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

Normal Aging, Mild Cognitive Impairment, and Alzheimer Disease

Ozioma C. Okonkwo, PhD; Michael L. Alosco, BA; H. Randall Griffith, PhD; Michelle M. Mielke, PhD; Leslie M. Shaw, PhD; John Q. Trojanowski, MD, PhD; Geoffrey Tremont, PhD; for the Alzheimer’s Disease Neuroimaging Initiative

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-tau181), and β-amyloid 1-42 (Aβ42) 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: Aβ42 ratio were associated with functional decline in controls. No abnormal CSF analyte was associated with functional decline in AD. Among controls, p-tau181 concentration was the most sensitive to functional decline, whereas in MCI it was Aβ42 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 Aβ42 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 Aβ42 abnormalities are at greatest risk of functional loss.

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CEREBROSPINAL FLUID (CSF) concentrations of total tau (t-tau), tau phosphorylated at threonine 181 (p-tau181), and β-amyloid 1-42 (Aβ42) 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). In contrast with the demonstrations of associations between CSF abnormalities and some indices of disease severity and progression such as cognitive decline, plaque density, and cerebral alterations, the relationship between CSF abnormalities and decline in everyday function has received limited attention. This constitutes a significant knowledge gap for several reasons.

First, functional restriction is a hallmark of AD and other dementias. 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.\(^7\) 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 A\(_\beta\) 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**

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 Disorders 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.\(^13,16\) 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, A\(_\beta\)\(_{42}\), and p-tau\(_{181}\) concentrations were performed using 0.5-mL aliquots and a multiplex platform (xMAP; Luminox Corp, Austin, Texas) with immunoassay kit–based reagents (INNO-BIA AlzBio3; Innogenetics NV, Ghent, Belgium; for research use–only reagents).

**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, \(\geq 0.80\)) and validity (correlations with measures of mental status, daily function, and clinical diagnosis, \(\geq 0.70\)).\(^17\) 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.
The biomarker effect of performance that is 1 SD above (ie, worse than) phosphor- lated at threonine 181; t-tau, total tau.

cerebrospinal fluid; MCI, mild cognitive impairment; p-tau181, tau Disease Neuroimaging Initiative study.

To examine whether the effect of CSF biomarkers on functional decline was mediated by cognition, we compared the relative fit of linear (time) and curvi-

teminal diagram 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 for potential interindividual variability in baseline scores and rate of change, respectively. In addition, they all included age, baseline FAQ scores, and their interactions with time as covari-

mality by fitting a series of random coefficient regressions in which the rate of functional decline among persons in the normal tau/normal Aβ42 group was contrasted with the rate of decline in the abnormal tau/normal Aβ42, normal tau/abnormal Aβ42, and abnormal tau/abnormal Aβ42 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 re-

As reported in previous studies, CSF levels of t-tau and P-tau181 and the t-tau:AB42 and P-tau181:AB42 ratios were significantly higher, whereas Aβ42 levels were significantly lower, in patients with MCI and those with AD com-

Finally, we examined whether individuals with a combina-

tenuated 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 func-

tional decline.

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.

**RESULTS**

**GROUP DIFFERENCES IN BASELINE CSF ANALYTES**

As reported in previous studies, CSF levels of t-tau and P-tau181 and the t-tau:AB42 and P-tau181:AB42 ratios were significantly higher, whereas Aβ42 levels were significantly lower, in patients with MCI and those with AD com-

**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.

**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 that added terms for potential interindividual variability in baseline scores and rate of change, respectively. In addition, they all included age, baseline FAQ scores, and their interactions with time as covari-

**Table 2. CSF Biomarker Concentrations and Ratios at Baseline**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Control (n=195)</th>
<th>MCI (n=195)</th>
<th>AD (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-tau, mean (SD), pg/mL</td>
<td>69.65 (30.32)</td>
<td>103.54 (60.93)</td>
<td>121.57 (57.56)</td>
</tr>
<tr>
<td>Abnormal, %</td>
<td>18.4</td>
<td>44.6</td>
<td>65.0</td>
</tr>
<tr>
<td>Aβ42, mean (SD), pg/mL</td>
<td>205.63 (55.07)</td>
<td>163.31 (54.93)</td>
<td>143.51 (41.01)</td>
</tr>
<tr>
<td>Abnormal, %</td>
<td>37.7</td>
<td>74.4</td>
<td>91.0</td>
</tr>
<tr>
<td>P-tau181, mean (SD), pg/mL</td>
<td>24.84 (14.59)</td>
<td>35.68 (18.10)</td>
<td>41.73 (19.96)</td>
</tr>
<tr>
<td>Abnormal, %</td>
<td>36.0</td>
<td>70.3</td>
<td>87.0</td>
</tr>
<tr>
<td>T-tau/Aβ42 ratio, mean (SD)</td>
<td>0.39 (0.27)</td>
<td>0.75 (0.62)</td>
<td>0.92 (0.48)</td>
</tr>
<tr>
<td>Abnormal, %</td>
<td>34.2</td>
<td>69.7</td>
<td>88.0</td>
</tr>
<tr>
<td>P-tau181/Aβ42 ratio, mean (SD)</td>
<td>0.14 (0.13)</td>
<td>0.26 (0.18)</td>
<td>0.32 (0.19)</td>
</tr>
<tr>
<td>Abnormal, %</td>
<td>47.4</td>
<td>77.9</td>
<td>94.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** Aβ42, β-amyloid 1-42; AD, Alzheimer disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau181, tau phosphorylated at threonine 181; t-tau, total tau.

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; Aβ42, 192 pg/mL; P-tau181, 23 pg/mL; t-tau/Aβ42 ratio, 0.39; and p-tau181/Aβ42 ratio, 0.10) established in a previous Alzheimer’s Disease Neuroimaging Initiative study.

Significantly different from controls.

Significantly different from MCI group.

<table>
<thead>
<tr>
<th>CSF ANALYTES</th>
<th>Diagnostic Group</th>
<th>Abnormality</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal, %</td>
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<td>70.3</td>
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</tbody>
</table>
Table 3. Trajectories of Functional Change Across AD Spectrum as a Function of CSF Biomarkers and ADAS-Cog Scores

<table>
<thead>
<tr>
<th>Marker</th>
<th>Control group</th>
<th>MCI group</th>
<th>AD group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-tau</td>
<td>0.54 (0.53)</td>
<td>1.29 (1.60)</td>
<td>2.62 (1.76)</td>
</tr>
<tr>
<td>Aβ42</td>
<td>0.28 (0.52)</td>
<td>1.21 (1.56)</td>
<td>2.02 (2.09)</td>
</tr>
<tr>
<td>P-tau181</td>
<td>0.64 (0.53)</td>
<td>1.10 (1.60)</td>
<td>1.97 (2.01)</td>
</tr>
<tr>
<td>T-tau:Aβ42 ratio</td>
<td>0.44 (0.53)</td>
<td>1.17 (1.57)</td>
<td>2.14 (1.92)</td>
</tr>
<tr>
<td>P-tau:Aβ42 ratio</td>
<td>0.23 (0.52)</td>
<td>1.05 (1.59)</td>
<td>1.53 (2.16)</td>
</tr>
<tr>
<td>ADAS-Cog score</td>
<td>0.23 (0.53)</td>
<td>1.93 (1.58)</td>
<td>0.23 (1.53)</td>
</tr>
</tbody>
</table>

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. Aβ42 indicates β-amyloid 1-42; p-tau181, 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, Aβ42, p-tau181, and p-tau: Aβ42 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 change 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/protopypical 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-tau181 concentration emerged as the most sensitive to decline in FAQ score (R²=9.57), and ADAS-Cog score was the least sensitive. In the MCI group, Aβ42 level accounted for the most variance in FAQ score (R²=11.84), although the t-tau:Aβ42 ratio was virtually as sensitive (R²=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-tau181, 13% for t-tau:Aβ42, and p-tau:Aβ42 ratios, 12% for Aβ42, and 7% for t-tau—consistent with partial mediation.
Within each diagnostic group, the abnormal t-tau/abnormal \( A\beta_{42} \) 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 \( A\beta_{42} \) subgroup declined faster than those in the normal t-tau/normal \( A\beta_{42} \) subgroup, whereas those in the abnormal t-tau/normal \( A\beta_{42} \) subgroup did not. These findings were essentially replicated in the p-tau\(_{181}\) and \( A\beta_{42} \) analyses (Table 4 and Figure 4).

**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:\( A\beta_{42} \) ratio were 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 \( A\beta_{42} \) 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 \( A\beta_{42} \) abnormalities exhibited the fastest rate of functional decline.
Progressive diminution in, and eventual loss of, the ability to perform daily activities is a hallmark feature of AD. Consequently, decline in everyday function is a verifiable measure of disease progression in AD. The findings from this study therefore suggest that p-tau181 level is the strongest predictor of possible disease progression among controls, whereas Aβ42 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. 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. For instance, it may be that t-tau and p-tau181 levels were stronger correlates of FAQ score decline (compared with Aβ42 concentration) among controls because Aβ42 levels were already reduced in the earliest phase of AD. Nonetheless, because levels of p-tau181 reflect hyperphosphorylation of tau (a putatively AD-specific process), 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 Aβ42 was strongly correlated with functional decline. Previous reports have suggested that biomarker ratios may be more promising AD biomarkers compared with absolute biomarker levels. 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 Aβ42 findings and those who have abnormal tau/normal Aβ42 findings. For instance, in the present study we found that patients with MCI who had normal tau/abnormal Aβ42 findings experienced a more rapid functional decline compared with those with normal tau/normal Aβ42 findings, whereas those with abnormal tau/normal Aβ42 findings did not. This observation buttresses the earlier-noted finding that, among patients with MCI, abnormal Aβ42 levels were a better prognostic indicator of functional degradation and disease progression than tau alterations.

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.50,51 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 AD42 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.46-47 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-tau181. There is evidence that p-tau181 levels reflect neurofibrillary tangle formation31 and that the density of tangles correlates better with cognitive decline than plaque load.50,51 Therefore, it stands to reason that adjusting for cognition most attenuated the original relationship between p-tau181 level and rate of functional decline. Finally, consistent with reports from previous investigations,3,33,34 we found that, within each diagnostic group, individuals who had pathological concentrations of tau and Aβ42 experienced the steepest functional decline. This was most pronounced in the MCI group, in which those with abnormal tau/abnormal Aβ42 levels declined at about 2.5 times the rate of those with normal tau/normal Aβ42 levels (eg, abnormal t-tau/abnormal Aβ42 vs normal t-tau/normal Aβ42 = [0.90 + 1.40]/0.90). Because concurrent disturbances in tau and Aβ42 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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Author Affiliations: Departments of Neurology (Dr Okonkwo) and Psychiatry (Dr Mielke), Johns Hopkins School of Medicine, Baltimore, Maryland; Neuropsychology Program, Rhode Island Hospital (Mr Alosco and Dr Tremont), and Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University (Dr Tremont), Providence, Rhode Island; Department of Neurology, University of Alabama at Birmingham (Dr Griffith); and Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia (Drs Shaw and Trojanowski).

Correspondence: Ozioma C. Okonkwo, PhD, Department of Neurology, Johns Hopkins School of Medicine, 1620 McElderry St, Reed Hall East 2, Baltimore, MD 21205 (odzioma@jhmi.edu).

Author Contributions: Dr Okonkwo had full access to all the data reported in this manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Okonkwo, Alosco, Griffith, Trojanowski, and Tremont. Acquisition of data: Trojanowski. Analysis and interpretation of data: Okonkwo, Alosco, Griffith, Trojanowski, and Tremont. Drafting of the manuscript: Okonkwo, Alosco, Griffith, and Trojanowski. Critical revision of the manuscript for important intellectual content: Okonkwo, Griffith, Mielke, Shaw, Trojanowski, and Tremont. Statistical analysis: Okonkwo, Griffith, and Mielke. Obtained funding: Trojanowski. Administrative, technical, and material support: Alosco, Shaw, Trojanowski, and Tremont. Study supervision: Trojanowski and Tremont. Financial Disclosure: None reported.

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Role of the Sponsors: Data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or in the writing of this report.