

1: [JAMA. 2003 May 28;289\(20\):2663-72.](#)

[Related Articles,  
Links](#)



Comment in:

- [JAMA. 2003 May 28;289\(20\):2717-9.](#)

**Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial.**

[Rapp SR](#), [Espeland MA](#), [Shumaker SA](#), [Henderson VW](#), [Brunner RL](#), [Manson JE](#), [Gass ML](#), [Stefanick ML](#), [Lane DS](#), [Hays J](#), [Johnson KC](#), [Coker LH](#), [Dailey M](#), [Bowen D](#); [WHIMS Investigators](#).

Department of Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA. [srapp@wfubmc.edu](mailto:srapp@wfubmc.edu)

**CONTEXT:** Observational studies have suggested that postmenopausal hormone treatment may improve cognitive function, but data from randomized clinical trials have been sparse and inconclusive. The Women's Health Initiative Memory Study (WHIMS) is an ancillary study of the Women's Health Initiative (WHI) hormone therapy trials. On July 8, 2002, the estrogen plus progestin therapy in the WHI trial was discontinued because of certain increased health risks for women. **OBJECTIVE:** To determine whether estrogen plus progestin therapy protects global cognitive function in older postmenopausal women. **DESIGN, SETTING, AND PARTICIPANTS:** A randomized, double-blind, placebo-controlled clinical trial, WHIMS is an ancillary study of geographically diverse, community-dwelling women aged 65 years or older from 39 of 40 clinical centers within the WHI estrogen plus progestin trial that started in June 1995. Of 4894 eligible postmenopausal women aged 65 years or older and free of probable dementia at baseline, 4532 (92.6%) were enrolled in the estrogen plus progestin component of WHIMS. A total of 4381 participants (96.7%) provided at least 1 valid cognitive function score between June 1995 and July 8, 2002. **INTERVENTIONS:** Participants received either 1 daily tablet containing 0.625 mg of conjugated equine estrogen with 2.5 mg of medroxyprogesterone acetate (n = 2145) or matching placebo (n = 2236). **MAIN OUTCOME MEASURE:** Global cognitive function measured annually with the Modified Mini-Mental State Examination. **RESULTS:** The Modified Mini-Mental State Examination mean total scores in both groups increased slightly over time (mean follow-up of 4.2 years). Women in the estrogen plus progestin group had smaller average increases in total scores compared with women receiving placebo (P = .03), but these differences were not clinically important. Removing women by censoring them after adjudicated dementia, mild cognitive impairment, or stroke, and nonadherence to study protocol, did not alter the findings. Prior hormone therapy use and duration of prior use did not affect the interpretation of the results, nor did timing of prior hormone therapy initiation with respect to the final menstrual period. More women in the estrogen plus progestin group had a substantial and clinically important decline (> or =2 SDs) in Modified Mini-Mental State Examination total score (6.7%) compared with the placebo group (4.8%) (P = .008). **CONCLUSIONS:** Among postmenopausal women aged 65 years or older, estrogen plus progestin did not improve cognitive function when compared with placebo. While most women receiving estrogen plus progestin did not experience clinically relevant adverse effects on cognition compared with placebo, a small increased risk of clinically meaningful cognitive decline occurred in the estrogen plus progestin group.