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Cognitive effects of hormone therapy continuation or discontinuation in a sample of women at risk for Alzheimer's disease

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Abstract

Use of estrogen-based hormone therapy (HT), as a protection from cognitive decline and Alzheimer's disease, is controversial although cumulative data supports HT use when initiated close to menopause onset with estrogen formulations containing 17 β -estradiol (17 β -E) being preferable to conjugated equine estrogen formulations. Little is known regarding specific populations of women who may derive benefit from HT. Women with heightened risk for AD (aged 49–69), all of whom were taking HT for at least one year, most of whom initiated HT close to menopause onset, underwent cognitive assessment followed by randomization to continue or discontinue HT. Assessments were repeated at two years after randomization. Women who continued HT performed better on cognitive domains composed of measures of verbal memory, and combined attention, working memory, and processing speed measures. Women who used 17 β -E versus conjugated equine estrogen, whether randomized to continue or discontinue HT showed better verbal memory performance at the 2-year follow-up assessment. An interaction was also found with HT randomization and family history of AD in a first degree relative. All women offspring of patients with AD declined in verbal memory however, women who continued HT declined less than women who discontinued HT. Women without a first-degree relative with AD showed verbal memory improvement (likely due to practice effects) with continuance and declined with discontinuance of HT. Continuation of HT use appears to protect cognition in women with heightened risk for AD when initiated close to menopause onset.

Keywords

Hormone therapy; Alzheimer's disease; cognition; postmenopausal women

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Objective

Estrogen-based hormone therapy (HT) remains a controversial intervention for use in menopausal and postmenopausal women. Cumulative studies of HT use in middle-aged and older postmenopausal women suggest possible protection against normal age-related cognitive decline and Alzheimer's disease (AD)^{1, 2}. Negative cognitive findings appear to be related to type of HT formulation with better verbal memory associated with use of 17-beta estradiol (17 β -E) compared to conjugated equine estrogen (CEE)³. In addition, timing of initiation is associated with increased probable dementia when HT is started in late menopause (i.e., after 65 years of age)⁴. Little is known however, regarding use of HT in a population of younger postmenopausal women with heightened risk for late onset AD. Presence of the apolipoprotein- ϵ 4 (APOE- ϵ 4) and family history of AD are known risk factors for late onset AD and cognitive aging. History of depression is also considered a putative risk for cognitive decline and AD^{5, 6}. Herein, we present secondary analyses of cognitive findings from a two-year prospective brain imaging study and randomized trial of HT continuation (HT+) or discontinuation (HT-) in a sample of middle-aged postmenopausal HT users women (aged 49-69 years) with one or more of these risk factors.

Study design included brain imaging and extensive neuropsychological testing at baseline^{7, 3} and two-year follow-up after randomization (see ⁸ for imaging follow-up). We hypothesized that HT use would provide protection from age-related cognitive changes in a sample of women all of whom had elevated risk for dementia. We also explored relationships between HT continuation or discontinuation with APOE- ϵ 4 carriership, family history of AD, personal history of depression, surgical versus natural menopause, and use of progestogens.

Methods

Subjects were participants who completed an NIA funded longitudinal study that recruited cognitively normal (verified by neuropsychological assessment results within normal range for age and education in addition to clinically normal PET and MRI scans, and normal physical and neurological examinations) euthymic, postmenopausal women aged 49-69 years of age, with heightened risk for AD, all of whom were receiving estrogen-containing HT for at least one year. Heightened risk for AD was characterized as having a first-degree relative with AD, documented carriership of APOE- ϵ 4, and/or a history of major depression. Only women who were not in a current mood episode were recruited into the study. For the full list of inclusion and exclusion criteria please see Wroolie et al. ³. Following a baseline evaluation (time 1), subjects were randomized to HT continuation (HT+) or discontinuation (HT-) and re-evaluated at a two-year follow-up (time 2). No changes in HT regimens were implemented by the investigators prior to randomization or thereafter (in the HT+ group). Additionally, as part of the study agreement, no HT regimen changes were implemented by the participants' treating physician after randomization. Given the nature of the study design, participants were aware of their randomization condition (HT+ versus HT-), while members of the research team who performed evaluations and neuroimaging analyses were blinded to the randomization groups. Post randomization HT exposure was monitored and verified each year by estradiol blood levels.

An extensive neuropsychological evaluation that included measures of attention and processing speed, verbal and visual memory, executive functioning, and subjective memory complaints, was conducted at time 1 and time 2 by the study neuropsychologist. The measures included the Auditory Consonant Trigrams (ACT⁹), Benton Visual Retention Test (BVRT¹⁰), Buschke Selective Reminding Test (BSRT¹¹), Color Trail Making Test (Color Trails 1 & 2¹²), Rey-Osterrieth Complex Figure Test (RCFT^{13, 14}), Delis Kaplan Executive Function System (DKEFS¹⁵) Color-Word and Verbal Fluency Tests, Wechsler Adult Intelligence Scale-Third Edition (WAIS-III¹⁶) Digit Span, Letter Number-Sequencing, and Digit Symbol Coding, the Wechsler Memory Scale-third edition (WMS-III¹⁷) Logical Memory I and II, and the Memory Function Questionnaire (MFQ¹⁸). The two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI¹⁹) was utilized to estimate intellectual functioning. (See Wroolie, et al. ³ for complete description of neuropsychological measures.) Additionally, depressive symptoms were assessed by an evaluation by the study psychologist in addition to the 21-item Hamilton Depression Rating Scale (HDRS-21²⁰) every 3 months to ensure stable mood. No women experienced a major mood episode and HDRS-21 scores remained within a clinically normal range. Sixty-eight women completed the baseline assessment however, 14 were lost to the two-year assessment due to attrition. No differences in demographic or clinical characteristics existed between completers and dropouts. The present study reports on the effects of HT randomization of all women completers (N=54).

In order to reduce Type 1 errors due to multiple comparisons, data from individual measures were combined *a priori* into cognitive domains based on theory, common practice in the literature ^{21, 22,23, 24}, and standard clinical practice each measure is purported to assess²⁵. Composite scores of attention/working memory/processing speed, verbal memory, visual memory, executive functioning, and subjective memory using z-score transformations around the mean separately for baseline and final scores as follows:

- Attention/working memory/processing speed: WAIS-III Digit Span, Letter Number-Sequencing, and Digit Symbol Coding, ACT total, BSRT 1st trial learning, WMS-III Logical Memory 1st trial learning, Color Trails 1, DKEFS Word Reading.
- Verbal memory: BSRT trials 2-8 and delayed recall, WMS-III Logical Memory I and II (total, thematic and recognition scores)
- Visual memory: BVRT total and error scores, RCFT immediate and delayed recall
- Executive functions: DKEFS Color Word Inhibition, Color Word Inhibition/Switching, Verbal Fluency Category Switching and Accuracy, and Letter, Color Trails 2
- Subjective memory: Memory Function Questionnaire total score

Statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL) with significance set at the $p < .05$ level. ANCOVA analyses controlling for age, years of education, baseline cognitive domains, were used to examine the effects of HT continuation or discontinuation at the final assessment, two years later.

Since baseline findings showed differences in verbal memory between women (N=68) who used 17 β -E versus conjugated equine estrogen³, t-tests were conducted between 17 β -E and CEE users at the final assessment regardless of HT randomization. ANCOVA analyses controlling for age, years of education, and baseline cognitive domains were also conducted within the 17 β -E group. Due to the limited sample size in the CEE discontinuation group (N=5), a within group ANCOVA was not possible.

Because women were randomly assigned to HT+ or HT- groups and not according to specific risk factors or clinical variables, exploratory ANCOVA analyses were conducted to determine whether there were interactions between HT randomization controlling for the variables of APOE- ϵ 4 carriership, family history of AD, personal history of depression, surgical versus natural menopause, and use of progestogens. Chi-square and t-tests were conducted between HT randomization groups and clinical variables that were used in the ANCOVA analyses.

Results

In the parent study, 68 participants completed baseline brain imaging and neuropsychological testing. Four of these participants dropped out, one to abnormal brain imaging and three changed their mind about participating. Of the 64 participants who were randomized, four were lost to follow up, one randomized on and five randomized off discontinued participation. The active treatment group was favored in terms of numbers however no significant differences were found between women who completed or did not complete all baseline study procedures in terms of age, education, IQ, MMSE, years of endogenous estrogen, age at menopause, time since menopause, age at menarche, BMI, presence of the ApoE- ϵ 4 allele, family history of AD, depression history, type of estrogen, use of progestin, or whether they had natural or surgical menopause.

Demographic and clinical data of HT randomization groups are presented in table 1. No differences in age, education, FSIQ, BMI, endogenous and exogenous estrogen exposure, age at menarche, age at menopause, or estradiol level, were found between any HT + and HT- groups.

Because all women had an elevated risk for AD, carriership of one or two APOE- ϵ 4 alleles was higher (21/54 or 38.9%) than what is typically seen in population studies (23%)²⁶. In the *a priori* study design, women were randomly assigned to HT+ or HT- groups and not to risk factors or other clinical variables. A significant difference was found in the distribution of HT and APOE- ϵ 4 carriership groups but not for family history of AD, type of estrogen (i.e., 17 β -E versus CEE), progestogen use, natural versus surgical menopause, or history of depression (table 2). No significant differences in demographic or clinical variables were found within each estrogen type group for APOE ϵ 4 status (table 3). The most common risk factor was a history of depression (42/54) and there were no significant differences in the number of risk factor distributions ($\chi^2(3)=2.08$, $p=.56$) or antidepressant use ($\chi^2(1)=.63$, $p=.58$) between randomization groups.

HT Randomization

Results are presented in table 4. ANCOVA results showed a significant main effect in the verbal memory domain. The women randomized to stay on HT improved in this domain over time whereas the group randomized off declined. A significant main effect was also found in the domain of attention/working memory/processing speed at final assessment due to HT randomization when controlling for age and education. Both groups declined in the attention/working memory/processing speed domain however, the group that was randomized off HT showed a greater decline. There were no significant main effects for the visual memory and executive function domains or for subjective memory complaints.

Estrogen Type Results

17 β -E versus CEE—At the two-year follow up assessment, women who continued or discontinued 17 β -E had higher scores in the verbal memory domain than those who continued or discontinued CEE ($t(52)=2.56$, $p=.01$; .23 versus -.46), respectively. However, the difference in the verbal memory domain was less than 1 standard deviation whereas baseline difference was greater than 3 standard deviations ($t(52)=3.18$, $p<.01$; 1.37 versus -3.00).

17 β -E users—Results are presented in table 5. A significant main effect was found in the verbal memory domain due to HT randomization in the 17 β -E users. Both HT randomization groups declined however those women who discontinued 17 β -E had a greater decline than the women who continued 17 β -E. Similarly, both groups declined but the group that discontinued 17 β -E had a greater decline than the group that remained on 17 β -E. There were no significant main effects of 17 β -E randomization in the attention/working memory/processing speed, visual memory, executive functioning domains, or for subjective memory complaints.

Exploratory Analyses Results

Significant interactions were found between HT randomization and family history of AD in the domains of verbal and visual memory (table 6). Women with a family history of AD exhibited a decline in the domain of verbal memory whether randomized to continue or discontinue HT however, those who discontinued had a greater decline than those who continued HT. Women without a family history of AD improved when they continued and declined when they discontinued HT. No significant main effects for family history of AD were found in the verbal memory domain ($F(1)=.33$, $p=.57$). In the visual memory domain, women with a positive family history of AD showed a slight decline in the visual memory domain when they continued HT but showed a large improvement when they discontinued HT. An opposite pattern was seen in the women without a family history, i.e. they improved with HT continuation and declined with discontinuation (table 6). No significant main effects for family history of AD were found in the visual memory domain ($F(1)=3.00$, $p=.09$). No significant interactions or main effects were found between HT randomization, APOE- $\epsilon 4$ carriership, progesterone use, natural versus surgical menopause, or history of depression with any cognitive domains or subjective memory complaints (data not shown).

Discussion

The results of this study showed subtle, yet differential effects on cognition as a result of randomized continuation versus discontinuation of HT in a sample of women with elevated risk for AD. Two years after randomization of HT, women who continued HT performed better than women who discontinued HT on attention/working memory/processing speed and verbal memory domains. Although the women randomized to continue HT showed a slight improvement in verbal memory, this was likely due to practice effects (i.e. improvement on cognitive tests due to repeated administration). Essentially, the women who continued HT maintained whereas women who discontinued HT declined in specific cognitive abilities across the two years compared to their own baseline performance.

Given that overall cognitive performance among study women was considered to be within normal range for their age and education, it was expected that improvements would occur secondary to practice effects, particularly in the memory domains²⁷. Although the decline in the HT discontinuation group was less than one standard deviation and likely clinically insignificant, it suggests a loss of expected practice effects. The loss of practice effects has been shown to differentiate between cognitively normal adults, adults with mild cognitive impairment, and dementia over short- and long-term retesting with greater loss being associated with MCI and dementia²⁸⁻³⁰. All women remained cognitively normal but the loss of these practice effects in the HT discontinuation group suggests early cognitive changes that may not be clinically apparent.

Not surprisingly, both HT randomization groups declined in the attentional/working memory/processing speed domain because this domain included cognitive abilities that normally decline with aging. However, compared to the women who remained on HT, the women who discontinued HT showed a greater decline over time. The findings of less decline in the attentional/working memory/processing speed domain in the HT continuers compared to the discontinuers, corroborate our PET imaging findings³¹ where continuation of HT was associated with relative preservation of frontal and parietal cortical metabolism, areas shown to mediate these cognitive abilities^{32, 33}.

Subtle verbal and visual memory and processing speed declines are shown to predict AD years prior to diagnosis³⁴⁻³⁶ with verbal memory declines having the strongest association with conversion to AD in cognitively intact individuals with APOE-ε4^{37, 38}.

Neuropathological changes of AD are also associated with greater rates of decline in attention/working memory and episodic (verbal) memory^{39, 40} and the combination of verbal and working memory declines may accelerate normal age-related memory declines⁴¹. In this sample of cognitively intact women (verified by clinical neuropsychological assessment in addition to clinical evaluation of MRI and PET brain imaging), our findings suggest that continuation of HT may slow normal age-related cognitive changes. Normal age-related cognitive changes are thought to be heterogeneous across older adults⁴² and given the specificity of cognitive findings in this sample of women with elevated risk of AD, HT continuation may at least for some, slow early cognitive changes associated with AD (See⁴³ for a review of early cognitive changes of AD). However, further longitudinal investigation is necessary to determine what if any HT use has on early AD changes.

We previously reported that at baseline women using 17 β -E performed three standard deviations higher in verbal memory than women using CEE, and that their verbal memory performances were positively correlated with metabolic activity in Wernicke's and auditory association areas⁷. In this follow up study, we continued to find that women who either continued or discontinued 17 β -E performed significantly better in the verbal memory domain compared to women who either continued or discontinued CEE at the final assessment, although cognitive differences in relation to the type of estrogen was not as great. It remains to be determined whether regression to the mean and/or practice effects played a particular role for the smaller difference between estrogen type performance at the second assessment regardless, women who were using or had ever used CEE continued to exhibit lower verbal memory overall. Only one other small observational study evaluated cognitive differences between 17 β -E and CEE; this study similarly showed better verbal memory with 17 β -E compared to CEE⁴⁴.

In addition, the women who continued 17 β -E again, performed better in the verbal memory domain compared to those women who discontinued 17 β -E. These findings are consistent with our previously published imaging data that showed preserved precuneus/posterior cingulate metabolism (an area associated with verbal memory performance⁴⁵) in women who continued 17 β -E versus those women who either discontinued 17 β -E or remained on CEE³¹. Our findings are also consistent with animal studies that show neuroprotective effects of 17 β -estradiol in hippocampal and prefrontal structures and related cognitive functioning⁴⁶⁻⁴⁸ and suggest that CEE does not provide the same benefits as 17 β -E either in terms of brain metabolism or cognition.

Cross-sectional studies that compare HT use to never use show positive, neutral, and negative cognitive effects of HT use (see⁴⁹ for a review). Further examination of these cross-sectional studies suggests that HT formulation and timing of initiation may be responsible for the controversies in the literature. The women in our study all began using HT during the "window of opportunity" for HT use to be effective for cognition (i.e. during perimenopause or early postmenopause) and our findings are limited to women who were either current users or ever users within that time frame. Because women used various HT dosages, formulations, and routes of administration (i.e. oral versus transdermal), it was not possible to determine the cognitive effects of each specific type of HT administration or progestogen use. However, our findings support both human and animal studies that showed cognitive benefits with 17 β -E⁵⁰⁻⁵² but not with CEE⁴.

Interestingly, family history of AD moderated the effects of HT continuation or discontinuation on cognition. Family history of AD as well as female gender, are shown to be the most robust predictors of late onset AD besides advanced age⁵³⁻⁵⁵ regardless of APOE- ϵ 4 status. Declines in attention, memory, and executive functioning are possibly shown as early as the 6th decade of life, but certainly after 70 years of age in adult children of confirmed AD patients⁵⁶. Our findings suggest that HT may provide protection to verbal memory in women without a family AD history and possibly slow progression of verbal memory decline in women with a family history of AD during what may be a critical period for intervention. HT also appeared to be protective of visual memory consistent with other

studies but only in women without a family history of AD. To our knowledge, this is the only study that has demonstrated cognitive effects of HT in relation to adult AD offsprings.

Contrary to what was expected, we did not find any interactions between HT randomization and APOE-ε4 status, although power was reduced due to limited sample size. We also found no interactions between HT randomization and history of depression. However, the majority of women in the sample had a history of depression (42/54) thus the ability to detect randomization effects was limited. The window of opportunity theory posits that HT use in menopause transition or early post-menopause may slow cognitive changes. Recent data from the Cache County Study showed a 30% reduction in AD risk in women who started any type of HT within 5 years of menopause⁵⁷. The majority of women in our sample (89%) started HT during these early stages of menopause lending support to the window of opportunity theory. Timing of initiation of HT may be even more critical for women with heightened risk of AD. WHIMS, the largest double blind, randomized HT clinical trial showed negative cognitive effects with CEE use when started after the age of 65 years⁴. The majority of women in the current sample began HT either during menopause transition or in early post-menopause, a time when the benefits of HT may be realized.

Little is known regarding the duration of HT use or the age at which it should be discontinued and further research is needed. In the current sample there was no difference in total lifetime estrogen exposure (endogenous estrogen exposure and HT use) between randomization groups at baseline although obviously there was a two-year difference at the final assessment. Perhaps duration of lifetime estrogen exposure may serve as a better measure in estimating length of HT use which may be conferring protection of cognitive function. Longer lifetime estrogen exposure, including ever use of HT, is shown to be associated with better verbal memory, visual memory, working memory, as well as a general measure of cognitive decline however, these benefits are not likely evident until older age when interventions may not be effective^{58, 59} or may be harmful⁴. The women in our sample were cognitively intact and the differences found in cognitive changes with randomization suggest that subtle but distinct changes may take place at an earlier age with estrogen deprivation.

Limitations

Study limitations were mainly due to small sample size, especially in the CEE discontinuation group. Overall, our significant findings had small effect sizes and may not be clinically significant. However, the original study was powered for changes in regional cerebral metabolism and not cognition hence, these analyses were under powered. Comparisons between specific HT formulations as well as individual AD risk factors and HT randomization were not possible due to limited sample sizes. Most of the women in our sample had a history of depression however we could not determine the impact of any particular risk or combination of risks on cognition.

Conclusion

To our knowledge, this is the first study to examine the cognitive effects of HT continuation or discontinuation in a population of cognitively normal women, verified by

neuropsychological performances that fell within age-related normal limits as well as clinically evaluated brain imaging. Our findings suggest that HT use may confer protection/maintenance of cognitive functioning in women at heightened risk of AD, particularly those with a family history of AD, at least in women who are currently cognitively intact. Hormonal formulations that contain 17 β -E, rather than CEE, may be the most beneficial. Because family history of AD and APOE- ϵ 4 carriership are non-modifiable risks for AD, interventions that may prevent or slow the progression of AD could have a profound impact on incidence rates. The findings from the current study if replicated in large samples of postmenopausal women, may help to reconcile some of the controversy that exists in the literature however, further studies are warranted to help clarify HT use in regards to risk/benefit profiles and specific populations that may benefit.

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Table 1

HT group demographic and clinical variables

	HT+ N=30		HT- N=24		t	df	p
	Mean	SD	Mean	SD			
Age	58.2	4.37	57.9	5.01	-.26	52	.80
Education	16.0	2.08	16.5	1.93	.88	52	.39
FSIQ	122.8	6.72	122.6	8.40	-.07	52	.95
Endogenous Estrogen (years)	32.8	7.29	34.5	4.27	.98	51	.33
HT use (years)	10.7	4.94	9.9	6.64	-.51	52	.62
Age at Menarche	13.0	1.57	13.0	1.68	-.17	51	.87
Age at Menopause	46.7	6.63	48.1	4.46	.91	52	.37
Baseline BMI	25.7	4.04	25.1	3.04	-.68	52	.50
Final BMI	26.0	3.90	25.9	4.04	-.09	38	.93
Baseline estradiol	36.1	38.45	42.8	23.58	.73	52	.46

Table 2

HT group distributions

	HT+	HT−	$\chi^2(1)$	p
APOEε4+	8	13	4.24	.04
APOEε4−	22	11		
Family Hx of AD+	15	9	.84	.36
Family Hx of AD−	15	15		
17β estradiol	17	19	3.04	.08
CEE	13	5		
Estrogen with progestogen	20	14	.40	.53
Estrogen alone	10	10		
Natural Menopause	16	16	.73	.39
Surgical Menopause	13	8		
Depression Hx+	24	18	.19	.66
Depression Hx−	6	6		

Table 3

Type of HT and APOEε4 status

		17β estradiol (APOEε4- N=22) APOEε4+ N=14)				CEE (APOEε4- N=11) APOEε4+ N=7)					
		Mean	SD	t	df	p	Mean	SD	t	df	p
Age	APOEε4-	57.86	4.44				59.55	4.74			
	APOEε4+	57.21	4.28	.43	34	.67	58.00	6.02	.61	16	.55
Education	APOEε4-	16.32	1.96				15.59	2.25			
	APOEε4+	16.71	2.16	-.57	34	.57	16.00	1.53	-.42	16	.68
FSIQ	APOEε4-	124.2									
	APOEε4+	3	6.57				120.09	7.34			
		123.2	8.76	.37	34	.72	120.86	7.51	-.21	16	.83
		8									
Endogenous	APOEε4-	33.91	5.49				30.00	9.22			
Estrogen (years)	APOEε4+	35.31	3.61	-.82	33	.42	33.14	7.16	.81	16	.73
HT use (years)	APOEε4-	10.48	6.38				12.72	6.02			
	APOEε4+	8.07	4.21	1.25	34	.22	11.00	4.86	.64	16	.53
Age at Menarche	APOEε4-	13.16	1.71				12.55	1.63			
	APOEε4+	12.85	1.39	.56	33	.58	13.50	1.71	-1.19	16	.25
Age at Menopause	APOEε4-	47.68	5.80				45.86	7.23			
	APOEε4+	47.93	4.46	-.14	34	.89	47.00	6.35	-.34	16	.74
Baseline BMI	APOEε4-	25.25	4.16				26.81	2.65			
	APOEε4+	24.53	3.29	.55	34	.59	25.66	3.73	.78	16	.45
Final BMI	APOEε4-	25.41	3.99				27.31	3.45			
	APOEε4+	25.46	4.22	-.04	25	.97	26.96	4.15	.17	11	.87
Baseline estradiol	APOEε4-	41.00	42.01				40.27	32.88			
	APOEε4+	40.57	23.46	.04	34	.97	28.14	6.52	.95	16	.35

HT randomization group adjusted means (z-scores), standard deviations, and ANCOVA comparing treatment groups at time 2

Table 4

	HT continuers (N=30)				HT discontinuers (N=24)				Partial F test for HT treatment group at time 2		
	Time 1		Time 2		Time 1		Time 2		F*	df	η^2
	M	SD	M	SD	M	SD	M	SD			
Cognitive domain											
Att/WM/PS	.40	3.82	.08	.42	.88	3.58	-.10	.60	4.59	1,49	.04 .09
Verbal Memory	-.76	4.95	-.32	.83	.74	5.38	.40	1.03	7.01	1,49	.01 .13
Visual Memory	.14	2.68	.30	2.28	-.17	3.43	-.30	4.25	.28	1,47	.60 .01
Executive	-.35	2.75	-.07	.62	.43	3.72	.09	.67	.01	1,49	.94 .00
Functioning											
Subjective	.06	1.04	.17	1.05	-.08	.97	-.29	.88	1.80	1,20	.19 .08
Memory											

* All models were adjusted for age, education, and baseline cognitive domain scores; all models were significant at $p < .05$. Att/WM/PS= z-score composites of WAIS-III Digit Span, Letter Number-Sequencing, and Digit Symbol Coding, ACT total, BSRT 1st trial learning, WMS-III Logical Memory 1st trial learning, Color Trails 1, DKEFS Word Reading; Verbal Memory= z-score composites of BSRT trials 2-8 and delayed recall, WMS-III Logical Memory I and II (total, thematic and recognition scores); Visual Memory: z-score composites of BVRT total and error scores, RCFT immediate and delayed recall; Executive Functions: z-score composites of DKEFS Color Word Inhibition, Color Word Inhibition/Switching, Verbal Fluency Category Switching and Accuracy, and Letter, Color Trails 2; Subjective Memory: Memory Function Questionnaire

17 β -estradiol randomization group adjusted means (z-scores), standard deviations, and ANCOVA comparing treatment groups at time 2

Table 5

	17 β estradiol continuers (N=17)						17 β estradiol discontinuers (N=19)						Partial F test for HT treatment group at time 2		
	Time 1			Time 2			Time 1			Time 2			F*	df	η^2
	M	SD		M	SD		M	SD		M	SD				
Cognitive domain															
Att/WM/PS	.80	4.53	.14	.38	.38	1.20	3.89	-.07	.56	3.60	1.31	.07	.10		
Verbal Memory	.62	4.94	-.17	.75	2.03	4.26	.59	.98	4.77	1.31	.04	.13			
Visual Memory	.34	3.13	.13	2.35	-.03	3.68	.38	3.89	.21	1.29	.65	.01			
Executive	.05	2.31	-.07	.62	1.10	3.27	.23	.62	.66	1.31	.42	.02			
Functioning															
Subjective	.31	.92	.26	1.03	-.17	1.01	-.37	.95	1.38	1.13	.26	.10			
Memory															

* All models were adjusted for age, education, and baseline cognitive domain scores; all models were significant at p .05. Att/WM/PS= z-score composites of WAIS-III Digit Span, Letter Number-Sequencing, and Digit Symbol Coding, ACT total, BSRT 1st trial learning, WMS-III Logical Memory 1st trial learning, Color Trails 1, DKEFS Word Reading; Verbal Memory= z-score composites of BSRT trials 2-8 and delayed recall, WMS-III Logical Memory I and II (total, thematic and recognition scores); Visual Memory: z-score composites of BVRT total and error scores, RCFT immediate and delayed recall; Executive Functions: z-score composites of DKEFS Color Word Inhibition, Color Word Inhibition/Switching, Verbal Fluency Category Switching and Accuracy, and Letter, Color Trails 2; Subjective Memory: Memory Function Questionnaire

Table 6

Interaction of HT randomization and Family History of AD group baseline and adjusted means (z-scores), standard deviations, and ANCOVA comparing treatment groups at time 2

		HT continuers				HT discontinuers				Partial F test for HT treatment group at time 2		
		Time 1		Time 2		Time 1		Time 2		F*	df	η^2
		M	SD	M	SD	M	SD	M	SD			
Cognitive domain	+ FamHx	.97	3.13	.19	.47	2.18	4.70	.26	.56	2.09	1,47	.16
	-Fam Hx	-.17	4.44	-.02	.35	.10	2.60	-.32	.52			
Verbal Memory	+FamHx	-.15	4.75	-.50	.79	4.43	3.45	1.04	.91	6.29	1,47	.02
	-Fam Hx	-1.36	5.22	-.14	.87	-1.48	5.17	.02	.93			.12
Visual Memory	+ FamHx	.46	2.20	.33	2.52	.83	3.58	2.25	2.98	4.98	1,45	.10
	-Fam Hx	-.18	3.13	.28	2.11	-.78	3.32	-1.76	4.25			
Executive Functioning	+ FamHx	.22	3.11	.12	.65	2.62	3.41	.68	.53	.91	1,47	.35
	-Fam Hx	-.91	2.29	-.26	.54	-.88	3.35	-.27	.47			
Subjective Memory	+ FamHx	.13	1.03	.27	1.15	.14	.97	.87	.53	.91	1,18	.35
	-Fam Hx	.00	1.08	.87	.99	-.21	.98	-.60	1.04			

* All models were adjusted for age, education, and baseline cognitive domain scores; all models were significant at p .05. - Fam Hx continuers (N=15), -Fam Hx discontinuers (N=15), +Fam Hx continuers (N=15), +Fam Hx discontinuers (N=9); Att/Wm/PS= z-score composites of WAIS-III Digit Span, Letter Number-Sequencing, and Digit Symbol Coding, ACT total, BSRT 1st trial learning, WMS-III Logical Memory 1st trial learning, Color Trails 1, DKEFS Word Reading, Verbal Memory= z-score composites of BSRT trials 2-8 and delayed recall, WMS-III Logical Memory I and II (total, thematic and recognition scores); Visual Memory: z-score composites of BVRT total and error scores, RCFT immediate and delayed recall; Executive Functions: z-score composites of DKEFS Color Word Inhibition, Color Word Inhibition/Switching, Verbal Fluency Category Switching and Accuracy, and Letter, Color Trails 2; Subjective Memory: Memory Function Questionnaire