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Associations of Pituitary-Ovarian Hormones and White Matter Hyperintensities in Recently Menopausal Women using Hormone Therapy

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Abstract

Objective: Little is known about how menopausal hormone treatment (HT) may influence the development of white matter hyperintensities (WMH) in the brain. This study evaluated the associations of changes in levels of pituitary-ovarian hormones during HT and changes in WMH.

Methods: Women (n = 78 adherent to treatment) enrolled in the Kronos Early Estrogen Prevention Study (KEEPS) underwent brain MRI, and blood collection prior to and following 48 months of randomization to either 0.45 mg/d oral conjugated equine estrogen (o-CEE) daily, 50 μg/d transdermal 17β estradiol (tE2) or placebo pills and patches. Women in the active treatment groups also received oral 200 mg/d micronized progesterone the first 12 d of the month. Estradiol (E2), estrone (E1), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were measured in serum by high sensitive liquid chromatography/mass spectroscopy at baseline and following 48 months of HT. Longitudinal change in WMH volume was determined from FLAIR MRIs using a semi-automated image segmentation algorithm.

Results: Serum levels of FSH, LH, E1 or E2 did not associate with WMH volume at baseline. After 48 months of treatment, smaller increases in WMH associated with decreases in FSH from baseline in the tE2 group and increases in E1 in both tE2 and oCEE groups. Changes in LH did not associate with changes in WMH in any group.

Contributions: JMK conceived study, interpreted data and prepared the manuscript; VMM contributed to conception of the KEEPS, interpreted the hormone data and edited the manuscript; NT analyzed the brain volumes, performed the statistical analysis, and edited manuscript; TGL analyzed the data and edited manuscript; KK conceived and supervised imaging study of KEEPS, interpreted data and edited the manuscript

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Conclusions: Circulating levels of pituitary-ovarian hormones associate with changes in WMH volume in recently menopausal women using HT. Whether these relationships would be influenced by different doses of tE2 or oCEE remains to be determined.

Keywords

Estrogen; follicle stimulating hormone; luteinizing hormone; hormone therapy; menopause; Pituitary-Ovarian; white matter hyperintensity

Introduction

Sex hormones influence structure and function of the brain through both the organizational effects, those that remain once sex hormones are removed, and the activational effects, those that vary with fluxes in levels of hormones.[1–4] Age related declines in learning and memory associate with changes in brain structure which may, in part, be related to decreased levels of circulating estrogens during menopause. Therefore, it is important to understand how different formulations of menopausal hormone treatment (HT) impact brain structure following menopause.

For example, ventricular volumes and volumes of white matter hyperintensities (WMH) on brain MRI increased to a greater extent in women using oral conjugated equine estrogen (oCEE) than in those using placebo.[5] While the rates of change in ventricular volumes slowed to placebo rates after the HT was withdrawn, the WMH continued to increase 3 years after HT.[6] Additionally, women randomized to transdermal 17β estradiol (tE2) had less accumulation of β- amyloid than placebo, especially those who were positive for APOE ε 4, a risk factor for β- amyloid accumulation.[7] CEE consists of a complex of hormones, the most prominent of which is estrone sulfate and with oral administration would be further metabolized in the liver, contrary to the tE2 where, E2 would be absorbed directly into the peripheral circulation before being metabolized in the liver. Thus, the resulting circulating concentrations of E1 and E2 differ between the two treatment groups. Both E1 and E2 decrease secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary.[8] Gonadotropins may be involved in brain function as demonstrated in observational studies.[9] Specifically, rising levels of peripheral LH levels associate with cognitive deficits in older men and women, including patients with Alzheimer's disease.[10–13]

The relationship of changes in pituitary-ovarian hormone levels during menopausal HT and the change in WMH is unknown. Therefore, this study evaluated the associations of changes in pituitary-ovarian hormones with changes of brain structure in women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS) at Mayo Clinic.

Methods

The Kronos Early Estrogen Prevention Study (KEEPS; NCT00154180) was a randomized, placebo-controlled, double-blind multicenter clinical trial that evaluated the cardiovascular and cognitive effects of o-CEE, tE2, and placebo in women between 42 and 58 years of age who experienced natural menopause.[14] Women were within 5–36 months of their last

menstrual period and without cognitive impairment. An ancillary study to evaluate the effects of HT on brain structure by MRI was conducted at Mayo Clinic during the four years of KEEPS.[5] Women with contraindications for MRI, or those with neurologic disorders, were excluded. The study was approved by the Mayo Clinic institutional review board (no. 224104) and participants provided written informed consent.

MRI was performed before randomization (baseline) and 48 months after randomization to treatments of 0.45 mg/d o-CEE daily, 50 μg/d tE2 weekly or placebo pills and patches. Women in the active treatment groups also received oral 200 mg/d micronized progesterone for the first 12 d of each month. All participants underwent genotyping for the *APOE* ε4 allele, presence of which is associated with increased risk of Alzheimer's disease.

Brain MRI studies were performed on a single 1.5-tesla system, with an 8-channel phased array coil (GE Healthcare A T2-weighted fluid-attenuated inversion recovery (FLAIR) and a T1-weighted 3D high resolution magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence were included in the standardized protocol for anatomic segmentation and labeling of WMH. WM was segmented using a semi-automated segmentation algorithm on FLAIR-MRI by a single image analyst, who was blinded to the treatment status.[15] The total change in volume was then calculated for the WMH lesion volume during the 48 months of HT.

E1 (pg/mL), E2 (pg/mL), LH (IU/L), and FSH (IU/L) were measured by high sensitive liquid chromatography/mass spectroscopy from a single fasting serum samples collected at the same time of day at baseline prior to and 48 months after randomization. Hormone levels were measured at the clinical core laboratory at Mayo Clinic, Rochester, MN. Detailed methodology along with the intra-assay and inter-assay coefficients of variability (C.V.'s) for E2, estrone, LH, and FSH, have been reported previously and are included in Table 1.[8] In brief, total 17 β-estradiol and estrone were extracted with methylene chloride and after derivatization with dansyl chloride, high-pressure liquid chromatography (HPLC) was used prior to introduction of the derivatized sample extract into the tandem mass spectrometry (LC-MS/MS) (Agilent Technologies, Santa Clara, CA 95051). FSH and LH were measured by respective, specific two-site immunoenzymatic assays performed on a DxI 800 automated immunoassay system (Beckman Instruments, Chaska, MN 55318).

Statistical analysis

WMH volumes at baseline, changes in WMH volumes, baseline hormone values, and changes in hormone values were not transformed since they were approximately normally distributed in this particular sample. Analyses including WMH or change in WMH also included an adjustment for the log of total intracranial volume (TIV). We performed sensitivity analyses without adjustment for comparison. The baseline participant characteristics were described using means and standard deviations for continuous variables, or counts and percentages for categorical variables. The oCEE, tE2 and placebo groups were first compared using analysis of variance (ANOVA) or chi-square tests. Where the omnibus ANOVA test was significant, Tukey's HSD (honestly significant difference) test was used to assess pairwise comparisons of the groups. We reported the comparisons of each treatment group with placebo. Changes in WMH volumes and hormone levels were described and

tested in the same way, and then summarized using Pearson partial correlations (adjusted for log TIV) and Pearson correlations (without adjustment for log TIV).

To analyze the effects of *APOE* ε4 status and smoking on the associations of WMH with hormones, linear regression models were fitted with WMH as a response and one of the hormones, treatment group, smoking status, log (TIV), and *APOE* ε4 status as explanatory variables. First, full models were fit with a treatment group by *APOE* ε4 status interaction term in each model. The treatment x *APOE* ε4 status interactions were not statistically significant, and models without the interaction terms were then fit. Standard diagnostic tests indicated that the assumptions for all of the models in this study were met reasonably well.

Results

One hundred and eighteen women enrolled in KEEPS at Mayo Clinic were invited to participate in the ancillary KEEPS-MRI study. Of these, twelve declined participation and an additional five were excluded because of MRI contraindications or neurologic disorders. There were a total of 101 who underwent MRI at baseline; 78 participants who were compliant to treatment underwent MRI at month 48 and had hormone levels measured at both time points. At baseline, clinical characteristics including hormone levels, cardiovascular risk factors, and global cognitive function were similar across treatment groups (Table 2). There was a higher percentage of *APOE* ε4 carriers in the tE2 group compared to placebo (46%, p=0.01) (Table 3 and 4). The oCEE group had a higher WMH volume at baseline compared to placebo (p=0.002). Sensitivity analyses did not uncover an effect of baseline WMH differences on any of the associations.

At baseline, there were no statistically significant associations between FSH (p=0.81), LH (0.51), E1 (p=0.93) or E2 (p=0.79) levels and WMH volume. Significant changes in hormone levels were observed in the oCEE and tE2 groups over the 48 months of the study, but not in the placebo group (Table 5, Figure 1); statistically significant changes in total WMH volume were observed in all groups. During the four years of HT, a greater decrease in FSH in the tE2 group associated with a smaller increase in WMH volume (Table 6, Figure 2). In the tE2 and oCEE groups, a greater increase in E1 associated with a smaller increase in WMH volume (Table 6, Figure 2). These relationships remained the same when outliers in the tE2 group were excluded. There were no significant associations between changes in LH or E2 and changes in WMH. Testosterone and androstenedione were also measured in KEEPS. Values of these hormones did not associate with WHM volume and are not further described.

Neither *APOE* ε4 status nor smoking modified the association between changes in WMH and changes in any of the hormone levels.

Discussion

In recently menopausal women participating in KEEPS who were randomized to one of two common formulations of menopausal HT, greater decreases in FSH associated with smaller increases in WMH volume over time only in the tE2 group. In other words, the type of HT appears to influence circulating hormones differently[8] and a relationship was found between

their changing levels and specific brain structure changes over time. These results may be related to the stronger negative feedback mechanisms for E2 and FSH with tE2 compared to those involved with E1. Furthermore, conversion of estrone sulfate to E2 and feedback regulation of FSH may be less robust with oCEE compared to tE2. [8,16] These different relationships among the hormones and WMH may help explain why not all HT formulations have the same effect on neuropsychologically implicated menopausal symptoms such as mood and anxiety.[17] In addition, not all HT formulations may influence hypertension and small vessel ischemic disease, as these conditions associate with the presence of WMH.[18] Previously reported in KEEPS, WMH volume increased for all groups in KEEPS over time, although the rate of increase in WMH volume was only found to be statistically significantly greater in the oCEE group compared to placebo.[6] In the present study, greater increases in E1 associated with smaller increases in WMH volume in both the tE2 and oCEE groups suggesting an inhibitory effect of E1 on mechanisms associated with development of WMH.

The interrelationships of pituitary and ovarian hormones are expected to differ based on whether HT is used, and if used, the formulation and route of administration. The current study found no association between changes in FSH and WMH volume in the placebo or oCEE group. The findings in the tE2 group support the concept that the changes in WMH may be related to pituitary-ovarian hormones. The results also are consistent with previous KEEPS MRI findings that indicate tE2 has a greater effect than oCEE on preserving the dorsolateral prefrontal cortex compared to placebo.[6] Although the trends are the same, the range of values for E1 in the tE2 group and E2 in the oCEE are narrow, thus precluding evaluations of dose effects. Estrogen receptors have greater affinity for E2 than E1 and E1 may be converted to E2 all of which may affect an individual response to the hormone. Thus, evaluating other doses or ranges of HT treatments should be explored.

Previous studies show that differences in levels of FSH and LH in postmenopausal women associate with various clinical outcomes. For example, for postmenopausal women not using HT, low FSH levels associated with an increased risk of prediabetes and diabetes,[19] as well as increased cardiovascular risk,[20] although the associations were partially explained by obesity or adiposity. Higher levels of peripheral LH correlated with cognitive deficits in aging women.[9] These studies examined individual levels of gonadotropin hormone, when indeed, it is more likely that pituitary ovarian hormone interactions may influence clinical outcomes. An interaction of the gonadotropin and ovarian hormones likely exerts effects through feedback loops, which may differ by tissue and anatomical location, in part, related to type and number of estrogen receptors.

In KEEPS, women randomized to transdermal E2 and who were *APOE* ε4 carriers had less accumulation of β-amyloid (a putative biomarker of Alzheimer disease pathology) than those on placebo, and o-CEE.[6,7] Although the mechanism of amyloid-beta protein formation are complex and likely explained by multiple factors, results of the current study related to FSH levels and WMH volumes are intriguing and may provide future area for study as a possible or partial explanation for amyloid-beta deposition. Previous studies of postmenopausal women not on HT found that elevated gonadotropin levels were significantly higher in women with Alzheimer's disease compared to cognitively normal

controls.[21] Whether or not treatment with HT, through its influence on gonadotropins, may decrease formation of amyloid-beta plaques remains to be determined.

Limitations

Women in KEEPS experienced natural menopause, therefore, the relationships noted in the present study may not apply to women who underwent oophorectomy or hysterectomy after or before the natural age of menopause. Other hormones, such as progesterone, testosterone, thyroid hormones, sex hormone binding globulin, and corticosteroids, were not included in this analysis. These hormones may affect the interpretability of the observed associations and menopausal state of the gonadotropic-pituitary axis. Furthermore, serum hormone levels reflect the total hormone level and not the free or bioavailable state since sex hormone binding globulin was not included in the analysis. Finally, our findings are based on observation of associations; thus, the results are hypothesis generating and may set the stage for future studies which could lead to enhanced understanding of hormonal interactions in women, with and without exogenous hormone treatment, as they age.

Conclusion

Changes in circulating levels of pituitary-ovarian hormones during menopausal HT associate with changes in WMH volume in recently menopausal women. The relationships seen may help explain why different HT formulations lead to different structural brain changes in menopausal women and differentially affect mood, anxiety, risk for hypertension, and small vessel ischemic disease. Whether these relationships would be influenced by different doses of either tE2 or oCEE remains to be determined and evaluating other doses of HT should be explored. Additionally, long term follow up in a larger cohort of women measuring all pituitary ovarian hormones would further clarify these relationships.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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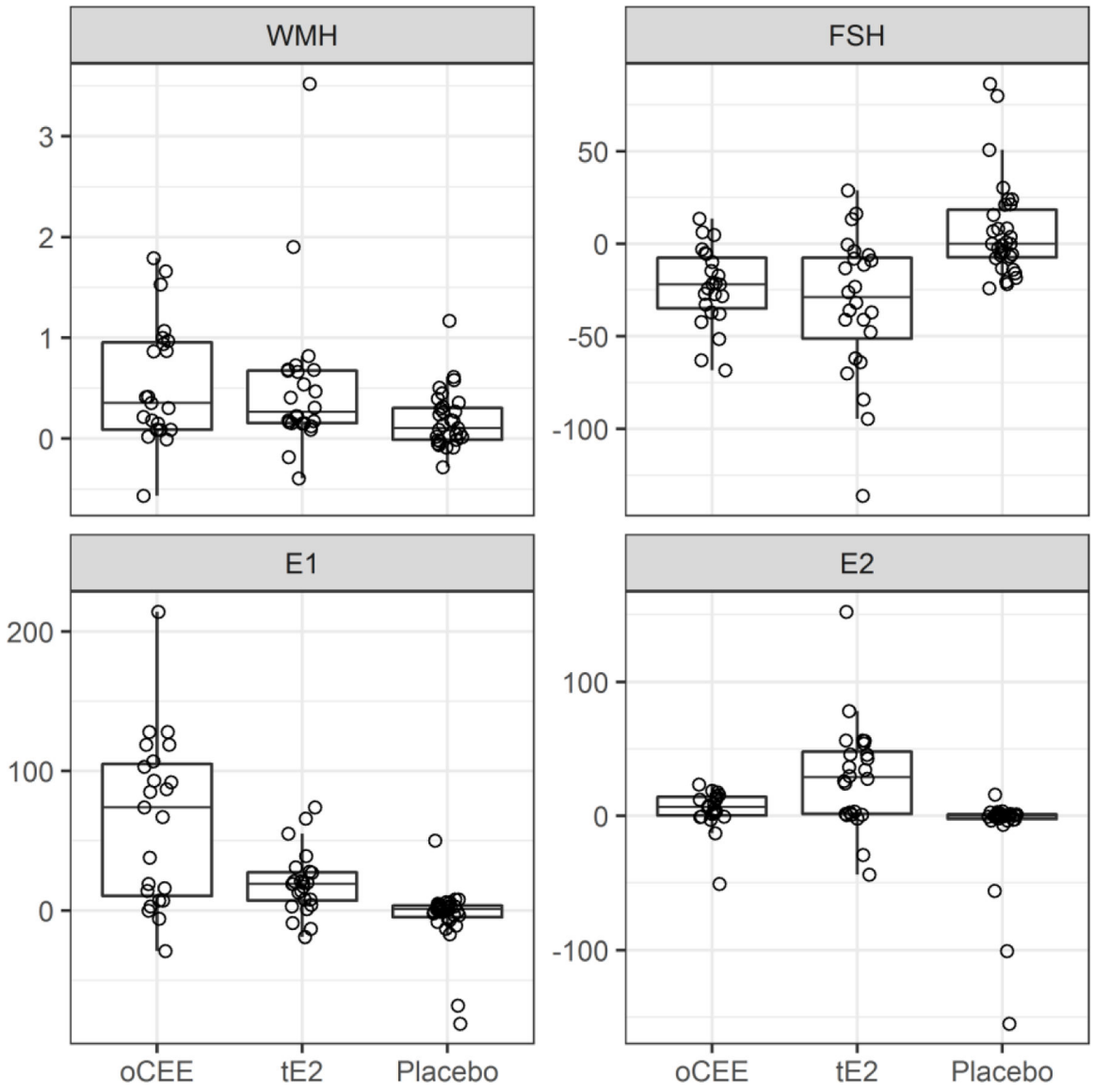

FIG. 1.

Boxplots of total change in WMH volume and total changes in hormones levels from baseline to month 48. The horizontal lines of the box from bottom to top show the 25th, 50th, and 75th percentiles of the data. The height of the box, 75th to 25th percentile, is the interquartile range (IQR). Whiskers extend 1.5*IQR from the box. Points farther out are considered outliers and drawn individually. E1, estrone; E2, estradiol, FSH, follicle-stimulating hormone; oCEE, oral conjugated equine estrogen; tE2, transdermal estradiol; WMH, white matter hyperintensity.

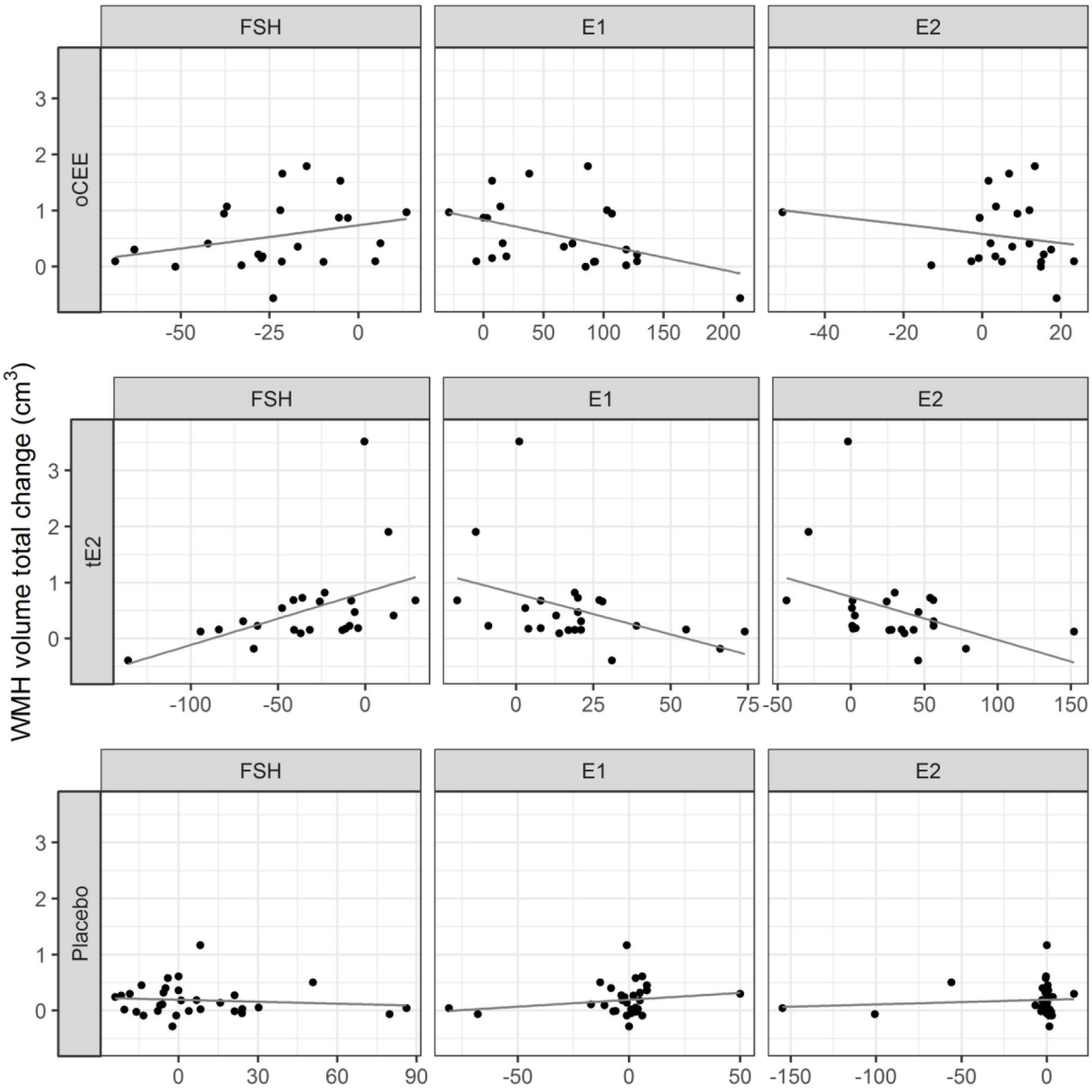

FIG. 2.

Scatterplots between total change in WMH volume and total changes in hormones levels by treatment group. The line represents the predicted linear relationship between the change in hormone and change in WMH. Each point represents a participant. E1, estrone; E2, estradiol, FSH, follicle-stimulating hormone; oCEE, oral conjugated equine estrogen; tE2, transdermal estradiol; WMH, white matter hyperintensity

Table 1:

Hormone intra and inter-assay Coefficients of Variability

Hormone	**Intra-assay C.V.**						**Inter-assay C.V.**					
17β estradiol (pg/mL)	0.23	0.50	0.74	35	151	405	0.29	0.50	0.77	32	140	382
Variation (%)	11.8	7.3	6.0	1.6	1.5	1.4	10.8	8.5	6.9	5.1	4.6	4.8
Estrone (pg.mL)	0.30	0.50	0.84	32	142	389	0.25	0.51	0.85	30	131	355
Variation (%)	17.8	7.5	6.1	2.5	1.7	1.2	12.0	9.5	7.9	7.4	7.1	6.6
Follicle Stimulating Hormone (mIU/mL)	8.6	47.1					6.5	16.7	58.0			
Variation (%)	32.	2.8					3.6	3.2	4.7			
Luteinizing Hormone (mIU/mL)	1.2	38.5					1.4	15.6	48.8			
Variation (%)	4.3	4.0					9.3	6.0	6.0			
Testosterone, high sensitivity (ng/dL)	0.65	4.3	48	118	832		0.69	4.3	45	117	841	
Variation (%)	7.4	6.1	9.0	2.3	0.9		8.9	6.9	4.0	3.6	3.5	

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C.V. = coefficient of variability

Table 2.

Characteristics of the participants at baseline

	oCEE (n = 23)	tE2 (n = 24)	Placebo (n = 31)	P-value	Effect size η^2
Age at baseline, year	53 (2)	53 (2)	53 (2)	0.51	0.02
Education				0.83	
High school or less	2 (9%)	1 (5%)	2 (6%)		
Some college / College graduate	16 (73%)	15 (68%)	19 (61%)		
Some graduate / Graduate	4 (18%)	6 (27%)	10 (32%)		
Smoking status				0.26	
Nonsmoker	16 (73%)	13 (57%)	24 (77%)		
Smoker (past or current)	6 (27%)	10 (43%)	7 (23%)		
Time past menopause, months	21 (11)	19 (8)	16 (9)	0.19	0.04
Treatment onset past baseline MRI, d	14 (30)	21 (31)	30 (68)	0.47	0.02
APOE ε4 carrier	2 (9%)	11 (46%)	7 (23%)	0.01	
Migraines	2 (9%)	0 (0%)	4 (13%)	0.24	
Global cognitive function (z-scores)	−0.09 (0.79)	0.03 (0.75)	0.21 (0.65)	0.33	0.03
Mean systolic blood pressure, mm Hg	125 (11)	120 (17)	121 (11)	0.36	0.03
Mean diastolic blood pressure, mm Hg	78 (6)	74 (9)	75 (7)	0.24	0.04
Waist circumference, cm	83 (21)	82 (12)	85 (11)	0.79	0.01
Body mass index, kg/m^2	29 (4)	26 (4)	27 (4)	0.06	0.07
Coronary arterial calcification present (Agatston score)	4 (17%)	2 (8%)	3 (10%)	0.61	
Carotid intima-media thickness (mm)	0.73 (0.11)	0.71 (0.09)	0.71 (0.08)	0.72	0.01
Low-density lipoprotein, mg/dL	123 (24)	122 (33)	115 (28)	0.53	0.02
High-density lipoprotein, mg/dL	69 (10)	72 (10)	72 (13)	0.74	0.01
Triglycerides, mg/dL	84 (49)	88 (37)	78 (44)	0.68	0.01
White matter hyperintensity volume, cm^3	2.77 (1.31)[a]	2.49 (1.60)[b]	1.52 (0.71)	0.002 *	0.05 *
FSH (IU/L)	96 (32)	98 (44)	78 (34)	0.08	0.06
LH (IU/L)	43 (14)	43 (18)	36 (15)	0.12	0.002
E1 (pg/mL)	31 (15)	30 (10)	32 (21)	0.93	0.01
E2 (pg/mL)	10 (12)	13 (15)	17 (34)	0.58	0.05

* models adjusted for log-transformed TIV

Abbreviation; oCEE = oral conjugated equine estrogens. FSH = follicle stimulating hormone, LH = luteinizing hormone, E1 = estrone, E2 = estradiol

Data are n (%) or mean (SD)

[a] Pairwise comparison to placebo < 0.01

[b] Pairwise comparison to placebo < 0.05

Table 3.

Linear regression analysis between total change in WMH volume (cm3) and hormones, model was fit with interaction between treatment group and APOE status.

	FSH		LH		E1		E2	
	Est (95% CI)	**P**	**Est (95% CI)**	**P**	**Est (95% CI)**	**P**	**Est (95% CI)**	**P**
Intercept	−8.0 (−20.8, 4.82)	0.22	−9.08 (−22.6, 4.43)	0.19	−9.75 (−22.4, 2.93)	0.13	−9.20 (−22.3, 3.85)	0.16
Hormone	0.006 (0.002, 0.01)	0.007	0.006 (−0.005, 0.02)	0.27	−0.005 (−0.008, −0.001)	0.008	−0.004 (−0.008, −0.000)	0.05
o-CEE	0.41 (0.05, 0.78)	0.03	0.24 (−0.12, 0.59)	0.19	0.53 (0.12, 0.93)	0.01	0.28 (−0.07, 0.63)	0.12
tE2	0.26 (−0.16, 0.68)	0.21	0.11 (−0.31, 0.53)	0.61	0.16 (−0.24, 0.56)	0.42	0.20 (−0.23, 0.62)	0.36
APOE	−0.27 (−0.74, 0.20)	0.25	−0.20 (−0.69, 0.29)	0.42	−0.22 (−0.69, 0.25)	0.35	−0.23 (−0.71, 0.26)	0.35
Smoker	0.21 (−0.07, 0.50)	0.14	0.25 (−0.05, 0.54)	0.10	0.23 (−0.06, 0.51)	0.12	0.24 (−0.05, 0.54)	0.10
TIV	1.12 (−0.65, 2.88)	0.21	1.28 (−0.59, 3.14)	0.18	1.36 (−0.38, 3.11)	0.12	1.29 (−0.51, 3.08)	0.16
o-CEE x APOE	0.87 (−0.06, 1.80)	0.07	0.81 (−0.17, 1.78)	0.10	0.87 (−0.06, 1.80)	0.07	0.82 (−0.13, 1.78)	0.09
tE2 x APOE	0.75 (0.07, 1.43)	0.03	0.62 (−0.08, 1.33)	0.08	0.62 (−0.05, 1.30)	0.07	0.68 (−0.01, 1.38)	0.05

Abbreviations; oCEE = oral conjugated equine estrogens, tE2 = transdermal estradiol, FSH = follicle stimulating hormone, LH = luteinizing hormone, E1 = estrone, E2 = estradiol, TIV = total intracranial volume

Table 4.

Linear regression analysis between total change in WMH volume (cm3) and hormones, model was fit without interaction between treatment group and APOE status.

	FSH		LH		E1		E2	
	Est (95% CI)	**P**	**Est (95% CI)**	**P**	**Est (95% CI)**	**P**	**Est (95% CI)**	**P**
Intercept	−5.22 (−18.2, 7.72)	0.42	−6.66 (−20.2, 6.91)	0.33	−7.03 (−19.7, 5.66)	0.27	−6.50 (−19.6, 6.60)	0.33
Hormone	0.005 (0.001, 0.01)	0.02	0.005 (−0.006, 0.02)	0.37	−0.004 (−0.008, −0.001)	0.01	−0.004 (−0.008, 0.001)	0.09
o-CEE	0.55 (0.19, 0.90)	0.003	0.38 (0.04, 0.71)	0.03	0.66 (0.26, 1.06)	0.001	0.42 (0.09, 0.76)	0.01
tE2	0.48 (0.11, 0.85)	0.01	0.31 (−0.04, 0.65)	0.08	0.36 (0.03, 0.69)	0.03	0.40 (0.04, 0.77)	0.03
APOE	0.17 (−0.14, 0.48)	0.27	0.18 (−0.14, 0.51)	0.27	0.17 (−0.13, 0.48)	0.26	0.18 (−0.13, 0.50)	0.25
Smoker	0.17 (−0.11, 0.46)	0.23	0.21 (−0.08, 0.50)	0.15	0.20 (−0.08, 0.48)	0.17	0.21 (−0.08, 0.49)	0.16
TIV	0.73 (−1.06, 2.51)	0.42	0.93 (−0.94, 2.80)	0.32	0.98 (−0.77, 2.72)	0.27	0.90 (−0.90, 2.70)	0.32

Abbreviations; oCEE = oral conjugated equine estrogens, tE2 = transdermal estradiol, FSH = follicle stimulating hormone, LH = luteinizing hormone, E1 = estrone, E2 = estradiol, TIV = total intracranial volume

Table 4a.

P-values comparing models with and without interaction between treatment group and APOE status (tables 2 and 3)

Hormone	P-value
FSH	0.054
LH	0.12
E1	0.09
E2	0.09

Abbreviations; FSH = follicle stimulating hormone, LH = luteinizing hormone, E1 = estrone, E2 = estradiol

Table 5.

Summary of total change in WMH volume and hormones levels adjusted for TIV

Total change	oCEE (n = 23)	tE2 (n = 24)	Placebo (n = 31)	Overall P-value	Pairwise P-value	
					oCEE / Placebo	tE2 / Placebo
WMH (cm^3)	0.54 (0.60)	0.52 (0.77)	0.18 (0.28)	0.06 *	0.12 *	0.11 *
FSH (IU/L)	−23 (21)	−33 (38)	7 (26)	<0.001	0.001	<0.001
LH (IU/L)	−6 (14)	−13 (16)	−3 (10)	0.04	0.81	0.04
E1 (pg/mL)	65 (60)	19 (22)	−4 (22)	<0.001	<0.001	0.07
E2 (pg/mL)	5 (15)	29 (39)	−10 (34)	<0.001	0.22	<0.001

Data are mean (SD)

Abbreviations; oCEE = oral conjugated equine estrogens, tE2 = transdermal estradiol, FSH = follicle stimulating hormone, LH = luteinizing hormone, E1 = estrone, E2 = estradiol, TIV = total intracranial volume, WMH = white matter hyperintensity

* models adjusted for log-transformed TIV

Table 6.

Pearson's partial correlations (p-values) between total change in WMH volume and total changes in hormones levels from baseline to month 48 for each treatment group. Models adjusted for the TIV.

	oCEE (n = 23)	tE2 (n = 24)	Placebo (n = 31)
FSH	0.24 (0.28)	0.46 (0.03)	−0.18 (0.34)
LH	0.11 (0.62)	0.10 (0.64)	−0.09 (0.64)
E1	−0.43 (0.04)	−0.41 (0.054)	0.21 (0.27)
E2	−0.18 (0.43)	−0.38 (0.08)	0.14 (0.46)

Abbreviations; oCEE = oral conjugated equine estrogens, tE2 = transdermal estradiol, FSH = follicle stimulating hormone, LH = luteinizing hormone, E1 = estrone, E2 = estradiol, TIV = total intracranial volume