ORIGINAL CONTRIBUTION

Cerebrospinal Fluid Abnormalities and Rate of Decline in Everyday Function Across the Dementia Spectrum

Normal Aging, Mild Cognitive Impairment, and Alzheimer Disease

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Objective: To investigate the effect of cerebrospinal fluid (CSF) abnormalities on the rate of decline in everyday function in normal aging, mild cognitive impairment (MCI), and mild Alzheimer disease (AD).

Design: Immunoassays of total tau (t-tau), tau phosphorylated at threonine 181 (p-tau$_{181}$), and β-amyloid 1-42 (Aβ$_{42}$) concentrations were performed in CSF obtained from participants in the Alzheimer's Disease Neuroimaging Initiative. Random effects regressions were used to examine the relationship among CSF abnormalities, cognitive impairment (assessed with the Alzheimer Disease Assessment Scale–cognitive subscale [ADAS-Cog]), and functional decline (assessed with the Pfeffer Functional Activities Questionnaire) and to determine whether the impact of CSF abnormalities on functional decline is mediated by cognitive impairment.

Setting: Fifty-eight sites in the United States and Canada.

Participants: One hundred fourteen cognitively intact adults, 195 patients with MCI, and 100 patients with mild AD.

Main Outcome Measure: Decline in the Pfeffer Functional Activities Questionnaire score.

Results: Abnormalities in all CSF analytes were associated with functional decline in MCI, and all but the t-tau: Aβ$_{42}$ ratio were associated with functional decline in controls. No abnormal CSF analyte was associated with functional decline in AD. Among controls, p-tau$_{181}$ concentration was the most sensitive to functional decline, whereas in MCI it was Aβ$_{42}$ concentration. Cerebrospinal fluid biomarkers were uniformly more sensitive to functional decline than the ADAS-Cog score among controls and variably so in MCI, whereas the ADAS-Cog score was unequivocally more sensitive than CSF biomarkers in AD. The impact of CSF abnormalities on functional decline in MCI was partially mediated by their effect on cognitive status. Across all diagnostic groups, persons with both tau and Aβ$_{42}$ abnormalities exhibited the steepest rate of functional decline.

Conclusions: Abnormalities in CSF are associated with functional decline and thus with future development of AD in controls and patients with MCI. However, they do not predict further functional degradation in patients with AD. Persons with comorbid tau and Aβ$_{42}$ abnormalities are at greatest risk of functional loss.

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Group Information: A complete list of Alzheimer's Disease Neuroimaging Initiative investigators is available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Authorship_list.pdf.

CEREBROSPINAL FLUID (CSF) concentrations of total tau (t-tau), tau phosphorylated at threonine 181 (p-tau$_{181}$), and β-amyloid 1-42 (Aβ$_{42}$) have emerged as core biomarkers of Alzheimer disease (AD) owing to their intrinsic linkage to the pathognomonic features of AD (ie, neurofibrillary tangles and amyloid plaques).[1-4] In contrast with the demonstrations of associations between CSF abnormalities and some indices of disease severity and progression such as cognitive decline,[5] plaque density,[6] and cerebral alterations,[7,8] the relationship between CSF abnormalities and decline in everyday function has received limited attention.[5,9,10] This constitutes a significant knowledge gap for several reasons.

First, functional restriction is a hallmark of AD and other dementias.[11,12] Indeed, widely used dementia staging instruments (eg, the Clinical Dementia Rating Scale) lean heavily on reports of an individual's daily functioning in ascertaining dementia severity. Thus, decline in everyday function likely signals disease onset or progression among cognitively

normal older adults and those with mild cognitive impairment (MCI), respectively. Second, everyday function is an important outcome in AD clinical trials.[13] Therefore, it is useful to understand how it is related to biomarkers of AD. Third, unraveling associations between CSF abnormalities and functional decline, especially in preclinical AD, might be valuable information for patients and their care providers because they often wish to know what the future holds.

In this article, we investigate (1) whether CSF abnormalities are associated with decline in everyday function; (2) whether such associations, if existent, are comparable or differential across CSF analytes; (3) whether CSF analytes are more sensitive to functional decline than cognitive measures; (4) whether the impact of CSF abnormalities on functional decline is mediated by their effect on cognition; (5) whether the combination of abnormally high t-tau or p-tau$_{181}$ and abnormally low Aβ_{42} concentrations confers increased risk of functional decline; and (6) whether these effects are similarly present throughout the continuum from healthy cognitive aging to AD.

METHODS

PARTICIPANTS

The analyses presented herein were based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI; http://www.loni.ucla.edu/ADNI/). The ADNI was launched in 2003 by the National Institute on Aging and other entities (listed in the Funding/Support section) as a 5-year public-private partnership. Enrollment target was 800 participants—200 healthy control subjects, 400 patients with amnestic MCI, and 200 patients with mild AD—at 58 sites in the United States and Canada.

Diagnosis of amnestic MCI required patient-reported memory symptoms, objective memory difficulties (impaired delayed recall of Story A from the Logical Memory Test[14]), essentially normal functional activities, a Clinical Dementia Rating Scale global score of 0.5, and a Mini-Mental State Examination score of 24 or more. Patients with AD met the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria[12] for probable AD, had Mini-Mental State Examination scores ranging from 20 to 26 (inclusive), and had Clinical Dementia Rating Scale global scores of 0.5 or 1.0. Participants underwent evaluation at 6-month intervals for 2 (patients with mild AD) or 3 (controls and patients with MCI) years. Further details about the ADNI, including participant selection procedures and complete study protocol, have been presented elsewhere[1,15,16] and may be found online at http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI.htm.

The present analyses included all participants—114 controls, 195 patients with MCI, and 100 patients with mild AD—who had valid test results for all CSF biomarkers (ie, t-tau, Aβ_{42}, p-tau$_{181}$, t-tau:Aβ_{42} ratio, and p-tau$_{181}$:Aβ_{42} ratio) when the data download occurred in November 2008. **Table 1** details the participants' baseline characteristics. Informed consent was obtained from study participants and their families, and the study was approved by the local institutional review board at the participating sites.

CSF COLLECTION AND ANALYSIS

Full details of the collection and analysis of CSF samples in ADNI have been provided elsewhere.[1] Briefly, lumbar puncture was performed in the morning after an overnight fast. Assays of t-tau, Aβ_{42}, and p-tau$_{181}$ concentrations were performed using 0.5-mL aliquots and a multiplex platform (xMAP; Luminex Corp, Austin, Texas) with immunoassay kit–based reagents (INNO-BIA AlzBio3; Innogenetics NV, Ghent, Belgium; for research use–only reagents).

Table 1. Characteristics of Study Participants at Baseline

Variable	Diagnostic Group		
	Control (n=114)	MCI (n=195)	AD (n=100)
Age, mean (SD), y	75.54 (5.19)	74.46 (7.50)	74.85 (7.89)
Female sex, %	49.1	33.3	42.0
White race, %	91.2	95.4	99.0
Education, mean (SD), y	15.74 (2.86)	15.82 (3.00)	15.11 (3.30)
Using antidementia medication, %	0	54.9	92.0
APOE ε4+, %	23.7	53.8	69.0
GDS score, mean (SD)	0.86 (1.10)	1.67 (1.36)	1.67 (1.36)
CDR global score, %			
0.0	100.0	0	0
0.5	0	100.0	57.0
1.0	0	0	43.0
MMSE score, mean (SD)	29.09 (1.03)	26.91 (1.79)	23.54 (1.91)
ADAS-Cog score, mean (SD)	6.41 (2.90)	11.65 (4.50)	18.15 (6.18)
FAQ score, mean (SD)	0.16 (0.66)	3.81 (4.45)	12.71 (6.71)

Abbreviations: AD, Alzheimer disease; ADAS-Cog, the Alzheimer Disease Assessment Scale–cognitive subscale; APOE ε4+, possession of 1 or more copies of apolipoprotein E ε4 allele; CDR, Clinical Dementia Rating scale; FAQ, Pfeffer Functional Activities Questionnaire; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

FUNCTIONAL ASSESSMENT

Everyday function was assessed with the Pfeffer Functional Activities Questionnaire (FAQ).[17] The FAQ is an informant-report inventory that inquires into an older adult's ability to manage finances; complete forms; shop; perform games of skill or hobbies; prepare hot beverages; prepare a balanced meal; follow current events; attend to television programs, books, or magazines; remember appointments; and travel out of the neighborhood. Ratings range from normal (0) to dependent (3), for a total of 30 points. Higher scores indicate worse functional status. The FAQ has good reliability (item-total correlations, ≥0.80) and validity (correlations with measures of mental status, daily function, and clinical diagnosis, ≥0.70).[17] Within this ADNI sample, the FAQ demonstrated excellent reliability (Cronbach $\alpha = 0.93$). At baseline, with the exception of control participants who, not surprisingly, mostly had scores of 0 on the FAQ, FAQ scores in this cohort were largely devoid of floor and ceiling effects. For instance, no patient with MCI or AD had a score of 30.

COGNITIVE ASSESSMENT

Global cognition was assessed with the Alzheimer Disease Assessment Scale—cognitive subscale (ADAS-Cog).[18] The ADAS-Cog is the most widely used cognitive measure in AD clinical trials. It is brief and structured and assesses verbal learning and memory, language, orientation, ideational praxis, and constructional praxis. Scores range from 0 to 70, with higher scores reflecting poorer cognitive function.

Table 2. CSF Biomarker Concentrations and Ratios at Baseline

Biomarker[a]	Diagnostic Group		
	Control (n=114)	MCI (n=195)	AD (n=100)
T-tau, mean (SD), pg/mL	69.65 (30.32)	103.54 (60.93)[b]	121.57 (57.56)[b,c]
Abnormal, %	18.4	44.6	65.0
$A\beta_{42}$, mean (SD), pg/mL	205.63 (55.07)	163.31 (54.93)[b]	143.51 (41.01)[b,c]
Abnormal, %	37.7	74.4	91.0
P-tau_{181}, mean (SD), pg/mL	24.84 (14.59)	35.68 (18.10)[b]	41.73 (19.96)[b,c]
Abnormal, %	36.0	70.3	87.0
T-tau:$A\beta_{42}$ ratio, mean (SD)	0.39 (0.27)	0.75 (0.62)[b]	0.92 (0.48)[b,c]
Abnormal, %	34.2	69.7	88.0
P-tau:$A\beta_{42}$ ratio, mean (SD)	0.14 (0.13)	0.26 (0.18)[b]	0.32 (0.19)[b,c]
Abnormal, %	47.4	77.9	94.0

Abbreviations: $A\beta_{42}$, β-amyloid 1-42; AD, Alzheimer disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau_{181}, tau phosphorylated at threonine 181; t-tau, total tau.

[a] Percentage abnormal refers to the percentage of cases within each diagnostic group whose CSF biomarker values were worse than the cutoff values (t-tau, 93 pg/mL; $A\beta_{42}$, 192 pg/mL; p-tau_{181}, 23 pg/mL; t-tau:$A\beta_{42}$ ratio, 0.39; and p-tau_{181}:$A\beta_{42}$ ratio, 0.10) established in a previous Alzheimer's Disease Neuroimaging Initiative study.[1]

[b] Significantly different from controls.

[c] Significantly different from MCI group.

DATA ANALYSES

Group differences on the CSF measures were tested using single degrees of freedom contrast tests, corrected for inequality of variance. To examine the association among CSF abnormalities, cognitive impairment, and functional decline within each diagnostic group, we fitted a series of random coefficient regressions[19,20] that modeled change in FAQ scores as a function of baseline values on CSF biomarkers and the ADAS-Cog score. Abnormality on CSF biomarkers was defined using previously established ADNI thresholds (t-tau, 93 pg/mL; $A\beta_{42}$, 192 pg/mL; p-tau_{181}, 23 pg/mL; t-tau:$A\beta_{42}$ ratio, 0.39; and p-tau_{181}:$A\beta_{42}$ ratio, 0.10).[1] For the ADAS-Cog, we modeled the effect of performance that is 1 SD above (ie, worse than) group-specific means.[21] The biomarker × time terms were the primary effects of interest because they would reveal the impact of CSF abnormality or cognitive impairment on the rate of change in FAQ.

To quantify and compare the variation in functional decline accounted for by each CSF biomarker or the ADAS-Cog score, we calculated the proportional reduction—a pseudo-R^2 statistic—in the FAQ score's rate of change residual variation that was attained when each biomarker and its interaction with time was introduced into a model that only contained age, baseline FAQ score, and their interactions with time.[20] Higher R^2 values indicated that the variable being modeled accounted for a larger proportion of the unexplained variation in—and, thus, is more sensitive to—rate of change in FAQ.

To examine whether the effect of CSF biomarkers on functional decline is mediated by their effect on cognition, we tested a series of random coefficient regressions that added terms for ADAS-Cog and ADAS-Cog × time to each CSF biomarker model. Full mediation was assumed when a previously significant biomarker × time interaction became nonsignificant. Partial mediation was indicated when the biomarker × time effect was attenuated but remained significant. The percentage of the relationship between the CSF biomarker and functional decline that was mediated by cognition was computed as (original estimate – ADAS-Cog–adjusted estimate)/original estimate. Because mediation requires that the substantive and mediator variables be associated with the outcome, these analyses were performed only within diagnostic groups in which CSF biomarkers and ADAS-Cog were both significantly related to functional decline.

Finally, we examined whether individuals with a combination of abnormal tau and $A\beta_{42}$ findings experience a faster rate of functional decline relative to those with no or 1 CSF abnormality by fitting a series of random coefficient regressions in which the rate of functional decline among persons in the normal tau/normal $A\beta_{42}$ group was contrasted with the rate of decline in the abnormal tau/normal $A\beta_{42}$, normal tau/abnormal $A\beta_{42}$, and abnormal tau/abnormal $A\beta_{42}$ groups.

As a precondition for examining the effects of CSF abnormalities and ADAS-Cog scores on functional decline, we first examined the temporal course and rate of functional decline within each group by fitting group-specific random effects regressions that modeled change in FAQ scores as a function of time.[20] To determine the temporal course of functional decline, we compared the relative fit of linear (time) and curvilinear (time × time) polynomials for time using the Bayesian information criterion.[22] On the Bayesian information criterion, lower values indicate better fit. The polynomial specification for time (ie, linear or quadratic) that emerged as optimal was used in all subsequent analyses.

All random coefficient regressions outlined included random intercept and random slope terms to account or test for potential interindividual variability in baseline scores and rate of change, respectively.[20] In addition, they all included age, baseline FAQ scores, and their interactions with time as covariates; to further adjust for variations in baseline FAQ scores, analyses were begun at the 6-month assessment. Data analyses were performed using commercially available statistical software (SPSS, version 16.0; SPSS Inc, Chicago, Illinois).

RESULTS

GROUP DIFFERENCES IN BASELINE CSF ANALYTES

As reported in previous studies,[1,2,5] CSF levels of t-tau and p-tau_{181} and the t-tau:AB_{42} and p- tau_{181}:AB_{42} ratios were significantly higher, whereas $A\beta_{42}$ levels were significantly lower, in patients with MCI and those with AD compared with controls, and in patients with AD compared with those with MCI (**Table 2**).

TEMPORAL PATTERN OF CHANGE IN FAQ SCORE

Within each diagnostic group, the model that examined change in FAQ score as a function of linear time had a lower Bayesian information criterion statistic compared with the model that specified a quadratic function for time. For example, within the MCI group, the Bayesian information criterion statistic was 3618.45 for the linear model, whereas it was 3628.87 for the quadratic model. This was taken as evidence that, within each group, change in the FAQ score was better characterized as proceeding linearly. All subsequent analyses were performed using a linear function for time.

Table 3. Trajectories of Functional Change Across AD Spectrum as a Function of CSF Biomarkers and ADAS-Cog Scores[a]

Marker	Time[b]		Biomarker		Biomarker × Time[c]		
	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value	Δ R^2, %[d]
Control group							
T-tau	0.54 (0.53)	.31	−0.15 (0.15)	.33	0.24 (0.10)	.02	6.38
$A\beta_{42}$	0.28 (0.52)	.59	−0.02 (0.12)	.88	0.16 (0.08)	.046	5.32
P-tau_{181}	0.64 (0.53)	.23	−0.26 (0.13)	.04	0.21 (0.08)	.009	9.57
T-tau:$A\beta_{42}$ ratio	0.44 (0.53)	.41	0.02 (0.13)	.86	0.14 (0.08)	.08	4.26
P-tau:$A\beta_{42}$ ratio	0.23 (0.52)	.66	−0.12 (0.12)	.32	0.17 (0.07)	.02	7.45
ADAS-Cog score	0.23 (0.53)	.66	−0.03 (0.06)	.66	0.04 (0.04)	.33	1.06
MCI group							
T-tau	1.29 (1.60)	.42	−1.47 (0.61)	.02	0.79 (0.32)	.02	5.21
$A\beta_{42}$	1.21 (1.56)	.44	−0.87 (0.71)	.22	1.24 (0.37)	.001	11.84
P-tau_{181}	1.10 (1.60)	.50	−0.62 (0.66)	.35	0.99 (0.34)	.004	5.76
T-tau:$A\beta_{42}$ ratio	1.17 (1.57)	.45	−0.92 (0.67)	.17	1.21 (0.34)	.001	11.39
P-tau:$A\beta_{42}$ ratio	1.05 (1.59)	.51	−0.49 (0.74)	.51	1.22 (0.38)	.002	7.71
ADAS-Cog score	1.93 (1.58)	.22	0.34 (0.31)	.27	0.43 (0.16)	.009	7.40
AD group							
T-tau	2.62 (1.76)	.14	−0.76 (1.19)	.52	0.31 (0.38)	.42	1.60
$A\beta_{42}$	2.02 (2.09)	.34	1.84 (2.06)	.38	0.58 (0.70)	.41	−9.63
P-tau_{181}	1.97 (2.01)	.33	0.38 (1.72)	.83	0.52 (0.56)	.36	3.08
T-tau:$A\beta_{42}$ ratio	2.14 (1.92)	.27	1.07 (1.79)	.55	0.62 (0.64)	.34	−0.54
P-tau:$A\beta_{42}$ ratio	1.53 (2.16)	.48	−0.77 (2.61)	.77	1.20 (1.07)	.26	−3.74
ADAS-Cog score	3.45 (1.60)	.04	−0.56 (0.65)	.39	0.57 (0.22)	.01	33.69

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale–cognitive subscale. For other abbreviations, see Table 2.

[a] Models were adjusted for age, baseline Pfeffer Functional Activities Questionnaire (FAQ) scores, and their interactions with time. In addition, analyses were begun at month 6 to further correct for potential group differences in FAQ scores at baseline.

[b] Indicates the estimated semiannual rate of change in FAQ scores for those who have normal biomarker levels or whose ADAS-Cog scores are at the mean for their group.

[c] Indicates the estimated differential in semiannual rate of change in FAQ scores for those who have abnormal biomarker levels or whose ADAS-Cog scores are 1 SD above (ie, worse than) their group's mean.

[d] Indicates proportional reduction in the FAQ score's rate of change residual variation attained when each biomarker and its interaction with time were introduced into a base model that only contained age, baseline FAQ score, and their interactions with time. These R^2 statistics were computed thus: (base model residual variation − substantive model residual variation)/base model residual variation.

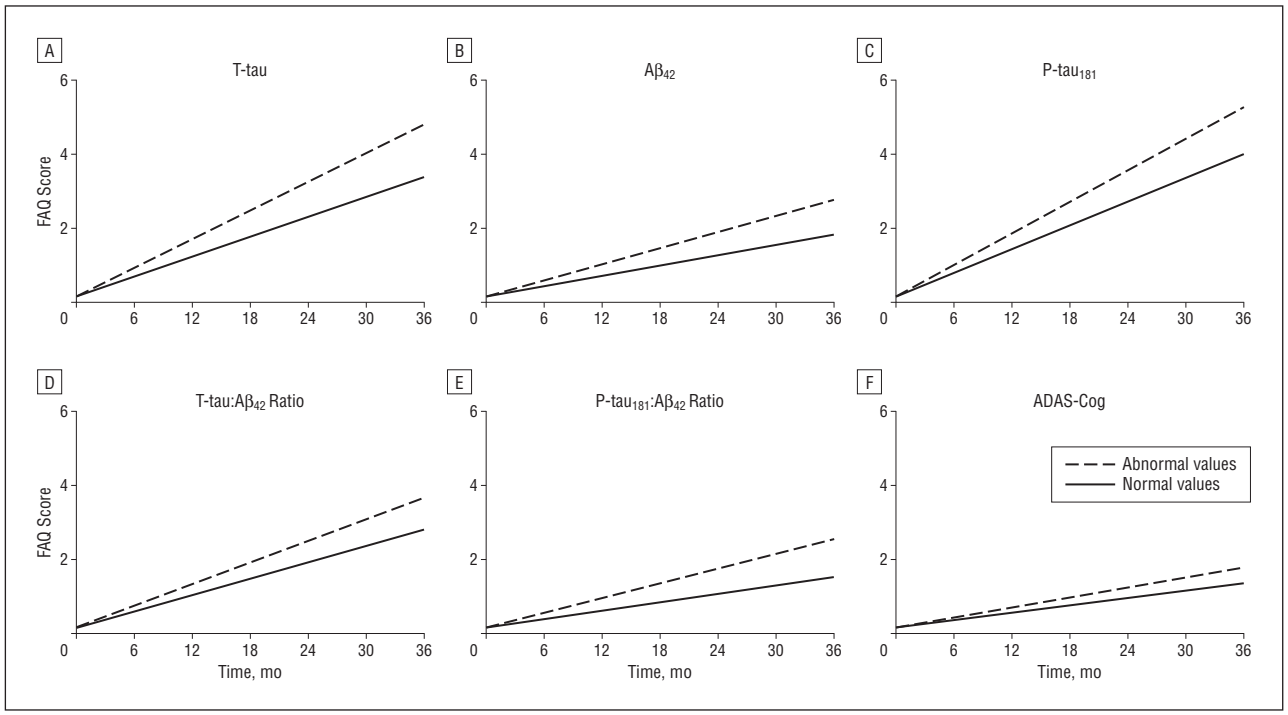

Figure 1. Change in Pfeffer Functional Activities Questionnaire (FAQ) scores as a function of cerebrospinal fluid biomarker concentrations and Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-Cog) scores among control subjects. $A\beta_{42}$ indicates β-amyloid 1-42; p-tau_{181}, tau phosphorylated at threonine 181; and t-tau, total tau.

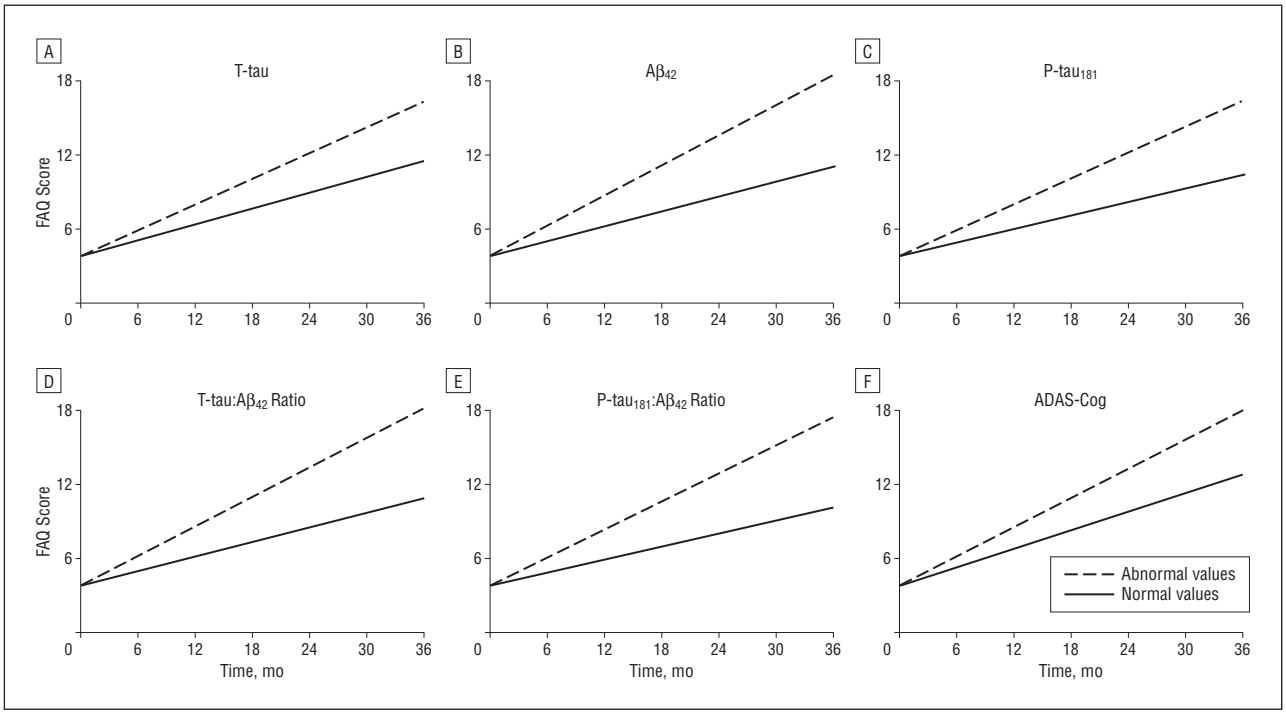

Figure 2. Change in Pfeffer Functional Activities Questionnaire (FAQ) scores as a function of cerebrospinal fluid biomarker concentrations and Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-Cog) scores among patients with mild cognitive impairment. $A\beta_{42}$ indicates β-amyloid 1-42; p-tau_{181}, tau phosphorylated at threonine 181; and t-tau, total tau.

RATE OF CHANGE IN FAQ SCORE

Score on the FAQ increased (ie, worsened) at a mean (SE) biannual rate of 0.04 (0.04) ($P=.28$) among controls, 1.23 (0.16) ($P<.001$) among patients with MCI, and 1.77 (0.19) ($P<.001$) among patients with AD. Although the mean rate of deterioration in FAQ scores among controls was nonsignificant, inspection of the random slope term revealed that there was significant interindividual variability around this mean value (estimate, 0.10 [SE, 0.02]; $P<.001$). Together these findings suggest that the FAQ duly captures longitudinal decline in everyday function across the dementia spectrum, albeit potentially less so among controls. Furthermore, the observed interindividual variability in slope trajectory, which was seen within each group, provided the basis for examining the impact of predictors (ie, CSF measures and the ADAS-Cog score) on rate of change in the FAQ.[20]

CSF BIOMARKERS, ADAS-Cog SCORES, AND RATE OF CHANGE IN FAQ SCORES

Among controls, only t-tau, $A\beta_{42}$, p-tau_{181}, and p-tau:$A\beta_{42}$ abnormalities were associated with a faster rate of functional decline. In MCI, all CSF measures and the ADAS-Cog score were significantly associated with the rate of functional decline. Finally, within the AD group, no CSF measure predicted rate of decline on the FAQ score. In contrast, the ADAS-Cog score significantly predicted FAQ decline (**Table 3**; **Figures 1**, **2**, and **3**). Of note, the random slope term in these analyses was significant ($P<.001$), indicating substantial between-person deviations from the mean/prototypical rate of change. The plots (Figures 1-3) present the prototypical change trajectories for illustrative purposes (eg, the t-tau graph in Figure 1 displays trajectories for the prototypical control with normal t-tau levels vs the prototypical control with abnormal t-tau levels).[20]

VARIANCE IN FUNCTIONAL DECLINE EXPLAINED BY CSF BIOMARKERS AND ADAS-Cog

Among controls, p-tau_{181} concentration emerged as the most sensitive to decline in FAQ score ($R^2=9.57$), and ADAS-Cog score was the least sensitive. In the MCI group, $A\beta_{42}$ level accounted for the most variance in FAQ score ($R^2=11.84$), although the t-tau:$A\beta_{42}$ ratio was virtually as sensitive ($R^2=11.39$). Among patients with AD, ADAS-Cog score accounted for 34% of the variance, whereas no CSF measure accounted for more than 3% (Table 3).

COGNITION AS A MEDIATOR OF CSF BIOMARKERS' EFFECT ON RATE OF DECLINE

The mediation analyses were performed only in the MCI group because it was the only group in which CSF biomarkers and ADAS-Cog scores significantly predicted the rate of functional decline. Adjustment for ADAS-Cog score did not obliterate the relationship between any CSF biomarker and rate of change in FAQ score. However, the relationships were attenuated—17% for p-tau_{181}, 13% for t-tau:$A\beta_{42}$ and p-tau:$A\beta_{42}$ ratios, 12% for $A\beta_{42}$, and 7% for t-tau—consistent with partial mediation.

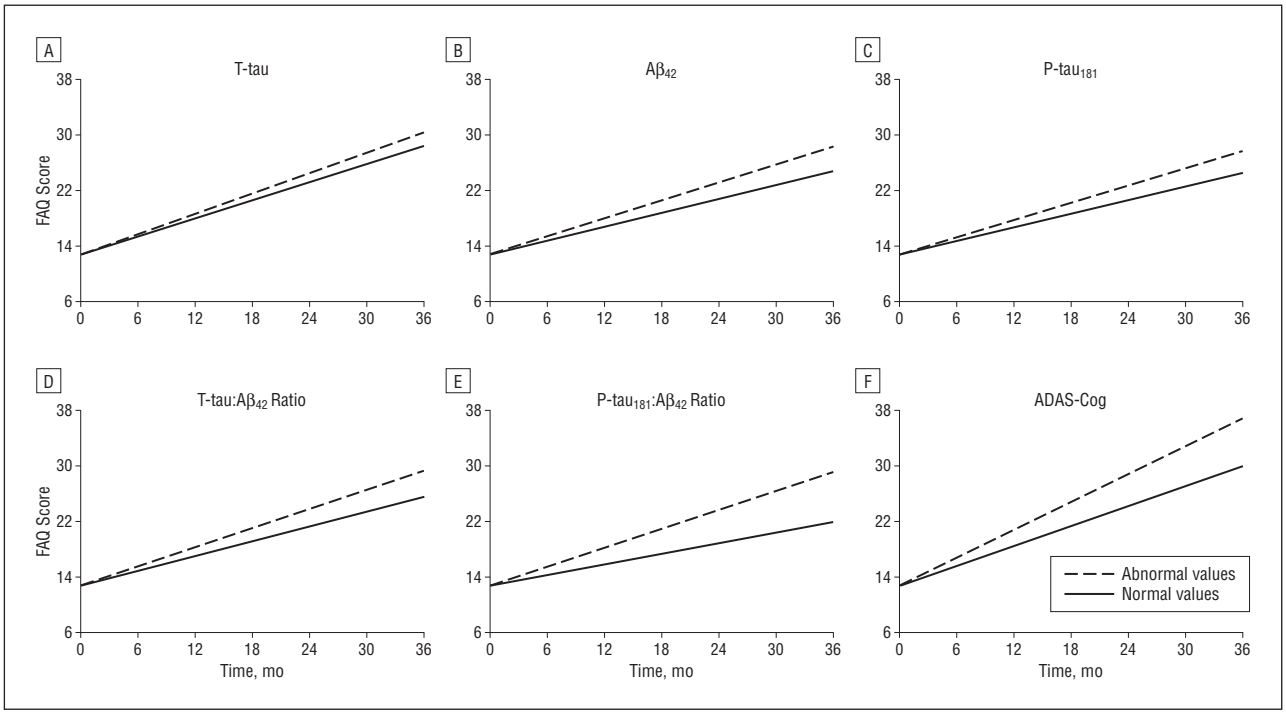

Figure 3. Change in Pfeffer Functional Activities Questionnaire (FAQ) scores as a function of cerebrospinal fluid biomarker concentrations and Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-Cog) scores among patients with Alzheimer disease. For other abbreviations, see Figure 2.

COMBINATION OF TAU AND Aβ$_{42}$ ABNORMALITIES AND RATE OF FUNCTIONAL DECLINE

Within each diagnostic group, the abnormal t-tau/abnormal Aβ$_{42}$ subgroup experienced the steepest rate of functional decline. However, within the AD group, this subgroup's rate of decline was statistically indistinguishable from that of the other 3 subgroups. Among patients with MCI, those in the normal t-tau/abnormal Aβ$_{42}$ subgroup declined faster than those in the normal t-tau/normal Aβ$_{42}$ subgroup, whereas those in the abnormal t-tau/normal Aβ$_{42}$ subgroup did not. These findings were essentially replicated in the p-tau$_{181}$ and Aβ$_{42}$ analyses (**Table 4** and **Figure 4**).

Table 4. Rate of Change in FAQ for Groups Defined by Combination of Tau and Aβ$_{42}$ Abnormalities[a]

Effect	Estimate (SE)	*P* Value
Control group		
Time	0.52 (0.52)	.32
Abnormal t-tau/normal Aβ$_{42}$ × time	0.17 (0.13)	.20
Normal t-tau/abnormal Aβ$_{42}$ × time	0.11 (0.09)	.19
Abnormal t-tau/abnormal Aβ$_{42}$ × time	0.36 (0.12)	.005
Time	0.63 (0.53)	.23
Abnormal p-tau$_{181}$/normal Aβ$_{42}$ × time	0.12 (0.10)	.24
Normal p-tau$_{181}$/abnormal Aβ$_{42}$ × time	0.06 (0.10)	.57
Abnormal p-tau$_{181}$/abnormal Aβ$_{42}$ × time	0.31 (0.10)	.002
MCI group		
Time	0.90 (1.56)	.57
Abnormal t-tau/normal Aβ$_{42}$ × time	−1.16 (1.30)	.37
Normal t-tau/abnormal Aβ$_{42}$ × time	0.87 (0.43)	.04
Abnormal t-tau/abnormal Aβ$_{42}$ × time	1.40 (0.40)	.001
Time	0.94 (1.58)	.55
Abnormal p-tau$_{181}$/normal Aβ$_{42}$ × time	0.74 (0.77)	.34
Normal p-tau$_{181}$/abnormal Aβ$_{42}$ × time	1.12 (0.60)	.06
Abnormal p-tau$_{181}$/abnormal Aβ$_{42}$ × time	1.44 (0.40)	.001
AD group		
Time	1.62 (2.14)	.45
Abnormal t-tau,/normal Aβ$_{42}$ × time	0.68 (1.30)	.60
Normal t-tau/abnormal Aβ$_{42}$ × time	0.71 (0.92)	.44
Abnormal t-tau/abnormal Aβ$_{42}$ × time	0.97 (0.91)	.28
Time	0.54 (2.42)	.82
Abnormal p-tau$_{181}$/normal Aβ$_{42}$ × time	1.38 (1.42)	.33
Normal p-tau$_{181}$/abnormal Aβ$_{42}$ × time	1.26 (1.28)	.32
Abnormal p-tau$_{181}$/abnormal Aβ$_{42}$ × time	1.61 (1.21)	.19

Abbreviations: FAQ, Pfeffer Functional Activities Questionnaire. For other abbreviations, see Table 2.

[a] Models adjusted for age, baseline FAQ, and their interactions with time. In addition, analyses were begun at month 6 to further correct for potential group differences in FAQ at baseline. Time indicates the estimated semiannual rate of change in FAQ for those who have normal tau (t-tau or p-tau, depending on the model being tested) and normal Aβ$_{42}$ concentrations. The other terms indicate the estimated difference in semiannual rate of change in FAQ between the normal tau/normal Aβ$_{42}$ subgroup and each of the other 3 subgroups.

COMMENT

With reference to the core questions this study investigated, our key findings were as follows: (1) All CSF analytes were associated with functional decline in MCI and all but t-tau:Aβ$_{42}$ ratio were associated with functional decline in controls, whereas no CSF analyte was associated with functional decline in AD. (2) Among controls, p-tau$_{181}$ concentration was the most sensitive to functional decline, whereas in MCI it was Aβ$_{42}$ concentration. (3) The CSF biomarkers were more sensitive than ADAS-Cog scores among controls and variably so in MCI, whereas the ADAS-Cog score was unequivocally more sensitive than CSF biomarkers in AD. (4) The impact of CSF biomarkers on functional decline in MCI is partially mediated by their effect on cognitive status. (5) Across all diagnostic groups, persons with a combination of tau and Aβ$_{42}$ abnormalities exhibited the fastest rate of functional decline.

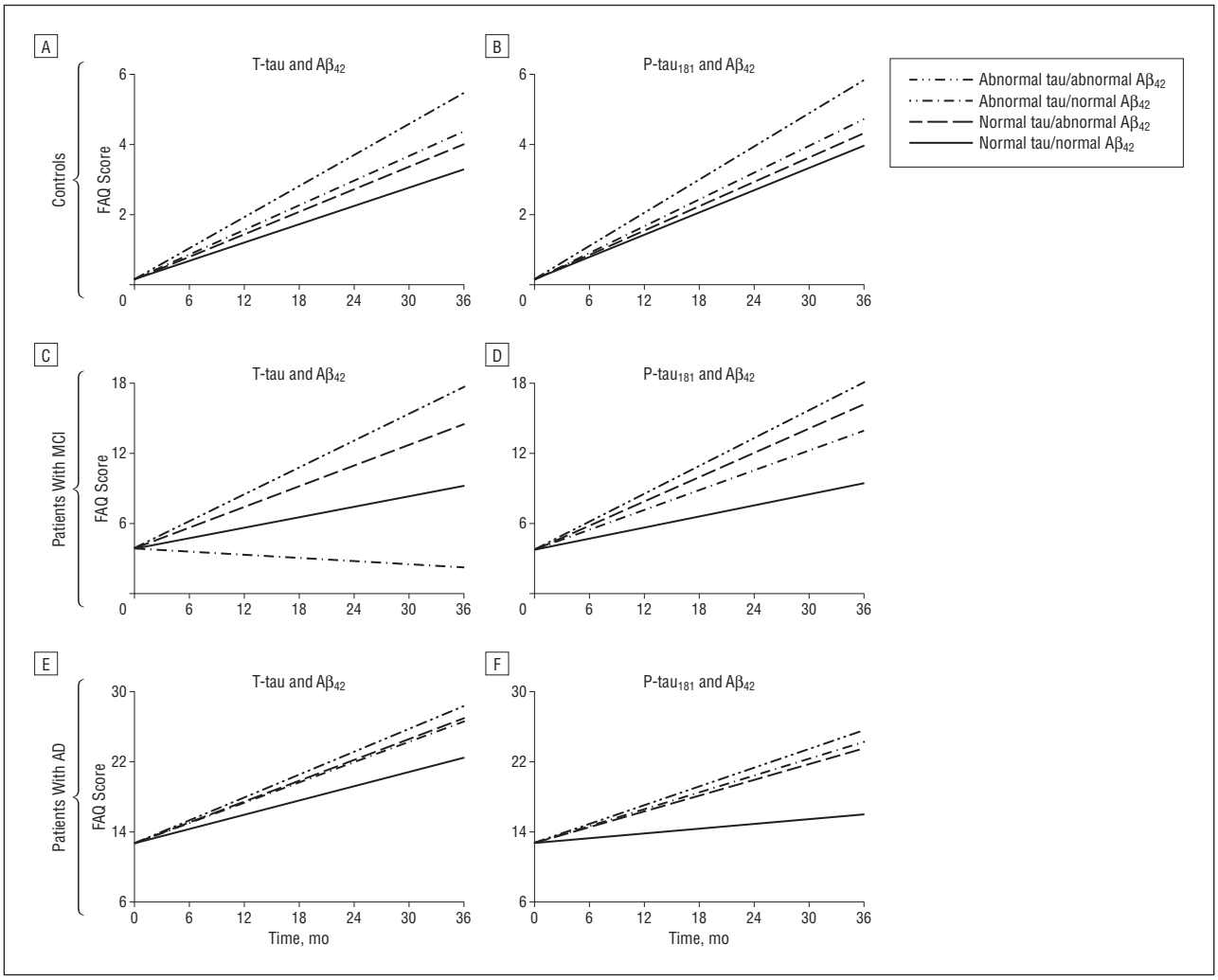

Figure 4. Change in Pfeffer Functional Activities Questionnaire (FAQ) scores as a function of concurrent tau and β-amyloid 1-42 ($A\beta_{42}$) abnormalities. AD indicates Alzheimer disease; MCI, mild cognitive impairment; p-tau_{181}, tau phosphorylated at threonine 181; and t-tau, total tau.

Progressive diminution in, and eventual loss of, the ability to perform daily activities is a hallmark feature of AD.[11] Consequently, decline in everyday function is a veritable measure of disease progression in AD.[13] The findings from this study therefore suggest that p-tau_{181} level is the strongest predictor of possible disease progression among controls, whereas $A\beta_{42}$ level is most potent in MCI. This conclusion is consistent with histopathological studies that suggest a temporal sequence in the manifestation of AD-related brain lesions wherein intraneuronal alterations precede the deposition of amyloid plaques.[23-25] Even so, we acknowledge that the temporal ordering of AD lesions and their presumed downstream effects on CSF analytes remain controversial issues deserving continued investigation.[6,7,26,27] For instance, it may be that t-tau and p-tau_{181} levels were stronger correlates of FAQ score decline (compared with $A\beta_{42}$ concentration) among controls because $A\beta_{42}$ levels were already reduced in the earliest phase of AD.[7,28,29] Nonetheless, because levels of p-tau_{181} reflect hyperphosphorylation of tau (a putatively AD-specific process),[3,30,31] our control findings suggest that, among cognitively intact elderly individuals, functional decline and eventual progression to AD may be most probable for individuals who already demonstrate pathognomonic features of AD.

Within the MCI and control groups, we found that ratio of tau protein to $A\beta_{42}$ was strongly correlated with functional decline. Previous reports have suggested that biomarker ratios may be more promising AD biomarkers compared with absolute biomarker levels.[5,32-35] However, a potential drawback to their application is that, by virtue of being ratios, they mask a likely nontrivial distinction between individuals who have normal tau/abnormal $A\beta_{42}$ findings and those who have abnormal tau/normal $A\beta_{42}$ findings. For instance, in the present study we found that patients with MCI who had normal tau/abnormal $A\beta_{42}$ findings experienced a more rapid functional decline compared with those with normal tau/normal $A\beta_{42}$ findings, whereas those with abnormal tau/normal $A\beta_{42}$ findings did not. This observation buttresses the earlier-noted finding that, among patients with MCI, abnormal $A\beta_{42}$ levels were a better prognostic indicator of functional degradation and disease progression than tau alterations.[36-38]

We were surprised to find that no CSF biomarker was predictive of functional decline among patients with AD.

The reason for this is not immediately clear, although it might be due to reduced variability in the CSF biomarkers. This would be consistent with previous studies that have shown that, on becoming abnormal, CSF biomarkers subsequently tend to remain stable for several years even as dementia progresses.[7,9,39-41] In addition, other studies have also failed to find associations between CSF biomarkers and indices of disease risk and burden in AD.[42]

Cerebrospinal fluid analytes hold great promise as biomarkers of AD[30] and, therefore, have potentially pivotal clinical utility.[43-45] However, their routine implementation in clinical practice is hampered by several factors, including lumbar puncture's relative invasiveness and potential for iatrogenesis, although the latter may not be as inexorable as originally believed.[45-47] Thus, clinical measures and peripheral fluid biomarkers are increasingly explored as viable alternatives.[31,32,48] In this study, we examined the comparative sensitivity of CSF biomarkers and scores on the ADAS-Cog, a brief measure of global cognition, to the rate of functional decline within each diagnostic group. Overall, our findings suggest that a cognitive screen that is brief, noninvasive, and easy to administer competes favorably with CSF biomarkers with regard to sensitivity to functional decline and hence disease progression, especially among patients with AD.[49]

Our mediation analyses showed that the greatest reduction in the variance accounted for by CSF biomarkers occurred for p-tau$_{181}$. There is evidence that p-tau$_{181}$ levels reflect neurofibrillary tangle formation[3,31] and that the density of tangles correlates better with cognitive decline and dementia than plaque load.[50,51] Therefore, it stands to reason that adjusting for cognition most attenuated the original relationship between p-tau$_{181}$ level and rate of functional decline. Finally, consistent with reports from previous investigations,[5,33,35] we found that, within each diagnostic group, individuals who had pathological concentrations of tau and Aβ_{42} experienced the steepest functional decline. This was most pronounced in the MCI group, in which those with abnormal tau/abnormal Aβ_{42} levels declined at about 2.5 times the rate of those with normal tau/normal Aβ_{42} levels (eg, abnormal t-tau/abnormal Aβ_{42} vs normal t-tau/normal Aβ_{42} = [0.90 + 1.40]/0.90). Because concurrent disturbances in tau and Aβ_{42} concentrations are considered diagnostic for AD, the accelerated decline in everyday function manifested by controls and patients with MCI who have these defining CSF alterations might represent a harbinger of their eventual progression to AD.[52]

Potential limitations of this study include the use of relatively gross measures of everyday function (FAQ) and cognition (ADAS-Cog) and the low ethnic diversity of the sample. In addition, the participants studied were enrolled in a clinical study, not an epidemiological study. It is unclear how these factors may have influenced our findings. Despite these limitations, this study is unique in being the first, to our knowledge, to examine several interrelated questions concerning the relationship between CSF biomarkers and rate of functional decline across the AD spectrum.

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REFERENCES

1. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al; Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease: neuroimaging initiative subjects. *Ann Neurol*. 2009;65(4):403-413.
2. Sunderland T, Linker G, Mirza N, et al. Decreased β-amyloid$_{1-42}$ and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. *JAMA*. 2003;289 (16):2094-2103.
3. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. *Lancet Neurol*. 2003;2(10):605-613.
4. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA*. 2009;302(4):385-393.
5. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/β-amyloid$_{42}$ ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol*. 2007;64(3):343-349.
6. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Aβ$_{42}$ in humans. *Ann Neurol*. 2006;59(3): 512-519.
7. Fagan AM, Head D, Shah AR, et al. Decreased cerebrospinal fluid Aβ$_{42}$ correlates with brain atrophy in cognitively normal elderly. *Ann Neurol*. 2009;65 (2):176-183.
8. Petrie EC, Cross DJ, Galasko D, et al. Preclinical evidence of Alzheimer changes: convergent cerebrospinal fluid biomarker and fluorodeoxyglucose positron emission tomography findings. *Arch Neurol*. 2009;66(5):632-637.
9. Snider BJ, Fagan AM, Roe C, et al. Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia of the Alzheimer type. *Arch Neurol*. 2009; 66(5):638-645.
10. Vemuri P, Wiste HJ, Weigand SD, et al; Alzheimer's Disease Neuroimaging Initiative. MRI and CSF biomarkers in normal, MCI, and AD subjects: predicting future clinical change. *Neurology*. 2009;73(4):294-301.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.
12. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.
13. Black R, Greenberg B, Ryan JM, et al. Scales as outcome measures for Alzheimer's disease. *Alzheimers Dement*. 2009;5(4):324-339.
14. Wechsler D. *Wechsler Memory Scale*. Rev ed. San Antonio, TX: Psychological Corp; 1987.
15. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement*. 2005;1(1):55-66.
16. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging*. 2008;27(4):685-691.
17. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37(3):323-329.
18. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.
19. Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. *SAS for Mixed Models*. 2nd ed. Cary, NC: SAS Institute Inc; 2007.
20. Singer JD, Willett JB. *Applied Longitudinal Data Analysis*. New York, NY: Oxford University Press; 2003.
21. Busse A, Angermeyer MC, Riedel-Heller SG. Progression of mild cognitive impairment to dementia: a challenge to current thinking. *Br J Psychiatry*. 2006; 189:399-404.
22. Schwarz G. Estimating the dimension of a model. *Ann Stat*. 1978;6:461-464.
23. Schönheit B, Zarski R, Ohm TG. Spatial and temporal relationships between plaques and tangles in Alzheimer-pathology. *Neurobiol Aging*. 2004;25(6):697-711.
24. Braak H, Del Tredici K. Alzheimer's disease: intraneuronal alterations precede insoluble amyloid-β formation. *Neurobiol Aging*. 2004;25(6):713-718, 743-746.
25. Troncoso JC, Martin LJ, Dal Forno G, Kawas CH. Neuropathology in controls and demented subjects from the Baltimore Longitudinal Study of Aging. *Neurobiol Aging*. 1996;17(3):365-371.
26. Price JL, Morris JC. So what if tangles precede plaques? *Neurobiol Aging*. 2004; 25(6):721-723, 743-746.
27. Korczyn AD. The amyloid cascade hypothesis. *Alzheimers Dement*. 2008;4(3):176-178.
28. Ingelsson M, Fukumoto H, Newell KL, et al. Early Aβ accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. *Neurology*. 2004; 62(6):925-931.
29. Jack CRJ Jr, Lowe VJ, Weigand SD, et al; Alzheimer's Disease Neuroimaging Initiative. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain*. 2009;132(pt 5):1355-1365.
30. Hampel H, Mitchell A, Blennow K, et al. Core biological marker candidates of Alzheimer's disease: perspectives for diagnosis, prediction of outcome and reflection of biological activity. *J Neural Transm*. 2004;111(3):247-272.
31. Frank RA, Galasko D, Hampel H, et al; National Institute on Aging Biological Markers Working Group. Biological markers for therapeutic trials in Alzheimer's disease: proceedings of the biological markers working group; NIA initiative on neuroimaging in Alzheimer's disease. *Neurobiol Aging*. 2003;24(4):521-536.
32. Sonnen JA, Montine KS, Quinn JF, Kaye JA, Breitner JC, Montine TJ. Biomarkers for cognitive impairment and dementia in elderly people. *Lancet Neurol*. 2008; 7(8):704-714.
33. Tapiola T, Alafuzoff I, Herukka SK, et al. Cerebrospinal fluid β-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol*. 2009;66(3):382-389.
34. Kapaki E, Paraskevas GP, Zalonis I, Zournas C. CSF tau protein and β-amyloid (1-42) in Alzheimer's disease diagnosis: discrimination from normal ageing and other dementias in the Greek population. *Eur J Neurol*. 2003;10(2):119-128.
35. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol*. 2006;5(3):228-234.
36. Hampel H, Teipel SJ, Fuchsberger T, et al. Value of CSF β-amyloid$_{1-42}$ and tau as predictors of Alzheimer's disease in patients with mild cognitive impairment. *Mol Psychiatry*. 2004;9(7):705-710.
37. Schoonenboom SN, Visser PJ, Mulder C, et al. Biomarker profiles and their relation to clinical variables in mild cognitive impairment. *Neurocase*. 2005;11(1):8-13.
38. Ivanoiu A, Sindic CJ. Cerebrospinal fluid TAU protein and amyloid β42 in mild cognitive impairment: prediction of progression to Alzheimer's disease and correlation with the neuropsychological examination. *Neurocase*. 2005;11(1):32-39.
39. Blennow K, Zetterberg H, Minthon L, et al. Longitudinal stability of CSF biomarkers in Alzheimer's disease. *Neurosci Lett*. 2007;419(1):18-22.
40. Sunderland T, Wolozin B, Galasko D, et al. Longitudinal stability of CSF tau levels in Alzheimer patients. *Biol Psychiatry*. 1999;46(6):750-755.
41. Zetterberg H, Pedersen M, Lind K, et al. Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. *J Alzheimers Dis*. 2007;12(3):255-260.
42. Engelborghs S, Sleegers K, Cras P, et al. No association of CSF biomarkers with APOEε4, plaque and tangle burden in definite Alzheimer's disease. *Brain*. 2007; 130(pt 9):2320-2326.
43. Hampel H, Buerger K, Zinkowski R, et al. Measurement of phosphorylated tau epitopes in the differential diagnosis of Alzheimer disease: a comparative cerebrospinal fluid study. *Arch Gen Psychiatry*. 2004;61(1):95-102.
44. Riemenschneider M, Wagenpfeil S, Vanderstichele H, et al. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. *Mol Psychiatry*. 2003;8(3):343-347.
45. Andreasen N, Minthon L, Davidsson P, et al. Evaluation of CSF-tau and CSF-Aβ42 as diagnostic markers for Alzheimer disease in clinical practice. *Arch Neurol*. 2001;58(3):373-379.
46. Peskind E, Nordberg A, Darreh-Shori T, Soininen H. Safety of lumbar puncture procedures in patients with Alzheimer's disease. *Curr Alzheimer Res*. 2009;6(3):290-292.
47. Peskind ER, Riekse R, Quinn JF, et al. Safety and acceptability of the research lumbar puncture. *Alzheimer Dis Assoc Disord*. 2005;19(4):220-225.
48. Carrillo MC, Blackwell A, Hampel H, et al. Early risk assessment for Alzheimer's disease. *Alzheimers Dement*. 2009;5(2):182-196.
49. Fleisher AS, Sun S, Taylor C, et al. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. *Neurology*. 2008;70(3):191-199.
50. Trojanowski JQ, Shin RW, Schmidt ML, Lee VM. Relationship between plaques, tangles, and dystrophic processes in Alzheimer's disease. *Neurobiol Aging*. 1995; 16(3):335-345.
51. Giannakopoulos P, Herrmann FR, Bussiere T, et al. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology*. 2003;60(9):1495-1500.
52. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol*. 1999;45(3):358-368.