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NEUROIMAGING

Sex and *APOE-ε4* carrier effects on early-onset Alzheimer's disease pathology

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Abstract

Background: Previously, we found that female sex is associated with greater pathology burden in early-onset Alzheimer's disease (EOAD) in the Longitudinal EOAD Study (LEADS). Here, we have expanded our analyses by adding *APOE-ε4* carrier status as a further predictor of EOAD pathologic burden.

Method: We included 180 EOAD LEADS participants with available *APOE* genotype, Flortaucipir PET, Florbetaben PET, and MRI data. Demographic and biomarker differences were analyzed using ANOVA. EOAD participants were split by sex and *APOE-ε4* carrier status. Box plots were created in R and a voxel-wise multiple linear regression in SPM12 yielded statistical brain maps of gray matter density (GMD), amyloid and tau burden.

Result: Compared to males, EOAD females showed significantly greater global amyloid uptake (mean SUVR, p=0.002) and greater tau SUVR in the MetaROI, Braak 3&4 and 5&6 regions (p=0.0007, p=0.001, p=0.01, resp., Table 1). Female *APOE-ε4* carriers showed greater tau SUVR in Braak regions 1&2 than female non-carriers (p<0.01, Figure 2B). Male *APOE-ε4* carriers showed trend-level thinner entorhinal cortex than male non-carriers (p=0.06, Figure 1). Interestingly however, female *APOE-ε4* non-carriers showed greater global amyloid SUVR than female carriers (p<0.01, Figure 2A). Further, *APOE-ε4* non-carriers showed significantly thinner medial temporal cortices than carriers in both sexes (M, p<0.05; F, p<0.01). Male *APOE-ε4* non-carriers

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also showed significantly lower mean cortical thickness than male carriers ($p<0.05$, Figure 1). Female *APOE-ε4* non-carriers showed trend-level lower mean cortical thickness than female carriers ($p=0.06$, Figure 1). The FWE corrected SPM12 maps showed significantly greater GM atrophy in the right temporal lobe and greater amyloid burden in a right lateralized occipitoparietal pattern in female *APOE-ε4* non-carriers compared to female carriers. Further, male *APOE-ε4* non-carriers showed greater tau uptake in the left frontal lobe than male carriers (Figure 3).

Conclusion: These results suggest that *APOE-ε4* non-carrier status is associated with greater atrophy, amyloid and tau deposition in EOAD. This might be due to the presence of other strong genetic drivers of disease pathology in EOAD.