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## Low plasma ApoE levels are associated with smaller hippocampal size in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort

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### Abstract

Apolipoprotein E (*APOE*) genotype is the strongest known genetic risk factor for sporadic Alzheimer's disease (AD), but the utility of plasma ApoE levels for assessing the severity of underlying neurodegenerative changes remains uncertain. Here we examined cross-sectional associations between plasma ApoE levels and volumetric magnetic resonance imaging (MRI) indices of the hippocampus from 541 participants [57 with normal cognition (NC), 375 with mild cognitive impairment (MCI), and 109 with mild AD] who were enrolled in the Alzheimer's Disease Neuroimaging Initiative. Across the NC and MCI groups, lower plasma ApoE levels were significantly correlated with smaller hippocampal size, as measured by either hippocampal volume

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or hippocampal radial distance. These associations were driven primarily by findings from carriers of an *APOE*  $\epsilon 4$  allele, and are consistent with prior reports that lower plasma ApoE levels correlate with greater global cortical Pittsburgh Compound B retention. In this high-risk group, plasma ApoE levels may represent a peripheral marker of underlying AD neuropathology in nondemented elderly individuals.

### Keywords

Alzheimer's Disease; mild cognitive impairment (MCI); magnetic resonance imaging (MRI); hippocampus; biomarkers; ADNI; apolipoprotein E (ApoE)

## INTRODUCTION

Apolipoprotein E (*APOE*) genotype is the strongest known genetic risk factor for sporadic Alzheimer's disease (AD) [1]. The risk of developing AD is highest in carriers of an  $\epsilon 4$  allele [2] and lowest in carriers of an  $\epsilon 2$  allele [3]. *APOE* affects several different mechanisms in AD pathophysiology, including the abnormal accumulation of  $\beta$ -amyloid (A $\beta$ ) [4].

Given the role of *APOE* genotype in AD risk, prior studies have examined the utility of plasma or serum levels of ApoE protein as a peripheral biomarker for the presence or severity of underlying AD. However, comparisons of plasma or serum ApoE between AD and control subjects have produced mixed results [5–11]. The cause of these discrepancies is uncertain, but may in part be due to differences in ApoE assays or *APOE* genotype distributions between studies. A wide range of technologies have been used to measure plasma and serum ApoE levels, including Western blotting [11], immunoturbidimetry [6,8], nephelometry [9], enzyme-linked immunosorbent assays (ELISAs) [7], and multi-analyte profile (MAP) platforms [10]. Studies that reported similar plasma ApoE levels in AD and controls [8,9] had lower proportions of  $\epsilon 4$  carriers in their AD groups than studies that reported lower plasma ApoE levels in AD [5–7]. The  $\epsilon 4$  isoform is the least stable [12] and is subject to enhanced degradation [13]. Significant associations between *APOE* genotype and plasma/serum ApoE protein levels are seen in clinical populations [7,8,14] and transgenic animal models [15], with the lowest levels seen in  $\epsilon 4$  carriers.

Alternatively, many of the studies comparing AD and control plasma/serum ApoE levels have relied on clinical diagnoses, which may not accurately represent the presence or absence of underlying AD neuropathology, and thus skew the results. A proportion of AD subjects may have had other underlying dementia etiologies and a proportion of normal control subjects may have had underlying incipient AD changes. Therefore, another approach to determining the utility of plasma/serum ApoE as an AD biomarker is to examine its association with other indices of AD neuropathology that are sensitive to changes that may occur before a clinical diagnosis of AD.

Three studies have examined the relationship of plasma ApoE levels and positron emission tomography (PET) imaging of A $\beta$  deposits using Pittsburgh Compound B (PiB) [7,16,17]. Analyses of data collected in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and

the Australian Imaging, Biomarkers, and Lifestyle (AIBL) studies found that lower plasma ApoE levels correlated with increased global cortical PiB retention on PET imaging [7,16]. However, in a smaller cohort of non-demented individuals enrolled in the Baltimore Longitudinal Study of Aging (BLSA), higher plasma ApoE levels correlated with increased PiB retention in medial temporal lobe regions [17].

Although these PiB studies suggest plasma ApoE levels may be associated with underlying brain A $\beta$  pathology, their conflicting results are difficult to reconcile. Therefore, we used the ADNI database to examine the association between plasma ApoE levels and another neuroimaging marker associated with AD pathology: hippocampal size as measured by magnetic resonance imaging (MRI). In addition to conventional hippocampal volumetry, we also employed a more advanced 3D shape deformation approach that incorporates hippocampal radial distances and allows for investigations of regionally specific ApoE associations. Previous work using this methodology has demonstrated that staged progression of subfield-specific atrophy is seen with clinical progression from presymptomatic to prodromal to dementia stages of AD [18]. We hypothesized that this surrogate measure of AD-associated neurodegeneration would provide greater sensitivity for detecting a relationship between plasma ApoE levels and underlying disease progression than conventional clinical indices.

## METHODS

### Subjects

ADNI is a large multi-center longitudinal study of the natural history and biological correlates of AD. It longitudinally collected detailed clinical, imaging, and laboratory data from 200 normal control (NC), 400 amnesic mild cognitive impairment (MCI), and 200 AD subjects over a 4-year period [19] (also see [adni.loni.usc.edu](http://adni.loni.usc.edu) and [ADNI-info.org](http://ADNI-info.org)). Participants were 55 to 90 years old at the time of enrollment. Exclusion criteria included significant neurologic disease other than AD, abnormal baseline MRI or contraindications to MRI, psychiatric disorders (including depression), alcohol or substance abuse or dependency within the last 2 years, and medical illnesses that could affect cognition or protocol compliance. A full list of inclusion/exclusion criteria can be found in the ADNI protocol ([www.adni-info.org/Scientists/ADNISTudyProcedures.aspx](http://www.adni-info.org/Scientists/ADNISTudyProcedures.aspx)).

The study cohort was classified into diagnostic groups based on cognitive and functional criteria. NC participants scored within age- and education-adjusted norms on the Logical Memory II (LM II) subscale from the Wechsler Memory Scale-Revised (WMS-R) [20], between 24 and 30 on the Mini Mental State Examination (MMSE) [21], and received a global score of 0 on the Clinical Dementia Rating Scale (CDR) [22]. MCI participants had memory complaints and scored below age- and education-adjusted norms on the LM-II subscale of the WMS-R. At baseline, their MMSE scores were between 24 and 30, their global CDR was 0.5, and their general cognition and activities of daily living were essentially intact. AD participants met the National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD [23], had MMSE scores between 20 and 26, and had global CDRs of 0.5 or 1.

## Image acquisition

All subjects were scanned at 1.5 Tesla magnetic field strength on scanners from 1 of 3 manufacturers (General Electric Healthcare, Siemens Medical Solutions, and Philips Medical Systems) with a scanner-specific standardized MRI protocol ([adni.loni.usc.edu/methods/documents/mri-protocols](http://adni.loni.usc.edu/methods/documents/mri-protocols)) at 58 different sites [24]. Additional image corrections including: GradWarp correction for geometric distortions due to gradient nonlinearity [25], “B1-correction” for image intensity nonuniformity [24], and “N3” bias field correction, for reducing intensity inhomogeneity [26]. Similar proportions of participants from each diagnostic group were imaged at each site and with each manufacturer’s scanners. Imaging data are maintained at a central repository at the Laboratory of Neuro Imaging at USC and are freely available for download ([adni.loni.usc.edu](http://adni.loni.usc.edu)).

Corrected images were downloaded and linearly registered to the International Consortium for Brain Mapping (ICBM-53) standard brain template [27], with a 9-parameter transformation (3 translations, 3 rotations, 3 scales) using the Minctracc algorithm [28]. Globally aligned images were re-sampled in an isotropic space of 220 voxels along each axis (x, y, and z), with a final voxel size of 1 mm<sup>3</sup>. We corrected for differences in head tilt and size by orienting each brain volume into the ICBM53 standardized coordinate system.

## Imaging analysis

The baseline images of our selected study sample underwent an automated hippocampal segmentation technique based on a machine-learning method called adaptive boosting (AdaBoost), which has been validated against manual segmentation in a subset of NC, MCI, and AD participants from the ADNI study [29], and yields results that are comparable or superior to other automated hippocampal segmentation methods [30]. Our training dataset consisted of manual hippocampal traces of 21 randomly chosen ADNI subjects (7 NC, 7 MCI, and 7 AD) created by a single human expert (intra-rater reliability Cronbach’s alpha = 0.98) who followed a widely used and extensively validated hippocampal tracing protocol [31]. Traces included the hippocampus proper, dentate gyrus and subiculum. The final AdaBoost classification algorithm was applied to the full imaging dataset. After hippocampal segmentation, the left and right hippocampal volumes were computed and retained for statistical analyses.

Traces were converted into hippocampal contours and transformed into 3D parametric surface mesh models, thus assuring normalization of the spatial frequency of the digitized surface points, which were then separated into top and bottom components [32]. Next, a medial core through the center of the hippocampus was computed. Radial distance was measured from the medial core to each corresponding surface coordinate point in the hippocampus. Individual hippocampal radial distance maps were combined across subjects to create group average distance maps for quantitative comparisons of surface morphology [32].

## Plasma ApoE Measurements

Fasting blood samples were collected at the baseline ADNI visit into K<sub>2</sub>EDTA coated tubes. Samples were spun at room temperature at 3000 RPM for 15 minutes within one hour of

collection. The plasma component was aliquoted into polypropylene tubes and stored at  $-80^{\circ}\text{C}$  prior to shipment to Myriad RBM for analysis with a 190-analyte multiplex immunoassay panel (Human Discovery MAP 1.0, Myriad RBM, Austin TX) on the Luminex xMAP platform (Luminex Corp., Austin TX). ApoE was one of 146 analytes that met ADNI quality control criteria (see [adni.loni.usc.edu/wp-content/uploads/2010/11/BC\\_Plasma\\_Proteomics\\_Data\\_Primer.pdf](http://adni.loni.usc.edu/wp-content/uploads/2010/11/BC_Plasma_Proteomics_Data_Primer.pdf) for details). Plasma ApoE levels were  $\log_{10}$ -transformed for statistical analyses. The NC group selected for plasma biomarker analyses included only subjects with CSF A $\beta$ 42 levels above the median level for the larger NC cohort, in order to increase the likelihood of identifying changes in plasma biomarkers in individuals with suspected early AD.

### Statistical methods

Statistical analyses were performed using SPSS 22 for Mac (IBM, Armonk NY). Demographic, plasma ApoE and lipid (total cholesterol and triglycerides), and hippocampal imaging data were compared between diagnostic and *APOE* genotype groups using analyses of variance (ANOVAs) or *t*-tests for continuous variables and Pearson's chi-square tests for categorical variables. Analyses were Bonferroni corrected for comparisons involving more than two groups. Correlational analyses were performed with Pearson's correlation coefficient. Relationships between plasma ApoE levels and hippocampal volumes and radial distance were studied with linear regression analyses adjusted for age, sex, and *APOE* genotype. 3D statistical maps were adjusted for multiple comparisons using permutation-based statistics with a threshold of  $p < 0.01$ .

## RESULTS

### Demographic data

We identified 562 ADNI participants with baseline MRI and plasma ApoE data. MRI scans from 8 participants failed automated hippocampal segmentation. An additional 13 participants had an *APOE* genotype of  $\epsilon 2/\epsilon 4$ . Data from these two subgroups were excluded from further analyses, which included the remaining 57 NC, 375 MCI, and 109 AD participants. Demographic data arranged by diagnostic group are shown in Table 1. The three diagnostic groups were similar in age, years of formal education, sex distribution, body mass index, and prevalence of hypertension. However, significant group differences were seen in ethnicity, prevalence of an *APOE*  $\epsilon 4$  allele, and MMSE scores, which were further investigated with Bonferroni corrected *post hoc* comparisons (critical  $p < 0.017$ ). The AD group had a higher proportion of non-Hispanic White participants than the MCI group ( $p = 0.009$ ). The AD group also had a higher proportion of *APOE*  $\epsilon 4$  allele carriers than the MCI ( $p = 0.007$ ) and NC groups ( $p < 0.001$ ), and the MCI group had a higher proportion of  $\epsilon 4$  carriers than the NC group ( $p < 0.001$ ). Therefore, ethnicity and presence/absence of an *APOE*  $\epsilon 4$  allele were included in subsequent comparisons between diagnostic groups. As expected, the NC group performed better on the MMSE than the MCI group, which in turn, performed better than the AD group (all  $p$ 's  $< 0.001$ ).

## Plasma ApoE levels

Raw and  $\log_{10}$ -transformed plasma ApoE levels across diagnostic groups are shown in Table 1. A three-way ANOVA revealed a significant effect of diagnosis [ $F(2,530)=3.25$ ,  $p=0.040$ ]. Bonferroni corrected post hoc analyses (critical  $p<0.017$ ) indicated that  $\log_{10}$ -transformed plasma ApoE levels were significantly higher in the NC group relative to both the MCI and AD groups (both  $p$ 's $<0.001$ ).  $\log_{10}$ -transformed plasma ApoE levels did not differ between the MCI and AD groups ( $p=0.12$ ), but across the entire cohort, were significantly lower in  $\epsilon 4$  carriers (mean=1.62, SD=0.18) than in  $\epsilon 4$  non-carriers [mean=1.79, SD=0.17;  $F(1,530)=7.73$ ,  $p=0.006$ ]. Among  $\epsilon 4$  carriers,  $\log_{10}$ -transformed plasma ApoE levels were significantly higher in heterozygotes ( $n=204$ ; mean=1.65, SD=0.15) than homozygotes [ $n=69$ ; mean=1.52, SD=0.20;  $t(271)=95.52$ ,  $p<0.001$ ]. There was no effect of ethnicity. Separate analyses indicated that  $\log_{10}$ -transformed plasma ApoE levels were positively correlated with age [ $r(541)=0.11$ ,  $p=0.012$ ] and significantly higher in women than men (Table 2;  $p<0.001$ ). Similar plasma total cholesterol and triglyceride levels were seen across diagnostic groups (Table 1). Raw plasma ApoE levels were significantly correlated with total cholesterol [ $r(527)=0.391$ ,  $p<0.001$ ] and triglyceride levels [ $r(527)=0.577$ ,  $p<0.001$ ].

## Hippocampal volumes

Hippocampal volumes across diagnostic groups are also shown in Table 1. Overall, measurements of right and left hippocampal volume were moderately correlated [ $r(541)=0.67$ ,  $p<0.001$ ], but significantly smaller hippocampal volumes were seen on the right relative to the left [ $t(540)=-3.22$ ,  $p=0.001$ ]. Analyses of right hippocampal volume using three-way ANOVA revealed a significant effect of clinical diagnosis [ $F(2,530)=6.75$ ,  $p=0.001$ ], but not of *APOE* genotype or ethnicity. Right hippocampal volumes were significantly smaller in the AD group relative to both the NC ( $p<0.001$ ) and MCI ( $p=0.001$ ) groups after Bonferroni correction (critical  $p<0.017$ ). Similar analyses of left hippocampal volume revealed a marginally significant effect of clinical diagnosis [ $F(2,530)=2.59$ ,  $p=0.076$ ], but not of *APOE* genotype or ethnicity. Left hippocampal volumes were significantly smaller in the AD group relative to the NC group ( $p=0.006$ ) after Bonferroni correction. Separate analyses revealed negative correlations between age and right [ $r(541)=-0.14$ ,  $p<0.001$ ] and left [ $r(541)=-0.20$ ,  $p<0.001$ ] hippocampal volumes. Additionally, larger hippocampal volumes were seen in women relative to men on both the right ( $p=0.009$ ) and left ( $p<0.001$ ) sides (Table 2).

## Correlations between plasma ApoE levels and hippocampal volumes

Multiple regression analyses were used to determine the relationship between hippocampal volumes and  $\log_{10}$ -transformed plasma ApoE levels. When data from all participants were included, the associations between plasma ApoE levels and right or left hippocampal volumes failed to reach significance after adjustment for age, sex, and presence/absence of an *APOE*  $\epsilon 4$  allele (data not shown). Inspection of right and left hippocampal volumes indicated that they became progressively smaller from the NC to MCI to AD groups (Table 1). Similar inspection of plasma ApoE levels indicated that although they decreased from the NC group to the MCI group, they remained similar between the MCI and AD groups

(Table 1). These results raised the possibility that plasma ApoE might only serve as a marker of the severity of underlying AD neuropathology at earlier stages of the disease due to potential floor effects at later stages.

Therefore, additional exploratory multiple regression analyses between plasma ApoE levels and hippocampal volumes were restricted to the NC and MCI groups. The results of these regression analyses, which incorporated right or left hippocampal volumes as dependent variables and were adjusted for age, sex, and presence/absence of an *APOE*  $\epsilon 4$  allele, are shown in Table 3. Plasma ApoE levels exhibited a significant positive correlation with left hippocampal volumes even after accounting for *APOE* genotype. Given the significant effects of *APOE* genotype on plasma ApoE levels reported above, we further subdivided this portion of the study cohort into *APOE*  $\epsilon 4$  carriers and non-carriers and found that the association between plasma ApoE levels and left hippocampal volume remained significant only in the presence of an  $\epsilon 4$  allele (Figure 1). Right hippocampal volumes in the NC and MCI groups were not significantly associated with plasma ApoE levels in any of the regression analyses. Similar results were obtained when these analyses were performed using raw plasma ApoE levels (Supplementary Table).

### Correlations between plasma ApoE levels and hippocampal radial distance

Additional multiple regression analyses were used to determine the relationship between hippocampal radial distance and plasma ApoE levels while controlling for age and sex. The 3D significance maps are shown in Figure 2. In the overall study sample, plasma ApoE levels were significantly correlated with left hippocampal radial distances, (permutation-corrected  $p=0.014$ ) but this finding did not survive correction for the presence of an *APOE*  $\epsilon 4$  allele (permutation-corrected  $p=0.23$ ). When we focused our exploratory analyses on the NC and MCI participants, significant associations between left hippocampal radial distance and plasma ApoE protein levels were present both before (permutation-corrected  $p=0.033$ ) and after correction for the presence of an *APOE*  $\epsilon 4$  allele (permutation-corrected  $p=0.047$ ). Although we still saw regionally significant associations between plasma ApoE levels and hippocampal radial distance among *APOE*  $\epsilon 4$  carriers in the NC and MCI groups, these results did not survive stringent permutation correction for multiple comparisons. Across the NC and MCI *APOE*  $\epsilon 4$  noncarriers, there were no significant associations between plasma ApoE protein levels and hippocampal radial distance.

## DISCUSSION

Our exploratory analyses of ADNI data for participants in the NC and MCI groups indicated a modest, but statistically significant association between lower plasma ApoE levels and smaller left hippocampal volumes and radial distances. This association was seen with global left hippocampal volumes, and was not driven by subfield-specific effects. It remained robust even after correction for age, sex, and *APOE* genotype, suggesting that plasma ApoE levels in this cohort may reflect both *APOE* genotype and the extent of underlying neurodegeneration. When the NC and MCI participants were subdivided into those with and without an *APOE*  $\epsilon 4$  allele, we found that the association between plasma ApoE levels and left hippocampal volume was driven primarily by *APOE*  $\epsilon 4$  carriers. Taken



together, these results suggest that plasma ApoE represents a potential peripheral marker of underlying AD neuropathology in nondemented elderly *APOE*  $\epsilon 4$  carriers, a cohort at high risk of subsequent progression to AD dementia.

Our findings are consistent with prior analyses of data from the ADNI [16] and AIBL [7] cohorts, which indicated that lower plasma ApoE levels were seen in *APOE*  $\epsilon 4$  carriers and were associated with another well-established AD biomarker, increased global cortical PiB retention. However, a third study from the BLSA showed an association in the opposite direction; increased plasma ApoE levels were associated with more pronounced medial temporal lobe PiB retention [17]. The seemingly counterintuitive direction of plasma ApoE-PiB association in the BLSA study is most likely due to different study cohort composition and/or plasma ApoE measurement techniques given that the authors reported higher rather than lower plasma ApoE levels in *APOE*  $\epsilon 4$  carriers relative to *APOE*  $\epsilon 3$  carriers [17] which contrasts with several other studies, including ours [7,8,14].

We observed a significant association between plasma ApoE levels and hippocampal size in NC and MCI but not AD subjects. Plasma ApoE levels in our MCI and AD cohorts were nearly identical, yet both groups had significantly lower ApoE levels than the NC group (see Table 1). We speculate that these data represent an early dynamic decline in plasma ApoE levels, which reach a floor in the early (MCI) and later (clinical AD) symptomatic stages of the disease. While this conclusion requires confirmation by longer longitudinal studies, a similar pattern has already been proposed for brain amyloidosis, as abnormal PiB retention appears to plateau in the early symptomatic stages of AD [33]. In contrast, measures of hippocampal volume showed a greater dynamic range than plasma ApoE levels through all stages of the disease in our ADNI sample. Therefore, plasma ApoE levels may only prove sensitive to progressive neurodegenerative changes in earlier stages of AD, prior to clinical dementia. An earlier ADNI study also related hippocampal volumes to plasma ApoE levels but failed to find a significant association between the latter two variables, possibly because of their inclusion of participants with clinical AD or use of less sensitive non-parametric statistics [16].

Plasma ApoE levels correlated with hippocampal volumes, even after accounting for *APOE* genotype. However, this effect was primarily driven by the associations found in  $\epsilon 4$  carriers. This result is consistent with prior work indicating that the presence of an *APOE*  $\epsilon 4$  allele is associated with greater or accelerated hippocampal atrophy [34–37]. *APOE* genotype may affect AD pathophysiology through multiple mechanisms [4]. One potential explanation for our findings may be found in the relationship between *APOE* genotype and A $\beta$  clearance from the brain. ApoE  $\epsilon 4$  has a lower affinity for A $\beta$  than does ApoE  $\epsilon 3$  [38]. Transgenic mice expressing human  $\epsilon 4$  alleles clear A $\beta$  more slowly than those expressing human  $\epsilon 2$  or  $\epsilon 3$  alleles [39]. Therefore, A $\beta$  clearance in  $\epsilon 4$  carriers may be particularly dependent on circulating ApoE levels. This mechanism might be expected to be more relevant to ApoE levels in the brain than in the plasma, but previous work with transgenic *APOE* mice indicates that *APOE* genotype has similar effects on brain and plasma ApoE levels [15]. Although ApoE does not appear to cross the blood-brain barrier [40], ApoE levels and isoforms modulate A $\beta$  clearance from the plasma [41], which may in turn affect A $\beta$  clearance from the brain.

Significant associations were seen between plasma ApoE levels and hippocampal volumetric indices on the left but not on the right. The root cause of the hemispheric asymmetry in our findings remains uncertain. However, a prior study of cerebrospinal fluid (CSF) biomarkers and hippocampal volumes in AD only showed significant correlations between CSF levels of total and phosphorylated tau and left (but not right) hippocampal volumes [42]. Previous work has also suggested that the effects of *APOE* genotype on hippocampal volumetrics in AD are more apparent on the left than on the right [37]. In that report, much like in the current study, smaller hippocampal volumes were found on the right side than on the left side, leading the authors to conclude the more advanced atrophy in the right hippocampus may have obscured the relationship between *APOE* genotype and hippocampal volumes on that side. Likewise, a recent analysis of the AddNeuroMed biomarker data reported stronger associations between putative plasma biomarker levels and hippocampal volumes in the left hemisphere relative to the right hemisphere [43]. While prior PiB studies in MCI and AD have not conclusively shown hemispheric asymmetry in amyloid deposition [44], PiB signal in the left, but not right, hemisphere in AD patients correlates with both cognitive performance and regional hypometabolism on FDG PET [45]. Alternatively, it has also been suggested that manual hippocampal volumetric analyses may be subject to asymmetric left-right biases [46]. This phenomenon could have theoretically impacted our results, even though our hippocampal indices were derived from automated segmentation, since the initial training set was developed through manual tracing. Although these results remain incompletely understood, they raise the possibility that the interactions between hippocampal volume and other AD biomarkers and risk factors may not always be bilaterally symmetric, particularly since greater hemispheric asymmetry in hippocampal volumes is associated with a higher likelihood of cognitive impairment [47].

A number of factors may limit the interpretation of our results. While hippocampal size is closely related to the clinical severity of AD [18,33] hippocampal atrophy can be seen in conditions other than AD [48]. The ADNI cohort is a convenience sample rather than an epidemiological cohort, which may reduce the generalizability of the results, particularly since a prior community-based study of plasma ApoE levels in non-demented elderly reported higher rather than lower levels in MCI relative to cognitively normal controls [49]. The subset of ADNI participants with plasma biomarker data may be more prone to selection bias than the larger ADNI study population [16], as it includes a much lower proportion of *APOE*  $\epsilon 4$  carriers (7%) than a prior study of the larger ADNI NC cohort, which reported an *APOE*  $\epsilon 4$  frequency of 26% [50]. Furthermore, the composition of the ADNI cohort was significantly weighted towards participants with MCI, and there were far fewer participants in the NC and AD groups. These last two factors may have impacted our ability to examine the associations between plasma ApoE levels and disease progression in presymptomatic AD. Finally, although the Myriad RBM ApoE assay targets all three isoforms, its relative sensitivity for individual isoforms has not yet been established (personal communication, Myriad RBM).

Our findings of a significant association between plasma ApoE levels and hippocampal size, when considered in conjunction with other cross-sectional studies suggesting similar associations between plasma ApoE levels and global cortical PiB uptake [7,16], raise the

possibility that this measure may represent a peripheral marker of underlying AD neuropathology, that may be most informative in early stages of the disease. Since the association between plasma ApoE levels and left hippocampal volumes was relatively modest and prior work suggests that alterations of ApoE levels measured from blood are present in other brain disorders [51], this marker may be more useful when considered in conjunction with other potential plasma or CSF markers of AD. Such panels may have particularly utility for enriching future AD prevention trials with participants at greatest risk for subsequent progression to AD-related dementia. It remains uncertain whether the changes in plasma ApoE levels in MCI and AD represent a cause or a consequence of underlying AD pathophysiology [7]. Further longitudinal studies of plasma biomarker data will allow for more comprehensive determinations of the value of plasma ApoE as a marker of early stages of AD neuropathology.

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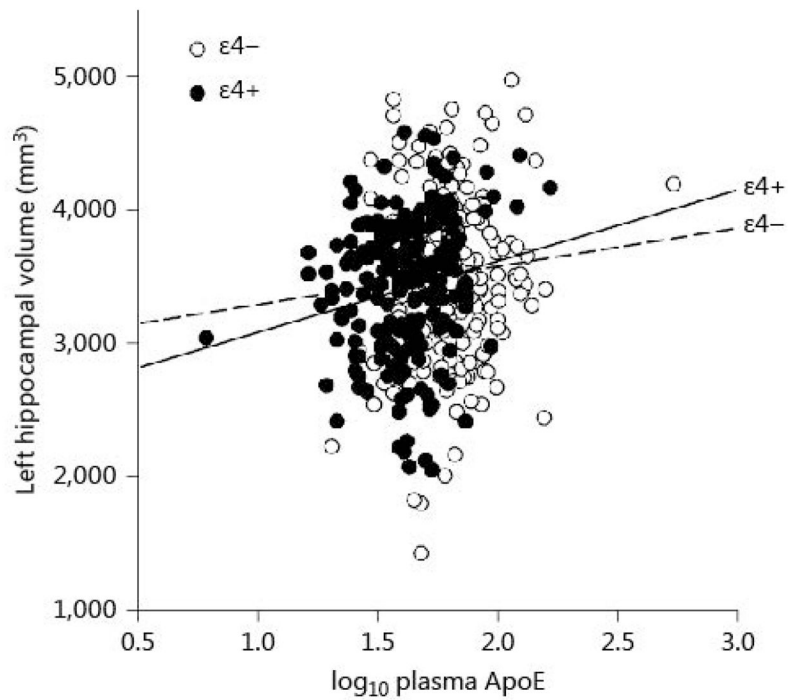
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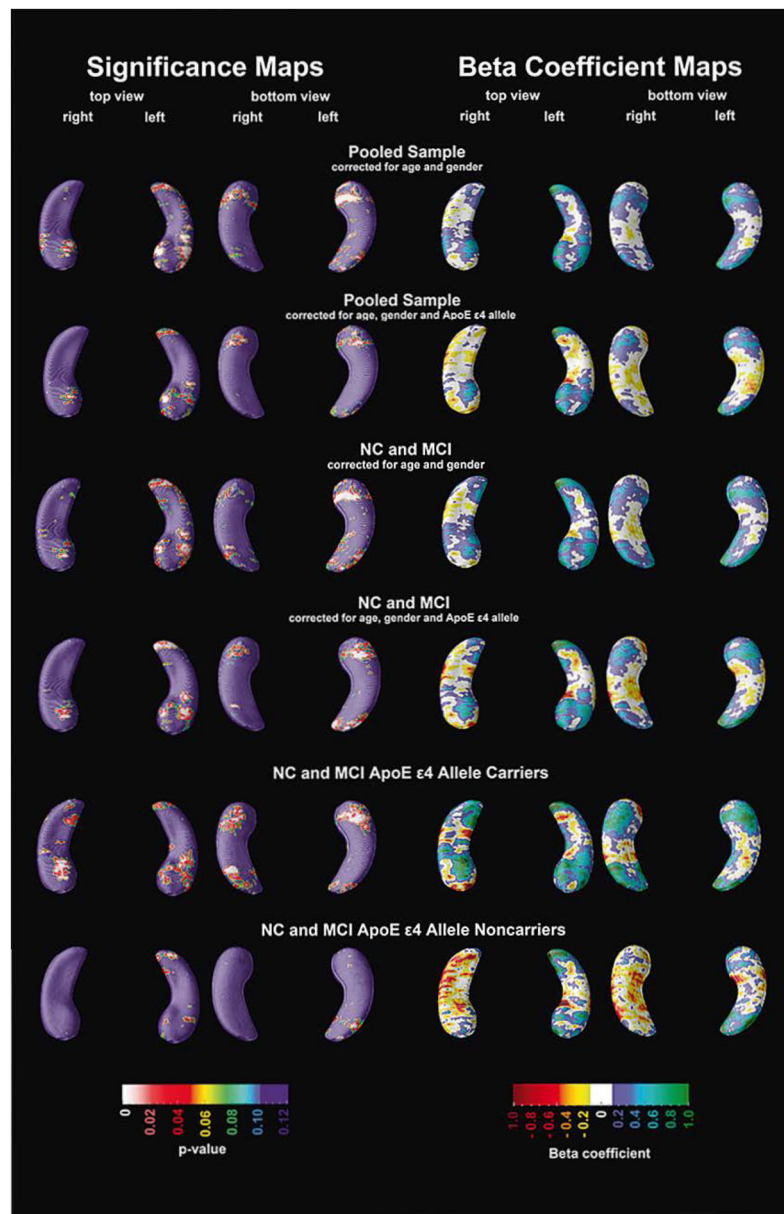
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**Figure 1.** Correlations between log<sub>10</sub>-transformed plasma ApoE levels and left hippocampal volumes in NC and MCI participants with and without an ε4 allele.



**Figure 2.** Three-dimensional significance and beta coefficient maps showing the regional associations between plasma ApoE levels and hippocampal radial distance.



**Table 1**

Demographic, plasma ApoE, and hippocampal volume data by diagnostic group

	NC	MCI	AD	F(2,538)/ $\chi^2$ (541)
N	57	375	109	
Age	75.2 (5.8)	74.8 (7.5)	74.8 (8.0)	0.07
Education	15.7 (2.7)	15.6 (3.1)	15.1 (3.2)	1.29
% Male	50.9%	63.7%	58.7%	3.85
% Non-Hispanic White	91.2%	89.1%	97.3% <sup>b</sup>	6.86*
MMSE	29.0 (1.0)	27.0 (1.8) <sup>a</sup>	23.6 (1.9) <sup>a,b</sup>	225.28*
Body mass index <sup>†</sup>	27.1 (4.0)	26.0 (4.0)	25.6 (3.7)	2.72
History of hypertension	50.9%	50.7%	46.8%	0.53
% ApoE $\epsilon$ 4 +	7.0%	52.3% <sup>a</sup>	67.0% <sup>a,b</sup>	55.31*
Plasma ApoE ( $\mu$ g/ml)	74.7 (25.6)	53.1 (33.1) <sup>a</sup>	56.6 (27.1) <sup>a</sup>	11.76*
Log <sub>10</sub> plasma ApoE	1.85 (0.14)	1.68 (0.19) <sup>a</sup>	1.71 (0.19) <sup>a</sup>	20.52*
Total cholesterol (mg/dL) <sup>‡</sup>	188.4 (41.1)	198.2 (42.2)	196.3 (39.3)	1.38
Triglycerides (mg/dL) <sup>‡</sup>	145.2 (93.0)	153.1 (140.5)	164.6 (107.8)	0.48
Hippocampal volume (mm <sup>3</sup> )				
Right	3709.0 (625.6)	3365.7 (607.0) <sup>a</sup>	3107.1 (617.4) <sup>a,b</sup>	18.57*
Left	3767.4 (579.2)	3433.1 (544.9) <sup>a</sup>	3190.2 (671.1) <sup>a,b</sup>	19.13*

Parentheses denote standard deviations. NC: normal control; MCI: mild cognitive impairment; AD: Alzheimer's disease; MMSE: Mini-Mental Status Examination score; ApoE: apolipoprotein E;

\*  $p < 0.05$ ;

<sup>a</sup>  $p < 0.017$  vs. NC;

<sup>b</sup>  $p < 0.017$  vs. MCI;

<sup>†</sup> F(2,537) due to missing data for 1 NC participant;

<sup>‡</sup> F(2,524) due to missing data for 1 NC, 9 MCI, and 4 AD participants.

**Table 2**

Sex differences in plasma ApoE levels and hippocampal volumes

	Men	Women	<i>t</i> (539)
N	332	209	
Log <sub>10</sub> plasma ApoE	1.67 (0.18)	1.75 (0.20)	-4.70*
Hippocampal Volume (mm <sup>3</sup> )			
Right	3293.2 (658.4)	3439.5 (573.9)	-2.64*
Left	3309.7 (592.3)	3593.7 (557.9)	-5.55*

Parentheses denote standard deviations.

\*  $p < 0.05$ .

**Table 3**

Multiple regression analyses for right and left hippocampal volumes in the NC and MCI groups.

<i>All NC and MCI participants</i>						
	Right Hippocampal Volume			Left Hippocampal Volume		
	$\beta$	<i>t</i>	<i>p</i>	$\beta$	<i>t</i>	<i>p</i>
Age	-0.124	-2.571	0.010	-0.177	-3.765	<0.001
Sex	0.088	1.789	0.074	0.172	3.597	<0.001
ApoE $\epsilon$ 4 allele	-0.108	-2.003	0.046	-0.066	-1.256	0.210
Log <sub>10</sub> plasma ApoE	0.026	0.042	0.637	0.109	2.045	0.041
Overall Model	<i>r</i> =0.192			<i>r</i> =0.299		
<i>NC and MCI ApoE <math>\epsilon</math>4 allele carriers</i>						
	Right Hippocampal Volume			Left Hippocampal Volume		
	$\beta$	<i>t</i>	<i>p</i>	$\beta$	<i>t</i>	<i>p</i>
Age	-0.132	-1.833	0.068	-0.108	-1.53	0.128
Sex	0.084	1.155	0.250	0.171	2.409	0.017
Log <sub>10</sub> plasma ApoE	0.098	1.381	0.169	0.156	2.248	0.026
Overall Model	<i>r</i> =0.203			<i>r</i> =0.285		
<i>NC and MCI ApoE <math>\epsilon</math>4 allele non-carriers</i>						
	Right Hippocampal Volume			Left Hippocampal Volume		
	$\beta$	<i>t</i>	<i>p</i>	$\beta$	<i>t</i>	<i>p</i>
Age	-0.115	-1.739	0.083	-0.220	-3.461	0.001
Sex	0.102	1.482	0.140	0.193	2.913	0.004
Log <sub>10</sub> plasma ApoE	-0.038	-0.549	0.583	0.049	0.741	0.459
Overall Model	<i>r</i> =0.153			<i>r</i> =0.301		