Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk APOE4 women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort

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Background The risk of dementia is higher in women than men. The metabolic consequences of estrogen decline during menopause accelerate neuropathology in women. The use of hormone replacement therapy (HRT) in the pre- vention of cognitive decline has shown conflicting results. Here we investigate the modulating role of APOE genotype and age at HRT initiation on the heterogeneity in cognitive response to HRT.

Methods The analysis used baseline data from participants in the European Prevention of Alzheimer's Dementia (EPAD) cohort (total n= 1906, women= 1178, 61.8%). Analysis of covariate (ANCOVA) models were employed to test the independent and interactive impact of APOE genotype and HRT on select cognitive tests, such as MMSE, RBANS, dot counting, Four Mountain Test (FMT), and the supermarket trolley test (SMT), together with volumes of the medial temporal lobe (MTL) regions by MRI. Multiple linear regression models were used to examine the impact of age of HRT initiation according to APOE4 carrier status on these cognitive and MRI outcomes.

Results APOE4 HRT users had the highest RBANS delayed memory index score (P-APOE*HRT interaction = 0.009) compared to APOE4 non-users and to non-APOE4 carriers, with 6–10% larger entorhinal (left) and amygdala (right and left) volumes (P-interaction= 0.002, 0.003, and 0.005 respectively). Earlier introduction of HRT was associated with larger right (standardized β= −0.555, p=0.035) and left hippocampal volumes (standardized β= −0.577, p=0.028) only in APOE4 carriers.

Conclusion HRT introduction is associated with improved delayed memory and larger entorhinal and amygdala volumes in APOE4 carriers only. This may represent an effective targeted strategy to mitigate the higher life-time risk of AD in this large at-risk population subgroup. Confirmation of findings in a fit for purpose RCT with prospective recruitment based on APOE genotype is needed to establish causality

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