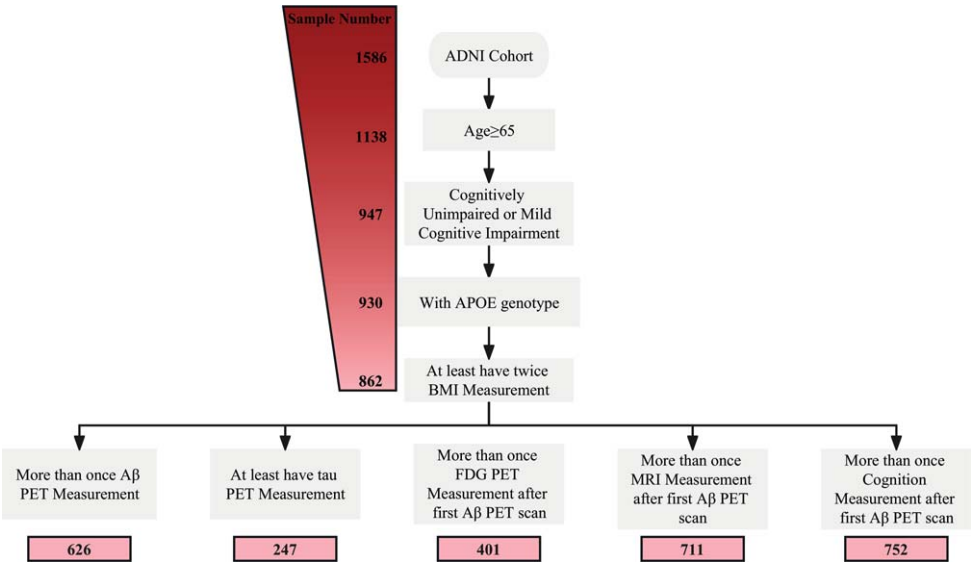

Fig. 1. The inclusion criteria of participants in this study. Only non-demented participants whose ages were not less than 65 years and with *APOE* ε4 genotype and at least two BMI measurements were recruited in this study. Part of them had longitudinal Aβ PET scans, FDG PET scans, MRI scans, cognitive assessments, and follow-up tau PET scans measured at around 5.5 years post-baseline Aβ PET scan.

ness (ΔCortical thickness), memory (Δmemory), and executive function (ΔExecutive function) using GLM models. We did these analyses in different Aβ PET (Aβ±) and *APOE* ε4 statuses (*APOE* ε4±) separately, controlling for age, sex, and diagnosis. We also included the duration of education as a covariate as we investigated cognitive changes. The equation of GLM model was as follow: ΔBiomarker ~ ΔBMI + Baseline Biomarker + Age + Sex + Diagnose, where Biomarker indicates the variables of images and cognitive scores used in GLM models as we described above.

Since we found that ΔBMI was significantly associated with ΔAβ PET, ΔFDG PET, ΔMemory, and ΔExecutive function in Aβ+ *APOE* ε4 non-carriers (see Figs. 2C, 3C, 4C, and 4D in Results), and marginally related to ΔCortical thickness and follow-up Tau PET (See Fig. 2D and 3D in Results), thus we further investigated whether these relationships differ among various BMI statuses (normal/overweight/obese) at baseline in Aβ+ *APOE* ε4 non-carriers.

RESULTS

Demographics

The characteristics of the 862 participants included in this study can be found in Table 1. In the cohort, 51.6% and 36.9% of participants were MCI and *APOE* ε4 carriers, respectively. Aβ+ individuals had older ages (estimate = 1.8 [95% confidence interval (CI), 1.0–2.7], $p < 0.001$), and larger prevalence of *APOE* ε4 carriers (odds ratio = 5.9 [95% CI, 4.3–8.1], $p < 0.001$) than Aβ- individuals. Longitudinally, 626, 401, 711, and 752 participants had ≥ 2 Aβ PET scans, FDG PET scans, MRI scans, and cognitive assessments, respectively. Additionally, 247 participants had a follow-up tau PET scan measured at a median of 5.5 years (IQR, 1.8; range, 4.0–9.8) post baseline Aβ PET scan.

Association between BMI changes and longitudinal Aβ accumulation

In Aβ − individuals, faster BMI decreases were related to steeper Aβ PET SUVR increases in *APOE* ε4 carriers (Fig. 2A, $\beta_{std} = -0.25$[95% CI, –0.46, –0.03], $p = 0.023$) but not in *APOE* ε4 non-carriers. In contrast, faster BMI decreases were associated with more rapid longitudinal Aβ accumulation in Aβ+ *APOE* ε4 non-carriers (Fig. 2C, $\beta_{std} = -0.29$[95% CI, –0.46, –0.11], $p = 0.001$) but not in *APOE* ε4 carriers.

Association between longitudinal BMI changes and follow-up tau deposition

Regarding the cortical tau deposition, we noticed that faster BMI decreases were marginally related to higher follow-up FTP SUVR (Fig. 2D,

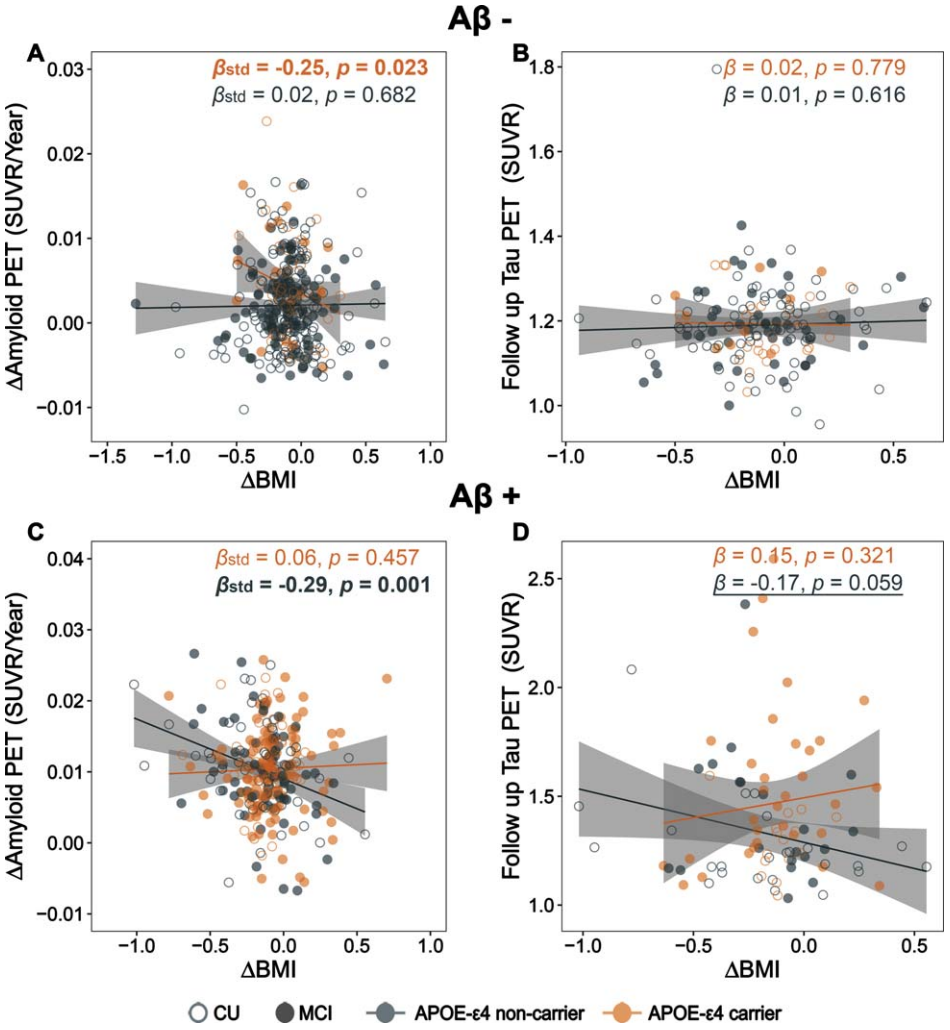

Fig. 2. Association of longitudinal BMI changes with longitudinal Aβ accumulation and follow-up tau deposition. Association of BMI change rates (ΔBMI) with (A, C) rates of Aβ accumulation (ΔAβ PET, SUVR/Year) in COMPOSITE region and (B, D) follow-up Temporal-MetaROI tau deposition in Aβ– and Aβ+ participants. The estimate (β) in (B, D) is not standard because we used a "log" link function from the Gaussian family in GLM models for the Temporal-metaROI Tau PET. Aβ, amyloid-β; BMI, body mass index; CU, cognitively unimpaired; MCI, mild cognitive impairment.

$\beta = -0.17$[95% CI, –0.35, 0.01], $p = 0.059$) in Aβ+ *APOE* ε4 non-carriers but not in *APOE* ε4 carriers. However, independent of *APOE* ε4 status, there was no correlation between ΔBMI and follow-up tau deposition in Aβ- individuals.

Association between BMI changes and longitudinal neurodegeneration

Only in Aβ+ *APOE* ε4 non-carriers did we find a significant or weak positive correlation between ΔBMI and ΔmetaROIs FDG SUVR (Fig. 3C, $\beta_{std} = 0.23$[95% CI, 0.03, 0.43], $p = 0.026$) and ΔTemporal-metaROI cortical thickness (Fig. 3D, $\beta_{std} = 0.15$[95% CI, –0.01, 0.32], $p = 0.067$).

Prediction of longitudinal cognitive decline

In Aβ+ individuals, faster BMI decreases were related to more rapid declines in memory (Fig. 4C, $\beta_{std} = 0.17$[95% CI, 0.02, 0.31], $p = 0.029$) and executive function (Fig. 4D, $\beta_{std} = 0.19$[95% CI, 0.04, 0.34], $p = 0.011$) in *APOE* ε4 non-carriers but not in *APOE* ε4 carriers. Among Aβ − individuals, faster BMI decreases-associated memory and executive function declines were found in both *APOE* ε4

Table 1
Demographics of participants in this study

	Aβ-/*APOE* ε 4−	Aβ-/*APOE* ε4+	Aβ+/*APOE* ε 4−	Aβ+/*APOE* ε4+
Sample size	369	84	175	234
MCI (No., %)	151 (40.9)	28 (33.3)	97 (55.4)[bd]	169 (72.2)[cef]
Age (median (IQR))	74.4 (9.4)	71.6 (7.8)[a]	77.8 (9.0)[bd]	74.6 (8.1)[ef]
Education (median (IQR))	17 (3)	16 (4)[a]	16 (4)[b]	16 (4)[c]
Females (N, %)	168 (45.5)	41 (48.8)	88 (50.3)	107 (45.7)
Aβ PET SUVR (median (IQR))	1.01 (0.07)	1.03 (0.10)[a]	1.28 (0.26)[bd]	1.38 (0.26)[cef]
Temporal-metaROI cortical thickness (mm) (median (IQR))	2.71 (0.19)	2.71 (0.20)	2.65 (0.22)[bd]	2.65 (0.25)[ce]
FDG SUVR (median (IQR))	1.30 (0.13)	1.29 (0.15)	1.27 (0.16)[b]	1.23 (0.19)[cef]
Memory (median (IQR))	0.86 (0.86)	0.80 (0.77)	0.51 (1.01)[bd]	0.30 (0.98)[cef]
Executive function (median (IQR))	0.74 (1.14)	0.65 (1.13)	0.32 (1.05)[bd]	0.16 (1.05)[ce]
Longitudinal Aβ PET ($n = 626$, duration of years: 4.1 (4.4, 0.9–9.3), scans: 3 (2, 2–6))				
Sample size	280	65	118	163
Duration, year (Median (IQR, range))	4.3 (4.9, 0.9–9.3)	5.8 (3.1, 1.9–9.0)	4.1 (4.0, 1.8–8.6)[bd]	4.0 (3.2, 1.8–9.1)[ce]
No. of scans (Median (IQR, range))	3 (2, 2–6)	3 (2, 2–5)	3 (2, 2–5)[bd]	3 (1, 2–5)[ce]
Tau PET measured at 5.5 years' post baseline Aβ PET ($n = 247$, duration of years: 5.5 (1.8, 4.0–9.8))				
Sample size	120	36	44	47
Interval from baseline Aβ PET scan, Years, Median (IQR, Range)	5.7 (1.7, 4.0–9.8)	5.1 (1.5, 4.0–9.4)	5.4 (1.8, 4.0–7.7)	5.2 (1.8, 4.0–8.1)
Longitudinal FDG PET ($n = 401$, duration of years: 2.0 (1.1, 0.8–8.1), scans: 2 (0, 2–4))				
Sample size	182	38	81	100
Duration, year (Median (IQR, range))	2.0 (0.3, 0.8–8.1)	2.0 (2.3, 1.5–6.8)	2.0 (2.5, 1.8–7.7)	2.0 (3.0, 1.7–7.5)
No. of scans (Median (IQR, range))	2 (0, 2–4)	2 (0, 2–3)	2 (0, 2–3)	2 (0, 2–3)
Longitudinal MRI ($n = 711$, duration of years: 4.0 (4.2, 0.3–9.2), scans: 5 (2, 2–10))				
Sample size	301	73	144	193
Duration, year (Median (IQR, range))	4.1 (4.6, 0.3–9.1)	4.9 (4.7, 0.8–9.2)	4.0 (3.9, 0.6–8.6)[bd]	3.0 (3.0, 0.5–9.0)[ce]
No. of scans (Median (IQR, range))	5 (3, 2–10)	5 (2, 2–9)	5 (2, 2–10)	5 (2, 2–9)
Longitudinal Cognition ($n = 752$, duration of years: 4.2 (4.5, 0.5–10.0), visits: 6 (3, 2–11))				
Sample size	309	77	155	211
Duration, year (Median (IQR, range))	5.1 (4.3, 0.9–10.0)	5.3 (4.1, 1.0–9.9)	4.1 (3.1, 0.9–9.5)[b]	4.0 (3.2, 0.5–9.8)[cef]
No. of tests (Median (IQR, range))	6 (3, 2–11)	6 (2, 3–11)	5 (3, 2–11)	5 (4, 2–11)[c]

Significantly different from [abc]Aβ − and *APOE* ε4 non-carriers, [de]Aβ − and *APOE* ε4 carriers, [f]Aβ+ and *APOE* ε4 non-carriers, $p < 0.05$, Mann-Whitney test and Fisher's exact test. Aβ, amyloid-β; BMI, body mass index; FDG, ^{18}F-fluorodeoxyglucose; IQR, interquartile range; MCI, mild cognitive impairment.

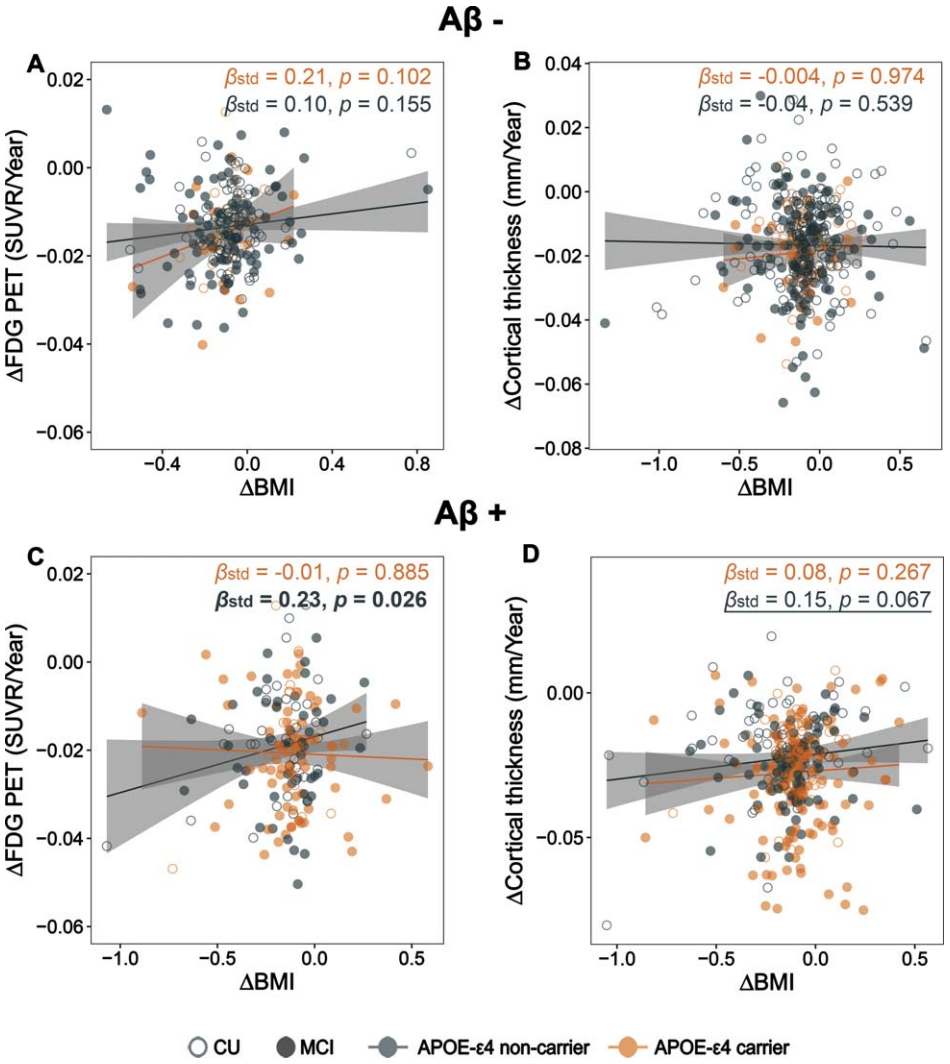

Fig. 3. Association of longitudinal BMI changes with longitudinal hypometabolism and Cortical thinning. Association of BMI rates (ΔBMI) with (A, C) metaROIs hypometabolism rates (ΔFDG PET, SUVR/Year) and Temporal-MetaROI cortical thinning rates (ΔCortical thickness, mm/Year) in Aβ– and Aβ+ older adults. Aβ, amyloid-β; BMI, body mass index; FDG, ^{18}F-fluorodeoxyglucose; CU, cognitively unimpaired; MCI, mild cognitive impairment.

carriers (Fig. 4A, $\beta_{std} = 0.25$[95% CI, 0.06, 0.43], $p = 0.008$; Fig. 4B, $\beta_{std} = 0.32$[95% CI, 0.13, 0.52], $p = 0.001$) and *APOE* ε4 non-carriers (Fig. 4A, $\beta_{std} = 0.11$[95% CI, 0.01, 0.22], $p = 0.030$; Fig. 4B, $\beta_{std} = 0.12$[95% CI, 0.01, 0.22], $p = 0.026$).

Associations of BMI changes with AD biomarkers in different baseline BMI status

We ultimately determined whether these relations vary among Aβ+ *APOE* ε4 non-carriers individuals with different baseline BMI statuses (normal/overweight/obese). We found that faster BMI decreases were linked to more rapid Aβ accumulation (Fig. 5A, $\beta_{std} = –0.44$[95% CI, –0.76, –0.12], $p = 0.006$), AD metaROIs hypometabolism (Fig. 5C, $\beta_{std} = 0.60$[95% CI, 0.23, 0.97], $p = 0.002$), Temporal-metaROI cortical thinning (Fig. 5D, $\beta_{std} = 0.36$[95% CI, 0.04, 0.67], $p = 0.025$) in normal BMI group but not in overweight and obese groups of Aβ+ *APOE* ε4 non-carriers. Additionally, we found faster BMI decreases were related to higher follow-up cortical tau deposition (Fig. 5B, $\beta = –0.78$[95% CI, –1.25, –0.31], $p = 0.001$) and faster executive function declines (Fig. 5F, $\beta_{std} = 0.36$[95% CI, 0.12, 0.60], $p = 0.003$) in the overweight group but not in nor-

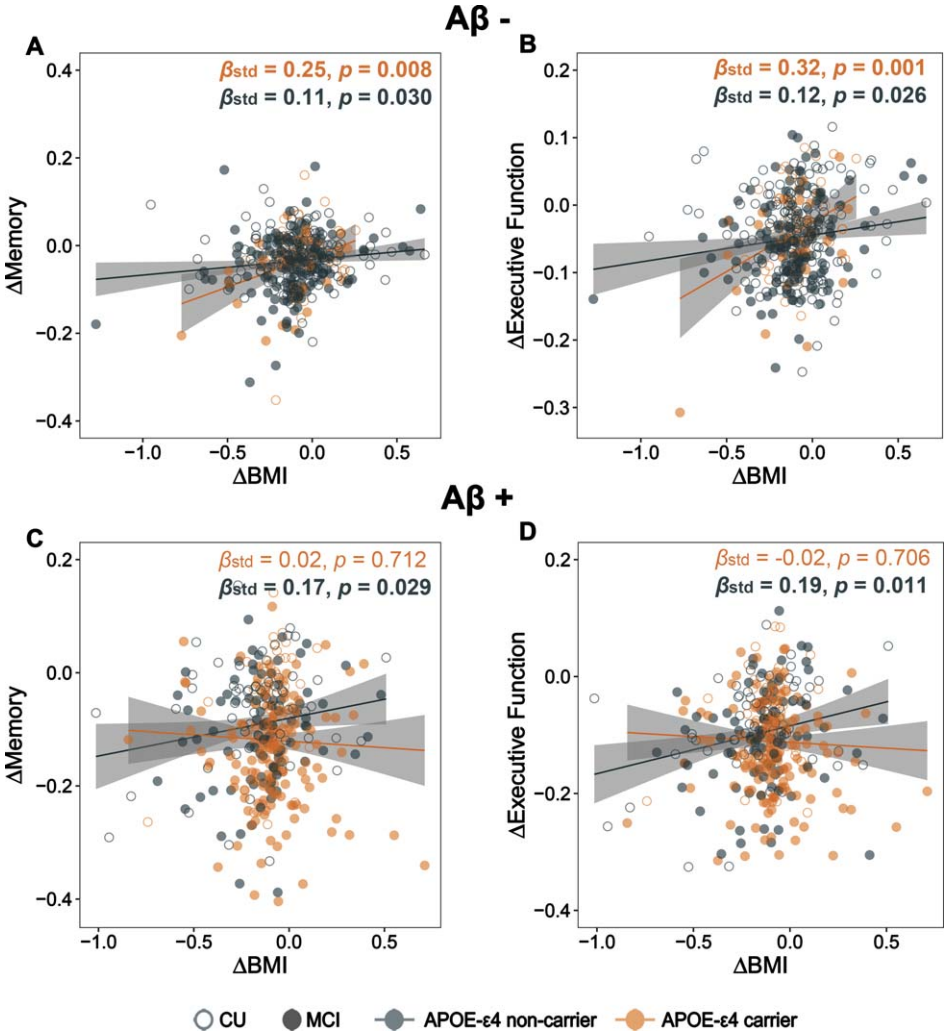

Fig. 4. Association of longitudinal BMI changes and longitudinal cognitive decline. Association of BMI rates (ΔBMI) with (A, C) memory changes (ΔMemory) and (B, D) executive function changes (ΔExecutive function) in Aβ– and Aβ+ older adults. Aβ, amyloid-β; BMI, body mass index; CU, cognitively unimpaired; MCI, mild cognitive impairment.

mal and obese groups. We also found faster BMI decreases were marginally related to higher follow-up cortical tau deposition (Fig. 5B, $\beta = -0.18$[95% CI, –0.38, 0.03], $p = 0.083$) and faster memory declines (Fig. 5E, $\beta_{std} = 0.29$[95% CI, –0.02, 0.60], $p = 0.065$) in normal groups.

DISCUSSION

In this study, we employed longitudinal imaging data to examine how the *APOE* ε4 genotype modifies the relationships between BMI declines and longitudinal changes in Aβ, tau, neurodegeneration, and cognitive decline in non-demented older adults. This demonstrated that faster BMI declines was significantly associated with faster rates of Aβ accumulation, AD typical hypometabolism, memory decline, executive function decline over time, more significant follow-up tau deposition, and faster longitudinal temporal-metaROI cortical thinning in Aβ+ *APOE* ε4 non-carriers (Fig. 6). Among Aβ+ *APOE* ε4 non-carriers with varying initial BMI status, we also discovered that the associations of BMI declines with AD pathologies and cognitive declines were primarily seen in persons whose body weights were normal or overweight at baseline. Regardless of *APOE* ε4 status, faster BMI declines were strongly linked to speedier memory and executive function decrease in Aβ − individuals. These findings may offer novel insights into the relationship between

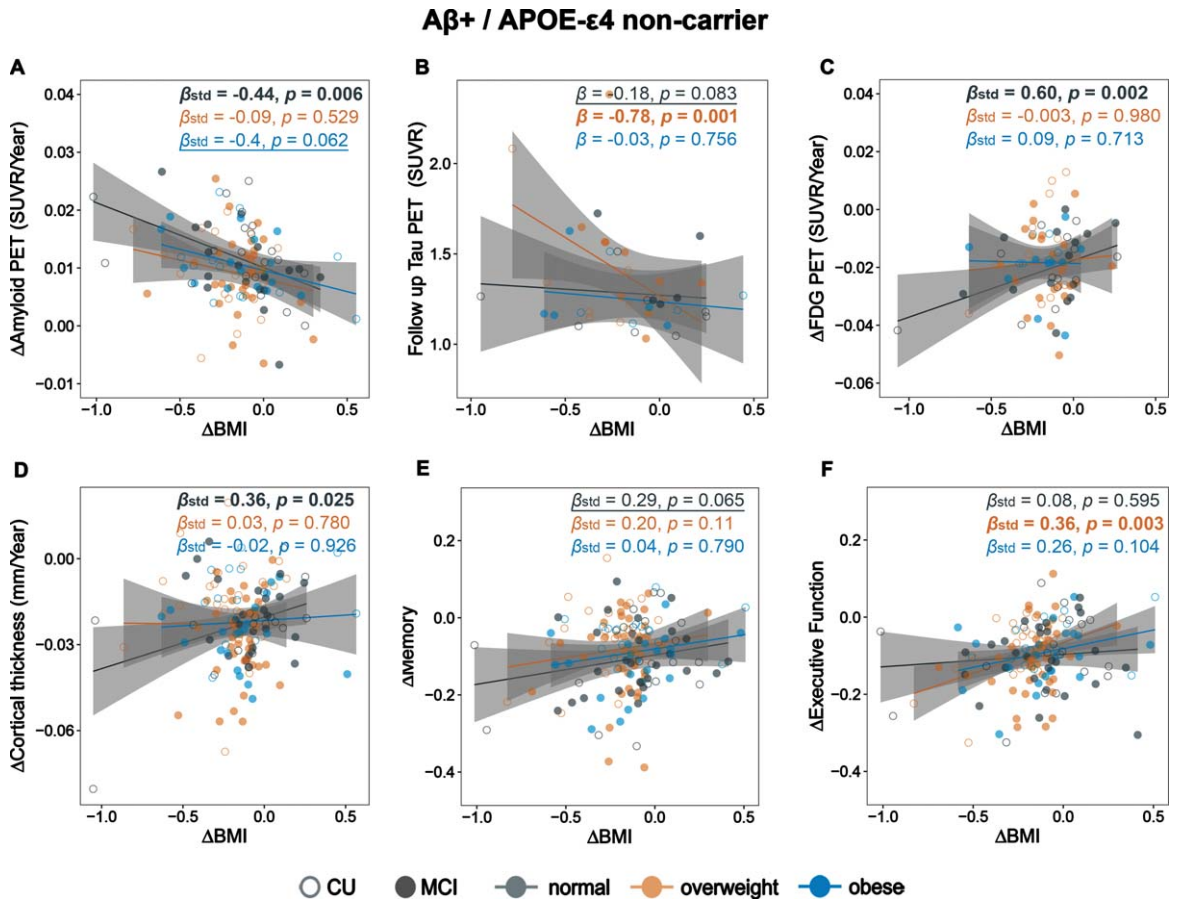

Fig. 5. Association of longitudinal BMI changes with Alzheimer's disease pathologies and cognitive changes in Aβ+ *APOE* ε4 non-carriers with different baseline BMI statuses. Association of BMI rates (ΔBMI) with (A) Aβ accumulation rates (ΔAβ PET, SUVR/Year), (B) follow-up Temporal-MetaROI tau deposition (SUVR), (C) metaROIs hypometabolism rates (ΔFDG PET, SUVR/Year), (D) Temporal-MetaROI cortical thinning rates (ΔCortical thickness, mm/Year), (E) memory changes (ΔMemory), and (F) executive function changes (ΔExecutive function) in normal, overweight, obese groups among Aβ+ *APOE* ε4 non-carriers. Only the estimate(β) in (B) is not standard because we used a "log" link function from the Gaussian family in GLM models for the Temporal-metaROI Tau PET. Aβ, amyloid-β; BMI, body mass index; FDG, ^{18}F-fluorodeoxyglucose; CU, cognitively unimpaired; MCI, mild cognitive impairment

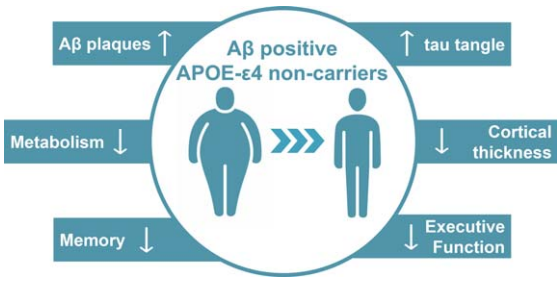

Fig. 6. Illustration of the association of body mass index changes with Aβ plaques, tau tangles, cortical metabolism, cortical thickness, memory, and executive function in Aβ PET positive *APOE* ε4 non-carriers.

BMI changes and AD pathogenesis in older adults with various *APOE* ε4 and Aβ PET statuses.

Consistent with our findings, one previous ADNI study [16] also found BMI changes were negatively correlated with cortical Aβ accumulation, although they did not analyze how the *APOE* ε4 allele affects this relation. We further found that BMI loss accelerated Aβ accumulation in Aβ+ *APOE* ε4 non-carriers but not in *APOE* ε4 carriers. Evidence from one animal study [37] suggested that high-fat diets induced increases in microglia and astrocyte expression in AD mouse models with *APOE* ε3 but not in those with *APOE* ε4. Of note, one recent ADNI study [38] reported that higher cerebrospinal fluid (CSF) soluble triggering receptor expressed on myeloid cell type 2, a biomarker of microglia activation, may be associated with attenuated Aβ accumulation and tau deposition. Together, it is likely that obesity-induced microglial

activation may attenuate Aβ and tau accumulation in Aβ+ *APOE ε*4 non-carriers.

To the best of our knowledge, no research has yet looked into the relationships between variations in BMI and the buildup of cortical tau in AD. A few cross-sectional studies [14, 26, 39] found that lower BMI was related to elevated CSF t-tau, tau/Aβ ratio, and p-tau. However, not all of them evaluated the influence of *APOE ε*4 alleles. Consistent with our findings, one recent study found [26] that higher BMI was associated with decreased CSF t-tau and p-tau in obese *APOE ε*4 non-carriers. In the present study, we extended the findings by showing the association between BMI changes and cortical tau deposition measured by tau PET. This showed that follow-up higher temporal-metaROI cortical tau deposition evaluated about five years after baseline Aβ PET was marginally correlated with BMI decreases in Aβ+ *APOE ε*4 non-carriers. Notably, this study's small sample size of tau PET images may limit us from observing significant effects. However, BMI decreases-related faster Aβ accumulation and higher follow-up tau deposition were observed in Aβ+ *APOE ε*4 non-carriers, further supporting the idea that BMI declines-related AD pathologic changes are not related to the presence of the *APOE ε*4 allele.

Our group [40] very recently reported that higher baseline BMI values were associated with faster declines in hippocampal volume and global cognitive decline over time in *APOE ε*4 non-carriers only. In line with our findings, two cross-sectional studies [13, 41] based on the ADNI cohort also reported a positive association between BMI and glucose metabolism. The present study further extends these findings by that ongoing body BMI declines may be closely linked to faster cortical hypometabolism, brain atrophy, and cognitive decline in Aβ PET positive *APOE ε*4 non-carriers. It has been observed that reduced levels of insulin and insulin signaling in AD brains [42]. One animal study [43] has demonstrated that *APOE ε*4 aggregation could inhibit insulin signaling with aging and a high-fat diet accelerates this inhibitory effects and related functions in *APOE ε*4-targeted but not in *APOE ε*3-targeted replacement mice. Together, it is likely that body weight increases in *APOE ε*4 non-carriers may be associated with reduced systemic inflammation and corresponding insulin resistance, thereby maintaining better glucose metabolism and brain structural and cognitive function. Further mechanism studies would be beneficial to explain why body weight increases are associated with fewer AD pathologies and cognitive decline in Aβ+ *APOE ε*4 non-carriers.

We subsequently determined whether the associations between body BMI declines, AD pathologies, and cognitive decline vary among baseline BMI status in Aβ+ *APOE ε*4 non-carriers. We observed that faster body BMI declines was linked to more rapid Aβ accumulation, hypometabolism, and cortical thinning in those with normal baseline BMIs exclusively. These findings suggest that BMI declines in Aβ+ *APOE ε*4 non-carriers with normal baseline BMIs requires extra care. Unlike other pathologies, we noticed that faster body BMI declines was associated with higher follow-up tau deposition and lower executive function in individuals with an overweight BMI at baseline. Nevertheless, these findings imply that BMI declines in older adults with normal or only overweight BMI at baseline may be more informative than those who were obese at baseline. Specifically, faster BMI declines rates imply more rapid progression of AD pathologies and cognitive decline in Aβ+ *APOE ε*4 non-carriers.

In Aβ − individuals, we found a significant negative association between BMI changes and longitudinal Aβ accumulation in *APOE ε*4 carriers but not in *APOE ε*4 non-carriers, suggesting faster BMI decreases may be related to more rapid Aβ accumulation in Aβ − *APOE ε*4 carriers. Consequently, tracking body weight changes may also help identify individuals with a high risk of accumulating Aβ plaques from Aβ − *APOE ε*4 carriers. We also observed that faster body BMI declines was related to more rapid cognitive decline in Aβ − individuals regardless of *APOE ε*4 status, suggesting that body BMI declines can also be used to track memory and executive function reduction in the absence of substantial Aβ pathology.

In this study, we used simultaneous longitudinal BMI data, Aβ PET images, FDG PET images, MRI images, and cognitive assessments, as well as follow-up tau PET images to determine how the *APOE ε*4 allele modulates the associations of body weight changes with Aβ plaques, tau tangles, hypometabolism, cortical thinning, memory decline and executive function decline in Aβ − and Aβ+ older adults. These findings provide novel imaging evidence for understanding the potential mechanism underlying body weight change-related AD pathophysiology alterations in the AD continuum. However, this study has limitations. First, BMI is a nonspecific measure of body composition that does not adequately reflect the distribution of body fat and

essential components of body composition in older adults [43, 44] thus, other body composition metrics, such as waist circumference and waist-to-hip ratio [45], may be more informative than BMI used in this study. Second, future studies are needed to use inflammatory and neuronal plasticity data to elucidate better the mechanism of the interaction of the *APOE* ε4 allele and obesity in the associations with AD pathophysiology. Third, the main results of the current study could be explained by reverse causation as the follow-up period is short and weight loss could be an early warning sign of the disease development.

In conclusion, this study reveals that the associations of body BMI declines with AD pathologies and cognitive function may vary among individuals with different *APOE* genotypes. The body BMI declines of older adults can be used as an indirect index to assess the ongoing abnormal AD pathologies and cognitive function changes in older adults with and without the *APOE* ε4 allele. These findings may provide a significant reference for better clinical management in older adults with a high risk of AD pathology and cognitive decline using longitudinal BMI data.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The dataset supporting the conclusions of this article is available in the ADNI repository (http://ida.loni.usc.edu). Derived data is available from the corresponding author on request by any qualified investigator subject to a data use agreement.

SUPPLEMENTARY MATERIAL

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