

## Original Investigation

# Associations Between Biomarkers and Age in the Presenilin 1 E280A Autosomal Dominant Alzheimer Disease Kindred

## A Cross-sectional Study

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**IMPORTANCE** Age-associated changes in brain imaging and fluid biomarkers are characterized and compared in presenilin 1 (*PSEN1*) E280A mutation carriers and noncarriers from the world's largest known autosomal dominant Alzheimer disease (AD) kindred.

**OBJECTIVE** To characterize and compare age-associated changes in brain imaging and fluid biomarkers in *PSEN1* E280A mutation carriers and noncarriers.

**DESIGN, SETTING, AND PARTICIPANTS** Cross-sectional measures of <sup>18</sup>F-florbetapir positron emission tomography, <sup>18</sup>F-fludeoxyglucose positron emission tomography, structural magnetic resonance imaging, cerebrospinal fluid (CSF), and plasma biomarkers of AD were assessed from 54 *PSEN1* E280A kindred members (age range, 20-59 years).

**MAIN OUTCOMES AND MEASURES** We used brain mapping algorithms to compare regional cerebral metabolic rates for glucose and gray matter volumes in cognitively unimpaired mutation carriers and noncarriers. We used regression analyses to characterize associations between age and the mean cortical to pontine <sup>18</sup>F-florbetapir standard uptake value ratios, precuneus cerebral metabolic rates for glucose, hippocampal gray matter volume, CSF Aβ<sub>1-42</sub>, total tau and phosphorylated tau<sub>181</sub>, and plasma Aβ measurements. Age at onset of progressive biomarker changes that distinguish carriers from noncarriers was estimated using best-fitting regression models.

**RESULTS** Compared with noncarriers, cognitively unimpaired mutation carriers had significantly lower precuneus cerebral metabolic rates for glucose, smaller hippocampal volume, lower CSF Aβ<sub>1-42</sub>, higher CSF total tau and phosphorylated tau<sub>181</sub>, and higher plasma Aβ<sub>1-42</sub> measurements. Sequential changes in biomarkers were seen at age 20 years (95% CI, 14-24 years) for CSF Aβ<sub>1-42</sub>, age 16 years (95% CI, 11-24 years) for the mean cortical <sup>18</sup>F-florbetapir standard uptake value ratio, age 15 years (95% CI, 10-24 years) for precuneus cerebral metabolic rate for glucose, age 15 years (95% CI, 7-20 years) for CSF total tau, age 13 years (95% CI, 8-19 years) for phosphorylated tau<sub>181</sub>, and age 6 years (95% CI, 1-10 years) for hippocampal volume, with cognitive decline up to 6 years before the kindred's estimated median age of 44 years (95% CI, 43-45 years) at mild cognitive impairment diagnosis. No age-associated findings were seen in plasma Aβ<sub>1-42</sub> or Aβ<sub>1-40</sub>.

**CONCLUSIONS AND RELEVANCE** This cross-sectional study provides additional information about the course of different AD biomarkers in the preclinical and clinical stages of autosomal dominant AD.

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There is growing interest in biomarker changes associated with the preclinical stages of Alzheimer disease (AD) and in the use of this information to help inform the design and statistical power of preclinical AD trials. Such trials are under way, predicated on an understanding that Alzheimer pathology and physiology begin decades before clinical symptoms of cognitive dysfunction arise.<sup>1,2</sup> Hypotheses about the evolution of abnormalities in biomarkers associated with AD led to revision of research and clinical guidelines for the use of biomarkers in the diagnosis of AD at 3 different stages of disease, including preclinical, mild cognitive impairment (MCI), and dementia.<sup>3,4</sup> Preclinical biomarker studies<sup>1,5,6</sup> in autosomal dominant AD (ADAD) have helped elucidate the evolution of biomarker abnormalities before onset of clinical symptoms.

In preparation for the recently started Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease treatment trial of an A $\beta$ -modifying agent,<sup>2</sup> we conducted an initial cross-sectional biomarker study in presenilin 1 (*PSEN1*; OMIM 104311) E280A mutation carriers and noncarriers to better understand preclinical biomarker change associated with age.<sup>5</sup> This study aimed to characterize associations among brain imaging and fluid AD biomarkers with mutation status and age, as well as to relate onset of progressive biomarker changes to this kindred's estimated median ages of 44 and 49 years, respectively, at clinical onset of MCI and dementia due to AD.<sup>7</sup> Our group previously reported that the mean cortical <sup>18</sup>F-florbetapir positron emission tomography (PET) measurements of fibrillar A $\beta$  burden begin to rise approximately 16 years before the kindred's respective median ages at MCI.<sup>5</sup> Herein, we extend our analyses to include <sup>18</sup>F-fludeoxyglucose PET, structural magnetic resonance (MR) imaging, cerebrospinal fluid (CSF), and plasma biomarker measurements from this cohort of clinically unaffected and affected research participants from the world's largest known single-mutation ADAD kindred.

## Methods

### Participants and Study Design

Participants provided their informed consent before study entry under guidelines approved by local institutional review boards. In those participants who were unable to provide consent because of cognitive impairment, a legal representative provided assent in accord with local laws and institutional regulations. This included agreement that information would not be provided about their *PSEN1* or apolipoprotein E (*APOE*) genotypes, which were obtained as previously described.<sup>7,8</sup>

The study was performed between September 1, 2011, and July 31, 2012. All biomarkers were collected within a 6-month time frame from clinical evaluations. Participant recruitment and enrollment, clinical and neuropsychological evaluations, and lumbar punctures were performed at the Universidad de Antioquia, Medellín, Colombia. The <sup>18</sup>F-fludeoxyglucose PET and MR imaging were performed at Hospital Pablo Tobón Uribe in Medellín. Plasma and CSF samples were shipped to and assayed by the Dominantly Inherited Alzheimer Network (DIAN) Biomarker Core laboratory at Washington University in St Louis, Missouri. <sup>18</sup>F-florbetapir PET was per-

formed at the Banner Alzheimer's Institute, Phoenix, Arizona, as previously described.<sup>5</sup> All data were analyzed at the Banner Alzheimer's Institute. Data were acquired by the study investigators, who were all blinded to the participants' genetic status except for some statisticians (A.R., P.T., W.L., and N.A.).

Fifty-four ADAD mutation carriers and noncarriers from the *PSEN1* E280A mutation kindred were recruited from the Alzheimer's Prevention Initiative's *PSEN1* E280A kindred Colombian registry at the Universidad de Antioquia. Inclusion criteria included an age range of 18 to 60 years. Cognitively unimpaired participants were required to show no cognitive impairment on a standard cognitive battery, including a Clinical Dementia Rating (CDR)<sup>9</sup> global score of zero and a Mini-Mental State Examination (MMSE)<sup>10</sup> score of at least 28. Cognitively impaired mutation carriers were required to have a CDR global score of at least 0.5, along with a clinical diagnosis of MCI or mild dementia (MMSE score  $\geq 18$ ) due to AD according to the National Institute on Aging-Alzheimer's Association diagnostic criteria terminology.<sup>11,12</sup> To ensure a broad age distribution among the cognitively unimpaired mutation carriers and noncarriers, enrollment was stratified into 2 age ranges of 18 to 34 years and 35 to 60 years. Participants were matched on age, sex, and education within 2 years to participants enrolled in the comparator group.

### Procedures

#### Clinical Ratings and Neuropsychological Tests

Participants were assessed using several tests. These included the MMSE, CDR, a Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease battery that was adapted for this Colombian population,<sup>7</sup> the Geriatric Depression Scale,<sup>13</sup> and Functional Assessment Staging.<sup>14</sup>

#### Brain Imaging

<sup>18</sup>F-fludeoxyglucose PET was performed on a 64-section PET/computed tomography imaging system (Biograph mCT; Siemens) using intravenous administration of 5 mCi (185 million Bq) of <sup>18</sup>F-fludeoxyglucose after a 30-minute radiotracer uptake period when resting in a darkened room, followed by a 30-minute dynamic emission scan (six 5-minute frames). Images were reconstructed with computed tomographic attenuation correction. Volumetric MR imaging data were acquired on a 1.5-T imaging system (Avanto; Siemens) with a T1-weighted, magnetization-prepared, rapid-acquisition, gradient-echo pulse sequence (echo time, minimum full; flip angle, 8°; number of excitations, 1; field of view, 22 cm; imaging matrix, 192  $\times$  192 pixels; and section thickness, 1.2 mm). All images were reviewed for quality and compliance in accord with the Alzheimer's Disease Neuroimaging Initiative recommendations.<sup>15</sup>

Precuneus to whole-brain cerebral metabolic rate for glucose (CMRgl) ratios were characterized from a bilateral region of interest (ROI) in each participant's <sup>18</sup>F-fludeoxyglucose PET image using an automated brain mapping algorithm (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) and the automatic anatomical labeling toolbox.<sup>16</sup> Hippocampal to total intracranial volume ratios were characterized from bilateral ROIs in each participant's T1-weighted MR image using a software package

(FreeSurfer 5.1; <http://surfer.nmr.mgh.harvard.edu>).<sup>17-19</sup> All images were visually inspected to verify ROI characterization.

SPM8 was used to deform each participant's <sup>18</sup>F-fluorodeoxyglucose PET image into the coordinates of a brain atlas, normalize the data for whole-brain measurements, and generate a statistical map of CMRgl differences between the cognitively unimpaired mutation carrier and noncarrier groups ( $P < .005$ , uncorrected for multiple comparisons).<sup>20,21</sup> For MR imaging, SPM8 was used in conjunction with the voxel-based morphometry toolbox and diffeomorphic anatomical registration using exponential Lie algebra to generate a statistical map of gray matter volume differences between groups ( $P < .005$ , uncorrected for multiple comparisons).<sup>22</sup> The false discovery rate was used to assess significance after correction for multiple comparisons.

#### CSF and Plasma Biomarkers

The lumbar punctures were performed before noon by a qualified physician at the Universidad de Antioquia after a minimum of 4 hours of fasting. In a seated position, an atraumatic 24G Sprotte needle and sterile polypropylene tubes were used for sample collection. In total, 6 to 12 mL of CSF was acquired in 0.3-mL aliquots, frozen at  $-70^{\circ}\text{F}$ , shipped on dry ice, and assayed in a single batch. Luminex xMAP bead-based assays (INNO-BIA AlzBio3; Innogenetics) were used to quantify CSF A $\beta$ 1-42, total tau, and phosphorylated tau<sub>181</sub>, as well as plasma A $\beta$ 1-42 and A $\beta$ 1-40 (INNO-BIA Plasma A $\beta$  Forms Multiplex Assay; Innogenetics). Sample aliquots were stored for longitudinal comparisons, future analyses, and data sharing.

#### Analysis of Associations Between Biomarker Measurements and Age

Curvilinear regression models were used to assess associations between prespecified biomarker measurements and age in the mutation carrier and noncarrier groups. Linear, quadratic, or sigmoidal regression curves were fitted to each biomarker within groups. Best-fitting models were selected based on goodness of fit to data ( $R^2$ ) and Akaike information criterion as previously described in detail.<sup>5</sup> Models were compared using a software package (GraphPad Prism; GraphPad Software, Inc). This approach determines how well the data support each model, taking into account goodness of fit (sum of squares) and the number of parameters in the model.

Best-fitting curves were used to determine the age at which biomarker measurements in carriers and noncarriers began to diverge based on an approximate  $t$  test ( $P \leq .05$ ), the same approach used in the DIAN study.<sup>1</sup> As complementary measures, to be consistent with other approaches, we also present 2 alternative methods for determining the age at biomarker change. First, when the initial part of the biomarker curve was found to be flat (ie, for <sup>18</sup>F-florbetapir PET and CSF phosphorylated tau<sub>181</sub> measurements), the point on the mutation carrier group regression curve at which the biomarker showed a significant slope inflection was used to estimate the age at significant biomarker initial change, consistent with our group's previous study<sup>5</sup> of cortical <sup>18</sup>F-florbetapir standardized uptake value ratio changes. Second, using a more conservative approach, the age at which the 95% CI zones for the carrier and noncarrier group curves be-

came separated is also presented. Results for these 2 alternative estimate methods are presented in table form for comparison with our primary measures. For all estimates of the age at biomarker change, 95% CIs were established using iterative Monte Carlo simulations (MATLAB; The MathWorks, Inc).<sup>5</sup>

## Results

### Participant Characteristics

Fifty-four research participants were successfully screened and enrolled into the study. <sup>18</sup>F-florbetapir PET, <sup>18</sup>F-fluorodeoxyglucose PET, MR imaging, CSF, and plasma measurements were acquired in each participant with only the following exceptions: 4 participants did not travel to Arizona for <sup>18</sup>F-florbetapir PET, and 2 participants declined to have <sup>18</sup>F-fluorodeoxyglucose PET. Participant characteristics, including representative clinical ratings and neuropsychological test scores, are summarized in **Table 1**. Seven of the cognitively impaired mutation carriers met diagnostic criteria for MCI due to AD, and 5 met criteria for mild dementia due to AD. The cognitively unimpaired mutation carrier and noncarrier groups did not differ significantly in their age, sex, education, APOE carrier proportion, clinical ratings, or neuropsychological test scores. Compared with unimpaired mutation carriers, cognitively impaired mutation carriers were older and had significantly lower education, clinical ratings, and neuropsychological test scores. Correlation analyses between years of education and each biomarker measurement revealed no significant associations. Therefore, years of education were not corrected for in group analyses.

### Cognitive Test Performance

Cognitive test performance for global measures, attention, executive function, and memory was evaluated for age-related onset and change, revealing evidence of cognitive decline up to 6 years before the kindred's estimated median age of 44 years at MCI diagnosis (95% CI, 43-45 years).<sup>7</sup> Cognitive changes were approximated to begin at age 38 years for CDR sum of boxes (95% CI, 33-42 years), MMSE (95% CI, 33-41 years), and Consortium to Establish a Registry for Alzheimer's Disease word list delayed recall (95% CI, 34-41 years) (**Figure 1**). Cognitive changes were approximated to begin at age 40 years (95% CI, 35-45 years) for letter fluency and at age 42 years for Trail Making Test A (95% CI, 33-47 years) and category (animal) fluency (95% CI, 36-45 years).

### <sup>18</sup>F-fluorodeoxyglucose PET

Unimpaired carriers had lower CMRgl in the prespecified precuneus ROI<sup>1,23-25</sup> than noncarriers ( $P = .02$ ). Lower CMRgl was associated with older age in the carrier group ( $P = .001$ ) but not in the noncarrier group ( $P = .30$ ). Regression modeling revealed a linear relationship between lower precuneus CMRgl and older age among the mutation carriers ( $R^2 = 0.31$ ). Carrier precuneus CMRgl began to diverge from noncarrier CMRgl at approximately age 29 years (95% CI, 20-34 years), about 15 years before the kindred's estimated median age at MCI onset (**Figure 1** and **Table 2**). Voxel-based analyses demonstrated

Table 1. Characteristics of Research Participants

Variable	Noncarriers (n = 22)	Unimpaired Carriers (n = 20)	Impaired Carriers (n = 12)
Age, mean (SD) [range], y	33 (9) [20-50]	32 (9) [20-44]	49 (5) [42-59] <sup>a,b</sup>
Sex, No.			
Male	9	8	4
Female	13	12	8
Educational level, mean (SD), y	11 (3)	12 (3)	8 (4) <sup>a,b</sup>
APOE carrier proportion, No. <sup>c</sup>			
2/3	1	1	1
2/4	1	3	0
3/3	14	10	8
3/4	5	6	2
4/4	1	0	0
Neuropsychological test score, mean (SD)			
CDR sum of boxes	0.0 (0.0)	0.1 (0.2)	3.5 (2.4) <sup>a,b</sup>
MMSE	29.8 (0.5)	29.8 (0.4)	22.3 (4.4) <sup>a,b</sup>
CERAD word list delayed recall	19.4 (3.1)	20.5 (3.0)	5.9 (3.3) <sup>a,b</sup>
Trail Making Test A <sup>d</sup>	48.3 (18.9)	39.6 (11.3)	143.5 (94.5) <sup>a,b</sup>
Category fluency, animals	19.8 (2.9)	21.5 (5.4)	10.3 (4.3) <sup>a,b</sup>
Verbal fluency, FAS	33.4 (6.3)	36.2 (11.9)	16.2 (8.8) <sup>a,b</sup>

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating (range, 0-18, with 0 a perfect score); CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination (range, 0-30, with 30 a perfect score).

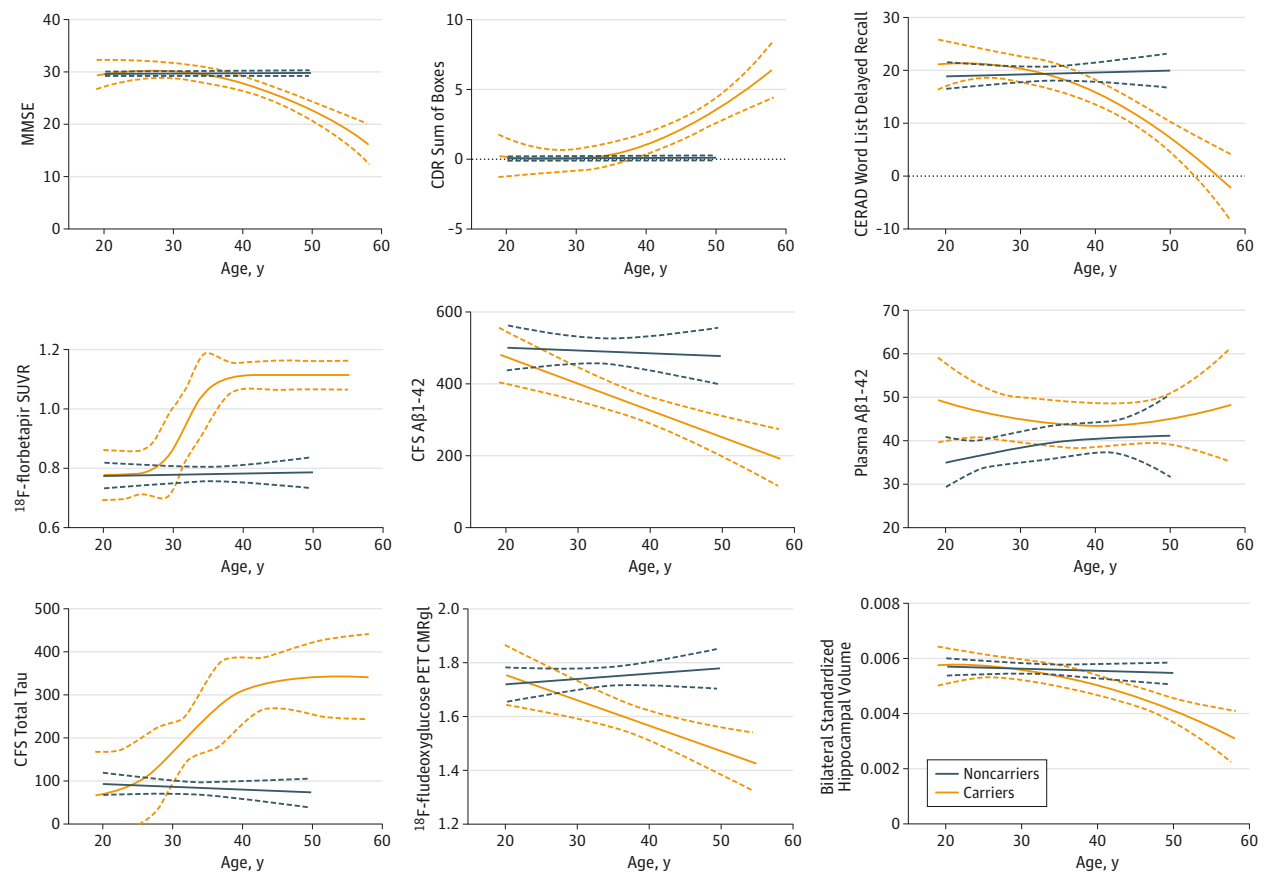
<sup>a</sup> P < .05 compared with noncarriers.

<sup>b</sup> P < .05 compared with unimpaired carriers.

<sup>c</sup> APOE information is missing for one impaired carrier for whom assent was not provided for APOE testing.

<sup>d</sup> No data were available for 2 impaired carriers.

Figure 1. Biomarker Measure Associations With Age



Shown are age-associated biomarker curves for mutation noncarriers and carriers. Some data points were withheld to protect individual identities associated with age. CDR indicates Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease;

CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; PET CMRgl, positron emission tomography precuneous cerebral metabolic rate for glucose; and SUVR, mean standardized uptake value ratio (previously reported<sup>5</sup>).

Table 2. Estimated Age at Onset of Biomarker Changes

Biomarker	No.	Age (95% CI) at Initial Change, y <sup>a</sup>	Years (95% CI) Before Kindred's Age at MCI Diagnosis <sup>a</sup>	Years Before Kindred's Age at Dementia Onset <sup>a</sup>	Age (95% CI) at Biomarker Slope Change, y <sup>b</sup>	Age (95% CI) at Significant Between-Group Difference, y <sup>c</sup>
CSF Aβ1-42 decline	54	24 (20-30)	20 (14-24)	25	NA	29 (27-34)
<sup>18</sup> F-florbetapir SUVR mean cortical increase	50	28 (20-32)	16 (11-24)	21	28 (27-33)	31 (27-34)
<sup>18</sup> F-fludeoxyglucose PET CMRgl precuneus reduction	52	29 (20-34)	15 (10-24)	20	NA	32 (26-36)
CSF total tau increase	54	29 (24-37)	15 (7-20)	20	NA	33 (25-41)
CSF phosphorylated tau <sub>181</sub> increase	54	31 (25-36)	13 (8-19)	18	31 (27-37)	35 (32-43)
Increased ratio of CSF phosphorylated tau <sub>181</sub> to Aβ1-42	54	31 (25-36)	13 (8-19)	18	31 (28-42)	34 (29-45)
Bilateral standardized hippocampal volume reduction	54	38 (33-43)	6 (1-10)	11	NA	42 (33-47)

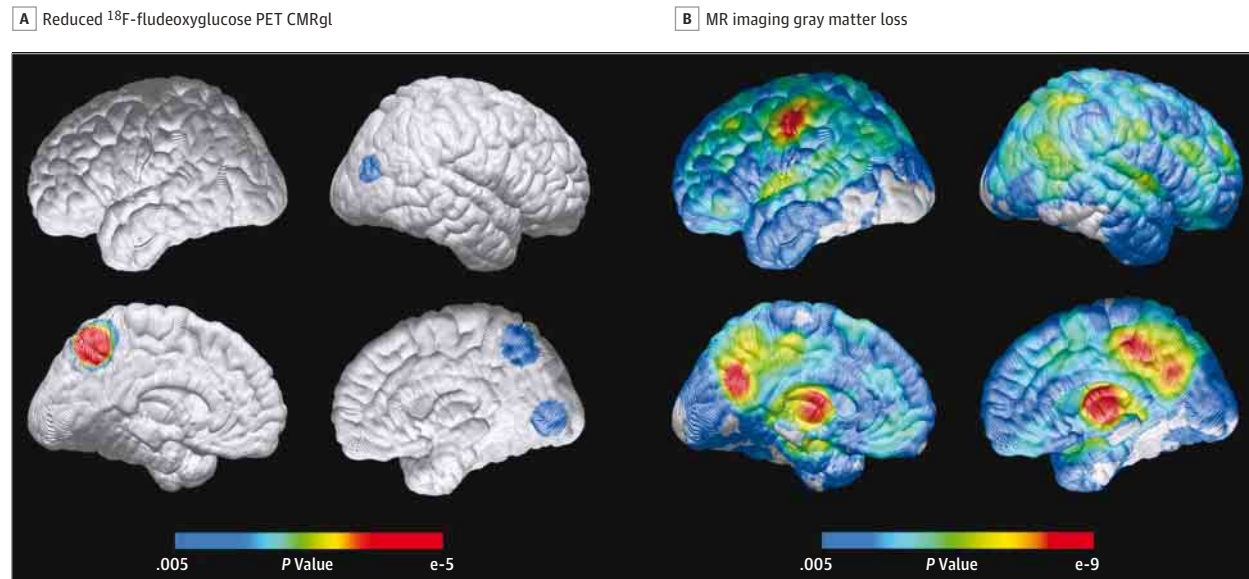
Abbreviations: CMRgl, cerebral metabolic rate for glucose; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NA, not applicable; PET, positron emission tomography; SUVR, standardized uptake value ratio.

<sup>a</sup> Estimates are based on the age at which biomarkers begin to diverge in the carrier and noncarrier groups using an approximate *t* test.

<sup>b</sup> Estimates are based on the age at which biomarkers begin to deviate from an initial zero slope in the carrier group. NA (not applicable) indicates that the biomarker did not have an initial slope of zero appropriate for this analysis.

<sup>c</sup> Estimates are based on the youngest age at which biomarker curves are significantly different in the carrier and noncarrier groups using 95% CIs.

Figure 2. Voxelwise Comparison of <sup>18</sup>F-fludeoxyglucose Positron Emission Tomography (PET)-Measured Cerebral Metabolic Rate for Glucose (CMRgl) and Volumetric Magnetic Resonance (MR) Imaging-Measured Regional Gray Matter in Unimpaired PSEN1 E280A Carriers and Noncarriers



Shown are group comparisons of unimpaired mutation carriers with age-matched noncarriers. A, Reduced <sup>18</sup>F-fludeoxyglucose PET CMRgl in cognitively unimpaired mutation carriers vs noncarriers. B, Magnetic resonance imaging gray matter loss in cognitively unimpaired mutation carriers vs noncarriers.

lower CMRgl among cognitively unimpaired mutation carriers than noncarriers in bilateral precuneus and occipital locations ( $P < .005$ , uncorrected for multiple comparisons) (Figure 2A).

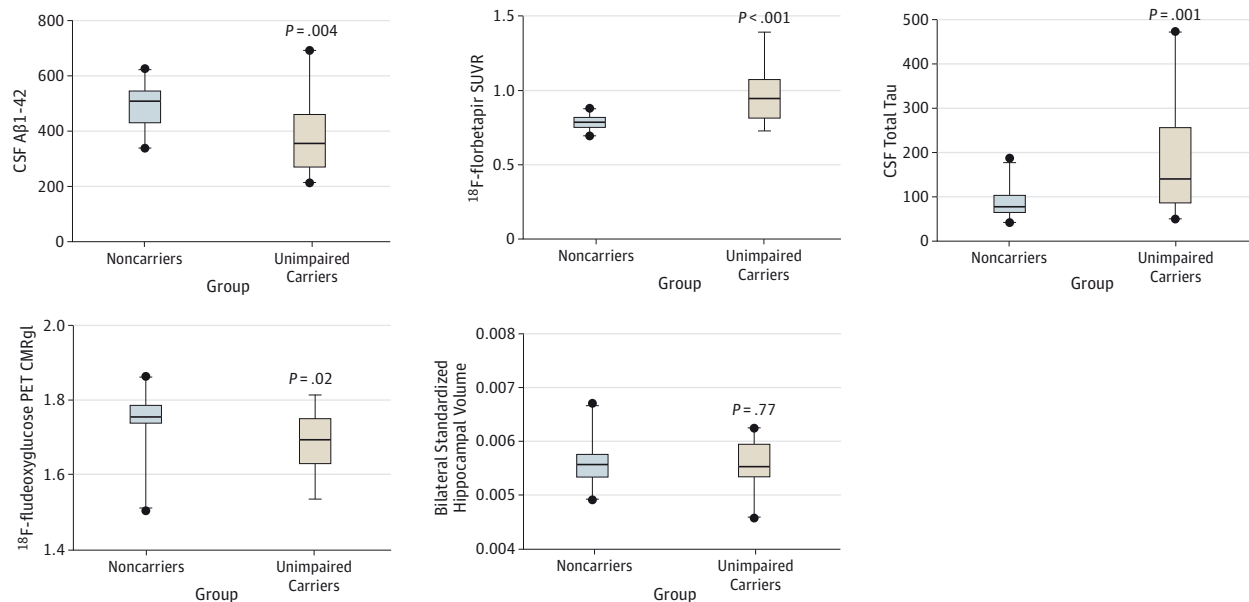
**Volumetric MR Imaging Measurements**

There were no overall group differences in prespecified hippocampal ROI<sup>1,26</sup> volume between unimpaired carriers and noncarriers ( $P = .77$ ) (Figure 3). However, smaller hippocampal volume was associated with older age in the mutation carrier group ( $P < .001$ ) but not in the noncarrier group ( $P = .41$ ). Regression models revealed that a quadratic curve best fit the association between age and hippocampal volume in the mutation carriers ( $R^2 = 0.48$ ). Mutation carrier hippocampal vol-

ume began to diverge from noncarrier volume at approximately age 38 years (95% CI, 33-43 years), 6 years before the kindred's median age at MCI onset (Figure 1 and Table 2). Post hoc evaluation of standardized whole-brain volume (smaller) and ventricular volume (larger) revealed similar age-related changes and estimated age at onset of divergence compared with hippocampal volume.

Cognitively unimpaired mutation carriers had significantly less gray matter than noncarriers in bilateral precuneus, posterior cingulate, lateral parietotemporal cortex, medial temporal lobe, and thalamus ( $P < .005$ , uncorrected for multiple comparisons) (Figure 2B). Based on these results, we performed post hoc age association ROI analyses of gray matter volume within the precuneus and posterior cingulate cor-

Figure 3. Biomarker Comparisons Between Unimpaired Carriers and Noncarriers



Shown are between-group cross-sectional comparisons between unimpaired *PSEN1* E280A mutation carriers vs noncarriers. Significant differences are seen in cerebrospinal fluid (CSF) A $\beta$ 1-42, amyloid positron emission tomography

(PET) ( $^{18}\text{F}$ -florbetapir standardized uptake value ratio [SUVR]<sup>5</sup>), CSF total tau, and  $^{18}\text{F}$ -fludeoxyglucose PET precuneus cerebral metabolic rate for glucose (CMRgl) but not in bilateral standardized hippocampal volume ( $P < .05$ ).

tex to assess for earlier changes than were identified in hippocampal volume. Similar to hippocampal volume, a quadratic fitted curve best represented the data and revealed an age of divergence between mutation carrier and noncarrier precuneus and posterior cingulate volumes of 38 years, similar to the age identified for hippocampal volume.

### CSF and Plasma Biomarkers

Unimpaired carriers showed reduced A $\beta$ 1-42 ( $P = .004$ ) and elevated total tau ( $P = .001$ ) compared with noncarriers (Figure 3). The CSF A $\beta$ 1-42 levels were reduced with age in the mutation carrier group ( $R = -0.62$ ,  $P < .001$ ) but not in the noncarrier group ( $R = -0.092$ ,  $P = .68$ ). Comparing linear, quadratic, and sigmoidal regression models revealed that a linear relationship between CSF A $\beta$ 1-42 levels and age was the best fit in the mutation carriers. Using the approximate  $t$  test, mutation carrier CSF A $\beta$ 1-42 began to diverge from noncarrier levels at approximately age 24 years (95% CI, 20-30 years) (Figure 1 and Table 2), about 20 years before the kindred's median age at MCI onset. Best fitting to sigmoidal curve models, CSF total tau and phosphorylated tau<sub>181</sub> levels were higher with age in the mutation carrier group ( $R^2 = 0.39$ ,  $P = .003$  and  $R^2 = 0.40$ ,  $P = .002$ , respectively) but not in the noncarrier group ( $R^2 = 0.071$ ,  $P = .21$  and  $R^2 = 0.037$ ,  $P = .39$ , respectively). Carrier CSF total tau levels began to diverge from noncarrier levels at approximately age 29 years (95% CI, 24-37 years), and phosphorylated tau<sub>181</sub> levels began to diverge at approximately age 31 years (95% CI, 25-36 years) (Figure 1 and Table 2). Carrier ratios of total tau to A $\beta$ 1-42 and phosphorylated tau<sub>181</sub> to A $\beta$ 1-42 in mutation carriers began to diverge from noncarrier levels at approximately age 31 years (95% CI, 25-36 years for both), best fitting sigmoidal-shaped curves ( $R^2=0.4$  for both).

Plasma A $\beta$ 1-42 levels were significantly higher in mutation carriers than in noncarriers (mean [SD], 45 [10] vs 39 [6] pg/mL;  $P = .03$ ) but were not significantly associated with age. Plasma A $\beta$ 1-40 levels were not significantly different between carriers and noncarriers (mean [SD], 130 [30] vs 138 [20] pg/mL;  $P = .35$ ).

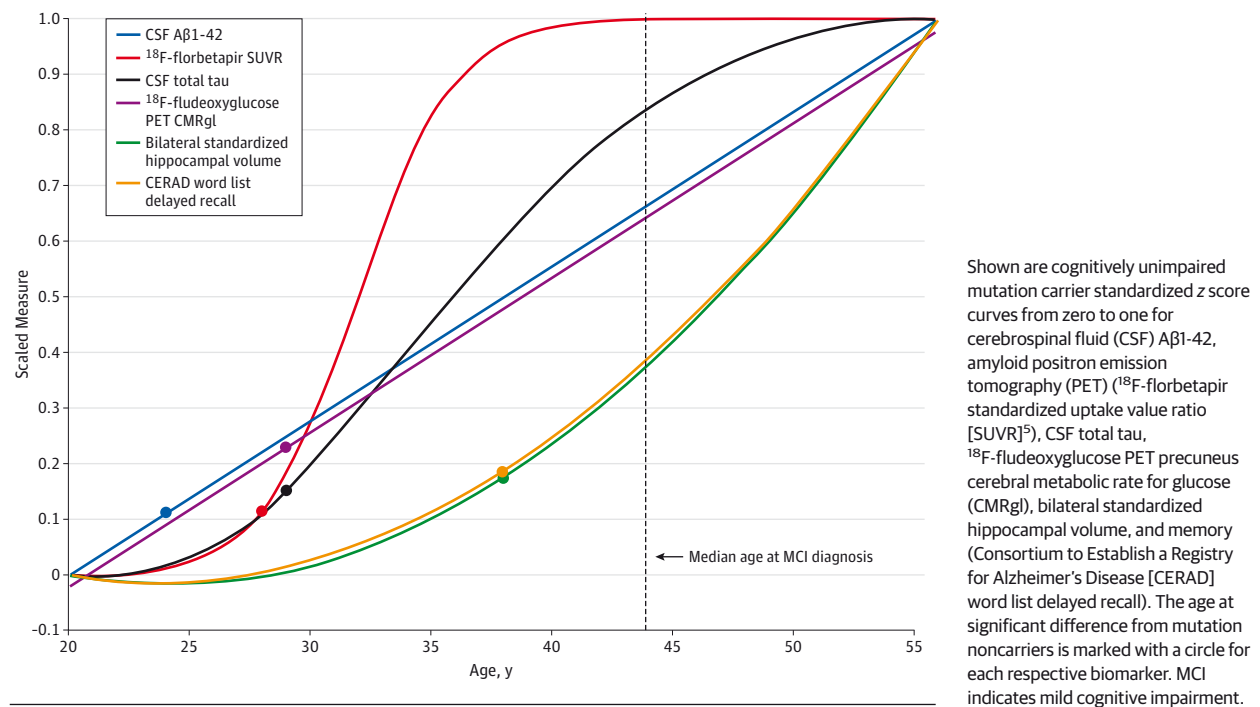
### Age-Related Biomarker Changes

To directly compare age-related biomarker changes, previously reported mean cortical to pontine  $^{18}\text{F}$ -florbetapir standard uptake value ratios,<sup>5</sup> CSF A $\beta$ 1-42 and total tau levels, precuneus CMRgl, and hippocampal volume were transformed to a minimum-maximum standard scale from zero to one, with increasing values representing higher abnormalities in the mutation carriers (Figure 4). Best-fitting regression models were used. The CSF and PET measures of A $\beta$  pathology began to diverge in the carrier and noncarrier groups at the youngest ages, followed soon by changes in CSF total tau and  $^{18}\text{F}$ -fludeoxyglucose PET, with hippocampal volume and notable cognitive changes closer to the age at MCI onset.

## Discussion

This cross-sectional study characterized and compared age-associated brain imaging and CSF AD biomarker changes in *PSEN1* E280A mutation carriers and noncarriers, estimating the number of years these changes occur before the kindred's estimated median ages at MCI and dementia onset. Findings from this study are largely consistent with previous cross-sectional studies<sup>1-27</sup> comparing ADAD mutation carrier biomarkers with the age at symptom onset. Furthermore, our results are con-

Figure 4. Age and Biomarker Associations and Comparison of Age at Onset of Biomarker Changes



sistent with the recently updated hypothetical models by Jack and colleagues<sup>3</sup> regarding the sequence of progressive preclinical AD pathology, namely, CSF and PET measures of Aβ pathology followed by CSF measures of tau pathology and regional CMRgl decline, followed by hippocampal atrophy and clinical progression. In addition, this time line of pathophysiological events is consistent with a recent longitudinal biomarker study<sup>28</sup> in late-onset sporadic AD that demonstrated amyloid PET changes 17 years before and hippocampal changes 4 years before a CDR of 1, suggesting similarities in preclinical biomarker progression between ADAD and late-onset sporadic AD.

Most previous biomarker studies in ADAD have focused on individuals close to the age at clinical onset, with smaller cohorts (often from families with mixed mutations), and that largely reported on a single-biomarker modality. Advantages of the present analysis include having a cohort not only with a single genetic variant but also from the same race/ethnicity and general geographic location and with similar cultural influences. Controlling for these genetic and demographic variations may result in reduced variability of data and greater accuracy for predicting estimated ages at symptomatic onset and biomarker trajectories than is possible in studies of families with mixed mutations. The DIAN study<sup>1,27,29</sup> assessed the age at biomarker change in 88 mutation carriers, combining 51 different mutation pedigrees. Consistent with the DIAN and other ADAD studies, cognitively unimpaired *PSEN1* E280A mutation carriers had significantly elevated plasma Aβ1-42 irrespective of a person's age, lower CSF Aβ1-42, higher fibrillar Aβ,<sup>1</sup> higher CSF total tau and phosphorylated tau<sub>181</sub> measurements,<sup>1,30</sup> lower CMRgl in the precuneus,<sup>1,24,25,31</sup> and volumetric reductions in the hippocampus and AD-related regions.<sup>3,6,32,33</sup> A recent report<sup>27</sup> of longitudinal data from the DIAN study showed in-

creases in CSF tau before the estimated year at symptom onset but showed decreases at later stages of disease, suggesting a late slowing of the neurodegenerative process.

Understanding how different biomarkers progress over the course of disease is important for tracking disease progress, prediction of outcomes, and stage-specific clinical trial design, as well as choosing and monitoring treatment effect. The shapes of age-associated curves presented herein are supportive of the recently updated hypothetical models by Jack and colleagues,<sup>3</sup> stating that some biomarkers appear to have more linear trajectories than others, with CSF tau, <sup>18</sup>F-fludeoxyglucose PET, and MR imaging likely lacking in sharp increases and dramatic plateaus as is seen in amyloid PET. The CSF Aβ1-42 changes were seen before amyloid PET changes as well. Unlike the updated models by Jack and colleagues, we found more distinct separation between <sup>18</sup>F-fludeoxyglucose PET and MR imaging curves, both markers of neurodegeneration.

Significant limitations of this study include the use of cross-sectional data to provide only a rough estimate of longitudinal biomarker trajectories, as well as the extent to which our biomarker findings can be generalized to other ADAD mutations, Down syndrome, or late-onset AD. The small sample size contributes to uncertainty in the characterization of best-fitting curves and the estimation of ages at which biomarkers begin to change. The 95% CIs for CSF and PET biomarker age at change (Table 2) were at least partially overlapping, lacking statistical power to definitively distinguish age at onset between most biomarkers. In addition, estimated age at change in biomarkers could be influenced by the specific methods applied herein, such as the sensitivity of the imaging or assay methods to detect those changes as well as the thresholds used to characterize a change. In addition, there may be more sen-

sitive measures of preclinical and early clinical cognitive decline, such as composite cognitive tests.<sup>34</sup>

## Conclusions

Longitudinal studies are needed to further characterize and confirm the findings presented herein. This study and the

recently started Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease treatment trial aim to clarify the extent to which AD biomarkers change in association with age. These studies and others in presymptomatic AD provide guidance to predict subsequent clinical progression and differential treatment response and to accelerate the evaluation of putative preclinical AD treatments.

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