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Original Article

Late-life body mass index and amyloid interaction on cognitive decline in unimpaired older adults

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ABSTRACT

Background: The late-life "obesity paradox" of reduced Alzheimer's disease (AD) risk is postulated to be driven by underlying preclinical/prodromal pathology. However, few studies have directly examined the joint associations of BMI and amyloid pathology with cognitive decline, especially in individuals with preclinical AD targeted in prevention trials.
Objective: To determine whether late-life BMI and amyloid pathology have independent or interactive associations with cognition in clinically unimpaired older adults.
Design: Secondary analyses of A4 randomized clinical trial and the companion observational LEARN Study (median follow-up 4.7 years).
Setting: Multicenter across 67 sites in US, Canada, Australia, and Japan.
Participants: We included 1663 participants (Placebo $n = 582$, Solanezumab $n = 563$, LEARN $n = 518$) who were baseline cognitively unimpaired and medically stable, mean age 71.5 ± 4.7 years, 60% women.
Measurements: BMI and global amyloid burden [Florbetapir PET] were measured at baseline. Cognition was measured longitudinally using Preclinical Alzheimer Cognitive Composite.
Results: Higher BMI and amyloid burden were independently associated with worse baseline cognition. Longitudinally, a BMI*Amyloid*Time interaction emerged: lower/normal BMI was associated with more favorable cognitive trajectory at low amyloid levels, but with faster cognitive decline when amyloid was substantially elevated.
Conclusions: Our cross-sectional findings support a negative association between obesity and cognitive aging up to late-life. Longitudinally, we observed an "obesity paradox", where higher/obese BMI was associated with more favorable cognitive trajectories in the presence of advanced amyloid pathology. Together, our findings suggest that future trials targeting obesity to slow late-life cognitive decline may benefit from preferentially enrolling younger individuals or those without substantial amyloid accumulation.

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1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide, which is projected to affect 153 million people by 2050, [1] placing an immense burden on patients, caregivers and healthcare systems. Despite recent advances in anti-amyloid therapy, [2,3] the search for safe, effective, and affordable AD treatment continues. In this context, there is growing interest in the contribution of modifiable risk factors on the risk and progression of AD.

Obesity represents one such target. Most commonly measured using body mass index (BMI) in research studies, obesity is a potentially modifiable risk factor for dementia including the clinical diagnosis of AD [4,5]. Given the growing prevalence of obesity globally [6], it represents a large potential opportunity for intervention and prevention. However, while there is relative consensus on the link between midlife obese BMI and increased risk for dementia/AD, [4] findings have been mixed for late-life obesity, with studies demonstrating negative, [7–9] neutral, [10] and most commonly protective effects [11–15]. This unexpected protective association has been termed the "obesity paradox", [9,13] and is postulated to reflect reverse causation in setting of weight loss from preclinical and/or prodromal AD [9,16,17]. Indeed, elevated amyloid burden has been linked to greater weight loss, even in cognitively unimpaired (CU) older individuals [18–20]. However, despite this known confound, most studies examining the effects of late-life BMI on cognitive decline relied on clinical syndromes and did not account for the presence or extent of underlying AD pathology. This presents a barrier to disentangling the relationship between obesity and cognitive decline from the influence of preclinical or prodromal amyloid pathology.

Clarifying this relationship is especially timely given the growing interest in using potent weight loss medications such as glucagon-like peptide-1 (GLP-1) receptor agonists [21] to slow late-life cognitive decline and AD progression in individuals with and without diabetes (e.g. evoke and evoke+ trials in early AD [22]). There has also been increasing focus on earlier intervention and secondary prevention in AD, [23] along with combination strategies that target both amyloid and vascular risk factors in older adults. Therefore, understanding how late-life BMI and preclinical amyloid pathology may jointly influence cognitive decline in at-risk individuals who may be candidates for AD prevention trials is of particular importance. The current study addressed this knowledge gap by leveraging longitudinal data from the A4 Study, [24] a unique resource of a large CU cohort with elevated amyloid burden, along with the companion LEARN Study of CU individuals without significant amyloid accumulation, [25] to examine whether late-life BMI and amyloid have interactive or independent associations with cognitive decline.

2. Methods

2.1. Participants

This study is a secondary analysis of longitudinal data from the A4 Study (a randomized clinical trial) and the LEARN Study (the companion observational arm). Detailed methods for the A4 and LEARN studies have been published previously [24,25] and are briefly described here. Participants were older adults aged 65–85 who were CU based on global Clinical Dementia Rating score of 0, Mini-Mental State Exam score (MMSE) of 25–30, [26] and Weschler Memory Scale-Revised Logical Memory IIa Delayed Recall score of 6–18 [27]. Individuals with unstable medical conditions were excluded. Stable hypertension, diabetes, hypercholesterolemia, mild-to-moderate small-vessel ischemic disease and other medical conditions were permitted. Eligible participants then underwent amyloid PET, and those with elevated amyloid were enrolled in A4 Study (NCT02008357) and randomized 1:1 to placebo or solanezumab. Eligible participants without elevated amyloid were enrolled in the LEARN Study (NCT02488720) until target enrollment was reached, and underwent the same cognitive assessments as the A4 Study participants. We included all available publicly released data (https://www.a4studydata.org) from the double-blind phase of the A4 Study and the corresponding period in LEARN. 5 participants with missing BMI ($n = 3$) or APOE genotype ($n = 2$) information were excluded from analysis. Participant flowchart is illustrated in Supplementary Figure 1, summarizing missing data that were excluded from primary and sensitivity analyses, which were excluded from those analyses. All participants provided written informed consent prior to the completion of any study procedures.

2.2. Amyloid PET imaging

Baseline brain amyloid burden was measured with 18F-Florbetapir PET. PET image processing and quantification were performed by Invicro (now Perceptive) using PMOD software (PMOD Technologies, Zurich, Switzerland), in accordance with specifications provided by Avid Radiopharmaceuticals (Eli Lilly and Company). Global amyloid burden was calculated across a six-region composite (medial orbital frontal, lateral temporal, parietal, anterior cingulate, posterior cingulate, and precuneus), as a standardized uptake value ratio (SUVR) using whole cerebellum as reference region [28]. SUVR values were converted to the standard Centiloid scale [29] using previously published methods [30]. Elevated amyloid status for A4 eligibility was assessed using an algorithm combining quantitative SUVR methods and qualitative visual read performed at a central laboratory.

2.3. BMI

Baseline BMI (kg/m^2) was calculated based on height and weight measured at baseline visit (weight divided by height-squared). There were 1620 participants with 2 or more longitudinal BMI measurements during the double-blind phase in A4 and corresponding period in LEARN (median 11.5, IQR 3–13 measurements). Longitudinal BMI was calculated based on weight measured at subsequent visits and baseline height. Longitudinal BMI percent change slopes were extracted and used in sensitivity analysis as described below.

2.4. Cognitive assessment

Longitudinal cognition was assessed every 6 months using the four-component Preclinical Alzheimer's Cognitive Composite Scale (PACC), [31] consisting of the Free Recall plus Total score from the Free and Cued Selective Reminding Test, [32] delayed recall on the Logical Memory IIa test, [27] Digit-Symbol Substitution Test from the Wechsler Adult Intelligence scale-Revised, [33] and MMSE [26]. Three versions of the component measures were alternated to minimize practice effects. Each component score was converted to a z-score and summed to generate a composite with negative scores indicating worse cognitive functioning.

2.5. Statistical analyses

We first examined baseline associations between BMI and amyloid burden using Pearson correlations, adjusting for baseline age and sex.

For cross-sectional analysis, a linear regression model was used to examine the interactive and independent effects of baseline BMI and amyloid burden (both modeled continuously, to leverage the full dynamic range of the variables [34]) on baseline PACC, adjusting for age, sex, education, APOE e4 carrier status, and study assignment (A4 versus LEARN).

For longitudinal analyses, natural cubic spline models were used in primary analyses to investigate the interactive effects of baseline BMI and amyloid burden (modeled as continuous variables) on longitudinal PACC trajectories, with two spline basis expansion terms for time [35]. Models were adjusted for baseline age, sex, education, APOE e4 carrier

status, cognitive test versions, and study/treatment (placebo versus solanezumab) assignment. The full model specifications are detailed in Supplementary Methods. To aid in the interpretation of spline model results, predicted PACC change from baseline to 240 weeks (median duration of follow-up) at representative levels of low versus high BMI (mean±1SD) and amyloid burden (25th, 50th and 75th percentiles) were calculated and presented in Table 2. Significant BMI-*Amyloid*Time interaction was visualized using predicted PACC trajectories across the same representative levels of BMI and amyloid burden, respectively.

The following sensitivity analyses were performed to assess the robustness of our primary findings: (1) Excluding individuals with very low (<18.5) or very high (≥40) BMI. (2) Modeling BMI as categories (normal, overweight, obese) instead of continuously, underweight individuals (BMI<18.5) were excluded from this analysis due to insufficient sample size (n = 9). (3) Excluding A4 participants who received solanezumab. (4) Adjusting for additional potential confounders (race, ethnicity, baseline systolic blood pressure, baseline heart rate [36,37], hemoglobin A1C, total cholesterol, current smoking [yes/no], alcohol use [number of drinks per week], self-reported physical activity [including both walking and aerobic exercise], depression [Geriatric Depression Scale [38]], and anxiety [State Trait Anxiety Inventory short form [39]]). (5) Adjusting for the effect of weight loss during study – we extracted individuals slopes of BMI percent change using unadjusted linear mixed effects models with time as the only predictor, and additionally modeled the effect of BMI slope by time on longitudinal cognition (the BMI Slope*Amyloid*Time term was not significant and was excluded from the model p = 0.46). (6) Repeating primary and sensitivity analyses using linear mixed effects models.

Lastly, we conducted an E-value analysis [40] to calculate the minimum strength of association between an unmeasured confounder with BMI, amyloid and PACC decline, in order to explain away our significant interaction of interest. We used sensitivity analysis model (4), which was adjusted for additional health and psychosocial factors that may affect BMI and/or cognition, to assess for potential unmeasured confounding beyond these variables. We first defined a meaningful standardized effect size for the BMI*Amyloid*Time interaction, using the difference in predicted PACC change from baseline to 240 weeks (median duration of follow up) across representative high vs low levels of BMI (mean±1SD) and amyloid (75th vs 25th percentiles). This standardized effect size is then converted to an approximate risk ratio using published methods [40] to calculate the E-value estimate and confidence interval.

All analyses were conducted using R version 4.5.2. Continuous variables were standardized prior to LME model entry except for PACC (already a z-score), to obtain standardized estimates. Correction for multiple comparisons were not performed and nominal p-values and 95% CIs were reported.

3. Results

A total of 1663 participants were included in the primary analyses, consisting of participants from A4 randomized to placebo (n = 582) and solanezumab (n = 563), and participants from LEARN (n = 518). Baseline characteristics of the cohort were summarized in Table 1. The distribution of baseline BMI and amyloid burden are illustrated in Supplementary Figure 2A. Cognition was measured longitudinally using PACC over a median of 4.7 years (IQR 4.0 to 5.0) (Supplementary Figure 2B).

3.1. Baseline associations between BMI, amyloid and cognition

There was no significant association between baseline BMI and amyloid burden, adjusting for age and sex ($r_{partial}$=−0.03, p = 0.22).

We first examined the cross-sectional associations of BMI and amyloid with cognition. There was no significant interaction between BMI and amyloid on baseline PACC (β=−0.02 [−0.13 to 0.09], p = 0.70).

Table 1
Participant demographics.

	Total	A4 Solanezumab	A4 Placebo	LEARN
	(N = 1663)	(N = 563)	(N = 582)	(N = 518)
Age (Years)				
Mean (SD)	71.5 (4.7)	72.0 (4.7)	71.9 (5.0)	70.5 (4.3)
Sex				
Female	998 (60%)	329 (58%)	352 (60%)	317 (61%)
Male	665 (40%)	234 (42%)	230 (40%)	201 (39%)
Education (Years)				
Mean (SD)	16.6 (2.7)	16.6 (2.7)	16.6 (2.9)	16.8 (2.6)
APOE e4				
No	873 (52%)	231 (41%)	241 (41%)	401 (77%)
Yes	790 (48%)	332 (59%)	341 (59%)	117 (23%)
Baseline Amyloid (Centiloid)				
Mean (SD)	46.8 (40.1)	66.2 (33.7)	65.9 (32.2)	4.3 (12.6)
Baseline BMI				
Mean (SD)	27.5 (5.0)	27.2 (5.0)	27.6 (5.1)	27.6 (4.8)
Baseline PACC				
Mean (SD)	0.3 (2.6)	0.0 (2.8)	0.0 (2.6)	0.9 (2.3)
Number of Cognitive Assessments				
Median (IQR)	11 (9–11)	11 (9–11)	11 (9–11)	11 (8–11)
Duration of Cognitive Follow-up (Years)				
Median (IQR)	4.7 (4–5)	4.6 (4–5)	4.7 (4–5)	4.8 (4–5)

BMI = Body mass index; IQR = Interquartile range; N = Number of participants; PACC = Preclinical Alzheimer's Cognitive Composite; SD = Standard deviation.

Instead, higher BMI and higher amyloid burden were independently associated with lower baseline PACC scores (BMI: β=−0.13 [−0.24 to −0.02], p = 0.02; Amyloid: β=−0.55 [−0.71 to −0.38], p < 0.001; Fig. 1).

3.2. BMI and amyloid effects on longitudinal cognitive decline

We then evaluated the association of baseline BMI and amyloid with longitudinal PACC decline. Using a natural cubic spline model, we found a significant BMI by amyloid by time interaction on longitudinal PACC scores (p = 0.002; full model results reported in Supplementary Table 1). Predicted PACC change from baseline to 240 weeks (median duration of follow-up) across representative levels of low versus high BMI (mean ±1SD) and amyloid burden (25th, 50th and 75th percentiles) were reported in Table 2. Predicted PACC trajectories across levels of BMI and amyloid burden were visualized in Fig. 2A. When baseline amyloid burden was low (13 Centiloid), lower BMI was associated with numerically higher PACC scores over time, with a numerically greater learning effect. However, the association between BMI and PACC decline changed as amyloid burden increased. When baseline amyloid burden was high (74 Centiloid), lower BMI was associated with greater PACC decline and was associated with worse cognition by the end of study period despite having a higher PACC scores at baseline.

3.3. Sensitivity analyses

We conducted sensitivity analyses to assess the robustness of the baseline BMI*Amyloid*Time interaction on longitudinal PACC, which remained significant (p < 0.05) in all sensitivity analyses. The number of participants included in each sensitivity analysis and the results of these models are summarized in Table 2. (1) We excluded individuals with very low (<18.5, n = 9) or very high (≥40, n = 37) BMI to ensure our results were not driven by extreme values, which revealed similar findings. (2) We modeled BMI as categories (normal, overweight, obese) instead of continuously. We found concordant results where normal BMI was associated with a more favorable cognitive trajectory when baseline amyloid burden was low, but was associated with accelerated cognitive decline when there was substantial amyloid pathology (Fig. 2B). Of note,

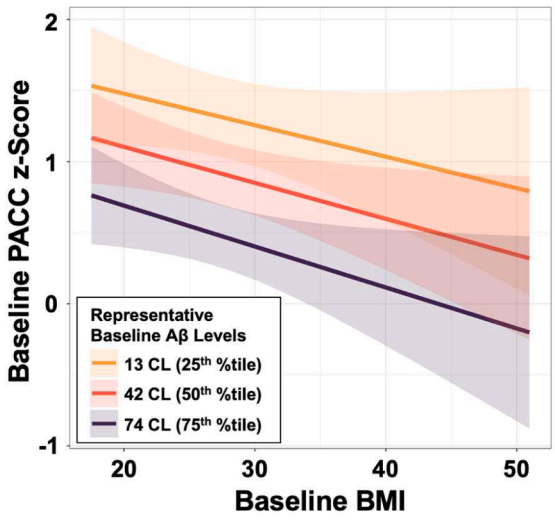

Fig. 1. Higher baseline BMI and amyloid burden were independently associated with lower baseline cognition. Using linear regression (adjusting for age, sex, education, APOE e4 carrier status, and study assignment), we found no significant interaction between BMI and amyloid burden on baseline PACC scores ($p = 0.70$). Instead, higher BMI (β=−0.13 [−0.24 to −0.02], $p = 0.02$) and higher amyloid burden (β=−0.55 [−0.71 to −0.38], $p < 0.001$) were independently associated with lower baseline PACC scores. Estimated PACC scores across baseline BMI and representative levels of amyloid burden (25th, 50th and 75thpercentiles) are illustrated. Aβ = β-amyloid; PACC = Preclinical Alzheimer's Cognitive Composite.

individuals who were overweight (BMI between 25 and 30) had intermediate cognitive trajectories between normal weight and obese individuals, which suggests that these relationships were unlikely to be driven only by individuals with low-normal BMI. (3) We excluded A4 participants who received solanezumab and found a significant BMI-*Amyloid*Time interaction in this smaller A4 placebo and LEARN subgroup. 4) We adjusted for additional health and psychosocial factors that may affect BMI and/or cognition (race, ethnicity, baseline systolic blood pressure, baseline heart rate, hemoglobin A1C, total cholesterol, smoking, alcohol use, self-reported physical activity, depression and anxiety), which revealed unchanged results. (5) We additionally adjusted for the effect of BMI change on cognitive decline. We found significant independent associations between greater weight loss and faster cognitive decline (BMI Slope*Time $p = 0.01$; Fig. 3B), as well as an unchanged baseline BMI*Amyloid*Time interaction on cognitive decline ($p = 0.001$; Fig. 3A). Lastly, we repeated the primary and sensitivity analyses using linear mixed effects models, which revealed a significant baseline BMI*Amyloid*Time interaction in all models (Supplementary Table 2). The full results from the primary linear mixed effects model are further presented in Supplementary Table 3.

3.4. E-value analysis

To complement the sensitivity analyses, we further calculated the E-value [40], which measures the minimum strength of association between an unmeasured confounder with both exposure and outcome in order to explain away the observed BMI*Amyloid*Time interaction on PACC. We used sensitivity model (4) which adjusted for additional health and psychosocial factors, and defined our contrast of interest as the difference in PACC change from baseline to week 240 (median duration of follow up) across high vs low levels of BMI (32 vs 22) and amyloid (74 vs 13 CL). We obtained an E-value estimate of 2.0, suggesting that an unmeasured confounder would have to be associated with baseline BMI, amyloid and PACC decline by an approximate risk ratio of 2.0 or greater (above and beyond the modeled covariates) to explain away the interaction of interest. Applying similar calculations to the confidence interval, an unmeasured confounder associated with both exposure and outcome by an approximate risk ratio of 1.5 or greater could move the confidence interval to include the null.

4. Discussion

In a study leveraging the seminal A4 Study with a large cohort of CU individuals with elevated amyloid burden, along with the companion

Table 2
Natural cubic spline model results examining the baseline BMI and amyloid interaction on longitudinal cognitive decline. Sensitivity analyses were conducted to examine the robustness of our primary finding of a significant interaction between baseline BMI, amyloid and time on longitudinal PACC scores. All models adjusted for baseline age, sex, education, APOE e4 carrier status, substudy/treatment assignment, cognitive test versions, and any additional covariates specified for the respective sensitivity analysis. To aid in the interpretation of spline model results, predicted PACC change from baseline to 240 weeks (median duration of follow-up) at representative levels of low versus high BMI (mean±1SD) and amyloid burden (25th, 50th and 75th percentiles) were calculated.

			Predicted PACC Change from Baseline to Week 240 at Representative Levels of Amyloid (25th, 50th, and 75th Percentile) and BMI (Mean ± 1 SD)		
	N	BMI* Amyloid* Time p	Low Amyloid (13 CL)	Mid Amyloid (42 CL)	High Amyloid (74 CL)
Primary analyses	1663	<0.001*	BMI 22: 0.38 [0.10 to 0.67] BMI 32: 0.11 [−0.12 to 0.33]	BMI 22: −0.79 [−1.06 to −0.52] BMI 32: −0.54 [−0.76 to −0.32]	BMI 22: −2.08 [−2.54 to −1.62] BMI 32: −1.25 [−1.61 to −0.90]
Sensitivity analyses					
Excluding individuals with very low (<18.5) or very high (≥40) BMI	1615	<0.001*	BMI 22: 0.35 [0.06 to 0.64] BMI 32: 0.19 [−0.05 to 0.42]	BMI 22: −0.82 [−1.10 to −0.54] BMI 32: −0.44 [−0.68 to −0.20]	BMI 22: −2.11 [−2.59 to −1.63] BMI 32: −1.13 [−1.53 to −0.73]
Modeling BMI as categories (normal, overweight, obese; excluding underweight)	1652	0.006*	Normal: 0.57 [0.24 to 0.90] Overweight: 0.01 [−0.26 to 0.27] Obese: 0.19 [−0.13 to 0.52]	Normal: −0.68 [−0.99 to −0.37] Overweight: −0.76 [−1.03 to −0.49] Obese: −0.38 [−0.68 to −0.08]	Normal: −2.05 [−2.59 to −1.52] Overweight: −1.61 [−2.10 to −1.11] Obese: −1.01 [−1.51 to −0.51]
Excluding Solanezumab group	1098	0.05*	BMI 22: 0.26 [−0.01 to 0.53] BMI 32: 0.07 [−0.16 to 0.30]	BMI 22: −0.71 [−1.05 to −0.37] BMI 32: −0.50 [−0.75 to −0.24]	BMI 22: −1.79 [−2.37 to −1.22] BMI 32: −1.12 [−1.55 to −0.69]
Adjusting for additional confounders (race, ethnicity, SBP, heart rate, A1C, total cholesterol, smoking, alcohol use, physical activity, depression, anxiety)	1636	0.002*	BMI 22: 0.40 [0.11 to 0.68] BMI 32: 0.10 [−0.13 to 0.33]	BMI 22: −0.74 [−1.01 to −0.47] BMI 32: −0.52 [−0.74 to −0.30]	BMI 22: −2.00 [−2.45 to −1.54] BMI 32: −1.21 [−1.56 to −0.85]
Adjusting for BMI percent change slope	1620	0.001*	BMI 22: 0.30 [0.02 to 0.59] BMI 32: 0.10 [−0.13 to 0.32]	BMI 22: −0.85 [−1.12 to −0.59] BMI 32: −0.52 [−0.73 to −0.31]	BMI 22: −2.13 [−2.59 to −1.67] BMI 32: −1.20 [−1.55 to −0.84]

A1C = Hemoglobin A1C; BMI = Body mass index; IQR = Interquartile range; *N* = Number of participants.
* $p < 0.05$
PACC = Preclinical Alzheimer's Cognitive Composite; SBP = Systolic blood pressure; SD = Standard deviation.

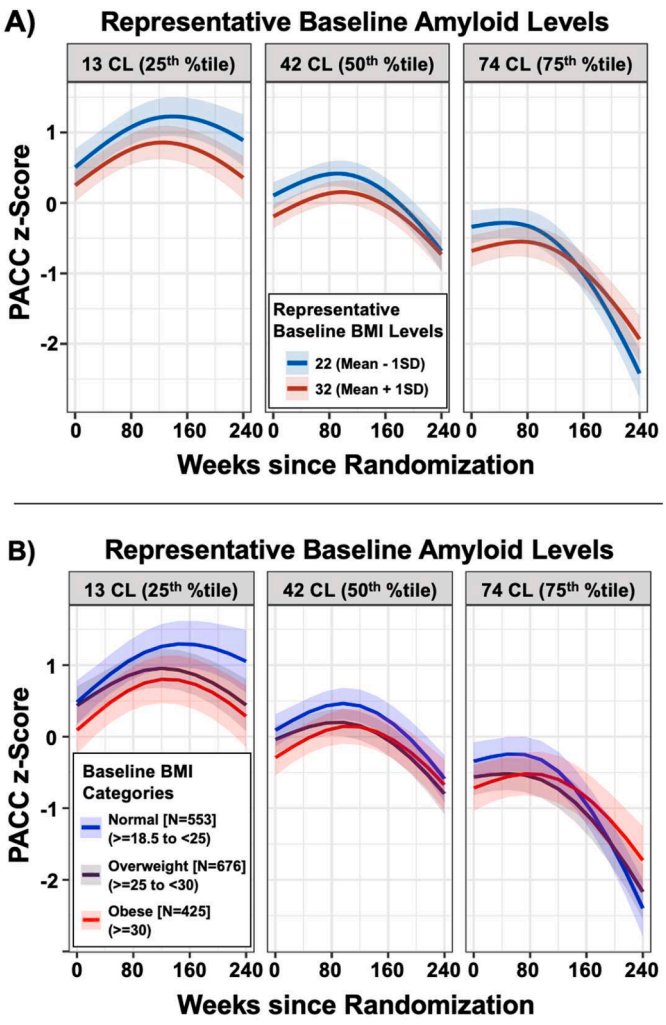

Fig. 2. Interactive association of baseline BMI (A) and BMI categories (B) with amyloid burden on longitudinal cognitive decline. (A) Natural cubic splines model revealed a significant BMI*Amyloid*Time interaction on longitudinal PACC scores (p = 0.002), adjusting for baseline age, sex, education, APOE e4 carrier status, substudy/treatment assignment, and cognitive test versions. To visualize this interaction, estimated longitudinal PACC trajectories at representative levels of BMI (mean±1SD) and amyloid burden (at 25th, 50th and 75th percentiles) are illustrated. PACC = Preclinical Alzheimer's Cognitive Composite. (B) BMI was modeled as categories: normal (BMI ≥18.5 and <25; n = 553), overweight (BMI ≥25 and <30; n = 676), and obese (BMI ≥30; n = 425), rather than continuously. Individuals who were underweight (BMI <18.5; n = 9) were excluded due to insufficient number. Natural cubic splines model revealed a significant Amyloid*BMI Category*Time interaction on longitudinal PACC scores (p = 0.006), adjusting for the same covariates. To visualize the interaction, estimated longitudinal PACC trajectories at different BMI categories and representative levels of amyloid burden (at 25th, 50th and 75th percentiles) are illustrated. PACC = Preclinical Alzheimer's Cognitive Composite.

LEARN study of CU individuals without significant amyloid accumulation, we demonstrated a complex relationship between late-life BMI and cognition, which was modified by amyloid pathology and time. At baseline, lower BMI was independently associated with better cognitive performance, regardless of amyloid burden. This observation supports obesity as a negative risk factor for cognitive aging up to late-life. By contrast, the relationship between BMI and longitudinal cognition was modified by amyloid burden. When there were low levels of baseline amyloid, lower/normal BMI was associated with more favorable cognitive trajectories. However, when amyloid burden was substantially elevated, lower/normal BMI was associated with greater cognitive decline, which remained robust in sensitivity analyses adjusting for the influence of longitudinal weight loss. Our findings align with the "obesity paradox" in context of advanced preclinical AD, and support a potential role of obesity in tempering cognitive decline in individuals with substantial amyloid pathology. Together with existing literature, our results suggest that future randomized clinical trials targeting obesity as a prevention strategy for late-life cognitive decline may benefit from preferentially enrolling older individuals with minimal to very early amyloid accumulations, or younger individuals prior to late-life.

Growing studies have demonstrated a link between midlife obesity and increased risk of late-life dementia including the clinical diagnosis of AD [4,10,13,15,17,41,42]. By contrast, the findings have been mixed for late-life obesity, with most studies demonstrating paradoxical protective associations with the risk of dementia/AD [11–15]. This reversal of associations from increased to decreased risk of dementia across mid- to late-life was well-demonstrated in several studies examining serial BMI measurements within the same individuals [9,42–44]. This late-life "obesity paradox" has been postulated to be driven by reverse causation, where lower BMI may reflect a greater proportion of individuals with weight loss secondary to incipient AD. Indeed, studies have demonstrated a relationship between AD neuropathology (particularly amyloid) and lower late-life BMI [18–20,45]. However, despite the known confounding influence of amyloid pathology on both weight and cognition, most studies examining obesity and dementia have relied on the clinical diagnosis of AD. Few have accounted for the presence or extent of underlying amyloid burden, making it difficult to distinguish the association between late-life obesity and cognitive trajectories from that of AD-related cognitive decline.

The current study addressed this knowledge gap by examining the joint associations between late-life BMI and baseline amyloid burden with cognitive decline in CU individuals from A4 and LEARN. In contrast to existing cohort studies, this study is unique in being enriched with individuals with substantially elevated amyloid burden, i.e. those with preclinical AD who would be candidates for AD prevention trials. At baseline, we observed no significant association between BMI and amyloid burden. Previous studies including cognitively impaired participants reported cross-sectional associations between lower BMI and higher amyloid burden [18,19,45–47]. However, similar cross-sectional associations have not been consistently observed in CU-only cohorts [20]. Instead, higher baseline amyloid burden in CU older adults has been associated with greater longitudinal weight loss. Collectively, these observations suggest that amyloid-associated weight loss may be a more prominent process during the prodromal period when there is emergence of early cognitive impairment.

We then examined the cross-sectional and longitudinal associations between late-life BMI and cognition across a broad range of preclinical amyloid pathology and identified two key findings. First, higher BMI and higher amyloid burden were independently associated with worse baseline cognition, supporting a negative impact of obesity on cognitive aging up to late-life. This finding is consistent with several studies linking late-life obesity, [7–9] and more studies of midlife obesity, [4,10,13,15,17,41,42] to worse cognition or increased risk of dementia. Our longitudinal analyses, however, revealed a more complex relationship, where the associations between late-life BMI and longitudinal cognitive decline differed by the degree of underlying amyloid pathology. When there was little amyloid, lower/normal BMI was associated with a numerically more favorable cognitive trajectory, consistent with the direction of our cross-sectional findings. By contrast, when there was substantial amyloid burden, lower/normal BMI was instead associated with accelerated cognitive decline, with incrementally slower cognitive decline as BMI increased to overweight and obese ranges. This interaction remained robust in sensitivity analyses addressing potential confounding factors. Given greater weight loss has been associated with faster cognitive decline, [18,48–50] we examined whether our primary finding may be driven by greater weight loss in those with lower

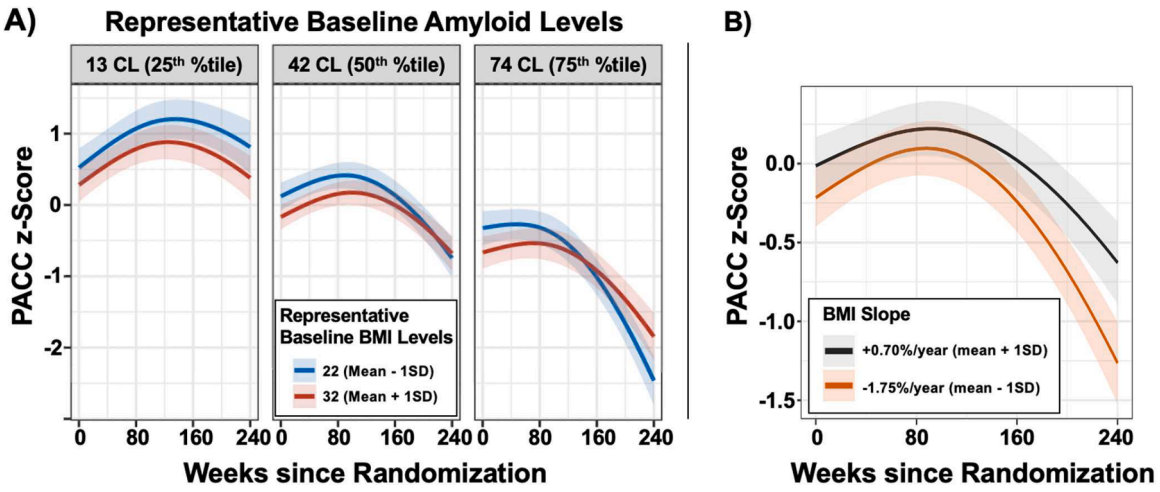

Fig. 3. Independent associations of baseline BMI by amyloid interaction (A) and BMI slope (B) with longitudinal cognitive decline. We conducted sensitivity analysis adjusting for the effect of weight loss during study. We extracted individuals slopes of longitudinal BMI percent change using unadjusted linear mixed effects models with time as the only predictor. In a natural cubic spline model adjusting for baseline age, sex, education, APOE e4 carrier status, substudy/treatment assignment, and cognitive test versions, we additionally adjusted for the effect of BMI slope by time (the BMI Slope*Amyloid*Time term was not significant and was excluded from the model $p = 0.46$). Results revealed that the baseline BMI*Amyloid*Time interaction on cognitive decline remained unchanged ($p = 0.001$; Panel A). There was additionally an independent association between greater weight loss and faster cognitive decline (BMI Slope*Time $p = 0.01$; Panel B). To visualize these associations, estimated longitudinal trajectories at representative levels of BMI (mean±1SD) and amyloid burden (at 25th, 50th and 75th percentiles) are illustrated in Panel A, and estimated longitudinal PACC trajectories at representative levels of longitudinal BMI slope (mean±1SD; percent change per year) are illustrated in Panel B. PACC = Preclinical Alzheimer's Cognitive Composite.

baseline BMI and elevated amyloid. Consistent with literature, our sensitivity analysis found a significant independent association between greater longitudinal weight loss and faster cognitive decline (baseline amyloid burden did not further modify this relationship), but our primary finding of an interaction between baseline BMI and amyloid on cognitive decline remained unchanged.

Few studies have examined the combined effects of obesity and amyloid burden on preclinical AD progression. Two prior studies (Harvard Aging Brain Study [HABS] and Wisconsin Registry for Alzheimer's Prevention [WRAP]) found that higher or obese BMI interacted with elevated amyloid to accelerate tau accumulation and cognitive decline—findings that contrast with ours [51,52]. These discrepancies likely reflect differences in cohort age and amyloid pathology. Specifically, HABS and WRAP included midlife participants, a period when obesity has been more consistently linked to dementia/AD risk, and were predominantly amyloid-negative (~30% positivity). Our cohort had a higher amyloid positivity rate (69%) and more advanced pathology (median Centiloid 42 vs. 11 in HABS). Recent work conceptualizes amyloid burden as a proxy for preclinical AD duration [53]. In this context, our findings suggest that obesity may negatively influence early preclinical AD but show a paradoxical protective association as amyloid pathology advances. Aligned with results from HABS and WRAP, a recent study of older adults from the National Alzheimer's Coordinating Center (NACC) cohort found that overweight and obesity were associated with greater risk of cognitive decline among cognitively unimpaired APOE ε4 carriers (who are known to exhibit earlier onset and higher burden of amyloid pathology [54]), but not among non-carriers, although amyloid burden was not explicitly measured [55]. The study further showed that the relationship between overweight/obesity and cognitive decline reversed across the clinical impairment spectrum, such that overweight/obese BMIs were associated with lower risk of cognitive decline in those with dementia (regardless of APOE status). While randomized trials are needed to confirm causality, these observational data collectively suggest that interventions targeting obesity (such as GLP-1 receptor agonists [21]) for the prevention or treatment of late-life cognitive decline, may benefit from preferentially enrolling individuals early in the disease spectrum (e.g. CU individuals without substantial amyloid accumulation) or younger individuals prior to late-life. In line with this hypothesis, recent trials of oral semaglutide in early symptomatic AD (mean age 72 years in evoke and evoke+) did not demonstrate significant slowing of cognitive or functional decline compared to placebo [56].

Future studies are also needed to clarify the pathways underlying the observed interaction between late-life BMI, amyloid and cognitive decline, including whether these relationships are mediated by tau and/or neurodegeneration. One possibility is that obesity may confer greater nutritional or energy reserves, allowing individuals to better tolerate the physiological stress associated with disease states such as amyloid-related hypothalamic dysfunction in AD [57], similar to protective associations observed in heart failure or chronic kidney disease [58,59]. More specific to AD, neuroprotective effects of leptin [60] may contribute to this paradoxical relationship. In animal models, leptin has been linked to improved neuronal survival and reduced amyloid-related tau phosphorylation and synaptic dysfunction [60–63]. Given obesity induces leptin resistance, [64] midlife obesity may increase risk of late-life AD through promoting resistance to leptin and its neuroprotective effects (in addition to inflammation and other cardiometabolic mechanisms). In late-life, when leptin resistance is further exacerbated by aging [65], higher leptin levels in obese individuals may paradoxically help preserve neuroprotective signaling amidst mounting amyloid pathology. Indeed, higher late-life leptin levels, independent of BMI/obesity, have been associated with slower tau accumulation, larger brain volumes, and lower AD/dementia risk [66,67]. While leptin administration improved memory performance in AD mouse model [68], future randomized clinical trials are needed to test whether augmenting leptin pathways can slow cognitive decline in advanced preclinical AD.

This study has several limitations. First, although BMI is a widely used and accessible measure of obesity, it is influenced by factors such as muscle mass and bone density. Future studies should confirm these findings using measures that better capture central adiposity (e.g. waist-to-hip ratio) [69]. Second, given this is a secondary analysis of publicly released data from the A4 randomized clinical trial and the companion observational LEARN study, our study was not designed to support a full causal inference framework, and our findings should be interpreted in context of these limitations. While our primary finding remained robust

after adjusting for longitudinal weight loss, we cannot fully exclude the possibility that lower baseline BMI may represent prior weight loss from more advanced preclinical disease, though its association with better (instead of worse) baseline cognition and the absence of a BMI–amyloid association at baseline lowers this concern. It is also important to note that inclusion in the A4 and LEARN studies conditioned on survival and being CU. As obesity is associated with increased mortality, obese individuals who survive to late-life without cognitive impairment may possess latent resilience factors unrelated to obesity, and may introduce potential survivor and collider bias. Future observational studies designed to support a causal inference framework are needed to disentangle the effects of obesity as a causal factor for late-life cognitive decline/impairment versus a marker for reserve/resilience, and randomized clinical trials are ultimately needed to confirm causality. Given growing literature highlighting the role of midlife and earlier modifiable risk factors on late-life cognitive decline, including earlier life BMI and BMI variability, it will be important to collect and examine these factors in future studies [4,70–75]. Finally, A4 and LEARN participants were predominantly non-Hispanic White, highly educated, and generally healthy, which may limit the generalizability of our findings. In context of known racial difference in the prevalence and burden of amyloid pathology [76–78], it will be important to examine the associations between late-life BMI, amyloid burden, and cognitive decline across more diverse cohorts in future studies.

In summary, in a predominantly amyloid-positive CU cohort, we examined the associations between late-life BMI and cognitive decline across a wide range of preclinical amyloid pathology. At baseline, lower BMI was independently associated with higher cognitive scores, suggesting a cumulative negative impact of obesity on cognitive aging up to late-life. Longitudinally, the association between BMI and cognition reversed when there was substantial amyloid pathology, and lower/normal BMI was instead associated with accelerated cognitive decline. Taken together with existing literature, our findings suggest that future prevention trials targeting obesity to slow late-life cognitive decline may benefit from preferentially enrolling older individuals with minimal to very early amyloid accumulation, or younger individuals in midlife.

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Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

ChatGPT was used to assist with debugging R codes. Codes and outputs were carefully reviewed and verified for accuracy.

Data statement

Publicly released data from A4 and LEARN studies can be requested at https://www.a4studydata.org.

CRediT authorship contribution statement

Wai-Ying Wendy Yau: Writing – original draft, Visualization, Formal analysis, Conceptualization. **Rema Raman:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Jasmeer Chhatwal:** Writing – review & editing, Conceptualization. **Jeremy J. Pruzin:** Writing – review & editing, Conceptualization. **Zahra Shirzadi:** Writing – review & editing, Conceptualization. **Neelum Aggarwal:** Writing – review & editing, Investigation. **Adam M. Brickman:** Writing – review & editing, Investigation, Conceptualization. **Petrice M. Cogswell:** Writing – review & editing, Investigation. **Jonathan Graff-Radford:** Writing – review & editing, Investigation. **Jay J. Pillai:** Writing – review & editing, Investigation. **Prashanthi Vemuri:** Writing – review & editing, Investigation. **Michael S. Rafii:** Writing – review & editing, Investigation, Conceptualization. **Roy Yaari:** Writing – review & editing, Investigation. **Paul Aisen:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Reisa Sperling:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Drs. Yau, Raman, Chhatwal, Aggarwal, Brickman, Cogswell, Graff-Radford, Vemuri, Rafii, Aisen, Sperling has received research support from NIH. Dr. Raman has received research support through her Institution from the Alzheimer's Association, American Heart Association, and Eisai (public-private partnership). Dr. Chhatwal has served as a consultant for ExpertConnect. Dr. Pruzin has served as a consultant for Eisai. Dr. Brickman is an advisor and/or board member for Cognition Therapeutics, Inc; CogState, Cognito Therapeutics, Inc., Tau Biosciences, ProPhase/IQVIA, and CogniMark outside the submitted work; in addition, Dr Brickman has received research support from Columbia University, and Mars Symbioscience. Dr. Cogswell has consulted for Eli Lilly regarding medical education and received honoria from Eisai Inc; she serves on Lilly and Eisai DSMBs but does not receive any compensation for these activities. Dr. Graff-Radford reports grants from NIH outside the submitted work; and serves as the site-PI for a clinical trial co-sponsored by Eisai and cognition therapeutics and the University of Southern California, and serves on the Data Safety and Monitoring Board for StrokeNET. Dr. Rafii has received grants from Esai and Eli Lilly and Company; has received consulting fees from AC Immune and Ionis; and has participated in data safety monitoring boards or advisory boards for Biohaven, Prescient Imaging, Positrigo, and Embic. Dr. Yaari is a full time employee and minor shareholder of Eli Lilly and Co. Dr. Aisen has research grants from NIH, the Alzheimer's Association, Lilly and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, Immuno-Brain Checkpoint, AltPep, Alector, Arrowhead and Neurimmune. Dr. Sperling has served as a consultant for AC Immune, Acumen, Genentech, Ionis, Janssen, Merck, Novartis, Oligomerix, Prothena, Renew, Shionogi, and Vaxxinity. Dr. Sperling is involved in public-private partnership clinical trials sponsored by Eisai and Eli Lilly but do not have any personal financial relationship with the companies.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100543.

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