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

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Abstract

Background—Postmenopausal hormone therapy with conjugated equine estrogens (CEE) may adversely affect older women's cognitive function. It is not known whether this extends to younger women.

Methods—1,326 postmenopausal women, who had begun treatment in two randomized placebo-controlled clinical trials of hormone therapy when aged 50–55 years, were assessed with an annual telephone-administered cognitive battery that included measures of global (primary outcome) and domain-specific cognitive functions (verbal memory, attention, executive function, verbal fluency, and working memory). The clinical trials in which they participated had compared 0.625 mg CEE with or without 2.5 mg medroxyprogesterone acetate (MPA) over an average of 7.0 years. Cognitive testing was conducted an average of 7.2 years following the end of the trials, when women had mean age 67.2 years, and repeated one year later.

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% confidence interval] intervention effect of 0.02 [−0.08,0.12]standard deviation units (p=0.66). Similarly, no overall differences were found for any individual cognitive domain (all p>0.15). Pre-specified 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, −0.02] and −0.25 [−0.42, −0.08], respectively, however this may be a chance finding. We are not able to address whether initiating hormone therapy during the menopause and maintaining therapy until any symptoms are passed affects cognitive function, either in the short or longer term.

Conclusions—CEE-based therapies produced no overall sustained benefit or risk to cognitive function when administered to postmenopausal women aged 50–55 years.

INTRODUCTION

The Women's Health Initiative Memory Study (WHIMS) demonstrated that postmenopausal hormone therapy with conjugated equine estrogens (CEE), when prescribed to women aged 65 years and older, produced deficits in global and domain-specific cognitive functioning.[1–3] On average these were small; however, deficits persisted for years after cessation of hormone therapy.[3] They occurred with decreases in brain volumes linked to increased incidence of cognitive impairment.[4,5]

In contrast, observational and cohort studies and considerable basic science research suggest that there may be a "window of opportunity," perhaps co-incident 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 as 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 ages 50–54 years has longer-term effects on cognitive function. We present its primary findings.

METHODS

The Women's Health Initiative (WHI) included two 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. Enrollment occurred from 1996–1999 at 40 academic research centers. Active therapies were 0.625 mg/day CEE in women post-hysterectomy and 0.625 g/day CEE combined with 2.5 mg/day MPA in women with a uterus and were compared to matching placebos. The trial among women without prior hysterectomy (CEE+MPA) was terminated July, 2002;[14] the trial among women with prior hysterectomy (CEE-Alone) was terminated February, 2004.[15] Study therapies were stopped at these times. Women were unmasked, but follow-up continued.

WHIMSY volunteers had begun screening for WHI enrollment when aged 50–54 years (and initiated their assigned WHI treatment when aged 50–55 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

Trained, 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:

- 12-point *East Boston Memory Test* (EBMT) for immediate and delayed verbal memory;[19]
- *Oral Trail Making Test* (OTMT), a modification of the Trail Making Test (TMT),[20] a validated measure of attention (Part A) and executive function (Part B),[21] scored as time in seconds;
- *Verbal Fluency-Animals* (VF-A) test totaling the number of unique spontaneously named animals in 1 minute;[22] and
- *Digit Span* (DS) subtest of the Wechsler Adult Intelligence Scale-Revised measuring attention and working memory with the longest correct span length recalled for digits forward and backward.[23]

Covariates and potential confounders

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 average proportion of assigned study medication use, based on pill counts. Years of on-trial exposure were computed by summing each woman's adherence rates (based on pill counts) across years of trial follow-up.

Statistical methods

Cognitive measures from two 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,[25] as pre-specified 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 and ordered so that higher values reflected better performance. A composite measure was computed by averaging normalized scores across tests. Pre-specified subgroup analyses were performed using tests of interactions. Primary analyses followed intention-to-treat, with women grouped according to treatment assignment.

RESULTS

WHIMSY enrolled 1,326 (of 1,372 potentially eligible women who agreed to contact). They averaged (range) 7.0 (3.9, 10.1) years of follow-up during the WHI trials, which ended 7.2 (5.4, 10.1) years prior to WHIMSY enrollment (Figure 1). Women averaged 67.2 (62.9, 73.5) at their first assessment. The second assessment was conducted on 1,168 (88.1%) women with mean age 68.1 years. Times between assessments for treatment groups were similar (p=0.64).

There was reasonable balance in important potential confounders at WHI enrollment between women who had been assigned active versus placebo therapy (Table 1, all p>0.05). 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>0.20).

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 versus placebo therapy (p=0.66). This finding was consistent for both CEE+MPA and CEE-Alone therapies (p=0.23). 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. CEE-Alone therapy was associated with 0.17 standard deviation worse mean scores on verbal fluency with a 95% confidence interval that excluded zero [−0.33,−0.02]; CEE+MPA was associated with 0.07 standard deviation better mean scores on this test, however its confidence interval included zero [−0.06,0.19]. 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=0.003; r =0.05, p=0.02), 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 (p>0.30).

The WHIMSY protocol pre-specified three subgroup analyses to compare treatment effects for women grouped by: assignment to unopposed or opposed CEE therapy (i.e. 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 two analyses. There was little evidence of differential effects for any measure of cognitive function, with one 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<0.001): compared to non-users, 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 with prior hysterectomy, we fitted a model that included treatment interactions with both hysterectomy status and prior use. Both interactions were independently statistically significant: women reporting prior hormone therapy use (interaction p=0.01) and those with prior hysterectomy (interaction p=0.03) 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 WHI, 28 (4.0%) reported use at some time during post-trial follow-up, compared to 24 (3.8%) among women who had been assigned to placebo (p=0.82). Post-trial use of hormone therapy had no associations with any cognitive function measure (all p>0.18).

Power projections for WHIMSY were based on the WHIMS Modified MiniMental State Exam global cognitive scores.[2] The recruitment goal of 2,240 women was projected to provide 91% power to detect a mean difference of 0.5 units in this test across two exams, which corresponds to 0.10 to 0.15 standard deviations for these test scores as collected at baseline in WHIMS. WHIMSY fell short of this recruitment goal, enrolling 1,326 women. Post hoc power projections based on observed data yielded 80% (90%) power to detect a mean difference of 0.15 (0.18) standard deviations, which translates to 0.65 (0.75) TICS-m units.

DISCUSSION

In a large heterogeneous cohort of postmenopausal women aged 50–55 years, WHIMSY tested whether random assignment to an average 7-year prescription of CEE therapies produced long-term cognitive benefits or deficits compared to 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 pre-specified subgroups of prior hysterectomy or prior use, however type 1 error was not controlled across the several domain-specific measures. There was also no evidence for differential treatment effects related to on-trial adherence or years of exposure. The original balance between treatment groups afforded by randomization did not appear to be eroded. WHIMSY fell short of its recruitment goal, but maintained adequate power to detect the relatively small mean differences targeted during its design.

Comparison to WHIMS

WHIMS found that prescribing 4–5 years of CEE-based therapy to women older than 65 years produced a mean relative decrement of 0.07 (standard error=0.03) standard deviations in global cognitive function, as assessed with the Modified Mini-Mental State Exam.[2] In the 2,304 of its women enrolled in the Women's Health Initiative Study of Cognitive Aging (WHISCA), this on-trial relative deficit was maintained through a mean (standard deviation) of 2.4 (1.1) and 4.0 (1.3) years after the termination of the WHI CEE-alone and CEE+MPA trials respectively, averaging 0.07 (0.03) standard deviations during post-trial follow-up.[3] The endurance of this effect on global cognitive function supports the choice of the TICS-m as the primary outcome measure for WHIMSY.

WHISCA found modest decrements in other domains WHIMSY assessed. A test of verbal memory (California Verbal Learning Test[26]) had an average [95% confidence interval] decrement of 0.039 [−0.028,0.106] on-trial and 0.013 [−0.056,0.082] post-trial standard deviations, neither statistically significant. A test of attention and working memory (Digit Span Forward and Backward) had average decrements of 0.064 [−0.009,0.146]on-trial and 0.039 [−0.034,0.112] post-trial, also not significant. A test of semantic verbal fluency similar to the measure used in WHIMSY had a larger on-trial average decrement of 0.083 [0.016,0.150], but little post-trial decrement: 0.006 [−0.063,0.075]. For each of these domains, post-trial relative decrements were smaller than on-trial decrements, only reaching nominal significance for verbal fluency (p=0.009). Because WHIMSY had fewer women 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 versus 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 one exception was verbal fluency, which appeared to be adversely affected among women assigned to CEE-alone therapy compared to CEE+MPA therapy and among women with prior (but not current) hormone therapy use compared to no prior use. WHISCA also found that post-trial differences between women who had been assigned to active versus 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 WHIMSY, it also found marginal differences in the post-trial effects of CEE-Alone versus CEE+MPA therapy on verbal fluency: women assigned to CEE-Alone therapy had mean (standard error) scores 0.092 (0.060) standard deviations worse than placebo, while women who had been assigned to CEE+MPA therapy averaged 0.039 (0.044) standard deviations better than placebo (interaction p=0.08).[3] While 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,[27] unchanged,[28,29] or harmed[30] by hormone therapy. Higher levels of endogenous estrogens have been associated with greater declines in verbal fluency in older women.[31] Because all women receiving CEE-Alone therapy had prior hysterectomy, which may be a risk factor on its own for cognitive impairment,[32] it may be that women's response to hormone therapy depends on whether loss of endogenous estrogens is gradual or precipitous.[33]

Magnitude of detectable intervention effects

WHIMSY had sufficient power to rule out mean treatment effects of 0.15 standard deviations, 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.[34]

The larger WHIMS and WHISCA trials, which featured more cognitive assessments over time, detected CEE-related mean decrements of 0.06 to 0.08 standard deviations in cognitive function.[1–3] Despite these relatively small mean differences, CEE-based therapy among women >65 years of age resulted in a 75% increase in the hazard for dementia and significant decrements in brain volumes.[4,35] It is possible that hormone therapy could have had a similar small effect on cognitive function in younger women that may have clinical significance, but for which WHIMSY was underpowered to detect. Two findings argue against this. First, both the primary outcome, a measure of global cognitive function, and the composite outcome formed by averaging all test scores, had essentially no treatment effects. Secondly, 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

WHIMSY 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 had no therapy for at least 3 months prior to randomization; their last menstrual period had occurred an average of 4 (no prior hysterectomy) to 8 years (prior hysterectomy) years before WHI enrollment. As volunteers for a clinical trial and post-trial follow-up, these women may not represent more general populations [Espeland, 2013]. Women had been unmasked to their treatment assignment, 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. Pre-treatment levels of cognitive function were not assessed, however the WHIMSY cohorts were well-balanced with respect to pre-treatment risk factors for cognitive impairment; covariate adjustment for these did not materially affect estimated treatment effects.

Summary

Our findings provide reassurance that CEE-based therapies when administered to women earlier in the postmenopausal period do not appear to convey long term adverse consequences for cognitive function. While we cannot rule out acute benefits or harm, these do not appear to be present to any degree an average of seven 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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References

1. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA. 2003; 289(2):2663–72. Medline 12771113. [PubMed: 12771113]
2. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004; 291(24):2959–68. Medline 15213207. [PubMed: 15213207]
3. Espeland MA, Brunner RL, Hogan PA, et al. 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. J Am Geriatr Soc. 2010; 58(7):1263–1271. Medline 20649689. [PubMed: 20649689]
4. Resnick SR, Espeland MA, Jaramillo SA, et al. Effects of postmenopausal hormone therapy on regional brain volumes in older women: The Women's Health Initiative Magnetic Resonance Imaging Study. Neurology. 2009; 72(2):135–142. Medline 19139364. [PubMed: 19139364]
5. Espeland MA, Tindle HA, Bushnell CA, et al. Brain volumes, cognitive impairment, and conjugated equine estrogens. J Gerontol A Biol Sci Med Sci. 2009; 64(12):1243–1250. Medline 19729392. [PubMed: 19729392]
6. Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. J Neurol Neurosurg Psychiatry. 2005; 76(1): 103–105. Medline 15608005. [PubMed: 15608005]
7. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. Ann Neurol. 2011; 69(1):163–169. Medline 21280086. [PubMed: 21280086]
8. Shao H, Breitner JCS, Whitmer RA, et al. Hormone therapy and Alzheimer disease dementia. Neurology. 2012; 79(18):1846–1852. Medline 23100399. [PubMed: 23100399]
9. Daniel JM, Bohacek J. The critical period hypothesis of estrogen effects on cognition: insights from basic research. Biochim Biophys Acta. 2010; 1800(10):1068–76. Medline 20100548. [PubMed: 20100548]
10. Barrett-Connor E, Laughlin GA. Endogenous and exogenous estrogen, cognitive function, and dementia in postmenopausal women: evidence from epidemiologic studies and clinical trials. Semin Reprod Med. 2009; 27(3):275–282. Medline 19401958. [PubMed: 19401958]

11. Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after menopause: a meta-analyses of treatment trials. Maturitas. 2010; 66(1):56–71. Medline 20202765. [PubMed: 20202765]
12. Taylor HS, Manson JE. Update in hormone therapy use in menopause. J Clin Endocrinol Metab. 2011; 96(2):255–264. Medline 21296989. [PubMed: 21296989]
13. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. 1998; 19(1):61–109. Medline 9492970. [PubMed: 9492970]
14. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288(3):321–333. Medline 12117397. [PubMed: 12117397]
15. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. JAMA. 2004; 291(14):1701–1712. Medline 15082697. [PubMed: 15082697]
16. Rapp SR, Legault C, Espeland MA, et al. Validation of a cognitive assessment battery administered by telephone. J Am Geriatr Soc. 2012; 60(9):1616–1623. Medline 22985137. [PubMed: 22985137]
17. De Jager CA, Budge MM, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. Int J Geriatr Psychiatry. 2003; 18(4):318–324. Medline 12673608. [PubMed: 12673608]
18. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study: a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials. 1998; 19(6):604–621. Medline 9875839. [PubMed: 9875839]
19. Albert M, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. Int J Neurosci. 1991; 57(3–4):167–178. Medline 1938160. [PubMed: 1938160]
20. Reitan, R. Trail Making Test. Manual for administration and scoring. Tucson, AZ: Reitan Neuropsychological Laboratory; 1975.
21. Mrazik M, Millis S, Drane DL. The oral trail making test: effects of age and concurrent validity. Arch Clin Neuropsychol. 2010; 25(3):236–243. Medline 20197294. [PubMed: 20197294]
22. Benton A. Differential behavioral effects in frontal lobe disease. Neuropsychologia. 1968; 6:53–60.
23. Wechsler, D. Manual for the Wechsler Adult Intelligence Scale-Revised WAIS-R. New York: Psychological Corporation; 1981.
24. De Craen AJ, Heeren TJ, Gussekloo J. Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. Int J Geriatr Psychiatry. 2003; 18(1):63–66. Medline 12497557. [PubMed: 12497557]
25. Littell, RC.; Milliken, GA.; Stroup, WW.; Wolfinger, RD. SAS System for Mixed Models. Cary, NC: SAS Institute, Inc; 1996.
26. Delis, DC.; Kramer, J.; Kaplan, E. The California Verbal Learning Test. New York: The Psychological Corporation; 1987.
27. Ryan J, Carriere I, Scali J, Ritchie K, Ancelin ML. Life-time estrogen exposure and cognitive functioning in later life. Psyschoneuroendocrinnology. 2009; 34(2):287–298.
28. Kang JH, Grodstein F. Postmenopausal hormone therapy, timing of initiation, APOE, and cognitive decline. Neurobiol Aging. 2012; 33(7):1129–1137. Medline 21122949. [PubMed: 21122949]
29. Almeida OP, Lautenschlager NT, Vasikaran S, Leedman P, Gelavis A, Flicher L. A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition, and quality of life. Neurobiol Aging. 2006; 27(1):141–149. Medline 16298249. [PubMed: 16298249]
30. Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Trial. Am J Med. 2002; 113(7):543–548. Medline 12459399. [PubMed: 12459399]

31. Laughlin GA, Kritz-Silverstein D, Barrett-Connor E. Endogenous oestrogens predict 4-year decline in verbal fluency in postmenopausal women: the Rancho Bernardo Study. Clin Endocrinol. 2010; 72(1):99–106. Medline 19508596.

32. Rocca WA, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. Neurodegener Dis. 2012; 10(1–4):175–178. Medline 22269187. [PubMed: 22269187]

33. Sherwin BB. Estrogen and cognitive aging in women. Neuroscience. 2006; 138(3):1021–1026. Medline 16310965. [PubMed: 16310965]

34. Evans DA, Grodstein F, Loewenstein D, Kaye J, Weintraub S. Reducing case ascertainment costs in US populations studies of Alzheimer's disease, dementia, and cognitive impairment – Part 2. Alzheimers Dement. 2011; 7(1):110–123. Medline 21255748. [PubMed: 21255748]

35. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004; 291(24):2947–2958. Medline 15213206. [PubMed: 15213206]

36. Espeland MA, Pettinger M, Falkner KL, et al. Demographic and health factors associated with enrollment in posttrial studies: The Women's Health Initiative Hormone Therapy trials. Clin Trials. 2013 EPub.

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For a list of all the investigators who have contributed to WHI science, please visit: https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

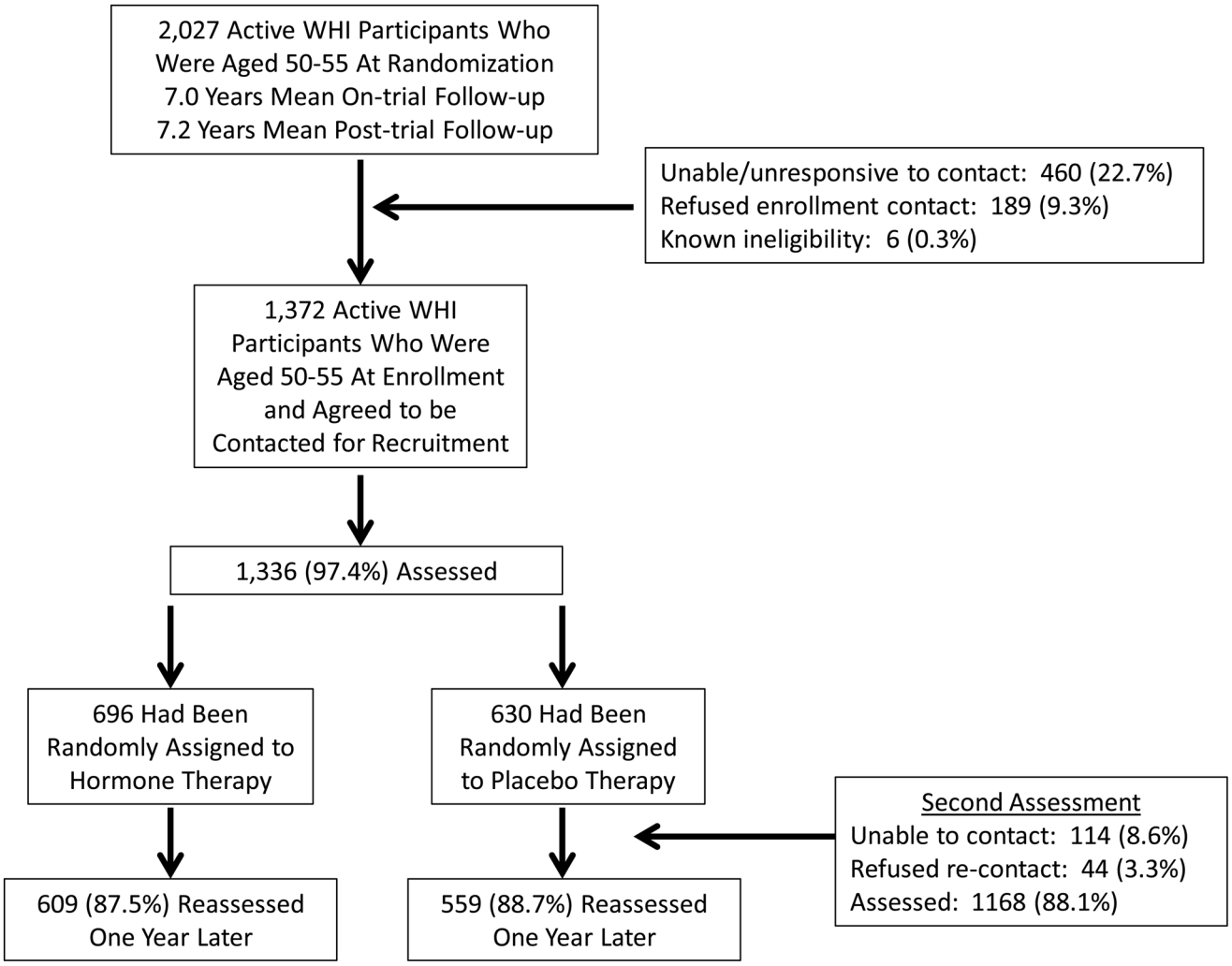

Figure 1.
CONSORT diagram describing WHIMSY enrollment and retention.

Table 1

Distribution of risk factors for cognitive impairment at the time of WHI randomization for WHIMSY participants grouped by WHI treatment assignment.

Risk Factor for Cognitive Impairment	WHI Assignment Mean (SD) or N (%)		p-value
	Hormone Therapy N=696	Placebo N=630	
Age, yrs	53.0 (1.3)	52.9 (1.3)	0.36
Age at Last Menstrual Period, yrs	46.1 (6.3)	46.1 (6.2)	0.89
Education			
High school or less	112 (16.3)	97 (15.5)	0.70
At least some college	577 (83.7)	530 (84.5)	
Race/Ethnicity			
African-American	85 (12.2)	80 (12.7)	
American Indian	2 (0.3)	3 (0.5)	
Asian	9 (1.3)	5 (0.8)	0.46
Hispanic	29 (4.2)	28 (4.4)	
Non-Hispanic White	557 (80.0)	509 (80.8)	
Other/Multiple	14 (2.0)	5 (0.8)	
Smoking Status			
Never	337 (48.6)	299 (47.7)	
Former	203 (31.5)	226 (36.0)	0.37
Current	106 (16.4)	102 (16.3)	
Alcohol Intake			
None	159 (22.9)	155 (24.8)	
<1 per day	471 (68.0)	401 (64.1)	0.27
≥1 per day	63 (9.1)	70 (11.2)	
Body Mass Index—kg/m^2			
<20	16 (2.3)	14 (2.2)	
20–25	208 (30.0)	170 (27.1)	
25–29	217 (31.3)	192 (30.6)	0.62
30–34	145 (20.9)	137 (21.9)	
≥ 35	107 (15.4)	114 (18.2)	
Hypertension Status			
No	547 (78.6)	497 (78.9)	0.94
Yes	146 (21.0)	131 (20.8)	
Missing	3 (0.4)	2 (0.3)	
Prior Cardiovascular Disease*			
No	542 (77.9)	510 (81.0)	0.30

Risk Factor for Cognitive Impairment	WHI Assignment Mean (SD) or N (%)		p-value
	Hormone Therapy N=696	Placebo N=630	
Yes	44 (6.3)	39 (6.2)	
Missing	110 (15.8)	81 (12.9)	
Hysterectomy			
No	432 (62.1)	382 (60.6)	0.59
Yes	264 (37.9)	248 (39.4)	
Age at Hysterectomy, yrs			
<30	30 (11.4)	35 (14.1)	
30–34	60 (22.8)	55 (22.2)	
35–39	59 (22.4)	52 (21.0)	0.70
40–44	51 (19.4)	57 (23.0)	
45–49	55 (20.9)	41 (16.5)	
50–54	8 (3.0)	8 (3.2)	
Years Since Last Regular Menstrual Period			
Prior hysterectomy	8.4 (7.5)	9.6 (8.6)	0.11
No prior hysterectomy	3.9 (3.4)	4.0 (2.8)	0.69
Prior Hormone Therapy At WHI Recruitment			
Never	336 (52.1)	279 (46.8)	0.090
Past	203 (31.5)	222 (37.2)	
Current	106 (16.4)	915 (15.9)	
Adherence (% expected)	0.82 (0.22)	0.83 (0.20)	0.41
Exposure: Adherence x Years	5.51 (2.47)	5.35 (2.53)	0.24

* Other CVD defined as MI, angina, PCTA, stroke, or CABG

Table 2

Mean cognitive function test scores averaged over time for women grouped by treatment assignment with adjustment for age and visit.

Cognitive Function Test	Treatment Assignment				Mean Standardized Difference HT Minus Placebo:* SD Units [95% CI]	p-value HT vs Placebo	p-value MPA vs No MPA
	CEE+MPA Mean (SE)	CEE+MPA Placebo Mean (SE)	CEE Mean (SE)	CEE Placebo Mean (SE)			
Global cognitive function							
TICS-m	38.08 (0.20)	38.26 (0.21)	37.67 (0.26)	37.28 (0.27)	0.02 [−0.08, 0.12]	0.66	0.23
Verbal Memory							
EBMT immediate	10.20 (0.07)	10.17 (0.07)	9.98 (0.09)	10.01 (0.09)	−0.00 [−0.09, 0.09]	0.97	0.70
EBMT delayed	9.88 (0.08)	9.78 (0.08)	9.57 (0.10)	9.59 (0.10)	0.02 [−0.07, 0.12]	0.67	0.49
Sum	20.08 (0.13)	19.95 (0.14)	19.55 (0.17)	19.61 (0.18)	0.01 [−0.08, 0.11]	0.82	0.56
Attention							
OTMT-A	8.95 (0.13)	8.57 (0.14)	8.97 (0.16)	8.93 (0.17)	−0.06 [−0.15, 0.03]	0.16	0.26
Executive function							
OTMT-B	43.26 (2.19)	42.14 (2.32)	46.76 (2.81)	50.02 (2.91)	−0.00 [−0.10, 0.10]	0.95	0.35
Verbal fluency							
VF-A	21.04 (0.25)	20.65 (0.27)	18.90 (0.33)	19.91 (0.34)	−0.05 [−0.15, 0.05]	0.29	0.02
Working memory							
Digits forward	8.33 (0.11)	8.60 (0.12)	8.64 (0.14)	8.48 (0.14)	−0.02 [−0.12, 0.08]	0.66	0.09
Digits backward	7.10 (0.11)	7.09 (0.12)	7.26 (0.14)	7.11 (0.15)	0.03 [−0.07, 0.13]	0.55	0.62
Sum	15.42 (0.20)	15.69 (0.22)	15.90 (0.26)	15.59 (0.27)	0.00 [−0.10, 0.11]	0.93	0.23
Composite	0.03 (0.04)	0.04 (0.05)	−0.09 (0.06)	−0.08 (0.06)	−0.01 [−0.11, 0.09]	0.78	0.94

*Ordered so that positive score indicates better cognitive function in HT; Logarithm transformations used for executive function

1Fitted mean (95% confidence interval) treatment effects for verbal fluency: CEE+MPA 0.07 [−0.06,0.19]; CEE −0.17 [−0.33,−0.02]

Table 3

Consistency of intervention effects for women grouped by characteristics at WHI enrollment: time since last menstrual period and prior use of hormone therapy.

Cognitive Function Test	Years Between WHI Enrollment and Last Menstrual Period**			Prior Use of Hormone Therapy			
	0–4 years N=643 Mean [95% CI]*	5+ years N=404 Mean [95% CI]*	p-value	No N=615 Mean [95% CI]*	Former N=425 Mean [95% CI]*	Current N=201 Mean [95% CI]*	p-value
Global cognitive function	0.10 [−0.04, 0.24]	−0.09 [−0.27, 0.09]	0.10	0.10 [−0.04, 0.25]	−0.11 [−0.29, 0.06]	0.06 [−0.20, 0.31]	0.17
Verbal memory	0.05 [−0.09, 0.18]	0.03 [−0.13, 0.20]	0.92	0.09 [−0.04, 0.23]	−0.01 [−0.17, 0.15]	−0.02 [−0.26, 0.22]	0.56
Attention	−0.06 [−0.17, 0.04]	−0.04 [−0.17, 0.09]	0.79	−0.08 [−0.18, 0.03]	0.01 [−0.11, 0.14]	−0.07 [−0.25, 0.12]	0.54
Executive function	0.02 [−0.12, 0.16]	0.09 [−0.09, 0.26]	0.56	−0.07 [−0.22, 0.07]	0.13 [−0.04, 0.30]	−0.04 [−0.29, 0.21]	0.18
Verbal fluency	0.07 [−0.07, 0.21]	−0.14 [−0.32, 0.04]	0.07	0.10 [−0.04, 0.24]	−0.25 [−0.42,−0.08]	0.04 [−0.21, 0.29]	0.008
Working memory	0.00 [−0.14, 0.15]	0.01 [−0.17, 0.19]	0.97	0.02 [−0.13, 0.17]	0.02 [−0.15, 0.20]	0.00 [−0.26, 0.26]	0.99
Composite	0.05 [−0.09, 0.19]	−0.01 [−0.19, 0.16]	0.56	0.07 [−0.07, 0.21]	−0.04 [−0.21, 0.13]	−0.01 [−0.26, 0.24]	0.61
Geriatric depression scale	−0.01 [−0.15, 0.13]	0.01 [−0.16, 0.19]	0.81	0.09 [−0.05, 0.23]	0.01 [−0.16, 0.18]	−0.24 [−0.49, 0.01]	0.07

*Positive value signals that women assigned to hormone therapy had better mean performance than women assigned to placebo; Logarithm transformations used for executive function

**Missing for N=279 women for last menstrual period (CEE+MPA: 137; CEE-Alone: 142) and N=85 for prior use of hormone therapy