Original Investigation

Hypothetical Preclinical Alzheimer Disease Groups and Longitudinal Cognitive Change

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IMPORTANCE Clinical trials testing treatments for Alzheimer disease (AD) are increasingly focused on cognitively normal individuals in the preclinical phase of the disease. To optimize observing a treatment effect, such trials need to enroll cognitively normal individuals likely to show cognitive decline over the duration of the trial.

OBJECTIVE To identify which group of cognitively normal individuals shows the greatest cognitive decline over time based on their cerebrospinal fluid biomarker profile.

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, cognitively normal participants were classified into 1 of the following 4 hypothetical preclinical AD groups using baseline cerebrospinal fluid levels of Aβ and tau or Aβ and phosphorylated tau (p-tau): stage 0 (high Aβ and low tau), stage 1 (low Aβ and low tau), stage 2 (low Aβ and high tau), and suspected non-AD pathology (SNAP) (high Aβ and high tau). The data presented herein were collected between August 1995 and August 2014.

MAIN OUTCOMES AND MEASURES An a priori cognitive composite score based on the following 4 tests previously shown to predict progression from normal cognition to symptom onset of mild cognitive impairment or dementia: Paired Associates immediate recall, Logical Memory delayed recall, Boston Naming, and Digit-Symbol Substitution. Linear mixed-effects models were used to compare the cognitive composite scores across the 4 groups over time, adjusting for baseline age, sex, education, and their interactions with time.

RESULTS Two hundred twenty-two cognitively normal participants were included in the analyses (mean follow-up, 11.0 years [range, 0-18.3 years] and mean baseline age, 56.9 years [range, 22.1-85.8 years]). Of these, 102 were stage 0, 46 were stage 1, 28 were stage 2, and 46 were SNAP. Individuals in stage 2 (low Aβ and high tau [or p-tau]) had lower baseline cognitive scores and a greater decline in the cognitive composite score relative to the other 3 groups ($\beta \leq -0.06$ for all and $P \leq .001$ for the rate of decline for all). Individuals in stage 0, stage 1, and SNAP did not differ from one another in cognitive performance at baseline or over time (11.0 years) and showed practice-related improvement in performance. The *APOE ε4* genotype was not associated with baseline cognitive composite score or the rate of change in the cognitive composite score.

CONCLUSIONS AND RELEVANCE These results suggest that, to optimize observing a treatment effect, clinical trials enrolling cognitively normal individuals should selectively recruit participants with abnormal levels of both amyloid and tau (ie, stage 2) because this group would be expected to show the greatest cognitive decline over time if untreated.

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Current evidence suggests that the neuropathological processes associated with Alzheimer disease (AD) begin a decade or more before the emergence of obvious cognitive impairment.[1] This preclinical phase of the disease is the focus of clinical trials because it is hypothesized that disease-modifying therapies are likely to be most successful when administered before the initial symptomatic phase, known as mild cognitive impairment (MCI), in which there is substantial synaptic and neuronal damage.[2-4] The primary objective of the present study was to examine which cognitively normal individuals with evidence of AD pathology are most likely to demonstrate cognitive decline over time. This information would have important implications for determining participant selection criteria for clinical trials because the rate of cognitive change over time must be sufficient to permit seeing a drug effect if one is present.

We tested whether individuals with differing biomarker profiles show different cognitive trajectories over time, as would be predicted by the hypothetical staging model of preclinical AD laid out by the Preclinical AD Workgroup sponsored by the National Institute on Aging and the Alzheimer's Association.[1] This model proposes that the preclinical phase of AD can be subdivided into 3 successive stages. Stage 1 is characterized by amyloid pathology but the absence of tau-related neurodegeneration. During stage 2, both amyloid pathology and tau-related neurodegeneration are evident. Finally, during stage 3, subtle cognitive decline becomes detectable in addition to amyloid and tau pathology. Individuals with normal measures of both amyloid and neurodegeneration are classified as stage 0. Furthermore, it has been proposed that individuals with evidence of neurodegeneration but normal levels of amyloid might be classified as having suspected non-AD pathology (SNAP).[5]

The participants in this study were part of a longitudinal cohort of individuals with normal cognition when first assessed. We used baseline cerebrospinal fluid (CSF) measures of amyloid (Aβ1-42), total tau, and phosphorylated tau (p-tau) to classify individuals into the hypothetical stages of preclinical AD and SNAP. These CSF biomarkers are particularly useful in addressing the objectives of the study because they directly reflect the levels of abnormal brain proteins associated with the AD pathology (ie, plaques and tangles).[6,7]

To our knowledge, only one prior study[8] has examined the combined effects of CSF measures of amyloid and tau on cognitive change among individuals who were cognitively normal at baseline. Vos et al[8] reported a greater decline on the Mini-Mental State Examination (MMSE) over a mean of 3.9 years among individuals with evidence of both amyloid and tau pathology (stage 2) compared with individuals classified as stage 0, stage 1, and SNAP. The only other 2 studies[9,10] to investigate the combined effects of amyloid and neuronal injury on cognitive change used imaging-based biomarkers (eg, magnetic resonance imaging), which do not provide a direct measure of tau-related neurofibrillary tangle pathology. These studies reported similar results as Vos et al,[8] but the mean follow-up period was limited to 2 to 4 years.

The availability of CSF samples at baseline (when the participants were cognitively normal), the extensive cognitive testing, and the unusually long duration of follow-up (mean, 11.0 years) allowed us to examine several questions of particular relevance to clinical trials in preclinical AD. First, the present study used a cognitive composite score covering multiple domains of cognition as the outcome, allowing us to determine whether prior findings regarding the MMSE generalized to a broader range of cognitive domains and to tests likely to be more sensitive to subtle cognitive change. Second, most prior studies that have examined rates of cognitive change among cognitively normal individuals have been of short duration (mean follow-up, 1-4 years),[8-10] have not included measures of tau pathology,[11-14] or did not examine possible interactions between amyloid and tau on the rate of change in cognition.[15-20] Third, it remains unclear whether the major genetic risk factor for AD, the *APOE ε4* (OMIM 107741) genotype,[21] modulates the associations between amyloid, tau, p-tau, and cognitive change. This consideration may be highly relevant for the selection of participants in clinical trials because subgroups with differing rates of decline would make it more challenging to identify drug effects.

Key Points

Question Do the long-term cognitive trajectories differ among individuals classified into hypothetical preclinical Alzheimer disease groups using baseline cerebrospinal fluid levels of Aβ, tau, and phosphorylated tau (p-tau)?

Findings In this cohort study of cognitively normal adults, individuals in stage 2 (low Aβ and high tau [or p-tau]) had significantly lower baseline cognitive composite scores and a greater decline in cognitive performance than individuals in stage 0, stage 1, and SNAP, who did not differ from one another over 11 years.

Meaning Abnormal levels of both amyloid and tau appear to be necessary for observing a marked decline in cognition among cognitively normal individuals.

Methods

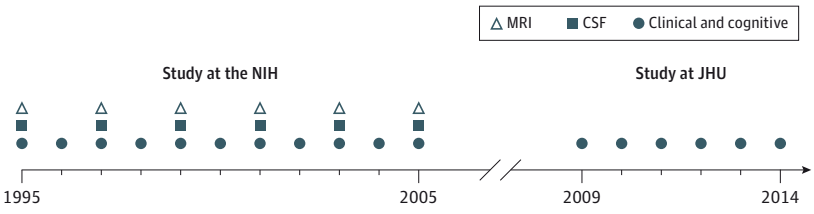
Study Design

The parent study from which these data are derived is BIOCARD, initiated at the National Institutes of Health (NIH) in 1995. By design, approximately 75% of the participants had a first-degree relative with dementia of the Alzheimer type. The study was stopped in 2005 for administrative reasons and reestablished at The Johns Hopkins University in 2009. During the initial study at the NIH, participants were administered a comprehensive neuropsychological battery annually. Magnetic resonance imaging, CSF samples, and blood specimens were obtained approximately every 2 years. **Figure 1** shows a schematic representation of the study design.

Selection of Participants

Recruitment was conducted by the staff of the geriatric psychiatry branch of the intramural program of the National Institute of Mental Health. At baseline, all individuals completed a comprehensive evaluation at the NIH consisting of a

Figure 1. Timeline Showing the Design of the BIOCARD Study



Shown are types of data collected each year for BIOCARD between 1995 and 2014. CSF indicates cerebrospinal fluid; JHU, The Johns Hopkins University; MRI, magnetic resonance imaging; and NIH, National Institutes of Health.

physical and neurological examination, an electrocardiogram, standard laboratory studies, and neuropsychological testing. Individuals were excluded from participation if they were cognitively impaired or had significant medical problems, such as severe cerebrovascular disease, epilepsy, or alcohol or drug abuse. eMethods 1 in the Supplement provides details regarding the selection of participants.

A total of 349 individuals were initially enrolled in the study after providing written informed consent. The analyses presented herein are based on 222 participants of the 335 who provided baseline CSF samples (eMethods 2 in the Supplement provides reasons for exclusion of individuals from analyses). The study was approved by The Johns Hopkins University Institutional Review Board.

Clinical and Cognitive Assessment of Participants

A cognitive and clinical assessment and a consensus diagnosis were completed annually at the NIH and at The Johns Hopkins University. Further details are provided by Albert et al.[22] Each participant included in our analyses received a consensus diagnosis by the staff of the Johns Hopkins BIOCARD clinical core. Each case was handled in the following similar manner: (1) clinical data pertaining to the medical, neurological, and psychiatric status of the individual were examined; (2) reports of changes in cognition by the individual and by collateral sources were reviewed; and (3) decline in cognitive performance based on review of longitudinal testing from multiple domains was established. We followed the diagnostic recommendations incorporated in the National Institute on Aging and the Alzheimer's Association working group reports for the diagnosis of MCI[23] and dementia due to AD.[24] eMethods 3 in the Supplement provides additional details. The clinical diagnoses were masked to CSF assessments.

The main outcome variable was an a priori–derived global cognitive composite score based on 4 individual measures that were identified previously to be the best combination of cognitive predictors of the time to progress from normal cognition to clinical symptom onset.[22] These measures were (1) Paired Associates immediate recall of the Wechsler Memory Scale–Revised, (2) Logical Memory delayed recall (Story A) score of the Wechsler Memory Scale–Revised, (3) Boston Naming, and (4) Digit-Symbol Substitution from the Wechsler Adult Intelligence Scale–Revised. These measures were administered annually at the NIH and are part of the annual neuropsychological battery at The Johns Hopkins University. To calculate the cognitive composite score, the individual measures were transformed to *z* scores and then averaged, with the requirement that at least 2 of the 4 scores were present at a given time point. eFigure 1 in the Supplement shows a histogram of baseline scores.

CSF Assessments

The CSF samples were analyzed with the same protocol used in the Alzheimer Disease Neuroimaging Initiative. This protocol used a kit (xMAP-based AlzBio3; Innogenetics) run on a suspension array system (Bio-Plex 200; Bio-Rad). Each participant had all samples (run in triplicate) analyzed on the same plate (eMethods 4 and eFigure 2 in the Supplement provide details regarding the CSF assay and baseline biomarker frequency distributions). Additional details have been published elsewhere.[25]

APOE Genotyping and Coding

APOE genotype was established in all but one of the cohort participants (n = 348). Genotypes were determined by restriction endonuclease digestion of polymerase chain reaction–amplified genomic DNA (performed by Athena Diagnostics, Worcester, Massachusetts). *APOE ε4* carrier status was coded by an indicator variable, with ε4 carriers coded as 1 if they had at least 1 ε4 allele and noncarriers coded as 0. Analyses that included *APOE* carrier status excluded individuals with the *ε2/ε4* genotype because the *ε4* allele increases AD dementia risk,[21] whereas the *ε2* allele decreases AD dementia risk.[26]

Statistical Analysis

Based on the observation that approximately one-third of cognitively normal older adults have AD pathology in their brains, as indicated by amyloid imaging[27-29] and neuropathological studies,[30-32] biomarker abnormality was defined as having CSF Aβ1-42 levels in the lower one-third of the distribution of participants (<374.5 pg/mL) or having tau (>74.9 pg/mL) or p-tau (>39.4 pg/mL) levels in the upper one-third of the distribution. The resulting proportion of individuals in the hypothetical preclinical AD groups (ie, stages 0, 1, and 2) was comparable to that reported in the literature.[5] The pattern of results was similar when using a median split or quintile split (eTable 1 and eTable 2 in the Supplement) to classify individuals into groups, suggesting robustness to cut point variations.

The data were analyzed using general linear mixed regression models, including linear effects of time, to test if the rate of change in cognition differed across the groups. Two main analyses were performed, one using CSF Aβ1-42 and tau to classify individuals into the 4 groups and the other using CSF

Table 1. Participant Characteristics at Baseline

Variable	Cohort as a Whole (n = 349)	Participants in Analyses (n = 222)
Age, mean (SD) [range], y	57.3 (10.4) [20.0-85.8]	56.9 (10.1) [22.1-85.8]
Follow-up time, mean (SD) [range], y	10.9 (4.6) [0-18.7]	11.0 (4.1) [0-18.3]
Female sex, No. (%)	201 (57.6)	133 (59.9)
White race/ethnicity, No. (%)	339 (97.1)	216 (97.3)
APOE ε4 carrier, No./total No. (%)	117/348 (33.6)	73 (32.9)
MMSE score, mean (SD)	29.5 (0.9)	29.5 (0.8)
Education, mean (SD) [range], y	17.0 (2.4) [12-20]	17.2 (2.3) [12-20]
Paired Associates immediate recall, mean (SD)	20.2 (3.4)	20.1 (3.4)
Logical Memory delayed recall, mean (SD)	12.3 (4.0)	14.8 (4.1)
Boston Naming % correct, mean (SD)	96.0 (5.3)	95.9 (5.3)
Digit-Symbol Substitution, mean (SD)	52.2 (11.7)	55.0 (12.6)
Cognitive composite score, mean (SD)	−0.1 (0.6)	−0.1 (0.6)

Abbreviation: MMSE, Mini-Mental State Examination.

Aβ1-42 and p-tau for classification. Group status was coded using binary predictors (0 or 1) for each group. The following predictors were included in both models, treating stage 0 as the implicit baseline: baseline age, sex, education, follow-up time, stage 1 indicator, stage 2 indicator, SNAP indicator, and the interaction (cross product) of each predictor with time. In these models, the stage indicator × time interaction terms test if the rate of change in the cognitive composite score differs between stage 0 and the other stages. The outcome variable in all analyses was the cognitive composite score (including baseline and all available follow-up scores, as defined in the Clinical and Cognitive Assessment of Participants subsection of the Methods section). Models were specified with a random intercept and slope.

To examine the role of the *APOE ε4* genotype on cognitive change, both models were rerun with inclusion of the indicator for the *APOE ε4* genotype and the *APOE ε4* genotype × time interaction term. In addition, to test if the cognitive trajectories within a given stage differ by the *APOE ε4* genotype, 4 mixed-effects models were run (one for each group) with the following predictors: baseline age, sex, education, *APOE ε4* genotype, time, baseline age × time interaction, and *APOE ε4* genotype × time interaction. The sex × time and education × time interactions were not included because they were not significant in any previous analysis.

Differences in baseline characteristics of participants in stage 0 compared with the other 3 groups were assessed using 2-tailed *t* tests or χ^2 tests, with a significance level of $P < .05$ uncorrected for multiple comparisons. All data analyses used a software program (R, version 3.2.1; R Project for Statistical Computing).

Results

The BIOCARD cohort as a whole, as well as subjects in the analysis, were primarily middle-aged at baseline, well-educated, and about one-third were *APOE ε4* carriers. Baseline characteristics for the BIOCARD cohort and for individuals in the analyses are listed in **Table 1**. **Table 2** lists baseline characteristics separately for the 4 groups (stage 0, stage 1, stage 2, and SNAP). The groups did not differ in sex, education, or MMSE score at baseline. However, compared with stage 0, individuals in stage 2 were older, were more likely to be *APOE ε4* carriers, had lower baseline cognitive composite scores, and were more likely to progress to MCI or AD dementia (Table 2 and eTable 2 in the Supplement). Individuals in stage 0 had more follow-up cognitive testing than the other groups.

The results from the mixed-effects models comparing the cognitive trajectories of individuals in stage 0 with the other groups are summarized in **Table 3**. The results were almost identical whether CSF Aβ1-42 and tau or CSF Aβ1-42 and p-tau were used to define group membership. In both models, there was a main effect of time (reflecting practice-related improvement in cognitive performance over time), a main effect of baseline age, and a baseline age × time interaction (signifying lower cognitive performance and less improvement in performance over time with increasing age). Higher education was associated with better cognitive performance but did not alter the rate of cognitive change over time.

Most important, the main effects of stage 1 and SNAP were not significant, nor were the interactions between stage 1 indicator × time and SNAP indicator × time. This finding suggests that there was no difference in either the mean cognitive composite score or the rate of change in the cognitive composite score over time between the stage 0 group and the stage 1 and SNAP groups. In contrast, the stage 2 indicator × time interactions were highly significant, indicating a more negative rate of change in cognition for the stage 2 group compared with the stage 0 group ($P < .001$). The mean cognitive performance was also lower in the stage 2 group compared with the stage 0 group. These results are shown graphically in **Figure 2**. Post hoc mixed-effects models directly comparing stage 1 and SNAP with stage 2 revealed a more negative rate of change in cognition for individuals in stage 2 compared with stage 1 and compared with SNAP. Compared with stage 1, the mean (SE) estimates were −0.074 (0.018) ($P < .001$) using p-tau and −0.068 (0.019) ($P < .001$) using tau. Compared with SNAP, the mean (SE) estimates were −0.074 (0.018) ($P < .001$) using p-tau and −0.060 (0.017) ($P = .001$) using tau. The results were similar using the individual cognitive measures as outcomes.

Table 2. Participant Characteristics at Baseline in Each of the 4 Preclinical Alzheimer Disease Groups

Variable	Stage 0 (n = 102)	Stage 1 (n = 46)	Stage 2 (n = 28)	SNAP (n = 46)
Groups defined by Aβ and tau				
Age, mean (SD), y	54.8 (10.3)	56.8 (8.1)	63.6 (9.9)[a]	57.6 (9.9)
Follow-up time, mean (SD), y	12.0 (3.5)	10.0 (3.6)[a]	8.6 (5.2)[a]	11.2 (4.3)
Female sex, No. (%)	62 (60.8)	27 (58.7)	16 (57.1)	28 (60.9)
White race/ethnicity, No. (%)	98 (96.1)	45 (97.8)	28 (100)[b]	45 (97.8)
APOE ε4 carrier, No. (%)	24 (23.5)	16 (34.8)	14 (50.0)[b]	19 (41.3)[b]
MMSE score, mean (SD)	29.6 (0.8)	29.4 (0.9)	29.6 (0.8)	29.5 (0.8)
Education, mean (SD), y	17.2 (2.4)	16.9 (2.4)	17.1 (2.1)	17.2 (2.2)
Paired Associates immediate recall, mean (SD)	20.3 (2.9)	20.0 (3.4)	20.3 (2.8)	20.7 (2.9)
Logical Memory delayed recall, mean (SD)	13.5 (3.8)	13.0 (3.9)	10.8 (4.5)[b]	12.8 (4.1)
Boston Naming % correct, mean (SD)	96.1 (5.9)	96.4 (5.7)	94.8 (6.0)	95.1 (6.5)
Digit-Symbol Substitution, mean (SD)	54.5 (11.6)	52.2 (12.5)	47.9 (13.0)[b]	53.4 (11.9)
Cognitive composite score, mean (SD)	0.0 (0.6)	−0.1 (0.7)	−0.3 (0.6)[b]	−0.1 (0.6)
CSF Aβ, mean (SD), pg/mL	447.7 (51.7)	315.3 (41.2)[a]	250.8 (71.8)[a]	476.9 (57.2)
CSF p-tau, mean (SD), pg/mL	30.7 (8.7)	26.6 (8.3)	60.5 (22.7)[a]	42.5 (13.5)[a]
CSF tau, mean (SD), pg/mL	56.8 (11.1)	45.4 (13.3)	109.6 (31.7)[a]	95.8 (30.0)[a]
Groups defined by Aβ and p-tau				
Age, mean (SD), y	56.0 (9.9)	57.1 (8.5)	63.1 (9.6)[a]	55.1 (11.1)
Follow-up time, mean (SD), y	12.4 (3.9)	10.2 (3.9)[a]	8.3 (4.7)[a]	10.2 (3.1)[a]
Female sex, No. (%)	60 (58.8)	25 (54.3)	18 (64.3)	30 (65.2)
White race/ethnicity, No. (%)	98 (96.1)	45 (97.8)	28 (100)[b]	45 (97.8)
APOE ε4 carrier, No. (%)	26 (25.5)	16 (34.8)	14 (50.0)[b]	17 (37.0)
MMSE score, mean (SD)	29.5 (0.8)	29.5 (0.9)	29.6 (0.7)	29.7 (0.7)
Education, mean (SD), y	17.3 (2.4)	17.1 (2.4)	16.8 (2.2)	17.0 (2.2)
Paired Associates immediate recall, mean (SD)	20.4 (2.9)	20.0 (3.5)	20.3 (2.5)	20.5 (2.9)
Logical Memory delayed recall, mean (SD)	13.3 (3.9)	13.0 (4.0)	10.8 (4.3)[b]	13.3 (4.0)
Boston Naming % correct, mean (SD)	95.9 (6.3)	96.0 (6.2)	95.5 (5.3)	95.5 (5.7)
Digit-Symbol Substitution, mean (SD)	54.1 (11.9)	53.1 (12.9)	46.5 (11.8)[b]	54.4 (11.3)
Cognitive composite score, mean (SD)	0.0 (0.6)	−0.1 (0.7)	−0.3 (0.6)[b]	0.0 (0.6)
CSF Aβ, mean (SD), pg/mL	454.2 (57.2)	308.1 (51.8)[a]	262.7 (69.7)[a]	462.5 (50.0)
CSF p-tau mean (SD), pg/mL	28.6 (7.2)	25.6 (6.9)	62.2 (20.7)[a]	47.1 (9.8)[a]
CSF tau, mean (SD), pg/mL	61.9 (20.3)	47.1 (16.7)	106.9 (34.5)[a]	84.7 (30.9)[a]

Abbreviations: CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; SNAP, suspected non–Alzheimer disease pathology.

[a] $P < .005$ for differences between stage 1, stage 2, and SNAP relative to stage 0.

[b] $P < .05$ for differences between stage 1, stage 2, and SNAP relative to stage 0.

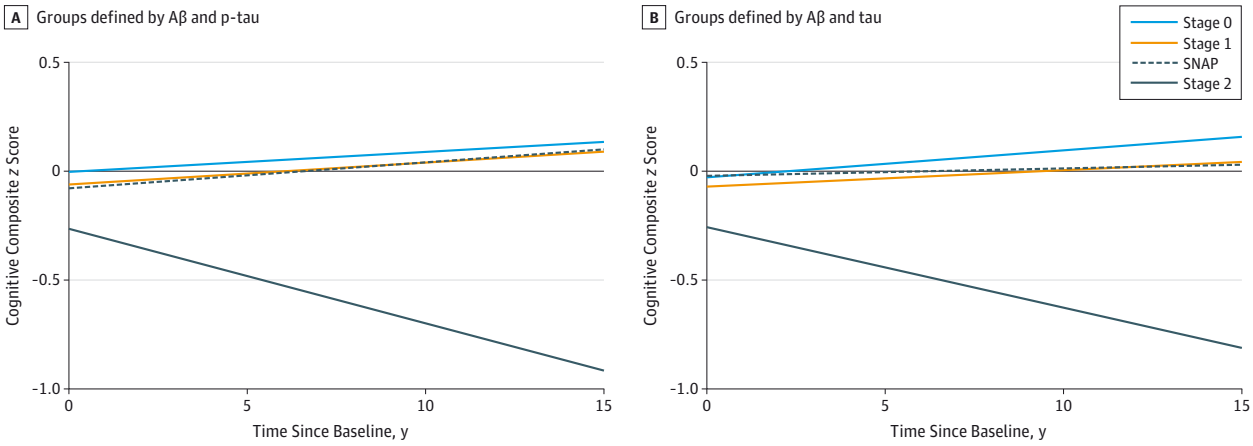
Table 3. Results of Linear Mixed-Effects Models[a]

	Groups Defined by Aβ and p-tau		Groups Defined by Aβ and tau	
Model Predictor	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Time	0.0905 (0.0318)	.005	0.0915 (0.0324)	.005
Baseline age	−0.0158 (0.0043)	<.001	−0.0157 (0.0043)	<.001
Male sex	−0.2590 (0.0779)	.001	−0.2508 (0.0777)	.002
Education	0.0466 (0.0164)	.005	0.0489 (0.0164)	.003
Stage 1 indicator	−0.0579 (0.0977)	.55	−0.0426 (0.0987)	.67
Stage 2 indicator	−0.2613 (0.1211)	.03	−0.2288 (0.1214)	.06
SNAP indicator	−0.0755 (0.0999)	.45	0.0068 (0.0980)	.94
Baseline age × time	−0.0017 (0.0004)	<.001	−0.0018 (0.0004)	<.001
Sex × time	−0.0029 (0.0068)	.67	−0.0019 (0.0068)	.78
Education × time	0.0011 (0.0014)	.45	0.0014 (0.0015)	.35
Stage 1 indicator × time	0.0009 (0.0085)	.92	−0.0048 (0.0088)	.58
Stage 2 indicator × time	−0.0526 (0.0116)	<.001	−0.0494 (0.0116)	<.001
SNAP indicator × time	0.0028 (0.0087)	.75	−0.0090 (0.0084)	.28

Abbreviations: p-tau, phosphorylated tau; SNAP, suspected non–Alzheimer disease pathology.

[a] Stage 0 was used as the implicit baseline in these models. Therefore, the estimates for stage 1, stage 2, and SNAP and their interactions with time reflect differences relative to stage 0.

Figure 2. Estimates of Longitudinal Cognitive Change for the 4 Hypothetical Preclinical Alzheimer Disease (AD) Groups



Shown are estimates from linear mixed-effects models predicting longitudinal cognitive composite scores over time among individuals classified into the 4 preclinical AD groups (stage 0, stage 1, stage 2, and suspected non–Alzheimer disease pathology [SNAP]) using baseline cerebrospinal fluid Aβ1-42 and phosphorylated tau (p-tau) (A) or Aβ1-42 and total tau (B) for classification. The estimates are adjusted for baseline age, sex, education, and their interactions with time. Stage 2 had a greater decline and lower baseline cognitive composite scores than the other groups, which did not differ from one another (Table 3).

The analyses were repeated with inclusion of the *APOE ε4* genotype and the *APOE ε4* genotype × time interaction term, but the results were unchanged, and effects involving the *APOE ε4* genotype were nonsignificant ($P > .40$ for all). Likewise, separate models for individuals in each stage showed no differences in the cognitive trajectories between *APOE ε4* carriers and noncarriers.

Discussion

This study compared the cognitive trajectories of individuals with different CSF AD biomarker profiles and normal cognition at baseline within the framework of 4 hypothetical groupings related to preclinical AD.[1,5] There was no difference in baseline cognitive performance or the rate of change in cognitive performance over a mean of 11.0 years among individuals in stage 1 (low levels of Aβ) or SNAP (high levels of tau or p-tau) compared with those in stage 0 (normal levels of both Aβ and tau or p-tau). By comparison, individuals in stage 2 (both low levels of Aβ and high levels of tau or p-tau) had lower cognitive performance at baseline and a more negative rate of change in cognition than the other 3 groups. Taken together, these results suggest that abnormal levels of both amyloid and tau are necessary for observing a marked decline in cognition among cognitively normal individuals.

These findings have important implications for the design of clinical trials aimed at individuals in the preclinical phase of AD. Our results suggest that, to optimize observing a treatment effect, clinical trials enrolling cognitively normal individuals should selectively recruit participants with abnormal levels of both amyloid and tau (ie, stage 2) because this group would be expected to show the greatest cognitive decline over time if untreated. If participants are selected solely on the basis of their amyloid status (eg, as in the A4 study[33]), then the ability to observe a significant treatment effect on cognition might be greatly diminished because a large proportion of untreated participants (those with abnormal amyloid but normal tau levels) would not be expected to show meaningful cognitive decline over the short time frame of a clinical trial. Our findings also suggest that, while *APOE ε4* carriers may be more likely to be further along the AD trajectory and therefore have an earlier age at onset,[12] the cognitive trajectories do not differ by ε4 carrier status after accounting for CSF amyloid and tau or p-tau levels. We do not have data regarding the effectiveness of antiamyloid drugs in reducing cognitive decline. However, our results suggest that, to the extent that amyloid and tau pathology arise independently and cognitive decline simply depends on their co-occurrence,[34-36] antiamyloid therapies may be effective in individuals with concurrent amyloid and tau pathology and in those with amyloid pathology only, who may subsequently develop tau pathology. However, if amyloid accumulation initiates a downstream cascade of tau-related neurodegeneration that becomes increasingly independent of amyloid itself,[37] then antiamyloid agents may only be effective if administered before the onset of the neurodegenerative process.

The present results are consistent with prior short-term longitudinal studies reporting a disproportionately greater rate of cognitive decline for individuals classified as stage 2 compared with stage 0, stage 1, and SNAP using CSF biomarkers[8] or neuroimaging-based biomarkers.[9,10] The study expands on prior findings in several ways. First, our cognitive outcome measure is clinically validated in the sense that it is based on neuropsychological tests previously shown to predict progression from normal cognition to MCI or dementia due to AD.[22] Both baseline cognitive composite score and the rate of change in the measures that comprise our cognitive composite score are associated with the time to onset of clinical symptoms, suggesting that these types of measures are useful for tracking AD progression in clinical trials. Second, our results demonstrate that the pattern of short-term cognitive trajectories observed

previously remains stable over the course of a decade. Third, we found that, although *APOE ε4* carriers were overrepresented among individuals classified as stage 2, the *APOE ε4* genotype did not modify the rate of change in cognition. Taken together, these 2 findings suggest that the *APOE ε4* allele does not significantly alter the rate of AD progression but is associated with an earlier age at onset of AD.[38,39] Fourth, higher education was associated with better cognitive performance after accounting for baseline CSF levels but did not modify the rate of change in cognition. This finding supports the view that education reduces the effect of AD neuropathology on cognition but does not alter the rate of disease progression.[40,41] Fifth, the present results point toward the usefulness of CSF biomarkers in identifying individuals at risk for cognitive decline at a significantly younger age (the mean baseline age for stage 2 was 63 years) than what has been reported by previous studies, which focused on individuals in their 70s at baseline.

Our study has several limitations. The participants are well educated, primarily of white race/ethnicity, and predominantly middle-aged at baseline, and most had a family history of dementia. Therefore, the results may not generalize to the population at large or to older cohorts. In addition, the sample size may have been too small to detect differences by the *APOE ε4* genotype. Future studies are necessary to determine if similar findings would be obtained using imaging-based biomarkers of amyloid and tau.

Conclusions

In summary, our data suggest that abnormal levels of both amyloid and tau appear to be necessary for observing cognitive decline among cognitively normal individuals. To optimize observing a treatment effect, clinical trials enrolling cognitively normal individuals should selectively recruit participants with abnormal levels of both biomarkers because this group would be expected to show the greatest cognitive decline over time if untreated.

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