

# Hormone Therapy, Genotype and Memory

Patient Questions & Answers · written in plain language for patient-facing use

## I read that hormone therapy helps memory. Is that true?

It's more specific than that. In this study of 1,178 women, hormone therapy use was associated with about 10% higher delayed memory scores — but only among women carrying a gene variant called APOE4. Women without that variant showed no equivalent memory difference. So the honest answer is that it appeared to help some women in this analysis, and the researchers are careful to say this shows an association rather than proving cause and effect.

## What is APOE4?

APOE is a gene everyone has, in several common variants. The APOE4 variant is the most significant common genetic risk factor for Alzheimer's disease, and it carries greater risk in women than in men. Roughly a third of the women in this study were carriers. Having it does not mean someone will develop Alzheimer's, and not having it does not mean they won't.

## Should I get tested for APOE4?

That's a decision worth making carefully with your provider rather than through a direct-to-consumer test. Knowing your APOE status has real emotional and practical implications, including how you might feel about a result you can't change, and it doesn't currently change standard treatment. If you're considering it, ask about genetic counseling as part of that conversation.

## What did they actually find in the brain scans?

Women with APOE4 who used hormone therapy had 6–10% larger volumes in two memory-related regions — the entorhinal cortex and the amygdala — compared with APOE4 carriers not using it. These were MRI measurements adjusted for overall brain size, so it isn't simply a matter of some people having larger heads.

## Why does the entorhinal cortex matter?

It's one of the first areas affected by Alzheimer's-related changes, often before the hippocampus, which is the region most people have heard of. Shrinkage there has been shown to predict progression from mild cognitive impairment to Alzheimer's better than hippocampal shrinkage does. That's why researchers chose to measure it.

## Does it matter when someone starts hormone therapy?

In this study, it appeared to. Among APOE4 carriers, the earlier hormone therapy was started, the larger the hippocampal volume observed. That relationship wasn't present in women without the variant. It fits a broader idea in menopause research called the critical window, where the menopausal transition may be a distinct period rather than just an earlier point in time.

## Why do women get Alzheimer's more often than men?

More than two-thirds of people with Alzheimer's are women, and that gap isn't fully explained by women living longer. One leading hypothesis is that the drop in estrogen during menopause affects the brain in ways that accelerate underlying disease processes. That's a large part of why researchers keep returning to menopause when studying dementia risk.

### Does this mean hormone therapy prevents dementia?

No, and this study wasn't designed to answer that. It looked at women at a single point in time and found associations between hormone therapy use, memory scores and brain volumes. It cannot show that the therapy caused those differences. The authors specifically call for a randomized trial before any conclusion about cause is drawn.

### The study group seems small. How much weight should I give this?

That's a fair reading. While the overall cohort was large at 1,178 women, only 29 to 31 APOE4 carriers were using hormone therapy — the group where the main findings appeared. The researchers name this as a limitation, along with missing information on hormone type and dose for some participants. Treat it as an interesting lead that needs confirming, not as settled guidance.

### So what should I actually do with this information?

Use it as a reason for a more specific conversation rather than a general one. If brain health is a concern for you, bring it up directly — alongside your symptoms, your family history, your cardiovascular risk and your own preferences. The useful takeaway from this research isn't a yes or a no about hormone therapy. It's that individual factors appear to matter more than a single rule applied to everyone.

#### 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       | <a href="https://doi.org/10.1186/s13195-022-01121-5">https://doi.org/10.1186/s13195-022-01121-5</a>                                                                                          |