

# Hormone therapy and brain structure in postmenopausal women

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**WHAT DID THE AUTHORS STUDY?** Many women who are going through menopause (see page e102, “About menopause”) have symptoms (e.g., “hot flashes”) that may be difficult. Some women choose to treat these symptoms through hormone replacement therapy. Hormones may include estrogen and progesterone.

Kantarci et al.<sup>1</sup> looked at the effects of hormone therapy on brain structure in postmenopausal women. Other studies have not fully explained whether hormone replacement therapy influences brain health.

The women in this study were recruited from the Kronos Early Estrogen Prevention Study (KEEPS). This study assigned women randomly (by a “coin toss”) to early hormone therapy after menopause, or placebo (a “sugar pill”). The goal of the study was to understand the effects of early hormone replacement on brain structure. Such changes may predict long-term brain health and risk of later dementia.

**WHY IS THIS STUDY IMPORTANT?** With menopause, estrogen and progesterone levels decrease in women. Hormonal therapy can treat many symptoms of menopause, but it also may affect thinking ability (cognition) and brain structure. In studies of women over the age of 65, hormone therapy was associated with decreased overall cognition and decreased sizes in brain structures that may affect cognition.<sup>2</sup> The authors wanted to see if hormone therapy in women who were younger and started treatment early after menopause also affected the size of brain structures that may be involved with cognition.

**HOW WAS THIS STUDY PERFORMED?** All of the participants from KEEPS were between 42 and 56 years old, free of a neurologic disorder and had recently entered menopause. These women were divided into 3 groups: (1) estrogen by mouth, (2) estrogen by a patch on the skin, and (3) placebo. In those who received estrogen treatment, 200 mg of progesterone a day by mouth was also given for 12 days at the beginning of each month to protect the lining of the uterus.

All the women underwent MRI to examine brain structure. They had at least another MRI at the 18 months, 36 months, or 48 months follow-up appointments. They also had cognitive testing at the start of the study.

The researchers looked at the changes in several brain measures over time. They measured the size of the whole brain. They also measured the size of the ventricles, which are normal spaces in the brain that are filled with spinal fluid. If there is loss of brain tissue, these spaces often enlarge. Finally, they measured something called white matter hyperintensity. The white matter is the “wiring” that connects nerve cells in different parts of the brain. When small blood vessels that supply the white matter narrow, this can make the “wiring” appear bright or “hyperintense” on MRI. This may cause decreases in whole brain volume.

In addition, the women also took cognitive examinations to test changes in overall cognition.

**WHAT WERE THE RESULTS OF THE STUDY?** Ninety-five women were included in the study. Twenty-nine participants were in the oral estrogen group, 30 participants were in the transdermal (patch) estrogen group, and 36 participants received placebo. Women in all groups were about 1½ years past menopause.

Compared to those taking placebo, those in the oral estrogen group had higher rates of increased ventricular size, especially in those who were treated later in menopause. The transdermal estrogen group also had higher rates of increased ventricular volume compared to placebo, but not to the degree of the oral estrogen group. The researchers found that the larger ventricles in the estrogen group participants were associated with decreases in brain volume and increases in white matter hyperintensities. The 2 estrogen groups did not differ from each other in brain structure measures. Despite these changes, there were no changes in overall cognition scores between the 3 groups.

**WHAT DID THE AUTHORS CONCLUDE?** The authors concluded that the group that received oral estrogen had increased ventricle size but no changes in cognition compared to the placebo group. They also suggested that both decreased whole brain volume and increased white matter hyperintensity volume may have contributed to the increased ventricle size. These findings suggest that oral estrogen may change brain structure but not cognition in women who recently underwent menopause.

**WHAT WERE THE STRENGTHS AND LIMITATIONS OF THE STUDY?**

A strength of the study is that it was a high-quality study that looked at women both with and without treatment. The study is also unique because it studied early treatment after menopause. A final strength of the study is that it was able to analyze the change in brain structure and cognition over 4 years. The main limitation is the small number of participants in the study. This can make it harder to see small differences between groups. It could possibly explain why changes in cognitive testing were not seen. It could also explain why the differences between the transdermal estrogen and placebo groups were less secure.

**WHAT IS NOT KNOWN YET?** The long-term effects of hormone therapy are still unclear. It is not known

whether the brain structure changes reported in this study will last or will worsen over longer periods of time. We do not know whether hormone therapy will affect cognitive performance if these women are followed longer over time. It is also unclear whether similar changes would be seen if these women stop hormone treatment. Further follow-up of these participants is necessary. Studies that include a larger number of participants may also provide clearer answers.

**REFERENCES**

1. Kantarci K, Tosakulwong N, Lesnick TG, et al. Effects of hormone therapy on brain structure: a randomized controlled trial. *Neurology* 2016;87:887–896.
2. McCarrey AC, Resnick SM. Postmenopausal hormone therapy and cognition. *Horm Behav* 2015;74:167–172.

## Section Editors

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# About menopause

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**WHAT IS MENOPAUSE?** Menopause is the natural process when a woman stops having menstrual cycles because her ovaries are producing less estrogen and progesterone. It is defined as having no menstrual cycles for 12 consecutive months.

**WHEN DOES MENOPAUSE OCCUR?** The average age at onset for natural menopause is 51–52 years. Some women may go through menopause in their forties or late fifties. Menopause also results from surgical removal of the ovaries.

**WHAT ARE THE SYMPTOMS AND CONDITIONS ASSOCIATED WITH MENOPAUSE?** A woman may have vaginal dryness, hot flashes, insomnia, night sweats, dry skin, thinning hair, and mood changes before or during menopause. Osteoporosis (thinning of the bones) may also occur. There is also an increased risk of heart disease after menopause.

**HOW IS MENOPAUSE CURRENTLY TREATED?**

Hormone treatments may include estrogen replacement. Progesterone is also added if a woman still has her uterus to protect against uterine cancer. Hormone therapy may improve menopausal symptoms such as night sweats and hot flashes, though it may increase the risk of blood clots. Starting hormone treatment after the age of 65 may also be associated with an increased risk of dementia. Given these risks and benefits, women should talk with their health care providers to determine the best course of management of these symptoms.

**FOR MORE INFORMATION**

National Institute on Aging

[nia.nih.gov/health/publication/menopause](http://nia.nih.gov/health/publication/menopause)

[nia.nih.gov/health/publication/hormones-and-menopause](http://nia.nih.gov/health/publication/hormones-and-menopause)

North American Menopause Society

[www.menopause.org](http://www.menopause.org)

# Neurology®

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