

Hormone Therapy, Genotype and Memory

Executive Summary for practitioners

REPORT	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, Minihihane AM
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DESIGN	Cross-sectional analysis · EPAD cohort · 1,178 women

OVERVIEW

This analysis examined whether APOE genotype and the age at which hormone therapy begins explain the long-standing inconsistency in research on hormone therapy and cognition. Using baseline data from 1,178 women in the European Prevention of Alzheimer's Dementia cohort, recruited across ten countries, the researchers tested the independent and interactive effects of APOE4 carrier status and hormone therapy use on cognitive testing and on MRI volumes of the medial temporal lobe. The hypothesis was that benefit is concentrated in a subgroup rather than distributed across all women — which, if true, would help explain why whole-group studies have produced conflicting results.

KEY FINDINGS

- Hormone therapy use was associated with approximately **10% higher delayed memory scores in APOE4 carriers**, with no equivalent association in non-carriers.
- APOE4 hormone therapy users showed **6–10% larger entorhinal and amygdala volumes** than APOE4 non-users on MRI.
- Among women not using hormone therapy, APOE4 carriers scored about 3% **lower** on delayed memory than non-carriers — the direction reversed among users.
- Earlier initiation of hormone therapy was associated with larger hippocampal volumes, an association present only in APOE4 carriers.
- In non-APOE4 carriers, amygdala volumes were **smaller** among hormone therapy users, a divergence the authors flag as needing further investigation.
- Effect sizes for spatial navigation testing were large in APOE4 carriers and absent in non-carriers.

CLINICAL IMPLICATIONS

This does not change prescribing today, and the authors are explicit about that. What it changes is how to read the existing literature. Trials that pool all women together may average away an effect concentrated in roughly a third of the population. For practitioners fielding questions about hormone therapy and dementia risk, the accurate current position is that the evidence is genotype-dependent and not yet causal — which is a more precise and more defensible answer than either reassurance or alarm.

PATIENT IMPACT

Patients increasingly arrive having read that hormone therapy either causes or prevents dementia, often from coverage of trials conducted in women over 65 on oral formulations. This research supports a more specific conversation: response appears to vary by individual factors including genotype and timing, the strongest signals here are associations rather than proof, and a personalized assessment is more useful than a general rule. It also provides useful context for why women carry disproportionate Alzheimer's risk in the first place.

IMPLEMENTATION CONSIDERATIONS

- **Clinical:** Frame hormone therapy and cognition as an area of active, genotype-dependent research rather than settled either way.
- **Clinical:** Where a patient raises family history of Alzheimer's, note that APOE status is one of several factors and that testing carries its own counseling implications.
- **Communication:** Distinguish clearly between association and causation when patients bring in coverage of this or similar studies.
- **Practical:** Keep a plain-language summary available for patients who ask specifically about brain health and hormone therapy.

LIMITATIONS & CONTEXT

This is a cross-sectional analysis, which precludes any causal conclusion. The APOE4 hormone therapy subgroup was small at 29 to 31 women, too few to stratify by estrogen-only versus combined preparations. Data on age at menopause, and on any gap between menopause and starting therapy, was unavailable. Hormone formulation, route and dose were not recorded for all participants. The authors' own stated conclusion is that a randomized trial with prospective recruitment by APOE genotype is required to establish causality.

RECOMMENDED NEXT STEPS

1. Prepare a consistent response for patients asking whether hormone therapy protects against dementia.
2. Review any existing patient materials that state a definitive position on hormone therapy and cognition.
3. Track the randomized trial literature recruiting on APOE genotype as it develops.
4. Where cognitive concerns are raised, document them and assess independent of the hormone therapy decision.

RESEARCH SOURCE CITATION

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