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Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women

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

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APPROXIMATELY 10% OF PERSONS older than 65 years and about 50% of those older than 85 years have Alzheimer disease (AD).¹ At present, this represents approximately 4 million persons in the United States, and that number is projected to increase to 14 million by the year 2040.²

Postmenopausal women may have a greater risk of developing AD than men,³ perhaps due to lower endogenous estrogen levels following menopause.^{4,5} Estrogen's protective effects on the brain may include promoting cholinergic activity, reducing neuronal loss and stimulating axonal sprouting and dendritic spine formation, reducing ce-

Context Postmenopausal women have a greater risk than men of developing Alzheimer disease, but studies of the effects of estrogen therapy on Alzheimer disease have been inconsistent. On July 8, 2002, the study drugs, estrogen plus progestin, in the Women's Health Initiative (WHI) trial were discontinued because of certain increased health risks in women receiving combined hormone therapy.

Objective To evaluate the effect of estrogen plus progestin on the incidence of dementia and mild cognitive impairment compared with placebo.

Design, Setting, and Participants The Women's Health Initiative Memory Study (WHIMS), a randomized, double-blind, placebo-controlled clinical trial, began enrolling participants from the Women's Health Initiative (WHI) estrogen plus progestin trial in May 1996. Of the 4894 eligible participants of the WHI study, 4532 (92.6%) postmenopausal women free of probable dementia, aged 65 years or older, and recruited from 39 of 40 WHI clinical centers were enrolled in the WHIMS.

Intervention Participants received either 1 daily tablet of 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (n=2229), or a matching placebo (n=2303).

Main Outcome Measures Incidence of probable dementia (primary outcome) and mild cognitive impairment (secondary outcome) were identified through a structured clinical assessment.

Results The mean (SD) time between the date of randomization into WHI and the last Modified Mini-Mental State Examination (3MSE) for all WHIMS participants was 4.05 (1.19) years. Overall, 61 women were diagnosed with probable dementia, 40 (66%) in the estrogen plus progestin group compared with 21 (34%) in the placebo group. The hazard ratio (HR) for probable dementia was 2.05 (95% confidence interval [CI], 1.21-3.48; 45 vs 22 per 10000 person-years; $P=.01$). This increased risk would result in an additional 23 cases of dementia per 10000 women per year. Alzheimer disease was the most common classification of dementia in both study groups. Treatment effects on mild cognitive impairment did not differ between groups (HR, 1.07; 95% CI, 0.74-1.55; 63 vs 59 cases per 10000 person-years; $P=.72$).

Conclusions Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women. These findings, coupled with previously reported WHI data, support the conclusion that the risks of estrogen plus progestin outweigh the benefits.

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See also pp 2663, 2673, and 2717.

rebral ischemia by improving blood flow and reducing cholesterol levels, and modulating expression of the apolipoprotein E gene.^{6,7}

Support for the estrogen deficiency hypothesis as one cause of dementia comes from reported positive associations between exogenous estrogen and cognitive performance in older women without dementia.⁸⁻¹⁴ In addition, case-control,^{15,16} cross-sectional,¹⁷ and prospective studies^{11,18-22} have reported a lower risk of dementia for women taking compared with those not taking postmenopausal estrogen. Two recent meta-analyses of estrogen and dementia reported risk reductions of 29%²³ and 34%,²⁴ yet several prospective observational studies found no protective effect of estrogen on either cognition or the incidence of dementia.^{21,22,25,26} In addition, clinical trials of unopposed estrogen in women with AD have shown no beneficial effect on cognitive performance.²⁷⁻²⁹ Moreover, recent reviews point to serious methodological problems in most studies.^{30,31} Thus, the mixed findings underscore the need for a large, well-designed randomized controlled trial.

The Women's Health Initiative Memory Study (WHIMS),³² an ancillary study to the 2 larger Women's Health Initiative (WHI) hormone therapy trials, is examining whether postmenopausal estrogen supplementation (both estrogen alone and estrogen plus progestin) reduces the risk of all-cause dementia (primary outcome) and subclinical (mild) cognitive impairment (secondary outcome) in healthy women aged 65 years or older. Study drug administration in the planned 8.5-year trial for estrogen plus progestin was discontinued after 5.6 years because women in the intervention group were at increased risk for heart disease, stroke, pulmonary embolism, and breast cancer compared with women receiving placebo, and these risks outweighed the beneficial effects of estrogen plus progestin on colon cancer and osteoporotic fracture.³³ The WHI estrogen-only hormone therapy trial, which enrolled women with a prior hysterectomy, continues,

as does the WHIMS component of this trial. The data reported herein are from the estrogen plus progestin and the placebo components of the WHIMS.

METHODS

WHI Hormone Therapy Trials: Participant Enrollment

The WHIMS trial was started in June 1995. All participants who were enrolled in the WHIMS trial first met enrollment criteria and then provided written consent to participate in the WHI hormone therapy trials. The eligibility criteria and recruitment procedures for the WHI hormone therapy trials³⁴ and more specific information about the estrogen plus progestin trial have been published.³³ Briefly, in the WHI estrogen plus progestin trial, women 50 through 79 years of age at initial screening and with an intact uterus were potentially eligible. A 3-month washout period was required before baseline evaluation of women using postmenopausal hormones at initial screening. Major exclusions related to competing risks (invasive cancer in the past 10 years; breast cancer at any time or suspicion of breast cancer at baseline screening; acute myocardial infarction, stroke, or transient ischemic attack in the previous 6 months; or known chronic active hepatitis or severe cirrhosis), safety (blood cell counts indicative of disease; severe hypertension; or current use of oral corticosteroids), and adherence or retention concerns (unwillingness or inability to complete baseline study requirements).

Participants had 3 screening visits before enrollment. At the third screening visit, if the participants complied with taking study medication during the 28-day run-in phase (participants could have up to 2 run-in phases and still be eligible for the trial), met all inclusion and exclusion criteria, remained interested in participating, and signed an informed consent for the WHI estrogen plus progestin trial, they were randomly assigned to take either 1 daily tablet that contained conjugated equine estrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (PremPro, Wyeth Pharmaceuticals, Philadel-

phia, Pa), or a matching placebo (also provided by Wyeth Pharmaceuticals). Randomization was determined using a permuted block algorithm that was stratified according to age group and clinical center site with implementation by the WHI Clinical Coordinating Center (CCC) (Fred Hutchinson Cancer Research Center, Seattle, Wash). Participants were given their next supply of study pills semiannually. They returned annually for clinic visits and were contacted semiannually for safety and outcomes ascertainment.

WHIMS Participant Enrollment

Thirty-nine of the 40 WHI clinical centers elected to participate in the WHIMS trial. Women were enrolled in the WHIMS trial between May 28, 1996, and December 13, 1999. The trial was designed to evaluate the effects of the combination of estrogen with and without progestin vs placebo on all-cause dementia (primary outcome), mild cognitive impairment (MCI) (secondary outcome), and global cognitive functioning (reported in Rapp et al³⁵). However, the early discontinuation of study drug administration of estrogen plus progestin in the WHI trial resulted in the early, unplanned examination of this same component within the WHIMS.

Participants were recruited during WHI hormone therapy trial enrollment from participants in the estrogen plus progestin trial who were aged 65 years or older and free of probable dementia, as determined by the WHIMS protocol (described below). No other inclusion/exclusion criteria were required. In addition, prospective WHIMS participants were asked to name a friend or family member (ie, the designated informant) who could provide information regarding the participant's cognitive and behavioral functioning. At a WHI screening visit, prospective WHIMS participants were informed about the study objectives, design, and requirements, and written informed consent was obtained. Ninety-nine percent of the WHIMS participants were enrolled within less than 6 weeks of WHI hormone therapy randomiza-

tion, and 45 women (1.0%) were enrolled after randomization (FIGURE 1).

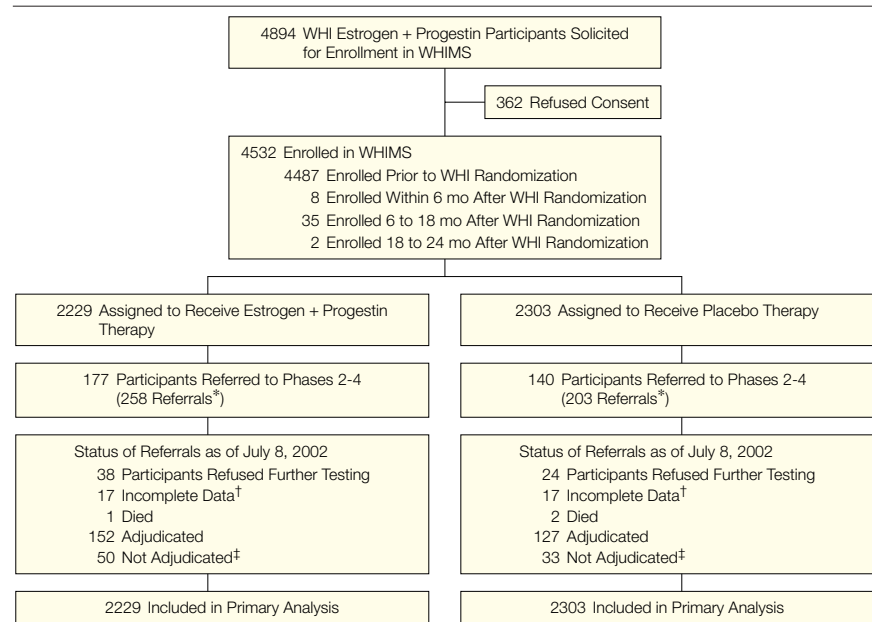
Of the 4894 women eligible for the estrogen plus progestin component of the WHIMS, 4532 (92.6%) had consented to participate. Study coordination for the WHIMS was provided by the WHIMS CCC, the central administrative and data site (Wake Forest University Health Sciences, Winston-Salem, NC). The National Institutes of Health and the institutional review boards for all participating institutions approved the WHI and WHIMS protocols and consent forms.

WHIMS Detection of Probable Dementia and MCI

A detailed description of the WHIMS protocol has been published previously.³² Technicians who were centrally trained and certified by the WHIMS CCC collected all WHIMS-specific data. In addition, some baseline data collected in the WHI hormone therapy trials (eg, demographic characteristics) were used in the WHIMS analyses. To maintain strict quality control in the administration of WHIMS-related measures, all technicians were centrally recertified semiannually.

The WHIMS dementia ascertainment protocol was divided into 4 phases. In phase 1, all participants completed the Modified Mini-Mental State Examination (3MSE)³⁶ at baseline and annually thereafter. The 3MSE was used to screen for global cognitive impairment and to track changes in global cognitive function (reported in Rapp et al³⁵). Initially, participants with 3MSE scores of 72 or lower (for participants with ≤ 8 years of education) or of 76 or lower (for participants with ≥ 9 years of education) were identified for an expanded neuropsychological battery and clinical examination (phases 2 and 3), with an estimated sensitivity of 80% and specificity of 85% based on earlier studies.^{37,38} After 16 months, the protocol was altered to increase the sensitivity (at the expense of specificity) of the 3MSE to ensure that we successfully detected any women with MCI or dementia. New cut points of 80 or lower (for participants

Figure 1. Enrollment and Flow of Participants Through WHIMS



WHI indicates Women's Health Initiative; WHIMS, Women's Health Initiative Memory Study. Asterisk indicates that a patient could be referred at any annual visit; dagger, 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, or scheduling conflict; double dagger, all probable dementia cases, a random sample of 10% of all no dementia cases, and a random sample of 50% of all mild cognitive impairment cases were adjudicated.

with ≤ 8 years of education) and 88 or lower (for participants with ≥ 9 years of education) were implemented prospectively.^{37,39} Participants scoring below these cut points on their yearly cognitive screening went on to phases 2 and 3 of the WHIMS protocol.

In phase 2 of the WHIMS, certified technicians administered a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery.⁴⁰ The battery contains tests measuring verbal fluency (animal category),⁴¹ naming (15-item Boston Naming Test),⁴² verbal learning and memory (10-item, 3-trial word list memory task with delayed recall, and recognition tasks),⁴³ constructional praxis (4 line drawings are copied and later recalled),⁴⁴ and executive function (Trail-Making Test, parts A and B).⁴⁵ Certified technicians also administered standardized interviews to assess behavioral symptoms, such as generalized anxiety, major depression, and alcohol abuse,⁴⁶ and the 15-item Geriatric Depression Scale.⁴⁷ Lastly, both the participant and her des-

ignated informant were administered separately a standardized set of 36 items (yes/no) that assessed observed cognitive and behavioral deficits (memory, language, orientation, personality/behavior, basic and instrumental activities of daily living, social and intellectual activities, and judgment and problem solving).³² All participants in phase 2 also completed phase 3.

In phase 3 of the WHIMS, participants were evaluated by a physician (ie, geriatrician, neurologist, or geriatric psychiatrist) who was identified by the local WHIMS clinical center and approved by the WHIMS CCC as having the experience required for diagnosing dementia. WHIMS clinicians were provided with a detailed protocol for their portion of the assessment. The clinicians reviewed all data collected on the WHIMS participant in phases 1 and 2 and completed a structured medical history, which focused particularly on possible causes of cognitive impairment, and a physical and neuropsychiatric examination. The local expert 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.⁴⁸ Mild cognitive impairment was operationally defined as poor performance (10th or lower percentile) on modified CERAD tests in at least 1 area of cognitive function, a report of some functional impairment reported by the designated informant but not in a basic activity of daily living, no evidence of a psychiatric disorder or medical condition that could account for the decline in cognitive function, review of past 3MSE scores or phase 2 through 4 data that suggested a decline from the woman's baseline functioning score, and an absence of dementia.⁴⁹ If the clinician suspected probable dementia, the participant went on to phase 4 of the WHIMS trial, in which she was referred for a computed tomography scan of the brain (without contrast) and laboratory blood tests to rule out possible reversible causes of cognitive decline and dementia. If dementia was judged present, the clinician was required to specify the most probable etiology based on all findings. In classifying the participants' dementia, the clinician followed the WHIMS protocol, which was based on *DSM-IV* criteria and included detailed descriptions for diagnosis of vascular dementia and AD, as well as other dementia-related classifications. All clinical and test data were then transmitted to the WHIMS CCC for review and central adjudication.

Adjudication Process

The central adjudication committee at the WHIMS CCC consists of 3 board-certified specialists (2 neurologists and 1 geriatric psychiatrist) with extensive experience in diagnosing dementias. The adjudicators independently reviewed all probable dementia cases identified by the local clinician, a random sample of 50% of MCI cases, and a random sample of 10% of cases without dementia. All information on a given participant's test scores, except the field clinician's classification, was provided to 2 of the 3 adjudicators, who independently evaluated

the data and assigned a classification. The field clinician's diagnostic assessment was then shared with each adjudicator, who independently made a revised diagnosis. If all the adjudicators agreed, this was considered the consensus diagnosis. If they disagreed, the adjudicators discussed the case and attempted to make a consensus classification. The adjudication committee and a geriatric psychologist, discussed all cases of disagreement until they reached a consensus classification. The same process was followed to reach consensus on the etiologic classification of the dementia. Regardless of the participants' classification, all continued to be screened annually thereafter with the 3MSE.

Blinding

All WHIMS-certified technicians, local WHIMS physicians, and WHIMS adjudicators were blinded to participants' treatment assignment. The certified technicians and local physicians were held to the same rigorous blinding protocol that is present throughout the WHI. That is, official unblinding (to address safety issues) occurred through a designated unblinding officer at each site. The unblinding officer was the only individual authorized to access unblinding information in the WHI database and to provide this information to the clinic's consulting gynecologist. This information was not recorded in the participants' clinic files or provided to any individuals involved in outcomes ascertainment or coding. The adjudicators were independent of the clinical center clinicians; data provided to them were blinded.

Adherence

Adherence data for hormone therapy were collected annually after randomization. According to WHI criteria, a participant became nonadherent by stopping study medication by her own decision or for protocol-based safety issues, by taking less than 80% of her pills between dispensing and collection, or by starting prescribed hormone therapy 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 on hormone therapy.

Statistical Analyses

The WHIMS trial was designed to provide more than 80% statistical power to detect an observed 40% relative reduction in the incidence rate of clinically diagnosed all-cause dementia associated with randomization to receive hormone therapy either with or without progestin.²⁷ Based on a projected enrollment of 8300 women, approximately 165 incident cases of all-cause dementia were expected over 5 years. When the estrogen plus progestin component of the WHI trial was terminated, 61 cases of all-cause dementia were identified. Post hoc calculations indicate that the WHIMS estrogen plus progestin trial provided 80% statistical power to detect a hazard ratio (HR) of 1.89 at the 5% significance level. Survival analyses were conducted on intention-to-treat principles for all eligible WHI estrogen plus progestin participants enrolled in the WHIMS (4532/4894, [92.6%]). One hundred fifty-one participants in the WHIMS had only a baseline 3MSE score. Mean (SD) baseline 3MSE scores did not differ significantly between the 2 intervention groups for these participants (estrogen plus progestin, 94.15 [4.1] and placebo, 95.18 [4.1], $P = .28$). A survival time equal to zero was assigned to these 151 participants and they were included in the overall mean survival.

We compared the effect of estrogen plus progestin and placebo on the primary outcome of probable dementia. All events up to July 8, 2002, when the study drug in the WHI estrogen plus progestin trial was discontinued, were included in the analyses and were adjudicated as described in the section "Adjudication Process." Hazard ratios and nominal 95% confidence intervals (CIs) from unadjusted Cox proportional hazards models⁵⁰ were compared between the treatment and placebo groups. Given the wide range of clinical and behavioral outcomes ex-

amined in the WHI estrogen plus progestin trial, some nominal CIs may exclude 1 based on chance alone. The time to event was defined as the number of days from randomization into the WHI estrogen plus progestin trial to the date of the 3MSE that initiated the referral for additional cognitive testing resulting in the first postrandomization diagnosis. Participants without a diagnosis were censored at their last follow-up contact before July 8, 2002. Cumulative hazards ratios are presented. A significance level of less than .05 was used for all primary analyses. WHIMS analyses for the effects of estrogen plus progestin on global cognitive function are reported elsewhere.³⁵

Secondary analyses were conducted for participants with a diagnosis of MCI only and of probable dementia or MCI. Cox proportional hazards models were fitted separately with treatment assignment and 1 of the following 10 baseline factors as independent variables: age; education; self-reported history of stroke or diabetes; prior use of hormone therapy, unopposed estrogen, estrogen plus progestin, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), or aspirin; and baseline 3MSE scores. In each of the 10 models, the interaction between treatment assignment and the factor was tested; HRs are presented for subgroups defined by these factors and a Bonferroni adjustment was used to control for type I error (.05/10=.005). Additional secondary analyses also were conducted censoring participants 6 months after they became nonadherent and when they started using statins. We used SAS release 8.2 (SAS Institute Inc, Cary, NC) for the statistical analyses.

The monitoring of the WHI hormone therapy trial was conducted semiannually by an independent data and safety monitoring board. Trial-monitoring guidelines for early stopping considerations have been published.⁵¹ Although not part of the stopping rules, the WHIMS data were reviewed in conjunction with the overall assessment of risk/benefit by the monitoring board.

RESULTS

Figure 1 depicts the enrollment and referrals to additional cognitive testing (phases 2-4) for the WHIMS cohort. Participants could be referred to phase 2 more than once if they did not meet diagnostic criteria for probable dementia or MCI. The total number of referrals for phases 2 through 4 in the estrogen plus progestin group were 213 in phase 2, 201 in phase 3, and 40 in phase 4. In the placebo group, the total number of referrals were 165 in phase 2, 157 in phase 3, and 27 in phase 4.

Of the 58 participants (62 referrals) who refused further testing at least once, 22 (38%) had subsequent visits at which a diagnosis was made. Furthermore, of the 32 participants (34 referrals) with incomplete data, 13 (41%) also had a diagnosis at a subsequent visit. The mean (SD) time between the last 3MSE and the date of randomization into the WHI for all WHIMS participants was 4.05 (1.19) years.

TABLE 1 lists baseline characteristics of WHIMS participants by treatment assignment at enrollment into the

Table 1. Baseline Characteristics and Adherence of WHIMS Estrogen Plus Progestin Subtrial Participants, by Treatment Assignment

Variable	Estrogen + Progestin (n = 2229)	Placebo (n = 2303)	P Value
Age, No. (%), y			
65-69	1040 (46.7)	1081 (46.9)	.49
70-74	779 (35.0)	829 (36.0)	
≥75	410 (18.4)	393 (17.1)	
Education, No. (%)			
<High school	150 (6.7)	148 (6.5)	.33
High school/GED	446 (20.0)	498 (21.7)	
<4 y of college	894 (40.2)	870 (37.9)	
≥4 y of college	734 (33.0)	779 (33.9)	
Smoking status, No. (%)			
Never	1176 (52.8)	1172 (51.9)	.58
Previous	876 (39.8)	930 (41.1)	
Current	149 (6.7)	158 (6.9)	
History of stroke, No. (%)	23 (1.0)	44 (1.9)	.01
History of diabetes, No. (%)	156 (7.0)	149 (6.5)	.48
Prior hormone therapy use, No. (%)			
Any	485 (21.8)	516 (22.4)	.60
Estrogen only	305 (13.7)	323 (14.0)	.74
Estrogen + progestin	222 (10.0)	236 (10.3)	.74
Other prior medication use, No. (%)			
Statins (HMG-CoA reductase inhibitors)	266 (12.0)	225 (9.8)	.02
Aspirin, regular use	627 (28.1)	682 (29.6)	.27
3MSE total score at WHI enrollment			
Mean (SD)	95.45 (4.21)	95.62 (3.88)	.16
Level, No. (%)			
95 to 100	1535 (69.3)	1617 (70.9)	.13
Above screening cutpoint to 94*	534 (24.1)	544 (23.9)	
At or below screening cutpoint*	146 (6.6)	119 (5.2)	
Adherence, No. (%)			
Year 1	1496 (71.2)	1823 (83.3)	<.001
Year 2	1223 (60.5)	1534 (73.2)	
Year 3	1087 (54.2)	1381 (66.3)	
Year 4	899 (49.6)	1143 (61.0)	
Year 5	364 (43.7)	507 (56.3)	
Year 6	10 (32.3)	27 (61.4)	

Abbreviations: 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.

*Screening cutpoint was ≤80 for women with ≤8 years of formal education and ≤88 for women with ≥9 years of formal education.

WHI trial. Other demographic data are described elsewhere.³⁵ Nearly half of the participants were 65 to 70 years old. No significant differences were found between study groups at baseline, including smoking, except for the slightly lower prevalence of stroke ($P=.01$) and the slightly higher percentage of participants using statins ($P=.02$) in the estrogen plus progestin group. Adherence rates were lower each year for participants assigned to receive estrogen plus progestin compared with participants assigned to receive placebo ($P<.001$).

Probable Dementia

Overall, 61 participants from 31 of the 39 clinical centers (range, 0-4 partici-

pants per clinical center) were diagnosed with probable dementia: 40 (66%) in the estrogen plus progestin group and 21 (34%) in the placebo group (TABLE 2). The rate of women experiencing probable dementia in the estrogen plus progestin group was twice that of women in the placebo group (HR, 2.05; 95% CI, 1.21-3.48; 45 vs 22 per 10 000 person-years, $P=.01$) (FIGURE 2). Cumulative hazards ratios indicate that the 2 groups began to diverge 1 year after randomization and that the differences continued through 5 years of follow-up (Figure 2). Twenty-eight participants in the estrogen plus progestin group and 13 in the placebo group were diagnosed with probable de-

mentia after the 3MSE cut point for referral to further cognitive screening was changed. These data support the improved sensitivity in identifying probable dementia cases achieved by implementing the revised cut points on the 3MSE. After excluding 265 participants at higher risk for developing dementia at baseline (ie, participants with 3MSE scores at or below the screening cut point), the HR for probable dementia was 2.64 (95% CI, 1.26-5.53), with 24 and 10 cases in the estrogen plus progestin and the placebo groups, respectively.

Probable Dementia Types

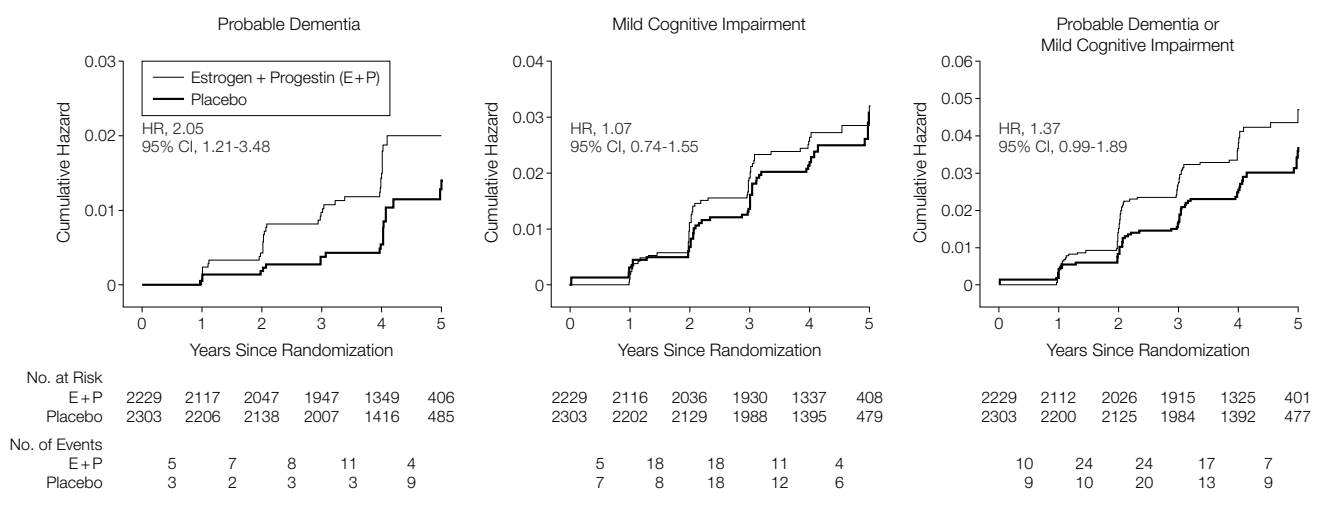
Alzheimer disease was the most common classification in both the estrogen plus progestin (20 [50.0%]) and the placebo (12 [57.1%]) groups ($P=.79$, TABLE 3). Seventy-five participants had a stroke during follow-up (39 in the estrogen plus progestin group and 36 in the placebo group), but only 1 participant diagnosed with probable dementia (who was in the estrogen plus progestin group) had a stroke during the trial before her diagnosis. Two other participants diagnosed with probable dementia in the estrogen plus progestin group had a history of stroke.

Table 2. Cases of Probable Dementia and Mild Cognitive Impairment: Frequencies and Rates for 10 000 Person-Years

Outcome	Estrogen + Progestin (n = 2229)	Placebo (n = 2303)	HR (95% CI)
Probable dementia, No.	40	21	
Follow-up, mean (SD), y	4.01 (1.21)	4.06 (1.18)	
Rate per 10 000 person-years	45	22	2.05 (1.21-3.48)
Mild cognitive impairment, No.	56	55	
Follow-up, mean (SD), y	3.99 (1.23)	4.04 (1.20)	
Rate per 10 000 person-years	63	59	1.07 (0.74-1.55)
Probable dementia or mild cognitive impairment, No.	85	66	
Follow-up, mean (SD), y	3.97 (1.24)	4.03 (1.21)	
Rate per 10 000 person-years	95	71	1.37 (0.99-1.89)

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

Figure 2. Cumulative Hazards Ratios for a Diagnosis of Probable Dementia and Mild Cognitive Impairment



CI indicates confidence interval; HR, hazard ratio. Data shown only through 5 years of follow-up because numbers at risk are too small after this point for precise estimates.

Diagnoses from local clinicians were compared with those from central adjudicators to determine the rate of agreement (TABLE 4). In the estrogen plus progestin group, 80% of the diagnoses made by local clinicians agreed with the diagnoses of those made by the central adjudicators, as did 76% in the placebo group ($\kappa=0.66$, 95% CI, 0.59-0.74). Of the 82 clinician diagnoses of no dementia in the estrogen plus progestin group, 78 were adjudicated as no dementia and 4 as MCI. In the placebo group, 56 of the 61 clinician diagnoses of no dementia were adjudicated as no dementia and 5 as MCI. Most disagreements resulted in a less serious classification by the central adjudicators. Sixty-six cases were diagnosed with probable dementia by local clinicians, 42 in the estrogen plus progestin group, and 24 in the placebo group, yielding an HR of 1.88 (95% CI, 1.14-3.10; $P=.01$).

At some point during the trial, 2534 participants were nonadherent. When nonadherent participants were censored 6 months after first becoming nonadherent, the number of probable dementia cases that occurred before censoring was reduced to 21 in the estrogen plus progestin group and to 6 in the placebo group. The risk of being diagnosed with probable dementia was 3.22 times greater in the estrogen plus progestin group (95% CI, 1.25-8.29; $P=.02$) (data not shown in tables).

The percentage of participants using statins in the estrogen plus progestin and placebo groups was 12.0% and 9.8%, respectively, at baseline ($P=.02$) (Table 1); 13.4% and 14.1% at year 1 ($P=.49$); 16.6% and 19.7% at year 3 ($P=.01$) and 24.3% and 23.1% at year 6 ($P=.85$) (data not shown in tables). After censoring at the time participants started using statins during the trial, the estrogen plus progestin group had 33 cases and the placebo group had 18 cases of probable dementia. The risk of being diagnosed with probable dementia among participants not starting statins was 1.93 times greater in the estrogen plus progestin group (95% CI, 1.09-3.43; $P=.03$) (data not shown in tables).

Mild Cognitive Impairment

In the estrogen plus progestin group, 45 participants were diagnosed with MCI who did not proceed to probable dementia during trial follow-up, 11 with MCI followed by probable dementia, and 29 with probable dementia not preceded by an MCI diagnosis, compared with 45, 10, and 11, respectively, in the placebo group. The risk of being diagnosed with MCI was not statistically different between the women in the estrogen plus progestin group and those in the placebo group (HR, 1.07; 95% CI, 0.74-1.55; 63 vs 59 cases per 10000 person-years; $P=.72$) (Table 2, Figure 2). The risk of being diagnosed with MCI or probable dementia was increased by 37% for women taking estrogen plus progestin compared with placebo (HR, 1.37; 95% CI, 0.99-1.89; 95 vs 71 cases per 10000 person-years, $P=.06$) (Table 2 and Figure 2). Figure 2 shows that these rates began to separate in the first year.

Dementia Risk by Subgroup

TABLE 5 shows the rates per 10000 person-years of probable dementia diagnoses for the 10 subgroups defined at baseline by dementia-related variables and treatment assignment. No interaction between treatment assignment and these factors reached statistical significance ($P>.05$ for all). In separate models including the main effects of treatment and a factor, the HR for treatment remained similar to the unadjusted ratio (range, 1.95-2.14) (data not shown).

Effects of Age and Baseline 3MSE Scores

In their respective models, main effects for age and baseline 3MSE scores alone were statistically significant ($P<.001$ for both). Specifically, the risk of developing probable dementia was 3.54 times (95% CI, 1.57-8.00) greater for women aged 70 to 74 years, and 12.22 times (95% CI, 5.60-26.65) greater for women

Table 3. Classification of Probable Dementia Cases by Treatment Assignment

Dementia Type	No. (%) of Cases	
	Estrogen + Progestin (n = 40)	Placebo (n = 21)
Vascular dementia	5 (12.5)	1 (4.8)
Alzheimer disease	20 (50.0)	12 (57.1)
Other dementia types		
Mixed type	5 (12.5)	3 (14.3)
Normal pressure hydrocephalus	2 (5.0)	0
Parkinson	0	1 (4.8)
Frontal lobe type	2 (5.0)	0
Alcohol related	1 (2.5)	0
Other dementia	3 (7.5)	2 (9.5)
Etiology unknown	2 (5.0)	2 (9.5)

Table 4. Comparison of Diagnosis Between Central Adjudicators and Local Clinicians by Treatment Assignment

	No. (%) of Cases	
	Estrogen + Progestin (n = 152)	Placebo (n = 127)
In agreement	121 (80)	97 (76)*
In disagreement	31 (20)	30 (24)
Disagreement resulted in more serious classification	8 (26)	6 (20)
From no dementia to MCI	4	5
From MCI to probable dementia	4	1
Disagreement resulted in less serious classification	23 (74)	24 (80)
From probable dementia to MCI	9	8
From MCI to no dementia	14	16

Abbreviation: MCI, mild cognitive impairment.
* $\kappa = 0.66$; 95% confidence interval, 0.59-0.74.

aged 75 to 80 years than for women aged 65 to 69 years. The risk of developing probable dementia was 3.78 times (95% CI, 1.91-7.50) greater for women with baseline 3MSE scores ranging from above the screening cut point to 94, and 24.84 times (95% CI, 13.19-46.75) greater for women with baseline 3MSE scores at or below the screening cut point, than for women with baseline 3MSE scores ranging from 95 to 100.

COMMENT

To our knowledge, the WHIMS is the largest among randomized clinical trials

assessing the effects of estrogen plus progestin on dementia and MCI, and it provides the most detailed characterization of a cohort at baseline and follow-up, the longest follow-up time, an extensive and well-documented battery of cognitive assessments, and rigorous quality control in ascertainment of events. Of the 4532 participants in the estrogen plus progestin component of the WHIMS trial, 61 were diagnosed with probable dementia; 40 (66%) in the estrogen plus progestin group compared with 21 (34%) in the placebo group. Overall, the risk of prob-

able dementia for women in the estrogen plus progestin group was twice that of women in the placebo group, and evidence of an increased risk began to appear as early as 1 year after randomization, with differences persisting over 5 years of follow-up. In additional analyses assessing the influence of baseline risks associated with dementia, the higher risk of probable dementia for women in the treatment group remained. Controlling for adherence did not alter the findings. The pattern of results was similar for all-cause probable dementia and for the specific clas-

Table 5. Rate of Diagnosis of Probable Dementia and Hazard Ratios Among Subgroups of Women Defined at Baseline, by Treatment Assignments

Subgroup	Estrogen + Progestin		Placebo		HR (95% CI)*	P Value
	No.	Rate per 10 000 person-years	No.	Rate per 10 000 person-years		
Age, y						
65-69	6	14	2	5	3.25 (0.66-16.11)	.60
70-74	12	38	9	26	1.47 (0.62-3.49)	
≥75	22	144	10	65	2.34 (1.11-4.94)	
Education						
<High school	7	128	3	51	2.65 (0.69-10.26)	.98
High school/GED	6	34	4	20	1.80 (0.51-6.38)	
<4 y of college	15	41	7	20	2.02 (0.82-4.96)	
≥4 y of college	12	41	7	22	1.97 (0.77-5.00)	
History of stroke						
No	39	44	20	22	2.08 (1.21-3.57)	.96
Yes	1	122	1	64	2.22 (0.14-35.89)	
History of diabetes						
No	37	44	16	18	2.51 (1.39-4.51)	.14
Yes	3	53	4	70	0.74 (0.17-3.30)	
Prior hormone therapy						
No	35	50	19	26	1.98 (1.13-3.47)	.73
Yes	5	25	2	10	2.69 (0.52-13.85)	
Prior use of estrogen only						
Some	4	32	2	15	2.15 (0.39-11.75)	.95
Never	36	47	19	24	2.04 (1.17-3.56)	
Prior use of estrogen + progestin						
Some	1	11	0	NA	NA	.98
Never	39	49	21	25	2.00 (1.18-3.40)	
Prior use of statins						
No	37	47	19	22	2.16 (1.24-3.76)	.56
Yes	3	29	2	23	1.23 (0.21-7.37)	
Prior use of aspirin						
No	27	42	12	18	2.35 (1.19-4.63)	.55
Yes	13	52	9	33	1.69 (0.72-3.95)	
Total 3MSE score at WHI enrollment						
95-100	11	17	5	8	2.45 (0.85-7.07)	.50
Above screening cutpoint to 94†	13	64	5	24	2.75 (0.98-7.71)	
At or below screening cutpoint	16	306	11	244	1.38 (0.64-2.98)	

Abbreviations: CI, confidence interval; GED, General Educational Development (test); HR, hazard ratio; NA, not applicable; 3MSE, Modified Mini-Mental State Examination; WHI, Women's Health Initiative.

*No interaction between subgroups and treatment assignment reached statistical significance ($P > .05$ for all).

†Screening cutpoint is ≤ 80 for women with ≤ 8 years of formal education and ≤ 88 for women with ≥ 9 years of formal education.

sifications of probable dementia (ie, AD, vascular dementia, and other etiologies). These results are unexpected and in striking contrast to most of the earlier research on the effects of hormone therapy on AD and dementia.

Most research on hormone therapy and cognition of postmenopausal women evaluates cognitive function, not dementia.³⁵ The less extensive research on the possible role of hormone therapy for the prevention of dementia is primarily observational and focuses on AD as opposed to all-cause dementia. These studies vary substantially in terms of the participants' characteristics and the study design (eg, sample size, years of follow-up), as well as in the use of cognitive tests or test batteries for determination of dementia status.³⁰ In a meta-analysis of 14 epidemiologic studies assessing the risk of AD, the overall odds ratio associated with estrogen use was 0.56.³⁰ Early and less rigorous epidemiologic studies showed no "protective" effects of estrogen, unlike the later and larger investigations. It is probable that a greater proportion of women used estrogen alone in the earlier studies. However, for the most part, investigators did not distinguish between estrogen alone vs estrogen plus progestin, and when these distinctions were made, benefits regarding prevention of AD were found for both treatments. In contrast, in one observational study, investigators noted a slight improvement in cognitive function for those women taking estrogen alone, but a decline among those women taking estrogen plus progestin therapy.⁵²

In the estrogen plus progestin component of the WHIMS, cases of probable dementia appeared in the first year of intervention in both the active hormone and the placebo groups (Figure 2). This observation suggests that some participants already had cognitive decline at baseline. Thus, rather than slowing progression of the symptoms associated with probable dementia, estrogen plus progestin increased progression to probable dementia. An alternative possibility is that the distribution of pre-existing cognitive decline favored the placebo group. However,

this is unlikely because when low baseline 3MSE scores were deleted from the analyses, an increased risk for probable dementia in the estrogen plus progestin group remained (HR for probable dementia, 2.64).

The short interval required to see an effect of estrogen plus progestin on dementia may have implications for understanding the pathogenesis of dementia related to hormonal therapy. One hypothesis relates to the increased risk of stroke seen in the results of the WHI estrogen plus progestin trial. Although the risk of probable dementia was increased even in WHIMS participants without previous or incident strokes, we cannot determine from these data whether small, undetected cerebrovascular events were more likely to occur in the estrogen plus progestin participants or whether such events could have increased risk for probable dementia. Recent studies suggest an overlap in pathophysiological mechanisms and clinical symptoms between AD and vascular dementia. As noted by Kalaria et al,⁵³ standard clinical diagnostic methods tend to favor a designation of AD over vascular dementia when both may be present. Jellinger et al⁵⁴ suggested that in ischemic vascular dementia, cognitive decline is often associated with small widespread lesions (microinfarcts or lacunae) that may both interact with early AD and promote Parkinson disease. Furthermore, early AD and microinfarcts may interact in promoting probable dementia.⁵⁴ Silent brain infarcts more than doubled the risk of dementia in 1015 participants (52% women) in the Rotterdam Scan Study.⁵⁵ Autopsy data from the Nun Study⁵⁶ support this hypothesis. In addition, in the Cardiovascular Health Study (N=3608), magnetic resonance imaging brain scans, apolipoprotein E4 levels, and measures of cognitive function were all strong predictors of AD and dementia.⁵⁷

Few observational studies have distinguished between the effects of estrogen alone and estrogen plus progestin on dementia. Basic science studies have produced many insights regard-

ing possibly beneficial roles of unopposed estrogens in brain function. Although some studies suggest the effects of unopposed estrogen may be transitory or even harmful,^{58,59} on balance most studies support the protective effects of estrogen in both in vitro and in vivo studies.⁶⁰⁻⁶⁶ However, far less is understood regarding the effects of progesterone. In the few studies that do exist—in cell culture systems,⁶⁷ rat models,⁶⁸ and cynomolgus monkeys⁶⁹—the combination of estrogen plus progesterone appears to reverse the positive effects of estrogen alone.

The risks for probable dementia associated with estrogen plus progestin continued throughout the study, suggesting that mechanisms that require longer-term exposure may also be in place. The manifold effects of exogenous and endogenous hormones on brain function deserve greater scrutiny in unraveling possible pathogenetic mechanisms, including identifying individuals at high risk of hormone therapy-related consequences.

Studies support a prospective association between diabetes and cognitive decline and dementia,⁷⁰⁻⁷² although findings are complex and data on this relationship in women are limited (see Coker and Shumaker⁷³ for a recent review). In the current analyses, history of diabetes was self-reported. Few cases of prior diabetes were reported and no relationship was identified between diabetes and dementia. Similarly, there is a growing body of literature on the potential protective effects of statins on cognitive decline and dementia.⁷⁴⁻⁷⁶ Controlling for prior statin use and censoring for onset of statin use after randomization did not alter the effects found in the current study. Data were not available on family history of dementia or apolipoprotein E4 levels for the WHIMS participants. Thus, we were unable to test for a possible interaction between these factors and hormone treatment for dementia.

Despite the significant negative effect of estrogen plus progestin on risk for developing probable dementia, our findings need to be kept in perspec-

tive. Although participants assigned to active therapy were at twice the risk for dementia, the absolute risk is relatively small. That is, for every 10 000 postmenopausal women aged 65 years or older with risk factor profiles similar to those of WHIMS participants who took estrogen plus progestin for 1 year, 45 would be diagnosed with probable dementia vs 22 women taking placebo. This increased risk would result in an additional 23 cases of dementia per 10 000 women per year. The total number of cases of dementia was small in the WHIMS (n=61). This is in keeping with both the age of the cohort and the expectation that healthier, cognitively and behaviorally competent women were more likely to have enrolled in this complex and rigorously conducted clinical trial. This effect of enrolling healthy participants on clinical trial results has been previously reported, at least in epidemiologic research.⁷⁷

The WHIMS results are specific to the use of conjugated equine estrogen plus medroxyprogesterone acetate, and may not apply to other estrogen/progestin combinations, doses, or routes of administration. However, no current evidence is available showing that other estrogen plus progestin therapies would lead to substantially different outcomes. The WHIMS estrogen plus progestin trial was restricted to women aged 65 years or older. Some investigators have suggested that for hormone therapy to prevent probable dementia, women must initiate its use around the menopause.⁷⁸⁻⁸⁰ This alternative hypothesis cannot be tested in the WHIMS. However, within the age distribution included in the WHIMS, probable dementia occurred at all ages and almost 50% of the study participants were 65 to 70 years of age at study onset.

Petersen et al⁸¹ have stated that MCI as defined by memory impairments (or what some now term the "amnesic" form of MCI) often represents very early AD. However, the belief that persons with isolated cognitive impairments in domains other than episodic memory are at the same risk for a later diagnosis of AD or another form of dementia

is more controversial.⁸² Because consensus has not been achieved on these competing points of view, we chose to analyze the MCI outcomes alone and combined with probable dementia. When viewed independently from probable dementia, the study groups showed no statistical differences in the risk of developing MCI. The risk of developing either MCI or probable dementia increases by 37% for women taking estrogen plus progestin compared with women in the placebo group ($P=.06$). One possible explanation for the lack of an effect of estrogen plus progestin on MCI alone may relate to the greater variability in cognitive status and greater heterogeneity in possible underlying diseases among the participants with MCI as opposed to the participants with probable dementia. Both of these factors limit the predictive power of MCI as well as its use as a classification in clinical practice. The ongoing follow-up of the full WHIMS cohort, including those participants identified as having MCI, and future studies in which consensus has been achieved on a more precise MCI designation, may help to clarify this point.

Study drug administration in the WHI estrogen plus progestin trial was stopped on July 8, 2002, after an average exposure to the hormones of 5.6 years³³; however, monitoring of important clinical (including cognitive) outcomes in these women continues in both the WHI and the WHIMS trials. Of particular interest in the WHIMS estrogen plus progestin cohort is the degree to which the negative effects of the hormone treatment have on dementia are sustained over time. The WHI estrogen-alone trial continues, as does the WHIMS estrogen-alone component with its assessments of global cognitive functioning, MCI, and probable dementia. As with the estrogen plus progestin component of the WHIMS, the WHIMS estrogen-alone study is the largest of its kind with the same rigor in design and outcome ascertainment as the WHIMS estrogen plus progestin trial. Given the current findings, the results of the estrogen-alone component assume added significance

because they may elucidate the impact of estrogen alone on the cognitive status of postmenopausal women. Furthermore, that either study component of WHIMS will be repeated in the near future, if ever, is not likely.

The WHIMS results demonstrate that estrogen plus progestin therapy increases older women's risk for probable dementia. Furthermore, estrogen plus progestin does not protect against MCI. Thus, estrogen plus progestin should not be prescribed with the expectation that it will enhance cognitive performance in postmenopausal women. When considered in conjunction with the WHI results reported earlier, the WHIMS estrogen plus progestin data reinforce the conclusion that the risks of estrogen plus progestin outweigh the benefits.

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