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Amyloid-beta burden predicts prospective decline in body mass index in clinically normal adults

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ABSTRACT

In the present study, we tested the hypothesis that higher amyloid-beta (Aβ) burden at baseline is associated with greater longitudinal decline in body mass index (BMI) in clinically normal adults. Participants from the Harvard Aging Brain Study (n = 312) and the Alzheimer's Disease Neuroimaging Initiative (n = 336) underwent Aβ positron emission tomography at baseline. BMI was assessed longitudinally over a median of >4 years. Linear mixed models showed that higher baseline Aβ burden was significantly associated with greater decline in BMI in both the Harvard Aging Brain Study ($t = -1.93$; $p = 0.05$) and Alzheimer's Disease Neuroimaging Initiative cohorts ($t = -2.54$; $p = 0.01$), after adjusting for covariates, including cognitive performance and depressive symptoms. In addition, the association of Aβ burden with longitudinal decline in BMI persisted in both cohorts after excluding participants with diabetes/endocrine disturbances and participants classified as underweight or obese (BMI <18.5 or >30). These findings suggest that decline in BMI in clinically normal adults may be an early manifestation related to cerebral amyloidosis that precedes objective cognitive impairment. Therefore, unintentional BMI decline in otherwise healthy individuals might alert clinicians to increased risk of Alzheimer's disease.

1. Introduction

Studies suggest that higher body mass index (BMI) during midlife is associated with an increased risk of dementia, including Alzheimer's disease (AD) (Fitzpatrick et al., 2009; Kivipelto et al., 2005; Whitmer et al., 2005). However, the inverse relationship

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has also been reported in late-life, whereby lower BMI at older ages is associated with an increased risk of cognitive decline (Besser et al., 2014; Corrada et al., 2006; Fitzpatrick et al., 2009; Hughes et al., 2009; Johnson et al., 2006). Given that weight loss may co-occur with the development of AD pathology before the diagnosis of dementia, a low BMI in late-life may be a consequence of the disease (Buchman et al., 2005; Johnson et al., 2006; Kivimaki et al., 2018; Mathys et al., 2017).

AD has a long "preclinical" phase defined by elevated amyloid-beta (Aβ) in the absence of significant cognitive symptoms (Jack et al., 2018; Sperling et al., 2014, 2011). Cross-sectional studies using positron emission tomography (PET) or cerebrospinal fluid have found associations between AD pathology (Aβ and/or tau) with lower BMI in clinically normal adults (Hsu et al., 2016; Thirunavu et al., 2019; Vidoni et al., 2011). However, longitudinal studies are needed to understand the temporal nature of the association, that is, whether decreases in BMI represent an early manifestation of AD pathology. To our knowledge, only one longitudinal study has examined this question in clinically normal adults and found no association between AD pathology and prospective BMI change, perhaps due to the modest sample size ($n = 100$) and/or limited follow-up data (up to 2 years; Vidoni et al., 2011). Larger sample sizes and longer follow-up periods may be needed to detect associations in the preclinical phase of AD.

In the present study, we tested the hypothesis that higher Aβ burden at baseline would be associated with greater longitudinal decline in BMI in individuals who were clinically normal at baseline. To do so, we leveraged Aβ-PET and longitudinal BMI data (1–8 years of longitudinal follow-up; median of more than 4 years) from 2 large cohorts of clinically normal individuals: the Harvard Aging Brain Study (HABS) and the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2. Materials and methods

2.1. Participants

Data were obtained from 2 independent cohorts: HABS and ADNI. For HABS, study protocols were approved by the Partners HealthCare Institutional Review Board. All participants in HABS provided written informed consent before study procedures. For ADNI, the institutional review boards of all participating sites provided approval for the study. All participants in ADNI provided written informed consent.

Inclusion criteria for both studies have been published previously (Aisen et al., 2010; Dagley et al., 2017). To be included in the present study, participants were required to be classified as clinically normal at the time of their first available Aβ-PET scan, which was considered baseline in this study. Clinically normal was defined by a global Clinical Dementia Rating of 0 (Morris, 1993), Mini-Mental State Examination score $\geq$27 with educational adjustment (Folstein et al., 1975), and performance within education-adjusted norms on Logical Memory Delayed Recall (Wechsler, 1987). In the ADNI sample, the subjective memory complaint group was also considered clinically normal, given that they met the aforementioned requirements. We required that participants contribute at least 2 BMI data points to the analysis (baseline and at least one follow-up data point), given that the present study focused on change in BMI. We excluded BMI values that changed more than 5 standard deviations from baseline to avoid possible outlier effects or data recording errors. This value was chosen based on a visual inspection of the distributions of BMI change values; large gaps in the distribution were identified around 5 standard deviations above and below the mean in both HABS and ADNI. This resulted in exclusion of <1% of the data points in each cohort (11 longitudinal data points in HABS and 4 longitudinal data points in ADNI).

2.2. Aβ positron emission tomography

Detailed Aβ-PET protocols have been previously described for both HABS and ADNI (Johnson et al., 2016; Landau et al., 2012). Different Aβ tracers were used in each cohort. HABS used ^{11}C–Pittsburgh Compound B (PiB), and ADNI used ^{18}F–florbetapir. For consistency purposes, we used non–partial volume corrected Aβ PET data for all analyses, given that partial volume corrected values were not publicly available in ADNI. Because analyses were carried out in each cohort independently, we used the cortical Aβ-PET composite that has been routinely used in each cohort. In HABS, PiB-PET measurements were represented as a distribution volume ratio across a composite of frontal, lateral temporal and parietal, and medial parietal regions, with cerebellar gray matter serving as the reference region. In ADNI, florbetapir measurements were represented as a cortical summary standard uptake value ratio across a composite of lateral and medial frontal, anterior, and posterior cingulate, lateral parietal, and lateral temporal regions. The whole cerebellum served as the reference region in ADNI. The standard uptake value ratio values for ADNI were accessed and downloaded from the LONI website (http://adni.loni.usc.edu/) in March 2019.

2.3. Clinical and cognitive assessments

In HABS, each participant had their height and weight measured annually. In ADNI, height and weight were measured at study entry and weight was measured at subsequent follow-up visits. These values were converted to metric units to calculate BMI (kilograms divided by meters squared).

Cognition was assessed longitudinally in both cohorts using the Preclinical Alzheimer Cognitive Composite-5 or PACC-5 (Donohue et al., 2014; Papp et al., 2017). This composite was developed to be sensitive to early cognitive changes in AD (Donohue et al., 2014). For HABS, the PACC-5 was calculated using the Mini-Mental State Examination, Logical Memory Delayed Recall, Digit Symbol Coding Test, Free and Cued Selective Reminding Test (Free plus Cued Recall), and Animal Fluency. For ADNI, the PACC-5 was calculated using the Mini-Mental State Examination, Logical Memory Delayed Recall, Trail-Making Test B, the Delayed Word Recall from the Alzheimer's Disease Assessment Scale–Cognitive Subscale, and Animal Fluency. To calculate the PACC-5 composite, z scores of the individual components were computed for each time point and then averaged together. This average was then standardized to the mean and standard deviation of the baseline sample within each cohort.

Depressive symptoms were measured at baseline and each follow-up visit in HABS and ADNI using the Geriatric Depression Scale (GDS). In HABS, depressive symptoms were measured with a full-length, 30-item questionnaire (Yesavage et al., 1982) and in ADNI they were measured with an abbreviated, 15-item questionnaire (Sheikh and Yesavage, 1986). To harmonize across the 2 cohorts, we calculated a 15-item GDS score for HABS participants and used this score in all analyses.

Metabolic and endocrine conditions that could influence BMI were identified (Bays et al., 2007). For HABS, we relied on self-reported diabetes or the use of diabetes medication. In ADNI, information on diabetes was not specifically collected, and therefore, we relied on self-reported endocrine dysfunction (yes or no), which was collected in the medical history questionnaire. In both cohorts, systolic blood pressure was measured in participants' dominant arm in a seated position.

2.4. Apolipoprotein E genotyping

A blood sample was collected in each study for genotyping of apolipoprotein E (*APOE*). Heterozygotes and homozygotes for the ε4 allele were collapsed into a single category. Data on *APOE* were available for 300/312 HABS participants and all 336 ADNI participants.

2.5. Statistical analyses

Statistical analyses were performed using R, version 3.2.4. T-tests and χ^2 tests were used to determine differences in demographic and clinical variables between HABS and ADNI. We ran a series of linear mixed models to investigate the association of baseline Aβ burden with BMI change over time. In all analyses, longitudinal BMI values served as the outcome variable and the interaction of baseline Aβ burden with time served as the independent variable of interest. A random intercept for BMI and rate of change over time (slope) were included as model parameters for each participant. Time was operationalized as years from baseline. Baseline age and sex, and their interactions with time, were included as covariates. Because poorer cognition and depressive symptoms might lead to reduced BMI in late life (McMinn et al., 2011; Morley and Kraenzle, 1994), we further adjusted for cognitive performance and depressive symptoms at each visit. In addition, given known associations between blood pressure and BMI (Domonkos Tarnoki et al., 2013), we also adjusted for systolic blood pressure at each visit.

In post hoc analyses, we examined whether *APOE* ε4 status moderated the association between Aβ burden with BMI change because previous studies have suggested a stronger relationship in *APOE* ε4 carriers compared to noncarriers (Blautzik et al., 2018; Hsu et al., 2016). We also tested whether the association of Aβ burden with BMI change was driven by metabolic or endocrine disturbances. To do so, we repeated the primary analysis after excluding participants with diabetes in HABS or endocrine dysfunction in ADNI as well as participants who were underweight (BMI <18.5) or obese (BMI >30). This allowed us to test whether the association of Aβ burden with BMI change persisted in a normal or close-to-normal BMI sample without diabetes or endocrine disturbances, after adjusting for the aforementioned covariates (i.e., age, sex, cognitive performance, depressive symptoms, and systolic blood pressure).

All tests were 2-tailed and performed separately in HABS and ADNI. Aβ burden and BMI were considered as continuous variables in all analyses. Age was centered at the mean in each cohort; 72.2 years in HABS and 74.6 years in ADNI, and females were the reference group in both cohorts.

3. Results

3.1. Cohort differences in demographics

Table 1 summarizes the baseline characteristics of the participants included in the present study and highlights the demographic and clinical differences between HABS and ADNI. At baseline, relative to ADNI, HABS participants were significantly younger, had fewer years of education, had a higher proportion of females to males, had a lower proportion of Aβ-positive individuals, and scored higher on the GDS short form (i.e., endorsed a greater number of depressive symptoms). On average, HABS participants were followed for approximately 6 months longer than ADNI participants (HABS: 5.0 years, ADNI: 4.3 years) and had one additional visit (HABS: 6 visits; ADNI: 5 visits). There were no significant cohort differences in baseline BMI or the proportion of *APOE* ε4 carriers.

3.2. Higher Aβ burden is associated with faster BMI decline

Higher Aβ burden at baseline was associated with greater decline in BMI over time in both cohorts (Table 2 and Fig. 1; $\beta = -0.20$ and -0.33 for HABS and ADNI, respectively; these β values are not directly comparable because different Aβ-PET tracers were used in each cohort). With respect to covariates, in HABS, older age at baseline was significantly associated with faster decline in BMI (baseline age-by-time interaction, $p = 0.004$). In ADNI, there was an effect of older age with lower baseline BMI ($p < 0.001$); however, a longitudinal association between older age and decreasing BMI was not observed (baseline age-by-time interaction, $p = 0.41$). In HABS, cognitive performance was not associated with BMI ($p = 0.85$), although a significant positive association was observed in ADNI ($p = 0.05$). In HABS, there was a significant negative association between depressive symptoms and BMI ($p = 0.002$), whereas no significant association was observed in ADNI ($p = 0.64$). In both cohorts, greater systolic blood pressure was associated with greater BMI ($p < 0.01$).

3.3. Post hoc analyses

When we examined the possible 3-way interaction effects of Aβ burden, *APOE* ε4 status, and time on BMI change, this 3-way interaction was not significant in HABS (β= 0.04, standard error [SE] = 0.22, $t = 0.19$, $p = 0.85$). This same interaction was at trend level in ADNI (β= 0.51, SE = 0.26, $t = 1.92$, $p = 0.06$), whereby Aβ burden was more strongly associated with declining BMI in *APOE* ε4 noncarriers compared to carriers. In post hoc analyses, we also tested whether the association of Aβ burden with BMI change could be attributed to metabolic or endocrine disturbances. After excluding participants with diabetes or endocrine dysfunction as well as underweight or obese participants, the association of higher

Table 1
Baseline demographic and clinical characteristics by cohort

Variables	HABS (n = 312)	ADNI (n = 336)	*p* value
Age in years, mean (SD)	72.23 (7.46)	74.62 (6.46)	<0.001
Education in years, mean (SD)	15.86 (2.96)	16.48 (2.60)	0.005
Females, n (%)	190 (61)	177 (53)	0.05
APOE ε4 carriers, n (%)	88 (29)[a]	91 (27)	0.67
Aβ-PET DVR/SUVr, mean (SD)	1.17 (0.19)	1.12 (0.18)	–
Aβ+, n (%)	77 (25)	111 (33)	0.02
BMI, mean (SD)	26.81 (4.50)	27.43 (5.04)	0.10
Weight, kg, mean (SD)	76.2 (15.27)	77.2 (15.76)	0.40
Height, mean (SD)	66.23 (3.91)	66.03 (3.99)	0.52
Underweight (BMI <18.5), n (%)	7 (2)	1 (0.3)	0.03
Obese (BMI >30), n (%)	77 (25)	81 (27)	0.94
GDS (short form)	1.23 (1.34)	0.88 (1.15)	<0.001
Diabetes (HABS) or endocrine dysfunction (ADNI), n (%)	32 (10)[b]	143 (43)[c]	–
Years of follow-up after baseline, median (SD)	5.00 (2.04)	4.34 (1.96)	<0.001
Total number of visits, median (SD)	6.00 (1.94)	5.00 (1.36)	<0.001

We did not directly compare the mean Aβ PET values from the 2 cohorts given that different tracers were used.

Key: ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE* ε4, apolipoprotein E ε4; Aβ, amyloid-beta; BMI, body mass index; DVR, distribution volume ratio; GDS, Geriatric Depression Scale; HABS, Harvard Aging Brain Study; PET, positron emission tomography; SD, standard deviation; SUVr, standard uptake value ratio.

[a] Missing *APOE* ε4 data on 12 participants in HABS.

[b] Missing diabetes information on 13 participants in HABS.

[c] Missing endocrine dysfunction information on 4 participants in ADNI.

Table 2
Associations of Aβ burden with longitudinal decline in BMI by cohort

Model variables	β estimate	SE	t value	*p* value
BMI ~ (Aβ × time) + (age × time) + (sex × time) + (time-varying cognitive performance) + (time-varying depressive symptoms) + (time-varying systolic blood pressure)				
HABS (n = 312)				
Time	0.12	0.12	1.00	0.31
Aβ	−1.98	1.34	−1.48	0.14
Age	−0.05	0.03	−1.46	0.15
Sex	0.29	0.52	0.55	0.58
Cognitive performance	−0.013	0.07	−0.19	0.85
Depressive symptoms	**−0.07**	**0.02**	**−3.07**	**0.002**
Systolic blood pressure	**0.01**	**0.001**	**3.01**	**0.003**
Aβ × time	**−0.20**	**0.10**	**−1.93**	**0.05**
Age × time	**−0.01**	**0.003**	**−2.88**	**0.004**
Sex × time	0.01	0.04	0.31	0.76
ADNI (n = 336)				
Time	**0.32**	**0.15**	**2.06**	**0.04**
Aβ	**−3.29**	**1.46**	**−2.25**	**0.03**
Age	**−0.17**	**0.04**	**−4.02**	**< 0.001**
Sex	−0.78	0.54	−1.45	0.15
Cognitive performance	**0.13**	**0.06**	**1.98**	**0.05**
Depressive symptoms	0.01	0.02	0.47	0.64
Systolic blood pressure	**0.01**	**0.002**	**6.09**	**<0.001**
Aβ × time	**−0.33**	**0.13**	**−2.54**	**0.01**
Age × time	−0.003	0.004	−0.82	0.41
Sex × time	−0.05	0.05	−0.95	0.34

Separate models were run in HABS and ADNI. Bolded values are significant.
Key: Aβ, amyloid-beta; ADNI, Alzheimer's Disease Neuroimaging Initiative; BMI, body mass index; HABS, Harvard Aging Brain Study; SE, standard error.

Aβ burden with BMI change remained significant in both HABS (β= −0.22, SE = 0.11, $t = -1.11$, $p = 0.04$) and ADNI (β = −0.36, SE = 0.17, $t = -2.19$, $p = 0.03$), suggesting that the primary results were not driven by these factors.

4. Discussion

The present study demonstrated that higher Aβ burden at baseline, as measured by PET, was associated with greater decline in BMI over time. This association was significant in 2 independent cohorts of clinically normal adults after adjusting for age, sex, cognitive performance, depressive symptoms, and blood pressure. The association between higher Aβ burden and greater longitudinal decline in BMI also remained significant after excluding participants with diabetes/endocrine dysfunction and participants considered underweight or obese. This latter result indicates that the association of Aβ burden with longitudinal decline in BMI was not driven by the presence of diabetes/endocrine conditions or by individuals with very high or low BMIs. Together, these findings suggest that declining BMI in clinically normal adults may be an early indicator of elevated Aβ burden.

Our results are in agreement with several cross-sectional studies in clinically normal older adults demonstrating that lower BMI is associated with higher levels of Aβ burden as measured by PET (Hsu et al., 2016; Thirunavu et al., 2019) or with cerebrospinal fluid markers of Aβ and tau (Ewers et al., 2012; Vidoni et al., 2011). Similar relationships have also been reported at autopsy in non-demented older adults, whereby lower BMI proximate to death was associated with increased AD pathology (Buchman et al., 2006). Interestingly, in that study, the relationship was specific to AD pathology, as neither cerebral infarcts nor Lewy body pathology was related to BMI. Our findings are also consistent with recent work in autosomal dominant AD, showing that mutation carriers have significantly lower BMI than noncarriers, and that this difference is evident more than 10 years before expected symptom onset (Müller et al., 2017). The present longitudinal results build on the previously mentioned cross-sectional findings by demonstrating that higher Aβ burden at baseline was associated with greater decline in BMI over time. The relatively large sample size (>300 in each cohort) and long follow-up period (a median of >4 years) likely yielded increased power to detect associations in the preclinical stage of the disease, given that a prior longitudinal study in ADNI with a smaller sample size (n = 100) and only up to 2 follow-up visits did not observe a significant association (Vidoni et al., 2011).

Some researchers have suggested that cognitive impairment itself contributes to late-life weight loss (Gustafson, 2006); however, the participants in the present study were clinically normal at baseline, which argues against this explanation. Furthermore, the association of higher Aβ burden with declining BMI was significant after adjusting for cognitive performance in both cohorts, suggesting that worsening cognition was not driving the effect. Depressive symptoms have also been linked to both late-life weight loss (McMinn et al., 2011; Morley and Kraenzle, 1994) and AD pathology across the clinical course of the disease (Donovan et al., 2018; Gatchel et al., 2017; Rapp et al., 2008). Importantly, the association between baseline Aβ burden and change in BMI was independent of GDS scores in both cohorts, suggesting that this association cannot be explained by depressive symptoms. In the HABS sample alone, we found that higher depressive symptoms were significantly associated with lower BMI. This finding is consistent with the idea that weight loss is a key feature of depression in late-life (Morley, 2001) and may be due to apathy toward normally appetitive behaviors (Mann, 2005).

When we examined the influence of *APOE* ε4 genotype on the association between Aβ burden and BMI decline, we found that it did not moderate the association in HABS; however, there was a trend toward significance in ADNI, whereby Aβ-related decline in BMI was stronger in *APOE* ε4 noncarriers compared to carriers. The literature has been mixed with regards to whether *APOE* ε4 genotype moderates the relationship between Aβ burden and BMI. Two prior cross-sectional studies reported no moderating effect of *APOE* ε4 status (Ewers et al., 2012; Thirunavu et al., 2019), whereas 2 other cross-sectional studies found that Aβ burden was associated with lower BMI in *APOE* ε4 carriers, but not noncarriers (including one from HABS; Blautzik et al., 2018; Hsu et al., 2016). The reasons for the discrepancies are not clear and require further investigation.

Post hoc analyses also investigated whether the association between Aβ burden and BMI decline was related to the presence of diabetes/endocrine dysfunction or underweight/obese individuals. Importantly, the results remained largely unchanged after excluding such participants despite significantly reduced sample sizes (HABS = 195 and ADNI = 155). These findings suggest that the association of elevated Aβ burden with BMI decline is observable even in individuals with normal or close-to-normal BMIs at baseline and in those without diabetes or endocrine dysfunction.

The biological mechanisms underlying the relationship between higher Aβ burden and accelerated decline in BMI remain unclear. One possibility is that Aβ accumulation (or possibly Aβ-associated tau pathology) may interfere with the functioning of the hypothalamus, which serves to regulate body weight and systemic metabolism (Ishii and Iadecola, 2016). It has been suggested that altered hypothalamic function may reduce leptin levels and cause a hypermetabolic state, which can accelerate weight loss (Hiller and Ishii, 2018; Ishii et al., 2014). Another possibility is that AD pathology and/or downstream neurodegeneration may reduce olfactory function (Bacon et al., 1998; Growdon et al., 2015), increase anxiety (Hanseeuw et al., 2018; Ramakers et al., 2013) or increase apathy (Lanctot et al., 2017), all of which can decrease food intake

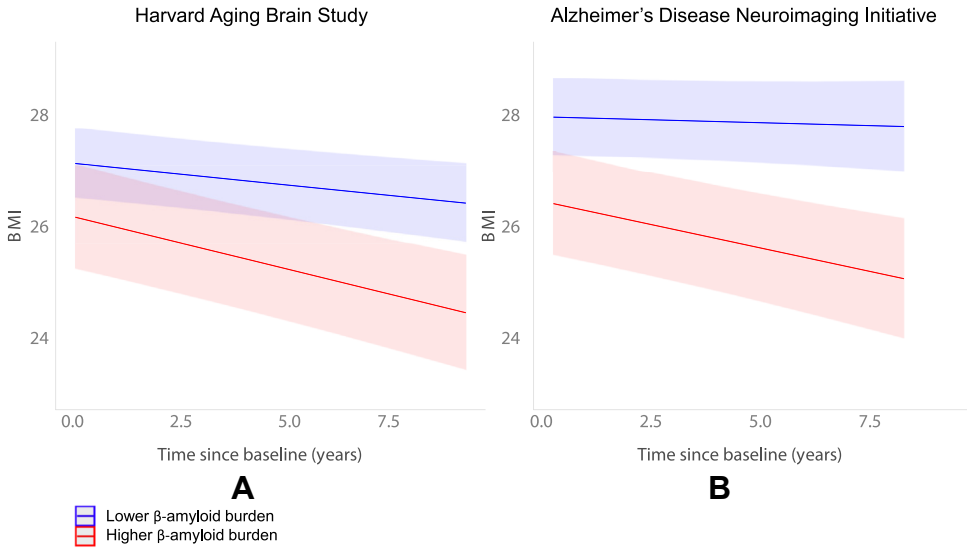

Fig. 1. Higher baseline Aβ burden was associated with accelerated decline in body mass index. For visualization purposes, modeled longitudinal change in body mass index (BMI) is depicted at lower and higher levels of Aβ based on Aβ values at the 10th and 90th percentiles, respectively, in each cohort. The plots demonstrate that greater Aβ burden at baseline is associated with more rapid decline in BMI over time in (A) the Harvard Aging Brain Study and (B) the Alzheimer's Disease Neuroimaging Initiative. Shaded regions represent the 95% confidence intervals.

and cause a decline in BMI. Alternatively, it may be that metabolic changes associated with a decline in BMI instigate or exacerbate Aβ deposition or that a common upstream process drives both Aβ and decline in BMI (e.g., inflammatory processes; Morris et al., 2014).

Strengths of the present study were the replication of our findings across 2 independent cohorts with Aβ-PET imaging and BMI follow-up data over a median period of >4 years. In addition, HABS and ADNI used different Aβ tracers (PiB and florbetapir, respectively), suggesting that the results are not dependent on a specific Aβ tracer. There were also several limitations. First, we relied on BMI as our outcome measure, as this was the only anthropometric measure available in both cohorts. However, BMI does not differentiate between fat tissue and lean muscle mass and therefore may not be an optimal measure of adiposity (Burns et al., 2010). Future studies using more accurate measurements of body composition (e.g., imaging adipose tissue) may provide a better understanding of the relationship between Aβ burden and weight loss in preclinical AD. Second, we did not include measures of tau pathology in the present study, as tau PET was collected several years after Aβ PET in both HABS and ADNI. Future studies should investigate whether decline in BMI is accelerated in individuals with both elevated Aβ and tau deposition. Third, since ADNI did not collect information on diabetes specifically, we relied on self-reported endocrine dysfunction. Fourth, given the sample size of each cohort, there may have been insufficient power to conduct analyses moderated by *APOE* ε4 status; therefore, these analyses should be interpreted cautiously. Fifth, longitudinal physical activity was not assessed in HABS or ADNI. It may, however, be an important confounder given that reduced physical activity is associated with weight loss in older adults (Baumgartner et al., 1999) and may also accelerate Aβ-related cognitive decline and neurodegeneration (Rabin et al., 2019). Finally, participants in HABS and ADNI are generally well educated, predominantly Caucasian, and generally healthy (i.e., may underrepresent individuals with high vascular risk). These factors may limit the generalizability of our findings and it will be important to replicate our results in more diverse cohorts.

5. Conclusions

We provide new evidence from 2 independent, well-characterized cohorts that higher Aβ burden at baseline is associated with greater decline in BMI in clinically normal adults. Importantly, this association persisted after adjusting for several important covariates, including cognitive performance, depressive symptoms, and metabolic or endocrine dysfunction. These findings lend credence to the idea that declining BMI in late life may not only be due to normal age-related processes, but may also be an early indicator of elevated Aβ burden.

CRediT authorship contribution statement

Jennifer S. Rabin: Methodology, Conceptualization, Writing - original draft, Data curation, Formal analysis, Writing - review & editing. **Zahra Shirzadi:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Walter Swardfager:** Conceptualization, Writing - original draft, Writing - review & editing. **Bradley J. MacIntosh:** Conceptualization, Writing - original draft, Writing - review & editing. **Aaron Schultz:** Data curation, Writing - original draft, Writing - review & editing. **Hyun-Sik Yang:** Methodology, Conceptualization, Writing - original draft, Writing - review & editing. **Rachel F. Buckley:** Writing - original draft, Writing - review & editing. **Jennifer R. Gatchel:** Writing - original draft, Writing - review & editing. **Dylan Kirn:** Writing - original draft, Writing - review & editing, Project administration. **Jeremy J. Pruzin:** Writing - original draft, Writing - review & editing, Conceptualization. **Trey Hedden:** Writing - original draft, Writing - review & editing, Conceptualization. **Nir Lipsman:** Writing - original draft, Writing - review & editing, Conceptualization. **Dorene M. Rentz:** Writing - original draft, Writing - review & editing, Conceptualization. **Sandra E. Black:** Writing - original draft, Writing - review & editing, Conceptualization. **Keith A. Johnson:** Writing - original draft, Writing - review & editing, Conceptualization, Funding acquisition. **Reisa A. Sperling:** Methodology, Conceptualization, Writing - original draft, Funding acquisition, Writing - review & editing. **Jasmeer P. Chhatwal:**

Methodology, Conceptualization, Writing - original draft, Funding acquisition, Writing - review & editing.

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