

# Low serum levels of ApoE associate with hippocampal atrophy in the ADNI cohort

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## Background:

Alzheimer's Disease (AD) has a long latent stage. However, there is no reliable presymptomatic biomarker yet. Considering the ease of access to peripheral blood samples, there has been significant interest in serum or plasma protein biomarkers.

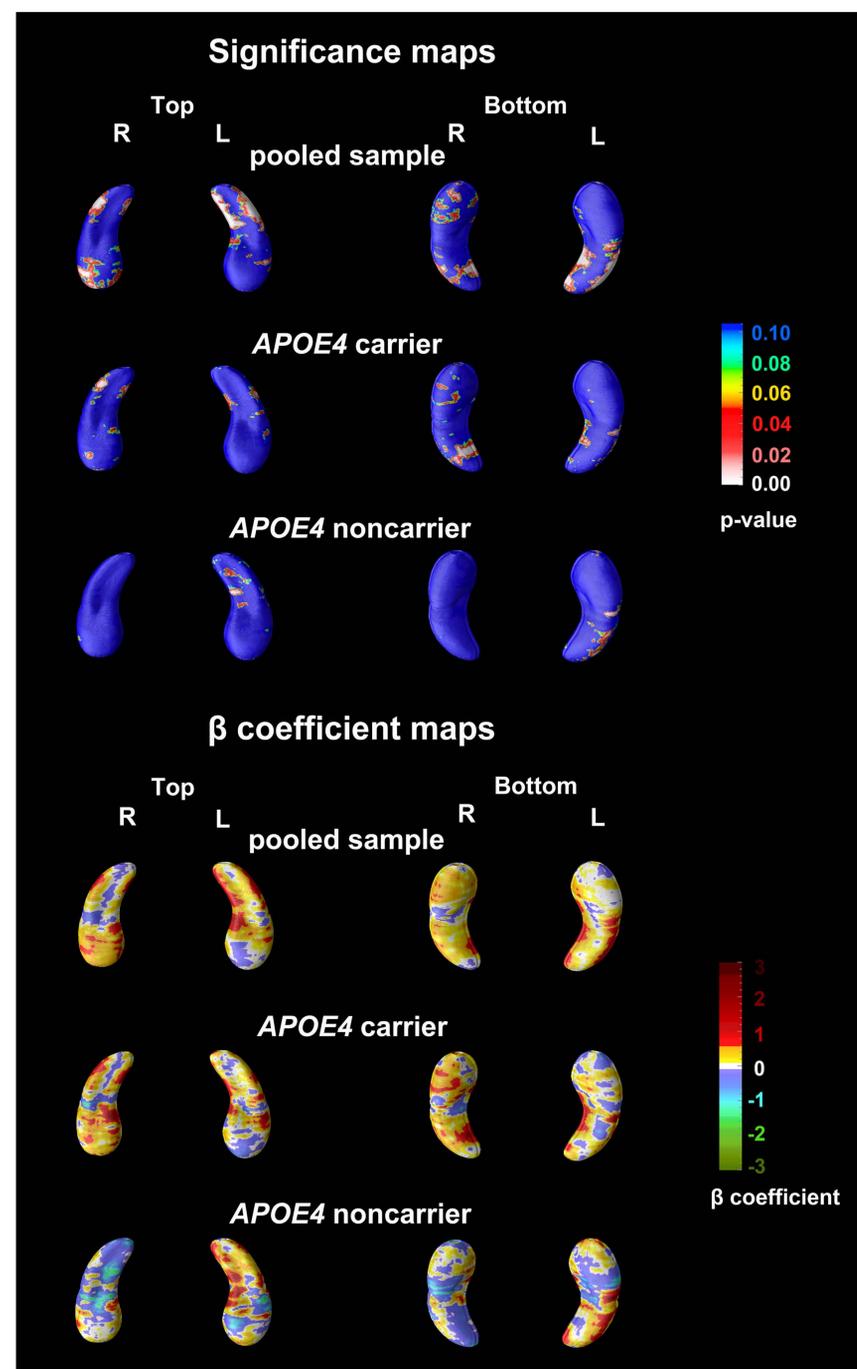
## Methods:

We analyzed the imaging and plasma protein biomarker data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. Our sample included 475 subjects – 58 normal controls (NC), 310 MCI and 107 AD subjects of whom 244 were apolipoprotein E4 gene (*APOE4*) carriers and 231 *APOE4* non-carriers. Baseline EDTA plasma samples were collected and analyzed with a 190 analyte multiplex immunoassay panel based on the Luminex xMAP platform. Hippocampal segmentations were created from 1.5T 3D T1-weighted brain MRI scans, with a novel automated segmentation technique based on the AdaBoost machine learning method. Hippocampal thickness was analyzed with the radial distance technique. We applied linear regression models to study the associations between hippocampal radial distance and several promising plasma protein AD biomarkers – apolipoprotein E (ApoE), apolipoprotein J (ApoJ), brain derived neurotrophic factor (BDNF), heat shock protein 40 (HSP40), interleukin 6 (IL6) and tumor-necrosis factor  $\alpha$  (TNF $\alpha$ ). Our linear regression models were adjusted for age and gender in the pooled sample. Considering a possible modulation by *APOE4* genotype, we also ran separate analyses in the *APOE4* carrier and non-carrier groups. For multiple comparisons correction, we used permutations with a threshold of  $p < 0.01$ .

**Table 1.** Demographic and biomarker data [mean (SD)]

| Variable      | <i>APOE4</i> carriers (N=244) | <i>APOE4</i> non-carriers (N=231) | p-value |
|---------------|-------------------------------|-----------------------------------|---------|
| Age, yr       | 74.21 (6.907)                 | 75.85 (7.771)                     | 0.015   |
| Gender, M/F   | 153/91                        | 144/87                            | 0.934   |
| Education, yr | 15.40 (3.101)                 | 15.94 (2.935)                     | 0.053   |
| MMSE          | 25.86 (2.387)                 | 27.09 (2.310)                     | <0.001  |

**Figure 1.** Significance and  $\beta$  coefficient maps showing the association between plasma ApoE levels and hippocampal radial distance



## Results:

The demographic comparisons of *APOE4* carriers and non-carriers are presented in **Table 1**. The groups were well balanced with respects to gender and education. There were significant between-group differences in mean age and MMSE score at baseline.

Plasma ApoE levels showed significant positive associations with hippocampal radial distance in the CA1 and subicular regions bilaterally in the pooled sample (left  $\beta=0.28$ ,  $p_{\text{corrected}}=0.001$ ; right  $\beta=0.23$ ,  $p_{\text{corrected}}=0.046$ ; **Figure 1**, top row). Regionally significant positive associations were present bilaterally in *APOE4* carriers (left  $\beta=0.14$ ; right  $\beta=0.27$ ; **Figure 1**, middle row). The association pattern in *APOE4* non-carriers was different from that seen in *APOE4* carriers especially on the right where it took a negative direction (left  $\beta=0.19$ ; right  $\beta=-0.18$ ; **Figure 1**, bottom row). ApoJ, BDNF, TNF $\alpha$  and IL6, failed to show significant association with hippocampal radial distance (maps not shown).

## Conclusions:

Decreased plasma levels of ApoE, a protein known to have amyloid  $\beta$  binding properties and to play an important role in amyloid  $\beta$  clearance, have been reported in AD. Studies have indicated that plasma ApoE protein levels may reflect disease status. Previous works using a young cohort at-risk for familial Alzheimer's disease (FAD) and another using NC and early-stage AD subjects, have shown that *APOE4* carriers have lower levels of plasma ApoE compared to *APOE4* noncarriers. Here, we report that lower plasma ApoE protein levels correlate with smaller hippocampal radial distance, a measure of hippocampal atrophy and an established biomarker for AD, in the pooled sample and among *APOE4* carriers. This association appears to be more largely driven by the *APOE4* carrier subgroup.

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