HHS Public Access

Author manuscript

J Steroid Biochem Mol Biol. Author manuscript; available in PMC 2015 August 24.

Published in final edited form as:

J Steroid Biochem Mol Biol. 2010 February 28; 118(0): 304–310. doi:10.1016/j.jsbmb.2009.11.007.

Postmenopausal Hormone Therapy and Cognitive Outcomes: the Women's Health Initiative Memory Study (WHIMS)

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Abstract

This review discusses major findings from the Women's Health Initiative Memory Study (WHIMS). WHIMS reported hormone therapy (HT) - conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA) - increased the risk for dementia (HR 1.76 [95% CI, 1.19-2.60]; P=0.005) and global cognitive decline, with a mean decrement relative to placebo of 0.21 points on the Modified Mini Mental State Examination (3MS) (P=0.006) in women age 65 and older.

A subset of WHIMS participants joined the ancillary WHI Study of Cognitive Aging (WHISCA) trials, in which domain-specific cognitive tests and mood were measured annually. Compared with placebo, CEE+MPA had a negative impact on verbal memory over time (p=0.01); and CEE-Alone was associated with lower spatial rotational ability (p=<.01) at the initial assessment, but the difference diminished over time.

The ancillary WHIMS-MRI study measured subclinical cerebrovascular disease to possibly explain the negative cognitive findings reported by WHIMS and the increased clinical stroke in older women reported by the WHI. WHIMS-MRI reported that while CEE+MPA and CEE-Alone were not associated with increased ischemic brain lesion volume relative to placebo; both CEE +MPA and CEE-Alone were associated with lower mean brain volumes in the hippocampus (p=0.05); frontal lobe (p=0.004);and total brain (p=0.07). HT-associated reductions in hippocampal volumes were greatest in women with baseline 3MS scores ≤ 90.

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Keywords

hormone therapy; cognition; brain MRI; cerebrovascular disease

(1) Introduction

In the mid-1990s, when the Women's Health Initiative Memory Study (WHIMS) was conceived, hormone therapy was commonly prescribed for postmenopausal symptoms. Conjugated equine estrogen alone and in combination with medroxyprogesterone acetate, were the most frequently used formulations in the United States between 1982-1992 [1]. These agents were thought by many to benefit women's cognitive function. Women's increased risk of developing dementia was attributed to lower endogenous estrogen levels following the menopause [2-5]. Controlled laboratory studies in women supported the view that memory impairment associated with loss of estrogen after natural or surgical menopause could be reversed to pre-menopausal levels with estrogen replacement therapy [6-10]. Prospective epidemiological studies reported a lower risk for dementia among women taking exogenous postmenopausal hormone therapy [11-18]. These human studies and a substantial basic science literature touting estrogen's neuroprotective effects on neural cells in the laboratory, including promotion of cholinergic activity, stimulation of axonal sprouting and dendritic spine formation, reduction of cerebral ischemia by vasodilatation and modulation in expression of the apolipoprotein E gene, gave added weight to the hypothesis that loss of endogenous estrogen at menopause put women at increased risk for accelerated cognitive declines and dementia [19,20].

On the other hand, a number of prospective observational studies found no protective effect of estrogen on either cognitive functioning [21-23] or dementia [24]. Clinical trials of unopposed estrogen in women with Alzheimer's disease (AD) showed no beneficial effects on cognitive performance [25-27]. Also, meta-analyses described methodological problems in many studies [28,29]. These mixed findings pointed to the need for a large, well-designed, randomized controlled trial on the effects of postmenopausal hormone therapy on cognitive outcomes including dementia.

The Women's Health Initiative Hormone Therapy (HT) trials, initiated in 1992, were focused on whether conjugated equine estrogen with medroxyprogesterone acetate (CEE +MPA) or CEE-Alone would reduce the risk of coronary heart disease, increase the risk of breast cancer and reduce the risk of hip fracture and other fractures. These large clinical trials provided a unique opportunity for cognitive scientists to study the critical questions about the effects of estrogen therapy on cognitive functioning and incident dementia, in the ancillary WHIMS hormone trials. Following is a review of the design and results of the WHI HT trials, WHIMS, and its ancillary studies - the WHI Study of Cognitive Aging (WHISCA) and the WHIMS-MRI Study.

(2) Design of WHI Hormone Therapy Trials

The WHI randomized HT trials were designed to evaluate postmenopausal HT and prevention of disease, with coronary heart disease as the primary outcome and hip fracture,

other fractures, other cardiovascular disease, and endometrial, colorectal, and other cancers as secondary outcomes [30]. A geographically diverse group of approximately 27,000 postmenopausal women aged 50-79 at enrollment were randomized to CEE 0.625mg /day with MPA 2.5 mg/day (16,608) for women with intact utreri or CEE-Alone (10,739) for women with prior hysterectomy versus placebo. Study drug administration for the WHI HT trials was planned for 8.5 years [31,32][W1].

(3) Results from the WHI HT Trial

The WHI HT trials were discontinued earlier than planned due to an unsatisfactory risk benefit ratio (Table 1). The CEE+MPA trial terminated in July, 2002 after a mean of 5.2 years follow-up due to significantly more non-cognitive adverse events associated with HT compared to placebo. Women randomized to CEE+MPA were at increased risk for heart disease, stroke, pulmonary embolism and breast cancer compared to placebo. These risks outweighed the beneficial effects of CEE+MPA on colon cancer and osteoporotic fracture [33]. In 2004, the WHI CEE-Alone trial was terminated early, after mean follow-up of 6.8 years, because the NIH considered the excess risk of stroke in the active hormone group, compared to placebo, to be unacceptable in healthy women in absence of benefit for coronary heart disease, the primary outcome of the WHI HT trials [34].

(4) Design of WHIMS

Ancillary to the WHI HT trials, WHIMS was the first large, long-term study to address the cognitive effects of CEE-based HT among older postmenopausal women. WHIMS consisted of two parallel, randomized, double-blind, clinical trials of CEE+MPA or CEE-Alone compared to placebo. The primary objective was to examine whether postmenopausal HT reduced the risk of all-cause dementia and, secondarily, mild cognitive impairment and global cognitive functioning in healthy women age 65-79 (mean age 69 years at WHIMS baseline). Enrollment began in May, 1996 among eligible WHI HT trial participants; 4,532 (92.6%) consented to participate in the WHIMS CEE+MPA trial and 2,947 (92.1%) consented to participate in the WHIMS CEE-Alone trial. The WHIMS study designs, eligibility criteria, and recruitment procedures have been described previously [35][W2]. Briefly, WHIMS participants underwent screenings of global cognitive functioning with the Modified Mini-Mental State Examination (3MS) [36] at enrollment and annually. Women who scored below an education-adjusted cut point on the 3MS underwent a more comprehensive neuropsychological evaluation with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery [37], an assessment of mood and a neuro-psychiatric examination by a specialist who classified the women into one of three categories—Normal, Mild Cognitive Impairment (MCI) or Probable Dementia (PD). If a classification of PD was made, the participant underwent laboratory tests and non-contrast x-ray computerized tomography or MRI of the brain. Final study classification of Normal, MCI, or PD was adjudicated at the WHIMS Clinical Coordinating Center at the Wake Forest University School of Medicine by a panel of experts that included a two neurologists, a geriatric psychiatrist and a geropsychologist.

(4a) Results of the WHIMS CEE+MPA Trial

Early termination of the WHI CEE+MPA trial in July 2002 ended the treatment phase of the ancillary WHIMS CEE+MPA trial with an average of 4.05 (SD=1.19) years follow-up. Of 4,532 participants, 61 cases of PD were adjudicated of which 40 (66%) had been assigned to active HT and 21 (34%) to placebo. The hazard ratio for PD was 2.05 (95% CI 1.21 – 3.48). The rate of dementia per 10,000 person-years was 45 in the HT group compared to 22 in the placebo group. This increased risk would result in an additional 23 cases of dementia per 10,000 women per year, (P=0.01) (Table 2). Treatment effects on MCI did not differ between groups (HR, 1.07; 95% CI, 0.74 – 1.55) with 63 versus 59 cases per 10,000 person years (P=0.72) [38]. With respect to global cognitive functioning, more women in the CEE +MPA group had a substantial and clinically important decline in 3MS total scores (6.7%) compared with the placebo group (4.8%; P=0.008) [39].

(4b) Results of the WHIMS CEE-Alone Trial

The WHIMS CEE-Alone trial also ended earlier than planned in February 2004 due to early termination of the WHI CEE-Alone parent study, with an average follow-up of 5.21 (SD=1.19) years. Among 2,947 participants, 47 were diagnosed with PD, of whom 28 were assigned to CEE and 19 to placebo (HR, 1.49; 95% CI 0.83 – 2.66). The incidence of PD was 49% higher among women assigned to CEE compared to placebo; with the incidence of dementia 37 versus 25 per 10,000 person years, respectively (P=0.18). This finding suggests an increased risk of 12 additional cases of dementia per 10,000 women per year (Table 2). For incident MCI, 76 women assigned to CEE compared to 58 in the placebo group were adjudicated (HR 1.34;95% CI, 0.95-1.89) [40]. As a measure of global cognitive functioning during follow-up, the mean (SD), 3MS scores were 0.26 (0.13) units lower among women assigned to CEE compared with placebo (P=0.04) [41].

(4c) Results of Pooled CEE+MPA and CEE-Alone Data

When the CEE+MPA and CEE-Alone data were pooled, per the original WHIMS protocol, the overall HR for PD was 1.76 (95% CI, 1.19-2.60, P=0.005) (Table 2) [40]. Pooled HT data also showed a mean (SD) decrement of 0.21 (.08) units on the 3MS score (P=0.006) [41].

(5) Design of the Women's Health Initiative Study of Cognitive Aging (WHISCA)

WHISCA was a two-armed, randomized placebo controlled, clinical trial designed to assess the efficacy of CEE-based postmenopausal HT on age-related changes over time in several domain-specific cognitive functions including verbal and figural memory, working memory, attention, spatial reasoning, speed of mental processing, executive function and motor performance. WHISCA tested whether HT was associated with less decline in memory and other specific cognitive functions over time: women receiving active HT were expected to show less change in memory over time and exhibit a lower incidence of memory impairment compared to placebo. The WHISCA trials also tested whether the addition of MPA to CEE treatment would modify the effect of CEE on cognitive aging, with the expectation that

women receiving CEE-Alone would show greater memory benefits compared with women receiving combined CEE+MPA and that women receiving the combined formulation would show less longitudinal decline on measures of spatial ability then women receiving CEE-Alone [42].[W3]

Funded by the National Institute on Aging, and ancillary to the WHI and the WHIMS HT Trials, WHISCA was conducted at 14 of the 39 WHIMS sites, selected to maximize geographic and racial/ethnic diversity and retention of participants. Of 3,494 eligible WHIMS participants, WHISCA enrolled 2,304 (66%) women age 66 to 84 (mean 73.9, SD 3.8) who were not demented between October, 1999 and June, 2001. Participants had been previously randomized to CEE+ MPA or CEE-Alone versus placebo in the WHI HT trials. Written informed consent was obtained from all participants, and the Institutional Review Board at each clinic site approved the consent form. Annual assessments of cognitive function and affect were conducted for all WHISCA participants and were planned to continue until the original WHI termination date of 2005 [42].

(5a) Results from the WHISCA CEE+MPA Trial

Of 2,089 CEE+MPA trial participants in WHIMS, 1416 (68%) agreed to participate in WHISCA. Compared to the 673 eligible women who did not enroll in WHISCA, those who joined were slightly younger, more highly educated, had higher scores at baseline on the 3MS global cognitive screening test ($P<0.001$), were more likely to be Caucasian ($P<0.001$), hypertensive ($P<0.01$), or to report moderate/severe vasomotor symptoms at WHI baseline ($P<0.05$). The WHISCA CEE+MPA and placebo groups were not significantly different at WHI baseline for demographic and health-related characteristics or for global cognitive function [42]..

The combined estrogen formulation had a negative impact on verbal memory over time compared to placebo ($P= 0.01$), but other cognitive domains were not affected. The negative effect was evident only after long-term hormone therapy. CEE+MPA did not influence global affect or depressive symptom scores [43].

(5b) Results from the WHISCA CEE-Alone Trial

Of 1361 WHIMS CEE-Alone trial participants eligible for WHISCA, 866 (64%) agreed to participate. Compared to women who were eligible but did not join WHISCA, those who joined tended to be younger, better educated, had never smoked ($p=0.003$), or were more likely to have 3MS scores >95 ($p=0.001$). They did not differ significantly with respect to heart disease, hypertension, race/ethnicity, or age at menonpause.

Compared with placebo, treatment with CEE-Alone was associated with lower spatial rotational ability ($p < 0.01$) at initial assessment (after 3 years of treatment), but the difference diminished with continued treatment. CEE-Alone did not significantly influence change in other cognitive functions and affect [44]

(6) Design of the WHIMS MRI Study

WHIMS reported that HT increased the risk for dementia [38,40] and global cognitive decline in women age 65 and older [39,41]. The WHI reported that both CEE+MPA and CEE-Alone were associated with increased risk of clinical stroke [33,34,45] and other adverse vascular events such as increased coronary heart disease and pulmonary embolism [33]. With these findings and those from the literature that silent stroke and white matter disease are more prevalent and predate clinical stroke [46], the question arose: Are hormone therapy's harmful cognitive effects in older women mediated by cerebrovascular disease? The objective of WHIMS MRI was to determine whether clinically silent cerebrovascular disease on cerebral MRI was associated with assignment to HT compared to placebo at WHI enrollment. We hypothesized that women randomized to CEE-based HT would have significantly increased ischemic lesion volumes on brain MRI.

WHIMS-MRI compared neuroradiologic outcomes among women with an average on-trial HT exposure to CEE+MPA of 4.0 years or CEE-Alone of 5.6 years versus placebo. Brain scanning was conducted an average of 8.02 years following randomization to CEE+MPA or 7.97 years to CEE-Alone; and 3.0 years after termination of the CEE+MPA trial or 1.4 years after termination of the CEE-Alone trial.

The primary outcome measure of WHIMS MRI was total ischemic lesion volume on brain MRI, measured in cubic centimeters (ccs) [47][W4]. Secondarily, lesion volumes in the basal ganglia and in the white and gray matter outside the basal ganglia were measured. Standardized imaging and reading protocols were developed by investigators at the central reading and MRI quality assurance center at the University of Pennsylvania.

Ischemic lesion volumes generally corresponded to small vessel ischemic disease (ischemic white matter disease and lacunar infarctions). This process is accepted as a non-necrotic, ischemic effect on myelin that is secondary to the effects of aging, hypertension and other small vessel pathologic processes of the brain [48.49]. Ischemic lesion volumes within the basal ganglia reflect lacunar infarcts [46]. The earliest reports of this vasculopathy were by anecdotal observations which were quickly superseded by semi-quantitative, human observer scoring systems such as those used in the Cardiovascular Health Study (infarct-like lesions) [50] and the Rotterdam Study (white matter lesions) [51]. While these systems are strongly correlated with each other in terms of rank order, their scores are not directly comparable, and these manual systems have limited reproducibility and restricted dynamic ranges [50,52]. The methodology for detecting and quantifying ischemic tissue used in WHIMS MRI reflects the evolution in image processing from manual human observer to automatic, quantitative computerized digital image analytical techniques that are not only correlated with human observers and the semi-quantitative scoring systems, but are very reproducible and offer a greater dynamic range [53,54].

A key secondary outcome for WHIMS MRI was whether regional and total brain volumes differed by WHI treatment assignment [55]. To quantify regional brain volumes, the T1-weighted volumetric scans were first pre-processed according to a standard protocol [56] consisting of alignment to the AC-PC plane, removal of extracranial material, and

segmentation of brain parenchyma into gray matter, white matter, and cerebrospinal fluid. Regional volumetric measurements were obtained with an automated computer-based template warping method based on a digital atlas labeled for brain lobes and individual structures [57].

(6a) Results from WHIMS MRI

Following Institutional Review Board approval, WHIMS-MRI recruitment began in January, 2005 and was completed in April, 2006. Enrollment for this study has been previously reported[58], but briefly, exclusion criteria included the presence of items that would make the MRI procedure hazardous (pacemakers, prohibited medical implants, and foreign bodies); or conditions that were severe enough to preclude MRI. Of the 2,859 active WHIMS participants in the 14 WHIMS-MRI sites at the beginning of the study, 2,345 (82.0%) were contacted about enrollment in WHIMS-MRI, and 1,527 (65.1%) consented. MRI scans were completed on 1,424 participants (61%) and 1,403 met study criteria for central reading. Of 1,403 participants, 883 had previously been enrolled in the CEE+MPA trial (436 active and 447 placebo) and 520 in the CEE-Alone trial (257 active and 263 placebo).

As in other MRI studies that enrolled from existing cohorts, women who were eligible and willing to consent for WHIMS-MRI tended to be younger, healthier, more highly educated, and had higher levels of global cognitive functioning (higher 3MS scores) than other members of the WHIMS cohort [58]. Also, the enrollment rate of WHIMS-MRI aligned with other major MRI studies, and there was no evidence that enrollment was differentially related to on-trial treatment assignment.

In this analysis of older women enrolled in the WHIMS HT trials and WHIMS MRI, who were evenly matched within trials on demographic and clinical characteristics, we found no marked differences within or across trials by treatment assignment (CEE + MPA or CEE-Alone versus placebo) on total ischemic lesion volume – the primary outcome of the WHIMS-MRI study [47]. Table 3 shows that after initial adjustment for clinical site, age at randomization, time from randomization to MRI scan, intracranial volume and risk factors (education, smoking, BMI, prior cardiovascular disease, hypertension, and diabetes), women previously assigned to CEE+MPA therapy had total geometric mean (SE) ischemic lesion volumes of 5.10 (0.21) cc compared to 4.70 (0.20) cc for women previously assigned to placebo (p=0.25). Among women previously assigned to CEE-Alone therapy, geometric total lesion volumes were 5.41 (0.30) cc compared to 5.35 (0.29) cc among women assigned to placebo (p=0.91). Further, we found no differences in ischemic lesion volumes in the basal ganglia or in the white and gray matter outside the basal ganglia. We also examined subgroups of women defined separately by baseline 3MS scores and compliance to study medication; no differential treatment effects were detected.

(6b) Secondary MRI Outcomes: Total and Regional Brain Volumes

Total and regional brain volumes, adjusted for total intracranial volume, served as markers of brain atrophy. Women assigned to CEE-based therapy during the WHI had smaller mean hippocampal, frontal lobe, and total brain volumes compared to those who had been

assigned to placebo [55]. After adjustment for dementia risk factors, age, time since enrollment, intracranial volume, and clinical site, mean (SE) differences on pooled trial data were −0.10 (0.05) cc for the hippocampus (p=0.05); −2.37 (0.81) cc for the frontal lobe (p=0.004); and −3.32 (1.84) cc for total brain volume (p=0.07) (Table 4). The magnitudes of these differences were inversely related to the level of 3MS at enrollment into WHIMS. Women whose baseline 3MS scores were less than 90 had mean (SE) HT-related decrements in adjusted brain volumes of 16.93 (7.71) cc, compared to 7.40 (4.34) cc for women with baseline scores of 90-94 and 01.41 (2.10) cc for women with baseline scores of 95 or greater (p=0.07). No other sub-groupings were associated with differential treatment effects [55].

(7) Summary of WHIMS Studies and Critical Next Steps

WHIMS was the first large, long-term clinical trial to address the effect of CEE-based postmenopausal HT on the incidence of all-cause dementia and global cognitive decline. We hypothesized that CEE with and without MPA would decrease the incidence of dementia and delay the onset of global cognitive decline. Following early termination of the WHI HT trials due to increased adverse non-cognitive events, WHIMS reported that CEE+MPA doubled the incidence of dementia, compared to placebo, and failed to reduce global cognitive decline. In 2004, the WHIMS CEE-Alone trial reported a 49% increase in the incidence of dementia. WHISCA, an ancillary study to WHIMS, aimed at measuring the effects of CEE-based HT on age-related changes over time, reported that CEE+MPA was associated with decrements in verbal memory after several years of treatment. CEE-Alone was associated with lower spatial rotational ability at the initial assessment, but the association diminished with continued treatment. Investigators concluded that CEE does not appear to have enduring effects on rates of domain-specific cognitive change in older postmenopausal women.

WHIMS-MRI, an ancillary study to WHIMS, was conducted to investigate the effects of CEE-based HT on silent cerebrovascular disease as a possible way of explaining the adverse cognitive findings in WHIMS and the adverse vascular events reported by the WHI. There was no difference in total ischemic lesion volume on brain MRI conducted, on average, 8 years following randomization of women to CEE-based therapy or placebo in the WHI. However, WHIMS-MRI did report small but significant decrements in brain volume that were most notable in women with lower scores on the 3MS at WHIMS baseline.

It should be noted that the WHIMS and WHISCA trials and the WHIMS MRI study were restricted to women who were were 65 years or older at enrollment. Thus, findings in these women, in whom menopause occurred years earlier, cannot be generalized to younger menopausal or perimenopausal women who are considering CEE-based hormone therapy for relief of menopausal symptoms.

Ancillary to the WHI HT trials, the WHIMS and WHISCA trials have provided important data with respect to the effect of postmenopausal therapy. CEE-based hormone therapy has been shown to be of no benefit for prevention or delay of dementia, mild cognitive impairment, global cognitive decline, or age-related declines in memory and other domain-

specific cognitive functions in women age 65 years and older. To the contrary, CEE-based postmenopausal therapy was associated with adverse effects on cognition that persist for years following randomized therapy. Further, the WHIMS's results indicate that women with the lowest scores on the 3MS at WHI baseline may be most vulnerable to the adverse effects of CEE-based therapy. At 8 years post-randomization to CEE-based HT in WHIMS, women with the lowest baseline 3MS scores showed the greatest HT-related reduction in hippocampal volumes. These findings suggest that the effect of CEE-based postmenopausal hormone therapy on the brain may be complex, requiring longitudinal brain MRI study for clarity.

Acknowledgment

The National Heart, Lung, and Blood Institute of the National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, Maryland, USA, funded the Women's Health Initiative and the Women's Health Initiative Memory Study, and the WHIMS MRI Study. Wyeth Pharmaceuticals, Inc., St. Davids, Pennsylvania, USA co-funded the Women's Health Initiative Memory Study and provided the active and placebo hormone therapy formulations. Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA, co-funded the Women's Health Initiative Memory Study. The Women's Health Initiative Study of Cognitive Aging was funded by the Department of Health and Human Services and the National Institute on Aging, National Institutes of Health, Bethesda, Maryland. Dr. Resnick is supported by the Intramural Research Program, National Institute on Aging, National Institutes of Health. Lists of participating centers and investigator groups appear in articles cited.

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Table 1

Clinical events, hazard ratios and nominal 95% confidence intervals associated with assignment to CEE-based hormone therapy compared to placebo reported by the Women's Health Initiative.

Clinical Event	CEE+MPA trial HR [95% CI]	CEE - Alone Trial HR [95% CI]
Stroke	1.41 [1.07-1.85]*	1.39 [1.10-1.77]*
Coronary Heart Disease	1.29 [1.07-1.85]*	0.91 [0.75-1.12]
Pulmonary Embolism	2.13 [1.39-3.25]*	1.34 [0.87-2.06]
Breast Cancer	1.25 [1.00-1.59]*	0.77 [0.59-1.01]
Death	0.98 [0.82-1.18]	1.08 [0.88-1.32]
Colorectal Cancer	0.63 [0.43-0.92]*	1.08 [0.75-1.55
Hip Fracture	0.66 [0.45-0.98]*	0.61 [0.41-0.91]*

* 95% Confidence interval excludes 1.0

Table 2

WHIMS CEE+MPA and CEE-Alone Trials: Incidence of Probable Dementia, by Treatment Assignment

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

Abbreviations: CI, confidence interval; HR, hazard ratio

Table 3

WHIMS MRI: Geometric mean (SE) ischemic brain lesion volumes (cc) by treatment assignment*

	WHIMS-MRI E+P Trial		WHIMS-MRI E-Alone Trial		p-values		
Variable	CEE+MPA N=436	Placebo N=447	CEE-Alone N=257	Placebo N=263	CEE+MPA vs Placebo	CEE-Alone vs Placebo	HT vs No HT
White and gray matter (outside of basal ganglia)	4.57 (0.19)	4.18 (0.17)	4.84 (0.26)	4.77 (0.26)	0.21	0.87	0.27
Basal ganglia	0.65 (0.01)	0.65 (0.01)	0.68 (0.02)	0.71 (0.02)	0.89	0.66	0.88
Total brain lesion volume	5.10 (0.21)	4.70 (0.20)	5.41 (0.30)	5.35 (0.29)	0.25	0.91	0.32

*After adjustment for trial, clinical sites, age, time from randomization to MR scan, intracranial volume, education, smoking, body mass index, prior cardiovascular disease, hypertension, and diabetes

Table 4

WHIMS MRI: Mean (SE) volumes by treatment assignment after adjustment for age, time since enrollment, intracranial volume, clinic site, prior HT, 3MS scores, and risk factors*

	Total Brain Volume Mean (SE)	Ventricle Volume Mean (SE)	Hippocampal Volume Mean (SE)	Frontal Lobe Volume Mean (SE)
Pooled trials				
HT	798.37 (1.30)	37.62 (0.55)	5.69 (0.04)	282.72 (0.57)
Placebo	801.69 (1.29)	37.15 (0.55)	5.79 (0.04)	285.09 (0.57)
Difference	−3.32 (1.84)	0.47 (0.78)	−0.10 (0.05)	−2.37 (0.81)
p-value	0.07	0.55	0.05	0.004
E+P Trial				
CEE+MPA	800.92 (1.63)	37.84 (0.68)	5.72 (0.04)	283.61 (0.72)
Placebo	803.11 (1.63)	36.53 (0.68)	5.83 (0.04)	285.46 (0.72)
Difference	−2.19 (2.32)	1.31 (0.97)	−0.11 (0.06)	−1.85 (1.03)
p-value	0.35	0.18	0.09	0.07
E-Alone Trial				
CEE-Alone	794.53 (2.21)	37.53 (0.95)	5.63 (0.06)	281.47 (0.95)
Placebo	799.03 (2.16)	37.85 (0.94)	5.75 (0.06)	284.25 (0.94)
Difference	−4.50 (3.13)	−0.33 (1.36)	−0.12 (0.09)	−2.78 (1.36)
p-value	0.15	0.81	0.18	0.04

*Education, ethnicity, smoking, body mass index, prior cardiovascular disease, hypertension, and diabetes