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Long Term Effects of Conjugated Equine Estrogens Therapies on Domain-Specific Cognitive Function: Results from the Women's Health Initiative Study of Cognitive Aging (WHISCA) Extension

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Abstract

Objectives—Conjugated equine estrogen (CEE) therapies when initiated among older women have been shown to produce small decrements in global cognitive function. We are interested whether these persist after cessation and extend to specific cognitive domains.

Design—Randomized controlled clinical trial

Setting—Fourteen clinical centers of the Women's Health Initiative

Participants—2,304 women aged 65-80 years and free of probable dementia at enrollment

Intervention—0.625 mg/day of CEE, with or without medroxyprogesterone acetate (MPA, 10 mg/day), and matching placebos

Measurements—Annual administrations of a battery of cognitive tests during and following the trial

Methods—General linear models were used to compare on-trial and post-trial mean standardized test scores between treatment groups, with adjustment for baseline risk factors for cognitive impairment.

Results—Assignment to CEE-based therapies was associated with small mean relative decrements in global and several domain-specific cognitive functions on-trial, which largely persisted through up to 4 years post-trial. The strongest statistical evidence was for global cognitive function: 0.07 standard deviation decrements both on-trial (p=0.007) and post-trial (p=0.01). Among domain specific scores, the mean relative decrements were slightly smaller, were less significant, and tended to be larger for CEE-alone therapy.

Conclusions—CEE-based therapies, when initiated after age 65 years, produce a small broad-based decrement in cognitive function that persists after their use is stopped. The differences in

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cognitive function however are small and would not be detectable or have clinical significance for

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*Authors can be listed by abbreviations of their names.

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an individual woman. Differences in effects among cognitive domains suggest that more than one mechanism may be involved.

Keywords

Postmenopausal hormone therapy; Cognitive function; Women's health

INTRODUCTION

The Women's Health Initiative Memory Study (WHIMS) randomized clinical trial found that assigning conjugated equine estrogen (CEE) therapy, alone or combined with medroxyprogesterone acetate (MPA), to women aged 65-80 years was associated with slightly worse mean scores in global cognitive function compared to assigning placebo therapy.[1,2] These effects were observed within the first three to four years of the trial follow-up and remained fairly constant several years thereafter. The Women's Health Initiative Study of Cognitive Aging (WHISCA) examined whether these therapies influenced domain-specific cognitive function at initial assessment, an average of 3.0 years after randomization to CEE-based therapies or placebos, and subsequent age-related rates of change in eight cognitive domains over the remaining average 2.6 years of on-trial follow-up.[3] Only small mean differences in cognitive test scores between treatment groups were found at women's initial WHISCA assessments and for the rates that scores changed over subsequent follow-up.[4,5] Together, these findings suggest that if the use of these agents produces an initial decrement in at least some aspects of cognitive function during the first few years, this decrement does not markedly widen or diminish thereafter. Concerns whether this initial on-trial decrement continues after hormone therapy is discontinued arise from a recent report that the volumes of the frontal lobe and hippocampus were smaller among a subset of these women, 1.4-3.0 years after the prescription of WHIMS CEE-based therapies ended.[6]

In this paper, we re-analyze WHISCA data to estimate the average relative decrement in cognitive function test scores associated with CEE-based therapies over the course of the trial. We then examine the degree these relative decrements persist during up to 5 years of post-trial follow-up. Scaling treatment effects in standard deviation units, we compare on-trial and post-trial effect sizes across domains. Finally, we examine whether there are differences between CEE alone therapy and CEE plus progestin therapy on the size and duration of effects.

Methods

The WHIMS[7] began enrolling its 7,145 participants from the parent Women's Health Initiative (WHI) hormone therapy trials[8] May, 1996. These women were between 65-79 years of age at initial screening, were appropriate candidates for postmenopausal hormone therapy, and were free of dementia as assessed with a standard protocol. Women without a uterus were randomly assigned with equal probability to take one daily tablet that contained either 0.625 mg of CEE (Premarin™, Wyeth-Ayerst Philadelphia, PA) or a matching oral placebo in the WHI CEE-Alone trial. In a similar manner, women with a uterus were randomly assigned to take one daily tablet that contained either 0.625 mg of CEE with 2.5 mg medroxyprogesterone acetate (PremPro™, Wyeth-Ayerst Philadelphia, PA) or placebo in the WHI CEE+MPA trial.

The WHISCA enrolled 2,304 participants from 14 of the WHIMS clinical sites beginning in September, 1999. These women had been randomly assigned to WHI treatments an average (standard deviation) of 3.0 (0.7) years prior to enrollment in WHISCA. The National

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Institutes of Health and Institutional Review Boards for all participating institutions approved protocols and consent forms. Informed written consent was obtained from all participants.

The WHI CEE+MPA trial was terminated earlier than planned, in July, 2002, because significantly more non-cognitive adverse events occurred among women assigned to hormone therapy compared to placebo.[9] In February, 2004, the WHI CEE-Alone trial was terminated earlier than planned because the excess risk of stroke in the hormone therapy group was judged to be unacceptable for healthy women in the absence of benefit for coronary heart disease, the primary outcome of the WHI hormone therapy trials.[10] At the conclusion of each trial, study medications were ceased and women were informed of findings and encouraged to consult with their physicians.

Annual follow-up of the WHISCA women continued after the termination of the WHI trials. Women were re-consented for extended follow-up during 2004-5, which continued until September, 2007. Results from all cognitive assessments from initial WHISCA enrollment to the end of extended follow-up are presented in this report.

Cognitive assessments

A battery of cognitive measures was collected annually on WHISCA participants.3 It included the Primary Mental Abilities Vocabulary test to assess verbal knowledge;11 letter and semantic fluency tests to assess verbal fluency;12،13 the Benton Visual Retention Test (BVRT) to assess short-term figural memory;[14] the California Verbal Learning Test (CVLT) to assess verbal memory;15 the Digit Span Forward and Backward Test to assess attention and working memory;16 the Card Rotations Test to measure spatial ability;17 the Finger Tapping Test to assess fine motor speed;18 and the Modified Mini Mental State (3MS) Exam to assess global cognitive function.[19] Quality control was maintained through recertification of test administrators twice during the first year and annually thereafter.

Demographic and clinical cognitive risk factors

Baseline demographic, lifestyle, and clinical factors related to the risk of cognitive impairment were collected via self-report and standardized assessments.[8]

Statistical methods

The primary analysis defined in the WHISCA protocol compared the on-study rates of change in domain-specific cognitive function between treatment groups.[4] In this re-analysis, we used a different approach. We examined mean differences between treatment groups in the cognitive function scores over time to estimate average on-trial and post-trial relative decrements associated with hormone therapy. We first standardized individual scores on each outcome measure by dividing their difference from the cohort mean at the initial WHISCA exam by the standard deviation (SD) of scores at this time. For cognitive domains assessed by more than one outcome measure, we averaged the standardized scores of these outcomes and renormalized these averages to have standard deviations of one. The means (SD) of cognitive tests used to create these standardized domain scores were as follows. Global cognitive function was based on the 3MS: 95.91 (3.70). Verbal knowledge was based on the Primary Mental Abilities Vocabulary test: 36.48 (9.80). Verbal fluency was a composite of letter and category tests: 39.64 (12.49) and 28.95 (6.25). Verbal memory was a composite of CVLT-A, CVLT-A Long Delay, and CVLT-A Short Delay tests: 28.63 (6.37), 9.12 (3.08), and 8.37 (3.11). Figural memory was based on BVRT: 7.14 (3.80). Attention and working memory was based on Digit Span forward and backward tests: 7.44 (2.05) and 6.66 (2.01). Spatial ability was based on the Card Rotations Test: 54.68 (27.70). Fine motor was an average of finger tapping tests from the dominant and non-dominant hands: 37.50

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(6.69). Scores from the BVRT were subtracted from zero so that higher scores expressed better performance. Covariate-adjustment was used to control for differences in the two CVLT word lists that were alternated over time.

The balance of risk factors for cognitive impairment between treatment groups was assessed with logistic regression. Cognitive score means over time (as measured from randomization date) were developed from general linear models fitted by maximum likelihood estimation.[20] To reduce the effects of rare extreme scores, those exceeding ±4 SDs were re-coded to be ±4. Estimates of on-trial and post-trial average relative treatment effects were developed from these models by including these markers as time-varying covariates. Because WHISCA did not begin until a year after the completion of WHI enrollment, the only baseline measure of cognitive function was the 3MS collected by WHIMS, which was included as a covariate in all analyses. Additional terms were included in models to adjust for the time on WHISCA (to control for learning effects). To contrast CEE-Alone and CEE +MPA treatment effects, we additionally included risk factors for cognitive impairment in models to account for differences in the trial cohorts. Women were analyzed according to treatment assignment (i.e. intention to treat).

RESULTS

Table 1 presents a description of the 2,304 WHISCA participants at the time of their enrollment in the WHI. Although there were differences in the characteristics of women between trials with respect to many factors, within both trials randomization provided good balance between active intervention and placebo. Figure 1 describes follow-up. Of the original cohort, 1933 (84%) women consented to and attended at least one post-trial cognitive assessment. With respect to the factors in Table 1 and compared to those who did not participate in post-trial follow-up, these women at WHI enrollment tended to be younger, non-smokers, free of diabetes or cardiovascular disease, and prior users of oral contraceptives and to have higher 3MS scores (all $p<0.05$). Post-trial participation rates were similar between women assigned to active versus placebo therapy ($p=0.21$). Among women from the WHI CEE+MPA trial, the average (standard deviation) on-trial pre-WHISCA, on-trial WHISCA, and post-trial follow-ups were 3.0 (0.7), 2.6 (0.9), and 4.0 (1.3) years. Among women from the WHI CEE-Alone trial, these averages were 3.0 (0.7), 3.6 (0.4), and 2.4 (1.1) years. None of these averages differed significantly between women assigned to active versus placebo therapy (all $p>0.10$).

Table 2 provides a comparison of the on-trial and post-trial mean test scores and the estimated relative treatment effects for each standardized domain score, with mean effect sizes expressed in terms of standard deviation units. During the trials, CEE-based therapies were associated with a mean (standard error) relative decrement in global cognition of 0.073 (0.027) SD units; during post-trial follow-up, this relative decrement was 0.070 (0.025) SD units and the average relative decrement across the full span of follow-up was 0.071 (0.025) SD units. Each of these decrements in global cognitive function was statistically significant $p\leq0.01$ and the on-trial and post-trial mean decrements were of similar magnitudes ($p=0.89$). Figure 2a portrays the fitted mean global cognitive function scores collected during WHISCA follow-up. In this cohort, relative decrements occurred, on average, 3-4 years from WHI enrollment and were maintained across time. Note that the termination of the CCE+MPA trial occurred an average of 5.6 (1.0) years from WHI enrollment and the termination of the CEE-Alone trial occurred an average of 6.6 (0.6) years from WHI enrollment for these women. As indicated in the figure, 6 years from randomization only 32% of the measurements occurred during the trial and in later years, almost all occurred after the termination of the trials.

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There was a mean on-trial relative decrement for each domain-specific cognitive function; these reached statistical significance ($p \leq 0.05$) for verbal knowledge, verbal fluency, figural memory, and fine motor speed. The magnitudes of effect sizes were uniformly smaller during the post-trial and none were significant on their own, however on-trial and post-trial decrements differ significantly only for verbal fluency ($p=0.009$). Figure 2b portrays the pattern over time of the means for verbal fluency, for which the initial relative decrement, which was apparent as early as Year 1, dissipated from 6 years on during follow-up.

There was little difference in the relative effects of CEE+MPA versus CEE on global cognitive function, both during on-trial and post-trial follow-up (Table 3). For three domains, however, there was some evidence of differences between the two drug regimens. For figural memory ($p=0.05$), spatial ability ($p=0.04$), and fine motor speed ($p=0.01$), the on-trial decrements appeared to be limited to CEE therapy and were not apparent for CEE +MPA therapy. For the spatial ability, the differences in the effect sizes between regimens persisted into the post-trial follow-up ($p=0.01$).

DISCUSSION

To investigate whether CEE therapies affected age-related cognitive decline, the WHISCA investigators predefined rates of changes in annual cognitive test scores from the time of WHISCA enrollment to be the primary outcomes of the trial. For women who had been prescribed CEE-based therapies an average of 3 years earlier, they found that no significant improvement in the trajectories of these slopes related to hormone therapy. Instead, CEE-Alone appeared to have produced a small average relative decrement in spatial ability that waned during WHISCA follow-up and CEE+MPA therapy was associated with a continued small deleterious relative effect on age-related declines in verbal memory.[4,6] Overall, however, there was little evidence that continued prescription of the CEE-based therapies produced widening differences in cognitive functions across multiple domains.

The analyses reported here differ from those pre-defined in the WHISCA protocol[3] in four important ways. First, they are focused on estimating differences in the average cognitive scores over time rather than the slopes of these differences. Second, visits are ordered according to time from initial prescription of WHI treatments, rather than time from WHISCA enrollment. Third, rather than analyzing scores from individual tests, we have combined some to form domain scores. Finally, both on-trial and post-trial data are considered.

We derive three principal points, and take up each in turn. First, CEE-based therapies were associated with small, but detectable, mean on-trial decrements in global cognitive function that were largely maintained for several years after the conclusion of the trials. In pooled analyses, CEE-based therapies were associated with on-trial decrements among the individual domains whose magnitudes spanned those for global cognitive function and some of which reached statistical significance on-trial, but none post-trial. Finally, while the magnitude of the CEE-Alone and CEE+MPA effects on global cognition were fairly comparable throughout follow-up, CEE-Alone therapy appeared to be associated with greater adverse domain-specific effects.

Enduring Deficits in Global Cognitive Function

For the full WHIMS cohort, the pooled on-trial mean decrement in 3MS scores associated with assignment to CEE-based therapies was about 0.05 SD units,[1,2] which was slightly lower than seen during follow-up of the WHISCA cohort. The reason for this is likely that the first few years following randomization were included in the WHIMS estimates, when differences were just beginning to emerge; the on-trial estimates from WHISCA more

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heavily reflect the later years of the WHIMS trial, when differences were more marked. These average differences in cognitive function are small and would not be detectable or have clinical significance for an individual woman. Of some concern is that these appear to persist long after cessation of hormone therapy and likely are linked to the smaller regional brain volumes as evident in MRI scans taken up to three years following the termination of these trials. It appears that these smaller volumes are an expression of how CEE-based therapies affect cognitive function: women who developed cognitive impairment after assignment to these therapies have smaller brain volumes than non-impaired women while women who developed cognitive impairment after assignment to placebo did not.[21]

The potential mechanisms for this broad-based effect are presently not known. Candidates include disruption of balance between neurogenesis and apoptosis, a loss of estrogen sensitivity and reversal of neuroprotective effects following prolonged hypoestrogenicity, or actions of equine estrogens on glial cells.22-26 Despite the increase risk of (predominantly ischemic) stroke associated with CEE-based therapies,[27] data from the WHIMS-MRI study suggest that the principal pathway for its adverse effect on cognition is not through an increase of ischemic lesions.28 Whether these adverse effects are limited to initiation of hormone therapy in women over the age of 65 and to only CEE-based therapies is unknown. The magnitudes of these effects are small, however they may translate to significant increases in the risk of dementia and mild cognitive impairment.29,30

Effects on Domain-Specific Cognitive Functions

Much has been written about the potential beneficial effects of hormone therapy on specific cognitive domains in younger women and laboratory animals.[22,31-33] In general, beneficial effects have been most consistently found for verbal memory and attention, however evidence for positive effects have been found for many domains. In older women, the evidence for domain-specific benefit is less clear.[22,32,34] In general, we found the on-trial adverse effects of hormone therapy on individual cognitive domains to be more-or-less comparable in magnitude to those on global cognitive function, but less statistically significant. The lower power to detect differences for individual domains was not attributable to measurement error (the within-subject longitudinal correlations of domain specific tests were at least as high as for global cognitive function), but was likely due to the lack of a domain-specific baseline test score for use as a covariate (using baseline global cognitive function for this purpose did not improve power uniformly across all domains). The smallest on-trial adverse effects were found for verbal memory, raising the possibility that there may have been some moderation of the general adverse effect by other mechanisms for this domain, however this is speculative.

Overall, the magnitudes of domain-specific post-trial adverse effects were smaller than on-trial effects, but not significantly so, with one exception. The on-trial effect on verbal fluency, which was the largest in magnitude of any domain, virtually disappeared during post-trial follow-up. Laughlin, et al. have reported that higher levels of endogenous hormones are associated with lower performance in verbal fluency,[35] which may signal an acute affect linked to elevated androgen levels, and these have been reported to suppress verbal fluency.[36,37] Thus, it is possible that this provides evidence a second mechanism is involved whereby CEE-based therapies adversely affect cognition.

Differences between CEE+MPA and CEE-Alone Therapies

While CEE-Alone and CEE+MPA therapy had fairly comparable on-trial and post-trial effects on global cognitive function, some differences appeared among domain-specific tests. CEE-Alone therapy was associated with on-trial decrements in verbal knowledge, verbal fluency, figural memory, spatial ability, and fine motor speed (all $p \leq 0.05$), while

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CEE+MPA therapy was not. Several possible explanations may exist. The longer duration of the CEE-Alone trial (an average of 4.0 versus 3.0 years) is one: the means of on-trial effects for the CEE-Alone women more heavily weight longer exposures, when treatment effects were largest. Also, the women from the CEE-Alone trial, tended to have greater pre-trial risk factors for cognitive impairment (including lower education, lower income, and more prevalent hypertension and cardiovascular disease) and lower levels of global cognitive function. These may identify women with greater levels of pre-existing disease cerebrovascular disease, for whom the adverse effect of CEE-based therapies may be greater.[6] Finally, it may be that MPA offers some protection against domain-specific adverse effects. If this is so, the strongest evidence for this may be for spatial ability: the on-trial adverse effect of CEE-Alone therapy on spatial ability continued post-trial, however no on-trial or post-trial effects for CEE+MPA therapy were seen. If MPA has a differential effect among global and domain-specific functions, this may be evidence of additional mechanisms linking hormone therapy to cognition.

Limitations

The WHISCA study was limited to postmenopausal women aged 65 years or older and only 0.625 mg/day CEE-based therapies. While we cannot rule out imbalances among treatment groups among women who enrolled in WHISCA with respect to unmeasured characteristics, none were detected among measured characteristics and extensive covariate-adjustment was used to promote balanced comparisons. We have not included data on the use of hormone therapies among WHISCA women following the WHI trials. Overall, this has been reported to be quite low, e.g. only 4% of participants who had been assigned to CEE+MPA therapy reported using any sort of hormone therapy one year after the termination of the trial.[38] We report the results from many inferences. Because of this, Type 1 error is inflated across the individual tests. The magnitude of the estimated mean effects, <10% of a standard deviation, are small and would be clinically undetectable for women.

Conclusions

CEE-based hormone therapies, when initiated among women aged 65 years or older and provided for an average of 5 to 7 years, produced small average decrements in global and several domain-specific cognitive functions that endured several years after cessation of use. No evidence of benefit for any cognitive domain was found, however differences in how CEE-Alone and CEE+MPA affect domain-specific cognitive test scores suggest that more than one mechanism may be involved.

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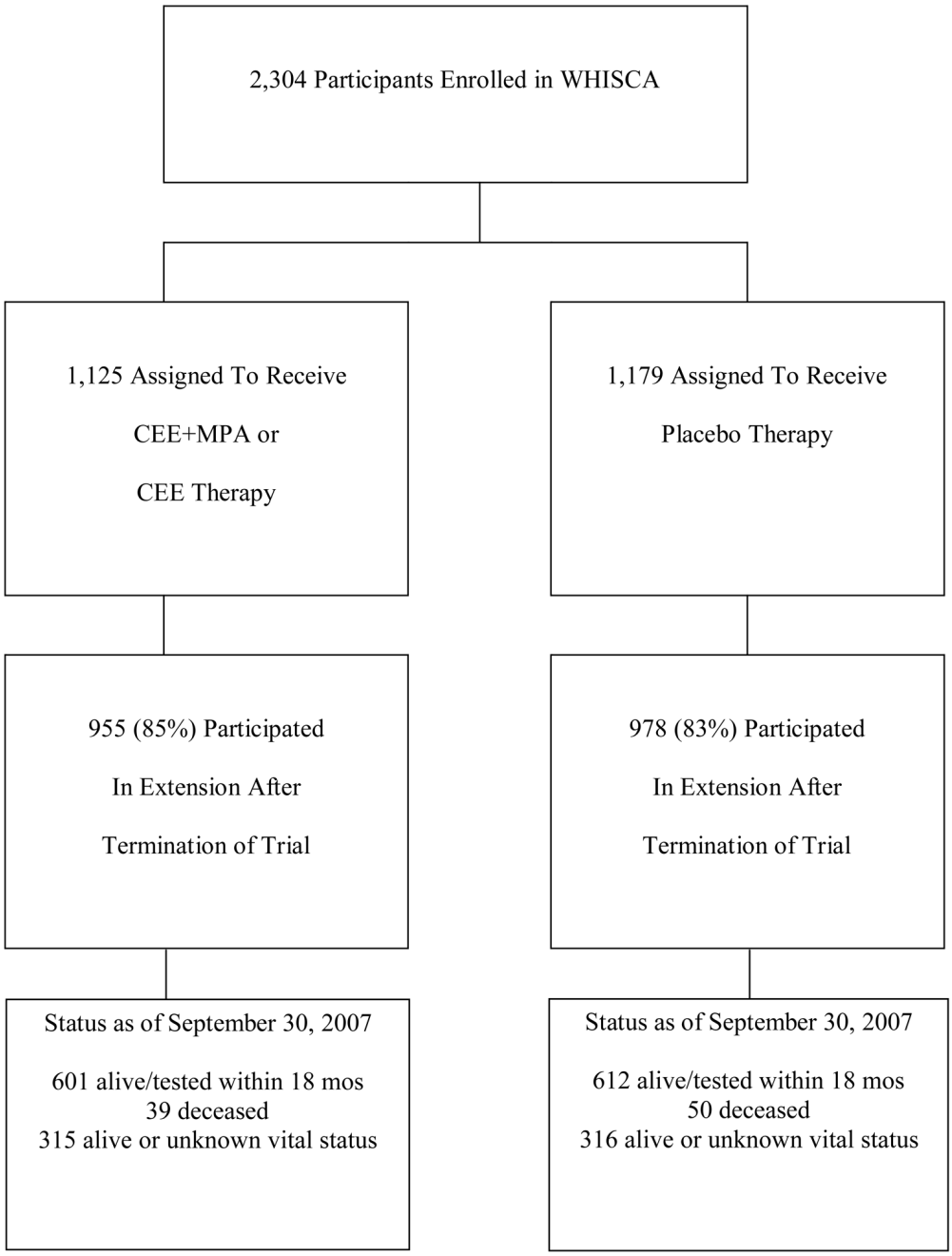

Figure 1.
Follow-up during WHISCA and the WHISCA Extension

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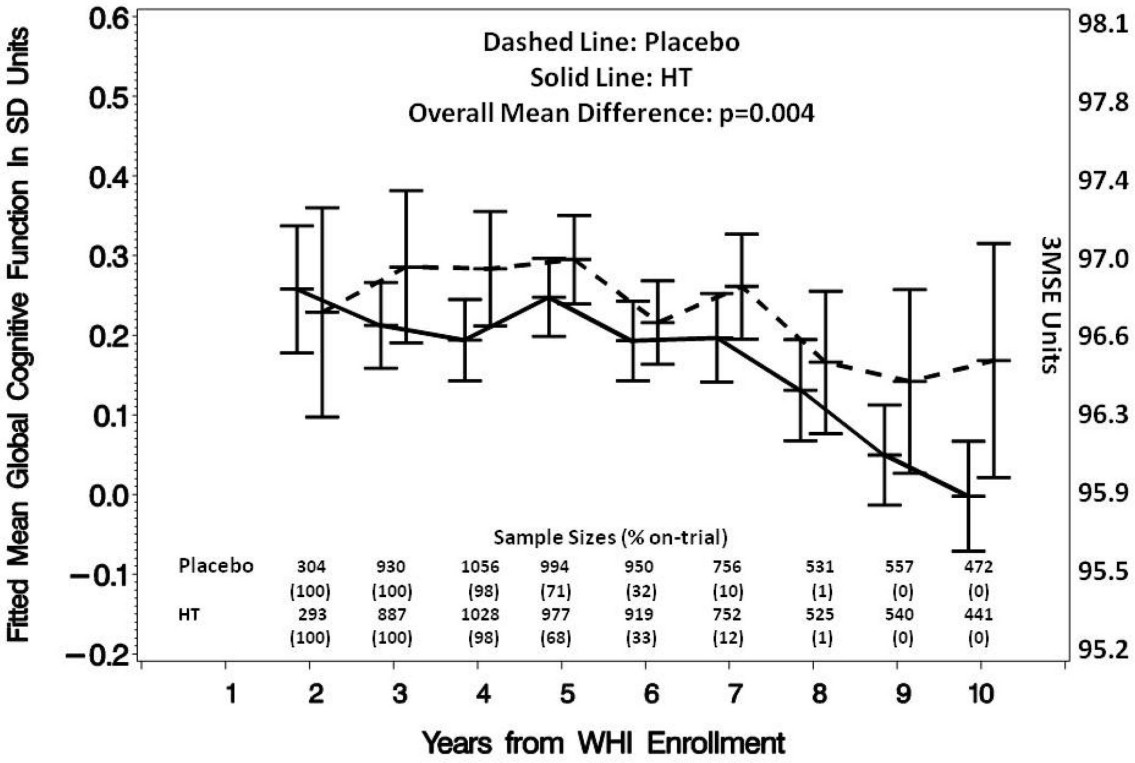

Figure 2a.

Fitted mean (with 95% confidence intervals) standardized global cognition test scores over time from women grouped by WHI treatment assignment with adjustment for baseline 3MS score, trial (CEE+MPA vs CEE-Alone), age, education, race/ethnicity, smoking status, body mass index, hypertension, alcohol intake, prior cardiovascular disease, diabetes, prior use of hormone therapy, and prior use of oral contraceptives. The left-hand axis provides units in the original scale. The lower panel provides the number of women who contributed to each data point and the percentage of measurements that were collected during on-trial.

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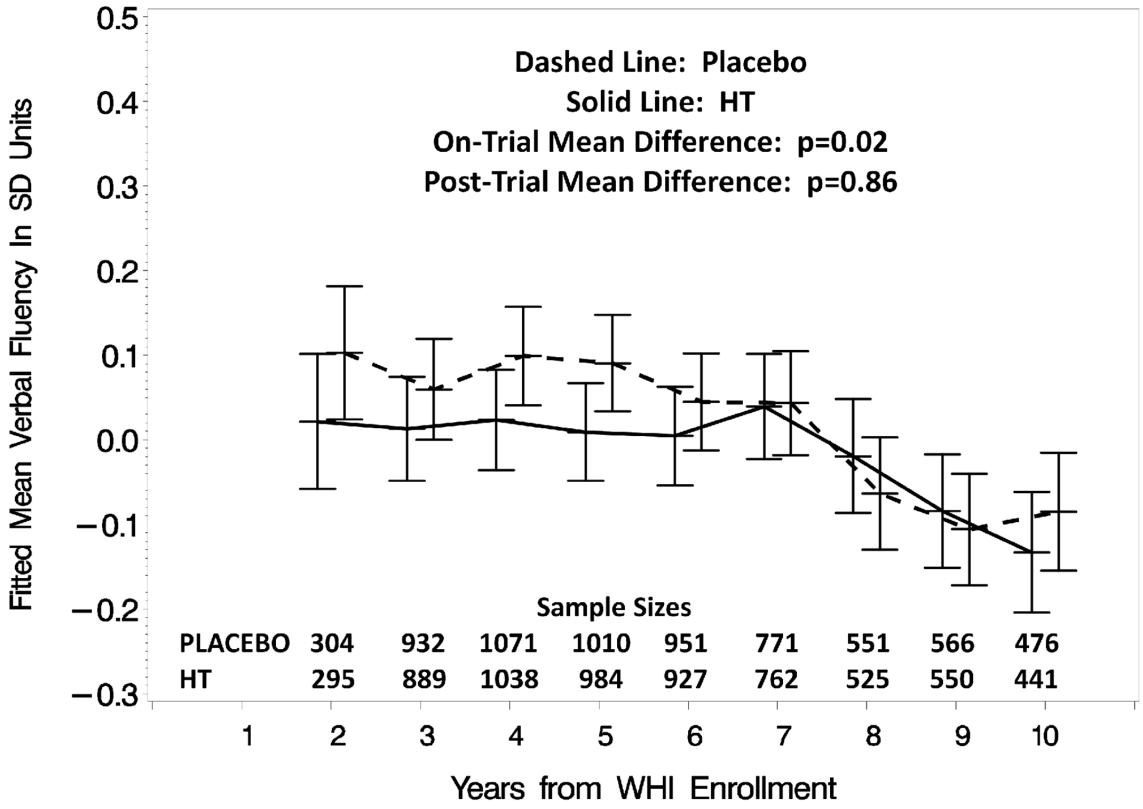

Figure 2b.

Fitted mean (with 95% confidence intervals) standardized verbal fluency test scores from women grouped by WHI treatment assignment with adjustment for baseline 3MS score, trial (CEE+MPA vs CEE-Alone), age, education, race/ethnicity, smoking status, body mass index, hypertension, alcohol intake, prior cardiovascular disease, diabetes, prior use of hormone therapy, and prior use of oral contraceptives.

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Table 1

Characteristics of participants at the time of enrollment into the WHI by treatment assignment: frequency and (percent).

Variable	WHISCA CEE+MPA Trial		WHISCA CEE-Alone Trial		Active vs Placebo p-value	Between Trials p-value
	CEE+ MPA	Placebo	CEE-Alone	Placebo		
Age--yrs, No. (%)					0.22	0.18
65-69	337 (49)	346 (48)	193 (44)	204 (45)		
70-74	258 (37)	260 (36)	169 (39)	163 (36)		
75+	96 (14)	121 (17)	72 (17)	85 (19)		
Education, No. (%)					0.92	<0.0001
< High school	31 (5)	35 (5)	26 (6)	27 (6)		
High school/GED	119 (17)	152 (21)	116 (27)	107 (24)		
> High school < 4 yr college	292 (42)	288 (40)	176 (41)	191 (42)		
≥ 4 yr college	247 (36)	251 (35)	116 (27)	127 (28)		
Ethnicity, No. (%)					0.29	<0.0001
American Ind/Alaskan Native	2 (0)	1 (0)	3 (1)	0 (0)		
Asian/Pacific Islander	8 (1)	9 (1)	7 (1)	2 (0)		
Black/African-American	31 (4)	32 (4)	38 (9)	44 (10)		
Hispanic/Latino	11 (2)	5 (1)	7 (1)	6 (1)		
White, non-Hispanic	633 (92)	676 (93)	372 (86)	393 (87)		
Other	6 (1)	4 (1)	7 (1)	7 (1)		
Smoking Status, No. (%)					0.70	0.31
Never	355 (52)	401 (56)	257 (60)	244 (54)		
Former	283 (42)	283 (39)	157 (37)	170 (38)		
Current	42 (6)	36 (5)	16 (4)	34 (8)		
Body mass index--kg/m^2, No. (%)					0.57	<0.001
< 25	216 (31)	243 (34)	110 (25)	110 (25)		
25-29	247 (36)	252 (35)	157 (36)	164 (37)		

Variable	WHISCA CEE+MPA Trial		WHISCA CEE-Alone Trial		Active vs Placebo p-value	Between Trials p-value
	CEE+ MPA	Placebo	CEE-Alone	Placebo		
30-34	141 (20)	152 (21)	96 (22)	109 (24)		
35+	86 (12)	77 (11)	70 (16)	65 (15)		
Hypertension status, No. (%)					0.85	<0.001
None	384 (56)	393 (54)	201 (46)	221 (49)		
Current / controlled*	93 (13)	96 (13)	83 (19)	79 (17)		
Current / uncontrolled	214 (31)	238 (33)	150 (35)	152 (34)		
Alcohol intake—drinks, No. (%)					0.88	<0.001
None	286 941)	298 (41)	211 (49)	225 (50)		
<1/day	304 (44)	330 (45)	189 (44)	173 (38)		
1-2/day	88 (13)	87 (12)	30 (7)	44 (10)		
≥3/day	12 (2)	12 (2)	4 (1)	8 (2)		
Prior CVD, No. (%)					0.54	<0.001
No	630 (91)	679 (93)	384 (88)	395 (87)		
History of stroke	7 (1)	7 (1)	5 (1)	8 (2)		
History of other CVD[ƒ]	54 (8)	41 (6)	45 (10)	49 (11)		
Diabetes, No. (%)					0.48	<0.001
No	653 (95)	681 (94)	390 (90)	403 (89)		
Yes	37 (5)	45 (6)	44 (10)	49 (11)		
Prior use of hormone therapy					0.85	<0.001
No	545 (79)	562 (77)	219 (50)	243 (54)		
Yes	146 (21)	165 (23)	215 (50)	209 (46)		
Ever use of oral contraceptives					0.55	0.02
No	482 (70)	515 (71)	336 (77)	329 (73)		
Yes	209 (30)	212 (29)	98 (23)	123 (27)		

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Variable	WHISCA CEE+MPA Trial		WHISCA CEE-Alone Trial		Active vs Placebo p-value	Between Trials p-value
	CEE+ MPA	Placebo	CEE- Alone	Placebo		
3MSE at WHI enrollment					0.72	<0.001
<90	39 (6)	37 (5)	39 (9)	37 (8)		
90-94	120 (17)	133 (18)	98 (23)	107 (24)		
≥95	532 (77)	557 (77)	297 (68)	308 (68)		

[*] Measured to be less than 140/90 mmHg.

[i] Other CVD defined as myocardial infarction, angina, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft

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Table 2

Mean on-trial, post-trial, and overall test scores and, expressed in standard deviation units, relative domain-specific treatment effects ([unk]active minus placebo): adjustment for baseline 3MS score, trial (CEE+MPA vs CEE-Alone), time since WHISCA enrollment, age, education, race/ethnicity, smoking status, body mass index, hypertension, alcohol intake, prior cardiovascular disease, diabetes, prior use of hormone therapy, and prior use of oral contraceptives.

Cognitive domain [Range]	On-trial		Post-trial		Overall		Consistency of on-trial and post-trial effects p-value
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	
Global cognitive function 3MSE [0-100]							
Active	96.58 (0.09)		96.44 (0.09)		96.51 (0.07)		
Placebo	96.84 (0.09)		96.68 (0.09)		96.76 (0.07)		
Domain treatment effect, SD	−0.073 (0.027)	0.007	−0.070 (0.028)	0.01	−0.071 (0.025)	0.004	0.89
Verbal knowledge PMA Vocabulary [0-50]							
Active	37.21 (0.24)		37.53 (0.24)		37.37 (0.23)		
Placebo	37.93 (0.24)		38.04 (0.24)		37.99 (0.23)		
Domain treatment effect, SD	−0.066 (0.032)	0.04	−0.053 (0.033)	0.11	−0.060 (0.031)	0.05	0.53
Verbal fluency Letter Fluency [≥0]							
Active	41.20 (0.32)		41.56 (0.33)		41.36 (0.29)		
Placebo	41.76 (0.32)		41.49 (0.32)		41.64 (0.29)		
Category Fluency [≥0]							
Active	28.05 (0.16)		28.18 (0.16)		28.11 (0.13)		
Placebo	28.60 (0.15)		28.32 (0.16)		28.47 (0.13)		
Domain treatment effect, SD	−0.083 (0.034)	0.02	−0.006 (0.035)	0.86	−0.048 (0.032)	0.13	0.009
Verbal memory CVLT-A [0-48]							
Active	27.33 (0.16)		27.38 (0.16)		27.35 (0.13)		
Placebo	27.77 (0.16)		27.68 (0.16)		27.73 (0.13)		
CVLT-A Long Delay [0-16]							
Active	9.16 (0.08)		9.10 (0.08)		9.13 (0.06)		

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Cognitive domain [Range]	On-trial		Post-trial		Overall		Consistency of on-trial and post-trial effects p-value
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	
Placebo	9.27 (0.08)		9.08 (0.08)		9.17 (0.06)		
CVLT-A Short Delay [0-16]							
Active	8.29 (0.08)		8.19 (0.08)		8.24 (0.06)		
Placebo	8.32 (0.08)		8.21 (0.08)		8.27 (0.06)		
Domain treatment effect, SD	−0.039 (0.034)	0.24	−0.013 (0.035)	0.70	−0.027 (0.030)	0.37	0.43
Figural memory	BVRT [0-26]						
Active	−6.93 (0.10)		−6.97 (0.10)		−6.95 (0.09)		
Placebo	−6.73 (0.10)		−6.88 (0.10)		−6.80 (0.09)		
Domain treatment effect	−0.062 (0.031)	0.05	−0.026 (0.032)	0.42	−0.045 (0.027)	0.09	0.28
Attention and working memory							
Digit Span Forward [0-14]							
Active	7.45 (0.06)		7.51 (0.06)		7.48 (0.05)		
Placebo	7.58 (0.06)		7.62 (0.06)		7.60 (0.05)		
Digit Span Backward [0-14]							
Active	6.56 (0.05)		6.60 (0.05)		6.58 (0.04)		
Placebo	6.66 (0.05)		6.67 (0.05)		6.67 (0.04)		
Domain treatment effect, SD	−0.064 (0.037)	0.08	−0.039 (0.037)	0.29	−0.053 (0.036)	0.14	0.21
Spatial ability							
Card Rotations Test [0-160]							
Active	60.30 (0.75)		59.08 (0.75)		59.70 (0.67)		
Placebo	61.55 (0.73)		60.52 (0.74)		61.04 (0.66)		
Domain treatment effect	−0.050 (0.039)	0.20	−0.040 (0.039)	0.31	−0.045 (0.038)	0.23	0.59
Fine motor speed							
Finger Tapping (dominant hand) [≥0]							
Active	39.37 (0.19)		39.02 (0.19)		39.20 (0.16)		
Placebo	39.73 (0.18)		39.37 (0.19)		39.55 (0.16)		

Cognitive domain [Range]	On-trial		Post-trial		Overall		Consistency of on-trial and post-trial effects p-value
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	
Finger Tapping (non-dominant hand) [≥0]							
Active	36.63 (0.17)		36.51 (0.17)		36.57 (0.16)		
Placebo	36.92 (0.17)		36.71 (0.17)		36.82 (0.15)		
Domain treatment effect, SD	−0.068 (0.034)	0.05	−0.045 (0.035)	0.20	−0.057 (0.030)	0.05	0.54

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Table 3

Mean on-trial, post-trial, and overall relative treatment effects: adjustment for baseline 3MS score, trial (CEE+MPA vs CEE-Alone), time since WHISCA enrollment, age, education, race/ethnicity, smoking status, body mass index, hypertension, alcohol intake, prior cardiovascular disease, diabetes, prior use of hormone therapy, and prior use of oral contraceptives.

Cognitive Domain	Mean Decrement in SD Units CEE-based Versus Placebo Therapy					
	On-trial		Post-trial		Overall	
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value
Global cognitive function						
CEE-Alone	−0.092 (0.039)	0.02	−0.081 (0.047)	0.09	−0.086 (0.035)	0.01
CEE+MPA	−0.080 (0.034)	0.02	−0.059 (0.032)	0.06	−0.069 (0.027)	0.01
CEE-Alone vs CEE+MPA		0.83		0.70		0.68
Verbal knowledge						
CEE-Alone	−0.100 (0.051)	0.05	−0.071 (0.054)	0.19	−0.089 (0.050)	0.07
CEE+MPA	−0.044 (0.041)	0.29	−0.040 (0.041)	0.33	−0.042 (0.039)	0.28
CEE-Alone vs CEE+MPA		0.39		0.65		0.46
Verbal fluency						
CEE-Alone	−0.118 (0.054)	0.03	−0.092 (0.060)	0.13	−0.099 (0.058)	0.09
CEE+MPA	−0.062 (0.044)	0.16	0.039 (0.044)	0.38	−0.004 (0.046)	0.94
CEE-Alone vs CEE+MPA		0.43		0.08		0.20
Verbal memory						
CEE-Alone	−0.040 (0.057)	0.49	−0.049 (0.062)	0.43	−0.043 (0.056)	0.44
CEE+MPA	−0.009 (0.047)	0.84	−0.020 (0.046)	0.67	−0.015 (0.044)	0.74
CEE-Alone vs CEE+MPA		0.68		0.71		0.69

Cognitive Domain	Mean Decrement in SD Units CEE-based Versus Placebo Therapy					
	On-trial		Post-trial		Overall	
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value
Figural memory						
CEE-Alone	−0.132 (0.048)	0.006	−0.009 (0.057)	0.88	−0.086 (0.044)	0.05
CEE+MPA	−0.008 (0.041)	0.85	−0.030 (0.040)	0.45	−0.020 (0.034)	0.57
CEE-Alone vs CEE+MPA		0.05		0.76		0.24
Attention and working memory						
CEE-Alone	−0.063 (0.054)	0.24	−0.088 (0.060)	0.14	−0.073 (0.051)	0.15
CEE+MPA	−0.077 (0.044)	0.08	−0.052 (0.044)	0.24	−0.064 (0.040)	0.11
CEE-Alone vs CEE+MPA		0.85		0.62		0.89
Spatial ability						
CEE-Alone	−0.137 (0.057)	0.02	−0.179 (0.063)	0.004	−0.153 (0.055)	0.005
CEE+MPA	0.013 (0.047)	0.78	0.019 (0.047)	0.68	0.016 (0.043)	0.70
CEE-Alone vs CEE+MPA		0.04		0.01		0.02
Fine motor speed						
CEE-Alone	−0.171 (0.053)	0.001	−0.120 (0.062)	0.06	−0.153 (0.048)	0.002
CEE+MPA	0.006 (0.045)	0.90	−0.002 (0.043)	0.97	0.002 (0.038)	0.96
CEE-Alone vs CEE+MPA		0.01		0.12		0.01

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