

# Effect of Postmenopausal Hormone Therapy on Cognitive Function: The Heart and Estrogen/progestin Replacement Study

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**PURPOSE:** To determine if hormone therapy results in better cognitive function in older postmenopausal women.

**SUBJECTS AND METHODS:** The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, placebo-controlled trial involving 2763 women with coronary disease. Women were assigned randomly to conjugated estrogen (0.625 mg) plus medroxyprogesterone acetate (2.5 mg) in one tablet daily or identical placebo; they were followed for a mean ( $\pm$  SD) of  $4.2 \pm 0.4$  years. Participants at 10 of the 20 HERS centers were invited to enroll in the cognitive function substudy. At the end of the trial, we measured cognitive function in 517 women in the hormone group and 546 in the placebo group using six standard tests: the modified Mini-Mental Status Examination, Verbal Fluency, Boston Naming, Word List Memory, Word List Recall, and Trails B. Cognitive function was not measured at baseline.

**RESULTS:** The mean age of participants at the time of cogni-

tive function testing was  $71 \pm 6$  years. There were no differences in age-adjusted cognitive function test scores between the two treatment groups, except that women assigned to hormones scored worse on the Verbal Fluency test than women assigned to placebo ( $15.9 \pm 4.8$  vs.  $16.6 \pm 4.8$ ,  $P = 0.02$ ). Adjustment for other potential confounders and restriction of the analyses to women who had been adherent to study medication did not change the results.

**CONCLUSION:** Among older postmenopausal women with coronary disease, 4 years of treatment with postmenopausal hormone therapy did not result in better cognitive function as measured on six standardized tests. Whether these results also apply to elderly women without coronary disease cannot be determined from this study. *Am J Med.* 2002;113:543-548. ©2002 by Excerpta Medica, Inc.

The findings of several randomized trials suggest that estrogen therapy improves cognition in postmenopausal women without pre-existing dementia (1-7). However, all of these trials were small (18 to 64 participants), several reported improved cognition in the estrogen-treated group but did not compare these changes with those in the placebo group (2,6,7), and most enrolled women who were recently menopausal (2,4-7) and likely to be suffering from menopausal symptoms. Relief of vasomotor symptoms and insomnia by estrogen therapy might have resulted in better concentration and improvement in cognitive performance (8).

The Heart and Estrogen/progestin Replacement Study (HERS) was a 4-year, randomized, placebo-controlled trial of daily oral conjugated estrogen plus medroxyprogesterone acetate for prevention of coronary heart disease

events (nonfatal myocardial infarction and coronary disease death) among 2763 postmenopausal women with established coronary disease. As an ancillary study, we measured the effect of this hormone regimen on cognitive function at the end of the trial among 1063 participants at 10 of the 20 HERS clinical centers. Our aim was to test the hypothesis that women treated with hormone replacement therapy would have better cognitive function at the end of the trial than women treated with placebo.

## SUBJECTS AND METHODS

The design, methods, baseline findings, and main outcomes of the trial have been published (9,10). Briefly, participants were postmenopausal women younger than 80 years old with established coronary disease and an intact uterus. Participants were assigned randomly to daily oral conjugated estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) in one tablet (Prempro, Wyeth-Ayerst, Radnor, Pennsylvania) or identical placebo. Randomization was stratified by clinical center. Participants, investigators, and those who assessed the outcomes were blinded to treatment status.

### *Measurements and Follow-up*

At baseline, participants completed questionnaires that included information on age, ethnicity, education,

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cigarette smoking, alcohol consumption, exercise, general health (poor, fair, good, excellent), health conditions, prior postmenopausal hormone use, and menopausal symptoms. All prescription and over-the-counter medications were recorded. Height and weight were measured, and participants completed the Medical Outcomes Survey depression scale. Women were classified as having hot flushes or trouble sleeping if they reported these symptoms in the prior week. Fasting lipoprotein levels were measured by the Lipoprotein Analytical Laboratory at Johns Hopkins Hospital. Cognitive function testing was not performed at baseline.

At follow-up visits that occurred every 4 months during the trial, compliance was measured by pill counts, and outcome and adverse events (including reported dementia) were ascertained. At the final visit at the end of the trial, all surviving participants at 10 of the 20 HERS clinical centers (see Appendix) were asked to participate in this ancillary study of the effect of postmenopausal hormone therapy on cognition. We invited 10 HERS centers to participate to yield an adequate number of participants for at least 90% power to detect a two-sided 10% or greater difference between the treatment groups in each of the six cognitive test scores.

Women who agreed to participate signed informed consent and completed a modified Consortium to Establish a Registry for Alzheimer's Disease battery (11) of six standard cognitive function tests: the modified Mini-Mental Status Examination, Verbal Fluency, modified Boston Naming, Word List Memory, Word List Recall, and Trails B. The modified Mini-Mental Status Examination is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory (12). Scores range from 0 to 100, with higher scores denoting better cognitive performance. Verbal Fluency (Category Fluency) tests semantic memory, verbal production, and language. Scores are based on the number of animals named in 1 minute (13), with higher scores denoting better cognitive function. Modified Boston Naming is a 15-item test of language that requires the subject to name objects presented in pictures. The test is scored based on the number of correct answers (maximum score of 15) (11). Word List Memory assesses the ability to remember 10 printed words on three separate trials (11) (maximum score of 30). Word List Recall tests the ability to remember the same 10 printed words after a delay of 10 minutes (maximum score of 10) (11). Trails B is a timed test measuring attention, visual scanning, visual sequential abilities, and executive function. Scores are based on the number of seconds required to complete the task, with lower scores denoting better cognitive function (14). These tests were chosen because they are reproducible and valid measures (11) that are also being used in other large trials of postmenopausal hormone therapy, including the Women's

Health Initiative Randomized Trial (15). Because depression can cause impaired cognitive function, participants also completed the Geriatric Depression Scale (16) at the time of cognitive function testing. Staff who administered the cognitive function tests attended a 2-day training session conducted by neuropsychologists who were experts in cognitive function measurement. Certification required correct administration and scoring of the tests documented by audiotaping of mock testing and expert review of scoring.

### Analysis

Baseline differences between treatment groups were compared using either the chi-squared test or the Student *t* test. We compared age-adjusted scores on the six cognitive function tests between treatment groups using multivariate linear regression. We then adjusted the cognitive function test scores for variables that differed between the treatment groups at the time of cognitive testing at  $P < 0.01$  (age, alcohol drinks per week, years menopausal, and use of statins), variables known to be associated with cognitive function (education, Geriatric Depression Scale score), and conditions that might affect cognitive function (general health status, hot flushes, and trouble sleeping). Because older women may be more likely to suffer cognitive decline, we also repeated the between-group analyses of age-adjusted cognitive function test scores, restricting the cohort to women who were aged  $\geq 70$  years. Finally, we repeated the between-group comparison of age-adjusted cognitive function test scores among women who reported taking more than 80% of assigned study medication during the entire follow-up and during the period since the prior study visit (about 4 months).

A score  $\leq 80$  on the modified Mini-Mental Status Examination is commonly used to define cognitive impairment (17). Using this cutoff, we compared the proportion of women who were cognitively impaired in the two treatment groups with multivariate logistic models adjusted for predictors of better cognitive test scores. Statistical analyses were performed using SAS Version 6.12 (SAS Institute, Cary, North Carolina).

## RESULTS

Between January 1993 and September 1994, the 10 HERS centers that participated in this ancillary study enrolled 1328 women; 662 were assigned randomly to estrogen plus progestin therapy and 666 to placebo. All participants were fluent in English. By the end of the trial, 61 women in the hormone group and 58 women in the placebo group had died. Twenty-eight women in the hormone group and 22 in the placebo group were willing but unable to complete cognitive testing because of physical problems such as visual impairment, hearing loss, or paralysis. Forty women in the hormone group and 28 in the

**Table 1.** Baseline Characteristics of 1063 HERS Participants Who Completed Cognitive Testing, by Treatment Group

Characteristic	Estrogen/Progestin	Placebo	P Value
	(n = 517)	(n = 546)	
	Number (%) or Mean $\pm$ SD		
Age (years)	66.3 $\pm$ 6.4	67.3 $\pm$ 6.3	0.01
White race	470 (90.9)	494 (90.5)	0.81
Education (years)	12.7 $\pm$ 2.7	12.7 $\pm$ 2.7	0.63
Current smoker	64 (12.4)	65 (11.9)	0.81
Drinks per week	1.5 $\pm$ 3.9	1.1 $\pm$ 2.8	0.07
Body mass index (kg/m <sup>2</sup> )	28.1 $\pm$ 05.3	28.5 $\pm$ 5.5	0.31
Exercise >3 times per week	222 (42.9)	224 (41.0)	0.53
Hot flashes	81 (15.7)	80 (14.7)	0.64
Trouble sleeping	240 (46.4)	252 (46.2)	0.93
LDL cholesterol (mg/dL)	142.3 $\pm$ 36.6	143.4 $\pm$ 36.6	0.64
HDL cholesterol (mg/dL)	50.5 $\pm$ 13.9	50.2 $\pm$ 13.2	0.73
Years since menopause	17.5 $\pm$ 7.8	18.6 $\pm$ 7.7	0.03
Medical Outcomes Survey depression score	0.04 $\pm$ 0.13	0.04 $\pm$ 0.13	0.88
Fair or poor health	115 (22.2)	126 (23.1)	0.75
Diabetes	103 (19.9)	102 (18.7)	0.61
Prior postmenopausal estrogen use	126 (24.4)	130 (23.8)	0.83
Medication use			
Statins	200 (38.7)	214 (39.2)	0.87
Aspirin	420 (81.2)	444 (81.3)	0.97
Nonsteroidal anti-inflammatory drugs	106 (20.5)	121 (22.2)	0.51
Multivitamins	142 (27.5)	158 (28.9)	0.59
Benzodiazepines	25 (4.8)	32 (5.9)	0.46
Dementia medications	0	0	
Sedative hypnotics	0	0	

HDL = high-density lipoprotein; HERS = Heart and Estrogen/progestin Replacement Study; LDL = low-density lipoprotein.

placebo group declined to give informed consent for the cognitive function measures, and 12 women in each treatment group did not attend the final visit. Thus, 1063 women completed cognitive function testing: 517 (78%) of the 662 women in the hormone group and 546 (82%) of the 666 women in the placebo group ( $P < 0.01$ ).

Participants who completed cognitive function testing were aged 44 to 79 years at the time of testing (interquartile range, 62 to 72 years; mean, 71  $\pm$  6 years). The baseline characteristics of women who were tested did not differ by treatment assignment, except that women in the hormone group were, on average, 1 year younger than those assigned to the placebo group ( $P = 0.01$ ) and had spent 1 year less in the postmenopausal period ( $P = 0.03$ ; Table 1).

The mean duration of study treatment among participants who completed cognitive function measures was 4.2  $\pm$  0.4 years. At the end of the first year of treatment, 83% (429/517) of women assigned to hormone therapy and 95% (519/546) of those assigned to placebo reported taking at least 80% of the study medication; by the end of the trial, these percentages had fallen to 78% (401/517) and 84% (460/546).

### Effects of Hormone Therapy on Measures of Cognitive Function

Women assigned to the hormone group scored slightly lower (worse) on the Verbal Fluency test (15.9 vs. 16.6,  $P = 0.02$ ) and on the Word List Memory test (19.7 vs. 20.1,  $P = 0.06$ ) than women assigned to placebo (Table 2). There were no differences in age-adjusted mean scores on the other four tests. The results did not change substantially after adjusting cognitive test scores for age, education, years postmenopausal, statin use, Geriatric Depression Scale score, alcohol drinks per week, hot flushes, and trouble sleeping (adjusted score on Verbal Fluency: 15.9  $\pm$  4.8 in the hormone group vs. 16.6  $\pm$  4.8 in the placebo group,  $P = 0.01$ ; adjusted score on the Word List Memory: 19.7  $\pm$  3.9 vs. 20.1  $\pm$  3.9,  $P = 0.04$ ).

Results were similar in analyses restricted to women in both groups who were 70 years or older at the start of the trial, and in analyses restricted to those who took at least 80% of assigned study medication during the entire trial or during the period from the next to last visit to the final study visit at which cognitive function testing was performed (about 4 months).

**Table 2.** Age-Adjusted Scores on Tests of Cognitive Function and Depression, by Treatment Group

Test (Score Range*)	Estrogen/Progestin (n = 517)	Placebo (n = 546)	Difference <sup>†</sup> (95% Confidence Interval)	P Value
	Mean ± SD			
Modified Mini-Mental Status (0–100)	93.1 ± 6.4	93.4 ± 6.4	−0.4 (−1.1 to 0.4)	0.36
Verbal Fluency (0–∞)	15.9 ± 4.8	16.6 ± 4.8	−0.7 (−1.3 to −0.1)	0.02
Boston Naming (0–30)	14.0 ± 1.4	14.1 ± 1.4	−0.1 (−0.3 to 0.1)	0.34
Word List Memory (0–30)	19.7 ± 3.9	20.1 ± 3.9	−0.5 (−1.0 to 0.02)	0.06
Word List Recall (0–10)	6.4 ± 2.1	6.6 ± 2.1	−0.1 (−0.7 to 0.4)	0.29
Trails B (0–300)	156.2 ± 77.5	151.5 ± 77.5	4.6 (−4.9 to 14.2)	0.34
Geriatric Depression Scale (0–15)	2.0 ± 2.6	2.0 ± 2.6	0.001 (−0.3 to 0.3)	0.99

\* Higher scores reflect better cognitive function on all tests except Trails B, where a lower score reflects better cognitive function. Higher scores on the Geriatric Depression Scale reflect more depressive symptoms.

<sup>†</sup> Estrogen/progestin group minus placebo group. A negative difference indicates a worse score in the estrogen/progestin group for all tests except Trails B and Geriatric Depression Scale.

At the end of the trial, 6.0% of women (31/517) in the hormone group and 4.8% (26/546) of those in the placebo group were cognitively impaired (adjusted odds ratio [OR] = 1.4; 95% confidence interval [CI]: 0.8 to 2.4;  $P = 0.2$ ). Similar results were seen when the analysis was confined to women who took at least 80% of assigned study medication during the trial (OR = 0.9; 95% CI: 0.5 to 1.8;  $P = 0.8$ ). Nine women in the hormone-treated group and 9 in the placebo group were reported to have developed dementia during the trial, but these diagnoses were not confirmed.

## DISCUSSION

Compared with placebo, 4 years of treatment with oral estrogen plus progestin did not result in better cognitive function in elderly women. Rather, the age-adjusted mean score on one of the six cognitive tests was statistically significantly worse among women assigned to hormones compared with those assigned to placebo. However, the absolute difference in scores between the groups was small and not likely to be clinically important. Similar proportions of the hormone and placebo groups were cognitively impaired (defined as a score  $\leq 80$  on the modified Mini-Mental Status Examination) at the end of the trial.

Biochemical and neurophysiologic studies have suggested several mechanisms by which estrogen may affect cognition or prevent dementia. Degeneration of cholinergic neurons and their tracts in the basal forebrain is one of the earliest and most pronounced neuropathologic changes in Alzheimer's disease and age-related cognitive decline (18,19). Studies in rodents suggest that estrogen prolongs survival of cholinergic neurons (20) and promotes cholinergic neural activity (21). Estrogen therapy might improve or prevent dementia due to vascular disease by favorably affecting lipoproteins (22), by reducing

cerebral ischemia (23) through central nervous system vasodilation, by reducing the smooth muscle injury response, or by reducing platelet aggregation (24). Nevertheless, we could not detect a benefit of 4 years of treatment with oral estrogen plus progestin on cognition.

All participants in HERS had documented coronary heart disease. Women with coronary disease may be at increased risk of cognitive decline (25) and of dementia due to both Alzheimer's disease and vascular disease (26). However, cognitive function among HERS participants appeared to be very similar to that of other populations of elderly women (27), as did the prevalence of cognitive impairment (28). About 20% of persons carry the apolipoprotein E (ApoE) allele, and this genotype is more common among persons with coronary disease and those with cognitive decline and dementia (27,29). Previous studies have suggested that estrogen therapy prevents cognitive decline only among persons who do not carry the ApoE allele (27). Unfortunately, we did not measure genetic variants of apolipoprotein. Thus, failure to detect a benefit of hormone therapy on cognitive function among HERS participants may, in part, be due to a high prevalence of ApoE among these women with heart disease.

Eleven randomized trials have evaluated the effect of various types of estrogen on cognitive function in nondemented postmenopausal women (1–7,30–33). Seven of these trials (1–7) concluded that estrogen therapy improved cognitive function, but substantial methodologic problems make the results difficult to evaluate. The trials were small (18 to 64 participants), and several used neuropsychiatric tests that are not validated (1,3,4). Two of the trials concluded that estrogen use improved cognitive function, although there was improvement in only one or two of several cognitive tests (1,3,7), and two trials reported that scores on cognitive tests improved after treatment with estrogen, but did not compare change in the

estrogen group with change in the placebo group (2,7). Participants in these trials were recently menopausal women, many of whom had vasomotor symptoms. Relief of symptoms and associated insomnia might have improved attention or concentration and resulted in better cognitive performance. In contrast, four trials did not show a benefit of estrogen therapy on cognitive function (30–33). Although participants in these negative trials were also recently menopausal, most did not have vasomotor symptoms, and this may have accounted for the lack of benefit of hormone therapy. These trials were also small (36 to 124 participants) and the duration of treatment was short (21 days to 3 months), and thus they had inadequate power to detect small benefits of hormone treatment on cognitive function and provided no information on longer duration of hormone use. In comparison, HERS was large (providing approximately 99% power to detect 5% or greater differences between the treatment groups in cognitive function) and the average duration of treatment was over 4 years. Similar to the other trials that found no effect of hormone therapy on cognitive function, the majority of women enrolled in HERS did not have vasomotor symptoms.

All prior trials have studied unopposed estrogen. In our trial, it is possible that the addition of medroxyprogesterone acetate negated a beneficial effect of estrogen. Because all hormone-treated women in HERS received estrogen and progestin, the trial provides no evidence regarding the effect of unopposed estrogen therapy on cognitive function. In HERS, not enough women were included and follow-up was not long enough to provide information on the risk of developing dementia. Estrogen therapy has also been hypothesized to improve function in women with known dementia, but a recent randomized trial found no benefit in women with documented Alzheimer's disease (34).

We did not measure cognitive function in HERS participants at the beginning of the trial. Because randomization of a large number of participants generally assures that groups are balanced at the beginning of a trial, lack of baseline measurement of cognitive function is unlikely to have introduced bias in the comparison of cognitive function at the end of the trial. Comparing change in cognitive function from baseline to the end of the trial between the treatment groups may, however, have provided more power to detect a difference. However, the 95% confidence intervals around the difference between mean cognitive function scores in the hormone and placebo groups were very narrow, making it unlikely that we missed more than a trivial difference between the treatment groups.

Some HERS participants died, were unable to complete cognitive function testing, or were lost to follow-up by the end of the trial when cognitive function was measured. This could potentially bias the comparison of cog-

nitive function in the treatment groups. At the end of the trial, women in the two treatment groups were still similar with regard to all variables measured, with the exceptions that the placebo group was approximately 1 year older than the hormone group and had spent 1 year more in the menopausal state. That hormone-treated women were somewhat younger than women in the placebo group should favor better cognitive function in the hormone group. After adjusting for this age imbalance, performance on the Verbal Fluency test was worse among women assigned to the hormone group, but there was no difference between the treatment groups on the five other cognitive function tests. Multivariate adjustment for other baseline predictors of cognitive function did not substantially change the results.

Because we did not measure cognitive function at baseline, we cannot determine the rates of development of cognitive impairment in the two treatment groups. However, given the level of cognitive function required to complete HERS enrollment procedures, it is unlikely that there were many women with cognitive impairment at baseline. Among older women similar in age to the HERS cohort, the incidence of new cognitive impairment has been reported to be about 1% per year (28). Because the HERS cohort was followed for 4 years, this rate would result in about the 5% prevalence of cognitive impairment that we observed at the end of the trial.

In summary, treatment with oral estrogen plus progestin therapy for 4 years did not result in better cognitive function compared with treatment with placebo in elderly women with coronary disease.

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## APPENDIX

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