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# Temporal Dynamics of $\beta$ -Amyloid Accumulation in Aging and Alzheimer Disease

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## Abstract

### Objective

To understand the time course of  $\beta$ -amyloid ( $A\beta$ ) deposition in the brain, which is crucial for planning therapeutic trials of  $A\beta$ -lowering therapies in Alzheimer disease (AD).

### Methods

Two samples of participants from the Alzheimer's Disease Neuroimaging Initiative were studied with [ $^{18}\text{F}$ ]Florbetapir (FBP)  $A\beta$  PET and followed for up to 9 years. Sample A included 475 cognitively normal (CN) older people and those with mild cognitive impairment (MCI) and AD and sample B included 220 CN  $A\beta$ - individuals. We examined the trajectory of FBP over time in sample A and the incidence rate of conversion from negative to positive  $A\beta$  PET scans in sample B.

### Results

The relationship between time and brain  $A\beta$  was sigmoidal, taking 6.4 years to transition from amyloid negative to positive and another 13.9 years to the onset of MCI.  $A\beta$  deposition rates began to slow only 3.8 years after reaching the positivity threshold. The incidence rate for scan positivity was 38/1,000 person-years, and factors associated with conversion were age, baseline FBP, and being a female *APOE*  $\epsilon 4$  carrier. Among CN  $A\beta$ - individuals, FBP slopes were associated with rates of memory decline and brain tau measured with [ $^{18}\text{F}$ ]Flortaucipir PET 5 years after baseline.

### Conclusions

Lowering brain  $A\beta$  must be accomplished early in the evolution of AD. Transitions of PET scans from  $A\beta$ - to  $A\beta$ + should be predictable, and it is reasonable to expect that lowering rates of  $A\beta$  even in early stages could produce clinically significant benefits.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](https://adni.loni.usc.edu)). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at [links.lww.com/WNL/B308](https://links.lww.com/WNL/B308).

## Glossary

**A $\beta$**  =  $\beta$ -amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CN** = cognitively normal; **FBP** = [ $^{18}\text{F}$ ]florbetapir; **FTP** = [ $^{18}\text{F}$ ]flortaucipir; **FWHM** = full width at half maximum; **MCI** = mild cognitive impairment; **ROI** = region of interest; **SMC** = subjective memory complaints; **SUVR** = standardized uptake value ratio.

The clinical manifestations of Alzheimer disease (AD) are preceded by an incubation period of decades, when the aggregation of  $\beta$ -amyloid (A $\beta$ ) and tau proteins into pathologic forms likely plays a major role.<sup>1,2</sup> The amyloid hypothesis, a widely held model of disease pathogenesis, postulates that A $\beta$  is the earliest initiating event in this pathologic chain.<sup>3</sup> However, because many therapeutic trials have lowered brain A $\beta$  without producing clinical improvement in patients with AD, this model has been questioned.<sup>4,5</sup> In turn, new approaches have suggested the use of anti-A $\beta$  treatments before the development of symptoms and even before the detection of brain A $\beta$  deposition in a "primary prevention" approach.<sup>6</sup>

Such early initiation of treatment requires knowledge of the time course of brain A $\beta$  deposition. Most existing longitudinal amyloid PET studies have been limited by sample size and follow-up duration. The Alzheimer's Disease Neuroimaging Initiative (ADNI) began collecting serial amyloid [ $^{18}\text{F}$ ]florbetapir (FBP) PET scans in 2010 and has continued for some participants to the present. In this study, we used up to 6 serial FBP scans and a maximum follow-up time of 9 years to estimate longitudinal A $\beta$  trajectories in impaired and unimpaired individuals who are likely to be on the AD pathway in order to estimate the temporal dynamics of amyloid accumulation over the full spectrum of AD. We then focused on amyloid-negative cognitively unimpaired participants to examine the rate of conversion to amyloid positivity and the factors associated with conversion.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

The ADNI protocol was approved by local institutional review boards and written informed consent was obtained from all participants.

### Study Design and Participants

Individuals in this report include 2 overlapping samples with at least 2 FBP scans in each participant, based on data available as of April 2020. This study had multiple goals. The first was the description of amyloid accumulation through the full time course of AD, beginning with amyloid negativity and extending to mild cognitive impairment (MCI) and AD. For this purpose, we required a sample of individuals who were on the Alzheimer continuum; i.e., patients with A $\beta$ + MCI and AD.<sup>7</sup> In order to include cognitively normal (CN) people who were amyloid-negative but might be on the AD continuum, we selected those CN individuals with increasing FBP slopes (>0) over time

because many A $\beta$ - individuals may never accumulate amyloid. This comprised sample A, and included a total of 475 participants, of whom 336 were A $\beta$ + at baseline (88 CN, 101 early MCI, 101 late MCI, 46 AD), and 139 CN individuals who were A $\beta$ - at baseline with an increasing FBP slope.

Additional goals of the study were to define the rate of conversion from an A $\beta$ - PET scan to an A $\beta$ + PET scan, to compare the baseline characteristics of converters vs non-converters (including cognition, hippocampal volume, and glucose metabolism), to define baseline factors predicting conversion, and to examine how rates of A $\beta$  accumulation are related to cognitive change and tau deposition. These goals required a separate sample of individuals who were all CN and A $\beta$ - at baseline. These individuals, who comprised sample B, were 220 CN individuals with baseline A $\beta$ - scans (regardless of slope) followed for up to 6 scans total (minimum 1.9, maximum follow-up time 9.1 years). The group of CN participants included 23% of participants who were recruited with subjective memory complaints (SMCs).<sup>8</sup> Sample A and sample B included 139 CN individuals in common.

ADNI participant characteristics have been previously described; individuals diagnosed with AD and MCI and who met standard diagnostic criteria and all CN participants had CDR scores of 0.<sup>9</sup> All were between ages 55 and 90 years at baseline, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any other significant neurologic diseases.

### Florbetapir-PET Imaging and Analysis

FBP images consisted of 4  $\times$  5-minute frames acquired at 50–70 minutes postinjection that were realigned, averaged, resliced to a common voxel size (1.5 mm<sup>3</sup>), and smoothed to a common resolution of 8 mm<sup>3</sup> full width at half maximum (FWHM). T1 MRI (magnetization-prepared rapid gradient echo) acquired concurrently with the baseline florbetapir images were used as a structural template to define cortical and reference regions in native space for each individual using Freesurfer (v5.3.0), as described previously.<sup>10</sup>

Baseline and follow-up florbetapir scans, acquired at approximately 2-year intervals, were coregistered to the baseline structural MRI scans used to calculate weighted cortical retention means from frontal, cingulate, parietal, and temporal regions that were averaged to create a cortical summary region. FBP means at each time point from this cortical summary region were divided by corresponding means of a composite reference region comprised of brainstem, whole

**Table 1** Characteristics of Cognitively Normal (CN) and Cognitively Impaired Participants Used to Estimate Amyloid Trajectories Over Time (Sample A)

	CN Aβ <sup>-</sup> /increasing slope	CN Aβ <sup>+</sup>	Cognitively impaired Aβ <sup>+</sup>
<b>N</b>	139	88	248
<b>SMC</b>	23	23	—
<b>EMCI/LMCI/AD</b>	—	—	37/28/35
<b>Age, y</b>	73.8 ± 6.7	75.7 ± 6.5	74.4 ± 7.6
<b>Sex, F</b>	56	62	45
<b>Education, y</b>	16.6 ± 2.5	16.4 ± 2.6	15.8 ± 2.8
<b>APOE ε4 carriers</b>	27	50	69
<b>FBP follow-up time, y</b>	4.7 ± 2.3	4.3 ± 2.1	3.6 ± 1.9
<b>% With 2/3/4/5/6 FBP scans</b>	36/26/27/11/<1	36/25/22/10/0	51/28/13/8/1/0

Abbreviations: AD = Alzheimer disease; EMCI = early mild cognitive impairment; FBP = [<sup>18</sup>F]florbetapir; LMCI = late mild cognitive impairment; SMC = subjective memory complaints. Values are % or mean ± SD.

cerebellum, and eroded WM that is optimized for longitudinal analyses.<sup>10</sup> Annualized rates of change (change in cortical summary standardized uptake value ratio [SUVR] units per year) were calculated for each individual using linear regression. In order to facilitate comparison of our results to other reference regions and PET tracers, SUVRs were converted to Centiloids,<sup>11</sup> with a modification to account for the composite reference used in this study. Specifically, we carried out an SUVR to Centiloids linear transformation to convert whole cerebellum-based SUVRs to whole cerebellum-based Centiloids as documented on the ADNI website (Centiloids = 196.9 × SUVR<sub>wholecerebrumFBP</sub> - 196.03) using all ADNI participants with a baseline FBP scan (489 CN, 585 MCI, and 220 AD). To adapt this approach for use with the composite reference region, we used the same participants and scans to calculate the best fit linear regression equation to convert composite reference-based SUVRs to composite reference-based Centiloids (Centiloids = 287 × SUVR<sub>compositerefFBP</sub> - 210).

### Determination of Amyloid Positivity

An Aβ positivity threshold of 0.82 (25.3 Centiloids/composite reference region) corresponds to the ADNI standard whole cerebellum-based florbetapir positivity threshold of 1.11 and is based on the mean and SD of young controls processed with the ADNI pipeline.<sup>12</sup>

### Structural Volumes and Glucose Metabolism

Hippocampal volume was defined on T1-weighted images acquired with the baseline florbetapir scan using Freesurfer v5.3 and adjusted using the association between hippocampal volume and total intracranial volume in healthy controls<sup>13</sup> to account for head size. Glucose metabolism measurement used preprocessed FDG-PET images concurrent with the baseline florbetapir scans spatially normalized to the standard <sup>15</sup>O-H<sub>2</sub>O PET template using SPM5. Mean FDG uptake

quantitation for each individual used study-independent and previously validated meta-regions of interest (ROIs) averaged together and divided by the mean of a pons and cerebellar vermis reference region.<sup>14</sup>

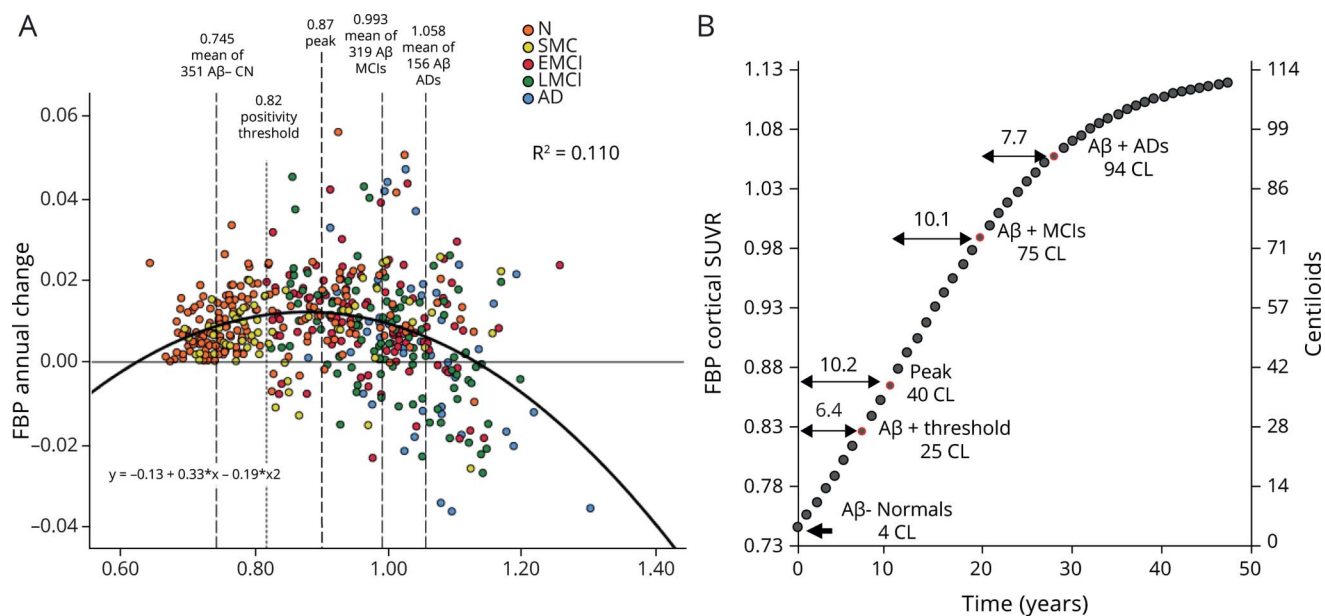
### Tau PET Scans

[<sup>18</sup>F]Flortaucipir (FTP)-PET images consisted of 6 × 5-minute frames acquired at 75–105 minutes postinjection, which were realigned, averaged, resliced to a common voxel size (1.5 mm<sup>3</sup>), and smoothed to a common resolution of 8 mm<sup>3</sup> FWHM (adni-info.org). FTP scans were coregistered to a contemporaneous MRI scan, and FTP SUVRs in the following Freesurfer-defined regions were calculated relative to inferior cerebellar gray matter uptake<sup>15</sup>: entorhinal cortex (Braak 1), temporal composite (entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal),<sup>16</sup> and extratemporal neocortex (Braak 56).

### Cognitive Assessments

We used previously validated longitudinal memory and executive function composite scores from the University of Washington that were derived from the ADNI neuropsychological battery using a nearly nonoverlapping sample of 800 ADNI normal controls, participants with MCI, and participants with dementia.<sup>17,18</sup> Composite scores had a mean of 0 and SD of 1 at baseline for the individuals in this sample. These composite scores were developed to address the varying difficulty of different word lists within the Auditory Verbal Learning Test and the Alzheimer's Disease Assessment Scale-cognitive subscale, which may affect the accuracy of measuring subtle differences in cognition cross-sectionally (between participants) and longitudinally (within participant). The mean follow-up time for longitudinal cognitive measurements was 4.9 ± 1.6 years. In addition, all participants underwent clinical follow-up at least annually, and status

**Figure 1** Time Course of  $\beta$ -amyloid ( $A\beta$ ) Accumulation for Individuals on the Alzheimer disease (AD) Pathway



(A) Cortical [ $^{18}$ F]florbetapir (FBP) annual change (composite reference region) is shown as a function of baseline FBP for all participants who are likely to be on the AD pathway. (B) The best-fit quadratic equation was used to estimate  $A\beta$ -related events on the AD pathway. Each point reflects 1 year of time with important temporal landmarks in red. CL = Centiloids; CN, N = cognitively normal; EMCI = early mild cognitive impairment; LMCI = late mild cognitive impairment; MCI = mild cognitive impairment; SMC = subjective memory complaints; SUVR = standardized uptake value ratio.

change (to MCI or dementia) was determined according to standard ADNI methods.<sup>9</sup>

### Cardiovascular and Other Risk Factor Assessment

At the baseline visit, all participants underwent a medical interview. We searched recorded text fields from this interview for the presence of standard cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and any smoking history. Participants were administered the Geriatric Depression Scale<sup>19</sup> and antidepressant use was recorded. This information was examined as dichotomous categories (except for depression) in relationship to subsequent conversion from amyloid negative to positive.

### Statistical Methods

We fit linear and quadratic equations to FBP slopes as a function of baseline FBP values for sample A participants and used the best-fitting equation to model approximate time between phases of  $A\beta$  accumulation. Starting from the average SUVR in the  $A\beta$ - CN subjects as time = 0 we used this equation to estimate the annual SUVR increase and plotted time vs SUVR to model this relationship. Subsequent analyses examined only baseline  $A\beta$ - CN participants (sample B). An individual was considered an amyloid “converter” if he or she had a baseline negative scan, crossed the threshold, and remained positive for subsequent FBP scans. Group differences between converters and nonconverters were examined using independent-samples *t* tests (continuous variables) and  $\chi^2$  tests (categorical variables) at  $\alpha = 0.05$ .

We examined regionwise baseline FBP comparisons between subsequent converters and nonconverters in 68 right and left subregions making up the cortical summary region used to determine  $A\beta$  positivity (see above). These comparisons used linear regression models to identify converter/nonconverter group differences (effect of interest) with age, sex, *APOE*  $\epsilon 4$  status, total FBP follow-up time, and number of scans as additional covariates ( $\alpha = 0.05$ , Bonferroni-Holm correction for multiple comparisons).

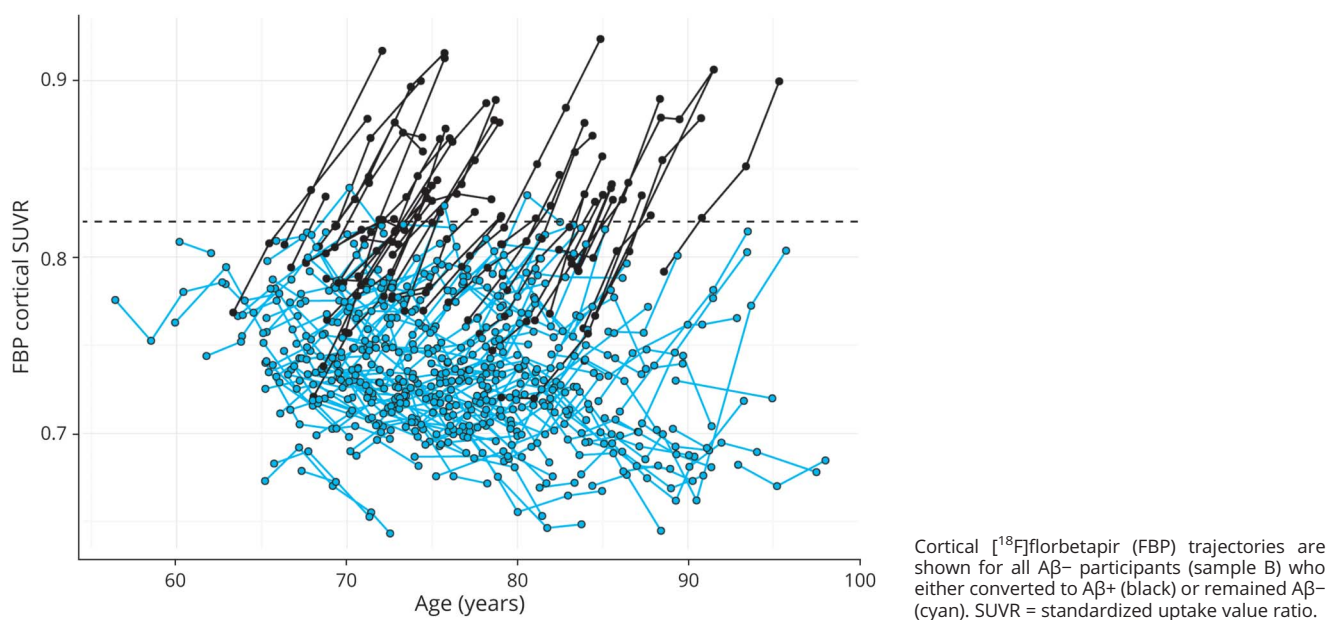
We examined continuous and dichotomous predictors of conversion to FBP-positive status using a Cox proportional hazards model, with age, presence of SMC, sex, *APOE*  $\epsilon 4$  status, baseline FBP, and baseline memory scores as predictors. The baseline FBP variable was modeled using continuous SUVRs and, separately, Centiloids categorized in 6 intervals of 5 Centiloids (<0, 0–5, 5–10, 10–15, 15–20, 20–25).

Linear regression models were carried out predicting subsequent tau with the following independent variables: annualized FBP slopes, baseline FBP, age, sex, education, and *APOE*  $\epsilon 4$ . Separate models were examined with entorhinal (Braak 1), temporal composite, and extratemporal neocortical tau (Braak 56) regions as outcomes.

Linear mixed effects models were carried out predicting, separately, time-varying longitudinal memory and executive function composite scores. Independent variables included time, age, sex, education, *APOE*  $\epsilon 4$ , presence of SMC, baseline



**Figure 2** Longitudinal  $\beta$ -amyloid ( $A\beta$ ) Trajectories for Cognitively Normal, Baseline  $A\beta$ -Negative Individuals



FBP, FBP slope, age  $\times$  time, sex  $\times$  time, *APOE*  $\epsilon 4 \times$  time, presence of SMC  $\times$  time, baseline FBP  $\times$  time, and FBP slope  $\times$  time, with a random effect of subject and an autoregressive covariance structure for repeated measurements.

### Data Availability

All data used in this article are available to the public at the ADNI data repository at the Laboratory of Neuroimaging ([adni.loni.usc.edu](http://adni.loni.usc.edu)). Derived data are available from the authors upon request.

## Results

Characteristics of sample A participants used to estimate the amyloid trajectory are shown in table 1.

### Temporal Dynamics of $A\beta$ Across the Spectrum of AD

We examined FBP slopes as a function of baseline FBP SUVRs for individuals in sample A. The quadratic function accounted for more variability ( $R^2 = 0.110$ ) than a linear model ( $R^2 = 0.028$ ) (figure 1A), so we used the quadratic equation ( $y = -0.19x^2 + 0.33x - 0.13$ ) to estimate time between phases of  $A\beta$  accumulation (figure 1B): 6.4 years from the mean of  $A\beta$ - cognitively normal participants (SUVR 0.745/SD 0.036, 4 Centiloids) to reach the FBP threshold (0.82, 25 Centiloids), 13.9 additional years from the threshold to the mean of  $A\beta$ + MCI participants (0.993; 75 Centiloids), and an additional 7.7 years to reach the mean of  $A\beta$ + AD participants (1.058; 94 Centiloids). The peak of this quadratic function and the inflection point of the sigmoidal function occurred at a baseline value of 0.87 SUVR (39 Centiloids) at an annual increase of 0.013 SUVR/year, indicating

that the rate of amyloid accumulation begins to slow only 3.8 years after conversion to amyloid positivity and well before the typical MCI level. Among the 248  $A\beta$ + impaired participants included in this analysis, 222 (90%) were past the  $A\beta$  accumulation peak; 70/227 (31%) of the  $A\beta$ + or  $A\beta$ - but increasing CN participants were past the peak. Whereas individuals on the descending limb of this function showed slowing rates of  $A\beta$  accumulation, some even showed evidence of negative slopes, indicating  $A\beta$  removal.

We evaluated several variables that can affect these estimates. Assuming that the starting SUVR for CN/ $A\beta$ - participants was either 1 SD lower or 1 SD higher than the mean increased or decreased the time to the threshold (10.2 vs 3.1 years) but had no effect on the relative timing of events. Restricting the sample to CN individuals who ultimately became  $A\beta$ + produced a time to threshold of 5.2 years and a time to peak of 8.6 years, whereas limiting the sample to those with an FBP slope greater than a previously defined test-retest reliability value ( $>1\%$ )<sup>10</sup> produced a time to threshold of 3.4 years and time to peak of 5.6 years.

We examined the 292 individuals with baseline FBP higher than the peak ( $>0.87$ ) in order to determine whether the decreasing and negative FBP slopes in some of those individuals reflect true decreases in the rate of amyloid accumulation or whether they are an artifact of atrophy or longitudinal increases in the composite reference region. FBP slope was not correlated with change in frontal, cingulate, temporal, or parietal volumes ( $R^2$  range 0.0004–0.02). In the same individuals, FBP slope calculated using the composite reference region was highly correlated with FBP slope calculated using a nonoverlapping cerebellar GM reference

**Table 2** Characteristics of Cognitively Normal, Baseline  $\beta$ -Amyloid ( $A\beta$ )– Participants (Sample B)

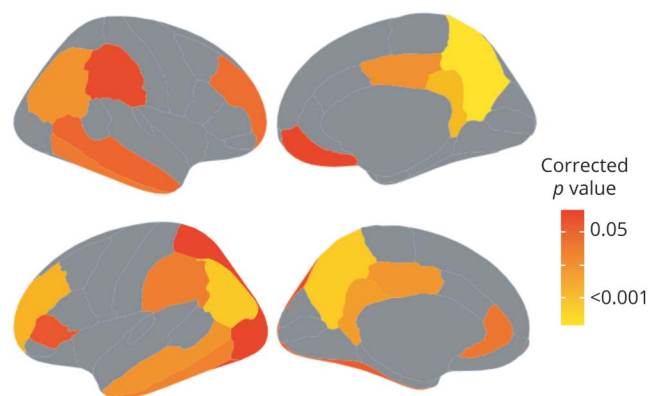
	Nonconverters	Converters	Group difference
<b>N</b>	178	42	
<b>Participant characteristics</b>			
SMC	41 (23)	13 (31)	
Age, y	73.7 $\pm$ 6.7	74.6 $\pm$ 6.4	
Sex, F	79 (44)	27 (64)	0.02
Education, y	16.8 $\pm$ 2.6	16.1 $\pm$ 2.4	0.095
APOE $\epsilon$ 4 carriers	32 (18)	14 (33)	0.028
APOE $\epsilon$ 2 carriers	30 (17)	6 (14)	
<b>Baseline and longitudinal <math>A\beta</math></b>			
Florbetapir PET follow-up time, y	5.2 $\pm$ 2.3	5.6 $\pm$ 2.0	
Florbetapir PET follow-up time to conversion, y	—	4.1 $\pm$ 1.8	NA
% With 2/3/4/5/6 FBP scans	26/29/29/16/<1	19/24/43/12/2	
Baseline amyloid cortical SUVR (composite ref)	0.74 $\pm$ 0.03	0.78 $\pm$ 0.02	<0.001
Baseline amyloid cortical uptake (Centiloids)	1.5	13.3	<0.001
Amyloid annual change (composite ref)	0.000 $\pm$ 0.005	0.014 $\pm$ 0.004	NA
<b>Baseline and longitudinal cognitive performance</b>			
Converted to MCI during follow-up	21 (12)	5 (12)	
Converted to AD during follow-up	4 (2)	1 (2)	
Follow-up time on cognition	4.8 $\pm$ 1.6	5.2 $\pm$ 1.5	
% With 2/3/4/5/6/7/8/9 cognitive measurements	1/7/21/30/30/8/2/<1	2/10/14/29/26/19/0/0	
Executive function composite	1.05 $\pm$ 0.79	0.97 $\pm$ 0.89	
Memory composite	1.15 $\pm$ 0.59	1.17 $\pm$ 0.59	
<b>Other biomarkers and risk factors</b>			
Temporoparietal FDG SUVR	1.32 $\pm$ 0.11	1.32 $\pm$ 0.12	
Hippocampal volume (adjusted), mm <sup>3</sup>	5,870 $\pm$ 1,127	6,018 $\pm$ 1,085	
FTP SUVR (entorhinal cortex) 5 years postbaseline <sup>a</sup>	1.12 $\pm$ 0.10	1.19 $\pm$ 0.13	0.004
FTP SUVR (temporal composite) 5 years postbaseline <sup>a</sup>	1.18 $\pm$ 0.08	1.23 $\pm$ 0.13	0.016
Smoking status	29 (16)	8 (19)	
Diabetes	20 (11)	2 (5)	
Hyperlipidemia	78 (44)	14 (33)	
Hypertension	89 (50)	17 (41)	
Cholesterol	193 $\pm$ 39	197 $\pm$ 33	
Antidepressant use	19 (14)	4 (12)	
Geriatric Depression Scale	0.93 $\pm$ 1.3	0.68 $\pm$ 0.88	

Abbreviations: AD = Alzheimer disease; FBP = [<sup>18</sup>F]florbetapir; FTP = [<sup>18</sup>F]flortaucipir; MCI = mild cognitive impairment; SMC = subjective memory complaints; SUVR = standardized uptake value ratio.

Values are n (%) or mean  $\pm$  SD. Significant ( $p < 0.05$ ) and marginally significant ( $0.05 < p < 0.10$ ) differences are shown comparing participants who subsequently converted to  $A\beta$ + vs those who did not convert.

<sup>a</sup> Data available in 55% of participants.

**Figure 3** Baseline Regional  $\beta$ -amyloid ( $A\beta$ ) Elevations



Regions in which [ $^{18}$ F]florbetapir (FBP) was higher at baseline in cognitively normal,  $A\beta^-$  participants who subsequently converted to  $A\beta^+$  compared to participants who did not convert (all  $p < 0.05$ , Bonferroni-Holm correction).

region ( $R^2 = 0.67$ ), indicating that longitudinal WM-related increases in the composite reference region are unlikely to explain the decreases we observed in the cortical summary ROI.

### Conversions to $A\beta$ Positive Status

The 220 CN participants in sample B who were  $A\beta^-$  at baseline had serial florbetapir scans for a minimum of 1.9 and maximum of 9.1 years (mean  $5.3 \pm 2.2$  years). Forty-two participants (19%) converted from  $A\beta^-$  to  $A\beta^+$  and remained  $A\beta^+$  at their last PET visit (figure 2). Conversion from  $A\beta^-$  to  $A\beta^+$  occurred at a mean of  $4.1 \pm 1.8$  years following the baseline scan. Three additional individuals converted from  $A\beta^-$  to  $A\beta^+$  but reverted to  $A\beta^-$  by their last PET visit and were not included as converters in these analyses. The crude incidence rate of conversion to  $A\beta^+$  status was 38 per 1,000 person-years of follow-up (42 converters over 1,093 total person-years). Figure 2 shows the trajectories of all participants who remained  $A\beta^-$  compared to those who converted. Converters included some individuals whose baseline scans showed SUVRs close to the threshold, but also many individuals with starting values that were well below the threshold. The trajectories of converters were for the most part unambiguously positive, showing little evidence of fluctuating values, a pattern that was more common in those who remained  $A\beta^-$ .

Table 2 shows the characteristics of sample B individuals who converted amyloid status or remained stable. Compared with the nonconverter group, the converter group included a significantly larger proportion of women and  $APOE \epsilon 4+$  individuals, but did not differ on age, education,  $APOE \epsilon 2$  status, total PET follow-up time, baseline cognitive function measured by the memory or executive function composites, conversions to a clinical diagnosis of MCI or dementia, or cardiovascular and health risk factors. Converters showed elevated baseline  $A\beta$  compared to nonconverters with a mean

Centiloid value of 13.3 compared to 1.5. The annual rate of change in the nonconverters averaged 0 (SD 0.005) SUVR/year and 0.14 (SD 0.004) in the converters. Among the 88/178 nonconverters who had positive  $A\beta$  slopes (but remained  $A\beta^-$ ), the annual rate of change was 0.006 (SD 0.004), which was 40% the magnitude of the increase among converters. There were no differences between groups on baseline FDG-PET or hippocampal volume.

### Regional FBP Baseline Elevations in Subsequent Converters

We identified brain regions that were already elevated in baseline  $A\beta^-$  participants who subsequently converted to  $A\beta^+$  compared with nonconverters. Participants who later converted were higher at baseline than nonconverters in 22 right and left temporal, medial and lateral parietal, cingulate, and medial and lateral orbitofrontal regions (figure 3).

### Predictors of Conversion

Initial Cox proportional hazard models did not show effects of sex and  $APOE \epsilon 4$ ; however, because these variables both differed between converters and nonconverters at baseline, we added an interaction term to the model. Results indicated that baseline florbetapir (measured as either continuous or as 6 ordinal Centiloid intervals) and older age were predictors of conversion (table 3). Compared with the lowest Centiloid group ( $<0$  Centiloids;  $n = 62$ ), all groups with baseline  $A\beta^-$  values at or above 5 Centiloids were at significantly greater risk of conversion during follow-up (figure 4A). Each decade increase in age above the mean was associated with an 11-fold greater risk of conversion (figure 4B). The sex  $\times$   $APOE \epsilon 4$  interaction was significant ( $p = 0.031$ ), and follow-up pairwise log rank tests indicated that  $APOE \epsilon 4-$  men and women did not differ ( $\chi^2 = 1.7, p = 0.19$ ) but  $APOE \epsilon 4+$  women were 3.22 times more likely to convert than  $APOE \epsilon 4+$  males ( $\chi^2 = 4.2, p = 0.039$ ; figure 4C).

Because baseline FBP was the major predictor of conversion, we examined the factors that were associated with elevated FBP within the negative range. In a regression model with the same predictors used in the proportional hazards model (except sex  $\times$   $APOE \epsilon 4$ , which was not significant and was removed from the model), female sex ( $\beta = 0.02, SE = 0.004, p = <0.001$ ), age ( $\beta = -0.001, SE < 0.001, p = 0.011$ ),  $APOE \epsilon 4$  positivity ( $\beta = 0.011, SE = 0.006, p = 0.047$ ), and marginally, presence of SMC ( $\beta = 0.01, SE = 0.005, p = 0.066$ ) were associated with elevated FBP.

### FBP Relationships With Subsequent Tau and Longitudinal Cognitive Measurements

Sample B CN participants had a minimum of 2 and a maximum of 9 years follow-up memory and executive function measurements over  $4.9 \pm 1.6$  years. We carried out mixed effects models with baseline FBP, FBP slope, age, education,  $APOE \epsilon 4$ , sex, and presence/absence of SMC as predictors of longitudinal memory. Only age ( $\beta = -0.004, SE = 0.001; p < 0.001$ ) and FBP slope ( $\beta = 1.50, SE = 0.749; p = 0.046$ ) and



**Table 3** Results of Cox Proportional Hazard Model

	Coeff	Cox HR	95% CI	p Value
<0 Centiloids (reference)		—	—	—
0–5 Centiloids	1.56	4.75	0.62–36.39	0.134
5–10 Centiloids	2.96	19.28	3.26–113.92	0.001
10–15 Centiloids	4.42	82.96	14.45–476.22	<0.001
15–20 Centiloids	4.34	76.60	13.71–428.01	<0.001
20–25 Centiloids	5.32	203.93	32.12–1,294.55	<0.001
Presence of SMC	0.63	0.53	0.26–1.12	0.097
<i>APOE</i> ε4	–0.88	0.41	0.12–1.49	0.177
Age	0.11	1.12	1.06–1.18	<0.001
Sex	–0.53	0.59	0.26–1.34	0.208
<i>APOE</i> ε4 × sex	1.70	5.47	1.17–25.5	0.031

Abbreviation: CI = confidence interval.

Model coefficients and corresponding hazard ratios (HRs) are shown with reference to a 74-year-old *APOE* ε4– cognitively normal man without a subjective memory complaint (SMC) with a baseline Centiloid value < 0.

marginally *APOE* ε4 ( $\beta = 0.024$ , SE = 0.01;  $p = 0.097$ ) predicted longitudinal decreases in memory composite scores. In a similar model examining longitudinal executive function outcomes, only age ( $\beta = -0.006$ , SE = 0.002;  $p = 0.005$ ) (and not *APOE* ε4, or baseline or longitudinal A $\beta$ ) predicted executive function decreases. To further investigate whether the subset of participants who converted to A $\beta$ + drove these effects, we re-examined these analyses without the converters with no substantive changes to the findings.

Fifty-five percent of sample B participants (93/178 non-converters and 28/42 converters) had FTP PET scans an average of  $5.3 \pm 1.4$  years after their baseline FBP PET scan. Among participants who converted to A $\beta$ +, conversion occurred  $0.6 \pm 1.7$  years before the FTP scan. In a regression model with baseline FBP, FBP slope, age, *APOE* ε4, sex, and presence/absence of SMC predicting entorhinal tau, only FBP slope was a significant predictor of entorhinal tau ( $\beta$  3.23, SD 1.3,  $p = 0.018$ ; overall model R<sup>2</sup> = 0.097). None of the variables was a significant predictor of the temporal composite or extratemporal neocortical tau (Braak 56) (all  $p > 0.05$ ).

## Discussion

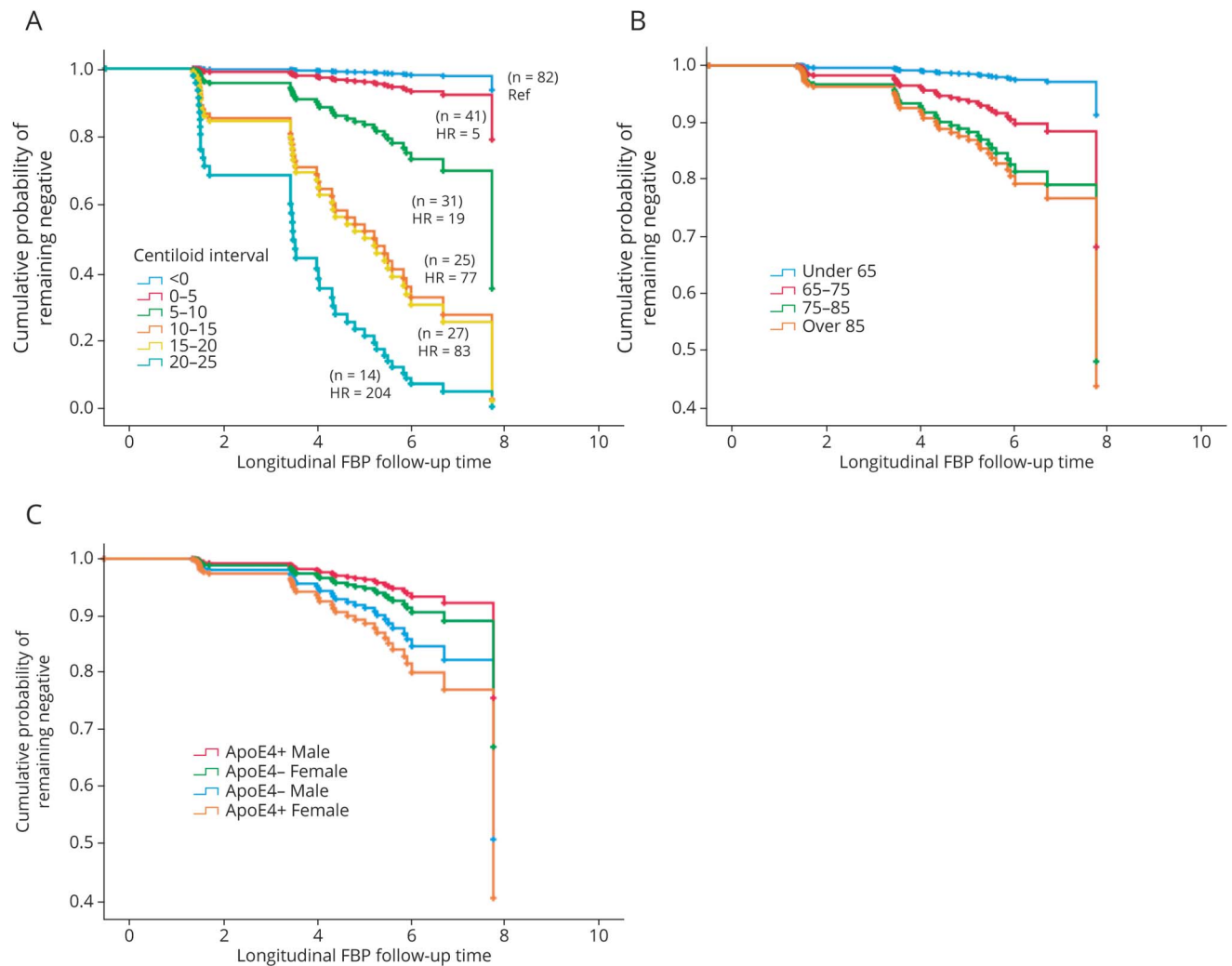
The long incubation period of AD, combined with the availability of brain biomarkers that can track protein aggregation, neurodegeneration, and cognition, provides a rare opportunity to track the evolution of disease. Whereas such studies have been possible for a while, small sample sizes and short follow-up durations have been limiting. In this report, we evaluated 1,659 longitudinal FBP scans in 782 participants and found evidence for a slowing of the rate of amyloid accumulation that occurs about 4 years after conversion from amyloid negative to

positive and 10 years before the average diagnosis of MCI. The time-varying accumulation of A $\beta$  conforms to hypothesized sigmoidal trajectories<sup>20</sup> as well as previous reports<sup>21–24</sup> indicating periods of about 20 years to progress from the amyloid positivity threshold to an A $\beta$  level typical of AD. Our results differ in showing very early deceleration of A $\beta$  deposition, which is a crucial observation in contemplating anti-amyloid therapies. Expecting clinical benefit through A $\beta$  removal when patients are diagnosed with MCI or clinical AD—10 to 18 years after the rate of accumulation has already begun to slow—may be unrealistic. On the other hand, we were able to detect memory change associated with FBP increases in CN participants in the amyloid negative range, offering the hope that an effective A $\beta$ -slowing intervention at an early stage could produce measurable cognitive benefit.

These findings may also explain the frequent observation in cross-sectional data that brain A $\beta$  deposition is bimodal, with few individuals near the actual threshold.<sup>25</sup> Whereas this reflects in part the likelihood that some individuals are not on a pathway to AD, it may also be a consequence of rapid A $\beta$  accumulation at the time of transition from negative to positive. This is also consistent with animal data showing that A $\beta$  aggregation follows a sigmoidal shape over time, including negative growth rates.<sup>26</sup> The detection of negative FBP slopes in individuals with higher baseline FBP values suggests the possibility that at late stages, the balance between A $\beta$  deposition and clearance becomes altered in humans, possibly related to diminished neural activity releasing A $\beta$ ,<sup>27</sup> or to increased immune clearance.

In those individuals who were amyloid-negative at baseline, the rate of amyloid deposition as measured with FBP slope

**Figure 4** Baseline Variables That Increase the Risk of Conversion to  $\beta$ -Amyloid ( $A\beta$ )<sup>+</sup>



Survival functions show (A) elevated risk of conversion with elevated [<sup>18</sup>F]florbetapir (FBP) shown as 5-Centiloid intervals (>0) relative to the reference group (Centiloids <0). (B) Older age (note that age was a continuous variable in the proportional hazards model but is shown as categorical for illustration purposes) and (C) increased risk of conversion among female versus male *APOE*  $\epsilon$ 4 carriers. HR = hazard ratio.

was related to subsequent cognitive decline and tau deposition. This cognitive decline was specific to memory. Previous reports, using both different subgroups of ADNI participants and other cohorts, have provided evidence that higher or rising brain  $A\beta$  even in the negative range is associated with harmful outcomes in terms of both brain tau and cognition.<sup>24,28-30</sup> Crucially, the combination of this observation with the finding that brain  $A\beta$  accumulation begins to slow before the onset of dementia is strong evidence that the detrimental effects of  $A\beta$  occur very early in the course of the disease. However, a very small proportion of participants developed MCI or dementia during the period of observation, so the clinical implications of these changes within the follow-up time of the study are not clear.

There are relatively few published estimates of incidence rates of amyloid PET positivity and they vary considerably, ranging from 3%/year<sup>31</sup> to 12%/year.<sup>32,33</sup> These rates are age-

dependent, but published data and our data are roughly comparable in age. Our estimate of 38/1,000 person-years, or about 4%/year, is thus on the lower end of reports. Although our sample size for estimating incidence rates ( $n = 220$ ) was smaller than our sample estimating rates of  $A\beta$  deposition over the entire spectrum of disease progression, individuals were followed on average for over 5 years; previous reports were in the range of 2.5 years. Longer observation may be particularly important in detecting conversions in those with starting FBP values that are further from the threshold; one might expect this to increase conversion rates. Thus, the low rates of amyloid conversion are surprising in our data.

The factors associated with conversion of PET scans from amyloid-negative to positive were not surprising. At baseline, subsequent converters were more likely to be female, *APOE*  $\epsilon$ 4 carriers, and have higher baseline FBP values. In contrast to a recent report using a different ADNI sample to examine

amyloid conversion,<sup>34</sup> we did not find that cognition was lower at baseline among subsequent converters, possibly because our sample was limited to CN controls. Measurements of neurodegeneration, depression, and cardiovascular risk factors were also no different between converters and non-converters at baseline, consistent with the hypothesis that these processes are either independent of, or sequential to, elevated brain A $\beta$ .

Accounting for time to conversion in the proportional hazard model shows that baseline FBP values, even if slightly elevated—above 5 Centiloids—greatly increased the risk of conversion. The sex  $\times$  *APOE* genotype interaction parallels results from large meta-analytic studies indicating stronger effects of the  $\epsilon 4$  allele for AD risk in women.<sup>35,36</sup> Increasing rate of conversion is also congruent with the prevailing view that *APOE*  $\epsilon 4$  accelerates the onset of AD to earlier ages.

Similar factors were related to higher baseline FBP, with the addition that those with SMC showed higher levels. Regional FBP PET values at baseline revealed a number of brain regions that were elevated in those who subsequently converted, suggesting regions that might be useful early. However, there were many such regions found in medial and lateral frontal and parietal lobes as well as inferior temporal cortex, raising the question as to which might be the “best” predictor of subsequent amyloid change. Many previous studies have selected varying combinations of these regions as best predictors of future A $\beta$  accumulation using ADNI data,<sup>37–40</sup> suggesting that there may be no single region that is invariably the best predictor given variability in samples, follow-up, and PET methods such as ligands and SUVR quantification.

The strengths of this study largely relate to the sample size, which was large for estimation of rates of change in FBP and moderate for estimation of conversion, and the follow-up time, which averaged 5 years and extended up to 9 years. We further examined possible methodologic factors that could underlie the deceleration and negative slopes of A $\beta$  accumulation and found no evidence that either longitudinal brain atrophy or changes in the PET reference region were driving these effects. Other strengths include the measurement of multiple biomarkers in the sample and the finding that multiple statistical approaches converged on similar indicators of amyloid progression. The major limitation of the study is the composition of the ADNI cohort itself, which is not fully representative of older individuals and individuals with dementia in the United States. In addition, some participants were enrolled in earlier phases of ADNI, before amyloid PET imaging was available, so that selective retention and dropout could mean that this is an unusually healthy group of people. Estimation of A $\beta$  trajectories included amyloid-negative individuals with rising levels of brain A $\beta$  in order to select a more “at risk” group for the modeling. However, many of these individuals may not be true amyloid accumulators and may never reach critical thresholds, or this may exclude

individuals who eventually progress. In addition, these trajectories are averages and include substantial variability based on the characteristics of the sample and a number of assumptions, including the proportion of A $\beta$ - individuals on the AD pathway, and the proportion of *APOE*  $\epsilon 4$  carriers.<sup>41</sup> We evaluated a number of these factors, such as the definition of the A $\beta$ - group, and found that some had modest effects on the timing estimates. Whereas many of these factors may contribute to underestimations or overestimations of the rates of amyloid deposition and conversion, the depicted results provide a reasonable estimate of event timing on the A $\beta$  pathway.

These findings indicate that among baseline amyloid-negative individuals, the rate of A $\beta$  deposition is related to later tau deposition and memory decline. As A $\beta$  accumulation continues past the threshold, accumulation begins to slow before overt clinical symptoms develop. The implications for amyloid-lowering therapies are obvious: they must occur very early, prior to or near the point of transition to amyloid-positive. On a more optimistic note, selection of amyloid-negative individuals to participate in such trials is practicable by using well-known variables that we confirm are associated with a likelihood of amyloid conversion including older age, female sex, *APOE* genotype, and higher baseline A $\beta$ . The presence of SMCs may also help establish higher baseline A $\beta$ . Findings that amyloid deposition rates are correlated with rates of memory decline and subsequent tau offer the hope that slowing A $\beta$  deposition could yield a cognitively meaningful outcome, even in amyloid-negative people. The findings in this report argue for the importance and feasibility of targeting anti-amyloid therapies to amyloid-negative individuals.

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<b>William J. Jagust, MD</b>	University of California Berkeley	Study design, drafting and editing the manuscript, interpretation of results, obtaining funding, study supervision
<b>Susan M. Landau, PhD</b>	University of California Berkeley	Study design, drafting and editing the manuscript, interpretation of results, data and statistical analysis

## Appendix 2 Coinvestigator

Coinvestigators are listed at <http://links.lww.com/WNL/B308>

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