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## APOE Effect on Amyloid- $\beta$ PET Spatial Distribution, Deposition Rate, and Cut-Points

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### Abstract

There are conflicting results regarding how *APOE* genotype, the strongest genetic risk factor for Alzheimer's disease (AD), influences spatial and longitudinal amyloid- $\beta$  (A $\beta$ ) deposition and its impact on the selection of biomarker cut-points. In our study, we sought to determine the impact of *APOE* genotype on cross-sectional and longitudinal florbetapir positron emission tomography (PET) amyloid measures and its impact in classification of patients and interpretation of clinical cohort results. We included 1,019 and 1,072 Alzheimer's Disease Neuroimaging Initiative participants with cerebrospinal fluid A $\beta_{1-42}$  and florbetapir PET values, respectively. 623 of these subjects had a second florbetapir PET scans two years after the baseline visit.

We evaluated the effect of *APOE* genotype on A $\beta$  distribution pattern, pathological biomarker cut-points, cross-sectional clinical associations with A $\beta$  load, and longitudinal A $\beta$  deposition rate measured using florbetapir PET scans. 1) *APOE*  $\epsilon 4$  genotype influences brain amyloid

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<sup>2</sup>Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://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: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_AcknowledgementList.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_AcknowledgementList.pdf).

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-1282r1>).

#### SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-181282>.

deposition pattern; 2) *APOE*  $\epsilon 4$  genotype does not modify A $\beta$  biomarker cut-points estimated using unsupervised mixture modeling methods if white matter and brainstem references are used (but not when cerebellum is used as a reference); 3) findings of large differences in A $\beta$  biomarker value differences based on *APOE* genotype are due to increased probability of having AD neuropathology and are most significant in mild cognitive impairment subjects; and 4) *APOE* genotype and age (but not gender) were associated with increased A $\beta$  deposition rate. *APOE*  $\epsilon 4$  carrier status affects rate and location of brain A $\beta$  deposition but does not affect choice of biomarker cut-points if adequate references are selected for florbetapir PET processing.

### Keywords

Alzheimer's disease; amyloid- $\beta$ ; cerebrospinal fluid; diagnosis; mild cognitive impairment; positron emission tomography

## INTRODUCTION

The presence of the apolipoprotein E gene (*APOE*)  $\epsilon 4$  allele is considered to be the strongest sporadic genetic risk factor for Alzheimer's disease (AD). The presence of one or two *APOE*  $\epsilon 4$  allele copies leads to earlier amyloid- $\beta$  (A $\beta$ ) deposition as measured by cerebrospinal fluid (CSF) and positron emission tomography (PET) A $\beta$  biomarkers [1, 2], but not to brain structural changes in the preclinical disease phase [3]. In addition, CSF A $\beta_{1-42}$  decrease seems to precede an increase in A $\beta$  PET standardized uptake value ratio (SUVR) [4], although CSF and PET A $\beta$  measures show a high agreement to classify healthy and cognitively impaired subjects based on amyloid pathology [5, 6].

Previous studies have reported that *APOE* genotype modifies the association between CSF A $\beta_{1-42}$  values and PET SUVRs in the same subjects [6, 7]. This could indicate that based on the *APOE* genotype brain amyloid deposition is captured differently by these two different A $\beta$  amyloid biomarkers. The gold standard to assess amyloid brain deposition is through neuropathology and several studies have shown that CSF A $\beta_{1-42}$  values [8] and A $\beta$  PET measures [9] are strongly correlated with brain amyloid deposits. However, there are no large studies with CSF and PET amyloid measures obtained at the same time, close to time of death, and with quantitative neuropathological brain amyloid deposition assessment.

In addition, even if the association between *APOE* genotype and AD risk has been consistently replicated, the results regarding its association with biomarker measures are conflicting. The results in clinically diagnosed AD subjects on the effects of *APOE* genotype on A $\beta$  PET burden [10–13] are inconsistent, and there is additional conflicting data on how *APOE*  $\epsilon 4$  carrier status affects the overall A $\beta$  burden and deposition in cognitively impaired subjects [11, 14–16]. Contradictory results could be related to sample selection, analytical methods, and the disease stage at which patients are recruited. Finally, there is limited evidence on spatial differences in *APOE*-related A $\beta$  PET distribution patterns, based on small samples of clinically diagnosed AD subjects [12, 13]. For all of the analyses, it is important to account for age in the model of biomarker changes, since age is the strongest demographic AD risk factor. This important adjustment for dementia biomarker research

would call for studies with larger sample sizes and detailed imaging as well as genotyping approaches.

Based on the described conflicting results, we aimed to investigate in a large biomarker cohort with longitudinal CSF and PET A $\beta$  biomarkers measurements if *APOE* genotype differentially affects: 1) A $\beta$  spatial distribution patterns, 2) A $\beta$  biomarker cut-points, 3) A $\beta$  burden in the different clinically defined groups, and 4) A $\beta$  PET deposition rate.

## MATERIAL AND METHODS

### Subjects

1,396 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with CSF A $\beta_{1-42}$  ( $n = 1,019$ ) and/or florbetapir PET scans ( $n = 1,072$ ) were included in this study (Table 1). Cognitively normal (CN) subjects with and without subjective memory complaints were analyzed together in the same group. A diagnosis of mild cognitive impairment (MCI) and AD was established as previously described [17]. Data was downloaded August 2015. The ADNI has been extensively reviewed elsewhere [18] (<http://www.adni-info.org> and Supplementary Methods).

### Standard protocol approvals, registrations, and patient consents

Protocols were submitted to Institutional Review Boards for each participating location and their written unconditional approval obtained and submitted to Regulatory Affairs at the ADNI Coordinating Center (ADNI-CC) prior to commencement of the study. Written informed consent for the study was obtained from all subjects and/or authorized representatives.

### CSF collection and A $\beta_{1-42}$ measurement

CSF samples were processed as previously described [19] (<http://www.adni-info.org/> and Supplementary Methods). A $\beta_{1-42}$  was measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use-only reagents) immunoassay kit-based reagents.

### Florbetapir PET scans processing

As previously described [6], we included florbetapir adjusted SUVRs developed in two different laboratories, i.e., the University of Utah (UU) and the University of California (UC) Berkeley.

The UU laboratory processed images using 3-dimensional stereotactic surface projections computed using Neurostat [20]. PET scans were downloaded from LONI using the post-processed group 4 images, i.e., coregistered and averaged frames, standardized image orientation and voxel size, and uniform resolution smoothed to 8 mm. Neurostat aligned the brain images along the AC-PC line and non-linearly warped the image into standard Talairach space. Longitudinal scans, for each subject, were coregistered to the baseline scan and a multi-step normalization was used to create a mean template. A peak pixel template was created from the mean template and applied to intra-subject serial scans to produce

surface projection maps, SSPs. Neurostat pre-defined brain regions in Talairach space were used to calculate the ROI regional values based on the SSP maps. Florbetapir images were normalized using both cerebellar and white matter (WM) values. Neurostat automatically defined the averaged cerebellar value. WM values were determined by sampling pixels from the amyloid image, in Talairach-space, starting at a much greater depth, thus bypassing the cortical ribbon. The Neurostat generated global value was used for the whole brain WM value. Averaged regional values from medial and lateral frontal, temporal and parietal cortices were normalized either using the cerebellum (CB) or WM as reference regions, to obtain the average CB and WM measures, respectively.

UC Berkeley laboratory used SPM5 software to co-register the florbetapir PET scans with the corresponding MRI scans, that previously were segmented and parcellated with Freesurfer (v 4.5) as described [21]. Fully pre-processed format (series description in LONI Advanced Search: “AV45 Coreg, Avg, Std Img and Vox Siz, Uniform Resolution”) were downloaded. Each subject’s first florbetapir image was coregistered using SPM5 to that subject’s MRI image (series description: ADNI 1scans \*N3;\* and ADNI GO/2 scans \*N3\*) that was closest in time to the florbetapir scan. Freesurfer processing was carried out to skull-strip, segment, and delineate cortical and subcortical regions in all MRI scans. The UC Berkeley laboratory estimated florbetapir means from grey matter in subregions were extracted within 4 large regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) [22]. Conventional (nonweighted) average of whole CB was selected as reference for the summary CB measure. Means from three Freesurfer-defined reference regions (whole CB, brainstem/pons, and eroded subcortical WM) were selected as reference for the summary composite measure. In addition, uptake values for 19 regions of interest (ROIs) in each brain hemispheres were estimated using Freesurfer software defined areas [23], and normalized using whole CB and composite reference.

623 and 621 participants had a second scan processed after a two-year follow-up at the UU and UC Berkeley laboratories, respectively.

### Statistical analysis

Cut-points were estimated using an unsupervised mixture modeling approach that empirically estimates the presence of different populations in the data [6, 24]. To compare the cut-points between the *APOE*  $\epsilon 4$  carrier and non-carrier groups, we calculated 1,000 bootstrapped samples with replacement for each *APOE* group and calculated the cut-point in each of the 1,000 bootstrapped samples. Linear regression models were applied to analyze associations with quantitative variables, as was the case of the comparison of amyloid burden in the different ROIs. Power transformations were applied as needed to normalize data distributions. A squared SUVR term was included to account for the nonlinear rate of amyloid deposition. False discovery rate (FDR) Benjamini-Hochberg correction was applied when multiple non hypothesis-based comparisons were performed. Results were considered significant if two-tailed *p*-values were  $\leq 0.05$ . Analyses were performed using R v. 3.2.2.

## RESULTS

### Florbetapir PET deposition patterns based on APOE genotype

*APOE*  $\epsilon 4$  carriers showed higher amyloid burden in all studied PET ROIs compared to non-carriers in analyses adjusted for age and clinical diagnosis ( $p < 0.0001$  for all areas). However, when adjusting for total amyloid burden instead of clinical diagnosis, *APOE*  $\epsilon 4$  non-carriers showed higher adjusted SUVRs for both CB and composite summary in two of the three parietal lobe regions compared to *APOE*  $\epsilon 4$  carriers who showed higher adjusted SUVRs in anterior cingulate and frontal regions (Table 2).

### Unbiased evaluation of A $\beta$ biomarker cut-points based on APOE genotype

The distribution of the 1,000 calculated CSF A $\beta_{1-42}$  and florbetapir PET cut-points overlapped between *APOE*  $\epsilon 4$  carriers and non-carriers for the CSF A $\beta_{1-42}$  values and the PET SUVRs when using WM and brainstem as references (average WM and summary composite) (Supplementary Figure 1), which lead to insignificant differences in cut-point values ( $<0.6\%$ ) between genotypes and less than 0.4% of the subjects were reclassified (Supplementary Table 1). Conversely, cut-points for PET indices with CB as reference (average CB and summary CB) showed a non-overlapping distribution, differing 3.2–7.9% based on *APOE*  $\epsilon 4$  carrier status, which led to a reclassification of 2.5 to 5.6% of the participants.

### Cross-sectional associations of A $\beta$ biomarker measures

Figure 1A and B depicts the distribution of CSF A $\beta_{1-42}$  and the summary composite SUVR values in the complete cohort as well as stratified by *APOE*  $\epsilon 4$  carrier status (Supplementary Figure 2 shows all biomarkers). Most of the A $\beta$  biomarker measures showed bimodal distributions for the three groups, although the frequencies, depicted by the height of the peaks, were reversed in *APOE*  $\epsilon 4$  carrier versus non-carrier groups. When further stratified by clinical diagnosis (Fig. 1C–H), subjects diagnosed as MCI and AD had more pathological A $\beta$  biomarker values and presented a higher peak in the pathological range (higher for PET adjusted SUVRs and lower for CSF A $\beta_{1-42}$  values) than CN participants indicating an increase of amyloid biomarker positivity across diagnostic categories.

In a multivariate model, we evaluated the association between different *APOE* genotypes and A $\beta$  biomarker values (Table 3). Overall the presence of one or more  $\epsilon 4$  alleles was associated with increased A $\beta$  burden and the  $\epsilon 2$  allele was only associated with a lower amyloid burden in the absence of the  $\epsilon 4$  allele. An interaction with clinical diagnosis was observed only in the *APOE*  $\epsilon 4$  carrier/non-carrier model (Supplementary Table 2). Interestingly, AD *APOE*  $\epsilon 4$  non-carriers showed a bimodal distribution of CSF and PET A $\beta$  values that was not present in *APOE*  $\epsilon 4$  carriers, while MCI subjects showed different frequencies of the bimodal distribution peaks based on *APOE*  $\epsilon 4$  carrier status (Fig. 1C–H). Older age and female gender were also associated with pathological A $\beta$  biomarker values.

### Longitudinal A $\beta$ burden changes associated with APOE

The baseline PET SUVRs plotted as a function of yearly changes showed the characteristic inverted “u” shape (Fig. 2). We observed that *APOE*  $\epsilon 4$  carriers (one or two copies) showed

a statistically significant upward shift of the values in three of the four analyses indicating that this group has a faster A $\beta$  deposition rate compared to *APOE*  $\epsilon 4$  non-carriers when accounting for baseline biomarker values (Table 3), whereas there was no significant effect for the  $\epsilon 2$  allele. Gender was not associated with longitudinal florbetapir PET changes in any of the analyses, whereas age was associated with increased deposition rates for measures that included WM as a reference.

## DISCUSSION

In this study, we found that 1) *APOE*  $\epsilon 4$  influences brain amyloid deposition pattern, 2) *APOE*  $\epsilon 4$  does not modify A $\beta$  biomarker cut-points estimated using unsupervised mixture modeling methods when WM and brainstem were included as references, 3) large differences in A $\beta$  biomarker values based on *APOE* genotype are due to increased probability of having AD neuropathology and are most significant in MCI subjects and 4) *APOE*  $\epsilon 4$  and age (but not gender) were associated with A $\beta$  deposition rate.

### A $\beta$ distribution patterns

Different brain A $\beta$  deposition patterns based on *APOE* genotype were only identified when the analysis was adjusted for total A $\beta$  burden. Two previous studies, including 52 and 84 AD subjects described increased A $\beta$  PET values in frontal and lateral frontotemporal regions [12, 13] in *APOE*  $\epsilon 4$  carriers whereas a third one described overall greater diffuse cortical A $\beta$  PET values in *APOE*  $\epsilon 4$  carriers [25]. Subject selection criteria and analytical approaches can explain differences between our results and these studies: two studies included only demented subjects [13], when *APOE*  $\epsilon 4$  carriers and non-carriers are close to the biomarker plateaus, in addition one of the former studies included atypical AD cases. The third study did include CN subjects for a wide range of ages, but did not adjust for global amyloid burden [25].

There are several explanations for discordant results between the adjusted and unadjusted models. Because the *APOE*  $\epsilon 4$  allele is such a strong risk factor for sporadic AD, the odds of having preclinical AD pathology in CN subjects and of having underlying AD pathology in cognitively impaired subjects is increased and therefore PET SUVRs may be higher [2, 26, 27]. Previously, *APOE* genotype has been described to be associated with different patterns of cognitive impairment and brain atrophy [28] with varying frequencies in different neuropathologically defined AD subtypes [29]. Therefore, it is not surprising that *APOE* genotype is associated with differences in amyloid deposition. This might indicate that vulnerability varies based on the presence or absence of *APOE*  $\epsilon 4$  and this can lead to differences in clinical expression. Nevertheless, the putative mechanisms suggested to lead to increased amyloid deposition in AD, such as decreased amyloid clearance [30], and the association of CSF ApoE levels with cognitive and MRI structural changes [31] do not explain why there is a preferential spatial vulnerability associated with *APOE* genotype.

### Selections of A $\beta$ biomarker cut-points based on *APOE* genotype

The mixture modeling analysis that we applied is an unsupervised, unbiased statistical approach to study independently the effect of *APOE* genotype with each studied A $\beta$

biomarkers cut-points, which has been successfully applied to estimate A $\beta$  biomarker cut-points and has shown less than 1% difference with previous cut-points estimated based on neuropathological cases [6, 9, 19]. This approach has not been applied separately to *APOE*  $\epsilon 4$  carriers and non-carriers.

Only CB-referenced florbetapir PET values showed differences in the distribution of the cut-points based on *APOE* genotype, which led to 2.5–5.6% of the participants being reclassified, whereas similar cut-points (<0.6% difference) were obtained for WM-referenced florbetapir PET and CSF A $\beta_{1-42}$  values in *APOE*  $\epsilon 4$  carriers and non-carriers.

A previous study analyzed the effect of *APOE* genotype on CSF and PET amyloid values [32] reporting no effects of *APOE* genotype using a different approach. This study was conditioned by the *a priori* choice of using CSF A $\beta_{1-42}$  cut-points to stratify PET A $\beta$  values, therefore conditioning the comparison of PET values based on *APOE* genotype and did not analyze each of these A $\beta$  biomarkers independently. In addition, the previous study looked at differences based on *APOE* genotype and not at changes in cut-points values. Last, it might have been underpowered to detect differences as the population with PET values included only 165 subjects and only one PET processing pipeline was evaluated.

There are several biological and technical factors such as acquisition, instrument, and image processing factors that can lead to differences between studies, which could explain why florbetapir PET cut-points were only affected when CB was selected as a reference [33]. Recent studies involving the same study population have evaluated differences based on the selected reference region to calculate A $\beta$  PET SUVRs [6, 34, 35]. Although there is a high correlation between cross-sectional amyloid measures using different pipelines on the same PET scans [6] and between scans of the same subjects obtained using different ligands [36], this is not the case for longitudinal changes [6, 34]. CB has been the most commonly used reference to calculate SUVRs, but it has several potential drawbacks [33, 35]: it is located close to the scanner's field of view limit (and therefore susceptible to truncation and scatter-related noise), has low signal level (cerebellar gray matter), and A $\beta$  deposits in CB are present in the latest A $\beta$  deposition stages, Thal phase 5 [37]. The latter would lead to lower SUVR values in the most advanced cases due to the presence of A $\beta$  deposition in the CB.

Using WM as the reference region has been compared to CB showing that reference selection may be important to detect alterations that are more likely linked to AD pathobiology [34] and increase statistical power to detect longitudinal changes [35]. Our results regarding A $\beta$  PET cut-points add further evidence for the use of WM references when florbetapir scans are processed.

### **Cross-sectional associations with baseline biomarker values**

Associations with *APOE* genotype have been reported to vary depending on the clinical status of the studied subjects. Whereas CN and MCI *APOE*  $\epsilon 4$  carriers consistently show higher A $\beta$  PET SUVRs than *APOE*  $\epsilon 4$  non-carriers, studies that included AD participants have described higher A $\beta$  PET SUVRs in *APOE*  $\epsilon 4$  carriers [10], higher A $\beta$  PET SUVRs in *APOE*  $\epsilon 4$  non-carriers [12], or a lack of differences [11].



Our results showed that in the different groups stratified by clinical diagnosis *APOE*  $\epsilon 4$  carriers had more pathological A $\beta$  biomarker values compared to *APOE*  $\epsilon 4$  non-carriers with patterns that clearly showed bimodal distributions belonging to two different populations, one with normal and another with pathological A $\beta$  values. MCI and AD *APOE*  $\epsilon 4$  non-carriers showed a large variance in A $\beta$  biomarker values with two distinct peaks (Fig. 1E–H), whereas only MCI *APOE*  $\epsilon 4$  carriers showed a low frequency for the peak in the normal range of values and no bimodal distribution was observed in AD *APOE*  $\epsilon 4$  carriers. Interestingly, the peaks in the pathological A $\beta$  range had a similar mode in *APOE*  $\epsilon 4$  carriers and non-carriers, indicating a similar distribution of the values in this population.

We infer that these observations are the consequence of A $\beta$  biomarker characteristics and/or clinical misdiagnosis. Based on the current AD biomarker model [26], it is expected that MCI and AD subjects with underlying AD pathology already have A $\beta$  biomarker values in the pathological ranges, because AD pathology in described autopsy assessed subjects begins decades before the onset of cognitive decline. Therefore, those cognitively impaired individuals diagnosed with MCI and AD with values in the normal range would likely not have AD pathology. Clinical misdiagnosis has been observed in clinico-pathological studies of subjects with a clinical diagnosis of AD [38] and there are several pathologies that can lead to MCI. Factors described above and differences in selection criteria and analytical approaches can explain divergent results previously observed for AD A $\beta$  biomarker studies.

### Longitudinal A $\beta$ deposition

We found a faster amyloid deposition in *APOE*  $\epsilon 4$  carriers, in a model that accounted for baseline amyloid levels and non-linear trajectories. There have been conflicting results regarding the association between *APOE* genotype and longitudinal amyloid biomarker changes [15, 39–42] that can be attributed to analytical and statistical aspects. For example, CSF A $\beta_{1-42}$  values reach a plateau earlier than PET amyloid values [6]. Therefore, it is not surprising that a high percentage of elderly AD and control *APOE*  $\epsilon 4$  carriers have reached this plateau and therefore do not show any further decrease in CSF A $\beta_{1-42}$  [41]. While PET SUVRs might reach a plateau at later stage, there is still a decreased amyloid deposition rate with increasing brain amyloid load [6, 15, 40]. Another important factor is the inclusion of baseline values when longitudinal changes are evaluated, because these lead to a large reduction in *APOE* genotype associated changes [40].

### Conclusions

Our results indicate that *APOE*  $\epsilon 4$  carrier status is associated with a preferential distribution of amyloid in the frontal cortex and anterior cingulate and leads to increased rate of amyloid deposition, which agrees with cross-sectional findings of higher amyloid burden in  $\epsilon 4$  carriers, without affecting A $\beta$  biomarker cut-points when adequate PET references are used in the processing pipeline. The neuropathological heterogeneity underlying subjects classified based on a clinical diagnosis can explain conflicting findings regarding *APOE* associations found in different studies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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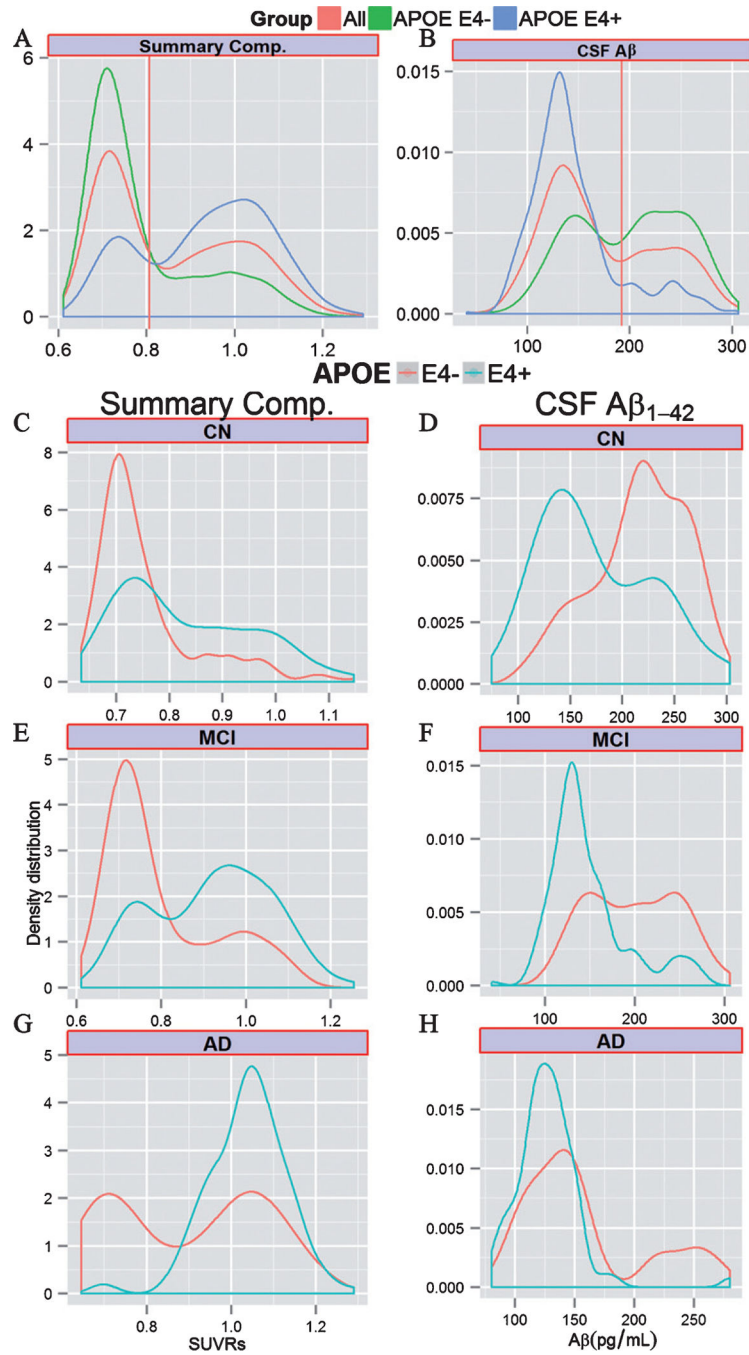
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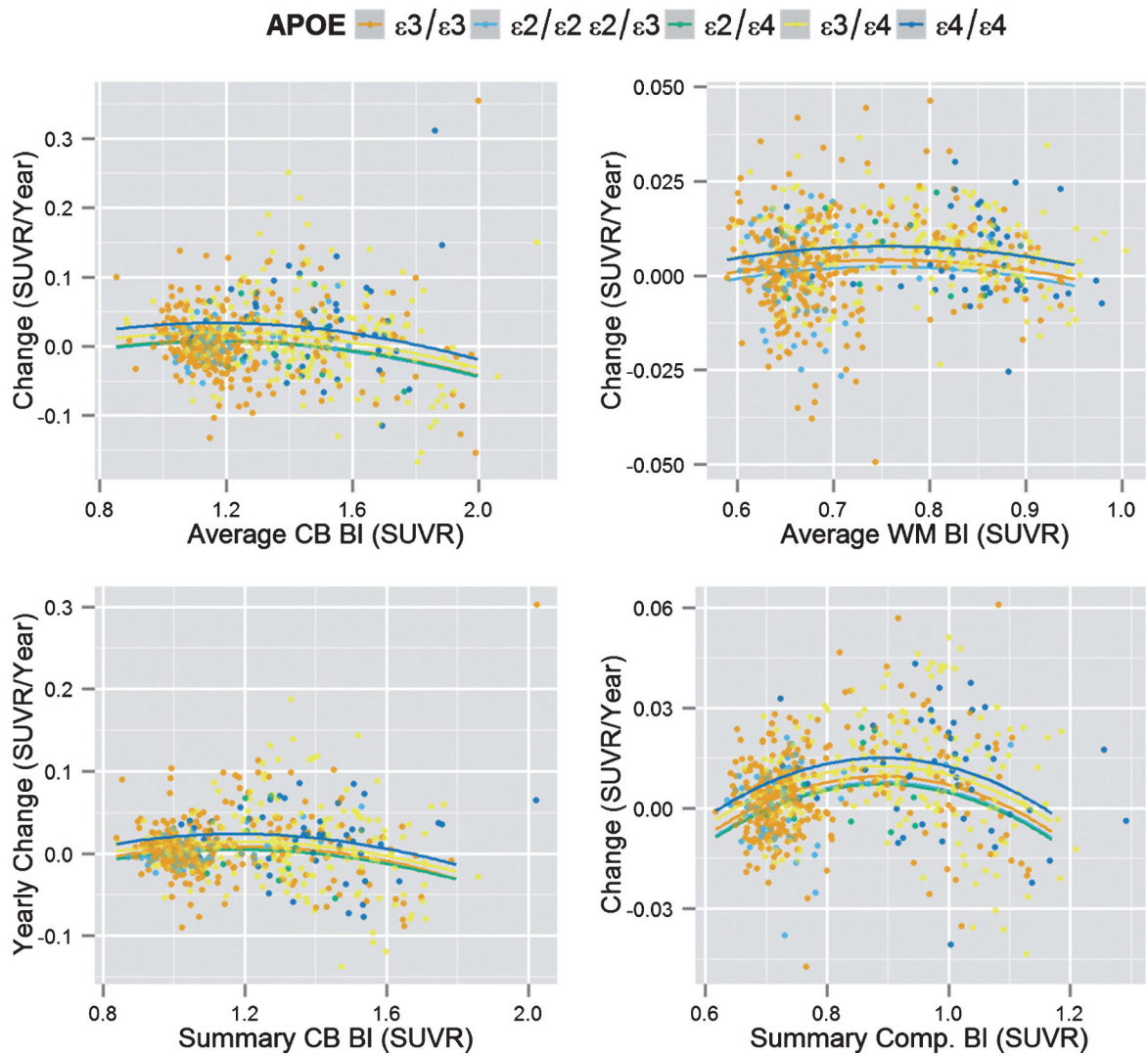
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**Fig. 1.** Cross-sectional Aβ biomarker values. Density distribution of Aβ amyloid biomarker values in the whole cohort (red) and stratified by *APOE ε4* carrier status (green for non-carriers and blue for carriers) for the summary composite florbetapir (A) and CSF Aβ<sub>1-42</sub> values (B). Distribution of summary composite florbetapir and CSF Aβ<sub>1-42</sub> values in the different clinical groups (C-H). The vertical red line represents the cut-point estimated using the whole sample. CB, cerebellum; CSF, cerebrospinal fluid; WM, white matter.



**Fig. 2.** Longitudinal A $\beta$  biomarker deposition. Baseline PET SUVR values (x-axis) versus longitudinal PET SUVR changes (y-axis) based on *APOE* genotype. BI, baseline; CB, cerebellum; CSF, cerebrospinal fluid; SUVR, standardized uptake value ratio; WM, white matter.

**Table 1**

## Demographics of the sample

	<b>Participants (<i>n</i> = 1,396)</b>
CSF A $\beta$ <sub>1-42</sub> (%)	73.0%
PET scan (%)	76.8%
Age at baseline (y) <sup>a</sup>	73.3 (7.2)
Gender (% male)	55.4%
Diagnosis	330 CN no SMC 103 SMC 667 MCI 296 AD
<i>APOE</i> $\epsilon$ 4 carriers (%)	54.9%
AV-45 Average CB <sup>b</sup>	1.25 (1.13–1.51)
AV-45 Average WM <sup>b</sup>	0.71 (0.65–0.84)
AV-45 Summary CB <sup>b</sup>	1.13 (1.01–1.39)
AV-45 Summary Composite <sup>b</sup>	0.80 (0.71–0.99)
A $\beta$ <sub>1-42</sub> (pg/mL) <sup>b</sup>	157.5 (130.0–220.0)

AD, Alzheimer disease; CB, cerebellum; CN, cognitively normal; CSF, cerebrospinal fluid; Coef., coefficient; MCI, mild cognitive impairment; SE, standard deviation; WM, white matter.



Differences in florbetapir PET adjusted SUVRs based on *APOE*  $\epsilon 4$  in models adjusted for total amyloid load. Positive coefficients indicate higher amyloid burden in  $\epsilon 4$  carriers, whereas negative coefficients represent higher amyloid burden in  $\epsilon 4$  non-carriers

**Table 2**

	Whole cerebellum normalized ROIs		Composite reference normalized ROIs	
	Coefficient	p	Coefficient	p
Rostral anterior cingulate	0.029	<0.0001	0.027	<0.0001
Medial Orbitofrontal region	0.023	<0.0001	0.019	<0.0001
Caudal anterior cingulate	0.014	0.014	0.019	<0.0001
Superior parietal lobe	-0.013	0.021	-0.015	0.0009
Rostral middle frontal	0.019	<0.0001	0.012	0.0014
Supramarginal gyrus	-0.011	0.0014	-0.009	0.0031
Inferior parietal gyrus	-0.005	0.38	-0.009	0.031
Superior frontal gyrus	0.009	0.019	0.006	0.036
Middle temporal region	0.000	0.96	-0.006	0.12
Lateral orbitofrontal region	0.003	0.73	0.006	0.16
Pars orbitalis	-0.001	0.96	-0.005	0.54
Isthmus cingulate	0.001	0.96	0.003	0.54
Pars triangularis	-0.004	0.42	-0.002	0.71
Pars opercularis	-0.006	0.18	-0.002	0.76
Caudal middle frontal lobe	-0.001	0.93	-0.001	0.81
Superior temporal gyrus	0.002	0.73	0.001	0.81
Precuneus	0.003	0.72	-0.001	0.81
Frontal pole	0.011	0.29	-0.002	0.81
Posterior cingulate	-0.002	0.89	0.0003	0.94

Adjusted for multiple comparisons using False discovery rate (FDR) Benjamini-Hochberg correction.

**Table 3**

Association with cross-sectional and longitudinal PET SUVR values

	Cross-sectional associations with PET SUVR values									
	Average CB		Average WM		Summary CB		Summary Comp.		CSF Aβ <sub>1-42</sub>	
	Coef. (SE)	p	Coef. (SE)	p	Coef. (SE)	p	Coef. (SE)	p	Coef. (SE)	p
Age (10 y)	0.032 (0.005)	<0.0001	0.060 (0.006)	<0.0001	0.027 (0.005)	<0.0001	0.037 (0.007)	<0.0001	-0.007 (0.001)	<0.0001
Gender (Female)	0.014 (0.008)	0.069	0.023 (0.009)	0.009	0.027 (0.008)	0.0009	0.047 (0.010)	<0.0001	0.0009 (0.019)	0.96
MCI	0.042 (0.009)	<0.0001	0.080 (0.010)	<0.0001	0.056 (0.009)	<0.0001	0.086 (0.011)	<0.0001	-0.12 (0.021)	<0.0001
AD	0.11 (0.014)	<0.0001	0.20 (0.013)	<0.0001	0.13 (0.012)	<0.0001	0.21 (0.015)	<0.0001	-0.26 (0.030)	<0.0001
<i>APOE</i> ε2/ε2 & ε2/ε3	-0.022 (0.014)	0.12	-0.046 (0.016)	0.004	-0.02 (0.015)	0.12	-0.05 (0.019)	0.006	0.088 (0.035)	0.012
<i>APOE</i> ε2/ε4	0.11 (0.03)	<0.0001	0.11 (0.032)	0.0006	0.12 (0.03)	0.0001	0.14 (0.037)	0.0001	-0.20 (0.083)	0.013
<i>APOE</i> ε3/ε4	0.092 (0.009)	<0.0001	0.12 (0.001)	<0.0001	0.11 (0.009)	<0.0001	0.14 (0.011)	<0.0001	-0.22 (0.022)	<0.0001
<i>APOE</i> ε4/ε4	0.11 (0.014)	<0.0001	0.18 (0.016)	<0.0001	0.15 (0.015)	<0.0001	0.22 (0.019)	<0.0001	-0.43 (0.035)	<0.0001

	Longitudinal associations with PET SUVR values							
	Average CB		Average WM		Summary CB		Summary comp.	
	Coef. (SE)	p	Coef. (SE)	p	Coef. (SE)	p	Coef. (SE)	p
Age (10 y)	0.0009 (0.003)	0.75	0.0015 (0.0007)	0.026	0.002 (0.002)	0.38	0.0002 (0.00008)	0.02
Gender (Female)	-0.0007 (0.004)	0.86	0.0005 (0.0009)	0.61	0.0006 (0.003)	0.83	0.0007 (0.001)	0.53
Baseline SUVR	0.18 (0.086)	0.036	0.20 (0.084)	0.019	0.23 (0.075)	0.002	0.38 (0.053)	<0.0001
Baseline SUVR*2	-0.077 (0.030)	0.011	-0.13 (0.055)	0.017	-0.10 (0.029)	0.0009	-0.21 (0.030)	<0.0001
<i>APOE</i> ε2/ε2 & ε2/ε3	-0.002 (0.007)	0.75	-0.002 (0.002)	0.26	-0.004 (0.005)	0.46	-0.002 (0.002)	0.36
<i>APOE</i> ε2/ε4	-0.0009 (0.015)	0.95	0.004 (0.004)	0.27	-0.04 (0.012)	0.73	-0.002 (0.004)	0.60
<i>APOE</i> ε3/ε4	0.011 (0.005)	0.017	0.004 (0.001)	0.0005	0.006 (0.004)	0.11	0.003 (0.001)	0.035
<i>APOE</i> ε4/ε4	0.024 (0.008)	0.002	0.004 (0.002)	0.0499	0.015 (0.006)	0.014	0.005 (0.002)	0.020

AD, Alzheimer disease; CB, cerebellum; CSF, cerebrospinal fluid; Coef., coefficient; MCI, mild cognitive impairment; SE, standard deviation; SUVR, standardized uptake value ratios; WM, white matter. Transformations differed in the different models.