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Amyloid-β Positivity Predicts Cognitive Decline but Cognition Predicts Progression to Amyloid-β Positivity

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ABSTRACT

BACKGROUND: Stage 1 of the National Institute on Aging–Alzheimer's Association's proposed Alzheimer's disease continuum is defined as amyloid-β (Aβ) positive but cognitively normal. Identifying at-risk individuals before Aβ reaches pathological levels could have great benefits for early intervention. Although Aβ levels become abnormal long before severe cognitive impairments appear, increasing evidence suggests that subtle cognitive changes may begin early, potentially before Aβ surpasses the threshold for abnormality. We examined whether baseline cognitive performance would predict progression from normal to abnormal levels of Aβ.

METHODS: We examined the association of baseline cognitive composites (Preclinical Alzheimer Cognitive Composite, Alzheimer's Disease Neuroimaging Initiative (ADNI) memory factor composite) with progression to Aβ positivity in 292 nondemented, Aβ-negative ADNI participants. Additional analyses included continuous cerebrospinal fluid biomarker levels to examine the effects of subthreshold pathology.

RESULTS: Forty participants progressed to Aβ positivity during follow-up. Poorer baseline performance on both cognitive measures was significantly associated with increased odds of progression. More abnormal levels of baseline cerebrospinal fluid phosphorylated tau and subthreshold Aβ were associated with increased odds of progression to Aβ positivity. Nevertheless, baseline ADNI memory factor composite performance predicted progression even after controlling for baseline biomarker levels and *APOE* genotype (Preclinical Alzheimer Cognitive Composite was trend level). Survival analyses were largely consistent: controlling for baseline biomarker levels, baseline Preclinical Alzheimer Cognitive Composite still significantly predicted progression time to Aβ positivity (ADNI memory factor composite was trend level).

CONCLUSIONS: The possibility of intervening before Aβ reaches pathological levels is of obvious benefit. Low-cost, noninvasive cognitive measures can be informative for determining who is likely to progress to Aβ positivity, even after accounting for baseline subthreshold biomarker levels.

Keywords: AD, Alzheimer's disease, Amyloid accumulation, β-amyloid, Biomarker trajectories, Cognition, MCI, Mild cognitive impairment

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Given its long prodromal period, Alzheimer's disease (AD) treatment should begin as early as possible (1). The National Institute on Aging–Alzheimer's Association (NIA-AA) research framework describes the A/T/(N) classification system, an approach to categorize individuals based on abnormal levels of amyloid, tau, and neurodegeneration. Early intervention may be possible after identifying amyloid-β (Aβ)–positive individuals who are still cognitively normal, defined as preclinical/stage 1 of the AD continuum proposed by the NIA-AA research framework (2). Yet, being Aβ-positive means significant pathology is already present. It may be critically important to identify at-risk individuals before they develop substantial amyloid burden (i.e., at stage 0) to improve treatment efficacy and slow progression to AD dementia.

Examinations of AD biomarkers primarily focus on biomarkers as predictors of cognitive decline, but here, our focus was on biomarker positivity as an outcome. Abnormal biomarkers precede clinical symptom onset by years or even decades (3–5). However, there is also evidence that cognition demonstrates subtle change earlier than is typically appreciated. Cognition begins to show accelerated change across individuals with a range of baseline Aβ values, including those who are Aβ negative (6,7). Delayed recall has been shown to demonstrate accelerating change prior to other biomarker and clinical measures (8–10). Change in amyloid is also correlated

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with change in cognition (11,12). Thus, Aβ accumulation, including subthreshold levels, is related to concurrent or future cognitive outcomes. However, none of these studies addressed whether baseline cognitive performance can predict progression to Aβ positivity as an outcome. According to the NIA-AA framework staging, Aβ positivity precedes cognitive impairment, consistent with serial models of AD trajectories. Here, we examined whether baseline cognition among Aβ-negative individuals could predict later progression to Aβ positivity, even among cognitively unimpaired individuals.

Increasing postmortem evidence indicates that abnormal tau appears in the brainstem during the earliest stages of AD—potentially before cortical Aβ plaque deposition—and tau is associated with poorer memory performance even in the absence of Aβ (13–16). However, individuals classified as A−/T+ are not considered to be on the AD continuum. Although tau deposition in the absence of Aβ might be age related rather than Alzheimer's related, we also examined whether individuals with elevated tau would be more likely to progress to Aβ positivity, indicating increased risk of AD.

METHODS AND MATERIALS

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, M.D. The primary goal of the ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD.

Participants from the ADNI-1, ADNI-GO, and ADNI-2 cohorts were included if they 1) had valid cognitive and cerebrospinal fluid (CSF) Aβ and phosphorylated tau (p-tau) data at baseline, 2) had at least 1 follow-up of amyloid data based on CSF or PET, 3) were Aβ negative at baseline, and 4) did not have a diagnosis of Alzheimer's dementia at baseline (see Table 1 for participant characteristics). In total, baseline and follow-up amyloid status were based on 585 assessments of CSF Aβ, 646 florbetapir PET scans, and 10 ^{11}C-Pittsburgh Compound B scans. Individuals were classified as Aβ stable if they had no abnormal amyloid levels at any follow-up, or as Aβ converter if they showed evidence of abnormal Aβ at a follow-up assessment. Individuals who were Aβ positive at multiple assessments followed by a subsequent reversion to Aβ-negative status on only a single time point were included as Aβ converters. Individuals who were Aβ positive at only one assessment, followed by reversion to Aβ-negative status, were excluded (n = 9). Individuals diagnosed as having MCI in the ADNI (17) were included if they were Aβ negative at baseline because our focus was to determine whether poorer cognition may precede amyloid positivity, and some of these Aβ-negative individuals with MCI may progress to Aβ positivity. Excluding them would truncate the distribution of cognitive performance, our predictor of primary interest. A total of 292 individuals were included (252 Aβ stable, 40 Aβ converters). Despite being Aβ negative, 138 (47.3%) were diagnosed with MCI at baseline.

Procedures were approved by the institutional review board of participating institutions and informed consent was obtained from all participants.

Table 1. Baseline Sample Characteristics of Aβ-Stable Versus Aβ-Converters

Measure	Aβ-Stable (n = 252)	Aβ-Converter (n = 40)
Age, Years	71.62 ± 7.20	71.69 ± 6.71
Male	128 (50.8)	25 (62.5)
APOE ε4 Status (ε4+)	41 (16.3)	12 (30.0)
MCI Diagnosis (MCI)	117 (46.4)	21 (52.5)
Education, Years[a]	16.21 ± 2.56	17.20 ± 2.22
Length of Follow-up, Years[a]	3.22 ± 1.59	4.30 ± 2.44
ADNI_MEM	0.89 ± 0.68	0.70 ± 0.59
PACC	−1.32 ± 3.31	−1.97 ± 3.03

Values are mean ± SD or n (%).

Aβ, amyloid-β; ADNI_MEM, Alzheimer's Disease Neuroimaging Initiative memory factor composite; MCI, mild cognitive impairment; PACC, Preclinical Alzheimer Cognitive Composite.

[a]Significant ($p < .05$) difference between the 2 groups.

CSF and Amyloid Imaging Measures

CSF samples were collected and processed as previously described (18). CSF $A\beta_{42}$ and p-tau were measured with the fully automated Elecsys immunoassay (Roche Diagnostics, Basel, Switzerland) by the ADNI biomarker core (University of Pennsylvania, Philadelphia, PA). Established cutoffs designed to maximize sensitivity in the ADNI study population were used to classify biomarker positivity [Aβ+: $A\beta_{42} < 977$ pg/mL; p-tau+: p-tau > 21.8 pg/mL] (http://adni.loni.usc.edu/methods) (19).

PET Aβ data were processed according to previously published methods (http://adni.loni.usc.edu/methods) (20,21). Mean standardized uptake value ratios were taken from a set of regions including frontal, temporal, parietal, and cingulate cortices using the whole cerebellum (florbetapir) or cerebellar gray matter (^{11}C-Pittsburgh Compound B) as a reference region. Established cutoffs to determine Aβ+ were used for ^{11}C-Pittsburgh Compound B–PET (standardized uptake value ratio > 1.44) and florbetapir-PET (standardized uptake value ratio > 1.11) (20).

CSF Aβ assessment was more common at earlier study time points, whereas PET assessments became more common at later time points. We included both modalities to maximize the number of individuals with baseline data and increase the length of follow-up assessment for dichotomized outcomes. However, it was necessary to restrict analyses of continuous baseline values to a single modality so that values were equivalent. CSF was chosen to examine continuous levels of baseline Aβ because it was available for more participants compared with PET.

Cognitive Measures

We used 2 composite measures of baseline cognition. The ADNI memory factor composite (ADNI_MEM) is based on a factor model of scores from 4 episodic memory tests: Rey

Auditory Verbal Learning Test, Alzheimer's Disease Assessment Scale–Cognition word list and recognition, Mini-Mental State Examination word recall, and Logical Memory immediate and delayed recall (22). The Preclinical Alzheimer Cognitive Composite (PACC) (23,24) is designed to detect amyloid-related cognitive decline and is based on delayed recall from the Alzheimer's Disease Assessment Scale–Cognition and Logical Memory, Mini-Mental State Examination total score, and Trail Making Test Part B time. ADNI_MEM and PACC scores were converted to *z* scores and coded such that higher scores reflect poorer performance. In a secondary analysis, we examined the ADNI executive function factor composite (25) to test whether a composite baseline executive function measure also predicted conversion to Aβ positivity.

Covariates

Age and *APOE* genotype (ε4+ vs. ε4−) were included because of their association with increased amyloid (26). Although age and cognitive performance are correlated, the variance inflation factor for these variables was ≤1.30 in all models, well below the common threshold indicating excessive multicollinearity. Length of follow-up was included to account for its effect on odds of observing eventual progression to Aβ positivity. Education was included to account for long-standing differences in cognitive ability or cognitive reserve that might influence the relationship between amyloid and cognition. In other analyses, baseline biomarkers were included to assess the effect of AD-related pathology on progression to Aβ positivity. P-tau status (p-tau+ vs. p-tau−) was included to account for differences in cognition owing to other AD-related pathology. An additional set of models included continuously measured CSF $A\beta_{42}$ and p-tau as covariates to determine whether subthreshold levels of pathology predict later progression to Aβ positivity. These measures were converted to *z* scores, and values of CSF $A\beta_{42}$ were reverse coded such that higher values of both indicated abnormality.

Statistical Analysis

We tested Aβ-stable and Aβ-converter groups for differences in the covariates using chi-square and *t* tests. Logistic regression models were used to test whether baseline cognition in Aβ-negative individuals was associated with increased odds of future progression to Aβ positivity. We chose this approach over a generalized linear mixed-effects logistic regression that included data from all time points because the issue of primary interest was the odds of progressing to Aβ positivity at any point during follow-up, not the odds of being Aβ positive at each individual time point (see Supplement for further discussion). The first set of models separately tested the ADNI_MEM and PACC, with baseline cognitive performance on these measures as predictors and group (Aβ stable or Aβ converter) as the outcome. The second set of models additionally included p-tau status to assess whether lower cognitive performance was driven by abnormal levels of p-tau, the other hallmark AD pathology. Although no subject met criteria for abnormal Aβ at baseline, that does not mean that they were completely free of pathology. Therefore, we ran a third set of models to determine whether poorer baseline cognition was driven by subthreshold levels of amyloid or tau. These models included continuous levels of CSF $A\beta_{42}$ and p-tau as predictors. All models included age at baseline, *APOE* genotype (ε4+ vs. ε4−), education, and length of follow-up as covariates. To determine whether effects were driven primarily by the subgroup with MCI at baseline, we conducted follow-up analyses excluding those individuals.

We also examined Cox proportional hazards models to test the association of baseline cognitive performance with time to conversion to Aβ-positive status (or censored at last follow-up). Two sets of models were run: the first included baseline cognitive performance as the predictor of interest; the second added continuous levels of baseline CSF $A\beta_{42}$ and p-tau. These models additionally controlled for age at baseline, *APOE* genotype, and education. The survival analyses are useful for directly addressing the question of differential follow-up time. However, they consider individuals with differential times to conversion differently, and the use of multiple modalities may further affect time to conversion. Because our primary question of interest was about progression to Aβ positivity at any point during follow-up, rather than its time to progression, we consider these models to be supplemental to the primary logistic regression analyses. Analyses were conducted with R version 3.5 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptive Statistics

Descriptive statistics are presented in Tables 1 and 2. There were no significant differences between groups for age (p = .94), gender (p = .18), or proportion of individuals with MCI (p = .47). Aβ converters were more likely to be *APOE* ε4+ at a trend level (p = .08). The Aβ-converter group had a higher average education (17.23 years vs. 16.2 years [$t_{56.7}$ = 2.78, p = .007]). The follow-up interval was significantly longer for the Aβ-converter group (4.3 years vs. 3.22 years [$t_{44.4}$ = 2.50, p = .02]). The mean time between baseline cognitive testing and the assessment at which Aβ converters first demonstrated progression to Aβ positivity was 2.8 years (interquartile range, 1.98–4.01 years). Of the 138 individuals who were Aβ negative

Table 2. Baseline Sample Characteristics of Cognitively Normal Versus MCI

Measure	Cognitively Normal (n = 154)	MCI (n = 138)
Age, Years	72.67 ± 5.97	70.47 ± 8.09
Male	80 (51.9)	73 (52.9)
APOE ε4 status (ε4+)	25 (16.2)	28 (20.3)
Education, Years[a]	16.50 ± 2.50	16.18 ± 2.57
Baseline CSF Aβ, pg/mL[a]	1488.68 ± 233.40	1443.50 ± 260.50
Baseline CSF p-tau, pg/mL[a]	19.47 ± 5.75	19.54 ± 7.86
ADNI_MEM[a]	0.59 ± 0.69	0.46 ± 0.57
PACC[a]	−3.25 ± 3.15	−3.40 ± 2.42

Values are mean ± SD or *n* (%).

Aβ, amyloid-β; ADNI_MEM, Alzheimer's Disease Neuroimaging Initiative memory factor composite; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; MCI, mild cognitive impairment; PACC, Preclinical Alzheimer Cognitive Composite.

[a]Significant (p < .05) difference between the 2 groups.

and had MCI at baseline, 21 (15%) progressed to Aβ positivity. The MCI group did not have significantly different levels of baseline CSF Aβ (p = .119) or p-tau (p = .930) compared with cognitively normal participants. However, individuals with MCI who progressed to Aβ positivity did have lower baseline CSF Aβ ($t_{25.9}$ = 3.158, p = .004) and higher p-tau ($t_{27.4}$ = 2.389, p = .024) compared with those with MCI that did not (see Supplemental Table S1).

Baseline Cognition Predicts Progression to Aβ Positivity During Follow-up

In the first set of models, Aβ-converters were also more likely to be *APOE* ε4+, have more education, and have longer duration of follow-up. Age was not significantly associated with progression to Aβ positivity in either model. After accounting for covariates, individuals with poorer performance on either cognitive composite at baseline showed higher odds of progressing to Aβ positivity at follow-up (ADNI_MEM: odds ratio [OR], 1.66; p = .013; PACC: OR, 1.66; p = .01). Full results of the regression models are presented in Figure 1.

The second set of models included a dichotomous classification for baseline CSF p-tau (Figure 2). Aβ converters were again more likely to be *APOE* ε4+, have more education, and have longer duration of follow-up. Age and dichotomous p-tau status were not significantly associated with progression to Aβ positivity in either model. After controlling for covariates, poorer baseline performance on either cognitive composite remained significantly associated with increased odds of progressing to Aβ positivity at follow-up (ADNI_MEM: OR, 1.64; p = .016; PACC: OR, 1.67; p = .011).

The third set of models addressed the question of whether subthreshold levels of AD pathology could account for the effect of lower cognitive performance on progression by including continuous CSF Aβ and p-tau measures (Figure 3). More abnormal baseline CSF Aβ and p-tau were associated with increased odds of progression to Aβ positivity (CSF Aβ: OR, 2.53–2.59; $p < .001$; CSF p-tau: OR, 1.51; p = .03). Note that for CSF Aβ, these values were all in the normal range according to standard cutoffs. After controlling for baseline biomarkers, the performance on the ADNI_MEM remained a significant predictor (OR, 1.61; p = .03), but the effect of the PACC was reduced to trend level (OR, 1.49; p = .071). Education and length of follow-up remained significant predictors of progression, whereas the effect of *APOE* ε4 status was reduced to trend level.

To determine whether these results may be driven by the MCI participants, we conducted analyses on cognitively normal and MCI groups separately. The large drop in sample size resulted in nonsignificant results for most analyses, but effect sizes of cognition predicting progression to Aβ positivity tended to be larger for the cognitively normal group.

Baseline performance on the ADNI executive function factor also significantly predicted later conversion at Aβ positivity. This effect remained when including dichotomous p-tau status but became nonsignificant when including continuous levels of baseline CSF Aβ and p-tau (see Supplemental Table S2).

Baseline Cognition Predicts Progression Time to Aβ Positivity

The Cox models were largely consistent with the logistic regression models (Figure 4, Supplemental Figure S1). In models including only baseline cognitive performance and covariates, *APOE* ε4 and higher education were associated with significantly higher risk whereas age was not. After accounting for covariates, lower cognitive performance was associated with increased risk of progression to Aβ positivity (ADNI_MEM: hazard ratio [HR], 1.48; p = .024; PACC: HR, 1.61; p = .006).

Additional Cox models were conducted including baseline CSF Aβ and p-tau to assess the impact of subthreshold pathology on risk of progression to Aβ positivity (Figure 4, Supplemental Figure S2). More abnormal baseline CSF Aβ and p-tau were associated with increased risk of progression to Aβ positivity (CSF Aβ: HR, 2.3; $p < .001$; CSF p-tau: OR, 1.5; $p < .001$). The PACC remained significantly associated with increased risk of progression (HR, 1.45, p = .04), whereas the

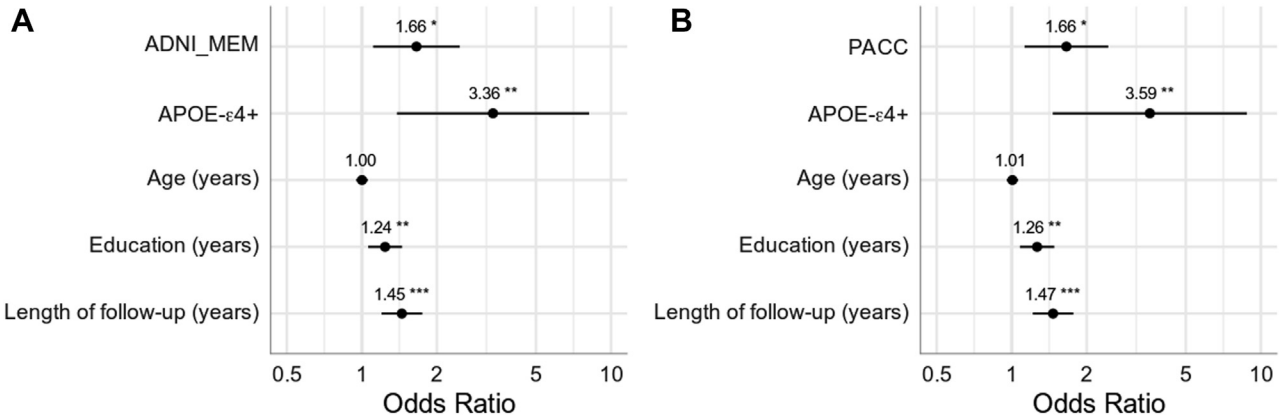

Figure 1. Baseline cognitive performance predicting future conversion to amyloid-β (Aβ) positivity. Results of 2 logistic regression models using **(A)** the Alzheimer's Disease Neuroimaging Initiative memory factor composite (ADNI_MEM) and **(B)** the Preclinical Alzheimer Cognitive Composite (PACC). Measures are all taken from baseline and predict future progression to Aβ positivity. Cognitive scores were converted to z scores and reverse-coded, such that higher scores indicate poorer performance. Odds ratios are presented with asterisks indicating significant estimates (*$p < .05$, **$p < .01$, ***$p < .001$). Lines represent 95% confidence intervals.

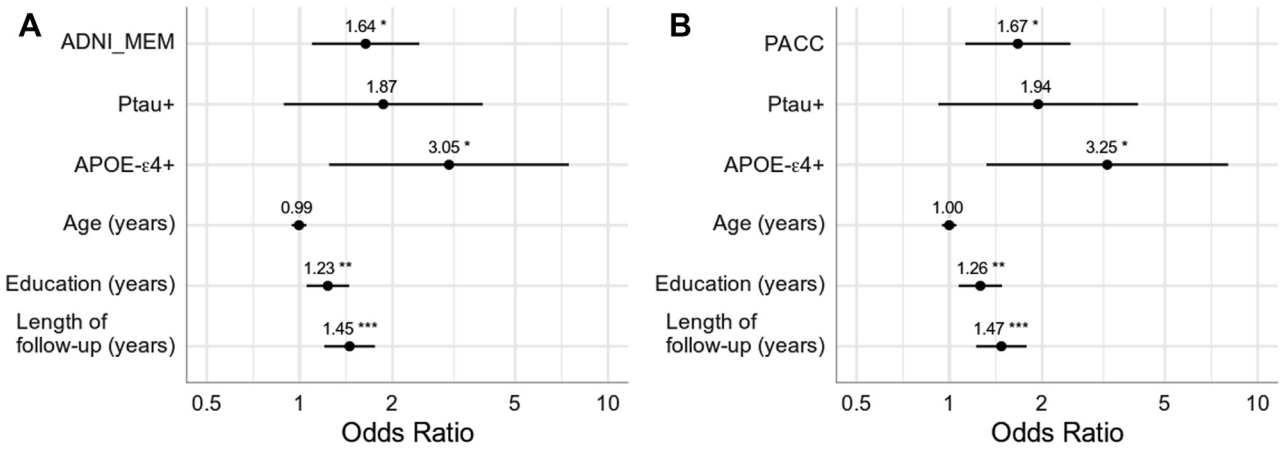

Figure 2. Baseline cognitive performance and phosphorylated tau–positive (Ptau+) status predicting future conversion to amyloid-β (Aβ) positivity. Results of 2 logistic regression models using **(A)** the Alzheimer's Disease Neuroimaging Initiative memory factor composite (ADNI_MEM) and **(B)** the Preclinical Alzheimer Cognitive Composite (PACC). Measures are all taken from baseline and predict future progression to Aβ positivity. Cognitive scores were converted to *z* scores and reverse-coded, such that higher scores indicate poorer performance. Ptau+ is entered as a dichotomous variable. Odds ratios are presented with asterisks indicating significant estimates (*$p < .05$, **$p < .01$, ***$p < .001$). Lines represent 95% confidence intervals.

effect of the ADNI_MEM was reduced to trend level (HR, 1.41; $p = .063$). Age was not associated with increased effects, and both *APOE* ε4 and education were reduced to trend level.

DISCUSSION

Cognitive Function Predicts Aβ Positivity

Here, we found that cognition can be a useful early risk indicator. The ability to identify individuals at risk before substantial Aβ accumulation would enhance prospects for slowing AD progression and may be useful for selection of participants in clinical trials. The NIA-AA research framework represents a move toward defining AD as a biological construct (2). However, as noted by the NIA-AA workgroups on diagnostic guidelines for AD (27), behavioral markers may still hold great promise for early identification. Cognitive measures can predict progression from MCI to AD as well as or better than biomarkers (28–31). It is not surprising that cognitive measures predict future cognition, but we found that cognitive measures can predict progression to Aβ positivity even after accounting for baseline biomarker levels. Furthermore, composite measures such as those used here may provide substantial boosts in sensitivity compared with individual test scores (32,33).

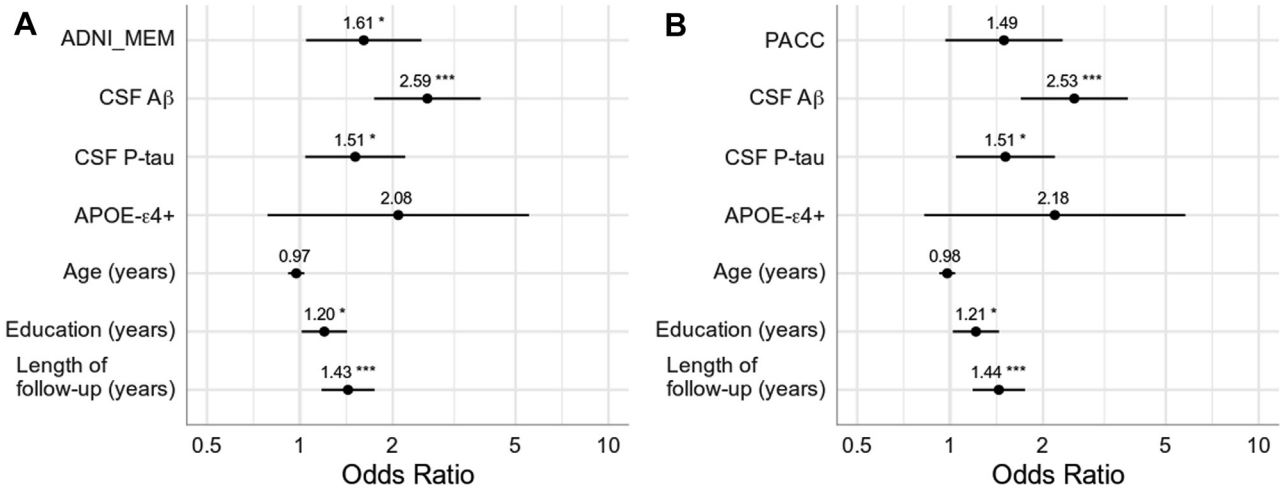

Figure 3. Baseline cognitive performance and continuous measures of cerebrospinal fluid (CSF) amyloid-β (Aβ) and phosphorylated tau (P-tau) predicting future conversion to Aβ positivity. Results of 2 logistic regression models using **(A)** the Alzheimer's Disease Neuroimaging Initiative memory factor composite (ADNI_MEM) and **(B)** the Preclinical Alzheimer Cognitive Composite (PACC). Measures are all taken from baseline and predict future progression to Aβ positivity. Cognitive scores were converted to *z* scores and reverse-coded, such that higher scores indicate poorer performance. CSF Aβ and P-tau were entered as continuous variables. Both measures were *z*-scored, and CSF Aβ was reverse-coded, such that higher values on both indicates abnormality. Odds ratios are presented with asterisks indicating significant estimates (*$p < .05$, **$p < .01$, ***$p < .001$). Lines represent 95% confidence intervals.

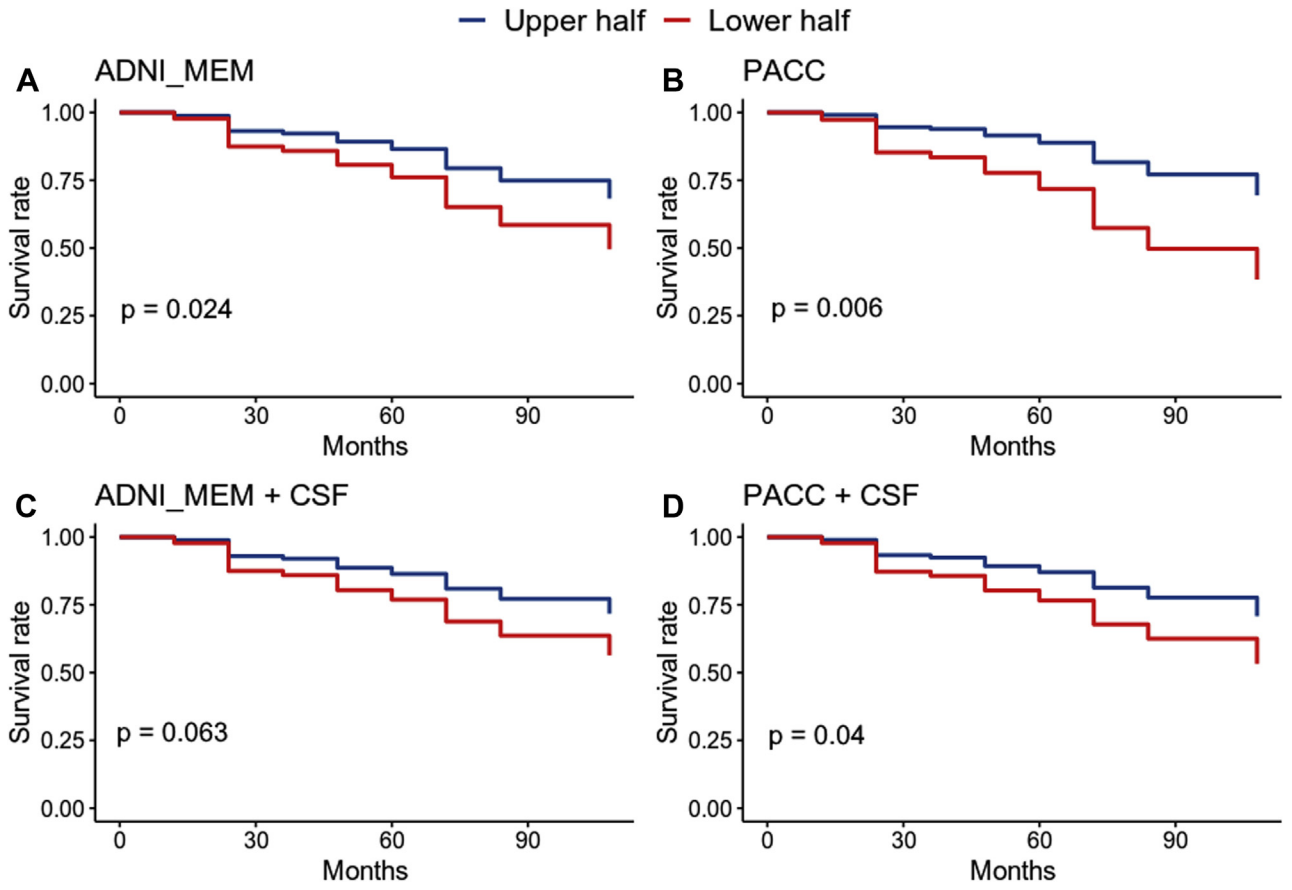

Figure 4. Survival estimates of progression to amyloid-β (Aβ) positivity based on baseline cognitive performance. Cox proportional hazard models were run using continuous measures of baseline performance. For display purposes, scores were grouped based on a median split and adjusted survival curves are shown for better (upper half) and worse (lower half) performance on baseline cognitive measures. Results from 4 models are presented: **(A)** Alzheimer's Disease Neuroimaging Initiative memory factor composite (ADNI_MEM) + covariates; **(B)** Preclinical Alzheimer Cognitive Composite (PACC) + covariates; **(C)** ADNI_MEM + covariates + baseline cerebrospinal fluid (CSF) Aβ and phosphorylated tau; **(D)** PACC + covariates + baseline CSF Aβ and phosphorylated tau. CSF Aβ and phosphorylated tau were entered as continuous variables. Covariates include: *APOE* ε4+ status, age at baseline, and education. The *p* values of hazard ratios for cognitive measures are shown for each model.

Impact of Subthreshold Aβ

Why would cognition predict future accumulation of AD pathology? There may be several potential explanations. Pathological processes may already be underway, and lower cognitive function may represent decline driven by subthreshold pathology. In a smaller (n = 35) study of ADNI participants, baseline cognition did not predict later progression to Aβ positivity (34). However, with the larger sample in our analysis, cognitive function was a significant predictor. Controlling for subthreshold Aβ in our analysis attenuated the effect of cognition, lending support to the idea that even low levels of Aβ are at least partially contributing to lower cognitive performance. This fits with growing evidence that subthreshold levels of Aβ are clinically relevant. Cognitive tests at this early stage seem to be more sensitive than dichotomous classifications of biomarker abnormality at current detection thresholds. As biomarker measures become more sensitive, classification of biomarker abnormality may more consistently appear before cognitive differences.

On the other hand, cognition still predicted future progression to Aβ positivity, even after controlling for subthreshold Aβ. Therefore, cognitive performance contributes independent information, and the effect is not driven solely by individuals closer to the Aβ-positivity threshold. Cognitive testing early on is also more practical, noninvasive, and far less costly than CSF or PET biomarkers.

Although CSF and PET measure different aspects of the amyloid process, both are considered valid indicators of abnormal Aβ, and use of both is consistent with the goals of the A/T/(N) framework. On the other hand, it may introduce some inconsistencies such as timing of conversion. Of the 40 Aβ-converters, only 6 (15%) were based on different modalities (baseline CSF negative; follow-up PET positive), largely because later follow-ups were with PET. Moreover, these measures show high concordance (35–37), such that it is likely that if an individual is positive on one, he or she would be positive on the other at some point in the near future. Most importantly, our primary analyses only assess if—not when—

someone converts to Aβ positivity, which should mitigate differences in these modalities.

The relevance of subthreshold pathology also has implications for the use of dichotomous versus continuous biomarker measures. Some have argued that making Aβ thresholds less conservative may improve sensitivity without a substantial sacrifice of specificity (38). Our findings suggest that current thresholds may not detect meaningful early Aβ accumulation, so the development of thresholds optimized for detecting the earliest stages of Aβ deposition is an important goal. Analysis of continuous measures should also be conducted when possible because continuous and binary A/T/(N) measures may lead to inconsistent inferences. An alternative approach is to examine Aβ accumulation over time. Several studies have examined individuals who do not meet the criteria for abnormal Aβ but do demonstrate evidence of change in Aβ (11,12,39–41). These studies find that change in Aβ levels is correlated with concurrent cognitive decline, commonly assumed to result from Aβ accumulation. Here, we shifted the focus to earlier in time and found that baseline cognition itself can predict later Aβ accumulation.

Non–AD-Related Processes and Ordering of AD-Related Changes

An alternative explanation for cognition predicting Aβ positivity is that lower cognitive function at baseline may result from non–AD-related processes. Individuals who progress to MCI while being Aβ negative exhibit different biomarkers and cognitive profiles and tend to be on a non-AD trajectory (42). As a whole, the Aβ-negative MCI group in our analysis did not differ from the cognitively normal group on baseline Aβ or p-tau, perhaps suggesting a non-AD etiology for cognitive impairment. However, the significant association between baseline cognition and later Aβ positivity suggests that such processes are still somehow a risk factor for AD. Indeed, 15% of Aβ-negative MCI participants did progress to Aβ positivity, at which point they would be classified as stage 3 in the AD continuum. This 15% had more abnormal levels of baseline Aβ (although still subthreshold) and p-tau compared with MCI participants who did not progress, suggesting that AD pathology may at least partially contribute to their cognitive impairment. Some individuals may be more sensitive to the effects of Aβ, such that even subthreshold levels result in cognitive impairment.

It is, of course, possible to have mixed etiology driving impairment whether it appears before or after an individual surpasses the threshold for Aβ positivity. Although the A/T/(N) framework is agnostic to the sequence of AD-related changes (43), these Aβ-negative (A−) MCI cases would not be considered to be on the AD continuum. As such, cognitive impairment prior to Aβ positivity is assumed to have a non-AD etiology. However, as pointed out in the NIA-AA framework, it is also uncertain that cognitive impairment arising after Aβ positivity is solely due to AD pathology (2). Indeed, it is well known that there can be significant AD pathology without cognitive impairment (44–46). Although the proposed NIA-AA research framework staging captures the typical progression, it will be beneficial to maintain a degree of flexibility to account for individuals who may progress through these stages in a nontypical trajectory.

Tau-PET studies have found that tau is confined to the medial temporal lobe and spreads to the rest of the isocortex only once Aβ is present (47–50). However, some have suggested that tau and Aβ develop independently, which may give rise to variable ordering in their progression (14,15,51). These different findings may raise questions about serial models of AD biomarker trajectories, i.e., that Aβ always precedes tau. We found that continuous—but not dichotomous—levels of CSF p-tau were associated with significantly higher odds of progression to Aβ positivity. Thus, some individuals with elevated tau and subthreshold Aβ do develop more typical AD-like profiles. Being at heightened risk of entering the AD continuum, they would be worth monitoring more closely.

Long-standing Individual Differences

Another explanation for why cognition predicts Aβ positivity is that lower baseline cognition might reflect long-standing individual differences. Lower cognitive function may reflect less efficient neural processing, which would in turn require higher activity. It has been proposed that elevated synaptic activity across the lifespan could result in increased release and aggregation of Aβ (52). Individuals with less efficient processing (indexed by lower cognitive function) may therefore be at greater risk of accumulating Aβ.

However, this idea may seem to be contradicted by the unexpected finding that higher education was associated with increased odds of progression to Aβ positivity. We propose two potential explanations. First, individuals with lower education may be at greater risk of becoming Aβ positive prior to their baseline visit, and thus would not have been included in our analysis. Those with lower education who remained Aβ negative until their baseline visit may be more resistant to Aβ deposition, and thus less likely to progress in the future. Second, the seemingly paradoxical education finding might be, in part, a function of ADNI ascertainment. Average education was 16+ years, yet only about 10% of this age cohort in the United States attained a 4-year college degree (53). ADNI participants were recruited at AD Research Centers, which are likely to attract people with concerns about memory and AD risk. There might, in turn, be a link between well-educated older adults with memory concerns and increased likelihood of progressing to Aβ positivity.

Are the Results Driven by MCI Cases?

We considered that the present results might be driven by the 47.3% of the sample diagnosed with MCI at baseline. However, ORs were in the direction of greater magnitude among cognitively normal participants when analyzed separately. It is also worth emphasizing that the results for the majority (52.7%) of the sample are consistent with typical disease progression because these non-MCI individuals did not have cognitive impairment prior to reaching Aβ positivity. Rather, differences within the range of normal cognitive function were informative about who is more likely to become Aβ positive.

Implications for Study Participant Selection

Use of Aβ positivity as inclusion criteria should be context dependent. Defined cut-points are necessary for clinical diagnosis and for clinical trials targeting Aβ pathology. Including only biomarker-confirmed MCI cases will reduce the number of false-positive diagnoses and provide more certainty that cognitive deficits arise from AD pathology. Our results suggest that early cognitive testing may also have utility as a screening tool for identifying who should receive biomarker assessments to more directly assess disease etiology or suitability for clinical trials. However, it would exclude Aβ-negative MCI cases who may later enter the AD continuum upon progression to Aβ positivity. If the goal is to understand the earliest stages of the AD continuum, it will be important to capture individuals who demonstrate putative atypical disease progression to better detect and identify sources of variability.

Summary

Despite much evidence for the standard model of biomarker and cognitive trajectories, the current results demonstrate the complex nature of disease progression. Differences in cognition that predict future progression to Aβ positivity may be driven by subthreshold pathology, perhaps suggesting a need to reconsider current biomarker thresholds or to focus more on approaches that measure Aβ accumulation. Additionally, higher levels of tau are associated with increased risk of becoming Aβ positive. Thus, elevated tau should be considered when identifying those at risk for developing AD. A subset of individuals with MCI but normal Aβ levels may similarly end up on the AD pathway, as indicated by later progression to Aβ positivity. Importantly, the results strongly suggest that cognition should not be considered important only as a late-stage end point of AD. Rather, even when cognitive function is still within the normal range, it can provide a sensitive, low-cost, noninvasive predictor of risk, potentially before current thresholds for Aβ positivity are reached.

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