

# Effect of Estrogen Plus Progestin on Global Cognitive Function in Postmenopausal Women

## The Women's Health Initiative Memory Study: A Randomized Controlled Trial

Stephen R. Rapp, PhD

Mark A. Espeland, PhD

Sally A. Shumaker, PhD

Victor W. Henderson, MD, MS

Robert L. Brunner, PhD

JoAnn E. Manson, MD, DrPH

Margery L. S. Gass, MD

Marcia L. Stefanick, PhD

Dorothy S. Lane, MD, MPH

Jennifer Hays, PhD

Karen C. Johnson, MD, MPH

Laura H. Coker, PhD

Maggie Dailey, PhD

Deborah Bowen, PhD

for the WHIMS Investigators

**D**ECLINING COGNITIVE FUNCTION is a growing public health concern for older adults, given the well-documented pattern of age-associated decrements in many areas of cognitive performance<sup>1</sup> and the increasing proportion of elderly individuals in the US population. The prevalence of age-associated memory impairment in the general older population is estimated to be between 17% and 34%.<sup>2-4</sup> In postmenopausal women, the effect of reduced sex hormones, especially estrogen and progesterone, on cognitive decline is of particular interest because of their modulating effects on

**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 ( $\geq 2$  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.

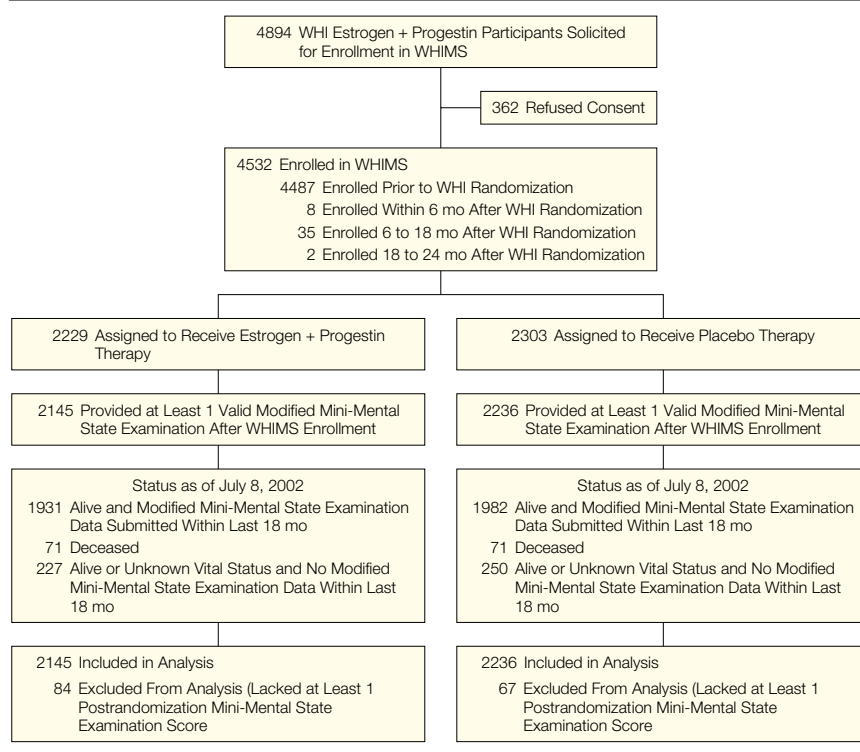
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**Author Affiliations** are listed at the end of this article.  
**Corresponding Author and Reprints:** Stephen R. Rapp, PhD, Department of Psychiatry and Behavioral

Medicine, Wake Forest University School of Medicine, 1 Medical Center Blvd, Winston-Salem, NC 27157 (e-mail: srapp@wfbmc.edu).

See also pp 2651, 2673, and 2717.

**Figure 1.** Flow Diagram of the Estrogen Plus Progestin Component of the Women's Health Initiative (WHI) Study

neurotransmitters,<sup>5</sup> neuroconnectivity,<sup>6,7</sup> and neuroprotection.<sup>8</sup> Estrogen receptors are widely distributed throughout the brain, but particularly in the hippocampus,<sup>9</sup> which has suggested a role of estrogen in episodic memory function.<sup>10</sup> Less is known about the effects of progesterone on the brain<sup>11,12</sup> although progesterone could theoretically amplify, modulate, or antagonize the effect of estrogen.<sup>13,14</sup>

The hypothesis that estrogen-containing hormone therapy improves cognition has mixed support. Both a positive association between use of estrogen and cognitive performance in postmenopausal women without dementia<sup>15-19</sup> and a failure to find improvement have been reported.<sup>20-24</sup> Recent systematic reviews<sup>12,25,26</sup> conclude that studies of the effects of estrogen are inconsistent, highlighting the need for large, carefully controlled randomized trials of hormone treatment.

The Women's Health Initiative Memory Study (WHIMS)<sup>27</sup> is an ancil-

lary study of the Women's Health Initiative (WHI) randomized trials of hormone therapy, specifically estrogen alone and estrogen plus progestin.<sup>28</sup> Both studies are described in an earlier article<sup>28</sup> and in a related article,<sup>29</sup> which analyzes dementia-related events. Because of the increased risk of dementia,<sup>29</sup> the results of longitudinal Modified Mini-Mental State Examinations (3MSEs) were evaluated to determine whether estrogen plus progestin modulates global cognition over time.

## METHODS

### Participants and Enrollment

The study design, eligibility criteria, and recruitment procedures of the WHI estrogen plus progestin trial have been described elsewhere.<sup>28,29</sup> Participants in the WHIMS estrogen plus progestin trial were recruited from women who were enrolled in the WHI estrogen plus progestin trial and who were aged 65 years or older and free of probable dementia as ascertained by the WHIMS proto-

col.<sup>27</sup> Prospective participants were informed about WHIMS and written informed consent was obtained. Thirty-nine of the 40 WHI clinical centers participated in WHIMS. Of the 4894 women in the WHI estrogen plus progestin trial who were approached for WHIMS participation, 92.6% (N=4532) consented. Study coordination for WHIMS was provided by the WHIMS clinical coordinating center located at Wake Forest University School of Medicine, Winston-Salem, NC. The National Institutes of Health and the institutional review boards for all participating institutions approved the WHI and WHIMS protocols and consent forms. The sample analyzed herein differs slightly from the sample described in the companion article<sup>29</sup> because it excludes 151 (3.3%) participants without at least 1 valid postenrollment 3MSE score (see "Results").

The main outcome in this analysis is global cognitive function measured with the 3MSE.<sup>30</sup> The 3MSE's 15 parts comprise 46 items that contribute to a total score that can range from 0 to 100, with a higher score reflecting better cognitive functioning. The test items measure temporal and spatial orientation, immediate and delayed recall, executive function (mental reversal, 3-stage command), naming, verbal fluency, abstract reasoning (similarities), praxis (obeying command, sentence writing), writing, and visuoconstructional abilities (copying). The 3MSE has demonstrated good internal consistency and temporal reliability,<sup>31,32</sup> sensitivity, and specificity for detecting cognitive impairment and dementia.<sup>31,33-38</sup> The  $\alpha$  coefficient of the 3MSE was .55 at baseline.

The 3MSE was administered at a screening visit and annually thereafter by a WHIMS technician trained and certified in its administration<sup>27</sup> and who was blinded to randomization assignment and symptom reports. Administration time averaged 10 to 12 minutes. The 3MSE was scored immediately by clinic staff and later by optical scanning. These 2 approaches were compared routinely throughout the trial to

identify scoring discrepancies, which were resolved by clinic staff. Enrolled participants were scheduled for their annual 3MSE assessments regardless of adjudicated dementia status.<sup>29</sup>

Demographic, health, and behavioral information was collected at baseline.<sup>28,29</sup> Women completed an inventory of 34 menopausal symptoms that they might have experienced during the prior 4-week period. Vasomotor symptoms (hot flashes and night sweats) were assessed with none, mild, moderate, or severe as response categories.

### Statistical Methods

The primary outcome measure for WHIMS is probable dementia. The trial was designed to evaluate hormone therapy with respect to this reported outcome.<sup>27,29</sup> The analyses we report herein were conducted to provide explanatory context to the primary results of WHIMS, although the 3MSE scores were not formally planned secondary end points and the trial was not specifically powered to detect treatment differences with respect to these measures. As a result, for the main comparisons of 3MSE score changes by treatment assignment, we have not adjusted *P* values and have used a 2-tailed significance level of .05.

The comparison of changes in 3MSE scores between estrogen plus progestin and placebo is based on a random coefficient mixed model analysis<sup>39</sup> in which the rates of change over time (ie, slopes and intercepts) for women were fitted as random effects.<sup>39,40</sup> The decision to use rates as the basis for inference was supported by the observed longitudinal patterns of scores. Analyses based on such rates show greater statistical power via computer simulation than those based on more complicated models, even if overall patterns are moderately nonlinear. We chose to report analyses on untransformed scores as they allow rates of change to be more easily interpreted and yielded inferences similar to analyses of transformed scores. Random (rather than fixed) effects models were expected to provide a more sensitive (and appropriately conservative) accounting of error.<sup>41</sup> The underlying distributions for

**Table 1.** Characteristics of WHIMS Subtrial Participants at WHI Enrollment by Treatment Assignment\*

Characteristic	Estrogen + Progestin (n = 2145)	Placebo (n = 2236)	<i>P</i> Value†
Age, y			
65-69	1004 (46.8)	1049 (46.9)	.51
70-74	750 (35.0)	807 (36.1)	
≥75	391 (18.2)	380 (17.0)	
Education			
<High school	138 (6.5)	144 (6.5)	.29
High school or GED	430 (20.1)	485 (21.8)	
>High school but <4 years of college	861 (40.3)	837 (37.6)	
≥4 years of college	708 (33.1)	759 (34.1)	
Race or ethnicity			
American Indian or Alaskan Native	4 (0.2)	6 (0.3)	.97
Asian or Pacific Islander	42 (2.0)	46 (2.1)	
Black	102 (4.8)	105 (4.7)	
Hispanic or Latino	49 (2.3)	45 (2.0)	
White, non-Hispanic	1920 (89.6)	1998 (89.6)	
Other	26 (1.2)	30 (1.4)	
Annual household income, \$			
<19 999	480 (23.2)	448 (20.8)	.39
20 000 to 34 999	615 (29.6)	664 (30.8)	
35 000 to 49 999	434 (20.9)	465 (21.6)	
50 000 to 74 999	319 (15.4)	323 (15.0)	
≥75 000	226 (10.9)	253 (11.8)	
Body mass index			
<25	667 (31.2)	746 (33.6)	.13
25-29	774 (36.2)	776 (35.0)	
30-34	445 (20.8)	473 (21.3)	
≥35	252 (11.8)	223 (10.0)	
Smoking status			
Never	1143 (53.9)	1150 (52.4)	.49
Former	845 (39.9)	896 (40.8)	
Current	131 (6.2)	150 (6.8)	
No. of alcoholic drinks consumed per week			
0	924 (43.1)	941 (42.2)	.81
1-6	926 (43.2)	977 (43.8)	
≥7	292 (13.6)	312 (14.0)	
Prior cardiovascular disease			
None	1956 (91.2)	2033 (90.9)	.03
Stroke	21 (1.0)	43 (1.9)	
Other‡	168 (7.8)	160 (7.2)	
Hypertension	767 (36.0)	789 (35.6)	.76
Diabetes			
Absent	1998 (93.2)	2088 (93.5)	.72
Present	145 (6.8)	145 (6.5)	
Moderate or severe vasomotor symptoms			
Absent	2025 (94.7)	2095 (94.1)	.39
Present	113 (5.3)	131 (5.9)	
Prior hormone therapy use			
Any	473 (22.0)	496 (22.2)	.92
Duration <10 y	389 (82.2)	408 (82.3)	.99
Time to initiation of hormone therapy after last menstrual period			
No later than 1 y	192 (43.9)	220 (47.4)	.53
1-4 y	89 (20.4)	84 (18.1)	
≥5 y	156 (35.7)	160 (34.5)	

(continued)

**Table 1.** Characteristics of WHIMS Subtrial Participants at WHI Enrollment by Treatment Assignment\* (cont)

Characteristic	Estrogen + Progestin (n = 2145)	Placebo (n = 2236)	P Value
Other medication use			
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors	257 (12.0)	219 (9.8)	.02
Aspirin (regularly)	603 (28.1)	663 (29.7)	.26
Modified Mini-Mental State examination score at WHI enrollment			
Mean (SD)	95.50 (4.21)	95.64 (3.87)	.28
Level			
95 to 100	1490 (69.9)	1574 (71.1)	.17
Above screening cut point to 94§	503 (23.6)	525 (23.7)	
At or below screening cut point§	138 (6.5)	114 (5.2)	
Baseline Modified Mini-Mental State examination factor z score, mean (SD)			
Verbal memory/fluency	-0.01 (1.03)	0.03 (0.96)	.24
Language/executive function	-0.01 (1.02)	0.02 (0.97)	.37
Orientation/visuoconstruction	-0 (1.02)	0.02 (0.94)	.49

Abbreviations: GED, General Educational Development test; WHI, Women's Health Initiative; WHIMS, Women's Health Initiative Memory Study.

\*Values are expressed as number (percentage) unless otherwise indicated. Group sizes and Modified Mini-Mental State Examination scores differ slightly from Shumaker et al<sup>28</sup> because 151 participants who lacked at least 1 postrandomization Modified Mini-Mental State Examination score were eliminated from this study. Excludes 37 women enrolled 6 months after WHI randomization who had no baseline examination.

†χ<sup>2</sup> test or t test were used.

‡Includes myocardial infarction, angina, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery.

§Screening cut point is ≤80 for women with 0-8 years of formal education and ≤88 for women with 9 or more years of formal education.

**Table 2.** Mean Modified Mini-Mental State Examination Scores by Time From WHI Randomization and Treatment Assignment

No. of Years Since Randomization	Treatment Assignment				Difference Between Treatments, Mean (95% CI)
	Estrogen + Progestin		Placebo		
	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	
0	2132	95.50 (4.21)	2215	95.63 (3.87)	-0.13 (-0.37 to 0.11)
1	2102	95.98 (4.10)	2188	96.20 (3.70)	-0.22 (-0.46 to 0.01)
2	2022	96.37 (3.92)	2095	96.50 (3.91)	-0.13 (-0.37 to 0.11)
3	2005	96.38 (4.36)	2083	96.74 (3.72)	-0.36 (-0.61 to -0.11)
4	1814	96.38 (4.96)	1875	96.90 (3.92)	-0.50 (-0.79 to -0.21)
5	833	96.71 (4.66)	901	96.87 (4.26)	-0.16 (-0.58 to 0.26)
6*	31	96.81 (2.39)	44	96.16 (8.63)	0.65 (-2.53 to 3.82)

Abbreviations: CI, confidence interval; WHI, Women's Health Initiative.

\*Includes 9 women who were tested at 7 years after randomization.

random intercepts and slopes were assumed to be Gaussian; similar results were obtained from parallel analyses in which data were transformed to permit asymmetrical distributions.

Our main analyses followed the intent-to-treat approach with supporting analyses limited to women adherent to treatment assignment. Subgroup analyses were planned and based on known risk factors for impaired cognition and/or possible confounders of

estrogen plus progestin therapy. The consistency of treatment effects across these subgroups was assessed with formal tests for interactions. Included among the subgroup comparisons was an analysis limited to cognitive examinations at times during which women were adherent to their study medications. Because of the relatively large number (n=17) of subgroups that were considered, we adopted a Bonferroni adjustment to control for type I error

and use 0.05/17 = .003 as the critical value for declaring significance for the subgroup analyses.

**RESULTS**

FIGURE 1 depicts the enrollment and follow-up status of the entire WHIMS cohort. Early in recruitment, 45 women (1.0%) were enrolled after their WHI randomization. Slightly fewer women assigned to estrogen plus progestin (n = 16; 0.7%) were enrolled postrandomization than those assigned to placebo (n = 29; 1.3%) (P = .07).

To assess our primary outcome measure—rates of change in 3MSE scores—analyses were restricted to 4381 women (96.7%) with at least 1 valid postenrollment 3MSE. The 151 women excluded from these analyses for this reason were slightly, but not significantly, more likely to have been assigned to receive estrogen plus progestin therapy (3.8% vs 2.9%; P = .11). These women had lower mean (SD) baseline 3MSE scores than women who were not excluded (94.62 [4.1] vs 95.57 [4.0]; P = .005). Among all the characteristics considered in this analysis, these women were significantly more likely to be current smokers (17.6% vs 6.5%; P < .001) and have lower family incomes (P = .02).

TABLE 1 lists characteristics at WHI enrollment of those WHIMS participants who had at least 1 follow-up 3MSE. Nearly half were younger than 70 years and most had at least a high school education. The 3MSE scores at baseline were comparable (P = .28). Most (70%) women scored 95 or above in each group and 6% scored below the preset WHIMS cut point that triggered the work-up to determine the presence of dementia.<sup>29</sup> The average span of measurement (times between first and last 3MSE) was 4.2 years (range, 0.9-7.0 years) and was similar in both groups (P = .99). The only significant group differences were lower prevalence of stroke (P = .03) and a higher percentage of participants using statins (P = .02) in the estrogen plus progestin group. The 3MSE scores tended to increase in both groups over the first 4 years (TABLE 2). However,

the placebo group had a pattern of slightly higher scores and a steadier increase compared with the estrogen plus progestin group. Differences were statistically significant (unadjusted *P* value) at years 3 and 4.

FIGURE 2 portrays 3MSE mean scores from random effects models, which use intrasubject longitudinal correlations to control for varying patterns of examination times among women. The relatively few data from visit 7 have been assigned to visit 6 in these plots for a more concise portrayal of patterns. Treatment group 3MSE mean scores tended to diverge only after 2 years (Table 2). Overall (first row of TABLE 3), mean (SD) 3MSE total scores increased 0.149 (0.021) units per year among women assigned to estrogen plus progestin and 0.213 (0.020) units per year among women assigned to placebo, providing a small statistically significant difference (*P* = .03).

Adherence to assigned study medication was significantly higher among women in the placebo group for each year (*P* < .01). Adherence rates for the estrogen plus progestin group were 71.2% for year 1 compared with 83.3% for the placebo group; 60.5% vs 73.2% for year 2; 54.2% vs 66.3% for year 3; 49.0% vs 60.6% for year 4; 45.1% vs 58.1% for year 5; and 35.8% vs 55.0% for years 6 or more, respectively. Analyses of differences between rates of 3MSE changes between the estrogen plus progestin and placebo groups were repeated with all data censored after the first occurrence of nonadherence. For this subset of visits, the fitted increase

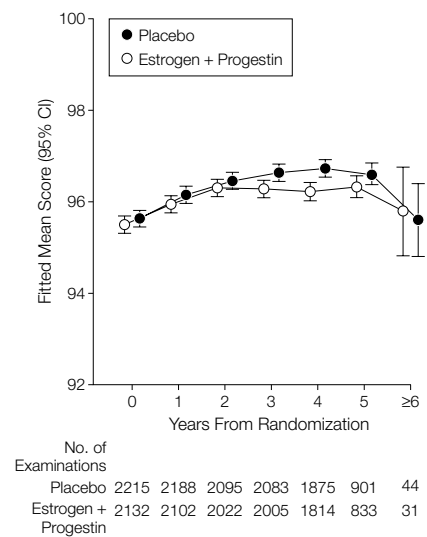
in scores was still marginally more favorable for women in the placebo group (*P* = .008; Table 3).

At baseline, 64 women reported a history of stroke: 21 (32.8%) were assigned to estrogen plus progestin and 43 (67.2%) were assigned to placebo (*P* = .009). During follow-up, 39 (1.8%) women in the estrogen plus progestin group and 36 (1.6%) in the placebo group were adjudicated to have strokes (*P* = .62). To examine the extent to which the lower 3MSE scores in estrogen plus progestin participants could be explained by cognitive effects associated with preexisting or incident strokes (the latter being increased by estrogen plus progestin),<sup>42</sup> we performed an analysis excluding women with prior stroke and censoring the 3MSE data in the remaining participants at the time of an incident stroke event. In these data, differences between the estrogen plus progestin and placebo cohorts remained significant (*P* = .03). The estimated mean slopes were 0.149 (0.021) for estrogen plus progestin and 0.213 (0.021) for placebo (Table 3).

Among the women included in our analyses, 61 were diagnosed as having probable dementia during our study: 40 were assigned to estrogen plus progestin and 21 were assigned to placebo (*P* = .01).<sup>29</sup> The mean (SD) 3MSE score triggering the more detailed neuropsychological and neuropsychiatric assessment and adjudication leading to these diagnoses was 78.1 (8.9) (range, 52-88). By protocol, these women were given the 3MSE annually. Thirty-eight women provided data 1 year after their

diagnosis of probable dementia, 19 after 2 years, and 9 after 3 years. Sixty-one women provided data 1 year prior to their diagnosis, 51 in 2 years prior, and 35 in 3 years prior. FIGURE 3 illustrates the 3MSE mean scores before, at the triggering visit, and after diagnoses of probable dementia for these women. Average 3MSE scores decreased during these years and were similar for both treatment groups. To determine whether the lower 3MSE scores of women diagnosed as having dementia explain the group differences, the primary 3MSE analyses were repeated after removing all scores from the triggering test forward. The differ-

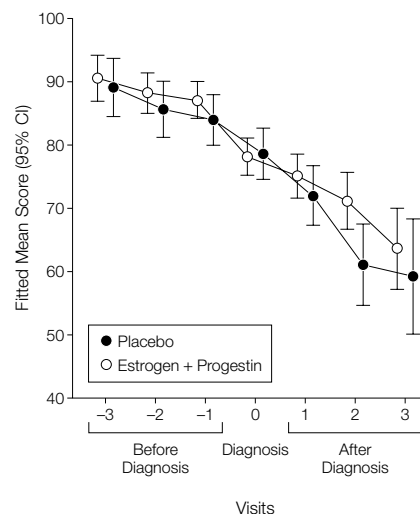
**Figure 2.** Mean Modified Mini-Mental State Examination Score (±95% Confidence Intervals) Over Time From Mixed Models by Treatment Assignment



**Table 3.** Mean Rates of Change in Modified Mini-Mental State Examination

Subgroup	Mean (SE) Rate of Change		Difference Between Treatments, Mean (95% Confidence Interval)	Interaction <i>P</i> Value
	Estrogen + Progestin	Placebo		
All women	0.149 (0.021)	0.213 (0.020)	-0.063 (-0.120 to -0.006)	.03
Excluded women				
Nonadherent	0.091 (0.024)	0.180 (0.023)	-0.089 (-0.154 to -0.024)	.008
History of stroke	0.149 (0.021)	0.213 (0.021)	-0.064 (-0.122 to -0.007)	.03
Probable dementia	0.191 (0.017)	0.241 (0.017)	-0.049 (-0.096 to -0.003)	.04
Probable dementia or mild cognitive impairment	0.207 (0.016)	0.247 (0.016)	-0.040 (-0.084 to 0.08)	.07
Nonadherent, history of stroke, probable dementia, mild cognitive impairment, and enrolled after randomization	0.166 (0.019)	0.228 (0.018)	-0.062 (-0.114 to -0.010)	.02

**Figure 3.** Mean Modified Mini-Mental State Examination Score ( $\pm$ SE) of Patients Diagnosed as Having Probable Dementia, at 1-3 Visits Prior, Time of Diagnosis, and 1-3 Visits Postdiagnosis, by Treatment Assignment



ence between average rates of 3MSE changes between the treatment groups remained statistically significant ( $P=.04$ ) in these analyses (Table 3). Additional analyses in which women were censored at the first diagnosis of either probable dementia or mild cognitive impairment yielded similar results, however the  $P$  value increased ( $P=.07$ ). Finally, analyses censoring these observations and those obtained after strokes, and removing both non-adherent women and those enrolled following randomization yielded fitted mean (SD) rates of change of 0.188 (0.018) for estrogen plus progestin and 0.246 (0.017) for placebo ( $P=.02$ ).

To determine whether the effect of estrogen plus progestin on cognitive performance was the same or different according to several baseline participant characteristics, we conducted a series of subgroup analyses. TABLE 4 lists fitted mean rates of change for women grouped by treatment assignment for selected subgroups with tests for interactions. The impact of treatment assignment on 3MSE scores was fairly consistent (based on tests of interaction) among all subgroups, and none

of these tests reached the adjusted statistical significance level ( $P<.003$ ).

Lastly, women assigned to estrogen plus progestin therapy were more likely to have large decreases in 3MSE scores. For example, declines of 2 SDs or more (ie,  $\geq 8$  units) occurred in 6.7% of women assigned to estrogen plus progestin compared with 4.8% of women assigned to placebo ( $P=.008$ ) for at least 1 follow-up visit compared with baseline scores. Increases of this magnitude occurred with similar frequency in the 2 groups (8.0% among women assigned to estrogen plus progestin and 7.0% for women assigned to placebo). Increases and decreases ranged from 2 to 10 units (FIGURE 4). The relative odds of 3MSE scores declining in estrogen plus progestin women increased with the magnitude of this loss. The 95% confidence intervals for odds ratios excluded 1.0 for losses of 8 units or more. The odds of increases in 3MSE scores were similar between treatment groups, regardless of the level of increase. The residual variances from linear models fitted to women's scores over time were nearly identical for the 2 treatment groups. When women with declines of at least 2 SDs and/or diagnoses of either dementia or mild cognitive impairment were removed from analyses, the mean (SD) rates of change were increased by 0.207 (0.016) for estrogen plus progestin and 0.247 (0.016) for placebo ( $P=.07$ ).

## COMMENT

Investigators recently concluded from the WHI that the combined postmenopausal hormone treatment of estrogen plus progestin increased risks for coronary heart disease, invasive breast cancer, stroke, and pulmonary embolism and that these increased risks outweigh benefits from reduced rates of colorectal cancer and hip fracture.<sup>42</sup> Potential effects of postmenopausal hormone treatment on cognition and dementia are a public health concern, and WHIMS was specifically designed to address this issue within the setting of the WHI hormone therapy trials.<sup>27</sup>

Plausible hypotheses have been offered for how hormone therapy might influence cognitive function,<sup>5-8,10,43-46</sup> but prior evidence regarding postmenopausal hormone therapy and cognition is limited and inconsistent. Some studies indicate protection<sup>17,18,47,48</sup> and others indicate little or no benefit from hormone therapy.<sup>21</sup> Also, in some studies, past but not current hormone use was associated with reduced cognitive decline.<sup>49</sup> Other studies have shown cognitive decline occurred in current users of combined estrogen plus progestin therapy,<sup>50</sup> but not among current users of unopposed estrogen.

Conclusions from previous randomized controlled trials of cognition in postmenopausal women have been hampered by generally small samples of women treated for relatively short periods.<sup>25,26,51</sup> Somewhat larger trials showed no treatment effects on a variety of tasks regarding attention<sup>22</sup> or memory.<sup>23</sup> In the Heart and Estrogen/progestin Replacement Study (HERS), 1063 older women (mean age, 67 years) with coronary disease were assessed once after a mean treatment interval of 4.2 years. The estrogen plus progestin and placebo groups differed on only 1 of 6 cognitive tasks (verbal fluency)—a difference that favored the placebo group.<sup>24</sup> In the analysis of 3MSE scores in the entire cohort of women aged 65 years or older in the WHI estrogen plus progestin trial, score changes did not differ significantly over 1 or 3 years.<sup>20</sup>

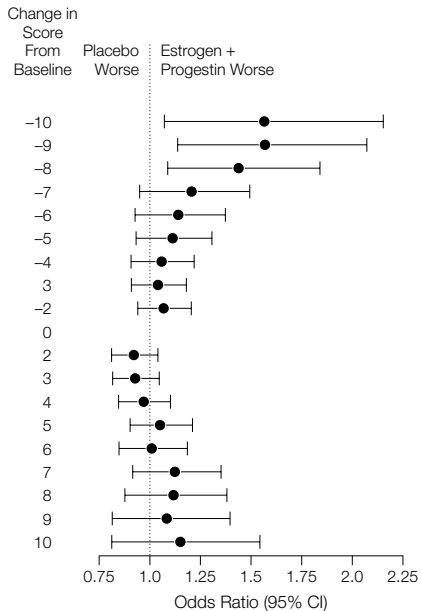
In the current WHIMS cohort, 4381 women provided baseline and at least 1 follow-up score on the 3MSE. Most women scored high at their initial testing and yet mean scores in both the estrogen plus progestin and placebo groups continued to improve through year 4, a finding that we attribute to a positive practice (learning) effect known to result from repeated administrations of cognitive tests.<sup>52-54</sup> In the present study, the mean rate of change in 3MSE scores over time was slightly less favorable in the estrogen plus progestin group than the placebo group (Figure 3) over an average follow-up of 4.2 years. This difference, while

**Table 4.** Mean Rates of Change in 3MSE Examination Scores Over Time\*

Subgroup	Estrogen + Progestin		Placebo		Difference Between Treatments	
	Rate of Change in Mean (SE) Score	P Value	Rate of Change in Mean (SE) Score	P Value	Mean (95% CI)	Interaction P Value
Age, y						
65-69	0.264 (0.030)	<.001	0.270 (0.029)	<.001	-0.006 (-0.088 to 0.076)	.17
70-74	0.124 (0.035)		0.246 (0.033)		-0.122 (-0.216 to -0.028)	
≥75	-0.116 (0.050)		-0.025 (0.050)		-0.091 (-0.023 to 0.048)	
Education						
<High school	0.061 (0.084)	.007	0.411 (0.081)	.006	-0.350 (-0.579 to -0.121)	.02
High school or GED	0.238 (0.047)		0.282 (0.043)		-0.043 (-0.168 to 0.082)	
>High school but <4 years of college	0.200 (0.032)		0.181 (0.034)		0.019 (-0.073 to 0.111)	
≥4 years of college	0.058 (0.036)		0.169 (0.035)		-0.111 (-0.209 to -0.013)	
Race or ethnicity						
American Indian or Alaskan Native	1.037 (0.579)	.18	-0.041 (0.467)	.01	1.078 (-0.278 to 2.434)	.47
Asian or Pacific Islander	0.295 (0.148)		0.264 (0.147)		0.030 (-0.378 to 0.438)	
Black	0.336 (0.101)		0.494 (0.099)		-0.158 (-0.434 to 0.118)	
Hispanic or Latino	0.130 (0.139)		0.394 (0.147)		-0.264 (-0.660 to 0.132)	
White, non-Hispanic	0.134 (0.022)		0.190 (0.021)		-0.056 (-0.117 to 0.005)	
Other	0.296 (0.194)		0.474 (0.180)		-0.178 (-0.695 to 0.339)	
Annual household income, \$						
<19 999	0.114 (0.044)	.48	0.232 (0.045)	.87	-0.119 (-0.242 to 0.004)	.40
20 000 to 34 999	0.141 (0.038)		0.235 (0.037)		-0.093 (-0.197 to 0.011)	
35 000 to 49 999	0.219 (0.046)		0.189 (0.044)		0.029 (-0.094 to 0.152)	
50 000 to 74 999	0.130 (0.053)		0.202 (0.052)		-0.072 (-0.217 to 0.073)	
≥75 000	0.202 (0.063)		0.183 (0.061)		0.019 (-0.153 to 0.191)	
Body mass index						
<25	0.080 (0.037)	.10	0.142 (0.035)	.04	-0.061 (-0.161 to 0.039)	.93
25-29	0.154 (0.035)		0.232 (0.035)		-0.078 (-0.174 to 0.018)	
30-34	0.206 (0.046)		0.286 (0.045)		-0.080 (-0.205 to 0.045)	
≥35	0.232 (0.061)		0.246 (0.066)		-0.015 (-0.191 to 0.161)	
Smoking status						
Never	0.133 (0.028)	.60	0.207 (0.028)	.23	-0.075 (-0.153 to 0.003)	.50
Former	0.178 (0.033)		0.238 (0.032)		-0.060 (-0.150 to 0.030)	
Current	0.154 (0.086)		0.106 (0.081)		0.048 (-0.183 to 0.279)	
No. of alcoholic drinks consumed per week						
0	0.156 (0.032)	.96	0.252 (0.032)	.15	-0.096 (-0.184 to -0.008)	.59
1-6	0.141 (0.032)		0.172 (0.031)		-0.032 (-0.118 to 0.054)	
≥7	0.147 (0.056)		0.232 (0.055)		-0.076 (-0.229 to 0.077)	
Prior cardiovascular disease						
None	0.135 (0.022)	.08	0.222 (0.021)	.24	-0.087 (-0.148 to -0.026)	.02
Stroke	0.166 (0.219)		0.176 (0.161)		-0.009 (-0.542 to 0.524)	
Other	0.321 (0.075)		0.095 (0.078)		0.226 (0.014 to 0.438)	
Hypertension						
Absent	0.109 (0.026)	.01	0.230 (0.025)	.25	-0.121 (-0.192 to -0.050)	.008
Present	0.224 (0.035)		0.183 (0.035)		0.041 (-0.055 to 0.137)	
Diabetes						
Absent	0.154 (0.021)	.44	0.216 (0.021)	.63	-0.061 (-0.120 to -0.004)	.39
Present	0.081 (0.082)		0.245 (0.082)		-0.165 (-0.392 to 0.063)	
Moderate or severe vasomotor symptoms						
Absent	0.141 (0.021)	.15	0.207 (0.021)	.21	-0.066 (-0.125 to -0.007)	.75
Present	0.290 (0.093)		0.314 (0.087)		-0.024 (-0.274 to 0.226)	
Prior hormone therapy use						
None	0.138 (0.024)	.34	0.197 (0.023)	.12	-0.058 (-0.123 to 0.007)	.75
Previous	0.189 (0.044)		0.270 (0.043)		-0.081 (-0.203 to 0.041)	
Duration <10 y	0.219 (0.043)		0.247 (0.042)		-0.028 (-0.146 to 0.090)	
Duration ≥10 y	0.056 (0.094)	.14	0.379 (0.091)	.18	-0.323 (-0.580 to -0.066)	.04
Time to initiation of hormone therapy after last menstrual period						
No later than 1 y	0.165 (0.063)	.62	0.146 (0.058)	.01	0.020 (-0.147 to 0.187)	.13
1-4 y	0.267 (0.089)		0.268 (0.093)		-0.001 (-0.254 to 0.252)	
≥5 y	0.166 (0.069)		0.396 (0.069)		-0.229 (-0.421 to -0.037)	
Use of hydroxymethyl glutaryl coenzyme A reductase inhibitors						
No	0.112 (0.023)	<.001	0.207 (0.023)	.54	-0.095 (-0.160 to -0.030)	.02
Yes	0.310 (0.048)		0.235 (0.044)		0.075 (-0.052 to 0.202)	
Regular use of aspirin						
No	0.137 (0.025)	.38	0.228 (0.024)	.24	-0.091 (-0.160 to -0.022)	.16
Yes	0.178 (0.039)		0.178 (0.038)		0 (-0.106 to 0.106)	
Baseline Modified Mini-Mental State Examination score						
95 to 100	0 (0.026)	<.001	0.034 (0.026)	<.001	-0.034 (-0.107 to 0.039)	.12
Screening cut point to 94	0.437 (0.047)		0.615 (0.046)		-0.178 (-0.305 to -0.051)	
At or below screening cut point	0.805 (0.090)		0.977 (0.099)		-0.173 (-0.436 to 0.090)	

\*A Bonferroni adjustment (0.05/17 = 0.003) was adopted for subgroup analyses.

**Figure 4.** Odds Ratio (95% Confidence Intervals) for Various Magnitudes of Modified Mini-Mental State Examination Score Changes From Baseline (Across All Follow-up Visits): Estrogen Plus Progestin vs Placebo



nominally statistically significant, is not clinically significant. Thus, estrogen plus progestin offers no benefit for global cognitive function and the small differences in mean change scores suggest that no clinically significant negative effect on cognition occurred either. However, we also found that significantly more women taking estrogen plus progestin registered substantial declines ( $\geq 2$  SDs) in 3MSE scores, suggesting that some women experienced a clear detrimental effect. The greater frequency of large declines among women assigned to estrogen plus progestin did not appear to result from increased variability in examination scores, which could happen if they were driven by short-term reversible changes in cognition. Removing these women from the analysis increased the mean rates of change and reduced the group differences to statistically non-significant levels.

The identification of subgroups of women who might be particularly vulnerable to adverse effects of estrogen

plus progestin on cognition is an important area of future research. Our subgroup analyses, which were based on 17 different baseline characteristics, failed to identify any women as having an especially high or low risk of cognitive changes. Thus, future studies will be needed to determine if any vulnerable subgroup can be identified.

The mechanisms by which estrogen plus progestin decreased 3MSE scores in some women are unknown, although effects of estrogen plus progestin on procoagulant<sup>55</sup> and proinflammatory<sup>56</sup> markers have been shown previously. Silent brain infarcts increase the risk of dementia and global cognitive decline.<sup>57</sup> Results from WHI<sup>42</sup> and HERS<sup>24</sup> indicate that estrogen plus progestin affects some clot-related events adversely. In WHIMS, the presence at baseline of cardiovascular disease or hypertension did not confound study analyses, and post-hoc exclusion of women with stroke did not substantially alter the conclusions.

The 2 WHIMS reports thus fail to support the hypothesis that estrogen plus progestin protects cognitive function in relatively healthy older postmenopausal women and are consistent with other data on cognitive function from the larger WHI estrogen plus progestin trial. Unlike the WHI data that showed no changes in 3MSE scores over 1 and 3 years,<sup>20</sup> WHIMS data revealed a small but important number of women in the estrogen plus progestin group who experienced an adverse effect on global cognitive function compared with placebo. This effect is not entirely explained by the presence of dementia or mild cognitive impairment.<sup>29</sup>

#### Limitations

Several methodological features of this study should be considered. Women in the WHIMS cohort were generally well educated, predominantly white, and in good health. However, there is no reason to believe that these results are not generally applicable to other women in this age group. Active treatment in this component of WHIMS was with estrogen plus progestin. The conclusions

here, like those of the earlier WHI study,<sup>20,42</sup> pertain to this specific formulation of hormone therapy and not to estrogen alone or to different formulations or routes of administration. The ongoing WHIMS trial of estrogen alone vs placebo will provide valuable information on this issue.

In WHIMS, menopause occurred some years before study enrollment. Therefore, our results pertain only to estrogen plus progestin initiated during the late postmenopausal period. Memory skills do not differ substantially between women during menopause and women in the early postmenopausal period.<sup>58</sup> Whether the present findings on global cognitive function apply equally to estrogen plus progestin initiated before the age of 65 years cannot be addressed by these data directly.

Nonadherence was higher in the estrogen plus progestin group than in the placebo group. However, a strict criterion for nonadherence (any assessment point at which the woman reported taking fewer than 80% of her pills) and excluding those who are not adherent from analyses did not change the overall results.

Lastly, the 3MSE is a screening measure for global cognitive function and it may be less sensitive to cognitive changes than a larger, more comprehensive neuropsychological battery. The Women's Health Initiative Study of Cognitive Aging (WHISCA) is an ancillary study to WHIMS designed to assess the efficacy of postmenopausal hormone therapy on age-associated cognitive decline. WHISCA includes 14 of the 39 WHIMS clinical sites and enrolled participants a mean (SD) of 3 (0.69) years after randomization into WHI. Approximately 61% of the WHISCA participants (n=1414) are in the estrogen plus progestin group. WHISCA participants undergo a detailed neuropsychological assessment annually, which involves a battery of measures that differs from those used in WHIMS. WHISCA was specifically designed to provide more specific and complementary data on the role of hormone therapy on cognitive function-

ing in postmenopausal women than that afforded by WHI and WHIMS. Thus, a kind of telescoping effect is created by studies within studies, each providing more detailed assessments in fewer women with different but complementary outcomes.

## Implications

In conclusion, this study adds important new information to the discussion regarding the effect of estrogen plus progestin on cognitive function in older postmenopausal women. Results from this analysis within a large, randomized trial do not support the use of combined estrogen plus progestin treatment to protect cognition in older women. Moreover, while most women did not experience a negative treatment effect on cognition, a small increased risk of clinically meaningful cognitive decline occurred in the estrogen plus progestin group.

**Author Affiliations:** Departments of Psychiatry and Behavioral Medicine (Dr Rapp) and Public Health Sciences (Drs Espeland, Shumaker, Coker, and Dailey), Wake Forest University School of Medicine, Winston-Salem, NC; Department of Geriatrics, University of Arkansas Medical Sciences, Little Rock (Dr Henderson); Department of Family and Community Medicine, University of Nevada, Reno (Dr Brunner); Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (Dr Manson); Department of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio (Dr Gass); Stanford Center for Research in Disease Prevention, Stanford University, Stanford, Calif (Dr Stefanick); Department of Preventive Medicine, State University of New York, Stony Brook (Dr Lane); Department of Medicine, Baylor College of Medicine, Houston, Tex (Dr Hays); Department of Preventive Medicine, University of Tennessee, Memphis (Dr Johnson); and Fred Hutchinson Cancer Research Center, Seattle, Wash (Dr Bowen).

**Author Contributions:** *Study concept and design:* Rapp, Espeland, Shumaker, Henderson, Manson, Gass, Coker, Dailey, Bowen.

*Acquisition of data:* Espeland, Shumaker, Brunner, Manson, Gass, Stefanick, Lane, Hays, Johnson, Coker. *Analysis and interpretation of data:* Rapp, Espeland, Shumaker, Henderson, Brunner, Manson, Gass, Stefanick, Hays, Johnson.

*Drafting of the manuscript:* Rapp, Espeland, Shumaker, Henderson, Brunner, Coker.

*Critical revision of the manuscript for important intellectual content:* Rapp, Espeland, Shumaker, Henderson, Brunner, Manson, Gass, Stefanick, Hays, Lane, Johnson, Coker, Dailey, Bowen.

*Statistical expertise:* Espeland, Shumaker, Brunner. *Obtained funding:* Rapp, Espeland, Shumaker, Brunner, Stefanick, Coker.

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