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Alzheimer's Biomarkers and Future Decline in Cognitive Normal Older Adults

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Abstract

Background—Identifying older adults at risk of cognitive decline represents a challenge as Alzheimer's disease (AD) modifying therapies move towards preclinical stages.

Objective—To investigate the relationship between AD biomarkers and subsequent change in cognition in a cohort of cognitively intact older adults.

Methods—84 cognitively normal subjects (mean age 72.0 years, 59% women) were recruited through the Massachusetts Alzheimer's Disease Research Center and the Harvard Aging Brain Study and followed over 3 years. Measurements of beta-amyloid 1-42 (Ab42), total Tau (t-Tau) and Tau phosphorylated at threonine 181 (p-Tau181) in the CSF at study entry were available in all cases. Baseline brain MRI, FDG-PET and PiB-PET data were available in the majority of participants. Relationship between baseline AD biomarkers and longitudinal change in cognition was assessed using Cox proportional hazard regression and linear mixed models.

Results—14% participants increased their global Clinical Dementia Rating (CDR) score from 0 to 0.5 during follow-up. A CDR score increase was associated with higher baseline CSF t-Tau and p-Tau181, higher global cortical PiB retention and lower hippocampal volume. The combination of high CSF t-Tau and low Aβ42 or low hippocampal volume was more strongly related to cognitive outcome than each single biomarker. Higher CSF t-Tau was the only biomarker associated with subsequent decline in MMSE score.

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Conclusions—Baseline CSF t-Tau and p-Tau181, *in vivo* amyloid load and hippocampal volume were all independently associated with future decline in cognition. The discriminatory ability of these biomarkers to predict risk of cognitive decline, however, was only modest.

Keywords

Biomarkers; cognitive decline; epidemiology; cerebrospinal fluid; neuroimaging

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia among older adults, affecting more than 30 million of people worldwide [1]. It is well recognized that the brain pathological changes that characterize AD, i.e. amyloid and tau pathology and synaptic and neuronal loss, develop slowly over many years, possibly decades, before patients manifest the first subtle cognitive changes [2, 3]. There is general agreement on the idea that disease-modifying treatments are likely to have maximal effect before extensive and irreversible brain damage has occurred, and ideally before symptom onset [4, 5], so clinical trials are moving accordingly towards the preclinical stages of AD [6]. This reinforces the importance of biomarkers to increase diagnostic accuracy, predict disease progression at early stages, and improve assessment of therapeutic efficacy in clinical trials [7].

AD biomarkers have been generally grouped into two categories reflecting the underlying neuropathology: 1. Biomarkers of brain amyloid-beta (Aβ) deposition: low cerebrospinal fluid (CSF) Aβ42 concentration [7] and positive PET amyloid imaging [8]. 2. Biomarkers of tau deposition, neuronal loss and neurodegeneration: increased levels of CSF total Tau (t-tau) and phosphorylated Tau (ptau-181) [9], decreased fluorodeoxyglucose (FDG) uptake on PET imaging [10], and regional cortical atrophy on volumetric MRI [11]. Most of these biomarkers have been validated in populations of symptomatic patients and are associated with high sensitivity and specificity for mild cognitive impairment (MCI) and AD dementia [9]. While several longitudinal follow-up studies have examined the potential role of AD neuroimaging biomarkers to predict subsequent decline in cognition among cognitively normal subjects [12–19], very few have examined the predictive value of combined CSF and neuroimaging biomarkers in this population; something that may prove key to accurately identifying candidates who could benefit most from therapies aimed at preserving cognition in the presence of brain AD pathology.

In the present study, we investigated the relation of several CSF and neuroimaging biomarkers of brain AD pathology (CSF Aβ42, t-tau and ptau-181, MRI-based hippocampal volume, *in vivo* brain amyloid load as reported by PiB-PET retention, and FDG-PET uptake), alone or in combination, and subsequent cognitive change over 3-year follow-up in 84 volunteers, aged 60 or older, with intact cognition at study entry.

MATERIALS AND METHODS

Subjects

Participants were community-dwelling volunteers, enrolled in longitudinal cohorts as part of the Massachusetts Alzheimer's Disease Research Center (MADRC) and the Harvard Aging Brain Study (HABS) [20]. Baseline and annual assessments included a general and neurological exam, the Washington University Clinical Dementia Rating Scale (CDR) [21], and a standard battery of neuropsychological tests [22]. As part of the study, participants were offered at baseline the possibility of undergoing additional exams including lumbar puncture (LP), brain MRI, amyloid PET imaging using Pittsburgh compound B (PiB-PET) and fluorodeoxyglucose (FDG) PET scan. Examiners performing annual neurological and neuropsychological assessments were blinded to biomarker results.

All participants, aged 60 or older, in the two cohorts with available CSF assessments and a global CDR score of 0 within a year of the LP were included in the study. The CDR is an assessment instrument that yields global and Sum of Boxes (CDR-SOB) scores. The global CDR is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to AD and related dementias: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The information to make each rating is obtained through a semi-structured interview with the patient and a reliable informant [23]. A global CDR of 0 corresponds to normal cognition, while 0.5, 1, 2, and 3 correspond to questionable, mild, moderate, and severe dementia, respectively. The CDR-SOB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18.

The study was performed using protocols reviewed and approved by the institutional review board of the Partners Health Care. Informed consent was obtained from each participant.

CSF exam

Baseline LPs were performed on fasting condition by trained neurologists using an atraumatic spinal needle. CSF was collected in 12-mL polypropylene tubes with standardized conditions. Within two hours, CSF samples were centrifuged at 1,000g for 10 minutes and 0.5 mL aliquots were frozen at −80°C awaiting further analysis. CSF Aβ42, t-tau, and p-tau181 were measured with Luminex xMAP® CSF Assay (Innogenetics® INNO-BIA AlzBio3), on the Luminex platform, according to the manufacturer's protocol (Fujirebio).

MRI-based hippocampal volumetry

Brain MRI data at baseline were available in 75% of the participants. Median time interval between MRI and CSF exam was 1.9 months (range 0–20 months). MRI scans were conducted with a Siemens Trio 3T scanner (Siemens Medical Systems, Erlangen Germany). High-resolution T1-weighted structural images were acquired using a 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence with the following acquisition parameters: repetition time=2300ms; echo time=2.98ms; inversion time=900ms; flip angle=9°; voxel size=1.0×1.0×1.2mm. Hippocampal volumes (mean of both sides) were

calculated using FreeSurfer Version 5.1 (http://surfer.nmr.mgh.harvard.edu/) and normalized to estimated intracranial volume according to our previously published protocols [24].

Amyloid PET scans

PiB-PET data at baseline were available in the same 75% of participants as brain MRI data. Median time interval between PiB-PET scans and CSF exam was 1.6 months (range 0–9 months). All scans were performed at the MGH PET facility. C11–PiB was synthesized as previously described [25]. PET data were acquired using a Siemens/CTI (Knoxville, TN) ECAT HR+ scanner. Before injection, 10-minute transmission images for attenuation correction were collected. After injection of 3.15 × 108 to 5.55 × 108 Bq of PiB, 60 minutes of dynamic data were acquired in 3-dimensional acquisition mode. PiB data were analyzed as distribution volume ratio ratios (DVR). For each participant, an index of PIB binding in cortical regions was calculated using the dynamic data via Logan graphical modeling within a large aggregate cortical region of interest consisting of frontal, lateral parietal and temporal, and retrosplenial cortices (the FLR region). PiB retention in the FLR region is substantial in patients clinically diagnosed with AD and has been used as a summary measure of PIB retention in previous studies [25].

FDG-PET scans

18F-fluorodeoxyglucose (FDG)-PET scans at baseline were available in the same 75% of participants as brain MRI. Median time interval between FDG-PET and CSF exam was 1.9 months (range 0–39 months). FDG-PET scans were performed at the MGH PET facility as previously described [26]. FDG was extracted from a MetaROI reflecting regions known to be vulnerable in AD (inferior parietal, inferior temporal, and precuneus cortex), and used as a marker of neurodegeneration. Cerebellum gray matter was used as region of reference to compute standardized uptake value ratio (SUVR) for this MetaROI.

Statistical analysis

Baseline characteristics of the participants were compared to their progression in global CDR score over the 3-year follow-up (progression to CDR > 0, yes/no), using Fisher exact test for categorical variables and Student’s t-test for continuous variables. Correlations between different biomarkers were assessed using non-parametric Spearman’s rank correlation coefficients.

We used multivariable Cox proportional hazard models to estimate hazard ratios for increasing global CDR from 0 to 0.5 or greater over follow-up, according to baseline biomarkers. Multivariate models were adjusted for gender, education, age, APOE status (at least one ε4 allele versus none), and MMSE score at the time of CSF exam. The ability of each biomarker to discriminate subjects whose global CDR increased from 0 to CDR 0.5 during follow-up from those who remained stable was evaluated using the area under the receiver operating characteristic (ROC) curves.

Linear mixed models were used to study the relationship between baseline biomarkers and repeated MMSE scores. The intercept and slope (time) were treated as random effects,

allowing them to vary between individuals. Time in years from baseline was included as a continuous linear term after verification that a quadratic term did not improve model fit.

Because their distributions were not Gaussian, MMSE score, MRI-based hippocampal volume, PiB-PET and FDG-PET retention values were log-transformed in the various analyses. We used z-scores to estimate standardized regression coefficients, which allow comparing the strength of relations between cognition change and the different biomarkers. These z scores were modeled as continuous variables to ensure that selection of a cut-off value did not drive the results. To investigate the relationship between combined CSF biomarkers, we dichotomized CSF t-Tau at the upper quartile and CSF Aβ42 at the lowest quartile. In sensitivity analysis, we re-ran the analysis after excluding 13 participants with a CDR global score of 0 but a CDR-SOB score >0 at baseline.

All P values were two tailed, and $P \leq 0.05$ was considered to be significant. In sensitivity analysis, we applied a Bonferonni correction to test whether the results were robust to multiple testing adjustments. All analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

84 cognitively normal subjects were included in this study. Their baseline characteristics are shown in Table 1. Mean age was 72.0 (SD=7.2) years, 59% were women, and the median duration of follow-up was 3.2 years. Our subjects had a relatively high average level of education (mean years of education: 17.2 [9.4]) and high cognitive performances at baseline (mean MMSE score: 29.1 [1.0]). Subjects who agreed to additional neuroimaging exams were significantly older than those who did not (mean age: 73.1 vs. 66.6 years, $p<0.001$); no differences were observed in any other parameter. During follow-up, 12 (14%) subjects showed an increase in global CDR from 0 to 0.5. There were no significant differences in clinical characteristics at baseline (including neuropsychological measures) between those whose global CDR increased and those who remained stable (Table 1). Among the various biomarkers analyzed, subjects who showed increased in global CDR had higher CSF t-tau and PiB-PET retention compared to subjects with stable global CDR. Spearman rank correlation coefficients between the biomarkers are presented in Supplementary Table 1.

Table 2 shows the multivariable analysis of the relationship between baseline biomarkers and the hazard of increase in global CDR from 0 to 0.5 during follow-up. After adjustment for age, gender, baseline MMSE score, APOE status, and education, an increase in global CDR was associated with higher CSF t-Tau, CSF p-Tau 181 and PiB-PET retention, and with lower MRI hippocampal volume. There was a 3-fold increase in hazard of progressing from CDR 0 to 0.5 for every standard deviation (SD) increase in CSF t-Tau (HR=3.14, 95% CI: 1.66–5.95). There was a 2.5 fold increase in hazard of progressing from CDR 0 to 0.5 per 1 SD decrease hippocampal volume (HR = 2.47, 1.28 to 4.79). CSF Aβ42 and FDG-PET uptake, however, were not associated with CDR change. After multiple comparisons, only CSF t-Tau and MRI hippocampal volume remained associated with a longitudinal increase in global CDR.

An analysis based on combined CSF biomarkers is presented in Table 3. Participants with CSF t-Tau levels in the upper quartile (4th quartile) had a higher risk of increase in global CDR during follow-up compared to those in the other quartiles (HR = 3.37, 95% CI: 1.29 to 8.80). No significantly higher risk was observed among participants with CSF Aβ42 levels falling in the lower quartile (HR=1.76, 95% CI: 0.71 to 4.37). The combination of these two biomarkers was most strongly related to cognitive outcomes, and became statistically significant for subjects with both high CSF t-Tau (upper quartile) and low CSF Aβ42 (lower quartile) (HR=5.65, 1.68 to 19.05).

Table 4 shows the association between the various AD biomarkers and the risk of increase in global CDR during follow-up, using cut-offs based on lowest or highest quartiles of distribution. CSF t-Tau and PiB-PET retention were the only two single biomarkers significantly associated with increase in global CDR. In combination analysis, high CSF t-Tau combined with low CSF Aβ42 (HR=4.46, 1.55 – 12.87) or with low hippocampal volume (HR=4.84, 1.83 – 12.82) were the strongest biomarker combinations associated with global CDR increase.

Supplementary Figure 1 shows ROC curves for the various single biomarkers to discriminate participants whose global CDR increased from 0 to 0.5 from those who showed no change. In these analyses, only PiB-PET retention (AUC [standard error]=0.73 [0.10], p=0.01) and CSF t-Tau level (AUC = 0.70 [0.08], p=0.006) had AUC significantly different from the null value of 0.50.

Table 5 shows the linear mixed model estimates of the relationship between baseline biomarkers and repeated MMSE scores over follow-up, adjusted for age, gender, APOE genotype, and education. CSF t-Tau was the only single biomarker significantly associated with subsequent decline in MMSE score (estimate $\beta = -0.066$, standard error = 0.03, p=0.02). The annual change in MMSE score according to baseline levels of CSF t-Tau is presented in Supplementary Figure 2. Subjects in the upper quartile for CSF t-Tau had a significantly lower MMSE score after 2 years (p=0.001) and 3 years (p=0.005) compared to those in the other 3 lower quartiles.

In sensitivity analysis, we excluded 13 participants with a global CDR of 0 but CDR- SOB score > 0 (= 0.5) at baseline. This analysis gave virtually identical results to those described above (Supplementary Tables 2 and 3).

DISCUSSION

We analyzed the relationship between baseline CSF and neuroimaging biomarkers of AD brain pathology and future change in cognition in a cohort of 84 cognitively normal subjects aged 60 or older who were followed longitudinally for approximately 3 years. At group level, CSF t-Tau and p-Tau 181, MRI hippocampal volume and PiB-PET retention were all independently associated with increase in global CDR score during follow-up. The combination of high CSF t-Tau and low CSF Aβ42 was more strongly related to cognitive outcome than either biomarker alone. Neither CSF Aβ42 nor FDG-PET uptake were associated with CDR change. Importantly, CSF t-Tau level was the only single biomarker

significantly associated with longitudinal decrease in MMSE score. However, when ROC curve analyses were conducted, only CSF t-Tau and PiB-PET retention showed AUC significantly greater than 0.50 (at approximately 0.70 in both cases), corresponding only to a modest discriminatory power to distinguish participants who exhibited a longitudinal decline.

AD biomarkers have been extensively investigated among AD and non-AD symptomatic patients. However, limited data are available on combined CSF and imaging biomarkers in cognitively normal populations, and these offer inconsistent results. While some studies have found that decreased CSF Aβ42 is associated with cognitive decline among normal older adults [27–30], others could not confirm these observations [31, 32]. Prior work by Palmqvist and colleagues. suggested that CSF Aβ42 can be used with high accuracy to determine whether a patient has increased brain amyloid deposition [33]. In that study, increased amyloid deposition by PET, but not CSF Aβ42, significantly correlated with disease stage among patients with mild cognitive symptoms. The same authors recently reported that the diagnostic accuracy of CSF biomarkers and amyloid PET for diagnosing early-stage AD is comparable [34]. A previously published report, with similar design to the present study, failed to demonstrate an association between CSF biomarkers and cognitive decline in non-demented elderly [31]. In that study, increased CSF t-Tau was the only CSF biomarker with a trend to correlate with increase in global CDR. In another study, CSF t-Tau and Aβ42, and PET amyloid load, all predicted cognitive decline without significant differences in their individual predictive ability [30]. Another recent exploratory analysis of a cognitively normal cohort followed up for a median of 3.1 years suggested that elevation in baseline brain amyloid level was associated with higher likelihood of cognitive decline [35]. A study based on ADNI subjects reported that structural MRI and CSF Tau had the strongest predictive value for progression from normal to MCI [36]. More recently, Soldan and colleagues found that, among cognitively normal adults, those with combined high CSF t-Tau or p-Tau and low CSF Aβ42 had significantly lower baseline cognitive scores and the greatest cognitive decline after follow-up [37].

It is worth noting that in our study we did not find an association between lower brain glucose metabolism, as measured by FDG-PET, and cognitive decline. Paradoxically, lower glucose metabolism tended to correlate with lower risk of increase in global CDR over follow-up (HR=0.65, 0.33–1.28). In agreement with this observation, recent studies reported that the brain hypometabolic pattern typically observed in symptomatic AD patients can be preceded by a hypermetabolic phase [38], pointing towards a potential compensatory mechanism at preclinical disease stages [39]. It is also interesting that in our study *in vivo* amyloid load was associated with cognitive change but CSF Aβ42 level was not. Of note, the kinetics of CSF Aβ42 in very early stages of the transition from normal cognition to very subtle cognitive changes in sporadic AD remains largely unknown. Data from studies on carriers of autosomal-dominant AD mutations [2, 40], as well as from experimental studies [41], suggest that CSF Aβ42 levels transiently increase during the early phase of brain amyloid deposition.

The current study is not without limitations. First, the relatively small cohort size and the limited number of events may have diminished the power of our study to detect subtle

effects on cognition of some of the biomarkers assessed. Second, our cohort contains a large proportion of participants more highly educated than the general population. The likely higher cognitive reserve in this population may alter the association of these biomarkers and cognition, and limits the generalizability of the findings [42]. Third, despite the finding of statistically significant associations between CSF and neuroimaging biomarkers and cognitive change at the group level in this study, the predictive value of these biomarkers, alone or in combination, to discriminate decliners from non-decliners at the individual level remained quite modest (as characterized by a low AUC) after 3-year follow-up. This is particularly relevant for the rational design of intervention studies in cognitively normal older adults at risk of AD, and highlights the need of further studies to define the value of AD biomarkers for predicting cognitive decline in those with normal cognition. Recently developed PET tau tracers that exhibit high affinity for neurofibrillary tangle pathology, like AV-1451, have now the potential to improve the predictive value of AD biomarkers in asymptomatic individuals [43, 44].

CONCLUSION

Higher CSF t-Tau and PiB-PET retention (*in vivo* amyloid load) were the single biomarkers that best predicted at the group level future decline in cognition in the cohort of 84 cognitively normal older adults studied here. The combination of high CSF t-Tau and low CSF Aβ42 or low hippocampal volume were significantly more predictive of future cognitive outcomes than any single biomarker. Our results reinforce the notion that AD pathology builds up slowly during a long preclinical phase of the disease that predates subtle changes in cognition. However, they also highlight the relatively modest performance of the biomarkers studied here, either alone or in combination, for predicting decline in cognition at the individual level among cognitively normal older adults after 3-year follow-up. These findings may prove relevant when designing preventive interventions within this time frame in asymptomatic subjects at risk of AD, and emphasize that efforts to optimize cutoff points of currently known biomarkers, as well as to develop and validate novel biomarkers with higher predictive value at the individual level are greatly needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics and Baseline Characteristics.

		Progression to CDR ≥ 0.5		
	Overall	No	Yes	
Baseline characteristics	**N=84**	**N=72**	**N=12**	**P-value**
Age, years, mean (SD)	72.0 (7.2)	71.9 (7.6)	72.6 (4.4)	0.78
Women, n (%)	49 (59)	44 (62)	5 (42)	0.22
Education level, years, mean (SD)	17.2 (9.4)	17.4 (10.1)	16.0 (2.4)	0.64
APOE ε4 positive, n (%)	28 (36)	22 (33)	6 (50)	0.33
Neuropsychological testing				
MMSE, mean (SD)	29.1 (1.1)	29.2 (1.1)	28.8 (1.1)	0.23
Global CDR, mean (SD)	0	0	0	
CDR sum of boxes, mean (SD)	0.1 (0.2)	0.1 (0.2)	0.2 (0.2)	0.13
Logical memory, mean (SD)	15.6 (3.4)	15.6 (3.6)	15.3 (2.1)	0.74
TMT-A, mean (SD)	33.6 (11.6)	33.7 (11.4)	32.8 (12.8)	0.81
TMT-B, mean (SD)	75.7 (30.7)	74.1 (29.6)	84.7 (36.4)	0.27
Benton naming test, mean (SD)	28.4 (1.9)	28.4 (1.9)	28.8 (1.7)	0.44
CSF biomarkers, pg/mL				
Aβ42, mean (SD)	445.5 (141.4)	450.9 (140.7)	412.9 (147.4)	0.39
Total Tau, mean (SD)	81.8 (38.1)	78.2 (36.5)	103.8 (41.5)	0.03
p-Tau 181, mean (SD)	35.7 (14.9)	35.1 (14.9)	39.6 (14.9)	0.33
MRI volumetry[a]				
Hippocampal volume, mm^3, mean (SD)	3706 (446)	3723 (423)	3588 (600)	0.43
PIB PET imaging[a]				
FLR region, DVR, mean (SD)	1.16 (0.19)	1.14 (0.17)	1.30 (0.26)	0.03
FDG PET imaging[a]				
Temporoparietal, SUVR, mean (SD)	3.25 (0.22)	3.25 (0.24)	3.50 (0.11)	0.94

DVR = distribution volume rario; CDR =Clinical Dementia Rating Scale; FLR = Frontal, lateral parietal and lateral temporal, and retrosplenial; SUVR = standardized uptake value ratio.

[a]MRI, PIB PET, and FDG PET imaging were available on 63/84 (75%) subjects of the sample.

Table 2

Association between Baseline Biomarkers and Risk of CDR ≥ 0.5 over the Follow-up.

	Hazard ratio (95% CI) of CDR ≥ 0.5[a]			
Baseline biomarkers	**Unadjusted**	**P value**	**Adjusted[b]**	**P value[b]**
CSF Aβ42	1.03 (0.67–1.57)	0.89	1.03 (0.63–1.67)	0.91
CSF total Tau	2.56 (1.51–4.33)	<0.001	3.14 (1.66–5.95)	<0.001
CSF p-Tau 181	1.53 (1.00–2.34)	0.05	1.65 (1.04–2.63)	0.03
MRI hippocampal volume	1.97 (1.20–3.21)	0.007	2.47 (1.28–4.79)	0.007
PIB FLR region	1.57 (1.03–2.40)	0.04	1.80 (1.00–3.22)	0.05
FDG temporoparietal region	0.76 (0.43–1.36)	0.36	0.65 (0.33–1.28)	0.21

FLR = Frontal, lateral parietal and lateral temporal, and retrosplenial.

[a] Standardized hazard ratios correspond to an increase (tau, p-Tau 181, PIB) or a decrease (Aβ42, MRI, FDG) of one standard deviation of the various biomarkers used as continuous variables.

[b] Adjusted for age, gender, MMSE score, APOE ε4, and years of education.

Table 3

Association between Combination of CSF Biomarkers and Risk of CDR ≥ 0.5 over the Follow-up.

	Hazard ratio (95% CI) of CDR ≥ 0.5			
Baseline CSF biomarkers	**Unadjusted**	**P value**	**Adjusted[a]**	**P value[a]**
CSF total Tau < 100 pg/mL	1	—	1	—
CSF total Tau ≥ 100 pg/mL[b]	3.37 (1.29 – 8.80)	0.01	3.52 (1.24 – 10.00)	0.02
CSF Aβ42 > 352 pg/mL	1	—	1	—
CSF Aβ42 ≤ 352 pg/mL[c]	1.76 (0.71 – 4.37)	0.22	1.85 (0.67 – 5.08)	0.24
Combination[d]:				
Low CSF Tau/High CSF Aβ42	1	—	1	—
Low CSF Tau/Low CSF Aβ42	1.27 (0.38 – 4.24)	0.69	1.66 (0.45 – 6.09)	0.45
High CSF Tau/High CSF Aβ42	2.34 (0.57 – 9.54)	0.24	3.26 (0.71 – 14.94)	0.13
High CSF Tau/Low CSF Aβ42	5.65 (1.68 – 19.05)	0.005	5.94 (1.49 – 23.71)	0.01

[a] Adjusted for age, gender, MMSE score, APOE ε4, and years of education

[b] Highest quartile of CSF Tau.

[c] Lowest quatile of CSF Aβ42.

[d] Based on highest and lowest quartiles of CSF Tau and Aβ42 respectively.

Table 4

Association between AD Biomarkers and risk of CDR ≥ 0.5 over the Follow-up.

	Hazard ratio (95% CI) of CDR ≥ 0.5[a]			
Baseline CSF biomarkers	**Unadjusted**	**P value**	**Adjusted[b]**	**P value[b]**
Single biomarker[b]:				
High CSF total Tau, ≥ 100 pg/mL	3.37 (1.29 – 8.80)	0.01	3.52 (1.24 – 10.00)	0.02
Low CSF Aβ42, ≤ 352 pg/mL	1.76 (0.71 – 4.37)	0.22	1.85 (0.67 – 5.08)	0.24
High PIB FLR, ≥ 1.17	2.56 (1.03 – 6.33)	0.04	3.09 (1.00 – 9.71)	0.05
Low FDG PET, ≤ 3.19	0.48 (0.16 – 1.44)	0.19	0.35 (0.11 – 1.12)	0.08
Low hippocampal volume, ≤ 3350 mm^3	1.77 (0.67 – 4.67)	0.25	1.70 (0.58 – 5.01)	0.34
Combination of biomarkers:				
High CSF Tau and low CSF Aβ42	4.46 (1.55 – 12.87)	0.006	3.78 (1.19 – 11.99)	0.02
High CSF Tau and low Hippocampal volume	2.65 (0.76 – 9.23)	0.13	2.96 (0.73 – 12.00)	0.13
High CSF Tau and High PIB FLR	2.70 (0.87–8.37)	0.09	2.25 (0.69 – 7.33)	0.18
Low CSF Aβ42 and high PIB FLR	2.85 (1.14 – 7.08)	0.02	3.49 (1.12 – 10.89)	0.03
Low CSF Aβ42 and low hippocampal volume	4.84 (1.83 – 12.82)	0.002	6.62 (1.71 – 25.58)	0.006
High PIB FLR and low hippocampal volume	4.10 (1.55–10.81)	0.004	5.27 (1.45 – 19.12)	0.01

[a] Highest or lowest quartile compared to the 3 other quartiles.

[b] High CSF total Tau and high PIB FLR correspond to highest quartile; low CSF Aβ42, FDG PET and hippocampal volume correspond to lowest quartile.

[c] Adjusted for age, gender, MMSE score, APOE ε4, and years of education

Table 5

General Linear Mixed Models Estimates of the Relationship between Baseline Biomarkers and MMSE Score at Baseline and over the Follow-up.

Biomarkers	Estimates (SE)[a]	P value[a]
Baseline MMSE		
CSF Aβ1-42	−0.01 (0.10)	0.91
CSF Tau	−0.10 (0.09)	0.28
CSF p-Tau 181	−0.13 (0.09)	0.16
MRI hippocampal volume	0.20 (0.13)	0.13
PIB FLR region	−0.16 (0.13)	0.21
FDG temporoparietal region	−0.88 (0.57)	0.58
Change in MMSE per year		
CSF Aβ1-42, continuous, x time	0.008 (0.03)	0.80
CSF Tau x time	−0.066 (0.03)	0.02
CSF p-Tau 181 x time	−0.042 (0.03)	0.14
MRI hippocampal volume x time	−0.001 (0.03)	0.99
PIB FLR region x time	−0.049 (0.04)	0.18
FDG temporoparietal region	0.009 (0.04)	0.82

MTL: medial temporal lobe; FLR: Frontal, lateral parietal and lateral temporal, and retrosplenial.

[a]Standardized estimates of mixed models, adjusted on age, gender, APOE ε4, and years of education