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Mark A. Espeland; Stephen R. Rapp; Sally A. Shumaker; et al.

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Conjugated Equine Estrogens and Global Cognitive Function in Postmenopausal Women

Women's Health Initiative Memory Study

Mark A. Espeland, PhD

Stephen R. Rapp, PhD

Sally A. Shumaker, PhD

Robert Brunner, PhD

JoAnn E. Manson, MD, DrPH

Barbara B. Sherwin, PhD

Judith Hsia, MD

Karen L. Margolis, MD, MPH

Patricia E. Hogan, MS

Robert Wallace, MD

Maggie Dailey, PhD

Ruth Freeman, MD

Jennifer Hays, PhD

for the Women's Health Initiative
Memory Study Investigators

AGE-ASSOCIATED MEMORY impairment affects an estimated one fifth to one third of older individuals and has important individual, family, and societal costs.^{1,2} In older postmenopausal women, the potential impact of declining levels of sex hormones on cognitive functioning has received particular attention because of estrogen's presumptive beneficial effects on neurotransmitters,³ neuroconnectivity,^{4,5} and neuroprotection.⁶ Observational studies have suggested that long-term hormone therapy may attenuate cognitive aging in postmenopausal women, although ran-

See also pp 2947 and 3005.

Context The Women's Health Initiative Memory Study (WHIMS) previously reported that estrogen plus progestin therapy does not protect cognition among women aged 65 years or older. The effect of estrogen-alone therapy, also evaluated in WHIMS, on cognition has not been established for this population.

Objectives To determine whether conjugated equine estrogen (CEE) alters global cognitive function in older women and to compare its effect with CEE plus medroxyprogesterone acetate (CEE plus MPA).

Design, Setting, and Participants A randomized, double-blind, placebo-controlled ancillary study of the Women's Health Initiative (WHI), WHIMS evaluated the effect of CEE on incidence of probable dementia among community-dwelling women aged 65 to 79 years with prior hysterectomy from 39 US academic centers that started in June 1995. Of 3200 eligible women free of probable dementia enrolled in the WHI, 2947 (92.1%) were enrolled in WHIMS. Analyses were conducted on the 2808 women (95.3%) with a baseline and at least 1 follow-up measure of global cognitive function before the trial's termination on February 29, 2004.

Interventions Participants received 1 daily tablet containing either 0.625 mg of CEE (n=1387) or matching placebo (n=1421).

Main Outcome Measure Global cognitive function measured annually with the Modified Mini-Mental State Examination (3MSE).

Results During a mean follow-up of 5.4 years, mean (SE) 3MSE scores were 0.26 (0.13) units lower than among women assigned to CEE compared with placebo ($P=.04$). For pooled hormone therapy (CEE combined with CEE plus MPA), the mean (SE) decrease was 0.21 (0.08; $P=.006$). Removing women with dementia, mild cognitive impairment, or stroke from the analyses lessened these differences. The adverse effect of hormone therapy was more pronounced among women with lower cognitive function at baseline (all $P<.01$). For women assigned to CEE compared with placebo, the relative risk of having a 10-unit decrease in 3MSE scores (>2 SDs) was estimated to be 1.47 (95% confidence interval, 1.04-2.07).

Conclusion For women aged 65 years or older, hormone therapy had an adverse effect on cognition, which was greater among women with lower cognitive function at initiation of treatment.

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domized clinical trial results are inconsistent.⁷⁻¹²

The Women's Health Initiative (WHI) includes 2 randomized trials of post-

menopausal hormone therapy: the estrogen-alone trial of conjugated equine estrogen (CEE) therapy in women with a prior hysterectomy and the estrogen

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Corresponding Author: Mark A. Espeland, PhD,

Department of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157 (mespelan@wfubmc.edu).

plus progestin trial of CEE combined with medroxyprogesterone acetate (CEE plus MPA) in women with an intact uterus.¹³ The Women's Health Initiative Memory Study (WHIMS) was designed as an ancillary study to evaluate the effect of either estrogen-alone or estrogen plus progestin on cognitive outcomes in an analysis pooled across the 2 trials.¹⁴

We previously reported that CEE plus MPA increased the risk of probable dementia and provided no benefit for global cognition.^{15,16} On March 1, 2004, the estrogen-alone trial of the WHI was terminated due to an excess risk of stroke and the lack of a significant effect on other cardiovascular disease outcomes.¹⁷

In this study, we evaluated the effect of postmenopausal hormone therapy on global cognition in the estrogen-alone trial and, consistent with the original design of WHIMS, in the pooled estrogen-alone and estrogen plus progestin cohorts. (An accompanying article reports the effects of estrogen plus progestin and estrogen-alone on incidence of probable dementia and mild cognitive impairment.¹⁸) This analysis was not specified in the original protocol but was conducted to help interpret the findings with respect to dementia.

METHODS

Participants

The study design, eligibility criteria, and recruitment procedures of the WHI estrogen plus progestin trial have been described.^{13,19} Women enrolled in the WHI estrogen-alone trial who were aged 65 to 79 years and free of dementia as ascertained by the WHIMS protocol¹⁴ were eligible and asked to enroll. Participating women provided written informed consent. Thirty nine of 40 WHI clinical centers participated in WHIMS. Early in the trial, follow-up was suspended by the main trial in 1 center and 47 women from this center were excluded from this study. The National Institutes of Health and institutional review boards for all participating institutions approved the WHI and WHIMS protocols and consent forms.

Of the 3200 women in the WHI estrogen-alone trial who were approached for WHIMS participation, 2947 (92.1%) consented and enrolled. To analyze the change in cognitive scores, we included only participants with at least 1 valid postbaseline Modified Mini-Mental State Examination (3MSE) score. We also excluded the relatively few women who were enrolled 6 months or more after initiation of their assigned WHI therapy, because treatment effects may be under way by this time. These exclusions were also applied to reanalyses of the estrogen plus progestin trial data, eliminating 37 women who were included in our earlier study.¹⁶

Main Outcome Measure

The main outcome measure was global cognitive function measured annually with the 3MSE.²⁰ Scores 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 moderate internal consistency and temporal reliability,^{21,22} with good sensitivity and specificity for detecting cognitive impairment.²¹⁻²⁸ The α coefficient of the 3MSE at baseline was .55.¹⁶

The 3MSE was administered during a WHI screening visit and annually thereafter by a technician who was trained and certified in its administration and masked to randomization assignment and reports of symptoms. 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. Women who scored below cut points based on education level were asked to complete an expanded neuropsychological battery and a neuropsychiatric clinical

examination to classify their dementia status.¹⁸ These cut points were initially a score of 72 or lower for women with 8 years or less of education and a score of 76 or lower for women with at least 9 years of education. After 16 months, the protocol was altered to increase these cut points to a score of 80 or lower and 88 or lower, respectively. Enrolled participants continued to be scheduled for their annual 3MSE assessments regardless of adjudicated dementia status.

Medical History

Information on demographic, health, and behavioral factors and physical measurements were collected at baseline as previously described.¹⁴ These included menopausal symptoms (hot flashes and night sweats) experienced during the prior 4-week period to assess presence and severity of vasomotor symptoms (none, mild, moderate, severe). Prior cardiovascular disease was defined by self-report of myocardial infarction, stroke, angina, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery. Regular use of aspirin was queried and use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) was ascertained by a medication inventory. Incidence of strokes during the trial was based on central adjudication of medical records.

Statistical Analyses

Changes from baseline 3MSE score across follow-up were compared between treatment groups using Wald tests from linear models fitted by maximum likelihood, with first-order autoregressive structure for the longitudinal correlation within study participants.²⁹ Treatment assignment was included in the model as a fixed effect to compare the mean difference in these changes between treatment groups over time. We decided to evaluate mean changes rather than rates of change (which were the basis of the earlier estrogen plus progestin trial analyses), because the changes in scores over the extended estrogen-alone trial

were markedly nonlinear and thus not well described by rates of change. We report analyses of untransformed scores because they allow more interpretable expressions of changes (and yielded inferences similar to the analyses of transformed scores). To parallel analyses defined by the WHIMS protocol for its primary outcome of probable dementia, we also pooled data from the estrogen-alone and estrogen plus progestin trials to estimate an overall effect of hormone therapy and assess by using interaction terms whether relative treatment effects varied between therapies.

Our main analyses follow a modified intent-to-treat approach. Women were analyzed according to randomization assignment; however, analyses were limited to women who consented to WHIMS, whose consent was obtained within 6 months of WHI randomization, and who took the 3MSE at least once after baseline. We also performed an analysis of only those women who were adherent to treatment assignment (a participant was defined as nonadherent by stopping study medication, taking <80% of study medications, or taking independently prescribed hormones). In other supporting analyses, we examined the balance of treatment assignment across subgroups defined by 17 factors expected to affect measured cognitive status (and ascribed potential importance only to comparisons associated with a nominal $P < .01$): age, education, ethnicity, family income, body mass index (calculated as weight in kilograms divided by the square of height in meters), smoking status, alcohol intake, prior vascular disease, hypertension, diabetes mellitus, moderate or severe vasomotor symptoms, prior hormone therapy, age at hysterectomy, bilateral oophorectomy, use of statins, regular use of aspirin, and baseline 3MSE score. We described the consistency of treatment effects across these subgroups, using interaction terms for inference.

We examined whether changes in 3MSE scores of various magnitudes occurred more frequently among women assigned to CEE and pooled CEE and

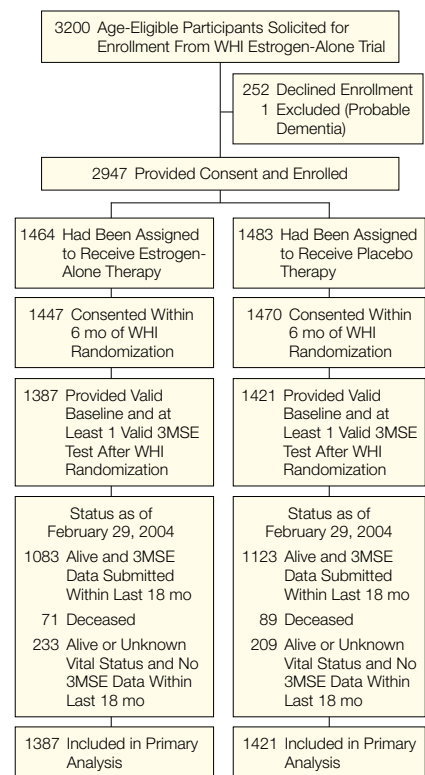
CEE plus MPA, by computing whether a woman's 3MSE scores had changed by 2, 4, 6, 8, 10, or 12 units from baseline at any time during follow-up. We used logistic regression to estimate the odds ratio of these changes between treatment groups and adjusted the odds ratio to approximate the relative risk.³⁰ Baseline 3MSE score and follow-up time were included as covariates in these analyses.

RESULTS

FIGURE 1 depicts the enrollment and follow-up status of the WHIMS estrogen-alone trial. The 139 WHIMS participants (4.7%) excluded from analyses due to enrollment 6 months or more after randomization (17 assigned to CEE and 13 assigned to placebo) or absence of follow-up data (60 assigned to CEE and 49 assigned to placebo) were equally distributed between groups. Women excluded in the analysis had lower mean baseline 3MSE scores than women who were included (mean [SD], 92.73 [5.80] vs 94.68 [4.64]; $P < .001$) and, among all the remaining characteristics considered in this analysis, the women excluded only differed in a higher rate of current (9.9% vs 7.2%) and former (41.4% vs 36.6%) smoking ($P < .001$). These women were included in the analyses of WHIMS primary outcomes.¹⁸

The baseline data for the WHIMS estrogen-alone trial participants that were included in these analyses are shown in TABLE 1. Approximately 45% were aged 65 to 69 years and two thirds had some education after high school. Most women (62%) had 3MSE scores of 95 or higher; 9.6% scored at or below the preset WHIMS screening cut points. The mean time between first and last 3MSE examinations was 5.4 years (range, 0.9-7.6) and was similar in both groups ($P = .86$). Women participated in 1 (4.0%), 2 (4.2%), 3 (5.3%), 4 (7.2%), 5 (23.5%), 6 (42.7%), 7 (12.9%), or 8 (0.2%) follow-up examinations. Overall, women assigned to CEE or placebo had comparable distributions of demographic, socioeconomic, and clinical characteristics. The

Figure 1. Study Flow of the Estrogen-Alone Trial of the Women's Health Initiative Memory Study



WHI indicates Women's Health Initiative; 3MSE, Modified Mini-Mental State Examination.

only statistically significant difference was regular use of aspirin at baseline, which was slightly more common among women assigned to placebo (31.1% vs 27.5%; $P = .04$).

The analyses for the companion estrogen plus progestin trial, which excluded 14 women assigned to CEE plus MPA and 23 assigned to placebo who consented to WHIMS more than 6 months after WHI treatment assignment, involved 4344 women (2131 assigned to CEE plus MPA and 2213 assigned to placebo) who were followed up for a mean of 4.2 years (range, 0.9-6.4 years). The baseline characteristics for the estrogen plus progestin trial were described previously.¹⁶ As self-described, women in the estrogen-alone trial, in addition to having had a hysterectomy, tended to be relatively less educated and were more likely to

Table 1. Baseline Demographic, Socioeconomic Status, and Clinical Characteristics of the WHIMS Estrogen-Alone Trial Participants at WHI Enrollment by Treatment Assignment*

Characteristics	CEE (n = 1387)	Placebo (n = 1421)
Age at screening, y		
65-69	620 (44.7)	637 (44.8)
70-74	521 (37.6)	492 (34.6)
≥75	246 (17.7)	292 (20.6)
Education		
<High school	128 (9.3)	128 (9.0)
High school or GED	330 (23.9)	337 (23.8)
>High school but <4 y of college	602 (43.6)	584 (41.3)
≥4 y of college	321 (23.2)	366 (25.9)
Race or ethnicity		
American Indian or Alaskan Native	10 (0.7)	6 (0.4)
Asian or Pacific Islander	21 (1.5)	12 (0.8)
Black	149 (10.8)	150 (10.6)
Hispanic or Latino	34 (2.5)	39 (2.8)
White, non-Hispanic	1151 (83.3)	1186 (83.7)
Other	17 (1.2)	24 (1.7)
Annual household income, \$		
<19 999	396 (29.6)	418 (30.5)
20 000 to 34 999	432 (32.3)	418 (30.5)
35 000 to 49 999	227 (17.0)	265 (19.3)
≥50 000	282 (21.1)	270 (19.7)
Body mass index		
<25	337 (24.4)	339 (24.0)
25-29	503 (36.4)	533 (37.8)
30-34	317 (23.0)	344 (24.4)
≥35	224 (16.2)	194 (13.8)
Smoking status		
Never	757 (55.2)	746 (53.3)
Former	523 (38.1)	546 (39.0)
Current	92 (6.7)	108 (7.7)
No. of alcoholic drinks consumed per week		
0	739 (53.4)	708 (50.1)
1-6	531 (38.4)	565 (40.0)
≥7	114 (8.2)	141 (10.0)
Prior cardiovascular disease		
None	1202 (86.7)	1233 (86.9)
History of disease†	185 (13.3)	186 (13.1)
Treatment for hypertension or blood pressure ≥140/90 mm Hg		
Absent	620 (44.7)	678 (47.8)
Present	767 (55.3)	741 (52.2)
Diabetes mellitus		
Absent	1236 (89.2)	1265 (89.3)
Present	149 (10.8)	152 (10.7)
Moderate or severe vasomotor symptoms		
Absent	1239 (90.0)	1265 (89.6)
Present	138 (10.0)	146 (10.4)
Prior hormone therapy use		
None	749 (54.0)	791 (55.7)
Duration <10 y	421 (30.4)	424 (29.9)
Duration ≥10 y	217 (15.6)	204 (14.4)

continued

be from an ethnic minority. Compared with women in the estrogen plus progestin trial, women in the estrogen-alone trial reported lower family incomes; weighed more; consumed less alcohol; had more cardiovascular disease, hypertension, diabetes mellitus, and vasomotor symptoms; and reported more use of hormone therapy in the past and for longer periods. The baseline mean (SD) 3MSE scores were 94.68 (4.64) and 95.69 (4.04), respectively, for the estrogen-alone and estrogen plus progestin trials ($P < .001$); this difference remained statistically significant after adjusting for the factors mentioned above, excluding hysterectomy. The overall mean (SD) 3MSE score across trials was 95.2 (4.3).

TABLE 2 shows that in both the CEE and placebo groups, 3MSE scores tended to increase with time on study during the first 4 years, and the placebo group tended to have slightly higher mean scores compared with the CEE group.

FIGURE 2 portrays mean 3MSE estimates from linear models using intra-participant longitudinal correlations to address the varying patterns of examination times among women. Means (SEs) by treatment assignment are provided for both trials, separately and combined. Across all treatment assignments, mean 3MSE scores initially increased from baseline throughout the first 3 to 5 years after randomization, with greater increases in the placebo groups. During longer follow-up in the estrogen-alone trial, the initial increases in mean 3MSE scores declined. Differences between active and placebo therapy emerged after 2 years.

During follow-up, the mean (baseline subtracted) 3MSE scores were 0.26 (SE, 0.13) units lower among women assigned to CEE compared with placebo in analyses without covariate adjustment ($P = .04$; TABLE 3). Similarly, in the estrogen plus progestin trial ($P = .58$), differences averaged 0.18 (0.10) units ($P = .055$). In the 2 trials combined, women assigned to hormone therapy had lower on-study mean (SE) 3MSE scores of 0.21 (0.08) units ($P = .006$).

Adherence to study medication in the estrogen-alone trial was greater among women assigned to the placebo group. Cumulative drop-out rates for CEE and placebo were 10.9% vs 8.0% (year 1), 20.5% vs 17.3% (year 2), 27.9% vs 24.4% (year 3), 34.7% vs 31.8% (year 4), 42.3% vs 38.8% (year 5), 49.5% vs 46.3% (year 6), and 59.4% vs 54.2% (year 7), respectively. During follow-up, some women (8.5% in CEE group and 11.0% in placebo group by year 6) initiated hormone therapy through their health care physicians. Baseline 3MSE score was inversely related to subsequent nonadherence ($P < .001$), based on logistic regression. Similar trends have already been reported for the estrogen plus progestin trial.¹⁶ When data were censored at the first occurrence of any nonadherence, mean (SE) 3MSE differences between treatment groups were slightly less (0.25 [0.14] for estrogen-alone trial [$P = .07$] and 0.14 [0.10] for estrogen plus progestin trial [$P = .17$], and 0.19 [0.08] overall [$P = .02$]). Again, differences between trials were not statistically significant ($P = .51$).

At baseline, 24 (1.7%) and 21 (0.99%) women in the active groups, and 29 (2.0%) and 42 (1.9%) women in the placebo groups of the estrogen-alone and estrogen plus progestin trials, respectively, reported a history of stroke. During follow-up, 33 (2.4%), 37 (1.7%), 39 (2.8%), and 32 (1.4%) women, respectively, had strokes. In analyses limited to women with no history of stroke and with follow-up censored after on-study strokes, the mean (SE) differences in 3MSE scores between treatment groups were 0.32 (0.14) for estrogen-alone trials ($P = .02$) and 0.18 (0.10) for estrogen plus progestin trials ($P = .055$), and 0.24 (0.08) for the pooled trials ($P = .002$). During follow-up, 88 women (6.5%) and 82 women (3.9%) in the active groups, and 62 women (4.5%) and 61 women (2.8%) in the placebo groups of the estrogen-alone and estrogen plus progestin trials, respectively, were classified as having probable dementia or mild cognitive impairment. Differences were moderated when follow-up was cen-

Table 1. Baseline Demographic, Socioeconomic Status, and Clinical Characteristics of the WHIMS Estrogen-Alone Trial Participants at WHI Enrollment by Treatment Assignment* (cont)

Characteristics	CEE (n = 1387)	Placebo (n = 1421)
Age at hysterectomy, y		
<40 y	405 (29.2)	420 (29.7)
40-49	627 (45.3)	629 (44.5)
50-54	171 (12.4)	182 (12.9)
≥55	182 (13.1)	182 (12.9)
Prior bilateral oophorectomy		
None or not available	834 (60.1)	828 (58.3)
Yes	553 (39.9)	593 (41.7)
Other prior medication use		
Statins (HMG-CoA reductase inhibitors)	155 (11.2)	183 (12.7)
Aspirin, regular use	381 (27.5)	441 (31.1)
3MSE total score at WHI enrollment		
Mean (SD)	94.63 (4.80)	94.73 (4.48)
Level		
95 to 100	867 (62.5)	879 (61.9)
Above screening cut point to 94‡	387 (27.9)	406 (28.6)
At or below screening cut point‡	133 (9.6)	136 (9.6)

Abbreviations: CEE, conjugated equine estrogen; GED, General Educational Development test; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; 3MSE, Modified Mini-Mental State Examination; WHI, Women's Health Initiative; WHIMS, Women's Health Initiative Memory Study.

*Data are No. (%) unless otherwise specified. Group sizes and 3MSE scores differ slightly from Shumaker et al.¹⁵ A total of 109 participants were eliminated because they lacked at least 1 postrandomization 3MSE score and 30 participants were eliminated because they were enrolled in WHIMS after start of hormone therapy.

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

‡Screening cut point is ≤80 for women with ≤8 years of formal education and ≤88 for women with ≥9 years of formal education.

sored at the first 3MSE leading to such classifications (mean [SE], 0.14 [0.11] for estrogen-alone trials [$P = .22$] and 0.09 [0.08] for estrogen plus progestin trials [$P = .30$], and 0.11 [0.07] overall [$P = .11$], with little difference between trials [$P = .71$]).

The largest declines in 3MSE scores from baseline tended to occur more frequently among women assigned to active therapy. FIGURE 3 contrasts treatment groups with respect to odds ratio for increases and declines in 3MSE scores, from baseline at any time during follow-up. For the estrogen-alone and the pooled trials, the odds ratios for declines of 8 points or more in 3MSE scores were 37% to 62% higher in the active treatment groups.³⁰ The estimated relative risk corresponding to and developed by adjustment of the odds ratio of the 10-unit decrease was 1.47 (95% confidence interval, 1.04-2.07).

As shown in Table 3, both within the estrogen-alone and estrogen plus progestin trials and overall, hormone therapy had a relatively greater ad-

verse effect for women whose baseline 3MSE scores were lowest (all $P < .01$). No other factors appeared to markedly influence the treatment effects of CEE or pooled hormone therapy.

COMMENT

We found that women aged 65 years or older assigned to CEE therapy had a slightly but significantly lower average cognitive function compared with women assigned to placebo, as measured by serial 3MSE scores during 5 to 7 years of follow-up. These differences appeared to emerge 1 to 2 years after initiation of therapy and persisted throughout the trial. The estimated magnitude of the difference attributable to CEE therapy was slightly smaller when analyses were limited to women who adhered to the study protocol. This adherence-related effect may be attributable to a tendency for women whose cognitive function is declining to become nonadherent, perhaps an effect of incident comorbidity or social stress. Baseline 3MSE score was a strong predictor of subsequent nonad-

herence, which supports this conjecture. The difference was not materially affected when data from women with a history of stroke or who experienced a stroke during the study were eliminated, suggesting that clinical strokes are not entirely responsible for the lower cognitive function we ob-

served in the active treatment groups. However, when women who developed cognitive impairment or dementia were excluded, the mean difference was moderated and was no longer statistically significant.

Cognition has been reported to be influenced by exogenous progestins^{3,31}

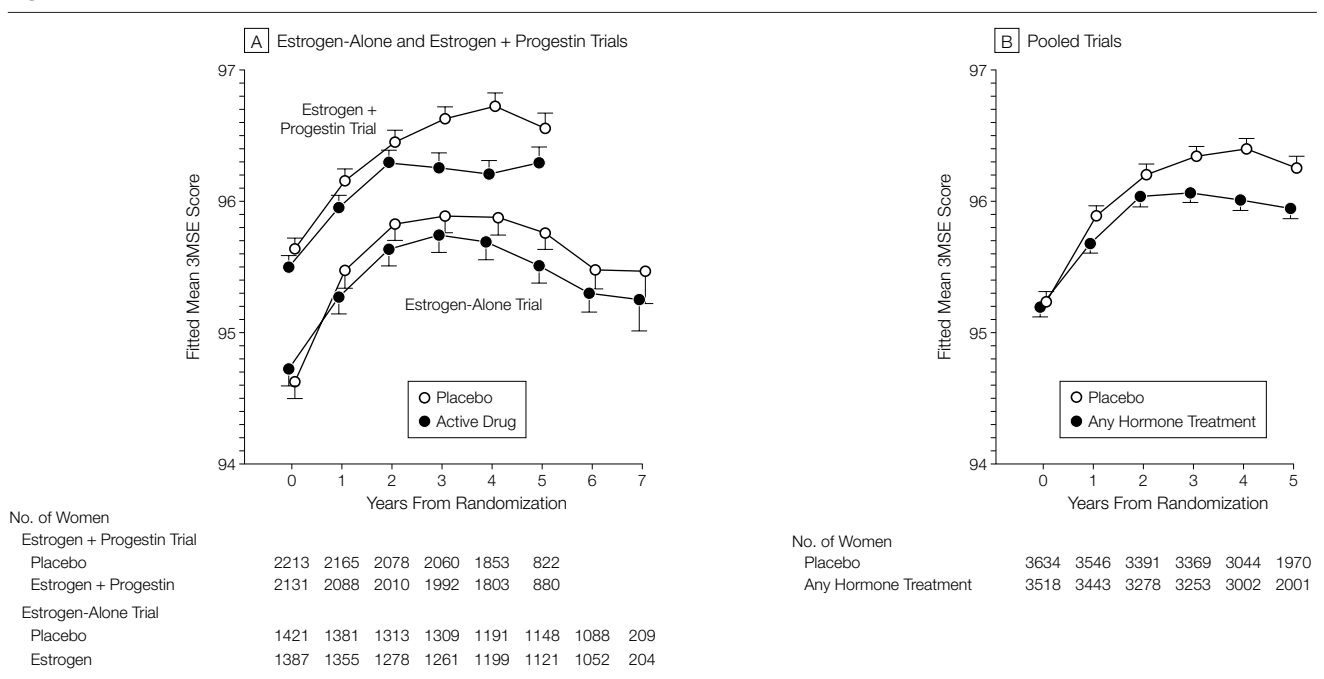
and differently by CEE and CEE plus MPA therapy.^{32,33} We found similar effects on 3MSE scores for CEE and CEE plus MPA therapy, although women in the 2 trials differed according to many factors at baseline, including cognitive function. The similarity of these effects, both overall and across many

Table 2. Mean Modified Mini-Mental State Examination Scores by Time From WHI Randomization and Treatment Assignment for Women in the Estrogen-Alone Trial

No. of Years Since Randomization	Treatment Assignment				Difference Between Treatments, Mean (95% CI)
	CEE		Placebo		
	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	
0	1387	94.73 (4.48)	1421	94.63 (4.80)	0.10 (-0.25 to 0.44)
1	1355	95.09 (4.49)	1381	95.54 (4.33)	-0.21 (-0.54 to 0.12)
2	1268	95.72 (4.32)	1313	95.93 (4.27)	-0.21 (-0.54 to 0.12)
3	1261	95.84 (4.88)	1309	96.05 (4.15)	-0.20 (-0.55 to 0.15)
4	1199	95.91 (4.56)	1191	96.08 (4.82)	-0.17 (-0.55 to 0.21)
5	1121	95.80 (5.62)	1148	96.06 (5.45)	-0.27 (-0.72 to 0.19)
6	848	95.53 (6.47)	879	95.98 (4.77)	-0.45 (-0.98 to 0.09)
7*	204	96.03 (5.74)	209	96.32 (4.41)	-0.28 (-1.27 to 0.71)

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; WHI, Women's Health Initiative. *Includes 24 women who were tested at 8 years after randomization.

Figure 2. Fitted Mean Modified Mini-Mental State Examination Scores for Estrogen-Alone and Estrogen Plus Progestin Trials and Pooled Trials



A, The mean (SE) Modified Mini-Mental State Examination (3MSE) scores from linear models by treatment assignment for the estrogen-alone (n=1387 assigned to conjugated equine estrogen [CEE] and n=1421 assigned to placebo) and estrogen plus progestin (n=2131 assigned to CEE in combination with medroxyprogesterone acetate [MPA] and n=2213 assigned to placebo) trials. For convenience, data from 2 women in the estrogen-alone trial collected at year 8 were pooled with year 7 data; similarly data from 42 women in the estrogen plus progestin trial collected at year 6 were pooled with year 5 data. P=.04 for CEE and P=.055 for CEE plus MPA for mean differences between active therapy and placebo. B, Pooled mean (SE) 3MSE scores from linear models by treatment assignment across trials for 3518 women assigned to estrogen plus progestin or estrogen alone and 3634 women assigned to placebo. P=.006 for the mean difference between active and placebo therapy.

Table 3. Mean Difference in Change From Baseline in 3MSE Scores Between Women Assigned to Active vs Placebo Therapy Among Women Overall and for Groups Based on Risk Factors for Cognitive Decline*

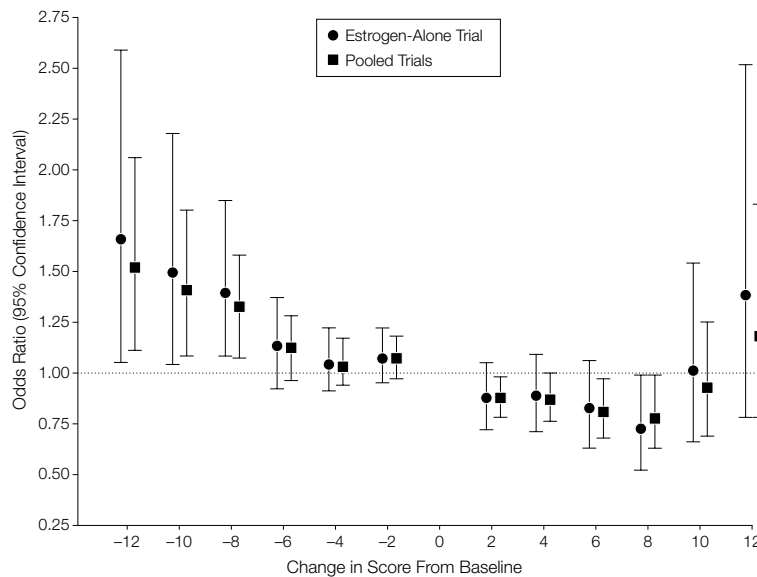
Subgroup	Estrogen-Alone Trial		Estrogen + Progestin Trial		Pooled Trials	
	Difference Between Treatments (CEE – Placebo), Mean (95% CI)	P Value	Difference Between Treatments (CEE + MPA – Placebo), Mean (95% CI)	P Value	Difference Between Treatments (Hormone Therapy – Placebo), Mean (95% CI)	P Value
All women	-0.26 (-0.52 to 0)	.04	-0.18 (-0.37 to 0)	.055	-0.21 (-0.37 to -0.06)	.006
Age, y						
65-69	-0.52 (-0.90 to -0.12)	.03	0 (-0.27 to 0.28)	.19	-0.21 (-0.44 to 0.02)	.34
70-74	0.18 (-0.26 to 0.61)		-0.36 (-0.67 to -0.05)		-0.13 (-0.38 to 0.13)	
≥75	-0.63 (-1.24 to -0.02)		-0.31 (-0.75 to 0.13)		-0.46 (-0.82 to -0.09)	
Education						
<High school	-0.62 (-1.50 to 0.27)	.67	-0.89 (-1.63 to -0.14)	.03	-0.75 (-1.32 to -0.18)	.04
High school or GED	-0.24 (-0.77 to -0.30)		-0.21 (-0.62 to 0.19)		-0.22 (-0.55 to 0.10)	
>High school but <4 y of college	-0.15 (-0.55 to 0.26)		0.13 (-0.17 to 0.43)		0.01 (-0.25 to 0.25)	
≥4 y of college	-0.48 (-1.01 to 0.05)		-0.38 (-0.70 to -0.05)		-0.41 (-0.69 to -0.13)	
Race or ethnicity						
White, non-Hispanic	-0.25 (-0.54 to 0.03)	.75	-0.19 (-0.39 to 0.01)	.63	-0.22 (-0.38 to -0.05)	.96
Other	-0.37 (-1.03 to 0.28)		-0.04 (-0.63 to 0.55)		-0.23 (-0.66 to 0.21)	
Annual household income, \$						
<19 999	-0.26 (-0.75 to 0.23)	.62	-0.08 (-0.48 to 0.33)	.27	-0.17 (-0.49 to 0.14)	.18
20 000 to 34 999	-0.50 (-0.98 to -0.02)		-0.45 (-0.79 to -0.10)		-0.46 (-0.74 to -0.18)	
35 000 to 49 999	0.03 (-0.60 to 0.66)		0 (-0.41 to 0.42)		0.01 (-0.34 to 0.37)	
≥50 000	-0.27 (-0.86 to 0.32)		-0.04 (-0.40 to 0.33)		-0.12 (-0.44 to 0.20)	
Body mass index						
<25	0.15 (-0.38 to 0.69)	.10	-0.27 (-0.60 to 0.06)	.31	-0.11 (-0.40 to 0.17)	.41
25-29	-0.26 (-0.69 to 0.17)		-0.34 (-0.66 to -0.03)		-0.31 (-0.57 to -0.05)	
30-34	-0.81 (-1.35 to -0.26)		-0.03 (-0.44 to 0.38)		-0.38 (-0.71 to -0.04)	
≥35	-0.19 (-0.87 to 0.50)		0.21 (-0.36 to 0.78)		0.01 (-0.43 to 0.45)	
Smoking status						
Never	-0.34 (-0.70 to 0.02)	.64	-0.23 (-0.49 to 0.03)	.57	-0.27 (-0.49 to -0.06)	.46
Former or current	-0.21 (-0.60 to 0.18)		-0.12 (-0.39 to 0.16)		-0.16 (-0.39 to 0.07)	
No. of alcoholic drinks consumed per week						
0	-0.50 (-0.87 to -0.14)	.06	-0.27 (-0.56 to 0.02)	.75	-0.38 (-0.61 to -0.15)	.13
1-6	0.12 (-0.31 to 0.54)		-0.15 (-0.43 to 0.13)		-0.04 (-0.28 to 0.20)	
≥7	-0.66 (-1.54 to 0.22)		-0.07 (-0.58 to 0.43)		-0.28 (-0.73 to 0.17)	
Prior cardiovascular disease†						
None	-0.21 (-0.49 to 0.07)	.22	-0.26 (-0.46 to -0.07)	.006	-0.24 (-0.41 to -0.08)	.44
History of disease	-0.70 (-1.43 to 0.03)		0.66 (0.03 to 1.29)		-0.04 (-0.52 to 0.43)	
Treatment for hypertension						
Absent	-0.15 (-0.54 to 0.24)	.37	-0.34 (-0.59 to -0.08)	.09	-0.26 (-0.48 to -0.04)	.61
Present	-0.39 (-0.75 to -0.03)		-0.01 (-0.28 to 0.26)		-0.18 (-0.40 to 0.04)	
Diabetes mellitus						
Absent	-0.22 (-0.50 to 0.06)	.17	-0.19 (-0.38 to 0.01)	.78	-0.20 (-0.36 to -0.04)	.19
Present	-0.83 (-1.64 to -0.01)		-0.29 (-1.03 to 0.44)		-0.58 (-1.12 to -0.03)	
Moderate or severe vasomotor symptoms						
Absent	-0.16 (-0.44 to 0.12)	.03	-0.22 (-0.41 to -0.03)	.11	-0.20 (-0.36 to -0.03)	.35
Present	-1.16 (-1.98 to -0.33)		0.45 (-0.35 to 1.25)		-0.48 (-1.04 to 0.09)	
Prior hormone therapy use						
Any	-0.17 (-0.53 to 0.19)	.38	-0.17 (-0.38 to 0.04)	.75	-0.17 (-0.35 to 0.02)	.31
None	-0.41 (-0.80 to -0.02)		-0.24 (-0.64 to 0.16)		-0.34 (-0.61 to -0.07)	
Age at hysterectomy, y						
<40	-0.09 (-0.58 to 0.39)	.44				
40-49	-0.51 (-0.90 to -0.11)					
50-54	-0.31 (-1.06 to 0.43)					
≥55	0.07 (-0.66 to 0.80)					
Prior bilateral oophorectomy						
None or not available	-0.44 (-0.78 to -0.09)	.13	-0.189 (-0.37 to -0.00)	.42	-0.26 (-0.43 to -0.09)	.23
Yes	-0.02 (-0.44 to 0.39)		1.16 (-3.47 to 3.10)		-0.01 (-0.38 to 0.36)	
Prior use of HMG-CoA reductase inhibitors						
No	-0.24 (-0.52 to 0.04)	.50	-0.24 (-0.44 to -0.04)	.15	-0.24 (-0.40 to -0.07)	.61
Yes	-0.52 (-1.29 to 0.24)		0.20 (-0.37 to 0.77)		-0.11 (-0.57 to 0.35)	
Baseline aspirin use						
No	-0.33 (-0.65 to -0.02)	.56	-0.22 (-0.45 to -0.00)	.50	-0.27 (-0.45 to -0.08)	.38
Yes	-0.16 (-0.65 to 0.33)		-0.08 (-0.43 to 0.27)		-0.11 (-0.40 to 0.17)	
Baseline 3MSE score						
95 to 100	-0.14 (-0.43 to 0.15)	.006	-0.07 (-0.27 to 0.12)	.003	-0.10 (-0.27 to 0.07)	<.001
Screening cut point to 94	-0.14 (-0.58 to 0.31)		-0.60 (-0.94 to -0.26)		-0.38 (-0.65 to -0.11)	
At or below screening cut point	-1.52 (-2.29 to -0.75)		-0.99 (-1.67 to -0.30)		-1.26 (-1.76 to -0.75)	

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; GED, General Educational Development test; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; 3MSE, Modified Mini-Mental State Examination; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative; WHIMS, Women's Health Initiative Memory Study.

*Results are provided separately for the estrogen-alone and estrogen plus progestin trials and pooled across trials, without covariate adjustment.

†Differences in results between estrogen-alone and estrogen plus progestin trials ($P = .01$).

Figure 3. Distribution of Changes in Modified Mini-Mental State Examination Scores From Baseline Between the Estrogen-Alone and Pooled Trials



No. of Women												
Estrogen-Alone Trial												
Placebo	42	64	111	211	405	699	912	544	321	176	84	37
Estrogen	54	77	123	217	400	697	863	510	285	138	73	36
Pooled Trials												
Placebo	74	113	209	422	866	1666	2186	1211	658	339	159	65
Any Hormone Therapy	108	151	258	446	864	1667	2049	1141	610	307	152	70

Changes in scores between treatment groups were at any time during follow-up from baseline controlling for baseline score and follow-up visit. Odds ratios comparing treatment assignments and 95% confidence intervals were from logistic regression. Any hormone therapy includes pooled data from the estrogen-alone and estrogen plus progestin trials.

subgroups, support pooled analysis, as was described in the original study protocol for the primary end point of probable dementia. The WHI found a similar increased risk of stroke for CEE and CEE plus MPA, although the overall incidence rates of strokes differed between the 2 trials.³⁴ A possible resonance between the adverse effects of hormone therapy on atherosclerotic and thrombotic cerebrovascular effects and cognitive outcomes may be further reflected in the higher numbers of women experiencing relatively large declines in 3MSE scores. For example, 54 (3.89%) of 1387 women assigned to CEE had declines in 3MSE scores of at least 12 units compared with 42 (2.96%) of 1421 women assigned to placebo in the estrogen-alone trial.

The adverse effect of hormone therapy appeared to be consistent across

many subgroups. Only baseline 3MSE score was associated with differential treatment effects. Among women whose scores exceeded 95, the mean decrement was small and not statistically different from 0. The mean decrement increased for lower 3MSE scores and was largest for those women who were below study 3MSE screening cut points; to enter the study, women must have been classified as not having probable dementia at that time according to additional testing and a standardized protocol.¹⁸ This finding occurred in both the estrogen-alone and estrogen plus progestin trial cohorts. Considering the age of these women, some degree of cerebrovascular disease and/or neuropathologic changes may have preceded their participation in WHIMS, and hormone therapy may have accelerated progress of underlying disease.

Although we cannot address this question directly, the findings from an ancillary magnetic resonance imaging study currently under way will test whether subclinical cerebrovascular pathological changes are more prevalent among women assigned to active hormone therapy.

The WHIMS findings stand in contrast to a considerable body of literature suggesting that exogenous estrogen helps to protect cognitive function in postmenopausal women. Many of these studies are observational in which, unlike our randomized trial, estrogen users may have reflected the so-called healthy user bias (ie, postmenopausal women who choose to take estrogen are generally healthier, better educated, and of a higher socioeconomic status than those who do not take estrogen).³⁵ Such demographic factors are independently associated with cognitive decline and dementia and thereby may confound the interpretation of observational study findings.

A second possible explanation for inconsistencies between prior studies and WHIMS is that estrogen has been reported to enhance verbal memory, with no effect on other domains of cognition.⁷ Although the 3MSE is a reliable and valid measure of global cognitive function, it does not capture performance in individual domains of cognition. It remains possible that differential beneficial (and/or detrimental) effects of estrogen on specific cognitive functions (eg, verbal memory) were not detected when, in fact, they had actually occurred. The results of the Women's Health Initiative Study of Cognitive Aging will help to address this important issue.

A third explanation may relate to a critical period during which hormone therapy must be initiated to protect cognitive functioning. Laboratory animal models^{36,37} suggest that giving estrogen 3 months not 10 months after ovariectomy produces memory performance similar to that of young control animals. Similarly, among older women, initiation of hormone therapy at meno-

pause may be associated with significantly less cognitive decline 20 years later compared with nonusers, whereas recent estrogen exposure may not be beneficial.³⁸ Former early users of estrogen but not current users may have a reduced risk of Alzheimer disease.³⁹ Unfortunately, this theory cannot be addressed in WHIMS because participants were all aged 65 years or older when they were recruited and treated. However, 45% of women in the estrogen-alone trial reported previous hormone therapy use, and they did not have higher scores than women reporting no prior use. In addition, results from the observational studies cited may be biased due to healthy user effects.

Although the difference in mean (SE) 3MSE scores between the CEE and placebo group was statistically significant ($P=.04$), the actual magnitude of the difference (0.26 [0.13] units) is too small to have relevance in clinical practice. This was also true for between-group differences in 3MSE scores in the CEE plus MPA¹⁶ and pooled CEE plus MPA and CEE-alone analyses. However, the statistically significant, albeit small, difference in mean 3MSE scores was robust across treatments and many subgroups, and indicates that in these large randomized clinical trials, hormone therapy did not improve global cognition in older postmenopausal women. In addition, both the CEE and pooled analyses showed that women receiving hormone therapy were significantly more likely to experience a marked decrease (≥ 8 units) in 3MSE scores compared with the placebo group. Such a decrease is meaningful and would likely alert a clinician to explore this further.

Although WHIMS participants were generally healthy and well educated, there is no compelling reason to believe that the results are not applicable to other women in this age group with similar demographic and health status characteristics. The WHI study tested only CEE and CEE plus MPA, the most commonly used postmenopausal hormone therapy preparations in the United States when WHI was de-

signed.⁴⁰ Outcomes of treatment might differ with other doses, formulations, or routes of delivery. The longer follow-up time of the estrogen-alone trial compared with the estrogen plus progestin trial indicated that the apparent practice (eg, learning) effect observed in both trials is overcome in time, yielding curved patterns for longitudinal scores. In adopting an analytical strategy more appropriate to data from the estrogen-alone trial, we decreased slightly the power for analyses of data from the estrogen plus progestin trial, in which the more parsimonious linear assumption was warranted. Overall, however, the 2 different analytical approaches to the estrogen plus progestin data yielded congruent results. Finally, as a brief screen for cognitive impairment, the 3MSE provides a coarser estimate than would a more detailed and comprehensive evaluation of cognitive functioning.

In conclusion, this large randomized clinical trial indicates that CEE, initiated in the late postmenopausal period, does not improve global cognitive function and may even adversely affect this outcome. The effects on cognition were similar to those observed with CEE plus MPA. Our results suggest that neither CEE nor CEE plus MPA should be initiated in older women for the purpose of protecting cognitive function. Furthermore, at least 1 subgroup of women was at particularly high risk for the adverse effects of hormone therapy on cognition—women with relatively low baseline cognitive function.

Author Affiliations: Departments of Public Health Sciences (Drs Espeland, Rapp, Shumaker, and Dailey, and Ms Hogan) and Psychiatry and Behavioral Medicine (Dr Rapp), Wake Forest University School of Medicine, Winston-Salem, NC; Women's Health Center, University of Nevada School of Medicine, Reno (Dr Brunner); Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (Dr Manson); Departments of Psychology and Obstetrics and Gynecology, McGill University, Montreal, Quebec (Dr Sherwin); Department of Medicine, George Washington University, Washington, DC (Dr Hsia); Division of Clinical Epidemiology, Hennepin County Medical Center, Minneapolis, Minn (Dr Margolis); Department of Epidemiology, University of Iowa College of Medicine, Iowa City (Dr Wallace); Department of Obstetrics and Gynecology and Women's Health, Montefiore Medical Center, Bronx, NY (Dr Freeman); and Center for Women's Health, Baylor College of Medicine, Houston, Tex (Dr Hays).

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Author Contributions: Dr Espeland had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Espeland, Rapp, Shumaker, Manson, Margolis, Dailey, Hays.

Acquisition of data: Rapp, Shumaker, Brunner, Manson, Hsia, Margolis, Wallace, Dailey, Freeman, Hays.

Analysis and interpretation of data: Espeland, Rapp, Shumaker, Manson, Sherwin, Hsia, Margolis, Hogan, Wallace, Dailey.

Drafting of the manuscript: Espeland, Rapp, Shumaker, Brunner, Sherwin, Hsia, Dailey, Freeman.

Critical revision of the manuscript for important intellectual content: Espeland, Rapp, Shumaker, Brunner, Manson, Sherwin, Hsia, Margolis, Hogan, Wallace, Dailey, Hays.

Statistical expertise: Espeland, Hogan.

Obtained funding: Espeland, Shumaker, Manson, Wallace.

Administrative, technical, or material support: Espeland, Rapp, Shumaker, Brunner, Manson, Sherwin, Margolis, Wallace, Dailey, Freeman, Hays.

Study supervision: Espeland, Rapp, Shumaker, Hsia, Margolis, Hays.

A current list of The Women's Health Initiative Memory Study Investigators appears on page 2956 (*JAMA*. 2004;291:2947-2958).

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