

Hormone Therapy, Genotype and Memory

Key Talking Points · eight points for patient conversations

POINT 01

Hormone therapy was associated with about 10% higher delayed memory scores — in APOE4 carriers only.

Among 1,178 women in the EPAD cohort, the association between hormone therapy and delayed memory was concentrated entirely in APOE4 carriers, with no equivalent finding in non-carriers.

POINT 02

The direction of the APOE4 memory gap reversed with hormone therapy use.

Among non-users, APOE4 carriers scored roughly 3% lower on delayed memory than non-carriers. Among users, APOE4 carriers scored highest of any group analyzed — the group expected to be most disadvantaged.

POINT 03

MRI showed 6–10% larger entorhinal and amygdala volumes in APOE4 hormone therapy users.

Volumes were adjusted for whole-brain size before analysis, so this is not a head-size artifact. The cognitive and imaging findings pointed in the same direction.

POINT 04

The entorhinal cortex matters because Alzheimer's reaches it first.

It is among the earliest regions affected, often before the hippocampus, and its shrinkage predicts progression from mild cognitive impairment better than hippocampal volume does.

POINT 05

Earlier initiation was associated with larger hippocampal volumes — again only in APOE4 carriers.

This aligns with the broader critical-window hypothesis, in which the menopausal transition represents a distinct period rather than simply an earlier point on the same curve.

POINT 06

This is cross-sectional data and cannot establish causation.

The authors call explicitly for a randomized trial recruiting prospectively on APOE genotype. Stating this clearly protects credibility when patients arrive with headline coverage.

POINT 07

The APOE4 hormone therapy subgroup was small — 29 to 31 women.

That is too few to separate estrogen-only from combined preparations, and it is the principal reason to treat this as hypothesis-generating rather than practice-changing.

POINT 08

Genotype may explain why the literature has looked contradictory.

Studies pooling all women can average away an effect present in only part of the population. That framing is often more useful to a patient than any single trial result.

RESEARCH SOURCE CITATION

TITLE	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
AUTHORS	Saleh RNM, Hornberger M, Ritchie CW, Minihane AM
SOURCE	Alzheimer's Research & Therapy
PUBLISHED	January 2023
URL	https://doi.org/10.1186/s13195-022-01121-5