

**Section 1
Chapter****Estrogens and cognition: perspectives and opportunities
in the wake of the Women's Health Initiative Memory Study****Women's Health Initiative Memory
Study (WHIMS) program:
emerging findings**

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Editors' introduction

The landmark Women's Health Initiative Memory Study (WHIMS) program has had an enormous impact on our understanding of how estrogens and estrogen-containing hormone therapy affect cognitive outcomes in postmenopausal women. It is the starting point and touchstone for any discussion on cognition and dementia in women. As reviewed in this chapter by principal WHIMS program investigators, the WHIMS comprised two large randomized placebo-controlled trials of conjugated equine estrogens with and without medroxyprogesterone acetate in women aged 65 years and older. In this study, the two hormone therapy formulations were associated with increased risk for probable dementia (hazard ratio 1.77, 95% confidence interval 1.22 to 2.58). They were also associated with a small adverse mean difference of 0.21 (0.06 to 0.37) points on the 100-point Modified Mini-Mental State examination. Adverse findings were similar for both hormone therapy formulations and for women with and without histories of prior hormone therapy use. The Women's Health Initiative Study of Cognitive Aging and the Women's Health Initiative Magnetic Resonance Imaging Study were conducted on subsets of WHIMS participants. The former found little evidence that conjugated equine estrogens with medroxyprogesterone acetate had a positive effect on cognitive aging. The latter found that the hormone therapy formulations were associated with decreased brain volumes, particularly among women with lower levels of cognitive function at baseline, but mean effects on ischemic lesions were not significant. No subgroups of WHIMS participants have been identified for which initiating hormone therapy appears to convey cognitive benefit.

Women's Health Initiative**Design of the Women's Health Initiative
Hormone Therapy Clinical Trial**

The Women's Health Initiative (WHI) trials of hormone therapy are landmarks in women's health research. These well conceived and well conducted randomized controlled clinical trials addressed whether the most prevalent form of postmenopausal hormone therapy in the USA should be prescribed to prevent cardiovascular disease, the leading cause of death in older women. Observational studies had supported this use in older women, who constituted a growing market share [1]. The WHI selected conjugated equine estrogens (CEE, 0.625 mg/day) as its estrogen therapy, because it had been extensively researched and was the most commonly prescribed postmenopausal estrogen therapy in the United States [2]. For women with a uterus, the WHI selected medroxyprogesterone acetate (MPA, 10 mg/day) to oppose CEE, because of its widespread use in the USA and because of prior research suggesting it conveyed similar cardiovascular risk profiles to other progestins [2, 3].

The stark finding of the WHI, that CEE therapy conveyed no cardiovascular benefits for older women, and indeed increased their overall risk of cardiovascular and cerebrovascular disease, has reverberated dramatically through the medical community and has led to a marked change in health care for women [4]. The findings are still widely studied and debated. While this chapter is focused on the impact of hormone therapy on cognition in older women, we first summarize the primary findings of the WHI on cardiovascular disease.

Section 1: Estrogens and cognition**Table 1.1** Hazard ratios and nominal 95% confidence intervals associated with assignment to hormone therapy reported by the Women's Health Initiative [6, 7].

Clinical event	CEE+MPA trial HR [95% CI]	CEE-alone trial HR [95% CI]
Stroke	1.41 [1.07, 1.85] ^a	1.39 [1.10, 1.77] ^a
Coronary heart disease	1.29 [1.07, 1.85] ^a	0.91 [0.75, 1.12]
Pulmonary embolism	2.13 [1.39, 3.25] ^a	1.34 [0.87, 2.06]
Death	0.98 [0.82, 1.18]	1.08 [0.88, 1.32]

Note: ^a95% Confidence interval excludes 1.0

Major findings of the Women's Health Initiative

The WHI trials of hormone therapy began in 1992 and were designed to continue until 2007 [2]. Following discovery of an unfavorable risk-to-benefit ratio of its non-cognitive endpoints, the CEE+MPA trial was discontinued in July, 2002 [5]. In March, 2004, the CEE-alone trial was also terminated earlier than planned due to an excess risk of stroke and the lack of a significant effect on other cardiovascular disease outcomes [6]. Table 1.1 summarizes the findings from these two trials for outcomes that may be most closely linked to mechanisms affecting cognitive function: stroke, coronary heart disease, pulmonary embolism, and all-cause death. Both trials found an increased risk for stroke associated with hormone therapy of about 40%. For CEE+MPA therapy, there was also an increased risk of coronary heart disease and pulmonary embolism. No significant interactions between treatment effect and age were found in either trial for these outcomes. When data are pooled across trials, a trend is evident for increased risks of these outcomes for women aged 60 and older compared to younger women; however, this finding is not as consistent within the individual trials [4].

The adverse risks for stroke within the CEE+MPA trial have been extensively studied [7]. Approximately 80% of the strokes were classified as ischemic. Increased rates of ischemic strokes accounted for the overall excess risk of stroke associated with CEE+MPA therapy.

Women's Health Initiative Memory Study

Design of the Women's Health Initiative Memory Study

The study design, eligibility criteria, and recruitment procedures of the WHIMS trials were described previously [8]. Participants were recruited from 39 WHI clinical sites; however, one was later dropped from the trial. To be eligible, women were between 65 and 79 years of age and free of dementia as ascertained by the WHIMS protocol (described below). Written informed consent was obtained; the National Institutes of Health and Institutional Review Boards for all participating institutions approved the protocols and consent forms.

Modified Mini-Mental State (3MS) examinations [9] were administered at baseline and annually thereafter by technicians who were trained and certified in their administration and masked to randomization assignment and reports of symptoms. Scores from the 3MS test may range from 0 to 100; a higher score reflects better cognitive functioning. The test includes items measuring temporal and spatial orientation, immediate and delayed recall, executive function, naming, verbal fluency, abstract reasoning, praxis, writing, and visuoconstructional abilities. Administration time averaged 10–12 minutes.

Women who scored below cutpoints based on education level proceeded to a second phase to classify their dementia status. At the start of the WHIMS, these cutpoints were ≤ 76 (for participants with nine or more years of education) and ≤ 72 (for participants with eight or fewer years of education). After 16 months the protocol was altered to increase the sensitivity of the 3MS by using cutpoints of ≤ 80 (for participants with eight or fewer years of education) and ≤ 88 (for participants with nine or more years of education). These second cutpoints were expected to provide a sensitivity of 80% and specificity of 85% based on earlier studies [8].

In the second phase of WHIMS screening, certified technicians administered a modified Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery [10]. This contained tests measuring verbal fluency, naming, verbal learning and memory, constructional praxis, and executive function. Technicians also administered standardized interviews to assess behavioral symptoms of generalized anxiety,

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major depression, and alcohol abuse [11] and the 15-item Geriatric Depression Scale [12]. Both the participant and her designated informant completed standardized interviews to identify acquired cognitive and behavioral deficits. An experienced local board-certified geriatrician, neurologist, or geriatric psychiatrist reviewed all data, completed a structured clinical evaluation, and classified women as having no dementia, mild cognitive impairment, or probable dementia, the latter based on standard DSM-IV criteria [13]. Clinicians were provided with reference scores for each test in the battery [14]. If the clinician suspected probable dementia, the participant was referred for a brain computerized tomography (CT) scan and laboratory blood tests to rule out possible reversible causes of cognitive decline and dementia and to classify subtypes of dementia.

A central expert panel adjudicated all probable dementia cases identified by the local clinicians, a random sample of 50% of mild cognitive impairment cases, and a random sample of 10% of no dementia cases. All information on participant's interviews and testing, except the field clinician's classification, was provided for initial classification by two independent adjudicators. The field clinician's diagnostic assessment was then shared with each adjudicator, who independently made a revised diagnosis. If the adjudicators agreed, this was considered the consensus diagnosis. If there was not agreement, discussions ensued among the entire adjudication committee until a consensus classification was made; however, agreement was generally high [15]. Regardless of their classification, all participants continued to be scheduled for annual 3MS tests.

The WHIMS has begun a Supplemental Case Ascertainment Protocol to identify additional classifications of probable dementia among women who had died or otherwise ceased full follow-up prior to a "determination" of cognitive status. The expectation has been that among these participants were women who would have been classified as having probable dementia had they completed the scheduled assessments. In order to capture these possible cases, the WHIMS, with the approval of the WHI, implemented a standardized telephone survey of proxies and/or family members of these women who provided consent. The survey consists of the Dementia Questionnaire [16], a standardized, validated instrument used to reliably diagnose dementia, and specifically Alzheimer's dementia, in deceased persons. It can be reliably administered

by telephone with good sensitivity and specificity [17], and includes items assessing memory and other cognitive functions, language, daily functioning, insight, and other medical and psychiatric difficulties. Data from these surveys are centrally adjudicated. Additional classifications of probable dementia are beginning to emerge from this protocol; however, these are not included in the results summarized below.

Major findings of the Women's Health Initiative Memory Study

The women who volunteered for and were enrolled in the WHIMS had mean ages of 69 years at enrollment. Approximately 40% of the 7,479 women had prior hysterectomy, and thus were drawn from the WHI CEE-alone trial (N = 2,947). The remainder, N = 4,532, were drawn from the CEE+MPA trial. Overall, about 30% reported use of hormone therapy at some time in the past, which, according to the WHI protocol, had been stopped at least three months prior to enrollment in the WHI. The early terminations of the WHI trials ended the WHIMS CEE + MPA and CEE-alone trials, with average follow-ups of 4.05 (SD = 1.19) and 5.21 (1.19) years, respectively [17].

At the time the primary publications from these trials were completed, central adjudication had yielded 108 cases of probable dementia and 310 cases of any cognitive impairment (i.e., probable dementia and/or mild cognitive impairment) [15, 17]. From these data, the hazard of probable dementia was increased by 76% among women assigned to hormone therapy compared to placebo ($p = 0.005$). The hazard of any cognitive impairment was increased by 41% ($p = 0.003$). The most common types of probable dementia were Alzheimer (52% overall), mixed (16%), and vascular (9%), with a trend towards greater numbers of each among women assigned to active therapy.

Adjudication of cases after the publication of these data has continued: 9 additional probable dementia cases and 17 additional cases of any impairment were identified as occurring during the follow-up periods of the trials. Figures 1.1 and 1.2 describe results of analyses of these completed data. The relative hazard of probable dementia associated with assignment to hormone therapy is now 1.77 [95% confidence interval: 1.22, 2.58]. For any impairment, the relative hazard is 1.36 [1.09, 1.69]. Treatment-related differences

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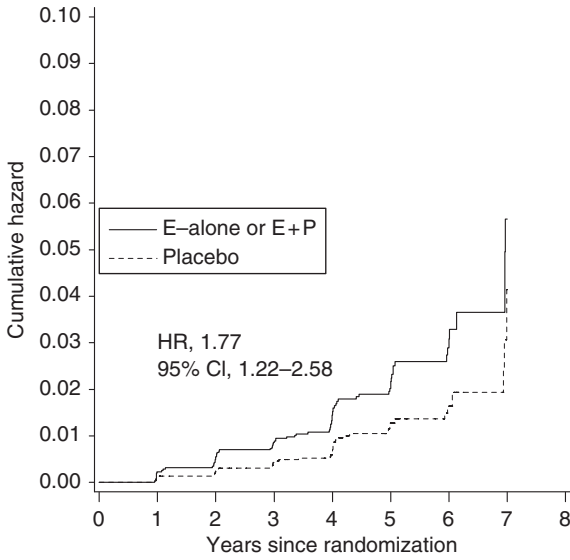


Fig. 1.1 Distribution of times until classification of probable dementia for women grouped by WHI treatment assignment.

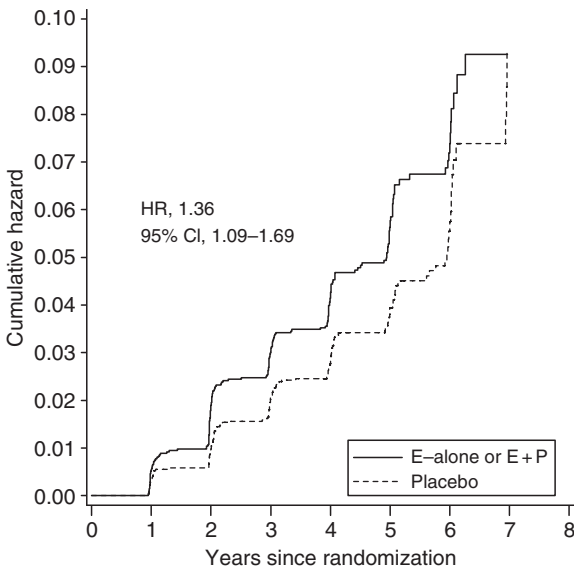


Fig. 1.2 Distribution of times until first classification of any impairment (probable dementia or mild cognitive impairment) for women grouped by WHI treatment assignment.

appear to emerge within the first two years of enrollment and extend throughout follow-up.

The WHIMS also found a small adverse effect of assignment to hormone therapy on global cognitive function, as measured by 3MS examinations [18, 19]. Figure 1.3 portrays, by year from randomization, the

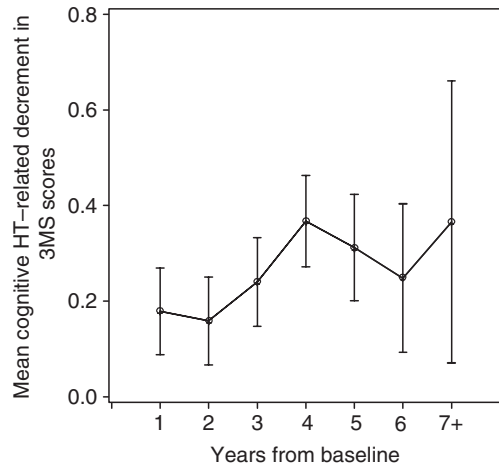


Fig. 1.3 Mean (\pm standard error) decrement in 3MS scores associated with assignment to hormone therapy, with adjustment for baseline 3MS score and age.

mean decrement in 3MS scores experienced by women assigned to hormone therapy relative to those assigned to placebo therapy. Covariate adjustment is made for baseline 3MS and age. Small relative decrements began to emerge within the first two years of therapy and continued throughout follow-up. The figure conveys no evidence that decrements diminish with time, even based on an intention-to-treat analysis in which non-adherence to medications was not factored. The average decrement in 3MS scores over time was 0.21 units ($p = 0.006$) on a scale ranging from 0–100 [19]. Such a deficit would clearly not be clinically detectable for an individual participant.

At the time of publication of the primary results of the trials, the hazard ratios of CEE-alone therapy versus its placebo and CEE+MPA therapy versus its placebo on the risk of probable dementia were 1.49 [0.83, 2.66] and 2.05 [1.21, 3.48], respectively [15, 17]. For any impairment, these were 1.38 [1.01, 1.89] and 1.37 [0.99, 1.89] [15, 17]. For the completed data described in this chapter, the hazard ratios of CEE-alone therapy versus CEE+MPA therapy on the risk of probable dementia were 1.55 [0.91, 2.65] and 2.05 [1.21, 3.47]; for any impairment, these were 1.34 [0.99, 1.80] and 1.39 [1.01, 1.92]. The mean relative deficits in on-trial 3MS scores were 0.26 [0.00, 0.52] and 0.18 [0.00, 0.37] [19]. Thus, the WHIMS found little evidence for a separate effect of MPA therapy when added to CEE therapy.

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The WHIMS has published the results of extensive subgroup analyses to examine the consistency of treatment-related effects on cognition among women grouped according to dementia risk factors and correlates of adherence to medications. These subgroups included age, prior use of hormone therapy, and history of cardiovascular disease. No factors have been found that appear to alter significantly the effect of CEE-based therapy, with or without MPA, on probable dementia or any impairment; however, power for these endpoints was low [17]. More definitive comparisons can be made for 3MS scores. Of the many factors examined, only one appears to identify women who are at greater potential risk for adverse effects [19, 20]. Women who scored relatively lower on the baseline measure of global cognitive function (3MS) on average had greater relative on-trial deficits in cognitive function ($p < 0.001$). The mean decrements in baseline cognitive function associated with hormone therapy were 0.10 [−0.07, 0.21] for women with scores of 95–100 at baseline, 0.38 [0.11, 0.65] for women with baseline scores above the screening cutpoint to 94, and 1.26 [0.75, 1.76] for women who scored at or below the screening cutpoint at baseline [19, 20]. These results suggest that the adverse impact of hormone therapy is most strongly expressed among women with underlying disease. It is important to note, however, that while subgroup differences were not statistically significant and the absolute risk was low, the relative hazard of probable dementia was greatest among women with baseline 3MS scores of 95–100: 2.82 [1.18, 6.70] [17]. Whether this results from the inability of 3MS tests to identify all women with underlying cognitive deficits, or for some other reason, is not known.

No subgroups emerged for which it appeared that hormone therapy had beneficial effects on cognition.

Women's Health Initiative Study of Cognitive Aging

Design of the Women's Health Initiative Study of Cognitive Aging

The Women's Health Initiative Study of Cognitive Aging (WHISCA) was designed to examine the impact of CEE-based therapy on longitudinal changes of cognitive tests targeting several different domains [21]. Participants were recruited from 14 of the 39

WHIMS sites. They were eligible for the WHISCA if they were English speaking, did not have probable dementia as determined by the WHIMS protocol, and provided written informed consent. The WHISCA was initiated after WHI randomization: its enrollees had been assigned to receive WHI treatment for 1.1–5.6 years (mean 3.0) prior to their initial WHISCA cognitive assessment.

The battery of cognitive measures used by WHISCA was designed to assess a broad range of cognitive functions (emphasizing tests that were expected to be sensitive to aging or the effects of hormones) and mood states. Included were assessments of verbal knowledge, phonemic and category fluency, short-term figural memory and visuo-construction, verbal learning and memory, attention and working memory, spatial rotational ability, fine motor speed, positive and negative mood states, and non-somatic features of depressed mood [21]. Test administrators were centrally trained using procedures consistent with those in the Baltimore Longitudinal Study of Aging [22]. Quality control was maintained through recertification of test administrators every six months for the first year and annually thereafter.

Major findings of the Women's Health Initiative Study of Cognitive Aging

The WHISCA enrolled 2,302 WHIMS participants [21]. In general, these women tended to be younger and healthier than the WHIMS women who chose not to enroll in WHISCA; however, there was good balance among treatment arms. To date, only WHISCA data from the CEE+MPA trial have been published [23]. When this trial was terminated in 2002, the 1,426 women enrolled in this trial had averaged 1.35 (SD = 0.61) years of WHISCA follow-up. Overall, none of the differences in this trial reached the protocol-specified criterion for statistical significance ($p < 0.01$). The largest difference between treatment groups was for verbal learning: women assigned to CEE+MPA therapy had slightly worse performance over time compared to women assigned to placebo. The primary conclusion from this analysis is that in these relatively healthy and cognitively intact women, there was little evidence that CEE+MPA therapy positively affected cognitive aging. The strongest signal was for a small adverse effect on changes in verbal learning over time.

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Women's Health Initiative Memory Study of Magnetic Resonance Imaging

Design of the Women's Health Initiative Memory Study of Magnetic Resonance Imaging (WHIMS-MRI)

The WHIMS-MRI was designed to contrast neuro-radiologic outcomes among women who had been assigned to active versus placebo therapy during the WHIMS trials. It was conducted in 14 of the 39 WHIMS clinical sites, which were selected based on interest, experience in conducting multi-center MRI studies, participation in the WHISCA, and availability of necessary equipment. All participants in these centers were to be solicited for potential screening to join WHIMS-MRI, regardless of their prior adherence or cognitive function. Exclusion criteria included the presence of pacemakers, defibrillators, neurostimulators, prohibited medical implants, and foreign bodies that could pose a hazard to the participant during the MRI procedure. Other exclusion criteria included shortness of breath, inability to lie flat, and conditions that could be exacerbated by stress severe enough to preclude an MRI (e.g., anxiety panic disorders, claustrophobia, uncontrolled high blood pressure, and seizure disorders).

The standardized WHIMS-MRI scanning protocol was developed by investigators in its central reading center at the University of Pennsylvania. Included were oblique axial spin density/T2-weighted spin echo images from the vertex to skull base parallel to the anterior commissure–posterior commissure (AC–PC) plane; oblique axial FLAIR T2-weighted spin echo images matching these slice positions; and oblique axial 3D T1-weighted gradient echo images from the vertex to the skull base parallel to the AC–PC plane. The primary outcome measure for the WHIMS-MRI was total ischemic brain lesion volume from central readings. With this methodology, these volumes generally correspond to leukoaraiosis, ischemic white matter disease, and small vessel ischemia [24] and are generated by non-necrotic processes, i.e., ischemic effects on myelin that are secondary to the effects of aging, hypertension, and other small vessel pathologies of the brain [25, 26]. Ischemic lesion volumes within the basal ganglia may reflect lacunar infarcts.

Important secondary outcome measures for WHIMS-MRI were regional brain volumes [27]. To measure these, the T1-weighted volumetric MRI scans were first pre-processed according to a standardized protocol consisting of alignment to the AC–PC plane, removal of extra-cranial 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 [28].

Major findings of the Women's Health Initiative Magnetic Resonance Imaging Study

Enrollment in the WHIMS-MRI began in January, 2005, two-and-a-half years after the termination of the CEE+MPA trial and nearly a year after the completion of the CEE-alone trial. As in prior MRI studies that enrolled participants from existing cohorts, those willing and eligible to participate tended to be younger, healthier, and more cognitively intact than other members of the cohort [29]. Importantly, the enrollment rate of the WHIMS-MRI aligned with other major MRI studies, and there was no evidence that enrollment was differentially related to on-trial treatment assignment. Of the 1,426 women scanned, images on 1,403 (98%) met study quality control criteria for inclusion in primary data analyses. Of these, N = 530 (N = 257 HT; N = 273 placebo) had been enrolled in the CEE-alone trial and N = 883 (N = 436 HT; N = 447 placebo) had been enrolled in the CEE+MPA trial.

The WHIMS-MRI found that the random assignment to active therapy that occurred during the WHI trials did not have statistically significant associations with total ischemic lesion volumes and lesion volumes in the basal ganglia. Overall, women who had been assigned to active therapy during the WHI trials had only slightly (and non-significantly more) total ischemic lesion volume than those who had been assigned to placebo [26]. After adjustment for risk factors, women previously assigned to CEE+MPA therapy had mean (SE) ischemic lesion volumes of 5.10 (0.21) ml compared to 4.70 (0.20) ml for women previously assigned to its placebo (p = 0.25). Within

the basal ganglia, these lesion volumes were 0.90 (1.19) ml versus 0.87 (1.08) ml respectively ($p = 0.92$). Among women previously assigned to CEE-alone therapy, mean ischemic lesion volumes were 5.41 (0.30) ml compared to 5.35 (0.29) ml among women previously assigned its placebo ($p = 0.91$). Within the basal ganglia, these lesion volumes were 0.91 (1.19) ml and 0.93 (1.23) ml respectively ($p = 0.90$). The hypothesis that the adverse effects of CEE-based therapy on cognition were primarily conveyed through increased lesion load and subclinical stroke is thus not supported by the WHIMS-MRI data. The slightly larger mean lesion volumes among women that had been assigned to CEE-based therapy were small and not statistically significant, despite the significantly increased incidence of ischemic strokes reported by the WHI [7].

The secondary outcomes of total and regional brain volumes, when adjusted for total intracranial volume, served as markers of brain atrophy. Women who had been assigned to CEE-based therapy during the WHI had smaller mean total, hippocampal, and frontal lobe brain volumes compared to those who had been assigned to placebo [27]. After adjustment for dementia risk factors, mean (SE) differences were 3.32 (1.84) ml for total brain ($p = 0.07$), 0.10 (0.05) ml for the hippocampus ($p = 0.05$), and 2.37 (0.004) ml for the frontal lobe ($p = 0.004$). When women were grouped according to their level of total ischemic lesion volume at the time of the MRI, no significant differences were found in the regional brain volumes between treatment groups among women in the lower quartile of lesion volumes (i.e., < 2 ml). However, differences were accentuated by about 40% among the three-quarters of women with ischemic lesion volumes ≥ 2 : 4.67 (2.20) ml for total brain volume ($p = 0.03$), 0.16 (0.06) ml for hippocampal volume ($p = 0.005$), and 3.01 (0.98) ml for frontal lobe volume ($p = 0.002$).

The magnitudes of these differences were inversely related to the level of 3MS at enrollment into the WHIMS. Women whose baseline 3MS scores were less than 90 had mean HT-related decrements in adjusted brain volumes of 20.31 (8.14) ml, compared to 7.09 (4.57) for women with baseline scores of 90–94 and 0.43 (2.23) for women with baseline scores of 95 or greater. No other subgroupings were associated with differential treatment effects [27].

To date, the WHIMS-MRI has found little difference between the adverse effects of CEE-alone and CEE+MPA therapy on MRI outcomes.

Summary and conclusions

Taken together, findings from the WHI, WHIMS, WHISCA, and WHIMS-MRI provide a coherent set of evidence on the impact of CEE-based therapy on cognitive function in women aged 65 years or older. Four major conclusions can be drawn from the collective results, which we discuss in turn.

First, there is consistently no evidence that CEE-based hormone therapy has protective effects on cognition for women aged 65 years or older. Collectively, these studies have assessed cognitively related clinical events (dementia, mild cognitive impairment, and stroke), performance on a range of cognitive assessment tools, and MRI outcomes. For each of these, no overall benefits were found. Furthermore, across a range of clinical subgroups, none has been identified for which there is evidence of a material benefit on cognition. Nearly half the women in the CEE-alone trial and one-fifth the women in the CEE+MPA trial reported use of hormone therapy in the past, which by protocol had been terminated at least three months prior to enrollment. The on-trial resumption of CEE-based therapy was not beneficial to these women's cognitive health, regardless of the duration and timing of prior use [18]; however, the WHIMS program was not designed to assess whether hormone therapy may have some benefits on cognition when administered to women at the time of menopause.

Second, CEE-based therapy appears to be associated, on average, with a small adverse effect on cognition that is sustained over time. Overall, the risks of dementia, mild cognitive impairment, and stroke are significantly increased; there is a mean decrement in global cognitive function; and there is evidence that brain atrophy is accelerated. Less striking, and non-significant, may be decrements in other measures of cognitive function; however, the earlier termination of the WHISCA trial limited the ability to detect these. The WHISCA cohort consisted of women with relatively high levels of education, whose cognitive function may be more resilient in the face of underlying increases in neuropathology [30]. Also less striking and not statistically significant were associations with increased levels of ischemic lesion volumes. The decrements in global cognitive function were evident and unabated throughout the later spans of the WHIMS follow-up. The decrements in brain volumes were evident more than two years after the termination of the WHI assigned therapies.

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The impact of CEE-based hormone therapy on cognition may be most strongly expressed among women with existing cognitive deficits. The only significant subgroup analyses across the range of outcomes has been that 3MS scores and brain volumes are more strongly adversely affected among women with lower cognitive function at baseline. Unfortunately, 3MS testing cannot be used as a means to identify accurately women without underlying cognitive deficits [20, 31], which may be why there remains an elevated risk for probable dementia among the relatively few high-scoring women who converted during follow-up.

Finally, it appears that the mechanism by which CEE-based therapy adversely affects cognition among older women is most likely complex and multifactorial. The WHI has clearly demonstrated that this therapy increases the risk of stroke, particularly ischemic stroke. While the absolute risk of clinical stroke is low, CEE-based therapy appears to increase this risk for women of all ages [7]. A second mechanism is expressed by an increased rate of brain atrophy, which appears to differentially affect women with evidence of existing disease. While the metabolic nature of this process has yet to be identified, it may not be strongly related to ischemic disease.

Observational data on US women can lead to spurious findings of health benefits of hormone therapy due to prescription practices [32, 33]. However, considerable evidence from well controlled basic science research remains that estrogens, and specifically components of CEE-based therapy, may have neuroprotective effects *in vitro* and in animal models [34]. These effects may be related to timing, dose, and duration of treatment [35]. The powerful evidence of the WHIMS program demonstrates that the beneficial effects of estrogens observed in basic science studies do not translate to cognitive benefits among older women, and signals that other overriding adverse consequences are in place to produce harm. Whether these are due to actions related to estradiol [36] or other components within CEE-based therapies [36, 37, 38], or differences among groups with respect to cognitive health and co-morbid conditions at the initiation of hormone therapy, requires further study.

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