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Beta-amyloid and cognitive decline in late middle age: Findings from the WRAP study

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Abstract

Introduction—The current study investigated the relationship between beta-amyloid (Aβ) and cognition in a late middle-aged cohort at risk for Alzheimer's disease (AD).

Methods—184 participants (mean age=60; 72% parental history of AD) completed a [C-11]PiB positron emission tomography scan and serial cognitive evaluations. A global measure of Aβ burden was calculated, and composite scores assessing learning, delayed memory, and executive functioning were computed.

Results—Higher Aβ was associated with classification of psychometric mild cognitive impairment (MCI) at follow-up ($p < .01$). Linear mixed-effects regression results indicated higher Aβ was associated with greater rates of decline in delayed memory ($p < .01$) and executive functioning ($p < .05$). *APOE* ε4 status moderated the relationship between Aβ and cognitive trajectories ($p's < .01$).

Discussion—In individuals at risk for AD, greater Aβ in late middle-age is associated with increased likelihood of MCI at follow-up and steeper rates of cognitive decline.

Keywords

Alzheimer's disease; amyloid imaging; preclinical Alzheimer's disease; mild cognitive impairment; cognition; APOE

1. Background

Beta-amyloid (Aβ) deposition is hypothesized to occur early in the development of Alzheimer's disease (AD), possibly 15-20 years prior to a dementia diagnosis [1, 2]. The reported relationship between Aβ and cognition measured at a single assessment in cognitively healthy individuals has been inconsistent, with some studies reporting modest associations [3-8] and others demonstrating no significant relationship [9-12]. However, longitudinal studies examining a variety of cognitive domains and ranging from 6-month to 10-year intervals more consistently reveal negative relationships between Aβ and cognition [13-21]. Moreover, genetic risk for AD (possession of the apolipoprotein E ε4 (*APOE* ε4) allele) may moderate this relationship [22-25].

Most studies have focused on the relationship between Aβ, *APOE*, and cognition in older adults (e.g., over age 65) at risk for AD with fewer investigations in middle age (e.g., ages 45-65). Since Aβ is hypothesized to accumulate early and then plateau [1, 26], it may be possible to detect a subtle, yet clinically meaningful, relationship between Aβ and cognitive decline in midlife while Aβ is accumulating and cognition begins declining. Higher Aβ in middle age may also provide earlier prediction of disease progression. The objective of this study was to examine whether Aβ is associated with longitudinal cognitive change in a late middle-aged cohort enriched for parental history of AD (Wisconsin Registry for Alzheimer's Prevention (WRAP)). The first aim investigated whether Aβ is associated with classification

of psychometric Mild Cognitive Impairment (MCI) at remote follow-up. The second aim was to determine whether Aβ is associated with longitudinal cognitive trajectories. The third aim explored whether *APOE* ε4 moderates the relationship between Aβ and cognitive trajectories. We hypothesized that higher Aβ would be associated with increased MCI and greater cognitive decline, and that the association between Aβ and cognitive decline would be strongest in *APOE* ε4 carriers.

2. Materials and Methods

2.1 Participants

Participants were selected from the WRAP, a late middle-aged, cognitively healthy longitudinal cohort (mean age = 53.6 years, SD = 6.6, at baseline) enriched for AD risk factors of *APOE* ε4 carrier status (40%) and parental history of AD (72%) [27]. The WRAP protocol includes a baseline neuropsychological evaluation (Wave 1), a second visit four years after baseline (Wave 2), and subsequent visits every two years (Waves 3-4). Because a subset of neuropsychological measures was not initiated until Wave 2, the current study design included data collected at Waves 2, 3, and 4, excluding Wave 1. Participants in the current sample (n = 184) also completed a neuroimaging procedure. The number of participants whose last visit was Wave 2, 3, or 4 was 6 (3%), 53 (29%), and 125 (68%), respectively. Of the 59 participants who had not completed Wave 4, only 2 (1%) were no longer enrolled in WRAP (1 due to dementia diagnosis, 1 deceased), and 57 remained enrolled but had not yet returned for follow-up due to the staggered enrollment of participants. The University of Wisconsin Institutional Review Board approved all study procedures and each participant provided signed informed consent before participation.

2.2 Study Procedures

2.2.1 MRI and PET acquisition—All participants completed a 70-minute dynamic [C-11]Pittsburgh compound B (PiB) positron emission tomography (PET) scan on a Siemens EXACT HR+ scanner and a T1-weighted anatomical scan on a GE 3.0 Tesla MR750 (Waukesha, WI) using an 8 channel head coil, typically acquired on the same day. The neuroimaging procedure was completed on average 1.4 years (SD = 1.4) after the Wave 2 WRAP visit. Anatomical scans were reviewed by a neuroradiologist (H.A.R.) for exclusionary abnormalities. Detailed methods for [C-11]PiB radiochemical synthesis, PiB-PET scanning, and distribution volume ratio (DVR) map generation have been described previously [12, 28]. Briefly, the reconstructed PET data time series were motion corrected, denoised, and coregistered to the T1-weighted anatomical scan, and data were transformed into voxel-wise DVR images representing [C-11]PiB binding using the time activity from the cerebellum gray matter as a reference function.

Eight bilateral AD-sensitive regions-of-interest (ROIs; angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus) were selected from the automated anatomical labeling (AAL) atlas and were standardized and reverse warped to native space. A composite measurement of global amyloid was calculated [29], and used as the measure of Aβ.

2.2.2 Cognitive measures—Cognitive composite scores were used to reduce measurement error and potential Type I error associated with conducting multiple comparisons. Three composite scores for each of waves 2-4 were calculated by transforming raw scores to z-scores using the means and standard deviations of the current sample at each wave and averaging the z-scores for the three measures (listed below) included in each composite score.

1. Learning: Rey Auditory Verbal Learning Test (RAVLT) [30] total trials 1-5, Wechsler Memory Scale-Revised Logical Memory subtest (WMS-R LM) [31] immediate recall, Brief Visuospatial Memory Test (BVMT-R) [32] immediate recall.
2. Delayed recall: RAVLT long-delay free recall, WMS-R LM delayed recall, BVMT-R delayed recall.
3. Executive functioning: Trail Making Test Part B (TMT B) [33] total time to completion, Stroop Neuropsychological Screening Test [34] color-word interference total items completed in 120 seconds, Wechsler Abbreviated Intelligence Scale-Revised (WAIS-R) [35] Digit Symbol Coding total items completed in 90 seconds. The z-score for TMT B was reversed prior to inclusion in the composite so that higher z-scores indicated better performance for all tests.

An estimate of literacy (Wide Range Achievement Test – 3rd Edition reading subtest) was included as a covariate [36].

2.2.3 Classification of MCI and cognitively normal—Participants were classified as cognitively normal (CN) or psychometric MCI (pMCI) based on neuropsychological performances at their most recent WRAP visit (mean (SD) = 1.7 (0.8) years following PiB-PET scan). The pMCI criterion was developed to identify participants with very mild impairment who may progress to a clinical diagnosis of MCI. Specifically, participants were classified as having pMCI if performances on at least two individual tests within a cognitive domain (learning, delayed recall, executive functioning), or one test in each of the three cognitive domains, were at least 1.5 standard deviations below the mean of an internally-derived robust normative sample [37, 38]. The robust normative sample included 476 WRAP participants that remained cognitively normal throughout the duration of the study.

2.3 Statistical analyses

All statistical analyses were conducted in SPSS version 22. Statistical significance was defined as $p < .05$ unless specified otherwise.

2.3.1 Relationship between beta-amyloid and follow-up cognitive status—A logistic regression analysis examined if Aβ predicted follow-up cognitive status at most recent visit (CN versus pMCI), controlling for covariates of age at PiB-PET scan, sex, literacy, number of years enrolled in WRAP, and interval (years) between PiB-PET scan and most recent neuropsychological evaluation.

2.3.2 Relationship among beta-amyloid and longitudinal cognitive trajectories—Linear mixed effects regression allows modeling of fixed effects (e.g., overall patterns on cognitive measures across visits) while accounting for random effects (e.g., variation associated with individual differences) and may detect decline on cognitive measures that does not exceed a specific clinical cut-off. Analyses were conducted with each cognitive composite score (learning, delayed recall, executive functioning) as an outcome variable. First, unconditional means and growth models adjusting for random effects of intercept and slope were examined for each of two covariance-variance structures (uncorrelated intercept and slope ('variance components') and correlation permitted between intercept and slope ('unstructured')). The final covariance-variance structure was selected based on model fit indices (Akaike Information Criterion). Subsequent conditional models included significant random effects plus fixed effects of sex, literacy, interval between Wave 2 cognitive evaluation and PiB-PET scan (years), Aβ (PiB DVR), time (age [centered] at each visit), and the interaction of time × Aβ. Time was operationalized as the age at each WRAP visit to provide more precise information about participants at each evaluation compared to a fixed time-structured variable. A Bonferroni correction was applied to correct for multiple comparisons (i.e., family-wise alpha = .05 was divided by 3; .05/3 = .017 significance level used for each outcome variable).

2.3.3 Effect of *APOE* ε4 on the relationship between beta-amyloid and longitudinal cognitive trajectories—Similar regression models were conducted, with additional fixed effects of *APOE* ε4 status (ε4 carrier vs non-carrier), *APOE* ε4 status × time, *APOE* ε4 status × Aβ, and *APOE* ε4 status × Aβ × time included in the models. To explore the three-way interaction, follow-up simple effects analyses were conducted. Specifically, the conditional model (sex, literacy, interval, Aβ, time, time × Aβ) was conducted within ε4 carrier and non-carrier groups separately.

3. Results

3.1 Sample characteristics

Sample characteristics are displayed in Table 1. At the WRAP visit conducted nearest to the PiB-PET scan, 30 participants (16%) were classified as pMCI and 154 as CN. At the most recent WRAP visit approximately 2 years following the PiB-PET scan, 28 (15%) were classified as pMCI and 156 remained CN. Of these 28, 17 were also classified as pMCI at the WRAP visit closest to the PiB-PET scan. Mean performances on the neuropsychological measures included in composite scores are displayed in Table 2.

3.2 Relationships among Aβ, AD risk factors, and cognitive status at follow-up

APOE ε4 carriers demonstrated significantly greater Aβ (M = 1.20) than non-carriers (M = 1.14), $t(124.39)$ = -2.47, $p < .05$. Figure 1 depicts Aβ by age at PiB-PET scan for *APOE* ε4 carriers and non-carriers. Higher Aβ was significantly associated with a greater likelihood of pMCI classification at the most recent follow-up visit, Wald $X^2(1) = 4.66$, $\beta = 2.64$, $p < .05$. The full model explained 18% of the variance in cognitive status (Nagelkerke R^2), and correctly classified 84.8% of cases (-2LL = 137.16, $X^2 = 19.78$, $p < .01$). Figure 2 displays the distribution of PiB DVR values for the CN and pMCI groups. A *post-hoc* analysis

indicated that Aβ was not significantly associated with cognitive status at the visit closest to the PiB-PET scan, Wald $X^2(1) = 1.86$, β=1.54, $p = .17$. Additional *post hoc* analyses included Wave 2 composite scores in addition to Aβ in the model as predictors. Results demonstrated that although the cognitive composite scores exhibited stronger relationships with cognitive status at follow-up, Aβ remained a significant contributor to follow-up cognitive status (all p's < .02).

3.3 Relationships between Aβ and longitudinal cognitive trajectories

Results from linear mixed effects regression models examining the relationship between Aβ, time, and composite score at each visit are presented in Table 3. A significant interaction between time and Aβ indicated higher Aβ was associated with increased rate of decline in delayed recall performance, $F(1,309.33) = 9.42$, $B = -.14$, $p = .002$ (Figure 3 middle left). The interaction between time and Aβ for learning performance did not reach statistical significance, $F(1,485.11) = 3.82$, $B = -.08$, $p = .051$ (Figure 3 top left). A significant main effect of time indicated that as individuals progressed through the study, learning performance decreased, $F(1,431.96) = 11.18$, $B = -.02$, $p = .001$. A smaller, though statistically significant effect was observed for the interaction between time and Aβ for executive functioning, indicating higher Aβ was associated with increased rate of decline in executive functioning performance, $F(1,444.95) = 5.87$, $B = -.09$; $p = .016$ (Figure 3 bottom left).

3.4 Effect of APOE ε4 on the relationship between Aβ and longitudinal cognitive trajectories

Results from linear mixed effects regression models examining the relationship between Aβ, time, *APOE*, and composite score at each visit are presented in Table 3. A significant three-way interaction among time, Aβ, and *APOE* was present for delayed recall, $F(1,347.01) = 20.92$, $p < .001$, and learning, $F(1,473.78) = 9.97$, $p < .01$ (Figure 3 right). The three-way interaction term neared the Bonferroni-adjusted alpha of .017 for the executive functioning composite score, $F(1,423.98) = 5.56$, $p = .02$. Simple effects analysis revealed a significant interaction between time and Aβ on delayed recall within *APOE* ε4 carriers, $F(1,144.08) = 24.57$, $B = -.36$, $p < .001$, but not within non-carriers, $F(1,165.88) = 0.44$, $B = .04$, $p = .51$. Similarly, a significant interaction effect was observed within *APOE* ε4 carriers for learning, $F(1,174.82) = 12.52$, $B = -.23$, $p = .001$, but was non-significant within the non-carriers, $F(1,300.58) = 0.37$, $B = .03$, $p = .54$.

Although PiB was included as a continuous variable, a *post-hoc* analysis used a median split procedure to explore potential differences between ε4 carriers and non-carriers with higher and lower Aβ levels. As depicted in Figure 3 (right), ε4 carriers with lower Aβ exhibited a lack of decline in contrast with ε4 carriers with high Aβ and non-carriers. The ε4+/low Aβ group comprised fewer participants (n=31; ε4+/high Aβ: n=42; ε4-/low Aβ: n=61; ε4-/high Aβ: n=50) and were younger than the ε4-/low Aβ group ($p < .05$). Moreover, the ε4+/low Aβ group comprised fewer participants that had not yet completed Wave 4 (∼50%) compared with the ε4+/high Aβ group (∼70%). With the exclusion of Wave 4 data, the interaction of time × *APOE* × Aβ remained statistically significant for both learning and delayed recall,

suggesting group differences could not be fully explained by fewer data points in the ε4+/low Aβ group.

4. Discussion

Although AD pathology begins years before clinical symptoms emerge [39], and cognitive impairment develops several years prior to an MCI or dementia due to AD diagnosis [40], the relationship between the earliest detectable pathology and cognitive change is not well understood. Prior longitudinal studies observed that older adults with greater Aβ exhibited increased rates of cognitive decline [13-21]. The current study adds that higher Aβ in midlife in those at risk for AD is associated with steeper cognitive decline resulting in a greater incidence of progression to pMCI.

4.1 Beta-amyloid predicts follow-up classification of psychometric Mild Cognitive Impairment

Approximately 15% was classified as pMCI at the evaluation nearest the PiB-PET scan and at the most recent cognitive evaluation. While Aβ was not associated with cognitive status at the visit closest to the PiB-PET scan, higher Aβ was associated with greater likelihood of pMCI classification at approximately two-year follow-up. Although neuropsychological performance demonstrated stronger relationships with follow-up cognitive status (previously shown in [41]), Aβ remained a significant contributor to the models, suggesting it may account for variance in follow-up cognitive status not explained by cognitive performance. These results are consistent with prior studies demonstrating greater rates of progression to MCI or dementia in participants with higher Aβ. For example, one study observed that 16% of older controls with high Aβ developed MCI or dementia within 2 years, and 25% progressed within 3 years [42]. The current sample is younger (mean age = 60) than that described by Villemagne and colleagues [42] (mean age = 73), and suggests that higher Aβ predicts progression to neuropsychological impairment that may precede a clinical MCI diagnosis. However, as the construct of pMCI represents a milder form of decline, it will be necessary to document whether these individuals progress to clinical diagnoses with continued follow-up.

4.2 High beta-amyloid is associated with cognitive decline

Aβ was associated with an increased rate of decline in delayed memory and executive functioning. Results indicated a stronger relationship between Aβ and delayed memory decline compared with learning and executive functioning, consistent with prior findings [8]. Previous cross-sectional studies of Aβ and cognition in the WRAP cohort have been mixed. For example, baseline cognitive performance did not differ between groups divided into Aβ-positive, Aβ-negative, and Aβ-indeterminate [12]. Additionally, no differences in precuneus amyloid load were observed between a “stable” and “decliner” group defined by RAVLT performance [41]. However, a recent cross-sectional study demonstrated greater age-related decline in processing speed among Aβ-positive compared to Aβ-negative participants, suggesting that ‘normal’ changes in cognition that occur with aging may be accelerated in the presence of amyloid pathology [43].

The current study differed from these prior studies in quantification of Aβ (composite measure across eight ROIs examined continuously) and the longitudinal method of measuring cognition (mean slopes across four years). By examining mean slopes, while accounting for individual differences through inclusion of random effects, the current analysis attempted to detect meaningful change, even if cognitive performance fell within a "normal" range. For example, decline in cognitive performance associated with higher Aβ remained within the normal range (declines from ∼z = 0.5 to ∼z = -0.5), and average performances on cognitive measures remained within normal limits at each visit. These results of subtle cognitive decline associated with Aβ may be difficult to detect via traditional clinical methods and cross-sectional designs, and are consistent with findings in longitudinal cohorts of older adults such as Baltimore Longitudinal Study of Aging (BLSA) [18], AIBL [20], and the Harvard Aging Brain study [17]. Our findings suggest that this Aβ-associated decline may be detected in younger ages than previously examined.

4.3 APOE ε4 moderates the relationship between beta-amyloid and cognitive decline

Similar to prior studies, *APOE* ε4 carriers exhibited higher Aβ than non-carriers [22, 44]. Furthermore, the presence of *APOE* ε4 moderated the association between Aβ and cognitive decline. Although some studies reported null effects of *APOE* genotype on rates of decline [20, 45], our results of a moderating effect of *APOE* are consistent with subsequent studies utilizing larger sample sizes and longitudinal follow-up [22-24]. The current results were driven by a significant interaction between Aβ and time within *APOE* ε4 carriers that was not observed within non-carriers. As displayed in Figure 3, the association between higher Aβ and time on memory performance in ε4 carriers was negative and demonstrated the steepest rate of decline. An unexpected positive association was observed between lower Aβ and time on memory performance in ε4 carriers. The latter result may be due to sampling bias, as ε4 carriers with low Aβ were less prevalent and younger than other participants, and included fewer participants that had yet to return for their fourth evaluation. However, results from a *post-hoc* analysis suggested that varied number of observations did not fully account for differences between ε4 carriers with high or low Aβ. It is possible that the sample size was too small to adequately investigate the interaction between Aβ and *APOE*, and follow-up studies on larger samples are required to replicate these findings. Interestingly, a very recent study of older adults within the AIBL cohort similarly reported unexpected findings of improved memory performance in ε4 carriers with low Aβ compared to non-carriers with low Aβ [46], which may warrant investigation of potential protective mechanisms in this group.

The mechanisms underlying the relationship between *APOE* ε4 and Aβ are becoming increasingly understood (see [47]). *APOE* ε4 carriers exhibit Aβ approximately 20 years earlier than non-carriers (e.g., age 55 compared to age 75). *APOE* ε4 may moderate cognitive decline and increase risk for AD by initiating and accelerating Aβ accumulation, aggregation, and clearance in the brain. *APOE* ε4 carriers could also be more vulnerable to Aβ-related toxicity due to Aβ-independent effects on neuronal integrity ([48]).

4.4 Limitations and future directions

The current study used a global composite measure of Aβ to summarize diffuse pathology in regions with reported increased PiB binding levels in AD; however, it is possible that regionally-specific relationships between Aβ and cognition are not captured. Furthermore, the PiB-PET scan was not acquired concurrently with the initial cognitive evaluation, complicating attempts to characterize the specific time course of Aβ development and cognitive decline. Additionally, the current study did not examine potential effects of neurofibrillary tangle pathology, neurodegeneration, or cerebrovascular disease on cognitive decline. However, incorporation of both Aβ and neuronal injury measures may provide the most accurate prognosis [49], and this is a future direction. Moreover, the sample is enriched for AD risk, and is a highly educated, mostly Caucasian sample from the Midwest region of the U.S. These results may not generalize to population-based samples of normally aging middle-aged adults.

Despite these limitations, results suggest that Aβ burden in late middle-age is associated with cognitive decline over a four-year period and predictive of pMCI diagnosis at follow-up in individuals at risk for AD. Furthermore, *APOE* ε4 carriers with greater Aβ may decline faster than ε4 carriers with low Aβ or non-carriers. These results suggest that identification of preclinical AD may be possible in cognitively healthy middle-aged adults with higher Aβ who may benefit most from clinical trials attempting to slow the rate of cognitive decline prior to the onset of clinical symptoms of MCI or dementia.

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Research in Context

Systematic Review

A literature review was conducted using PubMed and Web of Science databases to identify studies of beta-amyloid, PiB-PET, *APOE* genotype, and cognition. Although cross-sectional studies were mixed, longitudinal studies described consistent associations between greater beta-amyloid and memory decline. The majority of studies focused on elderly samples, with few on middle-aged individuals.

Interpretation

This study contributes to the literature by demonstrating that higher beta-amyloid is associated with steeper decline in delayed recall and executive functioning in a middle-aged cohort, resulting in greater progression to mild cognitive impairment. This relationship was strongest in *APOE* ε4 carriers.

Future directions

Research questions generated include further exploration of 1) distinct effects of beta-amyloid on cognition within *APOE* ε4 carriers, 2) cognitive decline on neuropsychological measures comprising composites and associated with beta-amyloid in particular brain regions, and 3) potential moderating effects of neurofibrillary tangle pathology, neurodegeneration, and cerebrovascular disease on cognition in middle age.

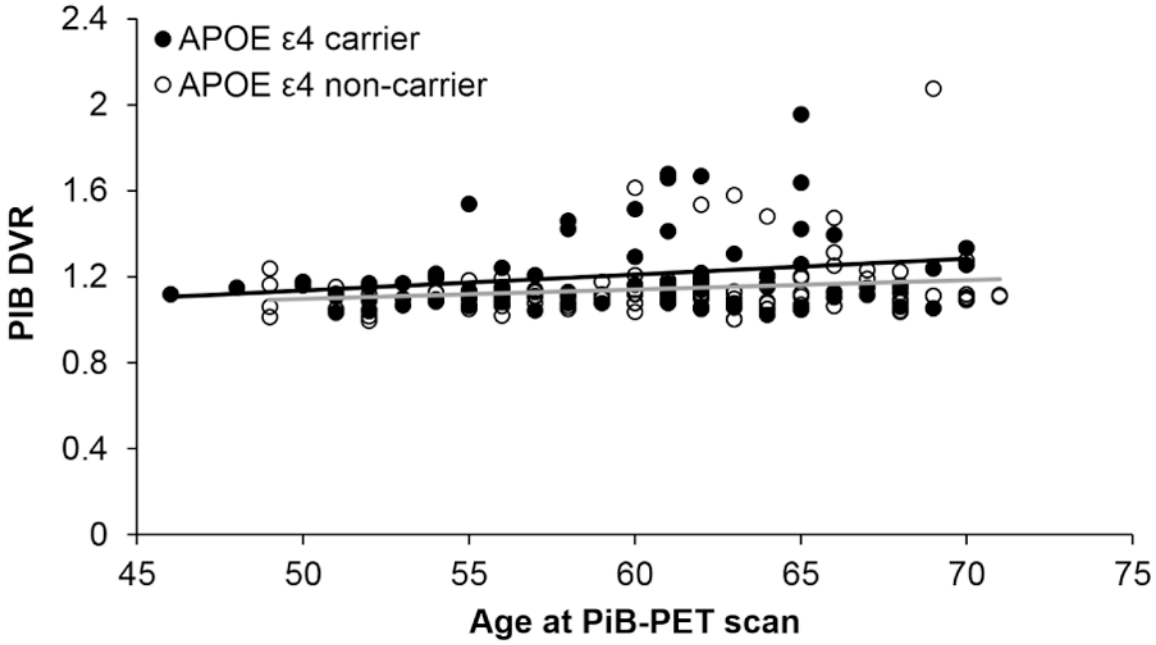

Figure 1. Relationship between Aβ burden (PiB DVR) and age at PiB-PET scan for APOE ε4 carriers and non-carriers

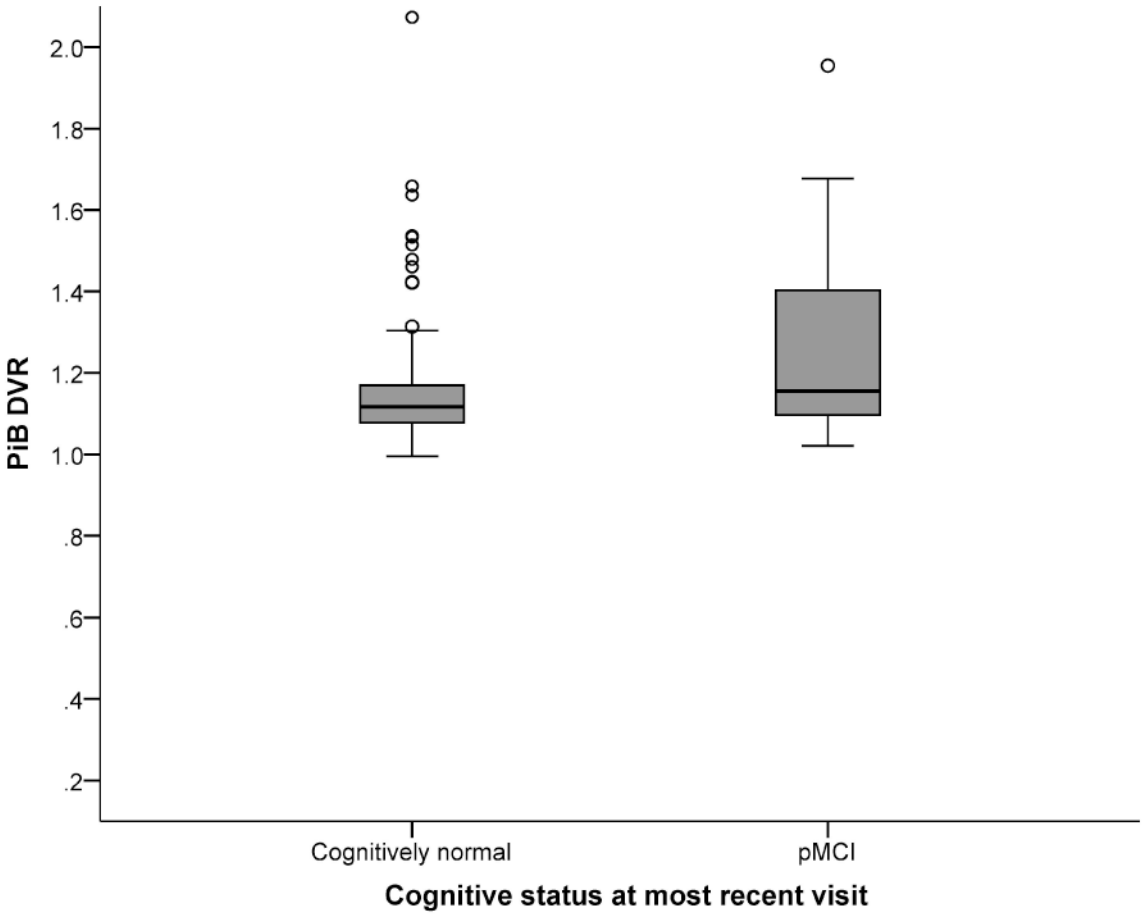

Figure 2.

Distribution of Aβ burden (PiB DVR values) for participants classified as cognitively normal or psychometric Mild Cognitive Impairment (MCI) at most recent cognitive evaluation.

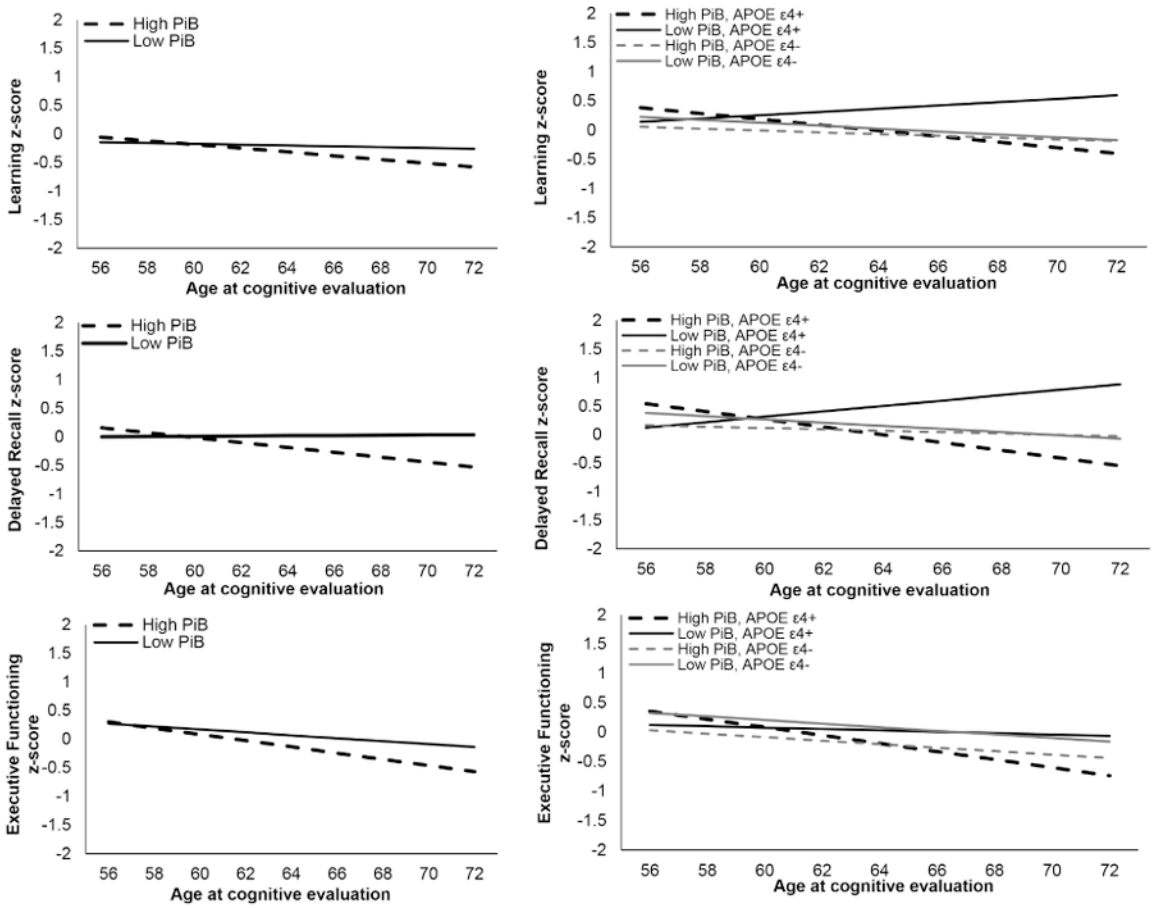

Figure 3.

Linear association between global PiB retention and standardized cognitive performance over time, adjusted for other predictors in models (Left). Linear association between *APOE* ε4 carrier status (carrier vs non-carrier), global PiB retention, and standardized cognitive performance over time, adjusted for other predictors in models (Right). High PiB was defined as 1 standard deviation above the sample mean and low PiB was defined as 1 standard deviation below the sample mean.

Table 1
Sample demographic and clinical characteristics

	Total Sample	Cognitively Normal at follow-up	Psychometric MCI at follow-up
N	184	156	28
Age			
At Wave 2 study visit	58.6 (5.8)	58.4 (5.9)	59.6 (5.2)
At PiB-PET scan	60.3 (5.8)	60.0 (5.9)	61.9 (5.0)
Sex (F/M; %F)	126/58 (69%)	107/49 (69%)	19/9 (68%)
Education (years)	16.1 (2.4)	16.1 (2.3)	15.7 (2.5)
WRAT-III standard score	106.8 (9.3)	106.7 (9.6)	107.7 (8.0)
Years enrolled in WRAP	7.7 (1.5)	7.6 (1.5)	8.3 (1.6)
APOE ε4 allele (ε 4/non- ε4; % ε4)	73/111 (40%)	61/95 (39%)	12/16 (43%)
Parental history of AD (+/-; %+)	133/51 (72%)	109/47 (70%)	24/4 (86%)
Cortical PiB DVR	1.2 (0.2)	1.1 (0.1)	1.3 (0.2)
Interval: PiB-PET & Wave 2	1.4 (1.4)	1.3 (1.3)	2.0 (1.5)
WRAP visit			
Interval: PiB-PET & most recent	1.7 (0.8)	1.8 (0.8)	1.3 (0.9)
WRAP visit			

PiB-PET = [C-11]Pittsburgh compound B Positron Emission Tomography, WRAT-III = Wide Range Achievement Test – 3rd Edition reading subtest, PiB DVR = [C-11]Pittsburgh compound B Distribution Volume Ratio. WRAP = Wisconsin Registry for Alzheimer's Prevention, *APOE* = apolipoprotein E, AD = Alzheimer's disease

Table 2

Neuropsychological performance (mean (SD)) at each visit

Cognitive measure	Wave 1			Wave 2			Wave 3			Wave 4		
Cognitive Status	CN	pMCI	All	CN	pMCI	All	CN	pMCI	All	CN	pMCI	All
N	156	28	184	156	28	184	150	28	178	106	19	125
Global cognition												
MMSE	N/A	N/A	N/A	29.4	29.4	29.4	29.4	29.0	29.3	29.3	29.1	29.3
				(0.9)	(1.0)	(0.9)	(1.0)	(1.5)	(1.1)	(1.0)	(1.8)	(1.2)
Learning												
RAVLT Trials 1-5 Total	51.8	48.4	51.3	51.2	46.5	50.5	52.1	45.4	51.1	51.7	45.0	50.7
	(7.9)	(8.5)	(8.1)	(8.1)	(9.6)	(8.5)	(8.3)	(7.5)	(8.6)	(7.8)	(9.1)	(8.4)
WMS-R Logical Memory I	N/A	N/A	N/A	30.7	25.7	29.9	30.4	23.5	29.3	30.0	23.2	29.0
				(6.0)	(6.6)	(6.3)	(5.6)	(5.8)	(6.1)	(5.6)	(4.9)	(6.0)
BVMT-R Immediate Recall	N/A	N/A	N/A	24.9	20.8	24.2	25.9	20.9	25.2	26.1	17.7	24.8
				(5.4)	(6.0)	(5.6)	(5.2)	(6.2)	(5.6)	(4.7)	(6.5)	(5.8)
Delayed Recall												
RAVLT Long Delay Free	10.6	9.4	10.4	10.7	8.8	10.4	10.9	8.3	10.4	10.9	8.3	10.5
Recall	(2.7)	(3.0)	(2.8)	(2.5)	(4.2)	(2.9)	(2.7)	(3.6)	(3.0)	(2.4)	(4.0)	(2.8)
WMS-R Logical Memory II	N/A	N/A	N/A	24.4	20.8	26.4	27.3	18.8	26.0	27.4	18.9	26.1
				(6.6)	(8.0)	(7.2)	(6.6)	(7.2)	(7.4)	(6.1)	(7.9)	(7.1)
BVMT-R Delayed Recall	N/A	N/A	N/A	9.7	8.4	9.5	9.9	8.1	9.6	10.2	7.4	9.8
				(1.8)	(2.7)	(2.0)	(1.8)	(2.5)	(2.0)	(1.5)	(2.7)	(2.0)
Executive Functioning												
Trailmaking Test Part B	61.0	69.5	62.3	58.9	68.1	60.2	58.7	71.5	60.7	60.3	85.4	64.1
	(18.9)	(19.5)	(19.2)	(20.1)	(20.1)	(20.3)	(17.0)	(20.0)	(18.1)	(17.5)	(22.7)	(20.4)
Stroop Color-Word	112.1	100.2	110.6	112.6	103.3	111.2	111.7	101.0	110.0	111.6	99.3	109.8
Interference	(18.9)	(18.2)	(19.2)	(18.8)	(18.4)	(19.0)	(17.1)	(20.2)	(18.0)	(18.9)	(20.4)	(19.5)
WAIS-R Digit Symbol	N/A	N/A	N/A	58.5	51.4	57.5	57.6	51.5	56.6	57.1	48.6	55.8
				(9.1)	(7.6)	(9.2)	(9.4)	(7.9)	(9.4)	(10.1)	(9.1)	(10.4)

CN = cognitively normal, pMCI = psychometric MCI, MMSE = Mini-Mental State Exam, RAVLT = Rey Auditory Verbal Learning Test, WMS-R = Wechsler Memory Scale – Revised, BVMT-R = Brief Visuospatial Memory Test – Revised, WAIS-R = Wechsler Adult Intelligence Scale – Revised; *Note*: MMSE, WMS-R Logical Memory, BVMT-R, and WAIS-R Digit Symbol were not added to the study until Wave 2

Table 3

Parameters resulting from linear mixed effects regression models

Variable	Learning			Delayed Recall			Executive Functioning		
Primary Model	***B* (SE)**	***p***	**95% CI**	***B* (SE)**	***p***	**95% CI**	***B* (SE)**	***p***	**95% CI**
Intercept	-3.49 (.54)	<.001*	-4.56, -2.43	-3.24 (.55)	<.001*	-4.33, -2.16	-1.70 (.58)	.004*	-2.85, -0.55
Sex (Female)	0.55 (.10)	<.001*	0.35, 0.74	0.48 (.10)	<.001*	0.28, 0.68	0.03 (.11)	.75	-0.18, 0.25
WRAT-III raw score	0.06 (.01)	<.001*	0.04, 0.08	0.06 (.01)	<.001*	0.04, 0.08	0.04 (.11)	.001*	0.02, 0.06
Interval (years)	-0.02 (.03)	.66	-0.08, 0.05	-0.04 (.03)	.24	-0.11, 0.03	-0.01 (.04)	.85	-0.08, 0.07
Time (age centered)	-0.02 (.01)	.001*	-0.03, -0.01	-0.02 (.01)	.01*	-0.03, -0.004	-0.04 (.01)	<.001*	-0.05, -0.02
PiB DVR	0.45 (.44)	.31	-0.42, 1.32	0.76 (.43)	.08	-0.09, 1.60	0.27 (.44)	.53	-0.59, 1.13
Time × PiB DVR	-0.08 (.04)	.051	-0.16, 0.00	-0.14 (.04)	.002*	-0.23, -0.05	-0.09 (.04)	.016*	-0.16, -0.02
Secondary Model									
Intercept	-3.80 (.55)	<.001*	-4.89, -2.72	-3.58 (.55)	<.001*	-4.67, -2.49	-1.83 (.60)	.003	-3.01, -0.65
Sex (Female)	0.58 (.10)	<.001*	0.38, 0.77	0.51 (.10)	<.001*	0.31, 0.71	0.04 (.11)	.68	-0.17, 0.26
WRAT-III raw score	0.07 (.01)	<.001*	0.05, 0.09	0.07 (.01)	<.001*	0.05, 0.09	0.04 (.01)	.001*	0.02, 0.06
Interval (years)	-0.01 (.03)	.70	-0.08, 0.05	-0.04 (.03)	.20	-0.11, 0.02	-0.01 (.04)	.82	-0.08, 0.06
APOE	0.10 (.12)	.40	-0.14, 0.34	0.04 (.12)	.76	-0.19, 0.26	0.08 (.13)	.52	-0.17, 0.33
Time (age centered)	-0.02 (.01)	.02	-0.03, -0.002	-0.02 (.01)	.07	-0.03, 0.001	-0.03 (.01)	<.001*	-0.04, -0.02
PiB DVR	-0.59 (.71)	.41	-1.97, 0.80	-0.77 (.68)	.25	-2.13, 0.56	-0.93 (.69)	.18	-2.29, 0.43
Time × PiB DVR	0.03 (.06)	.56	-0.08, 0.14	0.05 (.06)	.45	-0.07, 0.17	0.003 (.05)	.95	-0.10, 0.10
Time × *APOE*	0.01 (.01)	.69	-0.02, 0.03	0.01 (.01)	.35	-0.01, 0.04	-0.01 (.01)	.52	-0.03, 0.02
APOE × PiB DVR	1.82 (.90)	.04	0.05, 3.60	2.80 (.87)	.001*	1.09, 4.50	2.01 (.89)	.02	0.27, 3.75
Time × *APOE* × PiB DVR	-0.27 (.08)	.002*	-0.43, -0.10	-0.41 (.09)	<.001*	-0.59, -0.24	-0.18 (.07)	.02	-0.32, -0.03

WRAT-III = Wide Range Achievement Test – 3rd Edition reading subtest. Interval = Years between Wave 2 neuropsychological evaluation and PET scan. Time = age centered by mean age of sample at baseline neuropsychological evaluation (54.33). PiB DVR = [C-11]Pittsburgh compound B Distribution Volume Ratio centered by mean DVR value of sample (1.17). Outcome measures of delayed recall, learning, and executive functioning were standardized to z-scores prior to inclusion in models.

*Statistically significant using Bonferroni adjusted p-value (< .017)