Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women

Women's Health Initiative Memory Study

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Context The Women's Health Initiative Memory Study (WHIMS) previously found increased risk for dementia and no effect on mild cognitive impairment (MCI) in women treated with conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA).

Objective To determine the effects of CEE alone and CEE plus MPA on incidence of probable dementia and MCI in older women.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled clinical trials of CEE (estrogen-alone trial) or CEE plus MPA (estrogen plus progestin trial) in community-dwelling women aged 65 to 79 years, conducted from June 1995 to July 8, 2002 (estrogen plus progestin; n=4532), or to February 29, 2004 (estrogen-alone; n=2947), in 39 of the 40 WHI clinical centers.

Interventions In the estrogen-alone trial, 1 daily tablet containing either 0.625 mg/d of CEE vs matching placebo; in the estrogen plus progestin trial, 1 daily tablet containing CEE (0.625 mg/d) plus MPA (2.5 mg/d) vs matching placebos.

Main Outcome Measures Probable dementia and MCI.

Results In the estrogen-alone trial, 47 participants were diagnosed with probable dementia, of whom 28 were assigned to CEE and 19 to placebo (hazard ratio [HR], 1.49; 95% confidence interval [CI], 0.83-2.66). Incidence rates for probable dementia in the estrogen-alone trial were statistically similar to those in the estrogen plus progestin trial (45 vs 22 per 10000 person-years for CEE plus MPA vs placebo, respectively; $P=.11$). When data were pooled per the original WHIMS protocol, the overall HR for probable dementia was 1.76 (95% CI, 1.19-2.60; $P=.005$). After excluding participants with baseline Modified Mini-Mental State Examination scores at or below the screening cut point, the HR was 1.77 (95% CI, 0.74-4.23; $P=.20$) in the estrogen-alone trial and 2.19 (95% CI, 1.25-3.84; $P=.006$) in the pooled trials. In the estrogen-alone trial, 76 participants were diagnosed with MCI in the CEE group vs 58 in the placebo group (HR, 1.34; 95% CI, 0.95-1.89). In the combined trial data, the HR was similar (1.25; 95% CI, 0.97-1.60). In the estrogen-alone trial, 93 participants receiving CEE were diagnosed with either probable dementia or MCI vs 69 receiving placebo (HR, 1.38; 95% CI, 1.01-1.89; $P=.04$).

Conclusions Estrogen therapy alone did not reduce dementia or MCI incidence and increased the risk for both end points combined. Pooling data for estrogen alone and estrogen plus progestin resulted in increased risks for both end points. Use of hormone therapy to prevent dementia or cognitive decline in women 65 years of age or older is not recommended.

JAMA. 2004;291:2947-2958 www.jama.com

DEMENTIA IS AN AGE-ASSOCIATED illness that imposes severe functional impairment on individuals. In 2000, more than 4 million people in the United States had Alzheimer disease (AD), and that number is expected to increase to 13 million by 2050.[1] Milder cognitive impairment affects between one fifth and one third of older adults[2] and strongly predicts dementia and subsequent institutionalization.[3] Case-control studies,[4,5] cross-sectional studies,[6] and prospective studies[7-9] have reported an association between lower risk of dementia and postmenopausal estrogen supplementation. Meta-analyses of the potential protective effects of estrogen against dementia have reported risk reductions of 29%[10] and 34%.[11] However, prospective observational studies have not found a protective effect of estrogen on either cogni-

See also pp 2959 and 3005.

Author Affiliations, Financial Disclosures, and a List of the Women's Health Initiative Memory Study Investigators appear at the end of this article.
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tion or the incidence of dementia.[12,13] In addition, clinical trials of unopposed estrogen in women with AD showed no benefit on cognitive performance,[14-16] and methodological limitations, including the paucity of large, controlled clinical trials, have prevented clear conclusions.[17,18] The mixed findings to date leave unanswered questions about the efficacy of estrogen therapy in preventing cognitive decline and dementia in postmenopausal women.

The Women's Health Initiative Memory Study (WHIMS)[19] is a large, randomized, double-blind, placebo-controlled clinical trial examining whether postmenopausal hormone therapy (estrogen alone or estrogen plus progestin) reduces the risk of dementia in healthy women aged 65 to 79 years at baseline. The WHIMS is an ancillary study to the larger Women's Health Initiative (WHI) randomized clinical trials of hormone therapy that include a geographically diverse group of approximately 27 000 women. The estrogen plus progestin trial of the WHI was terminated in July 2002 due to significantly more noncognitive adverse events associated with conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) compared with placebo.[20] The WHI estrogen-alone trial was terminated on February 29, 2004, because the National Institutes of Health considered the excess risk of stroke in the active hormone group to be unacceptable in healthy women in the absence of benefit for coronary heart disease, the primary outcome.[21]

The objective of the WHIMS was to evaluate whether CEE or CEE plus MPA vs matching placebos decrease women's risk for dementia.

METHODS

WHI Hormone Therapy Trials

WHIMS participants initially met eligibility requirements, provided written informed consent, and enrolled in the WHI estrogen-alone trial (for women with prior hysterectomy) or the WHI estrogen plus progestin trial, and were randomized to receive either CEE, CEE plus MPA, or matching placebos (Wyeth Pharmaceuticals, Philadelphia, Pa).[22] In the estrogen-alone trial, women aged 50 to 79 years at baseline with a prior hysterectomy were screened for eligibility.[22] Those who had previously taken postmenopausal hormone therapy underwent a 3-month washout before initial screening.

Randomization was determined using a permuted block algorithm that was stratified by age and clinical center by the WHI Clinical Coordinating Center (CCC) at the Fred Hutchinson Cancer Research Center, Seattle, Wash. Study pills were dispensed and safety and outcomes assessments took place semiannually, and participants returned for clinic visits annually.

WHIMS Participant Enrollment

WHI participants eligible for the WHIMS were 65 to 79 years of age at baseline and free of probable dementia as ascertained by the WHIMS protocol.[19] Of 3200 age-eligible WHI participants, 2947 (92.1%) consented to participate and enrolled in the estrogen-alone trial. Similarly, of the 4894 women approached for the estrogen plus progestin trial, 4532 (92.6%) consented. Study coordination for the WHIMS was provided by the WHIMS CCC at Wake Forest University School of Medicine, Winston-Salem, NC.

The National Institutes of Health and the institutional review boards for the WHI CCC and each WHI clinical center approved the WHI and WHIMS protocols and consent forms. Monitoring of the WHI hormone therapy trials was conducted semiannually by an independent data and safety monitoring board. Trial monitoring guidelines for early stopping considerations have been published.[20]

WHIMS Protocol for Detecting Probable Dementia and Mild Cognitive Impairment

A detailed description of the WHIMS protocol for detecting probable dementia and mild cognitive impairment (MCI) has been published.[19] The protocol consisted of 4 phases. In phase 1, participants underwent a cognitive screening with the Modified Mini-Mental State Examination (3MSE)[23] at baseline and annually thereafter. Women who scored below an education-adjusted cut point on the 3MSE (≤72 for those with ≤8 years of formal education and ≤76 for those with ≥9 years of education; to increase sensitivity, after 16 months new cut points of ≤80 for those with ≤8 years of education and ≤88 for those with ≥9 years of education were implemented prospectively[24]) underwent phase 2 of the WHIMS, including a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery of neuropsychological tests[25] and standardized interviews to assess acquired cognitive and behavioral impairments.[26,27] In addition, a designated informant (friend or family member) was interviewed separately regarding acquired cognitive and behavioral impairments in the participant.

After completing phase 2, participants were evaluated by a local physician-specialist with experience in diagnosing dementia (phase 3). Using a standardized protocol provided by the WHIMS CCC, local physicians reviewed all available data and performed a clinical neuropsychiatric evaluation. The physician then classified the WHIMS participant as having no dementia, MCI, or probable dementia, based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria.[28] Our MCI classification was based on accepted criteria[29] at the time the WHIMS was initiated and was operationally defined as poor performance (10th or lower percentile based on CERAD norms[30]) on at least 1 CERAD test, a report of some functional impairment (but not severe enough to interfere with basic activities of daily living such as eating, dressing, grooming, etc) from the designated informant, no evidence of a psychiatric disorder or medical condition that could account for the decline in cognitive function, and an absence of adjudicated dementia. Women

suspected of having probable dementia underwent phase 4, including a noncontrast computed tomography brain scan and laboratory blood tests to rule out possible reversible causes of cognitive decline. If dementia was still suspected, the physician was required to provide the most probable etiology based on *DSM-IV* criteria for AD, vascular dementia (VaD), and other dementia-related classifications. All clinical and test data were then transmitted to the WHIMS CCC for review and central adjudication.

Central Adjudication of Probable Dementia and MCI

The central adjudication committee consists of 3 board-certified specialists (2 neurologists and 1 geriatric psychiatrist) with extensive experience in dementia. All cases judged as probable dementia by the local physician-specialists were independently reviewed by the central adjudicators, as well as 50% of MCI cases and 10% of cases without dementia. All test scores, lab test results, and other data on the WHIMS participant, except the field physician's classification, were provided to 2 adjudicators who independently evaluated the data and assigned a classification. The field physician's diagnostic assessment was then shared with each adjudicator, who could revise his or her diagnosis. If both adjudicators agreed, the consensus diagnosis was recorded. If the adjudicators disagreed, they discussed the case and if consensus was not achieved, the 3 adjudicators plus a geriatric psychologist familiar with the neuropsychological measures discussed the case until a consensus was reached. The same process was followed to reach consensus on the etiologic classification of dementia.

Quality Assurance of Data

Audiotapes of the WHIMS neuropsychological test battery and copies of the completed test booklets were sent to the WHIMS CCC. These materials were closely reviewed for administration and/or scoring errors, and written feedback was provided to technicians, who were recertified every 6 months.

All WHIMS-certified technicians, local WHIMS physicians, and WHIMS adjudicators were blinded to participants' treatment assignment. Official unblinding at the clinical sites to address safety concerns was handled by a designated unblinding officer, who was the only individual authorized to access unblinding information in the WHI database and to provide this information to the clinic's consulting gynecologist. The adjudicators were independent of the clinical center physicians and data provided to them were blinded.

Adherence

Adherence data on hormone(s) were collected annually after randomization. According to WHI criteria, a participant became nonadherent by (1) stopping study medication for any reason, whether by personal decision or for protocol-based safety issues; (2) taking less than 80% of her pills between dispensation and collection; or (3) starting prescribed hormone(s) outside of the main WHI hormone therapy trials. For these 3 criteria, the earliest nonadherence date was selected and follow-up data were censored 6 months later for secondary analyses examining the effect of nonadherence.

Statistical Analyses

The WHIMS was designed to provide more than 80% statistical power to detect an observed 40% relative reduction in all-cause dementia associated with either CEE or CEE plus MPA vs matched placebos.[19] Based on a projected enrollment of 8300 women, approximately 165 cases of all-cause dementia were expected over 5 years. When the estrogen-alone trial ended, there were 47 cases of all-cause dementia. Post hoc calculations indicate that the WHIMS estrogen-alone trial provided 80% statistical power to detect a hazard ratio (HR) of 2.07 at the 5% significance level. Survival analyses were conducted using intention-to-treat principles for the 2947 WHIMS estrogen-alone participants and for all 7479 participants. Analyses included all WHI participants who agreed to participate in the WHIMS, and treatment groups were based on their randomization assignment in the WHI hormone therapy trials. For the estrogen-alone analyses, all events up to termination of the study drug in the WHI estrogen-alone trial (February 29, 2004) were included in the analyses and were adjudicated as described above. Women who had MCI at baseline were excluded in the analyses of MCI and its combination with probable dementia.

Hazard ratios and nominal 95% confidence intervals (CIs) from unadjusted Cox proportional hazard models[31] were compared between the treatment and placebo groups. The time to event was defined as the number of days from randomization into the WHI trial to the date of the 3MSE that triggered the referral for additional cognitive testing resulting in the first post-randomization diagnosis. Participants without a diagnosis were censored at their last follow-up contact: before February 29, 2004, for the estrogen-alone trial and before July 8, 2002, for the estrogen plus progestin trial. Cumulative hazards are presented. Secondary analyses were conducted for participants with a diagnosis of MCI only, and either probable dementia or MCI. Cox proportional hazard models were fitted separately with treatment assignment and 1 of the following baseline factors as independent variables: age; education; race; smoking; self-reported history of cardiovascular disease, stroke, diabetes, or hypertension; prior use of hormone therapy, unopposed estrogen, statins (ie, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA]), or aspirin; and baseline 3MSE scores. In each of the 13 models, the interaction between treatment assignment and the factor was tested; HRs are presented for subgroups defined by these factors. A Bonferroni adjustment was used to control for type I error ($P = .05/13$ [.004]). Secondary analyses also were conducted, censoring participants 6 months

after they became nonadherent. A significance level of .05 was used for analyses other than the 13 models. Analyses were conducted with SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

FIGURE 1 depicts the enrollment and referrals to phases 2 through 4 for the estrogen-alone trial and for the pooled estrogen-alone and estrogen plus progestin trials. In the estrogen-alone trial, among those assigned to CEE, 184 participants were referred for further cognitive testing a total of 346 times; among the women assigned to placebo, 172 participants were referred 300 times. Of the 80 participants who refused further testing at least once, 13 (16%) had subsequent visits at which a diagnosis was obtained, and of the 86 participants with incomplete data, 11 (13%) also had a diagnosis from a subsequent visit. Overall, the percentages of women ever referred were 12.6% (CEE) and 11.6% (placebo) in the estrogen-alone trial, and 7.9% (CEE plus MPA) and 6.1% (placebo) in the estrogen plus progestin trial.[24]

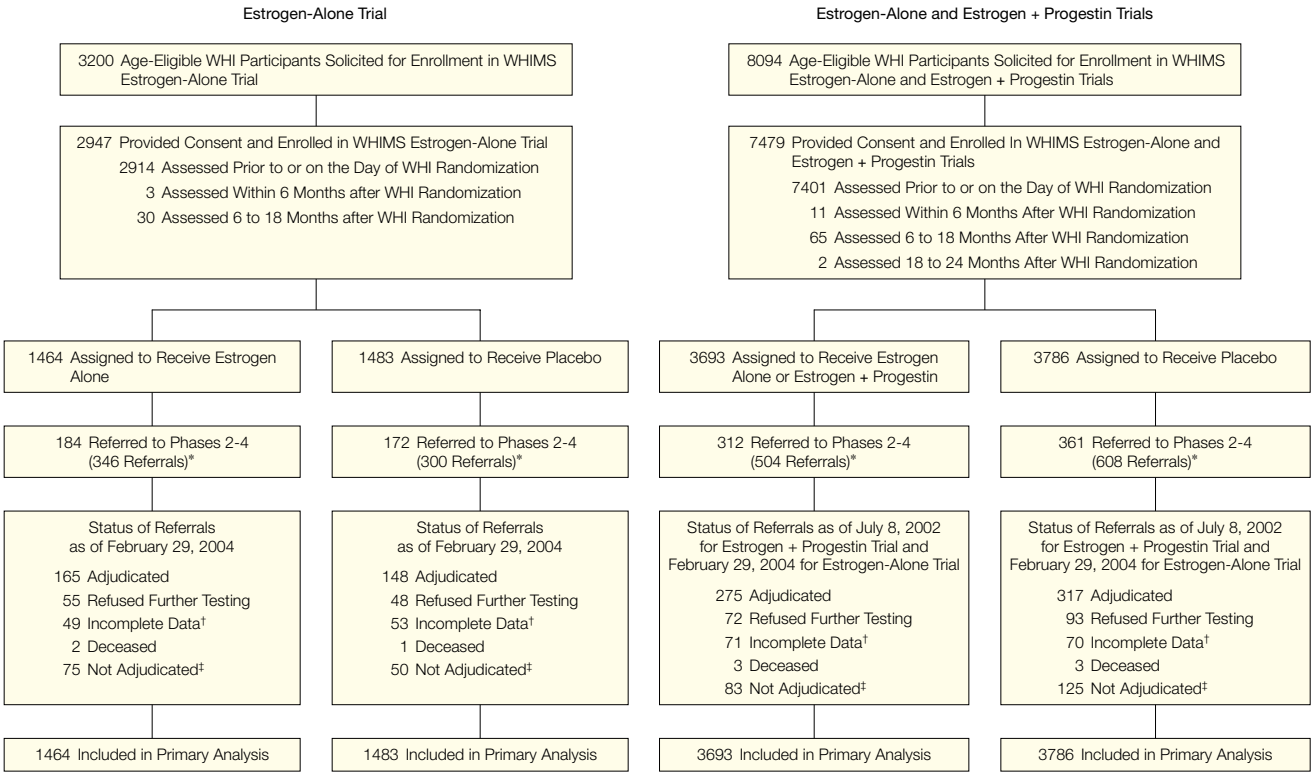
The average time between the last 3MSE and the date of randomization into WHI for women in the estrogen-alone trial was 5.21 (SD, 1.73) years, compared with 4.05 (SD, 1.19) years among women in the estrogen plus progestin trial.

TABLE 1 lists the distribution of risk factors for dementia at the time of WHI assignment for the participants in the estrogen-alone trial. No significant differences between the CEE and placebo groups were evident, except for the higher prevalence of hypertension ($P=.01$) in the CEE group. This difference in hypertension was maintained when combining women in both trials (Table 1). When compared with the women receiving estrogen plus progestin, women receiving estrogen alone were relatively less educated, had lower 3MSE scores at baseline, were more ethnically diverse, and were more likely to have had a history of stroke syndrome or coronary heart disease and to have used hormone therapy previously ($P<.001$ for all).

Probable Dementia

In the estrogen-alone trial, 47 participants were diagnosed with probable dementia, of whom 28 were assigned to receive CEE and 19 to receive matching placebo (TABLE 2). During follow-

Figure 1. Flow of Participants Through the WHIMS Estrogen-Alone Trial and the Combined Estrogen-Alone and Estrogen+Progestin Trials



WHI indicates Women's Health Initiative; WHIMS, WHI Memory Study.
*A participant could be referred at any annual visit.
†Data are incomplete because the participant did not return to the clinic for phases 2-4 for reasons including lack of transportation, illness, family/caregiver responsibilities, scheduling conflict, etc.
‡At least 10% of all no dementia cases and 50% of all cases of mild cognitive impairment were adjudicated.

up, the incidence of probable dementia was 49% higher among women assigned to receive CEE compared with those receiving placebo (37 vs 25 per 10 000 person-years) (FIGURE 2A). This negative trend did not reach statistical significance ($P = .18$). Incidence rates for probable dementia in the estrogen-alone trial were statistically similar to those in the estrogen plus progestin trial (45 vs 22 per 10 000 person-years for CEE plus MPA vs matching placebo, respectively; $P = .11$). In addition, the HR associated with assignment to active therapy in the estrogen-alone trial (1.49; 95% CI, 0.83-2.66) did not differ statistically from that for the estrogen plus progestin trial (2.05; 95% CI, 1.21-3.48) ($P = .44$), although the estrogen-alone HR was not significant. When data from the 2 trials were

Table 1. Distribution of Risk Factors for Dementia Between Women at Baseline, by Treatment Assignment

Variable	Estrogen Alone (n = 1464)	Placebo (n = 1483)	*P* Value	Estrogen Alone or Estrogen + Progestin (n = 3693)	Matching Placebos (n = 3786)	*P* Value
Age, No. (%)						
65-69 y	646 (44.1)	667 (45.0)	.05	1680 (45.5)	1735 (45.8)	.78
70-74 y	559 (38.2)	511 (34.5)		1336 (36.2)	1342 (35.5)	
≥75 y	259 (17.7)	305 (20.6)		676 (18.3)	709 (18.7)	
Education, No. (%)						
<High school	143 (9.8)	133 (9.0)	.32	293 (8.0)	281 (7.5)	.15
High school/GED	349 (23.9)	352 (23.8)		794 (21.6)	849 (22.5)	
>High school, <4 y college	629 (43.1)	609 (41.2)		1522 (41.4)	1478 (39.2)	
≥4 y college	337 (23.1)	383 (25.9)		1070 (29.1)	1161 (30.8)	
White race, No. (%)	1206 (82.7)	1236 (83.6)	.51	1989 (89.4)	2060 (89.7)	.72
Smoking status, No. (%)						
Never	789 (54.5)	770 (52.8)	.57	1965 (53.9)	1942 (52.2)	.34
Previous	553 (38.2)	571 (39.2)		1429 (39.2)	1501 (40.4)	
Current	105 (7.3)	117 (8.0)		254 (7.0)	276 (7.4)	
History of cardiovascular disease, No. (%)	187 (13.0)	171 (11.8)	.32	362 (10.0)	350 (9.4)	.43
History of stroke, No. (%)	26 (1.8)	31 (2.1)	.53	49 (1.3)	75 (2.0)	.03
History of diabetes, No. (%)	165 (11.3)	156 (10.6)	.52	321 (8.7)	305 (8.1)	.33
History of hypertension, No. (%)	681 (47.3)	617 (42.3)	.01	1485 (40.7)	1431 (38.3)	.03
Prior hormone therapy, No. (%)						
Any prior use	670 (45.8)	662 (44.7)	.56	1155 (31.3)	1178 (31.1)	.89
Prior use of estrogen alone	654 (44.7)	646 (43.6)	.57	959 (26.0)	969 (25.6)	.72
Prior use of estrogen + progestin	42 (2.9)	33 (2.2)	.27	264 (7.2)	269 (7.1)	.95
Other prior medication use, No. (%)						
Statins	169 (11.5)	187 (12.6)	.37	437 (11.8)	412 (10.9)	.19
Aspirin, regular use	410 (28.0)	458 (30.9)	.08	1037 (28.1)	1140 (30.1)	.06
3MSE total score at WHI enrollment						
Mean (SD)	94.6 (4.70)	94.6 (4.70)	.97	95.1 (4.39)	95.2 (4.29)	.28
Level, No. (%)						
95 to 100	891 (61.6)	908 (61.8)	.97	2426 (66.3)	2525 (67.3)	.27
Above screening cut point to 94*	411 (28.4)	419 (28.5)		945 (25.8)	963 (25.7)	
At or below screening cut point*	145 (10.0)	143 (9.7)		291 (8.0))	262 (7.0)	

Abbreviations: GED, General Educational Development (test); 3MSE, Modified Mini-Mental State Examination; WHI, Women's Health Initiative.
*Screening cut points were originally ≤72 for women with 0-8 years of formal education and ≤76 for women with ≥9 years. To increase sensitivity, new cut points of ≤80 and ≤88, respectively, were implemented prospectively.

Table 2. Incidence of Probable Dementia, by Treatment Assignment

	Estrogen-Alone Trial			Estrogen + Progestin Trial			Estrogen Alone or Estrogen + Progestin Trial		
	Treatment (n = 1464)	Placebo (n = 1483)	HR (95% CI)	Treatment (n = 2229)	Placebo (n = 2303)	HR (95% CI)	Treatment (n = 3693)	Matching Placebos (n = 3786)	HR (95% CI)
Probable dementia, No. (%)	28 (1.9)	19 (1.3)		40 (1.8)	21 (0.9)		68 (1.8)	40 (1.1)	
Follow-up, mean (SD), y	5.16 (1.77)	5.20 (1.71)		4.01 (1.21)	4.06 (1.18)		4.47 (1.56)	4.51 (1.52)	
Rate per 10 000 person-years	37	25	1.49 (0.83-2.66)	45	22	2.05 (1.21-3.48)	41	23	1.76 (1.19-2.60)

Abbreviations: CI, confidence interval; HR, hazard ratio.

pooled, the overall HR for probable dementia was 1.76 (95% CI, 1.19-2.60; *P*=.005) (Figure 2B). After excluding participants with baseline 3MSE scores at or below the cut point (overall n=553), the HR was 1.77 (95% CI, 0.74-4.23; *P*=.20) in the estrogen-alone trial and 2.19 (95% CI, 1.25-3.84; *P*=.006) in the pooled trials.

In the estrogen-alone trial, 42 participants in the placebo group experienced stroke during the trial compared with 39 in the CEE group. Only 1 participant experiencing a stroke in each group was classified with probable dementia. After deleting all participants who experienced a centrally adjudicated stroke during the trial, the HR for probable dementia was 1.51 (95% CI, 0.83-2.74; *P*=.18).

Probable Dementia Types

The distribution of types of dementia differed little between women assigned to CEE vs placebo in the estrogen-alone trial (TABLE 3). Of the dementia cases, overall 47% were classified as AD, 8.5% as VaD, and 19% as mixed type (having features of both AD and VaD). In the pooled data, the distribution of dementia classifications was similar: 52% AD, 9% VaD, and 16% mixed type.

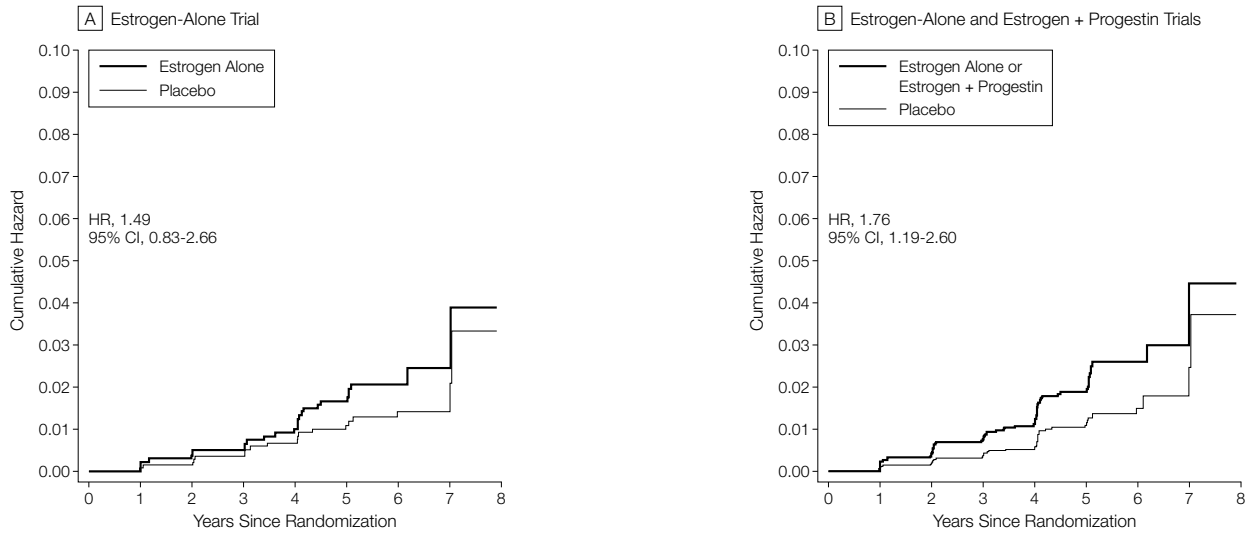
Local Clinician Diagnoses

Diagnoses from local clinicians were compared with those from central adjudicators (TABLE 4). Agreement between local clinicians and adjudicators was 75% in the estrogen-alone trial (κ=0.60; 95% CI, 0.52-0.68) and 77% in the estrogen plus progestin trial (κ=0.63; 95% CI, 0.58-0.69) (Table 4). Results were not affected by treatment assignment (*P*=.49). Most disagreements resulted in a less serious classification by the central adjudicators in both intervention groups (*P*=.14). In the estrogen-alone trial, 56 cases were diagnosed with probable dementia by local clinicians, 31 in the CEE group and 25 in the placebo group, yielding an HR of 1.26 (95% CI, 0.74-2.12; *P*=.40). In the combined trials, the HR was 1.54 (95% CI, 1.08-2.21; *P*=.02).

Adherence

In the estrogen-alone trial (as with the estrogen plus progestin trial), adherence decreased over time. For CEE and placebo, respectively, adherence rates were 77.2% and 84.1% (year 1), 66.3% and 71.6% (year 2), 59.8% and 63.1% (year 3), 52.9% and 57.8% (year 4), 45.6% and 52.1% (year 5), 42.0% and 47.8% (year 6), and 36.8% and 45.1% (year 7). In analyses limited to data censored 6 months after each participant's first assessed nonadherence, the HR for probable dementia associated with CEE was 1.55 (95% CI, 0.49-4.88; *P*=.45). Similar analyses of pooled data yielded an HR associated with hormone therapy of 2.38 (95% CI, 1.16-4.92; *P*=.02).

Figure 2. Times to Probable Dementia for Women Taking Estrogen Alone vs Placebo or Estrogen and Estrogen+Progestin Combined vs Placebo



No. at Risk

Estrogen Alone	1464	1377	1323	1280	1207	1031	539	80
Placebo	1483	1404	1360	1295	1227	1051	518	76

No. of Events

Estrogen Alone	3	4	2	5	9	2	3
Placebo	1	3	3	3	5	2	2

No. at Risk

Estrogen Alone or Estrogen + Progestin	3693	3494	3370	3227	2556	1437	550	80
Placebo	3786	3610	3498	3302	2643	1536	539	76

No. of Events

Estrogen Alone or Estrogen + Progestin	8	11	10	16	13	7	3
Placebo	4	5	6	6	14	2	3

Only participants followed up until 8 years are depicted, since very few women were followed up beyond that point. CI indicates confidence interval; HR, hazard ratio.

Mild Cognitive Impairment

Seventy-six participants were diagnosed with MCI in the CEE group, compared with 58 in the placebo group. The risk of being diagnosed with MCI in the CEE group was 34% higher than in the placebo group (HR, 1.34; 95% CI, 0.95-1.89). In the combined trials, the risk was similar (HR, 1.25, 95% CI, 0.97-1.60). Neither HR was statistically significant.

Of the women assigned to CEE, 93 were classified as having either MCI or probable dementia at some time during the trial, compared with 69 women assigned to placebo (TABLE 5). The incidence rates (per 10 000 person-years) of this composite end point were 126 and 91 for women assigned to CEE and pla-

Table 3. Classification of Probable Dementia Cases, by Treatment Assignment

	No. (%)					
	Estrogen-Alone Trial		Estrogen + Progestin Trial			
Dementia Type	Estrogen Alone (n = 28)	Placebo (n = 19)	Estrogen + Progestin (n = 40)	Placebo (n = 21)	Estrogen Alone or Estrogen + Progestin (n = 68)	Matching Placebos (n = 40)
Vascular	2 (7.1)	2 (10.5)	5 (12.5)	1 (4.8)	7 (10.3)	3 (7.5)
Alzheimer	13 (46.4)	9 (47.4)	20 (50.0)	12 (57.1)	33 (48.5)	21 (52.5)
Other						
Mixed	5 (17.9)	4 (21.2)	5 (12.5)	3 (14.3)	10 (14.7)	7 (17.5)
Normal-pressure hydrocephalus	0	0	2 (5.0)	0	2 (2.9)	0
Parkinson	0	0	0	1 (4.8)	0	1 (2.5)
Frontal-lobe	0	0	2 (5.0)	0	2 (2.9)	0
Alcohol-related	0	0	1 (2.5)	0	1 (1.5)	0
Other dementia	2 (7.1)	0	3 (7.5)	2 (9.5)	5 (7.4)	2 (5.0)
Etiology unknown	3 (10.7)	3 (15.8)	2 (5.0)	2 (9.5)	5 (7.4)	5 (12.5)
Not classified	3 (10.7)	1 (3.5)	0	0	3 (4.4)	1 (2.5)

Table 4. Agreement Between Local and Central Classifications, by Treatment Assignment

	Estrogen-Alone Trial		Estrogen + Progestin Trial			
Adjudications*	Estrogen Alone† (n = 165)	Placebo (n = 148)	Estrogen + Progestin‡ (n = 152)	Placebo (n = 127)	Estrogen Alone or Estrogen + Progestin (n = 317)	Matching Placebos (n = 275)
In agreement, No. (%)	123 (75)	114 (77)	121 (80)	97 (76)	244 (77)	211 (77)
In disagreement, No. (%)	42 (25)	34 (23)	31 (20)	30 (24)	73 (23)	64 (23)
Resulted in more serious classification, No. (%)	15 (36)	7 (21)	8 (26)	6 (20)	23 (32)	13 (20)
From no dementia to MCI, No.	7	6	4	5	11	11
From MCI to probable dementia, No.	7	1	4	1	11	2
From no dementia to probable dementia, No.	1	0	0	0	1	0
Resulted in less serious classification, No. (%)	27 (64)	27 (79)	23 (74)	24 (80)	50 (68)	51 (80)
From probable dementia to MCI, No.	10	10	9	8	19	18
From MCI to no dementia, No.	17	17	14	16	31	33

Abbreviation: MCI, mild cognitive impairment.
*More than 1 adjudication may be included for some participants.
†κ = 0.60 (95% confidence interval, 0.52-0.68).
‡κ = 0.63 (96% confidence interval, 0.58-0.69).

Table 5. Incidence of the Composite End Point of Probable Dementia or Mild Cognitive Impairment (MCI), by Treatment Assignment

	Estrogen-Alone Trial			Estrogen + Progestin Trial			Estrogen Alone or Estrogen + Progestin Trial		
	Treatment (n = 1463)	Placebo (n = 1479)	HR (95% CI)	Treatment (n = 2229)	Placebo (n = 2300)	HR (95% CI)	Treatment (n = 3692)	Matching Placebos (n = 3779)	HR (95% CI)
Probable Dementia or MCI, No. (%)	93 (6.4)	69 (4.7)		85 (3.8)	63 (2.7)		178 (4.8)	132 (3.5)	
Follow-up, mean (SD), y	5.05 (1.83)	5.14 (1.75)		3.97 (1.24)	4.04 (1.20)		4.40 (1.59)	4.47 (1.54)	
Rate per 10 000 person-years	126	91	1.38 (1.01-1.89)	95	68	1.44 (1.04-1.99)	110	78	1.41 (1.12-1.76)

Abbreviations: CI confidence interval; HR, hazard ratio.

cebo, respectively; the relative hazard associated with CEE was 1.38 (95% CI, 1.01-1.89; $P=.04$). These differences tended to emerge earlier than those for probable dementia (FIGURE 3A). These results did not differ significantly from those for the estrogen plus progestin trial ($P=.90$) (Figure 3B). The HR for this composite end point was 1.41 for the pooled data (95% CI, 1.12-1.76; $P=.003$).

TABLE 6 depicts the consistency of HRs from the estrogen-alone trial across subgroups defined by baseline risk factors for probable dementia. No significant heterogeneity was detected ($P>.004$ for all). These findings parallel those for the combined trials (Table 6).

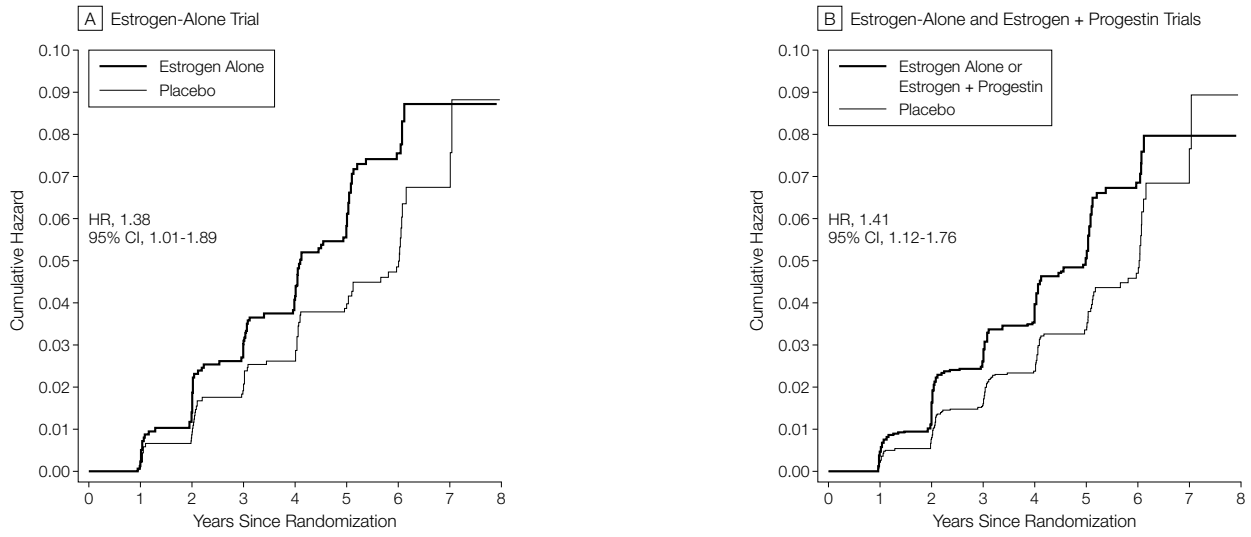
COMMENT

Previous preclinical, epidemiologic, and clinical trial data suggested that hormone therapy could benefit cognition and dementia among women with perimenopausal symptoms and postmenopausal women with dementia.[32] In the WHIMS, the first double-blind, placebo-controlled, long-term multicenter study of CEE and CEE plus MPA in postmenopausal women, both CEE and CEE plus MPA were associated with an increased incidence of dementia compared with placebo, although the association did not reach statistical significance in the smaller, but longer, estrogen-alone trial.

The number of MCI classifications in the treatment groups of the WHIMS trials were different (100 per 10 000 women for the estrogen-alone trial vs 63 per 10 000 women for the estrogen plus progestin trial). When risks of dementia and MCI were combined, effects of CEE and CEE plus MPA, compared with matching placebos, were similar in both hormone therapy trials. In general, MCI, particularly amnestic MCI, is viewed by most investigators as part of a continuum from normal cognitive functioning to dementia. The WHIMS classification of MCI required abnormality in any cognitive domain. Thus, it is possible that some women may have a nonamnestic type of cognitive impairment, not necessarily associated with an increased risk of dementia.[2] Reanalyses of the WHIMS classifications of MCI into amnestic and nonamnestic types may provide additional insights into this issue.

Previous investigators of hormone therapy have believed that the addition of MPA might somehow counteract the beneficial neurobiological or vascular effects of estrogen.[32-34] However, in the current studies of CEE alone and CEE plus MPA, an increased risk of dementia was found in both trials, although the difference from placebo was significant only in the estrogen plus progestin trial. Conjugated equine estrogens may contain estrogens with negative effects on risk of dementia, compared with 17β-estradiol alone. However, epidemiologic studies indicating a beneficial effect of hormones

Figure 3. Times to the First Occurrence of the Composite End Point of Probable Dementia or Mild Cognitive Impairment for Women Taking Estrogen Alone vs Placebo or Estrogen and Estrogen+Progestin Combined vs Placebo



No. at Risk								
Estrogen Alone	1463	1371	1299	1247	1171	991	517	73
Placebo	1479	1399	1347	1270	1199	1027	509	75
No. of Events								
Estrogen Alone	8	22	12	15	22	10	4	
Placebo	3	12	17	7	13	10	7	

No. at Risk								
Estrogen Alone or Estrogen + Progestin	3692	3483	3324	3161	2495	1392	528	73
Placebo	3379	3599	3472	3254	2591	1504	530	75
No. of Events								
Estrogen Alone or Estrogen + Progestin	18	46	36	32	29	13	4	
Placebo	9	22	37	20	22	14	8	

Only participants followed up until 8 years are depicted, since very few women were followed up beyond that point. CI indicates confidence interval; HR, hazard ratio.

most often used CEE.[32] Unless other studies demonstrate that different compounds bestow benefit, these data would generalize to all estrogens.[35]

Some studies indicate that the timing of hormone therapy may be important in disease prevention.[36] For example, in osteoporosis the primary positive effect of hormone therapy on bone loss is found in the immediate perimenopausal/postmenopausal period.[37] Some preclinical neurobiological studies suggest that timing of estrogen after ovariectomy may be important in preventing neuronal loss.[38,39] However, results of the WHIMS estrogen-alone and estrogen plus progestin trials demonstrate an increased

Table 6. Consistency of Hazard Ratios for Assignment to Active Therapy Across Subgroups Based on Baseline Risk Factors for Dementia, by Treatment Assignment

	Estrogen-Alone Trial				Estrogen + Progestin Trial			
	No. (Rate per 10 000 Person-Years)				No. (Rate per 10 000 Person-Years)			
Subgroup	Estrogen Alone	Placebo	HR (95% CI)	*P* Value	Estrogen + Progestin	Placebo	HR (95% CI)	*P* Value
Age, y								
65-69	6 (18)	4 (12)	1.54 (0.43-5.44)	.88	12 (16)	6 (8)	2.06 (0.77-5.50)	.65
70-74	13 (46)	8 (30)	1.52 (0.63-3.67)		25 (42)	17 (28)	1.48 (0.80-2.74)	
≥75	9 (71)	7 (47)	1.47 (0.55-3.94)		31 (110)	17 (55)	2.01 (1.11-3.63)	
Education								
<High school	6 (90)	3 (47)	1.84 (0.46-7.37)	.95	13 (107)	6 (49)	2.17 (0.83-5.72)	.93
High school/GED	6 (34)	4 (22)	1.55 (0.44-5.49)		12 (34)	8 (21)	1.65 (0.67-4.03)	
>High school, <4 y college	11 (35)	9 (29)	1.21 (0.50-2.92)		25 (37)	16 (25)	1.50 (0.80-2.82)	
≥4 y college	5 (28)	3 (15)	1.75 (0.42-7.33)		17 (36)	10 (19)	1.86 (0.85-4.07)	
Race								
Nonwhite	9 (73)	9 (74)	0.98 (0.39-2.47)	.27	15 (71)	13 (61)	1.16 (0.55-2.43)	.20
White	19 (31)	10 (16)	1.93 (0.90-4.15)		53 (37)	27 (18)	2.04 (1.28-3.24)	
Smoking								
Never	17 (42)	12 (30)	1.37 (0.66-2.88)	.59	40 (45)	23 (26)	1.74 (1.04-2.90)	.87
Some	11 (33)	6 (17)	1.93 (0.71-5.22)		26 (36)	15 (20)	1.86 (0.98-3.51)	
History of cardiovascular disease								
No	22 (34)	16 (24)	1.91 (0.48-7.63)	.69	58 (40)	34 (23)	1.77 (1.16-2.71)	.59
Yes	6 (67)	3 (35)	1.40 (0.73-2.66)		8 (51)	6 (39)	1.29 (0.45-3.72)	
History of stroke								
No	28 (38)	19 (26)	1.48 (0.83-2.64)		67 (42)	39 (24)	1.76 (1.19-2.62)	.94
Yes	0	0			1 (51)	1 (34)	1.59 (0.10-25.38)	
History of diabetes								
No	20 (30)	18 (27)	1.10 (0.58-2.09)	.06	57 (38)	34 (22)	1.72 (1.13-2.64)	.56
Yes	8 (108)	1 (13)	9.03 (1.13-72.2)		11 (84)	5 (36)	2.41 (0.84-6.94)	
History of hypertension								
No	10 (25)	11 (25)	0.98 (0.42-2.31)	.15	34 (35)	24 (23)	1.52 (0.90-2.57)	.32
Yes	18 (54)	7 (23)	2.40 (1.00-5.74)		33 (51)	14 (22)	2.30 (1.23-4.30)	
Prior hormone therapy								
No	21 (52)	11 (27)	1.95 (0.94-4.04)	.21	56 (51)	30 (27)	1.95 (1.25-3.03)	.34
Yes	7 (21)	8 (23)	0.87 (0.32-2.39)		12 (22)	10 (18)	1.22 (0.53-2.82)	
Prior use of estrogen only								
Never	21 (51)	12 (28)	1.78 (0.88-3.61)	.37	57 (49)	31 (26)	1.92 (1.24-2.97)	.38
Some	7 (21)	7 (21)	1.00 (0.35-2.84)		11 (24)	9 (20)	1.23 (0.51-2.98)	
Prior use of statins								
No	25 (38)	17 (26)	1.45 (0.79-2.69)	.83	62 (43)	36 (24)	1.79 (1.19-2.70)	.80
Yes	3 (37)	2 (21)	1.78 (0.30-10.65)		6 (32)	4 (22)	1.50 (0.42-5.32)	
Prior use of aspirin								
No	17 (31)	15 (29)	1.09 (0.54-2.18)	.12	44 (37)	27 (23)	1.63 (1.01-2.62)	.55
Yes	11 (54)	4 (17)	3.12 (0.99-9.79)		24 (53)	13 (26)	2.09 (1.06-4.10)	
3MSE total score at WHI enrollment								
95-100	8 (17)	2 (5)	4.04 (0.86-19.04)	.35	19 (18)	7 (7)	2.82 (1.18-6.70)	.36
Above screening cut point to 94*	6 (30)	6 (29)	1.04 (0.33-3.22)		19 (47)	11 (26)	1.81 (0.86-3.80)	
At or below screening cut point*	13 (197)	10 (151)	1.30 (0.57-2.96)		28 (237)	21 (189)	1.34 (0.76-2.34)	

Abbreviations: GED, General Educational Development (test); 3MSE, Modified Mini-Mental State Examination; WHI, Women's Health Initiative.
*See Table 1 footnote for explanation of cut points.

risk of combined probable dementia or MCI associated with both hormone regimens. Since women in the WHIMS were 65 years and older at baseline, delayed onset of treatment relative to menopause might have allowed irreversible neurodegeneration to occur that hormone therapy could not improve. Since the neuropathologic abnormalities of AD develop before clinical recognition of dementia,[40] dementia prevention trials in older women may not represent primary prevention of AD.

Approximately 45% of the women in the estrogen-alone WHIMS trial had previously taken hormone therapy. The HR is greater than 1 for women who had never taken hormone therapy (1.95; 95% CI, 0.94-4.04) compared with those who had (0.87; 95% CI, 0.32-2.39); however, these differences were not statistically significant. In the pooled analysis, the HRs of 1.95 (95% CI, 1.25-3.03) for those who had never taken hormone therapy and 1.22 (95% CI, 0.53-2.82) for those who had were not significantly different. Prior use of hormone therapy did not significantly affect the results. However, a small number of events occurred in each group.

The higher risk of dementia in women receiving estrogen alone and estrogen plus progestin combined could be due to adverse effects of vascular disease in the brain, as documented in epidemiologic studies. The high incidence of stroke in both trials would be consistent with such an adverse effect of hormone therapy on vascular disease in the brain. Earlier epidemiologic studies demonstrated a high prevalence of silent brain infarction (25%-35%), even among older women without a history of clinical stroke.[41,42] Also, dementia was more frequent among those who had relatively small primary lacunar infarcts and high-grade white matter lesions, probably due to small-vessel disease.[43,44] To investigate this further, magnetic resonance imaging will be performed on a subset of WHIMS participants to determine the extent of subclinical neurovascular disease, high-grade white matter infarcts and microinfarcts, and focal brain changes consistent with early stages of AD.

Hypertension and diabetes are important determinants of vascular disease in the brain and dementia.[45-47] In the estrogen-alone trial, hypertension was more prevalent in the CEE group vs the matching-placebo group (42.3% and 47.3%, respectively; $P=.01$). Both diabetes and hypertension were associated with higher HRs for the CEE group vs the placebo group. This was especially true for women with diabetes assigned to CEE, in whom the HR was 1.10 (95% CI, 0.58-2.09) for those with no history of diabetes and 9.03 (95% CI, 1.13-72.2) for those with a history of diabetes ($P=.06$). The HR was 0.98 (95% CI, 0.42-2.31) for those with no history of hypertension and 2.40 (95% CI, 1.00-5.74) for those with a history of hypertension ($P=.15$). These comparisons may not have reached statistical significance due to the small number of events in each subgroup. The effects of both diabetes and hypertension were substantially less in the pooled trial data. The results in the estrogen-alone trial, but not the pooled data, suggest a possible effect of hypertension, diabetes, and "vascular disease" in the brain. Disease in small vessels of the brain could be an independent determinant for risk of dementia. More likely, the neurovascular disease emphasizes the clinical presentation of AD in those with both vascular disease and pathologic processes consistent with AD, leading to clinically recognized dementia.[48] Thus, an alternative hypothesis is that, in women in the early stages of AD, neurovascular disease precipitates both dementia and MCI secondary to hormone therapy.[49,50]

The possibility that hormone therapy is associated with an increase in vascular disease in the brain and incidence of dementia could have important implications. Some participants in the estrogen-alone or estrogen plus progestin trials may have increased neurovascular disease but have not yet developed either MCI or dementia. Such women would remain at higher risk, not only for dementia, but also for clinical stroke. Further follow-up of the WHIMS participants is planned to determine whether an increased risk for dementia and MCI persists once treatment is discontinued.

In summary, the results of the WHIMS demonstrate an increased risk of dementia and MCI in the combined estrogen-alone and the estrogen plus progestin trials among women between 65 and 79 years of age at study entry. Use of hormone therapy to prevent dementia or MCI in women 65 years of age or older is not recommended.

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Financial Disclosures: Dr Shumaker has served as a consultant for Wyeth and Pfizer. Dr Lewis has received grants from Eli Lilly, Pfizer, and Novartis.

Author Contributions: Dr Shumaker, as principal investigator of the WHIMS trial, had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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Acquisition of data: Shumaker, Legault, Kuller, Rapp, Lane, Stefanick, Hendrix, Lewis, Masaki, Coker.

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Statistical expertise: Legault.

Obtained funding: Shumaker, Legault, Lane, Stefanick, Hendrix, Lewis.

Administrative, technical, or material support: Shumaker, Legault, Kuller, Rapp, Thal, Lane, Stefanick, Hendrix, Lewis, Masaki, Coker.

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Funding/Support: The Women's Health Initiative Memory Study was funded in part by Wyeth Pharmaceuticals through March 2003. Wake Forest University Health Sciences has provided support for the WHIMS. The WHI is funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, US Department of Health and Human Services. Wyeth Pharmaceuticals provided the study drug and the placebo to the WHI trial.

Role of the Sponsors: The authors are solely responsible for the design and conduct of the study; the collection, analysis, and interpretation of the data; and the preparation, review, and approval of the manuscript.

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You cannot acquire experience by making experiments. You cannot create experience. You must undergo it.
—Albert Camus (1913-1960)