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Postmenopausal hormone therapy, type 2 diabetes mellitus, and brain volumes

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ABSTRACT

Objective: To examine whether the effect of postmenopausal hormone therapy (HT) on brain volumes in women aged 65–79 years differs depending on type 2 diabetes status during post-intervention follow-up of a randomized controlled clinical trial.

Methods: The Women's Health Initiative randomized clinical trials assigned women to HT (0.625 mg/day conjugated equine estrogens with or without 2.5 mg/day medroxyprogesterone acetate) or placebo for an average of 5.6 years. A total of 1,402 trial participants underwent brain MRI 2.4 years after the trials; these were repeated in 699 women 4.7 years later. General linear models were used to assess the interaction between diabetes status and HT assignment on brain volumes.

Results: Women with diabetes at baseline or during follow-up who had been assigned to HT compared to placebo had mean decrement in total brain volume of −18.6 mL (95% confidence interval [CI] −29.6, −7.6). For women without diabetes, this mean decrement was −0.4 (95% CI −3.8, 3.0) (interaction $p = 0.002$). This interaction was evident for total gray matter ($p < 0.001$) and hippocampal ($p = 0.006$) volumes. It was not evident for changes in brain volumes over follow-up or for ischemic lesion volumes and was not influenced by diabetes duration or oral medications.

Conclusions: For women aged 65 years or older who are at increased risk for brain atrophy due to type 2 diabetes, prescription of postmenopausal HT is associated with lower gray matter (total and hippocampal) volumes. Interactions with diabetes and insulin resistance may explain divergent findings on how estrogen influences brain volume among older women. ***Neurology*®** **2015;85:1131–1138**

GLOSSARY

3MSE = Modified Mini-Mental State Examination; **BMI** = body mass index; **CEE** = conjugated equine estrogens; **CI** = confidence interval; **HT** = hormone therapy; **MPA** = medroxyprogesterone acetate; **WHI** = Women's Health Initiative; **WHIMS** = Women's Health Initiative Memory Study.

The Three-City Study reported that both lower and higher levels of endogenous estradiol were associated with increased risk for dementia among older women.[1] This relationship was modest among those without type 2 diabetes; however, among women with diabetes, those with higher estradiol levels were at remarkably increased risk. The hazard ratio for dementia associated with higher estradiol levels was 14.2 (95% confidence interval [CI] 1.6, 123) among women with diabetes compared with 3.4 (95% CI 0.1, 147) among those without diabetes (interaction $p < 0.05$). Others have reported that poor glucose regulation more adversely affects memory tasks among women than men,[2,3] which may also reflect a relationship with sex hormones. This potential interaction between diabetes and/or glucose dysregulation and sex hormones may

Supplemental data at Neurology.org

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explain discrepancies between earlier reports linking endogenous estrogens to cognitive function and impairment.[4–6]

The Women's Health Initiative Memory Study (WHIMS) confirmed results from several studies that diabetes is associated with smaller brain volumes and poorer cognitive function in older women.[7,8] Assignment to hormone therapy (HT) was found to be associated with increased risk of probable dementia, decreased cognitive function, and smaller total and regional brain volumes.[9–14]

We assessed whether an interaction existed between assignment to HT and diabetes on brain volumes and changes in brain volumes after controlling for other cognitive risk factors in WHIMS. Based on Three-City Study findings, we hypothesized that HT would have greater adverse effects on brain volumes in older women with diabetes than those without diabetes.

METHODS Volunteers for the WHIMS MRI study were recruited from 14 US academic centers. They had participated in the Women's Health Initiative (WHI) parallel placebo-controlled randomized clinical trials of 0.625 mg/day conjugated equine estrogens (CEE) with or without 2.5 mg/day medroxyprogesterone acetate (MPA).[15] At enrollment, women were aged 65–79 years and free of dementia. Compared with other WHIMS participants, those for whom MRI was obtained tended to be younger and more highly educated, to be nonsmokers, and to have fewer chronic diseases and better cognitive function.[16]

WHIMS-MRI assessed the long-term effects of HT on brain volumes.[11,14] Mean age at scanning, which occurred in 2005–2007, was 78.5 years (SD 3.7). In 2008–2010, women were invited to undergo repeat MRI.

Standard protocol approvals, registrations, and patient consents. Written informed consents were obtained. The NIH and institutional review boards approved protocols and consent forms. The WHIMS trial identifier is NCT00000611.

Diabetes and medications. At WHI enrollment, women self-reported a history of diabetes, age at onset, and diabetes treatment with medications or lifestyle modifications. During follow-up, women were annually asked to report new diagnoses of diabetes treated with oral hypoglycemic drugs or insulin; these reports have been validated.[17] A random sample had baseline fasting glucose measurements (n = 162), which were repeated at follow-up years 1 (n = 157), 3 (n = 150), and 6 (n = 145). Women were classified as having diabetes if they self-reported diabetes requiring medication or, for those with fasting (≥8 hours) glucose measurements, if levels were ≥126 mg/dL.

Covariates and potential confounders. We examined risk factors potentially related to risk of diabetes: age, education, family income, body mass index (BMI), waist girth, waist-to-hip girth ratio, hypertension, and cardiovascular disease. Prior hysterectomy determined whether women participated in the CEE-Alone or CEE + MPA trials. Information was collected via self-report and standardized assessments at WHI enrollment.[18] Modified Mini-Mental State Examination (3MSE) was used to assess global cognitive function.[15,19] *APOE* genotypes were imputed.[20]

MRI outcomes. Standardized and validated protocols were used for obtaining and processing MRI.[11,21,22] Volumes were measured using automated computer-based template warping to sum voxels in anatomic regions of interest. Intracranial volume was estimated as the total cerebral hemispheric volumes plus CSF within the ventricular and sulcal spaces. All supratentorial brain tissue was classified as normal or abnormal (ischemic) gray or white matter and assigned to anatomic brain regions.[21,23] We analyzed total (including ischemic lesion) brain, total gray matter, total white matter, frontal lobe, hippocampal, and ischemic lesion volumes.

The first MRI was conducted on 1,403 women. One woman reporting diabetes onset before age 30 and current insulin use (i.e., likely type 1 diabetes) was excluded. Scans from the remaining 1,402 women had been collected an average of 7.9 years (interquartile range 7.6, 8.4) after WHI enrollment. An average of 4.7 years (interquartile range 4.4, 4.9) later, a second MRI was conducted on 699 women. When the repeated scans were collected, 1,368 (97.6%) of the original scans for which an updated image analysis approach was suitable were reread.[24] Correlations between volumes from the initial reading and the reprocessing of the original scans were $r = 0.94$ (total brain), $r = 0.94$ (frontal lobe), and $r = 0.88$ (hippocampus).

Statistical methods. We assessed differences between intervention groups and between women with and without diabetes with respect to covariates and potential confounders using χ^2 and t tests. Linear mixed-effects models that included both the initial and rereading values as predictors, with control for (unstructured) intrasubject correlations, were fitted using restricted maximum likelihood (SAS software version 9.4).[24] This allowed 34 scans with missing rereadings to contribute, calibrated according to the rereading scale. Intracranial volume was included as a covariate to control for differences among participants. Additional (fixed-effect) covariates included clinical site and age. Diabetes status, HT assignment, and their interaction were used to assess relationships with brain volumes at the initial MRI and with changes in brain volumes between the initial and follow-up MRIs, using linear contrasts. Supporting analyses included additional covariates. Lesion volume distributions were right-skewed: logarithmic transformation (offset by 1) was used to improve their symmetry.[8] Among women with diabetes, we assessed whether HT effects varied according to diabetes duration and use of insulin and oral diabetes medications using tests of interactions. We examined whether the interaction between HT and diabetes on brain volumes varied by ischemic lesion volume burden and whether it might be accounted for by differences in baseline 3MSE scores.

RESULTS Of the 1,402 women, 72 (5.1%) met criteria for type 2 diabetes at WHI enrollment, 32 initiated diabetes medications and/or had elevated fasting glucose during the HT trials, and 20 initiated diabetes medications and/or had elevated fasting glucose after the trials ended but before their first MRI. At the first MRI, 30% of these 124 women had had diabetes for <5 years, 28% for 5–9 years, and 42% for ≥10 years. The distribution of diabetes duration was similar between treatment groups ($p = 0.48$).

Table 1 lists characteristics of the women at WHI enrollment by treatment assignment and diabetes status. Balance from the original randomization was maintained: no treatment group differences reached nominal $p < 0.05$. As expected, women with diabetes tended to be heavier and have larger waist girths than other women ($p < 0.001$). They were more likely to have hypertension, cardiovascular disease, and prior hysterectomy and had lower mean 3MSE scores ($p < 0.001$).

After adjustment for hysterectomy status, average on-trial follow-up was 5.6 years ($p = 0.67$) and average duration between trial termination and the first MRI was 2.4 years ($p = 0.94$) for both women with diabetes and others.

Treatment group differences in mean total brain volumes (table 2) depended on diabetes status (interaction $p = 0.002$). The average difference in total brain volume for women in the diabetes group who had been assigned to HT vs placebo was −18.6 mL (95% CI −29.6, −7.6); this average difference was −0.4 mL (95% CI −3.8, 3.0) among women without diabetes. Among women with diabetes, HT-associated decrements in brain volumes were evident in total gray ($p < 0.001$) but not total white matter ($p = 0.92$) volume and in hippocampal ($p = 0.006$) but not frontal lobe ($p = 0.24$) volume. Among women without diabetes, differences between treatment groups were consistently smaller than those

Table 1 Distribution of risk factors for atrophy and cerebrovascular disease among women enrolled in WHIMS-MRI at WHI enrollment

	Diabetes		No diabetes			
Risk factor for cognitive impairment	HT, n = 56	Placebo, n = 68	HT, n = 637	Placebo, n = 641	HT vs placebo, p value[a]	Diabetes vs no diabetes, p value
Age at WHI HT enrollment, y, mean (SD)	70.3 (3.7)	70.1 (3.9)	70.6 (3.6)	70.6 (3.6)	0.87	0.29
Education (missing = 2)						
High school or less	12 (21.4)	21 (30.9)	178 (28.0)	177 (27.7)	0.83	0.77
At least some college	44 (78.6)	47 (69.1)	458 (72.0)	463 (72.3)		
Race/ethnicity						
African American	7 (12.5)	12 (17.6)	25 (3.9)	21 (3.3)		
Non-Hispanic white	45 (80.4)	48 (70.6)	585 (91.8)	600 (93.6)	0.75	0.03
Other	4 (7.1)	8 (11.8)	27 (4.2)	20 (3.1)		
Annual income (missing = 45)						
<$35,000	32 (59.3)	44 (66.7)	312 (50.6)	333 (53.6)	0.21	0.02
≥$35,000	22 (40.7)	22 (33.3)	304 (49.4)	288 (46.4)		
Body mass index, kg/m^2, mean (SD) (missing = 5)	31.4 (6.4)	31.0 (5.3)	28.2 (5.1)	27.8 (5.5)	0.29	<0.001
Waist girth, cm, mean (SD) (missing = 3)	96.8 (13.2)	97.2 (11.4)	87.1 (12.4)	87.2 (12.6)	0.81	<0.001
Waist/hip ratio, mean (SD) (missing = 5)	0.87 (0.06)	0.87 (0.06)	0.82 (0.07)	0.82 (0.07)	0.15	<0.001
Hypertension status						
No	16 (28.6)	21 (30.9)	340 (53.4)	358 (55.8)	0.35	<0.001
Yes	40 (71.4)	47 (69.1)	297 (46.6)	283 (44.2)		
Prior CVD						
No	46 (82.1)	57 (83.8)	603 (94.7)	606 (94.5)	0.98	<0.001
History of other CVD[b]	10 (17.9)	11 (16.2)	34 (5.3)	35 (5.5)		
Prior hysterectomy						
No	29 (51.8)	35 (51.5)	407 (63.9)	411 (64.1)	0.94	0.007
Yes	27 (48.2)	33 (48.5)	230 (36.1)	230 (35.9)		
Baseline 3MSE score, mean (SD)	95.3 (4.3)	94.6 (4.7)	96.2 (3.4)	96.2 (3.3)	0.95	<0.001
APOE genotype (missing = 431)						
No ε4 allele	14 (66.7)	18 (81.8)	346 (75.9)	366 (77.5)	0.41	0.73
ε4 allele(s)	7 (33.3)	4 (18.2)	110 (24.1)	106 (22.5)		

Abbreviations: 3MSE = Modified Mini-Mental State Examination; CVD = cardiovascular disease; HT = hormone therapy; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study.
Women are grouped according to whether they had diabetes at the time of their initial MRI. Data are n (%) unless otherwise indicated.
[a] Analyses of variance or logistic regression.
[b] Other CVD defined as myocardial infarction, angina, postcutaneous transluminal coronary angioplasty, coronary artery bypass grafting, or stroke.

Table 2 Brain volumes at the first MRI scan for women grouped by HT assignment and diabetes status, with adjustment for intracranial volumes, clinical site, and age

Brain volume, mL	Diabetes, n = 124	No diabetes, n = 1,278	Interaction p value[a]
Total brain			
HT	850.2 (4.1)	864.4 (1.3)	
Placebo	868.8 (3.8)	864.8 (1.3)	0.002
95% CI for difference	−18.6 (−29.6, −7.6)	−0.4 (−3.8, 3.0)	
Total brain white matter			
HT	453.1 (3.7)	447.9 (1.1)	
Placebo	453.9 (3.4)	448.1 (1.1)	0.92
95% CI for difference	−0.8 (−10.6, 9.2)	−0.2 (−3.2, 2.8)	
Total brain gray matter			
HT	361.8 (3.5)	379.4 (1.1)	
Placebo	377.6 (3.2)	379.4 (1.1)	<0.001
95% CI for difference	−16.8 (−26.2, −7.4)	0.1 (−2.8, 2.9)	
Frontal lobe			
HT	302.5 (1.9)	305.8 (0.6)	
Placebo	307.3 (1.7)	307.4 (0.6)	0.24
95% CI for difference	−4.8 (−9.8, 0.2)	−1.6 (−3.2, −0.1)	
Hippocampus			
HT	5.58 (0.11)	5.79 (0.03)	
Placebo	6.02 (0.10)	5.81 (0.03)	0.006
95% CI for difference	−0.44 (−0.72, −0.15)	−0.03 (−0.11, 0.06)	

Abbreviations: CI = confidence interval; HT = hormone therapy.
Data are mean (SE) unless otherwise indicated.
[a] Wald test from general linear model.

in women with diabetes. Only for the frontal lobe did the 95% CI exclude 0.

In separate analyses (table e-1 on the *Neurology*® Web site at Neurology.org), we compared differences in ischemic lesion volumes (total and frontal lobe) between treatment groups. Neither reached statistical significance, and there was no evidence of an interaction with diabetes status ($p > 0.60$).

We found similar results when we repeated analyses described in table 2, this time eliminating the 52 women who did not meet criteria for diabetes at baseline but did during follow-up. Among the 72 women with diabetes at baseline, the mean decrement in total brain volume associated with assignment to HT was −14.2 mL (95% CI −28.5, −0.1), compared to −0.4 mL (95% CI −3.8, 2.9) among women without diabetes (interaction $p = 0.07$). Interactions were statistically stronger for total gray matter ($p = 0.004$) and hippocampal volume ($p = 0.009$). We also examined whether HT effects varied by BMI at baseline. Among women with BMI <25 kg/m^2, total brain volumes were an average 1.8 mL (SE 3.0) larger among women who had been assigned to HT vs placebo, and brain volumes were an average 4.1 mL (SE 2.7) smaller among women with BMI 25–29 kg/m^2 and 3.6 mL (SE 2.9) smaller among women with BMI ≥30 kg/m^2. However, a test of interaction based on these groupings did not reach statistical significance ($p = 0.30$).

At the first MRI, the 75th percentile of the distribution of total abnormal tissue, reflecting ischemic lesion burden, was 8.8 mL. The interaction between HT and diabetes on brain volume measures was similar for women below and above this 75th percentile cutoff (interaction $p = 0.93$).

In models including interactions of both diabetes status and baseline 3MSE scores with HT assignment on total brain volume, the interaction with diabetes status remained statistically significant ($p = 0.004$). Associations of 3MSE scores with total brain volumes and changes in total brain volumes, while in the expected direction, did not reach statistical significance (all $p > 0.20$) or vary between women with and without diabetes (all $p > 0.25$).

There were only marginal differences between the findings from the CEE-Alone and CEE + MPA trials (table e-1). The mean decrements in total brain volumes associated with assignment to HT vs placebo were −15.2 mL (95% CI −1.0, 0.7) and −21.5 mL (95% CI −37.0, −6.0) for CEE-Alone and CEE + MPA, respectively, among women with diabetes, compared with −1.1 mL (95% CI −6.8, 4.5) and 0.2 mL (95% CI −4.1, 4.5) among women without diabetes. In these subsets, interaction tests yielded $p = 0.10$ for the CEE-Alone trial and $p = 0.008$ for the CEE + MPA trial.

Additional covariate adjustment for all clinical and demographic factors in table 1 did not materially alter findings: interactions were similar for total brain ($p = 0.01$), total gray matter ($p = 0.002$), and hippocampus ($p = 0.02$) volumes. Including *APOE* genotype as a covariate (ε4 carrier vs noncarrier, with a separate category for missing data) yielded comparable findings.

Among women with diabetes, we examined whether HT-associated decrements in brain volumes varied by insulin use. Only 10 women reported using insulin during WHI screening, 3 more reported use prior to the end of the HT trial, and 4 more reported use between the end of the HT trial and their first MRI scan. While there was thus very limited information to assess whether insulin use moderated the impact of HT among women with diabetes, it did not appear to exacerbate its effects. Total brain volumes were an average of 22.3 mL (95% CI 9.2, 35.3) smaller for women who had been assigned to HT vs placebo among women not using insulin during follow-up but were an average of 9.7 mL (95% CI −41.9, 22.5) larger among the 17 women reporting insulin use

(interaction $p = 0.07$). Additional data are in table e-2. There was little evidence that decrements in brain volumes associated with assignment to HT varied by diabetes duration and on-trial use of oral medications among women with diabetes (all interaction $p > 0.10$).

MRI scans were repeated an average of 4.7 years after the initial scan in 42 women with diabetes (34% of those with initial scans) and 657 (51%) others. The rate of obtaining second scans was lower in the diabetes group ($p < 0.001$) and varied by other characteristics (table e-3); however, times between scans were similar regardless of diabetes status ($p = 0.54$) or HT assignment ($p = 0.94$). Mean volume losses between MRI scans for women grouped by HT assignment and diabetes were similar between treatment groups for each brain region for women with and without diabetes (table 3).

DISCUSSION While there is some evidence from cohort studies that use of HT short term or nearer to menopause may benefit brain structure, there is little evidence from cohort studies and clinical trials that long-term use of HT reduces brain atrophy.[25,26] The only large randomized controlled clinical trial to assess this possibility in older women is WHIMS, which has demonstrated that prescribing an average of 5.6 years of CEE-based therapies to women aged 65 to 79 results in long-term decrements in brain volumes that mediate the increased risk of cognitive impairment related to prescription of these therapies in older women.[11,12,14]

We now report that these HT-related decrements were primarily seen among women with diabetes or emerging diabetes, in whom gray but not white matter volumes and hippocampus but not frontal lobe volumes were reduced. Treatment effects were not markedly different between the CEE-Alone and CEE + MPA trials, did not appear to be affected by duration of diabetes or the use of oral diabetes medications, and were not attributable to insulin therapy (although power was limited). These effects appeared to stabilize by the time of the first MRI, i.e., an average of 2.4 years after study medications were terminated, so that there was no lingering effect on atrophy over the subsequent 4.7 years. HT did not appear to affect ischemic lesion volumes, as we have previously reported,[14] and there was no interaction with diabetes for these outcomes.

Our results are consistent with the Three-City Study report that the effect of higher endogenous estrogen levels on dementia risk is increased among women with diabetes vs those without.[1] Our findings of differential effects of HT in women with vs without diabetes are also in line with a report by Rasgon et al.,[27] in which women (mean age 58 years and 10 years of HT) were randomly assigned to either continue or terminate HT. Among 21 women with low insulin resistance, continuation of HT compared with termination was associated with significantly greater metabolic activity in the prefrontal cortex and better performance on tests of cognitive function 2 years later. In contrast, among the 21 women with higher levels of insulin resistance, those who continued HT had nearly identical declines in metabolic activity as those who terminated HT and somewhat worse cognitive function profiles. The authors concluded that any protective effect of HT when begun

Table 3 Loss of brain volume[a] across an average of 4.7 years (range 3.5–5.8) for women grouped by WHI treatment assignment and diabetes status

	Volume loss (cc) between MRI scans				
	Total brain	Total white	Total gray	Frontal lobe	Hippocampus
Diabetes					
HT (n = 16)	11.97 (4.83)	2.46 (5.03)	9.44 (4.90)	4.88 (1.94)	0.26 (0.11)
Placebo (n = 26)	18.00 (3.86)	3.46 (4.02)	14.21 (3.91)	6.82 (1.55)	0.21 (0.09)
Difference	−6.03 (6.18)	−1.00 (6.44)	−4.78 (6.27)	−1.94 (2.48)	0.04 (0.15)
	$p = 0.33$	$p = 0.88$	$p = 0.45$	$p = 0.44$	$p = 0.78$
No diabetes					
HT (n = 324)	16.09 (1.11)	0.36 (1.16)	15.61 (1.13)	6.72 (0.45)	0.32 (0.03)
Placebo (n = 333)	13.94 (1.10)	−2.06 (1.15)	16.04 (1.12)	6.47 (0.44)	0.27 (0.03)
Difference	2.14 (1.57)	−2.43 (1.63)	−0.42 (1.59)	0.24 (0.63)	0.04 (0.04)
	$p = 0.17$	$p = 0.14$	$p = 0.79$	$p = 0.70$	$p = 0.23$
Interaction	$p = 0.20$	$p = 0.61$	$p = 0.50$	$p = 0.39$	$p = 0.98$

Abbreviations: HT = hormone therapy; WHI = Women's Health Initiative.
Data are mean (SD).
[a] Positive means denote measured decreases; negative means denote measured increases; *p* values are from Wald tests from general linear model.

near to menopause is subsequently lost among women with insulin resistance.

HT did not affect cognitive function when prescribed proximal to menopause in a recent large randomized clinical trial.[28] Our findings suggest that later use of HT may harm older women with diabetes or emerging diabetes. All the women we examined had not used HT for at least 3 months prior to WHI enrollment, per protocol, and were a decade older than those studied by Rasgon et al. Among WHIMS women with diabetes, 51.6% reported prior use of HT, compared to 45.9% among those without diabetes ($p = 0.23$). The mean relative decrements associated with HT were similar among women with diabetes who reported prior use of HT and those who did not: −20.3 mL (95% CI −35.6, −4.9) vs −16.4 mL (95% CI −32.1, −0.6). Among women without diabetes, these values were 0.2 mL (95% CI −4.8, 5.2) and −0.9 mL (95% CI −5.5, 3.8). Thus, previous use of HT did not moderate our findings concerning initiation of HT after age 65.

If higher estradiol levels are associated with greater atrophy, it is plausible that the interactions we saw could be explained by the greater prevalence of high adiposity in type 2 diabetes, which is associated with higher levels of endogenous estrogens, potentially magnifying the effect of HT.[29] Three findings argue against this. First, including markers of adiposity (BMI and waist-to-hip ratio) as covariates did not materially influence the effects seen in the Three-City Study.[1] Second, while brain volumes among women assigned to HT vs placebo were slightly higher among women with BMI <25 kg/m^2 and slightly lower among overweight and obese women, this interaction was not significant, and inclusion of BMI and waist-to-hip ratios as covariates did not alter the significant interaction we observed between HT and diabetes. Finally, we have previously reported that higher BMI and weight gain are associated with better cognitive function in WHIMS.[30]

Type 2 diabetes results in a widespread loss of brain volume that is linked to decrements in cognitive function.[8,31,32] This increased atrophy is thought to result from glucose dysregulation, increased inflammation, and reduced circulation.[33–35] Estrogen plays a critical role in maintaining energy metabolism in the brain by increasing glucose transport and aerobic glycolysis.[36] In parallel, estrogen downregulates the use of alternative energy sources based on the metabolism of ketones and fatty acids, resulting in a "healthy cell bias."[37,38] Among older women with diabetes for whom the glucose-based energy metabolism promoted by estrogen is compromised, this downregulation of alternative energy sources may lead to increased atrophy of gray matter, which has greater metabolic demand relative to white matter. This may explain the interactions we see. In addition, diabetes may disrupt estrogen-mediated vasoprotection by shifting the balance of estrogen receptors alpha and beta,[39] which may restrict blood flow and further compromise energy metabolism. While adiposity also may interact with estrogen to alter its effects on energy regulation, and on brain oxidative stress,[40] our results support other factors related to diabetes interacting with HT to decrease brain volumes.

The volunteers we describe met eligibility criteria for HT and brain MRI and thus may not represent general populations.[16] MRI was not performed prior to WHI enrollment. Diabetes status was primarily based on self-report. Only half the women returned for a second MRI and rates were different among women with and without diabetes, so longitudinal findings may be influenced by differential follow-up. Power was limited, so further study is necessary to confirm these results. We used an intention-to-treat approach and have not assessed medication adherence in our analyses.

Prescription of CEE-based therapies to older women with type 2 diabetes may further accentuate their risk for brain atrophy, specifically of gray matter. These adverse effects may be attenuated in women without diabetes (although still evident in the frontal lobe), consistent with our earlier report that a compromised brain may be more vulnerable to adverse effects of HT.[11] Our findings support the healthy cell bias paradigm for the role of estrogen regulation of brain metabolism.

AUTHOR CONTRIBUTIONS

M.A.E. and S.M.R. contributed to the conceptualization of the study, its analysis and interpretation, and writing the manuscript. R.D.B., J.E.M., K.Y., C.H., L.V., S.C., B.J.E., R.C., and K.M. contributed to the interpretation of the study and the writing of the manuscript.

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