Long-Term Effects on Cognitive Function of Postmenopausal Hormone Therapy Prescribed to Women Aged 50 to 55 Years

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**IMPORTANCE** Postmenopausal hormone therapy with conjugated equine estrogens (CEEs) may adversely affect older women’s cognitive function. It is not known whether this extends to younger women.

**OBJECTIVE** To test whether prescribing CEE-based hormone therapy to postmenopausal women aged 50 to 55 years has longer-term effects on cognitive function.

**DESIGN** Trained, masked staff assessed participants with an annual telephone-administered cognitive battery that included measures of global and domain-specific cognitive functions. Cognitive testing was conducted an average of 7.2 years after the trials ended, when women had a mean age of 67.2 years, and repeated 1 year later. Enrollment occurred from 1996 through 1999.

**SETTING** Forty academic research centers.

**PARTICIPANTS** The study population comprised 1326 postmenopausal women, who had begun treatment in 2 randomized placebo-controlled clinical trials of hormone therapy when aged 50 to 55 years.

**INTERVENTION** The clinical trials in which the women had participated had compared 0.625 mg CEE with or without 2.5 mg medroxyprogesterone acetate over a mean of 7.0 years.

**MAIN OUTCOMES AND MEASURES** The primary outcome was global cognitive function. Secondary outcomes were verbal memory, attention, executive function, verbal fluency, and working memory.

**RESULTS** Global cognitive function scores from women who had been assigned to CEE-based therapies were similar to those from women assigned to placebo: mean (95% CI) intervention effect of 0.02 (−0.08 to 0.12) standard deviation units (P = .66). Similarly, no overall differences were found for any individual cognitive domain (all P > .15). Prespecified subgroup analyses found some evidence that CEE-based therapies may have adversely affected verbal fluency among women who had prior hysterectomy or prior use of hormone therapy: mean treatment effects of −0.17 (−0.33 to −0.02) and −0.25 (−0.42 to −0.08), respectively; however, this may be a chance finding.

**CONCLUSIONS AND RELEVANCE** CEE-based therapies produced no overall sustained benefit or risk to cognitive function when administered to postmenopausal women aged 50 to 55 years. We are not able to address whether initiating hormone therapy during menopause and maintaining therapy until any symptoms are passed affects cognitive function, either in the short or longer term.

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The Women’s Health Initiative Memory Study (WHIMS) demonstrated that postmenopausal hormone therapy with conjugated equine estrogens (CEEs), when prescribed to women 65 years and older, produced deficits in global and domain-specific cognitive functioning. On average, these were small; however, deficits persisted for years after cessation of hormone therapy. They occurred in conjunction with decreases in brain volume linked to increased incidence of cognitive impairment.

In contrast, observational and cohort studies and considerable basic science research suggest that there may be a “window of opportunity,” perhaps coincident with the loss of ovarian function during menopause, when hormone therapy may promote or preserve brain health.\(^{6-9}\) Meta-analyses of clinical trials and systematic literature reviews do not find consistent evidence of benefit\(^{10,11}\); however, the window-of-opportunity hypothesis remains of great interest and public health importance because hormone therapy continues to be widely prescribed for managing menopausal symptoms.\(^{12}\)

The Women’s Health Initiative Memory Study of Younger Women (WHIMSY) tested whether prescribing CEE-based hormone therapy to postmenopausal women aged 50 to 55 years has longer-term effects on cognitive function. We present its primary findings.

**Methods**

The Women’s Health Initiative (WHI) included 2 parallel placebo-controlled trials of CEE-based regimens.\(^{13}\) Volunteers were postmenopausal and appropriate candidates to receive these medications. Women currently using hormone therapy were eligible after a 3-month washout period. Enrollment occurred from 1996 through 1999 at 40 academic research centers. Active therapies were 0.625-mg/d CEE in women who had undergone hysterectomy and 0.625-g/d CEE combined with 2.5-mg/d medroxyprogesterone acetate (MPA) in women with a uterus and were compared with matching placebos. The trial among women who had not undergone hysterectomy (CEE-MPA) was terminated in July 2002;\(^{14}\) the trial among women who had undergone hysterectomy (CEE-alone) was terminated in February 2004.\(^{15}\) Administration of study therapies was stopped at these times. Group assignment was revealed, but follow-up continued.

The WHIMSY volunteers had begun screening for WHI enrollment when aged 50 to 54 years (and initiated their assigned WHI treatment when aged 50 to 55 years), were currently followed by the WHI, and had hearing acuity adequate for telephone interviews. All provided written informed consent; protocols were approved by local institutional review boards.

**Cognitive Function**

Tested, masked staff collected cognitive data with telephone-administered assessments that have been shown to be valid.\(^{16}\) The primary outcome was global cognitive function, assessed with the Telephone Interview for Cognitive Status-modified (TICS-m), a 14-question test with scores ranging from 0 to 50.\(^{17}\) Its selection paralleled use of global cognitive function as the primary cognitive outcome in WHIMS.\(^{18}\) Secondary outcomes included the following:

- Immediate and delayed verbal memory, assessed with the 12-point East Boston Memory Test;\(^{19}\)
- Attention and executive function, assessed with the Oral Trail Making Test, a modification of the Trail Making Test,\(^{20}\) a validated measure of attention (Part A) and executive function (Part B),\(^{21}\) scored as time in seconds;
- Verbal fluency, assessed with the Verbal Fluency–Animals test, scored as the number of unique spontaneously named animals in 1 minute;\(^{22}\) and
- Working memory, assessed with the Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised, which measures attention and working memory with the longest correct span length recalled for digits forward and backward.\(^{23}\)

**Covariates and Potential Confounders**

The WHI had collected baseline demographic, lifestyle, and clinical data related to the risk of cognitive impairment via self-report and standardized assessments.\(^{13}\) Adherence was computed as the mean proportion of assigned study medication use, based on pill counts. Years of on-trial exposure were computed by summing each woman’s adherence rates across years of trial follow-up.

**Statistical Methods**

Cognitive measures from 2 annual assessments were analyzed as repeated data to estimate women’s average level of cognitive function. General linear models with covariate adjustment were used to assess mean differences between intervention groups,\(^{24}\) as prespecified in the protocol. Results from generalized estimating equations were similar and are not reported. To facilitate comparisons among tests, measures were normalized by dividing the difference between individual scores and the cohort-wide mean by the scores’ standard deviation (SD) and ordered so that higher values reflected better performance. A composite measure was computed by averaging normalized scores across tests. Prespecified subgroup analyses were performed using tests of interactions. Primary analyses followed intention-to-treat, with women grouped according to treatment assignment.

**Results**

A total of 1326 women enrolled in WHIMSY (of 1372 potentially eligible women who agreed to be contacted). They had a mean (range) duration of follow-up of 7.0 (3.9-10.1) years during the WHI trials, which ended 7.2 (5.4-10.1) years prior to WHIMSY enrollment (Figure). The mean (range) age of participants was 67.2 (62.9-73.5) years at their first assessment. The second assessment was conducted with the participation of 1168 women (88.1%) with mean age of 68.1 years. Times between assessments for treatment groups were similar (\(P = .64\)).

There was reasonable balance in important potential confounders at WHI enrollment between women who had been...
assigned active vs placebo therapy (all \( P > .05 \)) (Table 1). Markers of exposure to therapy, based on average pill counts and the sum of pill counts across trial follow-up, were also similar between arms (\( P > .20 \)).

Table 2 presents mean cognitive function scores averaged over time, with adjustment for age and visit year. For TICS-m, there was essentially no difference in the mean scores between women who had been assigned to active vs placebo therapy (\( P = .66 \)). This finding was consistent for both CEE+MPA and CEE-alone therapies (\( P = .23 \)). Similarly, there were no overall treatment differences for any other measure of cognitive function, including the composite score. This held for CEE+MPA and CEE-alone therapies and for all cognitive measures, except verbal fluency. Assignment to CEE-alone therapy was associated with 0.17 SD worse mean scores on verbal fluency with a 95% confidence interval that excluded zero (\(-0.32 \text{ to } -0.02\)); CEE+MPA was associated with 0.07 SD better mean scores on this test; however, its confidence interval included zero (\(-0.06 \text{ to } 0.19\)). Covariate adjustment for the risk factors for cognitive impairment in Table 1 did not materially alter findings (data not shown).

Adherence and overall exposure were weakly correlated with higher executive function scores (partial \( r = 0.06, P = .003; r = 0.05, P = .02 \)) but had little correlation with scores from any other domains or the composite score. Adherence and overall exposure were not related to the size of the treatment effect for any measure of cognitive function, based on tests of interaction (all \( P > .30 \)).

The WHIMSY protocol prespecified 3 subgroup analyses to compare treatment effects: women were grouped by assignment to unopposed or opposed CEE therapy (ie, hysterectomy status), self-reported age at last menstrual period, and prior use of hormone therapy. Table 2 describes the subgroup analyses related to the type of CEE regimen; Table 3 summarizes the other 2 analyses. There was little evidence of differential effects for any measure of cognitive function, with 1 exception. For verbal fluency, worse treatment-related performance was seen among women reporting prior hormone therapy use that had ceased before WHI enrollment. Prior hormone therapy use was associated with longer time since last menstrual period (\( P < .001 \)): compared with nonusers, these times averaged 2.1 years longer for prior users and 0.2 years longer for current users. Because prior use of hormone therapy more often occurred among women who had undergone hysterectomy, we fitted a model that included treatment interactions with both hysterectomy status and prior use of hormone therapy. Both interactions were independently statistically significant: women reporting prior hormone therapy use (interaction \( P = .01 \)) and those who had undergone hysterectomy (interaction \( P = .03 \)) appeared to have treatment-attributable deficits in verbal fluency that were not apparent, on average, in other women.

Among women assigned to hormone therapy during the WHI, 28 (4.0%) reported use at some time during posttrial follow-up, compared with 24 (3.8%) of those who had been assigned to placebo (\( P = .82 \)). Posttrial use of hormone therapy had no associations with any cognitive function measure (all \( P > .18 \)).

Power projections for WHIMSY were based on the WHIMS Modified Mini–Mental State Exam global cognitive scores.\(^2\) The recruitment goal of 2240 women was projected to provide 91% power to detect a mean difference of 0.5 units in this test across 2 examinations, which corresponds to 0.10 to 0.15 SDs for these test scores as collected at baseline in WHIMS. Ultimately, WHIMSY fell short of this recruitment goal, enrolling 1326 women. Post hoc power projections based on observed data yielded 80% (90%) power to detect a mean difference of 0.15 (0.18) SDs, which translates to 0.65 (0.75) TICS-m units.

### Discussion

In a large heterogeneous cohort of postmenopausal women aged 50 to 55 years, WHIMSY tested whether random assignment to a mean 7-year prescription of CEE therapies produced long-term cognitive benefits or deficits compared with placebo. For the primary outcome of global cognitive function, and for specific cognitive domains and a composite of individual tests, no evidence for overall benefit or harm was found. There was some evidence that assignment to hormone therapy was associated with relatively poorer performance on verbal fluency among prespecified subgroups of prior hysterectomy or prior use of hormone.

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**Table 2**

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Prior use of hormone therapy</td>
<td>Compared with nonusers, these times averaged 2.1 years longer for prior users and 0.2 years longer for current users. Because prior use of hormone therapy more often occurred among women who had undergone hysterectomy, we fitted a model that included treatment interactions with both hysterectomy status and prior use of hormone therapy. Both interactions were independently statistically significant: women reporting prior hormone therapy use (interaction ( P = .01 )) and those who had undergone hysterectomy (interaction ( P = .03 )) appeared to have treatment-attributable deficits in verbal fluency that were not apparent, on average, in other women.</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed CEE therapy vs opposed CEE therapy</td>
<td>There was little evidence of differential effects for any measure of cognitive function, with 1 exception. For verbal fluency, worse treatment-related performance was seen among women reporting prior hormone therapy use that had ceased before WHI enrollment. Prior hormone therapy use was associated with longer time since last menstrual period (( P &lt; .001 )): compared with nonusers, these times averaged 2.1 years longer for prior users and 0.2 years longer for current users. Because prior use of hormone therapy more often occurred among women who had undergone hysterectomy, we fitted a model that included treatment interactions with both hysterectomy status and prior use of hormone therapy. Both interactions were independently statistically significant: women reporting prior hormone therapy use (interaction ( P = .01 )) and those who had undergone hysterectomy (interaction ( P = .03 )) appeared to have treatment-attributable deficits in verbal fluency that were not apparent, on average, in other women.</td>
</tr>
<tr>
<td>Age at last menstrual period</td>
<td>Adherence and overall exposure were weakly correlated with higher executive function scores (partial ( r = 0.06, P = .003; r = 0.05, P = .02 )) but had little correlation with scores from any other domains or the composite score. Adherence and overall exposure were not related to the size of the treatment effect for any measure of cognitive function, based on tests of interaction (all ( P &gt; .30 )).</td>
</tr>
</tbody>
</table>

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**Figure. Consolidated Standards of Reporting Trials Diagram Diagram Describing Women’s Health Initiative Memory Study of Younger Women Enrollment and Retention**

- 2027 Active WHI participants who were aged 50 to 55 years at randomization
- 1372 Active WHI participants who were aged 50 to 55 years at enrollment and agreed to be contacted for recruitment
- 1326 (96.6%) Assessed
- 610 Had been randomly assigned to placebo therapy
- 696 Had been randomly assigned to hormone therapy
- 114 (8.6%) Unable to contact
- 1168 (88.1%) Assessed
- 609 (87.5%) Reassessed 1 year later
- 559 (88.7%) Reassessed 1 year later
- 7.2 Years mean posttrial follow-up
- 7.0 Years mean on-trial follow-up
Table 1. Distribution of Risk Factors for Cognitive Impairment at the Time of Women’s Health Initiative (WHI) Enrollment for WHIMSY Participants Grouped by WHI Treatment Assignment

<table>
<thead>
<tr>
<th>Risk Factor for Cognitive Impairment</th>
<th>WHI Assignment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hormone Therapy (n = 696)</td>
<td>Placebo (n = 630)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>53.0 (1.3)</td>
<td>52.9 (1.3)</td>
<td>.36</td>
</tr>
<tr>
<td>Age at last menstrual period, mean (SD), y</td>
<td>46.1 (6.3)</td>
<td>46.1 (6.2)</td>
<td>.89</td>
</tr>
<tr>
<td>Education, No. (%)</td>
<td></td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>≤High school</td>
<td>112 (16.3)</td>
<td>97 (15.5)</td>
<td></td>
</tr>
<tr>
<td>At least some college</td>
<td>577 (83.7)</td>
<td>530 (84.5)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td>.46</td>
</tr>
<tr>
<td>African American</td>
<td>85 (12.2)</td>
<td>80 (12.7)</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>2 (0.3)</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>9 (1.3)</td>
<td>5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>29 (4.2)</td>
<td>28 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>557 (80.0)</td>
<td>509 (80.8)</td>
<td></td>
</tr>
<tr>
<td>Other/multiple</td>
<td>14 (2.0)</td>
<td>5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td></td>
<td></td>
<td>.37</td>
</tr>
<tr>
<td>Never</td>
<td>337 (48.6)</td>
<td>299 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>263 (37.9)</td>
<td>226 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>94 (13.5)</td>
<td>102 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake, No. (%)</td>
<td></td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>None</td>
<td>159 (22.9)</td>
<td>155 (24.8)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 Drink per day</td>
<td>471 (68.0)</td>
<td>401 (64.1)</td>
<td></td>
</tr>
<tr>
<td>≥1 Drink per day</td>
<td>63 (9.1)</td>
<td>70 (11.2)</td>
<td></td>
</tr>
<tr>
<td>BMI, No. (%)</td>
<td></td>
<td></td>
<td>.62</td>
</tr>
<tr>
<td>&lt;20</td>
<td>16 (2.3)</td>
<td>14 (2.2)</td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>208 (30.0)</td>
<td>170 (27.1)</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>217 (31.3)</td>
<td>192 (30.6)</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>145 (20.9)</td>
<td>137 (21.9)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>107 (15.4)</td>
<td>114 (18.2)</td>
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</tr>
<tr>
<td>Hypertension status, No. (%)</td>
<td></td>
<td></td>
<td>.94</td>
</tr>
<tr>
<td>No</td>
<td>547 (78.6)</td>
<td>497 (78.9)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>146 (21.0)</td>
<td>131 (20.8)</td>
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</tr>
<tr>
<td>Missing</td>
<td>3 (0.4)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Prior cardiovascular disease, No. (%)</td>
<td></td>
<td></td>
<td>.30</td>
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<tr>
<td>No</td>
<td>542 (77.9)</td>
<td>510 (81.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (6.3)</td>
<td>39 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>110 (15.8)</td>
<td>81 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy, No. (%)</td>
<td></td>
<td></td>
<td>.59</td>
</tr>
<tr>
<td>No</td>
<td>432 (62.1)</td>
<td>382 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>264 (37.9)</td>
<td>248 (39.4)</td>
<td></td>
</tr>
<tr>
<td>Age at hysterectomy, y, No. (%)</td>
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<td>.70</td>
</tr>
<tr>
<td>&lt;30</td>
<td>30 (11.4)</td>
<td>35 (14.1)</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>60 (22.8)</td>
<td>55 (22.2)</td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>59 (22.4)</td>
<td>52 (21.0)</td>
<td></td>
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<tr>
<td>40-44</td>
<td>51 (19.4)</td>
<td>57 (23.0)</td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>55 (20.9)</td>
<td>41 (16.5)</td>
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<tr>
<td>50-54</td>
<td>8 (3.0)</td>
<td>8 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Time since last regular menstrual period, mean (SD), y</td>
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<td>.11</td>
</tr>
<tr>
<td>Prior hysterectomy</td>
<td>8.4 (7.5)</td>
<td>9.6 (8.6)</td>
<td></td>
</tr>
<tr>
<td>No prior hysterectomy</td>
<td>3.9 (3.4)</td>
<td>4.0 (2.8)</td>
<td></td>
</tr>
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</table>

(continued)
Comparison With WHIMS

The results of WHIMS\(^a\) showed that prescribing 4 to 5 years of CEE-based therapy to women older than 65 years produced a mean (SE) relative decrement of 0.07 (0.03) SDs in global cognitive function, as assessed with the Modified Mini–Mental State Examination. In the 2304 of its participants who enrolled in the Women’s Health Initiative Study of Cognitive Aging (WHISCA), this on-trial relative deficit was maintained during a mean (SD) of 2.4 (1.1) and 4.0 (1.3) years after the

\[\text{Comparison With WHIMS}\]

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termination of the WHI CEE-alone and CEE+MPA trials, respectively, averaging 0.07 (0.03) SDs during posttrial follow-up. The endurance of this effect on global cognitive function supports the choice of the TICS-m as the primary outcome measure for WHIMS.

The WHISCA data revealed modest decrements in other domains that WHIMS assessed. A test of verbal memory (California Verbal Learning Test25) had a mean (95% CI) decrement of 0.09 (−0.14 to 0.02) on-trial and 0.07 (−0.14 to 0.01) posttrial SDs, neither statistically significant. A test of attention and working memory (Digit Span forward and backward) had mean (95% CI) decrements of 0.06 to 0.08 SDs in cognitive function.1-3 Despite these smaller than on-trial decrements, only reaching nominal significance.

The larger WHIMS and WHISCA trials, which featured more participants and less follow-up, it cannot rule out deficits (or benefits) as small as in WHISCA.

Subgroup Analyses
In general, the absence of differences in cognitive function between women assigned to active vs placebo therapy was consistent between CEE-alone and CEE+MPA regimens and for subgroups based on time since last menstrual period or prior hormone therapy use. The 1 exception was verbal fluency, which seemed to be adversely affected among women assigned to CEE-alone therapy compared with CEE+MPA therapy and among women with prior (but not current) hormone therapy use compared with no prior use. WHISCA also found that posttrial differences between women who had been assigned to active vs placebo therapy in the CEE-alone and CEE+MPA trials were similar for global cognitive function, verbal memory, and attention and working memory. Similar to WHIMS, it also found marginal differences in the posttrial effects of CEE-alone vs CEE+MPA therapy on verbal fluency: women assigned to CEE-alone therapy had mean (SE) scores 0.092 (0.060) SDs worse than those assigned to placebo, whereas women who had been assigned to CEE+MPA therapy had mean (SE) scores 0.039 (0.044) SDs better than those assigned to placebo (interaction P = .08). Although the magnitudes of these possible treatment-related differences in verbal fluency are small, the similarity in the trends across the trials raises the possibility that CEE-alone therapy may be associated with small longer-term adverse effects on verbal fluency. However, this finding could have resulted by chance.

Others have found verbal fluency to be improved,26 unchanged,27,28 or harmed29 by hormone therapy. Higher levels of endogenous estrogens have been associated with greater declines in verbal fluency in older women.30 Because all women receiving CEE-alone therapy had undergone hysterectomy, which may be a risk factor on its own for cognitive impairment,31 it may be that women’s response to hormone therapy depends on whether loss of endogenous estrogens is gradual or precipitous.32

Magnitude of Detectable Intervention Effects
The WHISY trial had sufficient power to rule out mean treatment effects of 0.15 SDs, within its original design specifications, supporting the use of its telephone-based battery. Telephone-based cognitive assessments are becoming more widely used in trials and cohort studies.23

The larger WHIMS and WHISCA trials, which featured more cognitive assessments over time, detected CEE-related mean decrements of 0.06 to 0.08 SDs in cognitive function.10 Although these relatively small mean differences, CEE-based therapy among women at least 65 years of age resulted in a 75% increase in the

Subgroup Analyses
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function—and the composite outcome formed by averaging all test scores had essentially no treatment effects. Second, there was no evidence that differences between intervention groups varied depending on markers of adherence or on-trial exposure. There was, across both arms, a trend for better adherence among women with higher levels of executive function; we interpret this as reflecting an increased ability to adhere to the study protocol rather than a treatment effect.

Limitations
The WHIMSY trial does not address whether initiating hormone therapy during menopause and maintaining therapy until symptoms pass affects cognitive function, either in the short or longer term. All enrollees received no hormone therapy for at least 3 months prior to randomization; their last menstrual period had occurred a mean of 4 (no prior hysterectomy) to 8 (prior hysterectomy) years before WHI enrollment. As volunteers for a clinical trial and posttrial follow-up, these women may not represent more general populations.43-46 Participants had been unmasked to their treatment assignment in the WHI, which could have influenced their willingness to participate in WHIMSY and their performance on cognitive tests; however, good balance was maintained between treatment groups for important risk factors for cognitive dysfunction. Pretreatment levels of cognitive function were not assessed; however, the WHIMSY cohorts were well balanced with respect to pretreatment risk factors for cognitive impairment; covariate adjustment for these did not materially affect estimated treatment effects.

Conclusions
Our findings provide reassurance that CEE-based therapies when administered to women earlier in the menopausal period do not seem to convey long-term adverse consequences for cognitive function. Although we cannot rule out acute benefits or harm, these do not appear to be present to any degree a mean of 7 years after cessation of therapy. One exception may be for minor longer-term disturbances of verbal fluency for women prescribed CEE alone; however, this may be a chance finding.

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