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Individual estimates of age at detectable amyloid onset for risk factor assessment

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Abstract

INTRODUCTION—Individualized estimates of age at detectable amyloid-beta ($A\beta$) accumulation, distinct from amyloid positivity, allow for analysis of onset age of $A\beta$ accumulation as an outcome measure to understand risk factors.

METHODS—Using longitudinal Pittsburgh compound B (PiB) PET data from Baltimore Longitudinal Study of Aging, we estimated the age at which each PiB+ individual began accumulating $A\beta$. We used survival analysis methods to quantify risk of accumulating $A\beta$ and differences in onset age of $A\beta$ accumulation in relation to *APOE* $\epsilon 4$ status and sex among 36 *APOE* $\epsilon 4$ carriers and 83 non-carriers.

RESULTS—Age at onset of $A\beta$ accumulation for the *APOE* $\epsilon 4$ – and $\epsilon 4$ + groups was 73.1 and 60.7, respectively. *APOE* $\epsilon 4$ positivity conferred a 3-fold risk of accumulating $A\beta$ after adjusting for sex and education.

DISCUSSION—Estimation of onset age of amyloid accumulation may help gauge treatment efficacy in interventions to delay symptom onset in Alzheimer's disease.

Keywords

APOE; Pittsburgh compound B; PET; amyloid imaging; age at onset

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INTRODUCTION

Cerebral amyloid-beta (A β) deposition is the defining characteristic of preclinical stages of Alzheimer's disease (AD) [1] and begins years before cognitive symptoms are evident [2]. The apolipoprotein E (*APOE*) ϵ 4 allele is the most influential known genetic risk factor for late-onset AD [3,4], and is associated with higher cortical A β burden in cognitively normal individuals [5–23].

Age at onset of AD is a phenotype of great clinical interest, as delaying onset will decrease population prevalence and disease burden [24]. Furthermore, finding characteristics associated with onset age might provide clues about disease mechanisms. Among AD risk genes, *APOE* exhibits the strongest relationship with the age at onset of AD [25,26], with the presence of one or more ϵ 4 alleles shifting the onset to earlier ages [27]. However, studies of *APOE* in relation to onset age of AD-related neuropathology are limited. Two cross-sectional studies [7,22] and a recent meta-analysis [23] have shown that A β deposition is more likely at younger ages in groups of *APOE* ϵ 4 carriers compared with non-carriers, suggesting an earlier age at onset of A β accumulation. However, the effect of *APOE* genotype on the age at onset of A β accumulation at the individual level has not been investigated. Individualized estimates of the age at onset of A β accumulation will allow for the analysis of onset age as an outcome measure to understand the effects of risk factors.

Here, we use longitudinal Pittsburgh compound B (PiB) positron emission tomography (PET) scans from the Baltimore Longitudinal Study of Aging to estimate the age at which each individual with A β pathology began exhibiting increases in cortical fibrillar A β , a measure distinct from the age of PiB positivity. We investigate both the risk of accumulating A β and the age at which this began in relation to *APOE* genotype and sex.

METHODS

Participants

Longitudinal positron emission tomography (PET) data were acquired using the radiotracer Pittsburgh compound B (PiB) for 132 participants, aged 55 and older, from the Baltimore Longitudinal Study of Aging (BLSA) neuroimaging substudy [28]. Research protocols were approved by local institutional review boards, and all participants gave written informed consent at each visit. At enrollment into neuroimaging substudy, participants were free of central nervous system disease (dementia, stroke, bipolar illness, epilepsy), severe cardiac disease (myocardial infarction, coronary artery disease requiring angioplasty or coronary artery bypass surgery), severe pulmonary disease, or metastatic cancer. A subset of the BLSA neuroimaging participants received PiB-PET scans beginning in 2005. At baseline PiB-PET, 3 of the 132 participants had diagnoses of mild cognitive impairment (MCI) and 2 had diagnoses of AD. Remaining individuals were cognitively normal at baseline. At last PiB-PET, 3 participants had diagnoses of MCI, 4 had AD, and one had dementia of unspecified etiology. Diagnoses of dementia and Alzheimer's disease (AD) were based on DSM-III-R [29] and NINCDS-ADRDA criteria [30], respectively. Mean (SD) age at baseline PiB-PET imaging was 77.1 (7.8). Participants were studied at 1 to 2-year intervals with up to 8 (mean 2.5, SD 1.8) repeated scans over up to 9 years. Participant demographics

for the whole sample and for each *APOE* group are presented in Table 1. Of the 36 $\epsilon 4$ carriers, 3 were $\epsilon 2/\epsilon 4$, 29 were $\epsilon 3/\epsilon 4$, and 4 were $\epsilon 4/\epsilon 4$. Of the 83 non-carriers, 16 were $\epsilon 2/\epsilon 3$ and 67 were $\epsilon 3/\epsilon 3$.

Mean (SD, range) age at baseline for males (n=71) and females (n=61) was 79.0 (6.8, 60.9–92.3) and 74.9 (8.5, 55.7–93.4) years, respectively. Sixteen (25.4%) of 63 males and 20 (35.7%) of 56 females with known *APOE* status were $\epsilon 4$ carriers.

Continuous variables were compared between *APOE* $\epsilon 4$ groups, as well as between males and females, using Wilcoxon rank sum tests. Proportions were compared using Fisher's exact test.

Image acquisition

Dynamic PiB-PET scans were acquired in 3D mode on a GE Advance scanner immediately following an intravenous bolus injection of a mean (SD) 14.7 (0.8) mCi of [^{11}C]-PiB. Participants were fitted with a thermoplastic head mask to minimize motion during scanning. PET data were acquired according to the following protocol for the duration of the frames: 4×0.25, 8×0.5, 9×1, 2×3, and 10×5 min (70 minutes total, 33 frames). Dynamic images were reconstructed using filtered back-projection with a ramp filter, yielding a spatial resolution of approximately 4.5 mm full width at half max at the center of the field of view (image matrix = 128×128, 35 slices, pixel size = 2×2mm, slice thickness = 4.25mm).

Magnetization-prepared rapid gradient echo (MPRAGE) images acquired on a 3T scanner (Philips Achieva, repetition time [TR]=6.8ms, echo time [TE]=3.2ms, flip angle=8°, image matrix=256×256, 170 slices, pixel size=1×1mm, slice thickness=1.2mm) were used as the MRIs whenever available; however, these images were unavailable for 19 of the 132 participants due to scanner changes over time. Six participants underwent an MPRAGE acquisition sequence on a 1.5T scanner (Philips Intera, TR=6.8ms, TE=3.3ms, flip angle=8°, image matrix=256×256, 124 slices, pixel size=0.94×0.94 mm, slice thickness=1.5 mm). Remaining 13 participants underwent a spoiled gradient-recalled (SPGR) acquisition sequence on a 1.5T scanner (GE Signa, TR=35ms, TE=5ms, flip angle=45°, image matrix=256×256, 124 slices, pixel size=0.94×0.94mm, slice thickness=1.5mm). A baseline MRI was matched with its concurrent or closest-in-time PiB-PET image for each participant. Seventeen participants did not have an MRI concurrent with any of their PiB-PET scans. The interval between the MRI and closest-in-time PiB-PET for these participants was 2.5 years (SD 1.1, range 1.0–4.6), excluding two participants who were claustrophobic and had a single MRI 10.5 and 14.7 years prior to PiB-PET.

Image processing

Time frames of each dynamic PET scan were aligned to the average of the first two minutes to correct for motion [31]. For registration purposes, we obtained static images by averaging the first 20 minutes of each dynamic PET scan. Follow-up PET scans were rigidly registered onto the baseline PET within each participant using 20-minute average images. Baseline MRIs were rigidly registered onto their corresponding 20-minute average. We generated a study-specific template using baseline 3T MPRAGE images in a diffeomorphic registration framework [32]. Corresponding 1.5T MPRAGE and 1.5T SPGR templates were generated

from the 3T template using a patch-based image synthesis method [33]. 3T MPRAGE template was segmented using FreeSurfer (version 5.1, <http://surfer.nmr.mgh.harvard.edu>) [34]. The appropriate MRI template was registered onto each subject's baseline MRI using diffeomorphic registration [35]. The FreeSurfer segmentation in template space was transformed accordingly onto the baseline PET scan, and then rigidly transformed onto each longitudinal PET scan using the within-subject transformations. Consecutive transformations were concatenated so that FreeSurfer segmentations were interpolated only once. Distribution volume ratio (DVR) images were calculated in the native space of each PET image using the simplified reference tissue model with the cerebellar gray matter as reference tissue [36]. Mean cortical DVR (cDVR) was calculated as the average of the DVR values in cingulate, frontal, parietal (including precuneus), lateral temporal, and lateral occipital cortical regions, excluding the sensorimotor strip.

Estimation of mean cDVR threshold

A two-class Gaussian mixture model was fitted to baseline mean cDVR data. The DVR value corresponding to the intersection of the probability density functions of the two classes was used to classify participants into PiB- and PiB+ groups based on their last visit. The longitudinal mean cDVR data are presented in Figure 1.

APOE genotype

APOE genotype was determined using standard procedures [37]. Thirteen participants with missing *APOE* genotype information were excluded in *APOE* analyses. *APOE* $\epsilon 4$ status was coded for each participant as 1 if at least one $\epsilon 4$ allele was present, and as 0 otherwise.

Nonlinear mixed effects model for estimating the age of onset of amyloid deposition

We estimated the age at which each PiB+ individual began exhibiting increases in mean cDVR using a nonlinear mixed effects model. This age reflects the age at earliest detectable amyloid accumulation, prior to surpassing the threshold for PiB positivity. The model included an intercept and a slope associated with age for the PiB- group. Subjects who were PiB+ at last visit were modeled using a two-part piecewise linear trajectory: they were assumed to follow the trajectory associated with the PiB- group until they reached detectable amyloid levels, beyond which they were modeled with a separate trajectory that had a different slope associated with age. Random effects included intercept and age at detectable amyloid accumulation, allowing for the estimation of these values for each individual. The rate of change in mean cDVR was assumed to be the same across individuals within each of the PiB groups. This assumption reduced the variability in the estimated parameters and allowed for the estimation of the age at detectable amyloid accumulation for individuals with a single PiB-PET scan. See Appendix for details. Once amyloid levels are detectable, individuals need to accumulate enough amyloid to surpass the mean cDVR threshold to be considered PiB+. We also calculated the age at which each individual became PiB+ based on the fitted model.

Survival analyses

The nonlinear mixed effects model allows for the estimation of the age at detectable amyloid accumulation only for the individuals who developed elevated levels of cortical A β over the course of the study. In order to accurately assess the risk of *APOE* genotype and sex on developing elevated levels of A β , we have to account for the possibility that individuals who remained PiB– during the study might have begun accumulating A β after their last visit. We therefore used survival analysis methods to examine the effects of *APOE* ϵ 4 status and sex on the age at detectable amyloid accumulation, adjusting for level of education. Age at detectable amyloid accumulation served as the time of event for the PiB+ individuals; those who had not developed cortical A β pathology by their last visit were right-censored. First, we compared the Kaplan-Meier curves for *APOE* ϵ 4 groups and for males and females. To study the effect of *APOE* ϵ 4 status and sex on the risk of reaching detectable amyloid levels, we used the Cox proportional hazards model. The Cox model allows for the quantification of risk, but does not inform about the differences in the age at onset across groups. To directly study the effect of *APOE* status and sex on the age at detectable amyloid accumulation, we used the accelerated failure time (AFT) model. The AFT model is given by

$\log T_i = x_i^T \beta + \sigma \varepsilon_i$, where T_i is time to event for i^{th} subject, x_i is a vector of independent variables, ε_i is random noise, and β and σ are parameters to be estimated. The Akaike Information Criterion (AIC) was used to select the best distribution (among exponential, log-logistic, Weibull, log-normal, and gamma distributions) for T_i in the AFT model. In survival analyses, sex was coded as 1 for males and 0 for females. All statistical analyses were conducted in R, version 3.0.2 (<http://www.r-project.org>).

RESULTS

Distribution of baseline age ($p=0.19$), proportion of females ($p=0.24$), years of education ($p=0.54$), number of PiB-PET scans ($p=0.28$) and follow-up duration ($p=0.29$) were comparable between the *APOE* groups (Table 1). Proportion of *APOE* ϵ 4 carriers ($p=0.24$ restricting the comparison to individuals with known *APOE* status), years of education ($p=0.63$), number of PiB-PET scans ($p=0.79$) and follow-up duration ($p=0.93$) were comparable between males and females. Females were younger than males at baseline ($p=0.004$).

The Gaussian mixture model yielded a mean cDVR threshold of 1.066 for classifying individuals into PiB– and PiB+ groups (Appendix, Figure A.1). Of 83 ϵ 4– and 36 ϵ 4+ individuals, 25 (30.1%) and 18 (50.0%) were PiB+ at last visit, respectively (Table 1). Of 71 males and 61 females, 30 (42.3%) and 17 (27.9%) were PiB+ at last visit, respectively. Proportion of PiB+ individuals at last visit was higher in the ϵ 4+ group compared to ϵ 4– as well as among males compared to females, but these differences did not reach statistical significance ($p=0.06$ and 0.10 , respectively). ϵ 4 carriers had significantly higher mean cDVR at last visit compared to non-carriers ($p=0.02$). Mean cDVR at last visit was 1.13 (SD 0.20) for males and 1.07 (SD 0.16) for females, but this difference was not significant ($p=0.18$).

The results of the nonlinear mixed effects model are presented in Table A.1, and predicted mean cDVR values for each individual are shown in Figure A.2. We estimated that

individuals in our sample began accumulating cortical fibrillar amyloid as measured by PiB-PET at age 69.3 (SD 8.1) on average. Estimated ages at detectable amyloid accumulation ranged from 54.0–88.8 years. After reaching detectable amyloid levels, individuals exhibited increases in mean cDVR by 0.024/year. There was a slight downward slope in the PiB– group showing decreases by 0.001/year in mean cDVR.

Using individual-level estimates, we calculated that individuals surpass the cDVR threshold at age 72.5 (SD 8.3, range 56.7–92.8) on average. Average within-subject interval between age at detectable amyloid accumulation and age at which the individual became PiB+ was 3.2 years (SD 0.4, range 1.5–4.0).

Kaplan-Meier curves (Figure 2) were statistically different between *APOE* $\epsilon 4$ carrier and non-carriers (log-rank test $p=0.0009$) but not between males and females ($p=0.26$). The Cox model showed that *APOE* $\epsilon 4$ carrier status was significantly associated with reaching detectable amyloid levels (chi-squared test $p=0.0006$) after adjusting for sex and years of education (Table 2). *APOE* $\epsilon 4+$ individuals had a 3-fold increase in risk of reaching detectable amyloid levels compared to the $\epsilon 4-$ individuals (hazard ratio [HR]=3.05, 95% CI 1.61–5.78). Neither sex nor level of education was significant ($p=0.12$ and 0.77 , respectively).

The log-normal distribution yielded the smallest AIC, and therefore was selected as the distribution function for the AFT model. The effect of *APOE* $\epsilon 4$ status on age at detectable amyloid accumulation was significant in the AFT analysis (chi-squared test $p=0.0005$), with $\epsilon 4+$ individuals reaching detectable amyloid levels 16.9% (95% CI 7.4–26.4) earlier on average compared to $\epsilon 4-$ individuals after adjusting for sex and years of education (Table 3). Neither sex nor level of education was significant ($p=0.25$ and 0.84 , respectively). Using the result of the AFT model in conjunction with the mixed effects model finding that the population-average age at detectable amyloid accumulation is 69.3, we approximated that the age at detectable amyloid accumulation is 73.1 (95% CI 68.2–76.1) and 60.7 (95% CI 53.6–65.1) years for the *APOE* $\epsilon 4-$ and $\epsilon 4+$ groups, respectively.

Analyses using precuneus DVR values instead of mean cDVR yielded similar results, with $\epsilon 4$ carrier status associated with a more than 3-fold risk of reaching detectable amyloid levels as well as an 18.2% earlier onset of amyloid accumulation (Appendix, Tables A.8 and A.9).

DISCUSSION

We estimated the age at onset of fibrillar cortical A β pathology using PiB-PET imaging in a longitudinal sample, and investigated its associations with *APOE* genotype, adjusting for sex and levels of education. On average, A β accumulation began at age 69.3 in our sample. *APOE* $\epsilon 4$ carrier status not only increased the risk of developing A β pathology, i.e., PiB positivity, but was also associated with an earlier onset of A β accumulation. There was a more than 12-year difference in the initiation of A β accumulation between *APOE* $\epsilon 4$ carriers and non-carriers, with $\epsilon 4+$ and $\epsilon 4-$ individuals beginning to accumulate at age 60.7 and 73.1

years, respectively. We found no significant effects of sex or education on level or timing of onset of A β accumulation.

Our finding that *APOE* ϵ 4 carrier status is associated with a higher risk of developing cortical fibrillar A β agrees with previous reports of *in vivo* amyloid imaging in cognitively normal healthy individuals showing higher cortical amyloid levels and a greater proportion of amyloid positive individuals in the *APOE* ϵ 4+ group [6,9,11,23,38,39]. In this paper, we extend these findings by introducing a novel approach to estimate the onset age of A β accumulation to allow investigation of factors that modify the initiation of A β deposition at the individual level. The earlier onset of A β in *APOE* ϵ 4 positive individuals is closely linked to the finding that the presence of the *APOE* ϵ 4 allele shifts the age at diagnosis of AD by about 10 to 15 years [3,27,40]. Our finding suggests that the onset of preclinical AD, which is characterized by asymptomatic amyloidosis [1], is also earlier in *APOE* ϵ 4 carriers, supporting the hypothesis that *APOE* ϵ 4 positivity shifts the entire disease timeline rather than accelerating disease progression. We and others have shown that after adjusting for age, *APOE* ϵ 4 status does not significantly affect rates of A β accumulation, measured by PiB-PET [2,5,21,41] or cerebrospinal fluid A β ₁₋₄₂ [21], suggesting that once the neuropathological changes are underway, the effects of *APOE* status on disease progression are less pronounced.

Our analyses using longitudinal data corroborate the findings in two cross-sectional samples that *APOE* ϵ 4 positivity is associated with an earlier onset of A β accumulation [7,22]. Fleisher et al. found that Florbetapir PET signal began showing increases at age 58, with positivity occurring at age 71 in cognitively normal adults [7]. *APOE* ϵ 4 carriers were found to become amyloid positive at age 56 on average, whereas non-carriers at age 76 [7]. In a study of cognitively normal adults, Jack et al. found that the ages at which 10% of individuals would be considered PiB-PET positive is 57 for *APOE* ϵ 4 carriers and 64 for non-carriers [22]. Our study is distinguished from these studies in several aspects: Our analyses were based on longitudinal rather than cross-sectional data, we characterized the age at onset of amyloid accumulation rather than age at amyloid positivity, and we estimated an onset age for each individual in addition to reporting averages by *APOE* group. We estimated that PiB signal began showing increases at age 69, with positivity occurring at age 72 in our overall sample. We further estimated that ages at detectable amyloid accumulation were 61 for *APOE* ϵ 4 carriers and 73 for non-carriers. Based on our finding that there is approximately a 3-year period between detectable amyloid accumulation and amyloid positivity, our results indicate that amyloid positivity occurs around age 64 for ϵ 4 carriers and 76 for non-carriers. The different findings across these studies might be due to the difference in radiotracers, definitions of amyloid positivity, and statistical approaches, the use of standardized uptake volume ratio versus DVR to quantify the amyloid levels, and the cross-sectional versus longitudinal nature of the datasets. Furthermore, our sample included individuals 55 and older, but the samples used in Fleisher et al. [7] and Jack et al. [22] had participants as young as 18 and 30, respectively. Inclusion of younger adults might have benefited the estimation of subtle trends at earlier ages that we were unable to extract in our sample. In addition, our initial sample of BLSA participants was selected for health, as they had remained healthy enough to participate over an 11-year follow-up at the initial PiB

studies. BLSA participants also have high levels of education, which might have a protective effect against amyloid deposition although this was not evident in our sample [42].

Sex differences in cortical A β levels or the proportion of amyloid positive individuals have previously not been observed among healthy individuals in large studies of PET imaging, including the BLSA, although a small study of 26 individuals found higher cortical amyloid burden in males [20]. The proportion of PiB+ individuals was not significantly different among males and females in our sample, and males and females did not differ significantly in terms of their risk or age at onset of A β accumulation, which agrees with the finding of Jack et al. [22]. The proportion of *APOE* ϵ 4+ individuals was higher among females than among males in our sample. This difference in older adults may in part reflect an earlier dropout of males due to the association between the ϵ 4 genotype and risk for cardiovascular disease [43], which occurs earlier in men than women.

Limitations of our study include the limited number of longitudinal follow-ups due to the relatively recent development of amyloid imaging. The majority of the estimated ages of detectable amyloid accumulation from the nonlinear mixed effects model are based on relatively few direct observations since only a few individuals went from being PiB– to PiB+ during the course of the study. Estimation of these ages for individuals who were PiB+ at their initial scan was based on the assumption that the rate of DVR change is constant across PiB+ individuals. Since PiB-PET measures fibrillar amyloid, our nonlinear mixed effects model estimates reflect the ages at which we start to measure a discernible change in PiB signal, not necessarily the age at which amyloid begins to accumulate. Our PiB-PET images were not corrected for partial volume effects, and therefore the mean cDVR measures may be confounded by effects of atrophy. Due to sample size limitations, we were unable to investigate different *APOE* allele combinations or the interaction of *APOE* status and sex in relation to A β . High education levels of the BLSA cohort may limit generalizability of our findings to individuals with lower levels of education.

In conclusion, individualized estimates of the onset age for detectable amyloid accumulation in conjunction with survival analysis methods allow for novel analyses using longitudinal amyloid data. Determination of onset age of amyloid accumulation is of critical importance for evaluation of treatments to prevent or delay AD and can inform the optimal time window for anti-amyloid interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's disease
BLSA	Baltimore Longitudinal Study of Aging
cDVR	Cortical DVR
DVR	Distribution volume ratio
HR	Hazard ratio
MCI	Mild cognitive impairment
PiB	Pittsburgh compound B

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Research in Context

1. Systematic Review

We searched PubMed for “amyloid”, “APOE”, “PiB”, and “Alzheimer”. Our review indicated that the age at onset of amyloid accumulation has not been explored at the individual level, and no longitudinal study to date has investigated the associations between the onset age of amyloid accumulation and *APOE* genotype.

2. Interpretation

APOE $\epsilon 4$ positivity confers a 3-fold risk of accumulating A β after adjusting for sex and education. The onset of A β accumulation occurs more than 12 years earlier for *APOE* $\epsilon 4+$ individuals compared to $\epsilon 4-$. Understanding the factors that influence the onset age of amyloid accumulation may help gauge treatment efficacy and inform the optimal treatment window in interventions to prevent or delay symptom onset in Alzheimer’s disease.

3. Future directions

Future work in larger samples with more follow-up visits will also evaluate additional risk factors that might modulate the age at onset of amyloid accumulation.

Figure 1.
Longitudinal mean cortical DVR versus age
Data within individuals are connected by lines. Colors indicate *APOE* $\epsilon 4$ genotype, and markers indicate sex. The dashed line corresponds to the mean cortical DVR threshold obtained from the Gaussian mixture model.

Figure 2.
Kaplan-Meier curves
Kaplan-Meier curves by *APOE* $\epsilon 4$ status.

Table 1Participant characteristics overall and by *APOE* ϵ 4 status.

Characteristic	Whole sample (n = 132)	<i>APOE</i> ϵ 4– (n = 83)	<i>APOE</i> ϵ 4+ (n = 36)
Baseline age, y, mean (SD)	77.1 (7.8)	77.6 (8.2)	75.4 (6.7)
Range	55.7–93.4	55.7–93.4	59.0–88.2
Female, n (%)	61 (46.2%)	36 (43.4%)	20 (55.6%)
MCI diagnosis at last visit, n (%)	3 (2.3%)	0	3 (8.3%)
Dementia diagnosis at last visit, n (%)	5 (3.8%)	3 (3.6%)	2 (5.6%)
Education, y, mean (SD)	16.9 (2.2)	16.9 (2.2)	16.6 (2.3)
Range	12.0–20.0	12.0–20.0	12.0–20.0
PiB+ at last visit, n (%)	47 (35.6%)	25 (30.1%)	18 (50.0%)
Mean cDVR at last visit, mean (SD)	1.10 (0.18)	1.07 (0.16)	1.17 (0.21)
Range	0.89–1.62	0.89–1.54	0.94–1.61
Number of PiB-PET scans, n (%)			
1	54 (40.9%)	29 (34.9%)	14 (38.9%)
2	25 (18.9%)	14 (16.9%)	10 (27.8%)
3	17 (12.9%)	14 (16.9%)	2 (5.6%)
4	17 (12.9%)	10 (12.0%)	7 (19.4%)
5	8 (6.1%)	6 (7.2%)	2 (5.6%)
6 to 8	11 (8.3%)	10 (12.0%)	1 (2.8%)
Years between first and last scan, mean (SD)	2.7 (2.9)	3.1 (3.1)	2.4 (2.5)
Range	0.0–9.0	0.0–9.0	0.0–7.8

APOE ϵ 4 status was missing for 13 participants. Abbreviations: PiB = Pittsburgh compound B; cDVR = Cortical distribution volume ratio; MCI = Mild cognitive impairment; AD = Alzheimer's disease.

Table 2

Cox model results.

Parameter	HR	95% CI	Chi-square <i>p</i> -value
<i>APOE</i> ε4	3.05	1.61–5.78	0.0006
Sex	1.65	0.88–3.12	0.12
Education	0.98	0.86–1.12	0.77

HR = Hazard ratio.

Table 3

Accelerated failure time (AFT) model results.

Parameter	Estimate	SE	Chi-square <i>p</i> -value
<i>APOE</i> ε4	−0.169	0.048	0.0005
Sex	−0.054	0.046	0.25
Education	0.002	0.010	0.84