

## ONLINE FIRST

# Longitudinal Change of Biomarkers in Cognitive Decline

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**Objective:** To delineate the trajectories of A $\beta$ 42 level in cerebrospinal fluid (CSF), fludeoxyglucose F18 (FDG) uptake using positron emission tomography, and hippocampal volume using magnetic resonance imaging and their relative associations with cognitive change at different stages in aging and Alzheimer disease (AD).

**Design:** Cohort study.

**Setting:** The 59 study sites for the Alzheimer's Disease Neuroimaging Initiative.

**Participants:** A total of 819 participants 55 to 90 years of age with normal cognition, mild cognitive impairment, and AD who were followed up during the period from 2005 to 2007.

**Main Outcome Measures:** Rates of change in level of A $\beta$ 42 in CSF, FDG uptake, hippocampal volume, and the Alzheimer Disease's Assessment Scale–cognitive subscale score during up to 36 months of follow-up by diagnostic group as well as prediction of cognitive change by each biomarker.

**Results:** Reductions in the level of A $\beta$ 42 in CSF were numerically greater in participants with normal cognition than in participants with mild cognitive impair-


ment or AD; whereas both glucose metabolic decline and hippocampal atrophy were significantly slower in participants with normal cognition than in participants with mild cognitive impairment or AD. Positive APOE4 status accelerated hippocampal atrophic changes in participants with mild cognitive impairment or AD, but did not modify rates of change in level of A $\beta$ 42 in CSF or FDG uptake. The Alzheimer Disease's Assessment Scale–cognitive subscale scores were related only to the baseline level of A $\beta$ 42 in CSF and the baseline FDG uptake in participants with normal cognition, which were about equally associated with change in FDG uptake and hippocampal volume in participants with mild cognitive impairment and best modeled by change in FDG uptake in participants with AD.

**Conclusion:** Trajectories of A $\beta$ 42 level in CSF, FDG uptake, and hippocampal volume vary across different cognitive stages. The longitudinal patterns support a hypothetical sequence of AD pathology in which amyloid deposition is an early event before hypometabolism or hippocampal atrophy, suggesting that biomarker prediction for cognitive change is stage dependent.

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**U**SING BIOMARKERS FOR THE early detection of Alzheimer disease (AD) is crucial for developing potential treatment. Previous studies have shown that A $\beta$ 42 and tau protein levels in cerebrospinal fluid (CSF),<sup>1</sup>

onstrated that the burden of AD pathology was reflected by the antemortem A $\beta$ 42 level in CSF,<sup>4</sup> the region-specific FDG uptake using PET,<sup>5</sup> and the hippocampal volume using MRI,<sup>6</sup> which suggests that these markers are indicative of the altered biological states in AD.

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region-specific fludeoxyglucose F18 (FDG) uptake using positron emission tomography (PET),<sup>2</sup> and hippocampal volume using magnetic resonance imaging (MRI)<sup>3</sup> were markers associated with AD. Postmortem examinations further dem-

Although lower levels of A $\beta$ 42 in CSF are associated with the risk of incipient AD,<sup>7</sup> CSF biomarkers appear to be relatively stable over time within individuals.<sup>8,9</sup> Greater hippocampal atrophy rates measured by serial MRI correlated with faster cognitive decline in normal aging

and early conversion to dementia in mild cognitive impairment (MCI) in previous studies.<sup>10-13</sup> Several longitudinal FDG-PET studies also suggested that regional hypometabolism predicted clinical progression or conversion to AD.<sup>14-17</sup> Because these time-varying biomarkers as well as the *APOE4* gene are all associated with AD or cognitive impairment, it is conceivable that they are correlated with one another.<sup>18-21</sup> However, very few studies have examined the dynamic change of 2 or more biomarkers simultaneously.<sup>22,23</sup> Longitudinal comparison of biomarker change is an important approach to assess the relative importance and pathological significance of each biomarker.

In our study, we aimed to delineate the trajectories of the A $\beta$ 42 level in CSF, FDG uptake, and hippocampal volume as well as the influence of the *APOE4* gene, and then evaluated their relative associations with cognitive function in participants with normal cognition (NC), MCI, or AD.

## METHODS

### STUDY POPULATION

A total of 819 research participants (229 with NC, 397 with MCI, and 193 with AD) were enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) from 59 centers in the United States and Canada during the period from 2005 to 2007. Full inclusion and exclusion criteria are detailed at <http://www.adni-info.org>. Briefly, screening criteria for entry into our study included the Mini-Mental State Examination score, the Clinical Dementia Rating scale, and an education-adjusted cutoff score on delayed recall of 1 paragraph from the Logical Memory subtest of the Wechsler Memory Scale-Revised.<sup>24</sup> All participants were recruited between the ages of 55 and 90 years and had at least 6 years of education. Participants who took specific psychoactive medications or who had other neurological disorders were excluded. After the baseline visit, subsequent visits occurred at 6- or 12-month intervals. Participants with NC or MCI were followed up for 3 years, whereas those with AD were followed up for 2 years at maximum.

### STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENTS' CONSENT

The study procedures were approved by the institutional review boards of all participating institutions. Written informed consent to obtain blood samples and to perform lumbar puncture, neuropsychological testing, and neuroimaging were obtained from all research participants or their representatives.

### GENETIC MARKER

Blood samples at baseline were collected, and *APOE* genotyping was performed at the University of Pennsylvania AD biomarker laboratory in Philadelphia. *APOE4* gene carriers were participants who had at least 1 *APOE4* allele.

### CSF PROTEINS

Cerebrospinal fluid samples were collected in the morning after overnight fast, shipped to the University of Pennsylvania AD biomarker laboratory, and analyzed using a standardized protocol.<sup>25</sup> Levels of A $\beta$ 42, total tau, and phosphorylated tau were mea-

sured (in units of picograms per milliliter) in each of the CSF aliquots using the multiplex xMAP Luminex (Luminex Corp, Austin, Texas) platform with Innogenetics (INNO-BIA Alz-Bio3; Ghent, Belgium; for research use-only reagents) immunoassay kit-based reagents. About 50% of all participants underwent lumbar puncture at baseline, after which 106 participants underwent a lumbar puncture every year for 3 years.

### FDG UPTAKE USING PET

The protocol to acquire ADNI PET data at sites nationwide is detailed at <http://adni.loni.ucla.edu/research/protocols/pet-protocols/>, and methods for FDG-PET analysis have been described previously.<sup>26</sup> Briefly, PET images were acquired 30 to 60 minutes after injection. Images were averaged, spatially aligned, interpolated to a standard voxel size, intensity normalized, and smoothed to a common resolution of 8-mm full-width at half-maximum. The PET volumes were intensity normalized to a single region comprising the cerebellar vermis and the pons defined by the Montreal Neurological Institute template. We used predefined regions of interest to reflect glucose metabolism. Mean FDG uptake was extracted and averaged from 5 regions of interest (right and left temporal gyrus, right and left angular gyrus, and posterior cingulate gyrus) for each participant. Baseline PET images were available for 404 participants, and more than 60% of these participants were followed up for 2 additional years with repeated PET scans.

### MRI HIPPOCAMPAL VOLUME

The 1.5-T MRI protocol, which was described elsewhere,<sup>27</sup> was standardized across all sites: 2 T1-weighted MRI scans, using a sagittal volumetric magnetization-prepared rapid gradient echo sequence, with an echo of 4 milliseconds, a repetition time of 9 milliseconds, a flip angle of 8°, and an acquisition matrix size of 256 × 256 × 166 in the x, y, and z dimensions with a nominal voxel size of 0.94 × 0.94 × 1.2 mm. The images were aligned, skull-stripped, and segmented. A quality-control center was designated to exclude scans with serious motion artifacts. FreeSurfer software (<http://surfer.nmr.mgh.harvard.edu>) was applied to obtain bilateral hippocampal volumes in units of cubic millimeters from this segmentation. Baseline MRI images were available for 811 participants, and more than 60% of these participants were followed up for 2 more years with multiple MRI scans.

### ASSESSMENT OF COGNITIVE FUNCTION

The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score was used as a dependent measure to examine relationships between biomarkers and cognitive change. This test contains 11 items covering language, memory, praxis, and comprehension function. The total score ranges from 0 to 70, and higher scores indicate poorer cognitive function. Baseline and multiple follow-up ADAS-cog assessments were available for all participants.

### STATISTICAL ANALYSES

Participants with 2 or more repeated measures had their data entered into the analyses. We first delineated the trajectories of different biomarkers and used repeated measures linear regression (an exchangeable, working-within-subject correlation model via a generalized estimating equation)<sup>28</sup> to estimate population average rates of change in levels of CSF proteins, FDG-PET regions of interest, hippocampal volume, as well as ADAS-cog scores for participants with NC, MCI, or AD.

To account for the residual correlation due to repeated measures on the same subject, we could have also used a more parametric, mixed-model approach. However, given that our focus was on the average rate of change in biomarkers (and not on the variance components), and because we wanted to derive a robust inference (standard errors not sensitive to the specified correlation model), we chose the generalized estimating equation approach rather than a parametric maximum likelihood approach.<sup>29</sup> Time-varying biomarkers were treated as the outcome and modeled by time and baseline age in the regression. In these models, a significant time coefficient indicated a nonzero rate of change. We also made intergroup comparisons of rates of change. In a separate analysis, we included *APOE4* allele carrier status in the model to evaluate its influence on the rate of change for each biomarker, reflected by the coefficient of the interaction term (*APOE4* × time).

We then examined the relation between the change of cognitive function and the change of different biomarkers. Time-varying ADAS-cog scores were treated as the outcome of interest and modeled by time and the change in biomarkers after adjusting for baseline age and baseline biomarker value. Values of  $R^2$  were calculated for each longitudinal model to represent the goodness of fit or the extent to which the marginal variance of cognitive function was explained by the model. Models differed by biomarker of interest and sample size because only a limited number of participants had all 3 biomarkers available. We conducted model comparisons by restricting participants to those with 2 biomarkers available ( $A\beta 42$  level in CSF and FDG uptake;  $A\beta 42$  level in CSF and hippocampal volume; or FDG uptake and hippocampal volume) so as to make models more comparable. All statistical analyses and graphics were performed in R version 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

The demographic features of all participants are summarized in **Table 1**. The sample size declined over time, and the number of repeated measures available for longitudinal analysis varied across different biomarkers and diagnostic groups (**Table 2**). The  $A\beta 42$  level in CSF (measured in units of picograms per milliliter per month) appeared to decrease faster in participants with NC ( $-0.46$  pg/mL/mo) than in participants with MCI ( $-0.26$  pg/mL/mo) or AD ( $-0.29$  pg/mL/mo), but intergroup differences were not significant; changes in total tau and phosphorylated tau levels in CSF for the most part were not significantly different from zero (Table 2). Brain regional glucose metabolic decline (measured in units of normalized intensity per month) was significantly slower in participants with NC ( $-7.4 \times 10^{-4}$  normalized intensity per month) than in participants with MCI ( $-1.9 \times 10^{-3}$  normalized intensity per month) or AD ( $-4.2 \times 10^{-3}$  normalized intensity per month) and slower in participants with MCI than in participants with AD (Table 2). The rate of MRI hippocampal atrophy (measured in units of cubic millimeters per month) was also significantly slower in participants with NC ( $-2.95$  mm<sup>3</sup>/mo) than in participants with MCI ( $-5.52$  mm<sup>3</sup>/mo) or AD ( $-8.01$  mm<sup>3</sup>/mo) and slower in participants with MCI than in participants with AD (Table 2). Cognitive function assessed by the ADAS-cog declined (increased in ADAS-cog score) in participants with MCI and declined even faster in participants AD, but it improved (decreased in ADAS-cog

**Table 1. Demographic Features of 819 Participants in the Alzheimer's Disease Neuroimaging Initiative at Enrollment**

Feature	ADNI Diagnostic Groups		
	NC	MCI	AD
Sample size, No.	229	397	193
Age, mean (SD), y	75.1 (5.0)	74.0 (7.5)	74.6 (7.5)
Sex, No.			
Male	119	256	102
Female	110	141	91
Education, mean (SD), y	16.0 (2.9)	15.7 (3.0)	14.7 (3.1)
MMSE score, mean (SD)	29.1 (1.0)	27.0 (1.8)	23.3 (2.1)
<i>APOE4</i> carriers, No. (%)	61 (26.6)	212 (53.4)	127 (65.8)

Abbreviations: AD, Alzheimer disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NC, normal cognition.

score) a little in participants with NC. The hypothetical average changes of these biomarkers and the ADAS-cog scores for a 75-year-old person in the 3 diagnostic groups are illustrated in our **Figure**.

The associations between *APOE4* status and the baseline value of biomarkers were significant in the NC group for  $A\beta 42$  level in CSF and FDG uptake and in the MCI group for all 3 biomarkers (**Table 3**). Positive *APOE4* status did not appear to modify the rate of change in the  $A\beta 42$  level in CSF or glucose metabolism in all 3 groups, but it accelerated hippocampal atrophy in the MCI and AD groups.

For participants with NC, although changes in cognitive function were not captured by any of these time-varying biomarkers,  $A\beta 42$  level in CSF ( $R^2=0.12$ ) appeared to better explain the total variance of ADAS-cog scores over time than did FDG uptake ( $R^2=0.07$ ) or MRI hippocampal volume ( $R^2=0.03$ ) (**Table 4**). For participants with MCI, changes in cognitive function were associated with all of these biomarkers, such that cognitive decline (increase in ADAS-cog score) was associated with the decrease in the  $A\beta 42$  level in the CSF, FDG-PET regional metabolism, and MRI hippocampal volume. Cognitive function at the MCI stage was about equally well modeled by FDG uptake ( $R^2=0.18$ ) and hippocampal volume ( $R^2=0.16$ ). For participants with mild AD, cognitive decline was still captured by FDG uptake and hippocampal volume, but not by the  $A\beta 42$  level in CSF. The variance of the ADAS-cog score during the course of dementia seemed better modeled by FDG uptake ( $R^2=0.36$ ) than by hippocampal volume ( $R^2=0.19$ ). We further conducted head-to-head comparisons in sample-size matched groups ( $A\beta 42$  level in CSF vs FDG uptake;  $A\beta 42$  level in CSF vs hippocampal volume; and FDG uptake vs hippocampal volume), and their relative contributions to model cognitive decline remained largely unchanged (eTable; <http://www.archneuro.com>).

## COMMENT

Annualized changes in the biomarkers of the  $A\beta 42$  level in CSF, FDG uptake, and hippocampal volume as well

**Table 2. Monthly Change in Biomarkers Among Study Population and Intergroup Rate Comparison<sup>a</sup>**

Biomarker	Mean (SE)					
	ADNI Diagnostic Group Monthly Change			Intergroup Comparison Coefficient (Group × Time)		
	NC	MCI	AD	NC <sup>b</sup> vs MCI	NC <sup>b</sup> vs AD	MCI <sup>b</sup> vs AD
	(n=36)	(n=54)	(n=16)			
Aβ42 in CSF, pg/mL	-0.46 (0.14) <sup>c</sup>	-0.26 (0.08) <sup>d</sup>	-0.29 (0.10) <sup>d</sup>	0.20 (0.16)	0.16 (0.17)	-0.04 (0.13)
Total tau in CSF, pg/mL	0.05 (0.07)	-0.04 (0.15)	-0.41 (0.25)	-0.09 (0.17)	-0.46 (0.26)	-0.38 (0.28)
Phosphorylated tau in CSF, pg/mL	0.05 (0.02) <sup>e</sup>	-0.01 (0.02)	-0.09 (0.06)	-0.05 (0.03)	-0.14 (0.06) <sup>e</sup>	-0.09 (0.06)
	(n=104)	(n=203)	(n=97)			
FDG uptake using PET, normalized intensity	-7.4 × 10 <sup>-4</sup> (3.0 × 10 <sup>-4</sup> ) <sup>e</sup>	-1.9 × 10 <sup>-3</sup> (2.1 × 10 <sup>-4</sup> ) <sup>c</sup>	-4.2 × 10 <sup>-3</sup> (4.6 × 10 <sup>-4</sup> ) <sup>c</sup>	-1.2 × 10 <sup>-3</sup> (3.6 × 10 <sup>-4</sup> ) <sup>d</sup>	-3.4 × 10 <sup>-3</sup> (5.4 × 10 <sup>-4</sup> ) <sup>c</sup>	-2.2 × 10 <sup>-3</sup> (5.0 × 10 <sup>-4</sup> ) <sup>c</sup>
	(n=228)	(n=390)	(n=191)			
Hippocampal volume using MRI, mm <sup>3</sup>	-2.95 (0.19) <sup>c</sup>	-5.52 (0.23) <sup>c</sup>	-8.01 (0.34) <sup>c</sup>	-2.57 (0.29) <sup>c</sup>	-5.03 (0.39) <sup>c</sup>	-2.49 (0.41) <sup>c</sup>
	(n=228)	(n=390)	(n=190)			
ADAS-cog score	-0.02 (0.01) <sup>e</sup>	0.12 (0.01) <sup>c</sup>	0.40 (0.04) <sup>c</sup>	0.14 (0.02) <sup>c</sup>	0.41 (0.04) <sup>c</sup>	0.28 (0.04) <sup>c</sup>

Abbreviations: AD, Alzheimer disease; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; FDG, fludeoxyglucose F18; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NC, normal cognition; PET, positron emission tomography.

<sup>a</sup>The study population's average rate (unit per month) was calculated using a generalized estimating equation approach, adjusting for baseline age. Sample sizes were limited to participants with 2 or more repeated measures during a 3-year follow-up period. Biomarker change is statistically significant if different than zero. Intergroup rate comparisons were tested in the longitudinal models with 2 diagnostic groups each time, and the intergroup rate difference was reflected by the coefficient of the interaction term (group × time).

<sup>b</sup>Referent group.

<sup>c</sup>*P* < .001.

<sup>d</sup>*P* < .01.

<sup>e</sup>*P* < .05.

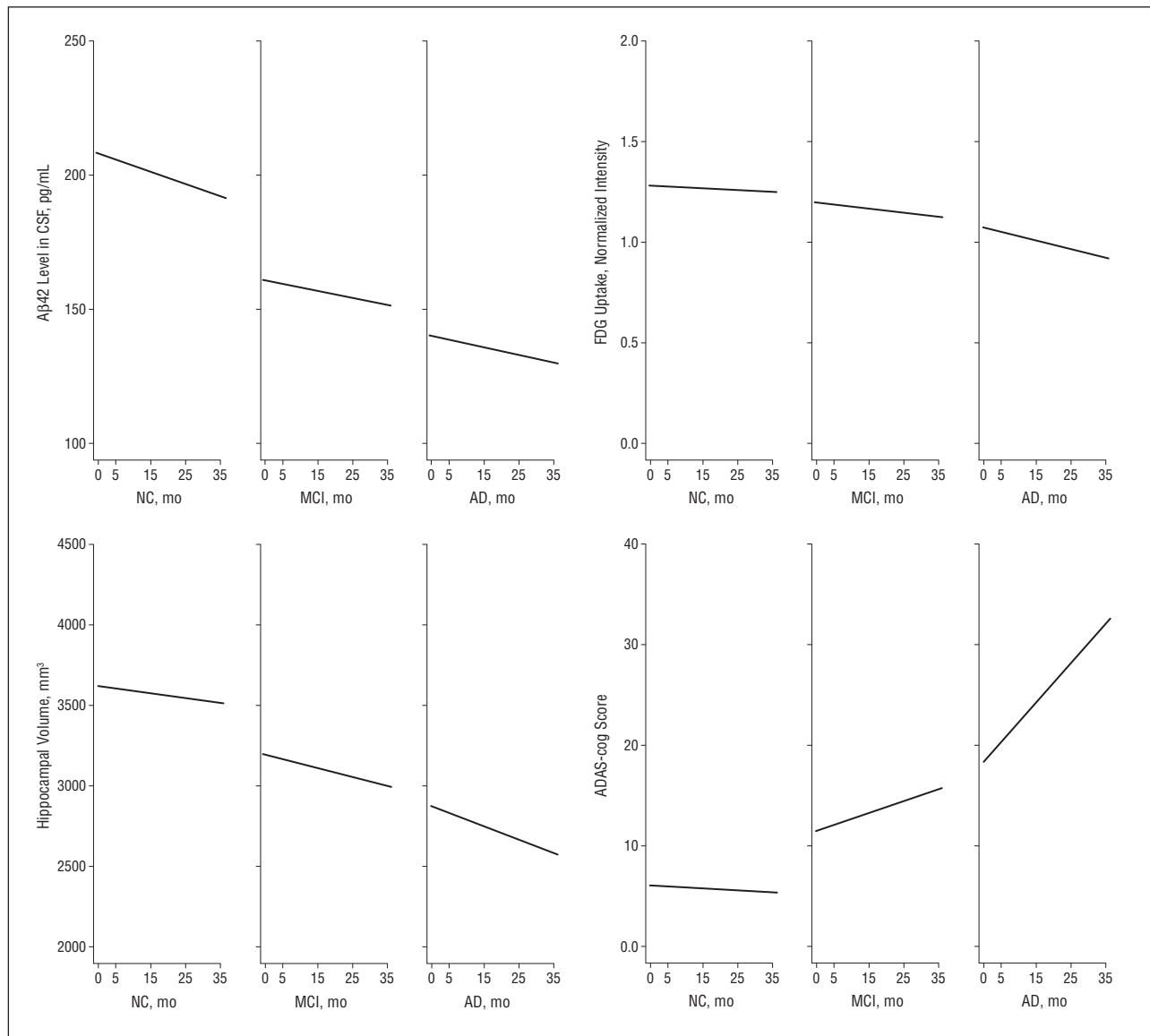
as cognitive function during the first 12 months of follow-up in ADNI have been reported.<sup>30</sup> We extended the follow-up study to up to 36 months and found evidence of significant change in the biomarkers of Aβ42 level, glucose metabolism, and hippocampal volume in all 3 groups of participants: NC, MCI, and AD. These biomarker trajectories showed that rates of change in the Aβ42 level were not different among the groups, but changes in glucose metabolism and hippocampal volume accelerated as cognitive function deteriorated. For participants with NC, cognitive change was not related to change in any of these biomarkers, although a model that included the Aβ42 level in CSF captured more variance than models that contained other biomarkers. The lack of association between cognitive change and biomarker dynamics in participants with NC may be due to only a subtle functional difference at this stage or to the limitation of our cognitive measurement tool. For participants with MCI, all 3 categories of biomarkers were related to cognitive decline, whereas for participants with AD, only glucose metabolism and hippocampal atrophy, and not the Aβ42 level in CSF, were related to cognitive decline. These findings imply that the Aβ42 level in CSF declines prior to the onset of cognitive impairment, in relation to aging or preclinical AD, whereas measures of neuronal dysfunction and injury (glucose metabolism and hippocampal atrophy) change with disease severity and stage.

Previous studies showed that, prior to cognitive impairment, *APOE4* carriers have accelerated memory decline,<sup>31</sup> greater MRI hippocampal atrophy rates,<sup>32</sup> and faster decline in regional FDG uptake using PET.<sup>33</sup> Our data in Table 3 demonstrated that *APOE4* was associated with

a baseline Aβ42 level in CSF and a baseline FDG uptake (but not a baseline hippocampal volume) in participants with NC, whereas in participants with MCI or AD, the presence of *APOE4* accelerated hippocampal atrophy (but not the Aβ42 level in CSF or FDG uptake). The influence of the *APOE4* gene on Aβ42 level in CSF and FDG-PET regional metabolism appeared to begin earlier than on hippocampal atrophy. There is evidence from pathological examinations and amyloid PET imaging showing that the *APOE4* gene increases the risk of AD through Aβ accumulation in the brain.<sup>34,35</sup> Therefore, the effect of *APOE4* on biomarkers at different stages may reflect the pathological sequence led by the pivotal event in AD, β-amyloid deposition.

The decrease in the Aβ42 level in CSF as an early event shown in our biomarker trajectories and the influence of *APOE4* on hippocampal atrophy that occurred after Aβ42 deposition in CSF and FDG uptake both imply that the FDG-PET marker changes after Aβ42 deposition in CSF but before hippocampal atrophy. Our study supports the hypothetical model of the AD pathological cascade proposed by Jack et al,<sup>36</sup> in which brain Aβ deposition heralds the onset of the entire AD pathological process and is followed by regional synaptic dysfunction or glucose hypometabolism that eventually culminates in cell loss or brain atrophy.

One of the unique features in our study is that we have follow-up information on the biomarkers of the Aβ42 level in CSF, FDG uptake, and hippocampal volume from our study participants, as well as ADAS-cog scores, to address the dynamics of the pathological course of AD. These biomarker dynamics have been examined by the ADNI



**Figure.** Hypothetical longitudinal changes in the Aβ42 level in cerebrospinal fluid (CSF), fludeoxyglucose F18 (FDG) uptake using positron emission tomography, hippocampal volume using magnetic resonance imaging, and Alzheimer Disease's Assessment Scale–cognitive subscale (ADAS-cog) score for a 75-year-old person at different cognitive states. AD indicates Alzheimer disease; MCI, mild cognitive impairment; and NC, normal cognition.

using a cross-sectional approach<sup>37</sup>; however, to translate cross-sectional results into actual patterns of change requires a strong assumption that all participants follow the same pattern of disease progression from normal all the way to dementia. We understand that this assumption may hold true for participants who developed MCI and for participants with AD, but it is unlikely for participants with NC who did not develop MCI. Nearly half of the participants with MCI developed AD during follow-up, but very few people changed from NC to MCI or AD in the ADNI. Participants with NC may be a very different group of people from those who used to be cognitively normal but currently have MCI or AD. Ideally, the longitudinal change of biomarkers could have been better delineated had our study continued with follow-up that was long enough to observe the same group of participants with NC transitioning to MCI and AD. Limited by this design, we might be observing biomarker dynamics

in aging but not necessarily disease progression in AD; therefore, we should be conservative about making inferences from participants who remained cognitively intact.

Previous longitudinal CSF studies showed that the decrease in the Aβ42 level correlated with cognitive decline in a healthy elderly population<sup>38</sup> but that the decrease might be too slight to detect later in the disease course,<sup>22,39,40</sup> which suggests that the level of Aβ42 in CSF might stabilize long before symptomatic dementia. These longitudinal CSF studies were, however, limited by, at most, 2 repeated measures and relatively small sample sizes. Our longitudinal study of CSF biomarkers is based on up to 3 repeated measures, which is the minimum number of time points allowing us to evaluate the variance of change. A baseline measure and 1 follow-up measure can only generate 1 single slope or change for each individual, and therefore there is no variance of slope to evaluate. The 2-point difference may result from either

**Table 3. Influence of *APOE4* Gene on Biomarkers Among Participants in the Alzheimer's Disease Neuroimaging Initiative<sup>a</sup>**

Biomarker	Coefficient, by ADNI Diagnostic Group		
	NC (n=36)	MCI (n=54)	AD (n=16)
Aβ42 level in CSF			
Age	2.45	0.30	0.92 <sup>b</sup>
Time	-0.38 <sup>b</sup>	-0.36 <sup>c</sup>	-0.41
<i>APOE4</i>	-52.34 <sup>c</sup>	-46.24 <sup>d</sup>	-0.71
<i>APOE4</i> × time	-0.32	0.20	0.15
	(n=104)	(n=203)	(n=97)
FDG uptake using PET			
Age	-9.4 × 10 <sup>-3d</sup>	-3.1 × 10 <sup>-3b</sup>	8.0 × 10 <sup>-3d</sup>
Time	-7.7 × 10 <sup>-4b</sup>	1.7 × 10 <sup>-3d</sup>	-3.7 × 10 <sup>-3d</sup>
<i>APOE4</i>	-5.0 × 10 <sup>-2b</sup>	-4.3 × 10 <sup>-2b</sup>	2.9 × 10 <sup>-2</sup>
<i>APOE4</i> × time	1.6 × 10 <sup>-4</sup>	5.0 × 10 <sup>-4</sup>	-6.4 × 10 <sup>-4</sup>
	(n=228)	(n=390)	(n=191)
Hippocampal volume using MRI			
Age	-33.19 <sup>d</sup>	-26.96 <sup>d</sup>	-25.18 <sup>d</sup>
Time	-2.72 <sup>d</sup>	-4.44 <sup>d</sup>	-6.56 <sup>d</sup>
<i>APOE4</i>	-67.50	-188.19 <sup>c</sup>	-152.47
<i>APOE4</i> × time	-0.81	-1.98 <sup>d</sup>	-2.04 <sup>c</sup>

Abbreviations: AD, Alzheimer disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; FDG, fludeoxyglucose F18; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NC, normal cognition; PET, positron emission tomography.

<sup>a</sup>Time-varying biomarkers were modeled by baseline age, time, *APOE4* status, and interaction between *APOE4* and time using a generalized estimating equation approach. Coefficients of the interaction term (*APOE4* × time) represented the influence of *APOE4* on rates of change. Sample sizes were limited to subjects with 2 or more repeated measures during the 3-year follow-up period.

<sup>b</sup>*P* < .05.

<sup>c</sup>*P* < .01.

<sup>d</sup>*P* < .001.

actual change or simply measurement error. In addition, if CSF biomarker measurement error exists, which is very likely for all laboratory tests, the magnitude of difference can be subject to the "regression toward the mean" effect. In other words, the more the baseline value deviates from the population mean, the larger the change is likely to be.

We used the ADAS-cog score to monitor cognitive function and mapped the change of biomarkers to the ADAS-cog score as a way to assess the extent to which pathological markers correlated with clinical progression over time. There is no gold standard for measurement of cognitive function, particularly when our outcome of interest includes multiple stages of AD from normal to overt dementia. We noticed that ADAS-cog scores in participants with NC even improved over time, and we recognized that the possible learning effect might hinder us from using the ADAS-cog to track cognitive change among healthy elderly people. Nevertheless, ADAS-cog is still the standard tool in many clinical trials to assess AD, which allows our results to be more interpretable across different studies.

There are several limitations in our study. First, research participants in the ADNI were volunteers and from

**Table 4. Goodness of Fit of Regression Analyses Modeling Cognitive Change by Biomarkers<sup>a</sup>**

GEE Model	Coefficient in GEE Model, by ADNI Diagnostic Group		
	NC (n=36)	MCI (n=54)	AD (n=16)
CSF Aβ model <i>R</i> <sup>2</sup>	0.12	0.12	0.26
Age	0.06	-0.01	-0.12
Time	-0.02	0.05	0.43 <sup>b</sup>
Baseline	-0.02 <sup>c</sup>	-0.03 <sup>c</sup>	0.12
Change	-0.02	-0.08 <sup>d</sup>	-0.15
	(n=104)	(n=203)	(n=96)
FDG-PET model <i>R</i> <sup>2</sup>	0.07	0.18	0.36
Age	0.02	0.03	0.13
Time	-0.02	0.08 <sup>b</sup>	0.18 <sup>b</sup>
Baseline	-6.27 <sup>c</sup>	-15.39 <sup>b</sup>	-29.83 <sup>b</sup>
Change	-3.11	-11.45 <sup>b</sup>	-36.00 <sup>b</sup>
	(n=228)	(n=390)	(n=190)
MRI hippocampal volume model <i>R</i> <sup>2</sup>	0.03	0.16	0.19
Age	0.08 <sup>d</sup>	-0.05	-0.18 <sup>d</sup>
Time	-0.03 <sup>c</sup>	0.05 <sup>c</sup>	0.24 <sup>b</sup>
Baseline	2.0 × 10 <sup>-4</sup>	-4.0 × 10 <sup>-3b</sup>	-4.1 × 10 <sup>-3b</sup>
Change	-4.6 × 10 <sup>-3</sup>	-0.01 <sup>b</sup>	-0.02 <sup>c</sup>

Abbreviations: AD, Alzheimer disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; FDG, fludeoxyglucose F18; GEE, generalized estimating equation; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NC, normal cognition; PET, positron emission tomography.

<sup>a</sup>Time-varying Alzheimer's Disease Assessment Scale-cognitive subscale scores were modeled by baseline age, time, baseline value, and change of biomarker. *R*<sup>2</sup> was the percentage of the outcome variance explained by the model.

<sup>b</sup>*P* < .001.

<sup>c</sup>*P* < .01.

<sup>d</sup>*P* < .05.

clinics, not from the general population. Although they all met the inclusion and exclusion criteria for NC, amnesic MCI, or mild AD, they were not newly diagnosed or incident cases. Within the same diagnostic group, participants were enrolled in our study at different stages in the disease course. Baseline evaluation did not adequately reflect their clinical states when they first had the disease. Therefore, we want to be clear that our target population is patients who come to the clinic rather than the general community; and we applied a generalized estimating equation approach to avoid the unverifiable assumption about their biological states at the beginning of cognitive impairment. Second, not all ADNI research participants underwent all biomarker examinations, especially lumbar puncture for CSF. Like many longitudinal studies, we had substantial missing data for biomarkers during the 36-month follow-up period. Although a generalized estimating equation approach can handle missing time points within individuals, there is no way that we can recover the actual biomarker profiles for those individuals who did not end up being in the analyses. The differences in sample size, particularly the smaller samples of individuals with longitudinal CSF samples compared with the other biomarkers, may limit our ability to draw inferences about the rela-

tive changes in these biomarkers. Participants whose data were used in the analyses might be different from those whose data were not included or who dropped out; we do not know whether this is informative censoring or random missing data. Nevertheless, we focused on the relative rates of change or associations with cognitive change but not true rates. The calculated biomarker values would be biased by informative censoring, but the interrelationship among these biomarkers might not be affected.

In sum, longitudinal patterns of biomarkers suggest that A $\beta$ 42 level in CSF, FDG uptake using PET, and hippocampal volume using MRI capture AD pathological states sequentially and that their predictive values for cognitive decline depend on the stage of the disease. Repeated measurement of these candidate biomarkers provides a potential approach for early diagnosis of AD.

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