Editors’ Note: Estrogen Receptor Genes, Cognitive Decline, and Alzheimer Disease

Dr. Oveisgharan et al. examined the association of 3 estrogen receptor variants with cognitive and neuropathologic features of Alzheimer disease (AD) in 1,711 women and 651 men in 2 longitudinal clinical pathologic studies of aging. They found that estrogen receptor (ER) DNA methylation and RNA expression, and to some extent ER polymorphisms, were associated with cognitive decline, tau tangle density, and global AD pathology score, particularly in women. In response, Dr. Brenner notes that the estrogen receptor GPER1 has been shown to have protective effects against the development of AD, whereas DNA methylation would impede GPER1 transcription, with methylation levels reflecting postmenopausal acceleration of epigenetic aging. Because earlier age of menopause and late initiation of hormonal therapy are associated with AD neuropathology, Dr. Brenner argues that early hormonal therapy after menopause could inhibit such methylation and protect against AD. Responding to these comments, the authors agree, citing similar findings in their prior work examining patients with surgical menopause. They note that they plan to examine epigenetic clocks in relation to reproductive period and surgical menopause. This exchange highlights our evolving understanding about the complex relationships among estrogen, menopause, epigenetics, hormonal therapy, and AD. It is important to note that hormone replacement therapy has not been beneficial in preventing dementia in randomized controlled trials (in fact, there has been a signal of harm), demonstrating the challenges of translating observational insights into therapeutic progress.

Aravind Ganesh, MD, DPhil, FRCP, and Steven Galetta, MD
Neurology® 2023;101:633. doi:10.1212/WNL.0000000000207840

Reader Response: Estrogen Receptor Genes, Cognitive Decline, and Alzheimer Disease

Steven Brenner (St. Louis)
Neurology® 2023;101:633–634. doi:10.1212/WNL.0000000000207841

I read the article by Oveisgharan et al.1 regarding the effect of low estrogen levels in the postmenopause period (MP) as a risk factor of Alzheimer disease (AD). Estrogen receptor (ER) DNA methylation seems to influence the development of AD.1 Earlier age of MP and late initiation of hormonal therapy (HT) are related to increased tau vulnerability if there is increased neocortical β-amyloid,2 indicating HT should be administered close to MP onset.2

Utilizing an “epigenetic clock” biomarker of aging, menopause accelerated biological aging in blood, while menopausal HT resulted in a lower epigenetic age in buccal epithelium.3 GPER1 has been shown to have neuroprotective and vascular protective effects and also affects and maintains metabolism.4 This would be protective against the development of AD; however, GPER1 DNA methylation would impede transcription, leading to cognitive decline and global AD indices.5 It is also involved in tumorigenesis.6

Author disclosures are available upon request (journal@neurology.org).
Estradiol affects memory through altering DNA methylation. Early HT after menopause could inhibit DNA methylation and protect against AD.


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**Author Response: Estrogen Receptor Genes, Cognitive Decline, and Alzheimer Disease**

Shahram Oveisgharan (Chicago) and David A. Bennett (Chicago)

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We thank Dr. Brenner for his interest in our paper. Consistent with his comments, in prior work, we found that surgical menopause was associated with Alzheimer disease pathology and cognitive decline and that its effects were mitigated in part by estrogen use. We also reported an association between reproductive period and methylation of the oxidative phosphorylation apparatus. We previously reported on epigenetic clocks, and based on the author’s suggestion, we plan to look at them in relation to reproductive period and surgical menopause.


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Cortical Proteins and Individual Differences in Cognitive Resilience in Older Adults

In the Research Article “Cortical Proteins and Individual Differences in Cognitive Resilience in Older Adults” by Zammit et al., the row for protein GFAP_1 in eTable 4 should appear in the pink section rather than the orange section. Thus, the number shown in the overlap for Motor and Cognition in the Venn diagram in Figure 3 should be 8; furthermore, the numbers for Motor alone and Cognition alone should be 5 and 34, respectively. The authors regret the error.

Reference

Structural Neuroimaging in Adults and Adolescents With Newly Diagnosed Focal Epilepsy

In the Research Article “Structural Neuroimaging in Adults and Adolescents With Newly Diagnosed Focal Epilepsy: The Human Epilepsy Project” by Bank et al., there were minor errors and omitted coinvestigators in Appendix 2. The updated Appendix 2 can be accessed here in links.lww.com/WNL/C674. The authors regret the errors.

Reference