Impact of Type 2 Diabetes and Postmenopausal Hormone Therapy on Incidence of Cognitive Impairment in Older Women

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OBJECTIVE

In older women, higher levels of estrogen may exacerbate the increased risk for cognitive impairment conveyed by diabetes. We examined whether the effect of postmenopausal hormone therapy (HT) on cognitive impairment incidence differs depending on type 2 diabetes.

RESEARCH DESIGN AND METHODS

The Women's Health Initiative (WHI) randomized clinical trials assigned women to HT (0.625 mg/day conjugated equine estrogens with or without [i.e., unopposed] 2.5 mg/day medroxyprogesterone acetate) or matching placebo for an average of 4.7–5.9 years. A total of 7,233 women, aged 65–80 years, were classified according to type 2 diabetes status and followed for probable dementia and cognitive impairment (mild cognitive impairment or dementia).

RESULTS

Through a maximum of 18 years of follow-up, women with diabetes had increased risk of probable dementia (hazard ratio [HR] 1.54 [95% CI 1.16–2.06]) and cognitive impairment (HR 1.83 [1.50–2.23]). The combination of diabetes and random assignment to HT increased their risk of dementia (HR 2.12 [1.47–3.06]) and cognitive impairment (HR 2.20 [1.70–2.87]) compared with women without these conditions, interaction $P = 0.09$ and $P = 0.08$. These interactions appeared to be limited to women assigned to unopposed conjugated equine estrogens.

CONCLUSIONS

These analyses provide additional support to a prior report that higher levels of estrogen may exacerbate risks that type 2 diabetes poses for cognitive function in older women. The role estrogen plays in suppressing non–glucose-based energy sources in the brain may explain this interaction.

Type 2 diabetes increases the risk of dementia and brain atrophy in older women (1–3). Two recent studies have reported that elevated estrogen levels exacerbate these risks. Among older women in the Three City Study, having higher levels of estradiol increased the estimated risk of dementia associated with diabetes by a factor of up to 14 (4). In the Women's Health Initiative (WHI), older women with diabetes who had been randomly assigned to 4–6 years of hormone therapy (HT) had significantly smaller gray matter volumes than those assigned to placebo; this difference was not apparent among women without diabetes (5). If these findings hold, estrogen may be an important risk

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factor to consider toward preventing cognitive decline in older women with diabetes owing to the role it plays in regulating glucose metabolism in the brain (6,7).

We use data from the long-term follow-up of the Women's Health Initiative Memory Study (WHIMS) (8,9) to examine whether there is further support for an interaction between estrogen and diabetes on three measures of cognitive function: incident dementia, any cognitive impairment, and performance on a test of global cognitive function over time. We compare the trajectories of these outcomes among women grouped by diabetes status and random assignment to receive HT or placebo. We also examine whether other factors known to be associated with diabetes (hypertension, obesity, cardiovascular disease, lower baseline cognitive function) contribute to the interactions and describe a potential mechanism for how the adverse consequences of HT in older women (8–10) may be of particular concern for those with diabetes.

RESEARCH DESIGN AND METHODS

WHIMS was an ancillary study to the Women's Health Initiative Hormone Therapy (WHI-HT) trials, which included both a randomized, double-blind, placebo-controlled clinical trial of conjugated equine estrogen treatment alone (CEE-alone) for women with prior hysterectomy and a parallel trial of CEE in combination with medroxyprogesterone acetate (CEE+MPA) for women with an intact uterus (11). The goal of WHIMS was to assess the impact of HT on cognitive impairment and cognitive function in women aged 65–80 years and free of dementia. WHIMS recruitment spanned from May 1995 to December 1999. After an unfavorable risk-to-benefit ratio for its noncognitive end points was discovered, CEE+MPA trial medications were terminated in July 2002. Medications in the CEE-alone trial were discontinued in February 2004 because of a greater risk of stroke and a lack of benefit for coronary heart disease. Annual follow-up of the WHIMS cohort continued postintervention. Through 2007, this was by in-person interviews. Subsequently, the study was extended as WHIMS-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO), with annual follow-up by telephone.

Diabetes and Diabetes Medications

At WHI-HT enrollment, data on history of diabetes, age at onset, and diabetes treatment with glucose-lowering medications or lifestyle modifications were based on self-report. During follow-up, women were queried about diabetes treatment; this has been found to be a valid indicator of diabetes status and well correlated with medication inventories and fasting glucose measurements (12). Prescription medication use (insulin or oral hypoglycemic therapy) was assessed at baseline and years 1, 3, 6, and 9 of follow-up and once again during extended follow-up.

Cognitive Impairment

The protocol for classifying cognitive impairment has previously been described (9,13,14). Global cognitive function was assessed annually by centrally trained, masked, and certified technicians and interviewers. During WHIMS (1995–2007), this was based on the 100-point Modified Mini-Mental State (3MS) exam (15). Subsequently, during WHIMS-ECHO, this was based on the 40-point Telephone Interview for Cognitive Status-modified (TICSm) (16).

In WHIMS, women who screened positive (according to age-/education-adjusted 3MS cut points) proceeded to extensive neuropsychological testing (including the Consortium to Establish a Registry for Alzheimer's Disease battery) and assessment of behavioral symptoms. They then received detailed neurological examinations and neuropsychiatric evaluations by experienced board-certified physicians. Cranial CT scanning and laboratory testing were performed for each suspected case of dementia to rule out possible reversible causes of cognitive decline and dementia.

In WHIMS-ECHO, when women screened positive for cognitive impairment (TICSm <31), a reliable and preidentified informant was interviewed by telephone using the validated Dementia Questionnaire (17) to assess the history of cognitive and behavioral changes, functional impairments, and health events that can affect cognitive functioning (e.g., stroke). Women were classified as no cognitive impairment, mild cognitive impairment, or probable dementia.

Longitudinal cognitive scores and supplemental information (e.g., cardiovascular events) were centrally reviewed for classification based on the DSM-IV (18). When cognitive scores were not obtained, the Dementia Questionnaire interviews of proxies were used to identify additional cases (13), an approach demonstrated to have high diagnostic validity (19).

Covariates and Potential Confounders

We examined risk factors for diabetes: age, education, family income, BMI, waist girth, hypertension, and prior cardiovascular disease. This information was collected via self-report and standardized assessments at WHI enrollment (20). Prior hysterectomy determined whether women participated in the CEE-alone or CEE+MPA trials. Apolipoprotein (apo)E genotypes were assigned based on rs429358 and rs7412 genotype results from imputation and harmonization of genetic data across WHI genome-wide association studies in 4,403 women included in our analyses. Imputation was conducted using the 1000 Genomes Project reference panel and the MaCH algorithm as implemented in Minimac ($R^2 = 0.98$ for each single nucleotide polymorphism in the study population) (21).

Statistical Methods

Proportional hazards regression was used to assess the interaction between diabetes status at enrollment and the incidence of probable dementia and any cognitive impairment (probable dementia or mild cognitive impairment) and to estimate hazard ratios (HRs) for the four subgroups defined by this 2×2 interaction. Log-log plots were used to confirm the appropriateness of the proportional hazards model. We repeated these analyses for three spans of follow-up: through a maximum of 6 years (when the majority of women had transitioned into the postintervention phase of follow-up), through a maximum of 12 years (roughly the time of our prior article on MRI outcomes) (5), and through a maximum of 18 years. We used age and baseline 3MS scores as covariates in all models but also examined the impact of additional covariate adjustment. To assess whether other factors related to diabetes (hypertension, obesity, prior cardiovascular disease) might account for the interactions between diabetes and postmenopausal HT that we described, we examined the degree to which inclusion of their interactions with treatment assignment as covariates affected results. We also assessed

whether there was an interaction between diabetes and HT on global cognitive function by fitting general linear models (22) to longitudinal 3MS scores. Because our earlier article on brain volumes reported some (nonsignificant) differences attributable to insulin use (5), we repeated analyses eliminating women who took insulin at baseline and/or during the intervention phase of the trials.

RESULTS

Our analyses include the 7,233 (96.7%) of 7,479 women who provided at least one assessment of cognitive function during follow-up and for whom diabetes status at baseline was recorded. The average (SD) durations of participation in the treatment phases of the WHI CEE+MPA and WHI CEE-alone trials were 4.7 (1.0) and 5.9 (1.5) years. These mean participation times in the treatment phases did not vary with treatment assignment ($P = 0.89$) but were 0.36 (SE 0.06) years shorter, on average, for women with diabetes compared with others ($P < 0.001$).

Women contributed an average of 7.7 years (interquartile range 6.0–9.8) of follow-up through 2007, when 3MS global cognitive assessments ceased. Their average follow-up (WHIMS and WHIMS-ECHO combined) until either censoring or classification with cognitive impairment was 9.9 years (6.0–15.0).

Table 1 describes women grouped according to treatment assignment and baseline diabetes. The balance between intervention groups provided by randomization was maintained among these women. Differences between those with and without diabetes were evident for all factors except age and apoE genotype.

Across follow-up, the conversion rates to probable dementia for women assigned to HT were 11.7% (of 274) in women with diabetes and 8.4% (of 3,282) in women without diabetes. Among women assigned to placebo, conversion rates were 7.2% (of 264 with diabetes) and 7.9% (of 3,413 without diabetes). Rates of any cognitive impairment (either mild cognitive impairment or probable dementia) in these four groups were 23.4% (HT with diabetes) 14.4% (HT without diabetes), 17.4% (placebo with diabetes), and 14.4% (placebo without diabetes). Figure 1*A* and *B* portrays cumulative hazards for dementia and any cognitive impairment for these groups.

Table 2 describes results from proportional hazards regression for probable dementia, with covariate adjustment for age and baseline 3MS. For portrayal of how relationships may have changed with longer follow-up, analyses were performed with follow-up censored at 6 years (when 67% of women had completed the intervention phase of the trials), 12 years (when time since interventions ended averaged 6.4 [range 3.8–8.7] years), and at 18 years. Results are provided for analyses pooled across the two trials and separately for the CEE-alone and CEE+MPA trials.

Through the first 6 years, the HR for conversion to probable dementia among women assigned to HT compared with placebo was 1.54 (95% CI 1.10–2.16) across trials and was of a similar magnitude between trials. The overall HR associated with diabetes was 1.45 (0.87–2.41). Over time, the HR associated with HT waned and its 95% CI no longer excluded 1: through 18 years, it was HR 1.15 (95% CI 0.98–1.35). The overall HR for conversion to dementia associated with diabetes remained fairly constant over time (e.g., 1.54 [1.16–2.06] at 18 years); however, there was some heterogeneity in this risk depending on HT assignment. The combination of diabetes and assignment to HT in the CEE-alone trial appeared to increase women's risk for cognitive impairment beyond what might be predicted from their separate effects (although interaction *P* values were only of marginal significance).

If the 239 women who took insulin at baseline and/or during the intervention phase of the trials are eliminated (181 who had diabetes at baseline and 58 who did not), among the remaining subset of women, the 18-year HRs relative to women on placebo without diabetes are 1.93 (95% CI 1.25–2.99) for women with diabetes on HT, 1.12 (0.95–1.33) for women on HT without diabetes, and 0.94 (0.52–1.73) for women on placebo with diabetes (interaction $P = 0.11$). Thus, while eliminating these women slightly altered the magnitudes of the HRs, some evidence for the interaction remained.

We also examined whether there was evidence that the interaction was attributable to other factors related to diabetes, including hypertension, history of cardiovascular disease, BMI, and baseline 3MS scores. When interactions between these factors and HT assignment were included as covariates in analyses, there was no material effect on estimates for the interaction between diabetes and treatment assignment in models with additional covariate adjustment (with *P* values for this ranging from 0.06 to 0.11). We also examined whether including an interaction term between apoE genotype and treatment assignment affected results: while presence of an apoE-4 allele was associated with HR 2.99 (95% CI 2.44–3.68) for probable dementia across 18 years, there was no interaction with treatment assignment ($P = 0.56$), and including this term in models did not appear to influence the interaction between diabetes and HT on cognitive outcomes.

There were 176 women who did not report diabetes at baseline but who converted to diabetes during the WHI HT trials, 70 of whom had been assigned to HT and 106 who had been assigned to placebo therapy. Compared with women without diabetes, there was little evidence for an interaction involving treatment assignment on probable dementia across the span of 18 years ($P = 0.38$).

Table 3 reports parallel analyses for the hazard of any cognitive impairment. At 6 years, assignment to HT compared with placebo was associated with an overall HR of 1.26 (95% CI 1.02–1.55). At this time, diabetes compared with no diabetes was associated with an overall HR of 2.40 (1.82–3.15). Among the CEE-alone trial, but not the CEE+MPA trial, there was some evidence of an interaction ($P = 0.04$) for increased risk among treated women who had diabetes compared with those who did not. While the overall hazard associated with HT waned to nonsignificance later during follow-up, the interaction between HT and diabetes in the CEE-alone trial continued to be evident at 12 and 18 years (both $P = 0.02$).

Assignment to HT relative to placebo was associated with an overall mean decrement in 3MS scores of −0.26 SD units (95% CI −0.40 to −0.11) throughout follow-up, which was similar in both trials (Supplementary Table 1). Diabetes compared with no diabetes was associated with an overall mean decrement of −0.72 SD units (−0.99 to −0.44). There was some evidence for greater

Table 1—Distribution of risk factors for cognitive impairment at WHI enrollment

	Diabetes (*N* = 538)		No diabetes (*N* = 6,695)			
Risk factor for cognitive impairment	HT (*N* = 274)	Placebo (*N* = 264)	HT (*N* = 3,282)	Placebo (*N* = 3,413)	HT vs. placebo *P*	Diabetes vs. no diabetes *P*
Age at WHI HT enrollment, years	71.1 (3.7)	70.7 (3.8)	71.0 (3.8)	71.0 (3.9)	0.79	0.61
Education (missing = 9)						
Not high school graduate	33 (12.1)	28 (10.6)	237 (7.2)	248 (7.3)	0.18	<0.001
High school graduate	56 (20.5)	56 (21.2)	711 (21.7)	772 (22.6)		
At least some college	118 (43.2)	125 (47.4)	1,357 (41.4)	1,310 (38.4)		
College graduate	66 (24.2)	55 (20.8)	974 (29.7)	1,078 (31.6)		
Race/ethnicity, *N* (%) (missing = 3)						
American Indian	2 (0.7)	3 (1.1)	12 (0.4)	9 (0.3)	0.97**	<0.001**
Asian/Pacific Islander	7 (2.6)	8 (3.0)	56 (1.7)	50 (1.5)		
African American	54 (19.7)	32 (12.1)	203 (6.2)	224 (6.6)		
Hispanic/Latino	13 (4.7)	7 (2.6)	71 (2.2)	78 (2.3)		
Non-Hispanic white	195 (71.2)	211 (79.9)	2,897 (88.3)	3,000 (87.9)		
Other/multiple	3 (1.1)	3 (1.1)	41 (1.2)	51 (1.5)		
Annual income, *N* (%) (missing = 253)						
<$20,000	102 (38.4)	84 (33.1)	784 (24.8)	7,891 (24.0)	0.41	<0.001
$20,000–34,999	89 (33.5)	75 (29.5)	968 (30.6)	1,012 (30.7)		
$35,000–$49,999	38 (14.3)	55 (21.6)	624 (19.7)	682 (20.7)		
≥$50,000	37 (13.9)	40 (15.8)	792 (25.0)	807 (24.5)		
BMI, kg/m^2 (missing = 39)	32.0 (6.7)	31.1 (5.5)	28.4 (5.5)	28.2 (5.6)	0.08	<0.001
Waist girth, cm (missing = 25)	99.0 (13.1)	97.7 (13.0)	88.0 (13.3)	87.8 (12.9)	0.24	<0.001
Hypertension status, *N* (%) (missing = 84)						
No	95 (35.7)	94 (36.2)	2.005 (61.7)	2,155 (63.8)	0.07	<0.001
Yes	171 (64.3)	166 (63.8)	1,243 (38.3)	1,220 (36.2)		
Prior CVD, *N* (%) (missing = 110)						
No	185 (68.3)	182 (70.0)	2,698 (83.4)	2,824 (84.1)	0.35	<0.001
History of other CVD*	86 (31.7)	78 (30.0)	536 (16.6)	534 (15.9)		
Prior hysterectomy, *N* (%)						
No	133 (48.5)	119 (45.1)	2,017 (61.5)	2,122 (62.2)	0.67	<0.001
Yes	141 (51.5)	145 (54.9)	1,265 (38.5)	1,292 (37.8)		
Baseline 3MS score	93.97 (4.77)	94.34 (5.23)	95.29 (4.29)	95.32 (4.20)	0.56	<0.001
ApoE genotype (missing = 2,830)						
No e4 allele	103 (76.3)	113 (79.6)	1,493 (74.0)	1,576 (74.8)	0.44	0.18
e4 allele(s)	32 (23.7)	29 (20.4)	526 (26.0)	531 (25.2)		

Data are mean (SD) unless otherwise indicated. *Other cardiovascular disease (CVD) defined as myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or stroke. **For inference, grouped as African American, Hispanic/Latino, Non-Hispanic white, or other.

treatment-related decrements among women with diabetes compared with those without (interaction $P = 0.04$) in the CEE-alone trial but not the CEE+MPA trial.

CONCLUSIONS

The presence of a relatively stable, long-term impact of diabetes on the risk for cognitive impairment and dementia in women is consistent with many other reports. For example, in a cohort of 1,118 women initially aged 38–60 years, diabetes was associated with an HR of 2.2 (95% CI 1.1–4.4) for developing dementia over 34 years of follow-up (1). Increased risks in older persons with diabetes are evident for both vascular dementia and Alzheimer disease (23,24) and for conversion from mild cognitive impairment to dementia (25). We have previously reported that diabetes leads to sustained decrements in cognitive function among WHI participants (26).

To facilitate presentation, we chose time frames (i.e., 6-year intervals) that overlap but do not equal reports of the primary findings from the treatment phases of the WHI trials (8,9), and we have included additional cases that were identified through longer follow-up and the supplemental case ascertainment protocol (13). Our findings through 6 years are consistent with these earlier reports: 95% CIs for the overall HRs associated with random assignment to CEE-based therapies for probable dementia (HR 1.54 [95% CI 1.10–2.16]) and cognitive impairment (1.26 [1.02–1.55]) both exclude 1, indicating increased risks associated with CEE-based HT in older women. Among women without diabetes, the 6-year HR associated with CEE therapy for dementia also excludes 1 (1.53 [1.07–2.19]); however, the HR for any cognitive impairment does not (1.19 [0.94–1.49]). These CIs both attenuate toward 1 with longer follow-up. This is consistent with hypotheses raised in these earlier WHI reports (27) that HT may accelerate the conversion to cognitive impairment and dementia among those already at proximal risk. In this scenario, women in the placebo group would eventually convert, as well, evening out the long-term numbers of observed cases.

Consistently throughout follow-up in analyses pooled across trials, the greatest hazards for probable dementia and any cognitive impairment were among women with diabetes who had been assigned to HT. Compared with women

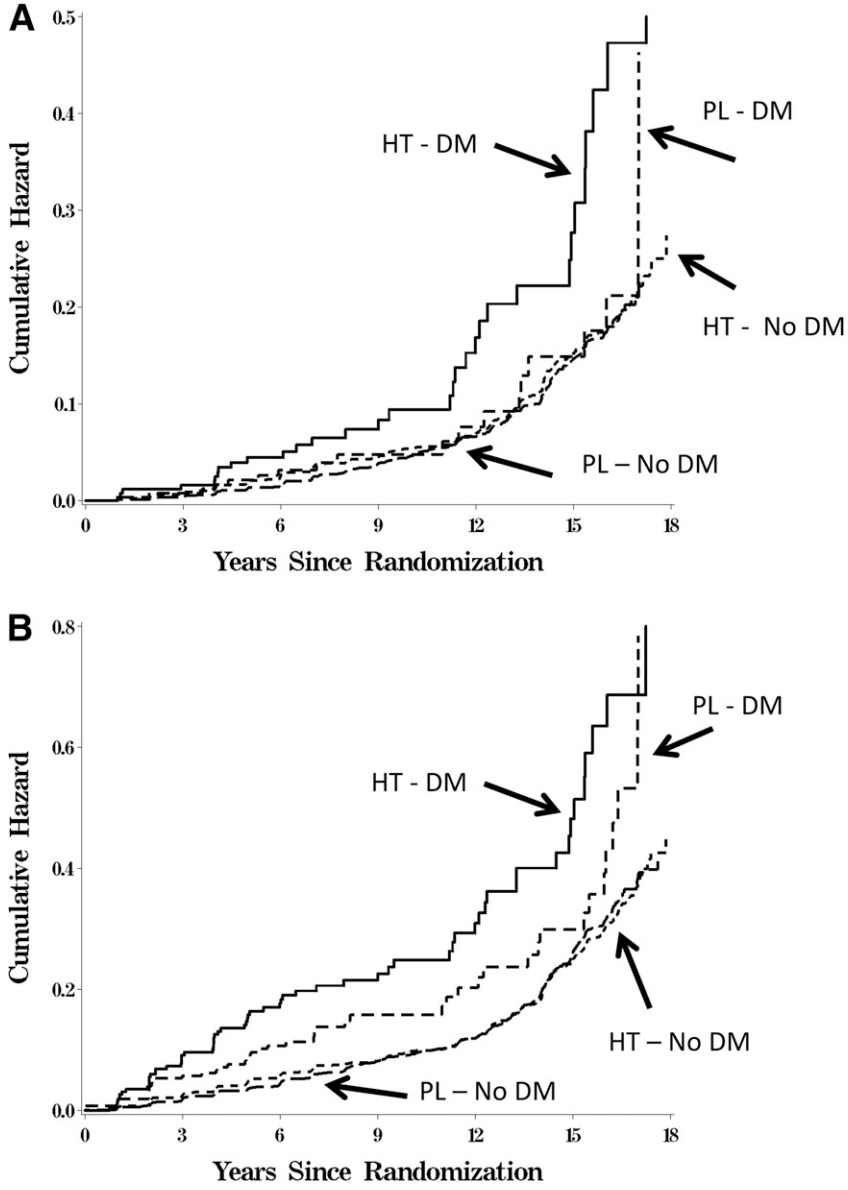

Figure 1—Cumulative hazard of probable dementia (*A*) and cognitive impairment (*B*) over 18 years for women grouped by diabetes (DM) and assignment to HT or placebo (PL).

without diabetes assigned to placebo, HRs exclude 1 and persist over time: for probable dementia, these were HR 2.29 (95% CI 1.16–4.52) through 6 years and 2.12 (1.47–3.06) through 18 years.

While the interactions that we report would not reach statistical significance after adjustment for multiple comparisons, they are consistent with our motivating hypotheses and of potential clinical concern. The presence of diabetes appears to accentuate the short-term (i.e., 6 years) effects of randomization to CEE-based HT on cognitive impairment and probable dementia. Evidence of this interaction appears to persist through 18 years of follow-up, more than a decade after prescription of HT was terminated. Qualitatively, these long-term interactions appear to be sustained among women participating in the CEE-alone trial but not among those participating in the CEE+MPA trial. This interaction is also statistically significant for cognitive function. It does not appear to be attributable to other factors related to diabetes that we examined, including hypertension, obesity, history of cardiovascular disease, or pretreatment cognitive function. It was also not apparent among women who had prediabetes (defined as those who converted to clinically overt diabetes during follow-up). Note that in the subset of women we analyzed, there were fewer women who converted to diabetes among those assigned to HT versus placebo, similar to what has been reported for the full WHI trials (28,29). We did not find evidence that insulin therapy altered the relationship.

During premenopause, estrogen promotes the glucose metabolism system in the brain to enhance glucose uptake, glucose metabolism, the conversion of pyruvate to acetyl-CoA, the TCA cycle, and mitochondrial oxidative phosphorylation to generate ATP (30–34). The impact of estrogen regulation of the bioenergetic system of the brain is to promote and sustain the use of glucose as the primary fuel to generate ATP in brain (34). In tandem, estrogen suppresses the fatty acid/ketone metabolism system of the brain (6,7). During the perimenopausal transition, estrogenic control of the glucose metabolism system in brain is dismantled and replaced with an adaptive reliance on ketone bodies as a compensatory fuel to generate ATP in brain (30,32–34). The introduction of estrogen agonists after menopause could result in reinstantiation of estrogenic suppression of the ketogenic system without commensurate recovery of glucose metabolism. If this were the case, it would be particularly deleterious for women with diabetes, as the diabetic brain has compromised glucose metabolism and thus a greater reliance on ketone bodies as a fuel source.

Interestingly, the interaction between diabetes and HT did not appear in women treated with CEE+MPA. This suggests that MPA continues to act as an antagonist to estrogen action in the brain, which is consistent with preclinical data (35,36). In these studies, MPA antagonized estrogen potentiation of critical aspects of glucose metabolism in the brain including mitochondrial function (35,36). These mechanistic postulates require that estrogen control of glucose metabolism in brain is no longer inducible in the postmenopausal diabetic brain, whereas suppression of the ketogenic system in brain remains responsive to estrogenic control. This hypothesis could be tested in female rodent models of diabetes over the course of reproductive senescence.

An alternative mechanism to account for our findings is that HT may mask the severity of diabetes, potentially leading

Table 2—HRs (95% CI) and numbers of cases for probable dementia for women grouped by diabetes status and WHI treatment assignment with covariate adjustment for baseline age and global cognitive function (3MS score)

	HT		Placebo therapy				
	Diabetes (*N* = 274)	No diabetes (*N* = 3,282)	Diabetes (*N* = 264)	No diabetes (*N* = 3,413)	HT vs. placebo	Diabetes vs. no diabetes	Interaction *P*
Through a maximum of 6 years of follow-up							
CEE-alone trial	2.59 (1.05–6.37) 6 cases	1.22 (0.70–2.13) 27 cases	0.35 (0.05–2.56) 1 case	1.00 (Ref) 23 cases	1.46 (0.86–2.48) *P* = 0.16	1.24 (0.56–2.74) *P* = 0.60	0.11
CEE+MPA trial	1.87 (0.65–5.38) 4 cases	1.81 (1.12–2.90) 50 cases	2.57 (1.04–6.37) 6 cases	1.00 (Ref) 26 cases	1.61 (1.04–2.50) *P* = 0.03	1.60 (0.82–3.11) *P* = 0.17	0.19
Combined	2.29 (1.16–4.52) 10 cases	1.53 (1.07–2.19) 77 cases	1.37 (0.62–3.06) 7 cases	1.00 (Ref) 29 cases	1.54 (1.10–2.16) *P* = 0.01	1.45 (0.87–2.41) *P* = 0.16	0.87
Through a maximum of 12 years of follow-up							
CEE-alone trial	2.02 (1.09–3.74) 12 cases	0.87 (0.61–1.24) 55 cases	0.45 (0.14–1.43) 3 cases	1.00 (Ref) 66 cases	1.02 (0.73–1.43) *P* = 0.90	1.27 (0.74–2.18) *P* = 0.38	0.01
CEE+MPA trial	2.10 (1.00–4.03) 9 cases	1.34 (0.98–1.82) 94 cases	1.74 (0.83–3.66) 8 cases	1.00 (Ref) 70 cases	1.32 (0.98–1.77) *P* = 0.07	1.60 (0.97–2.66) *P* = 0.07	0.77
Combined	2.10 (1.33–3.33) 21 cases	1.11 (0.88–1.40) 146 cases	1.01 (0.54–1.87) 11 cases	1.00 (Ref) 136 cases	1.18 (0.95–1.48) *P* = 0.14	1.46 (1.01–2.11) *P* = 0.04	0.11
Through a maximum of 18 years of follow-up							
CEE-alone trial	2.04 (1.22–3.40) 17 cases	0.91 (0.69–1.19) 96 cases	1.06 (0.57–1.98) 11 cases	1.00 (Ref) 116 cases	0.99 (0.77–1.28) *P* = 0.93	1.57 (1.06–2.33) *P* = 0.03	0.07
CEE+MPA trial	2.11 (1.24–3.60) 15 cases	1.24 (1.00–1.54) 179 cases	1.22 (0.60–2.49) 8 cases	1.00 (Ref) 152 cases	1.27 (1.03–1.56) *P* = 0.03	1.49 (0.98–2.29) *P* = 0.06	0.46
Combined	2.12 (1.47–3.06) 32 cases	1.10 (0.93–1.30) 275 cases	1.15 (0.72–1.84) 19 cases	1.00 (Ref) 268 cases	1.15 (0.98–1.35) *P* = 0.09	1.54 (1.16–2.06) *P* = 0.003	0.09

to differences in the management of diabetes and incident diabetes that affect the risk for dementia and cognitive impairment. We do not have adequate measures of diabetes control in the WHIMS cohort to explore this hypothesis. However, we note that termination of HT treatment did not result in an increase in diabetes detection (37), arguing against the role of HT in "masking" disease incidence. In addition, the use of insulin among women with baseline diabetes after termination of the WHI HT trials did not differ among treatment groups ($P = 0.73$).

Emergence of the interactions between HT and diabetes appeared to be expressed differently for probable dementia and any cognitive impairment. The largest difference appeared at 6 years, at which time there was little evidence (but few cases) for an interaction associated with probable dementia ($P = 0.87$) and only very modest evidence for an interaction associated with any cognitive impairment ($P = 0.22$). Later, as more cases accrued, the evidence for interactions for both probable dementia and any cognitive impairment became stronger, driven by cases from the CEE-alone cohort.

Our study is limited by the lack of assays of estradiol levels and the use of self-report and/or treatment to determine cases of diabetes. In addition, the shift in the protocol for identifying probable dementia and mild cognitive impairment during the longer term follow-up and the necessity to reconsent women for continued follow-up may have altered the case mix. The 3MS measure of global cognitive functioning has been used extensively and reliably in WHIMS (38,39); however, it is a screening instrument designed to offer a quick, global assessment of cognitive status. The 3MS is limited by its potential for ceiling effects, particularly in highly educated individuals. In a clinical setting, more sensitive measures of cognition would be more accurate at detecting transitions to mild cognitive impairment and/or dementia. The WHI only studied CEE-based HT. We are unable to examine in this study whether our findings generalize to younger women, who are the primary target at present for postmenopausal HT. The *P* values we report to support the interaction between HT and diabetes are marginal but suggest potential mechanisms underlying adverse effects of HT in vulnerable older women. In this study, we focused on diabetes and its effect in accentuating adverse effects of HT on cognition in older postmenopausal women, but other factors may also accentuate HT-associated adverse effects in vulnerable women.

Table 3—HRs (95% CI) and numbers of cases for cognitive impairment (i.e., mild cognitive impairment or probable dementia) for women grouped by diabetes status and WHI treatment assignment with covariate adjustment for baseline age and global cognitive function (3MS score)

	HT		Placebo				
	Diabetes (*N* = 274)	No diabetes (*N* = 3,282)	Diabetes (*N* = 264)	No diabetes (*N* = 3,413)	Hormone vs. placebo therapy	Diabetes vs. no diabetes	Interaction *P*
Through a maximum of 6 years of follow-up							
CEE-alone trial	3.91 (2.46–6.21) 25 cases	1.17 (0.84–1.63) 75 cases	1.47 (0.79–2.73) 12 cases	1.00 (Ref) 66 cases	1.38 (1.02–1.86) *P* = 0.03	2.39 (1.66–3.44) *P* < 0.001	0.04
CEE+MPA trial	2.31 (1.28–4.19) 13 cases	1.20 (0.88–1.65) 95 cases	2.44 (1.32–4.52) 2 cases	1.00 (Ref) 70 cases	1.17 (0.88–1.56) *P* = 0.29	2.13 (1.40–3.26) *P* < 0.001	0.57
Combined	3.30 (2.30–4.73) 38 cases	1.19 (0.94–1.49) 170 cases	1.96 (1.27–3.03) 24 cases	1.00 (Ref) 136 cases	1.26 (1.02–1.55) *P* = 0.03	2.40 (1.82–3.15) *P* < 0.001	0.22
Through a maximum of 12 years of follow-up							
CEE-alone trial	2.63 (1.77–3.91) 31 cases	0.95 (0.74–1.23) 115 cases	1.26 (0.77–2.08) 18 cases	1.00 (Ref) 124 cases	1.09 (0.86–1.37) *P* = 0.48	1.94 (1.42–2.64) *P* < 0.001	0.02
CEE+MPA trial	2.10 (1.30–3.40) 19 cases	1.07 (0.85–1.34) 156 cases	2.05 (1.20–3.49) 15 cases	1.00 (Ref) 142 cases	1.06 (0.86–1.32) *P* = 0.58	2.01 (1.40–2.86) *P* < 0.001	0.92
Combined	2.52 (1.86–3.41) 50 cases	1.02 (0.86–1.20) 271 cases	1.63 (1.13–2.34) 33 cases	1.00 (Ref) 266 cases	1.07 (0.92–1.26) *P* = 0.38	2.05 (1.63–2.59) *P* < 0.001	0.08
Through a maximum of 18 years of follow-up							
CEE-alone trial	2.35 (1.66–3.33) 38 cases	0.98 (0.80–1.19) 191 cases	1.28 (0.86–1.92) 27 cases	1.00 (Ref) 212 cases	1.07 (0.89–1.28) *P* = 0.49	1.77 (1.36–2.31) *P* < 0.001	0.02
CEE+MPA trial	1.86 (1.24–2.78) 26 cases	1.04 (0.88–1.23) 283 cases	1.73 (1.09–2.76) 19 cases	1.00 (Ref) 281 cases	1.05 (0.89–1.23) *P* = 0.58	1.76 (1.30–2.39) *P* < 0.001	0.93
Combined	2.20 (1.70–2.87) 64 cases	1.02 (0.90–1.16) 474 cases	1.50 (1.10–2.04) 46 cases	1.00 (Ref) 493 cases	1.06 (0.94–1.20) *P* = 0.34	1.83 (1.50–2.23) *P* < 0.001	0.08

Summary

The adverse effects of diabetes on the cognitive function of older women appear to be accentuated by unopposed CEE therapy. Whether these results apply to younger women is unknown, and the question of whether hormone therapy prior to menopause will yield comparable outcomes warrants further study.

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Appendix

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WHIMS, Wake Forest University School of Medicine. Sally Shumaker. For a list of all the investigators who have contributed to WHI science, please visit https://www.whi.org/about/SitePages/Study%20Organization.aspx.

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