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Association between central adiposity and cognitive domain function in recently postmenopausal women: an analysis from the KEEPS-Cog substudy of the Kronos Early Estrogen Preventive Study

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Abstract

Objective: To determine associations between central adiposity, cognitive function, and randomized menopausal hormone therapy (MHT) in a reanalysis of the Kronos Early Estrogen Prevention Study-Cognitive and Affective (KEEPS-Cog) substudy participants.

Methods: KEEPS randomized 727 women (ages 42-58) who were < 36 months postnatural menopause to oral conjugated equine estrogens (o-CEE), transdermal 17-β-estradiol (t-E2), or placebo for 48 months. Participants with diabetes, body mass index > 35 kg/m^2, coronary artery calcium score > 50 Agatston Units, and other cardiometabolic disease risk indicators were excluded from enrollment. In the ancillary KEEPS-Cog study, cognitive tests were completed at baseline, 18-, 36-, and 48-month postrandomization. In these analyses, cognitive variables were summarized as four cognitive domain-specific factor scores: verbal learning and memory, auditory attention and working memory, visual attention and executive function, and speeded language and mental flexibility. Waist-hip-ratio (WHR), an indicator of central adiposity, was measured at screening (baseline) and modeled as a covariate in linear latent growth models assessing associations of MHT with cognitive functions at baseline and over time.

Results: Higher baseline WHR was associated with poorer performance on all domain-specific cognitive outcomes at baseline and with changes in visual attention and executive function across time. Models including interaction effects were not significant for either o-CEE x WHR or t-E2 x WHR.

Conclusion: Central adiposity is a risk factor for domain-specific cognitive decline, and thus, cognitive health effects should be investigated in early postmenopausal women, even in women with low cardiovascular risk statuses.

Key Words: Central adiposity, Estrogens, Menopausal hormone therapy, Metabolic syndrome diseases, Waist-to-hip ratio.

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Weight gain, especially at the waist, is common during the peri/postmenopausal period.[1] This increase in waist girth and declining endogenous estrogens occurring after menopause are linked with decreases in insulin sensitivity and increases in inflammatory processes, which are all related to accumulation of intra-abdominal, visceral, or adipose tissue.[2,3] Compared with overall body adiposity, visceral adipose tissue has been associated with major health risks, including metabolic syndrome (MetS), insulin resistance, diabetes, hypertension, dyslipidemia, cardiovascular disease, Alzheimer disease, and related dementias (ADRD).[1,2,4–,8] While much is unknown about these disease processes, the molecular events driving the relationship between metabolic dysfunction and cognitive decline appear to be bidirectional.[9] Therefore, measures of central adiposity, such as the waist-to-hip ratio, may possibly serve as an early and convenient marker of risk for both metabolic as well as cognitive dysfunction.

Although clinical trials of menopausal hormone therapy (MHT) with either estrogen alone or estrogen plus progestin among recently postmenopausal women have shown no effect on cognition,[10,11] incident cognitive impairment was reported in the Women's Health Initiative Memory Study (WHIMS) for women ages 65 and older who were randomized to MHT.[12,13] Furthermore, in WHIMS, women with type 2 diabetes demonstrated a greater risk of incident cognitive impairment with the administration of MHT compared with women without diabetes, suggesting MHT effects on cognitive decline in women in later menopause with metabolic disturbances.[12,13] Of note, to date, there are no studies on cognitive harm in younger, early postmenopausal women who exhibit risk for, or already have, metabolic dysfunction. The participants in WHIMS were older than the women in KEEPS and other studies examining the cognitive effects of MHT soon after menopause, for example, the Early versus Late Intervention Trial with Estradiol (ELITE).[10] Other randomized clinical trials have shown an inverse relationship between diabetes and MHT in postmenopausal women, where MHT use in mid-life has an antidiabetic effect in women.[14-16] Together, these data suggest a complex relationship between endogenous estrogen, exogenous estrogens (MHT), and metabolic health and cognition in postmenopausal women.

Therefore, to further investigate the relationship between central adiposity, cognitive function, and MHT exposure in early postmenopausal women, we conducted a secondary analysis of data from an ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS) –the KEEPS Cognitive and Affective Study (KEEPS-Cog). While KEEPS and KEEPS-Cog excluded participants with diabetes at enrollment, women with prediabetes were included.[17–20] The original KEEPS trial randomized women to 4 years of treatment with one of two forms of MHT or placebo.[11,21]

In this secondary analysis, central adiposity was estimated by a measure of waist-to-hip ratio (WHR), a robust predictor of risk for glucose tolerance, insulin resistance, and type 2 diabetes mellitus (T2DM).[22-24] In our analysis, the selection of WHR over simple waist circumference (WC) was based on the ability of WHR to characterize visceral adipose tissue distribution.[25] Adipose tissue can have differential effects depending on where it develops, with peripheral depositions (eg, at the hips) being metabolically protective relative to central adiposity, which is associated with visceral adipose tissue.[26]

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TABLE 1. Baseline characteristics of KEEPS-Cog participants, N = 693

Treatment group	N (%)
Placebo	262 (37.8)
t-E2	211 (30.4)
o-CEE	220 (31.7)
Study center	N (%)
Brigham and Women's Hospital	81 (11.69)
Columbia University	113 (16.31)
Mayo Clinic Rochester	118 (17.03)
Albert Einstein College	69 (9.96)
University of California—San Francisco	51 (7.36)
University of Utah	92 (13.28)
University of Washington	37 (5.34)
Yale University	67 (9.67)
Kronos Longevity Research Institute	65 (9.38)
Age	Mean ± SD
Baseline age (y), n = 687	52.6 ± 2.6
Education	N (%)
Grade school or some high school	4 (0.58)
High school diploma or GED	49 (7.07)
Some college/vocational school	126 (18.18)
College graduate	274 (39.54)
Some graduate or professional school	31 (4.47)
Graduate or professional degree	197 (28.43)
Missing	12 (1.73)
Self-identified race/ethnicity	N (%)
Asian Indian	6 (0.87)
Black or African American	51 (7.36)
White	533 (76.91)
Chinese	6 (0.87)
Filipino	2 (0.29)
Hispanic or Latino	49 (7.07)
Japanese	1 (0.14)
Korean	1 (0.14)
Multiracial or Other	7 (1.01)
Missing	37 (5.34)
Baseline global cognition and cognitive domain factors scores	Mean standard score ± SD
Modified Mini-Mental State Examination Score (3MS), n = 619	96.6 ± 4.3
Verbal learning and memory (VLM), n = 662	50.0 ± 8.7
Auditory attention and working memory (AAWM), n = 662	50.0 ± 7.5
Visual attention and executive function (VAEF), n = 662	50.0 ± 7.3
Speeded language and mental flexibility (SLMF), n = 662	50.0 ± 7.9
Baseline Biometric and Biological measurements	Mean ± SD
Waist-to-Hip-Ratio (WHR) cm/cm, n = 683	0.82 ± 0.08
Waist Circumference, (WC) cm, n = 683	84.4 ± 11.8
HOMA-IR, n = 688	1.3 ± 2.4

Under self-identified race/ethnicity, multiracial or other is a category for anyone whose race/ethnicity did not fit any of the listed categories.

%, percentage; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; KEEPS-Cog, Kronos Early Estrogen Preventative Study-Cognitive and Affective; M, mean; n, the number of participants in a group; o-CEE, oral conjugated equine estrogen; t-E2, transdermal E2.

Notably, in the literature, WHR and metabolic dysfunction have been linked to deficits in specific cognitive domains, namely executive function and verbal memory.[6,9,27–29] Estrogen receptors in the brain are concentrated in regions serving executive function and memory.[30,31] However, there have been reports of contradictory effects of hormone therapy on both executive function and verbal memory in younger postmenopausal women.[32] Therefore, in these analyses, we assessed the relationship between central adiposity, MHT, and cognitive domain-specific outcomes.

We hypothesized that higher WHR measured at baseline would negatively associate with domain-specific cognitive functions at baseline and longitudinally, especially in participants who received placebo versus MHT, such that women with higher central adiposity at baseline would exhibit worse domain-specific cognitive function in all domains over the 4 years of the study. To test this hypothesis, we assessed (1) associations between baseline WHR and specific concurrently measured cognitive domains during the KEEPS-Cog, and (2) the interaction of baseline WHR and MHT on cognitive domain-specific function over time in linear latent growth models.

METHODS

Secondary analysis of clinical trial data

The Kronos Early Estrogen Prevention Study (KEEPS)—and its ancillary trial, the KEEPS Cognitive and Affective Study (KEEPS-Cog) was a multisite, randomized, placebo-controlled, double-blind clinical trial occurring between 2005 and 2012. Women in the KEEPS trial were aged 42-58 years and within 36 months of their last menstrual period (LMP; mean = 1.4 years since LMP) at enrollment. Women with surgical or induced menopause were not included in the study. Participants were randomized to one of three treatment arms, ie, placebo, oral conjugated equine estrogens CEE (o-CEE), or transdermal 17-β-estradiol (t-E2).[21] MHTs were paired with progesterone daily (d) for the first 12 days of each month to prevent detrimental endometrial effects of unopposed estrogen treatment. Specifically, participants randomized to o-CEE received o-CEE as Premarin (Pfizer), a 0.45 mg/d tablet, plus Prometrium (Abbott), a cyclical micronized progesterone (m-P) as a 200 mg/d oral capsule for 12 d/mo, and a placebo skin patch. Participants randomized to t-E2 received t-E2 as Climara (Bayer), a skin patch (50-μg/d) plus cyclical m-P at 200-mg/d oral capsule for 12 days and a placebo tablet. Those randomized to placebo followed the same dosing schedule, with inactive medications. The intervention phase continued for a duration of 48 months. A detailed description of the study has been previously published, including study sites, recruitment/screening methods, and inclusion/exclusion criteria.[33,34]

KEEPS-Cog enrollment was initiated approximately 1 month after the start of KEEPS; thus, 693 of 727 women enrolled in KEEPS were enrolled in KEEPS-Cog. Participants were randomized as follows: $N_{placebo} = 262$, $N_{t\text{-}E2} = 211$, $N_{o\text{-}CEE} = 220$ (Table 1). Participants with high cardiovascular risk were excluded from enrollment from KEEPS and thus from KEEPS-Cog based on a body mass index (BMI) > 35 kg/m^2, a coronary artery calcium (CAC) score > 50 Agatston Units (AU), and a history of clinical cardiovascular disease (including myocardial infarction, angina, congestive heart failure, stroke, transient ischemic attack, or thromboembolic diseases); participants with dyslipidemia (low density lipoprotein cholesterol > 190 mg/dL), and hypertriglyceridemia (triglycerides > 400 mg/dL) were also excluded[33,34] As noted, diabetes was an exclusion criteria; however, prediabetes, for example, insulin resistance was not exclusionary in either KEEPS or KEEPS-Cog.[33,34]

Ethics approval

Original study procedures and current analyses were approved by the Institutional Review Boards (IRBs) at all participating study sites as previously described.[11] The IRB protocol remains open for secondary data analyses.

Measurements/data collection

Cognitive testing—derivation of cognitive domain-specific factor scores

Cognitive testing was performed at screening (baseline), 18, 36, and 48 months, and comprised a full neuropsychological test battery. Cognitive tests (shown in Supplementary Table A, Supplemental Digital Content 1, http://links.lww.com/MENO/B433) were summarized with factor models into 4 cognitive domain factors: verbal learning and memory (VLM), = speeded language and mental flexibility (SLMF), visual attention and executive function (VAEF), and auditory attention and working memory (AAWM). A detailed description of the construction of the cognitive factors is fully described in Gleason et al.[11] A notable change from the Gleason et al publication is that the New York University Paragraph Learning trials tests were excluded from these analyses to adjust for VLM factor instability due to missing data. Tests in the VAEF included the Stroop Color Word Interference Test, Trail Making Tests A & B, WAIS-III Digit Symbol, and the Benton Visual Retention Test. Tests used in all cognitive factor scores are shown in Supplementary Table A.

Measurement of central adiposity

WHR, an estimate of central adiposity in our analysis, was measured at study visits by clinical research staff and calculated for all participants as a ratio of their waist circumference (a measure taken at the top of the iliac crest using a tape measure) divided by the hip circumference (a measure at the largest lateral extension of the hips). We used baseline values of WHR in all analyses.

Statistical analyses

We used linear latent growth models for these analyses.[35] The growth models were fitted with baseline WHR as a covariate to examine associations between WHR and changes in cognitive outcomes across time. Model outcomes or dependent measures included cognitive data, summarized as four latent cognitive factor scores described above.

Separate growth models were estimated with the same covariates for each of the four cognitive factor scores. The full model included two-way interactions (WHR x treatment) to examine whether the strength of the relationship between baseline WHR and the specified cognitive outcome differed between those in a treatment group (o-CEE or t-E2) versus those in the placebo group. Subject-specific random intercepts were included in each model. Education and treatment groups were included in the models as time-invariant covariates or fixed effects. Only participants with complete covariates at all cognitive visits were included in the analyses. However, data from women who were missing sporadic longitudinal outcomes remained in the analyses, ie, we used all available data points, including those with missing longitudinal values.

To verify that our models were appropriate to analyze our research questions, we tested assumptions for linear growth models, including linearity and normality in the data distribution. We also used graphical and analytical techniques to determine independence and homoscedasticity of errors. Maximum likelihood was used to estimate model parameters. Given the use of multiple growth models in these analyses, statistical significance was adjusted using the Benjamini-Hochberg method to control the False Discovery Rate (FDR).[36] The package *lavaan* in the statistics software R, version 4.20 (R Development Core Team; http://cran.r-project.org/), was used to explore the longitudinal data and model assumptions and estimate the model parameters.[37]

Comparative analyses: waist circumference (WC) and HOMA-IR as measures of central adiposity and associations to cognitive domain outcomes

The selection of WHR as the primary marker of risk in these analyses is based on a previous analysis of KEEPS-Cog data, which demonstrated cross-sectional associations between WHR and global cognition, but no relationship between homeostatic model assessment for insulin resistance (HOMA-IR) and global cognition.[7] In addition, we selected an estimate that would optimally predict the type of adipose deposition (eg, apple vs. pear phenotypes, ie, android or central obesity vs. gynoid obesity). Published reports have demonstrated that increased central adiposity (i e, WC), separate from general weight gain, precedes insulin resistance and type 2 diabetes mellitus (T2DM).[2]

To develop a fuller picture of the influence of WHR specifically, we conducted two comparative analyses of WHR to examine associations between baseline and longitudinal cognitive domain scores with (1) baseline WC and (2) baseline HOMA-IR. In the KEEPS study, fasting glucose and insulin values were measured at baseline from participants' blood samples at the Kronos Science Laboratories, and HOMA-IR was calculated with a standard equation (HOMA-IR = fasting glucose x fasting insulin/405).[38] Statistical analysis followed the same modeling approach as that used with the WHR analyses. Briefly, we fitted four separate linear latent growth models representing four cognitive factor domains with either baseline WC or baseline HOMA-IR as continuous covariates to examine associations between WC or HOMA-IR and changes in cognitive outcomes across time. Model fitting, model outcomes, two-way interactions, subject-specific random intercepts, and fixed effects followed the format for the WHR analyses. To minimize false-positive results, we also used FDR to correct for multiple hypotheses testing.

RESULTS

Participant characteristics

Table 1 provides a description of the women included in this secondary analysis of KEEPS-Cog data. Participants were largely non-Hispanic White. As intended with the parent study design, women were recently postmenopausal. Women also were generally in normal ranges for BMI (not shown) and other biometric parameters (Table 1 and Supplementary Table B, Supplemental Digital Content 2, http://links.lww.com/MENO/B434). According to the International Diabetes Federation (IDF), women with a WC ≥ 80 cm are at risk for MetS, and as defined by the World Health Organization (WHO), women with a WHR ≥ 0.85 are denoted to have central adiposity and are at increased risk for metabolic dysfunction, hypertension, and diabetes.[39]

The median and mean waist circumference values for the placebo, t-E2, and o-CEE groups are shown in Supplementary Table B, Supplemental Digital Content 2, http://links.lww.com/MENO/B434. Four hundred and twenty (61.5%) women in KEEPS-Cog with WC values were at risk for metabolic syndrome diseases using a WC cut point of ≥ 80 cm (Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/MENO/B435). The median and mean -values for WHR are provided in Supplementary Table B, Supplemental Digital Content 2, http://links.lww.com/MENO/B434; 196 (28.7%) women in KEEPS-Cog with WHR values were at risk for metabolic syndrome diseases using a WHR cut point of > 0.85 (Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/MENO/B435). The SD of the means and the minimum and maximum values suggest that between a third to nearly two thirds of women in KEEPS-Cog demonstrated elevated metabolic risk based on WC or WHR values.

Supplementary Table B, Supplemental Digital Content 2, http://links.lww.com/MENO/B434 displays descriptive values for baseline HOMA-IR as another index assessing baseline insulin resistance. A HOMA-IR value above 1.9 suggests early metabolic risk/insulin resistance, and a value > 2.9 indicates significant insulin resistance.[40] Using these HOMA-IR cut points, 62 (9.0%) of the women enrolled demonstrated early metabolic risk/insulin resistance, and 49 (7.1%) demonstrated insulin resistance in Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/MENO/B435.

Cognitive findings

Association between WHR and cognitive domain factor scores

Domain-specific cognitive results addressing the hypothesis that greater baseline central adiposity (ie, participants with a higher WHR) would associate with worse domain-specific cognitive outcomes are expressed in Table 2. The results for each cognitive factor domain are displayed in two models (ie, model 1 and model 2). Model 2 displays the full analyses, ie, model 2 included WHR * MHT (o-CEE or t-E2) interactions in comparison to placebo.

As shown in model 1 of Table 2 (in the row labeled Baseline WHR in bold font), WHR was negatively associated with cognitive performance for all four cognitive factors at baseline. That is, individuals with higher WHR values, on average, had significantly lower scores on all four latent outcomes. There were no associations between WHR and domain-specific cognitive outcomes when participants were randomized to treatment at baseline, as seen in Table 2, in the rows labeled Baseline WHR*Randomization to o-CEE*time and Baseline WHR*Randomization to t-E2*time.

For one of the cognitive domains factors, ie, visual attention and executive function (VAEF)—WHR at baseline was significantly and negatively associated with longitudinal cognitive performance during the treatment phase with an estimate (SE) of −0.066 (0.017) and a *P*-value of < 0.001 in model 1 and an estimate (SE) of −0.073 (0.026) and a *P*-value of 0.012 in model 2. These results suggest that baseline WHR was significantly associated with an average decrease in VAEF functions by 0.066 and 0.073 over the course of the study for model 1 and model 2, respectively. In addition, VAEF showed statistically significant associations with time in model 1 with an estimate (SE) of -0.014 (0.026) at a P-value < 0.001, and also in model 2 (Table 2), with an estimate (SE) of −0.012 (0.003) at a *P*-value < 0.001. For example, for model 1 this result shows that for every change in time (ie, either 12 or 18 mo), the average change in VAEF performance is expected to decrease by 0.014 and represents a significant change. We note that like the VAEF factor, verbal learning and memory (VLM) and speeded language and mental flexibility (SMLF) also showed statistically significant associations with time as shown in model 2 (Table 2), indicating that cognition declined modestly over the four years of follow-up (with estimates that ranged from −0.014 to −0.012 across the three cognitive domains).

Examination of the WHR moderating effects of the type of MHT on cognitive domain factors

Model 2 of Table 2 examined the effect of MHT (o-CEE or t-E_2) on associations between WHR and cognition for the four cognitive factors. That is, we estimated the effect of the interaction between baseline WHR and cognition across 4 years of placebo or each type of MHT ($WHR_{Baseline}$*o-CEE or $WHR_{Baseline}$*t-E2 on cognition at time point *t*). When the MHT type was added to the analysis, there were no significant modifying effects of WHR on the association between MHT and cognition for any of the cognitive factor outcomes (shown in the shaded rows of model 2 of Table 2 for each cognitive factor domain). The full Table 2 parameters are shown as Supplementary Table C, Supplemental Digital Content 4, http://links.lww.com/MENO/B436.

Comparative analyses: models using WC and HOMA-IR as risk indicators

Unlike WHR, neither baseline WC nor HOMA-IR was associated with longitudinal domain cognitive out-

TABLE 2. Waist-to-hip ratio (WHR) as a covariate on cognition in linear latent growth models (LGM)

	Verbal learning and memory				Speeded language and mental flexibility				Visual attention and executive function				Auditory attention and working memory			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
Variable	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***	**Estimate (SE)**	**Adj *P***
Intercept (level or initial status)																
Randomization to o-Cee	−0.079 (0.088)	0.370	−1.088 (0.864)	0.208	0.072 (0.083)	0.386	0.014 (0.914)	0.987	0.029 (0.081)	0.723	−0.948 (0.869)	0.275	−0.005 (0.082)	0.955	−0.356 (0.833)	0.669
Randomization to t-E2	−0.028 (0.090)	0.754	−0.179 (0.791)	0.821	0.029 (0.085)	0.734	0.506 (0.803)	0.528	−0.001 (0.083)	0.992	0.086 (0.820)	0.917	0.04 (0.081)	0.625	0.558 (0.722)	0.439
Baseline WHR	**−1.49 (0.426)**	**< 0.001**	**−1.966 (0.679)**	**0.0107**	**−2.171 (0.447)**	**< 0.001**	**−2.021 (0.710)**	**0.0107**	**−1.894 (0.4420**	**< 0.001**	**−2.268 (0.689)**	**0.004**	**−1.914 (0.411)**	**< 0.001**	**−1.871 (0.609)**	**0.0069**
Baseline WHR*Randomization to o-CEE*time	—	—	1.233 (1.053)	0.242	—	—	0.068 (1.112)	0.951	—	—	1.193 (1.065)	0.263	—	—	0.428 (1.013)	0.673
Baseline WHR*Randomization to t-E2*time	—	—	0.185 (0.973)	0.849	—	—	−0.586 (0.983)	0.551	—	—	−0.107 (1.010)	0.916	—	—	−0.637 (0.885)	0.472
Slope (by time)	−0.037 (0.049)	0.451	**−0.012 (0.005)**	**0.019**	−0.02 (0.038)	0.597	**−0.014 (0.004)**	**0.001**	**−0.14 (0.026)**	**< 0.001**	**−0.012 (0.003)**	**< 0.001**	−0.027 (0.019)	0.154	−0.004 (0.002)	0.071
Randomization to o-CEE*time	−0.005 (0.005)	0.316	0.01 (0.048)	0.830	−0.001 (0.004)	0.708	0.019 (0.038)	0.622	0.001 (0.003)	0.885	−0.019 (0.032)	0.547	−0.003 (0.002)	0.266	−0.008 (0.020)	0.679
Randomization to t-E2*time	−0.003 (0.005)	0.511	−0.049 (0.050)	0.333	−0.002 (0.004)	0.517	0.046 (0.040)	0.258	0.001 (0.003)	0.895	0.005 (0.037)	0.901	−0.001 (0.002)	0.572	−0.002 (0.021)	0.942
Baseline WHR*time	−0.002 (0.025)	0.984	−0.01 (0.041)	0.9143	−0.043 (0.019)	0.0567	−0.017 (0.034)	0.909	**−0.066 (0.017)**	**< 0.001**	**−0.073 (0.026)**	**0.012**	−0.004 (0.010)	0.9143	−0.006 (0.019)	0.9143
Baseline WHR*Randomization to o-CEE*time	—	—	−0.019 (0.059)	0.9143	—	—	−0.025 (0.046)	0.909	—	—	0.024 (0.040)	0.909	—	—	0.007 (0.025)	0.9143
Baseline WHR*Randomization to t-E2*time	—	—	0.056 (0.062)	0.6757	—	—	−0.059 (0.050)	0.472	—	—	−0.005 (0.045)	0.984	—	—	0.001 (0.026)	0.988

Baseline WHR was modeled as a covariate in LGM models to determine the relationship between WHR and cognition in four cognitive factor domains: Verbal Learning and Memory (VLM), Speeded Language and Mental Flexibility (SLMF), Visual Attention and Executive Function (VAEF), and Auditory Attention and Working Memory (AAWM). Model 1 represents the association between baseline WHR and cognition irrespective of treatment group. Model 2 represents associations between baseline WHR and cognition while comparing MHT treatment groups (oral conjugated equine estrogen [o-CEE] or transdermal E2 [t-E2]) to placebo. All models controlled for age and education (not shown). The shaded columns represent model 2 analyses, which included the MHT groups to assess cognitive outcomes. The two shaded complete rows represent MHT (ie, o-CEE or t-E2) versus placebo cognitive outcomes. Bolded values represent significant cognitive outcomes. The full table, including all covariates and statistical parameters, is included in the manuscript as Supplementary Table C, Supplemental Digital Content 4, http://links.lww.com/MENO/B436.

adj, adjusted.

comes (Supplementary Tables D, Supplemental Digital Content 5, http://links.lww.com/MENO/B437 and E, Supplemental Digital Content 6, http://links.lww.com/MENO/B438, respectively). Baseline WC was modestly associated with baseline scores for SLMF and VAEF cognitive domains, but effect sizes were small at −0.009 and -0.010, respectively. Baseline HOMA-IR was not associated with baseline cognitive performance.

DISCUSSION

In this secondary analysis of data from KEEPS-Cog, an ancillary study of KEEPS, we found significant cross-sectional associations between higher WHR and poorer domain-specific cognitive function expressed as four-factor scores at baseline. Higher baseline WHR is also associated with VAEF over 4 years of follow-up, suggesting that central adiposity may affect longitudinal executive function performance. Contrary to our hypothesis, there were no significant two-way interactions (ie, WHR*MHT) observed in the models; ie, there were no observed differences in cognitive domain functions between groups randomized to MHT versus placebo when WHR was a covariate in the analysis. Therefore, despite using central adiposity as a modifier in these analyses, the results were similar to previous analyses of KEEPS-Cog by Gleason et al,[11] ie, MHT—o-CEE or t-E2—did not associate with domain-specific changes in cognition versus placebo.

Association of WHR with cognitive domains

In a previous cross-sectional analysis of KEEPS data, Pal et al[7] found that WHR was linked cross-sectionally to poorer global cognition as measured with the Modified Mini-Mental State Examination (3MS). Our analysis extends these findings to domain-specific cognitive associations with WHR and demonstrates that for the visual attention and executive function domain, the associations are maintained longitudinally over 4 years of follow-up. Overall, these results are in line with our hypothesis that higher WHR would negatively associate with cognition and with previously published data showing that central adiposity was associated with longitudinal executive function.[6,27,28] On the other hand, our findings misalign with published evidence indicating associations between central adiposity and the cognitive domain of learning/memory.[9,29]

Importantly, these findings suggest that even a risk factor for central adiposity/metabolic syndrome is detrimental for domain-specific cognitive functions. KEEPS participants were at low risk for cardiovascular disease and were nondiabetic. Given these selection criteria and the relatively young age of women enrolled in KEEPS, it was particularly surprising to find associations between WHR and cognitive domain scores. Conversely, based on previous analysis of KEEPS-Cog highlighting that HOMA-IR did not associate with global cognition,[6] we anticipated that markers of metabolic dysfunction, like HOMA-IR, would not be associated with cognition for participants whose values were in normal ranges. Indeed, our comparative analysis revealed that HOMA-IR was not associated with cognitive domain scores cross-sectionally or longitudinally.

Like the KEEPS findings from Pal et al[7] wherein WC was associated with global cognition, our comparative analyses found that WC was associated with two specific cognitive domain scores at baseline; however, WC did not associate with any cognitive domain over time. Considering the findings of Pal and colleagues with the WC and cognition findings in these analyses, it is possible that global cognition measures may be sensitive to the acute molecular effects of central adiposity and not long-term metabolic function. In addition, Pal et al[7] used a cutoff of WC > 88 cm in their cognitive analyses, whereas we included all WHR values in our statistical models.

Biological actions of central adiposity relevant for cognition

The link between WHR and VAEF across time suggests that central adiposity may elevate risk for acquired cognitive syndromes like ADRD by affecting attentional processes and brain structures and regions supporting executive functioning (ie, lowering the cognitive reserve). Indeed, in an analysis of the Framingham Heart Study (FHS), Zade et al[6] reported a negative association between WHR with executive function and frontal brain volumes, a structure supporting executive function. An Alzheimer disease genetic risk factor [apolipoprotein E (*APOEε*4)] was implicated in these findings, as they observed a stronger negative association between WHR and executive function in carriers (*APOEε*4^+) versus noncarriers (*APOEε*4^-).[6] We did not assess differences between cognition in APOE carriers versus noncarriers in our analyses. Also, we did not find associations between HOMA-IR and any cognitive domain functions in these re-analyses, suggesting a more nuanced link between central obesity/metabolism and cognition in our study. Future studies in postmenopausal women with differing patterns of metabolic disturbances could help elucidate mechanisms relating central adiposity to VAEF-supported brain structures.

Central adiposity did not moderate MHT versus placebo cognitive domain-specific outcomes

Though it was hypothesized, baseline WHR did not modify cognitive domain-specific outcomes of MHT versus placebo at baseline or longitudinally in KEEPS-Cog. In other words, in these younger and generally cardiometabolically healthy women in KEEPS-Cog, central adiposity and metabolic health as estimated with WHR did not associate with MHT to predict cognitive performance. Therefore, as in previous analyses,[11] there were no observed associations between MHT and cognition in KEEPS-Cog.

In contrast, in a secondary analysis of data from the Women's Health Initiative (WHI) hormone trials, Kerwin et al[41] reported a complex relationship between body fat distribution as measured with WHR, obesity, and cognition in women ages 65-79. In their analyses, an increased WHR was protective for cognitive performance, but only for those with elevated body mass indices (BMI).[41] For women without obesity, the association between WHR and cognition was consistent with our findings.[41]

In WHIMS, an ancillary study of WHI, the findings of accentuated incident cognitive impairment in diabetic women ages 65 and older administered o-CEE (with or without medroxyprogesterone) compared with women administered placebo, demonstrate a cognitive interaction with MHT in conditions of diabetes or glucose intolerance.[12] Notably, there were statistically fewer women in the MHT group who converted to diabetic status over the 18 years of follow-up than in the placebo group.[12] These WHIMS findings highlight that there is a relationship between metabolism, MHT, and cognition. Although an association of both central adiposity and MHT with cognitive domain function in KEEPS-Cog was not identified in our analyses, our findings with WHR partially support the hypothesized relationship that higher central adiposity, a risk factor for poorer metabolic health, is negatively associated with cognition domain scores.

Menopause as both a biological and life-course event: alternative explanatory models

Like insulin, estrogen is believed to be a regulator not only of metabolism but also of homeostasis of multiple processes related to neuronal health.[2,42] Although MHT does not reduce risk for cognitive impairment or dementia,[10,11,43] cognitive deficits are associated with menopause in women who participated in the Study of Women's Health Across the Nation (SWAN).[44] Lastly, mechanisms involved in cognitive associations with WHR in these women early in the postmenopausal period could likely be linked to experiential factors like trauma and stress that can promote hormone changes leading to increased central adiposity.[45,46] Conversely, obesity and metabolic disease may have independent effects on cognition that can be modified by lifestyle factors.[9,28] Of note, one form of MHT, o-CEE, was found to have beneficial mood effects in the KEEPS-Cog, which could have contributed to the maintenance of cognition and metabolically healthier states in the women in KEEPs-Cog.[11]

Strengths and limitations

This study has strengths in its sample size and robust follow-up with repeated cognitive assessments. Moreover, despite not using a threshold or cutoff for WHR in the cognitive analyses, we still saw associations between WHR and domain-specific cognition. Yet, these analyses have noted limitations. This study assesses the association of central adiposity (WHR) and domain-specific cognitive outcomes, but not global cognition. Although WHR is an acceptable marker of central adiposity that can capture insulin resistance, it is only an indirect measure of metabolic health, and the overall sample used in this analysis was at low risk for metabolic dysfunction relative to the general population. Moreover, the women in the KEEPS-Cog study were predominantly non-Hispanic, White, and well-educated, thus limiting the generalizability of findings. Lastly, these findings assess the short-term effects of four years of MHT in generally healthy, recently postmenopausal women. It is possible that these null associations of WHR and cognitive decline may be a result of limited statistical power to detect small effect sizes.

Analysis across a longer time interval may reveal currently unrecognized effects of MHT treatment in the early postmenopausal women in KEEPS-Cog. The KEEPS continuation study (KEEPS-Continuation) assessed long-term cognitive and ADRD biomarker effects of MHT and may provide opportunities to further elucidate the relationships between central adiposity, metabolic health, and cognition.[47]

CONCLUSIONS

We examined the intersection of central adiposity, cognition, and MHT in recently postmenopausal women. We found that in nondiabetic women at low risk for cardiovascular disease, WHR was negatively correlated with multiple cross-sectional cognitive domain-specific scores at baseline and associated with visual attention and executive function longitudinally over the course of the 4-year study. Altogether, a picture emerges from the KEEPS-Cog and other data where higher central adiposity in the absence of outright metabolic dysfunction negatively associates with domain-specific cognition.

On the other hand, WHR did not appear to modify MHT's neutral effects on cognition. In total, these data support continued exploration of the role of central adiposity and metabolic health on cognition in aging women after menopause. Future studies could decipher molecular/behavioral links between estrogens, metabolism, lifestyle, mood, and cognition inflection points. For example, exploring how the mid-life event of menopause may serve as an initiating event with co-occurring and bidirectional lifestyle, sleep, mood, changes, and alterations in central adiposity and metabolic dysfunction that work synergistically to promote the development of MetS and neurodegeneration.

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REFERENCES

1. Opoku AA, Abushama M, Konje JC. Obesity and menopause. *Best Pract Res Clin Obstet Gynaecol* 2023;88:102348. doi:https://doi.org/10.1016/j.bpobgyn.2023.102348
2. Rettberg JR, Yao J, Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. *Front Neuroendocrinol* 2014;35:8-30. doi:10.1016/j.yfrne.2013.08.001

3. De Paoli M, Zakharia A, Werstuck GH. The Role of Estrogen in Insulin Resistance: A Review of Clinical and Preclinical Data. *Am J Pathol* 2021;191:1490-1498. doi:10.1016/j.ajpath.2021.05.011
4. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. *J Clin Endocrinol Metab* 2008;93(11 Suppl 1):S57-S63. doi:10.1210/jc.2008-1585
5. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis* 2017;11:215-225. doi:10.1177/1753944717711379
6. Zade D, Beiser A, McGlinchey R, et al. Apolipoprotein epsilon 4 allele modifies waist-to-hip ratio effects on cognition and brain structure. *J Stroke Cerebrovasc Dis* 2013;22:119-125. doi:10.1016/j.jstrokecerebrovasdis.2011.06.020
7. Pal L, Morgan K, Santoro NF, et al. Cardiometabolic measures and cognition in early menopause - Analysis of baseline data from a randomized controlled trial. *Maturitas* 2022;162:58-65. doi:10.1016/j.maturitas.2022.04.004
8. Swarup S, Ahmed I, Grigorova Y, Zeltser R Metabolic syndrome https://www.ncbi.nlm.nih.gov/books/NBK459248/
9. Stoeckel LE, Arvanitakis Z, Gandy S, et al. Complex mechanisms linking neurocognitive dysfunction to insulin resistance and other metabolic dysfunction. *F1000Res* 2016;5:353. doi:10.12688/f1000research.8300.2
10. Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. *Neurology* 2016;87:699-708. doi:10.1212/wnl.0000000000002980
11. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-cognitive and affective study. *PLoS Med* 2015;12:e1001833; discussion e. doi:10.1371/journal.pmed.1001833
12. Espeland MA, Brinton RD, Hugenschmidt C, et al. Impact of type 2 diabetes and postmenopausal hormone therapy on incidence of cognitive impairment in older women. *Diabetes Care* 2015;38:2316-2324. doi:10.2337/dc15-1385
13. Henderson VW. Three midlife strategies to prevent cognitive impairment due to Alzheimer's disease. *Climacteric* 2014;17(Suppl 2):38-46. doi:10.3109/13697137.2014.929650
14. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal hormone therapy and type 2 diabetes prevention: evidence, mechanisms, and clinical implications. *Endocr Rev* 2017;38:173-188. doi:10.1210/er.2016-1146
15. Espeland MA, Hogan PE, Fineberg SE, et al. Effect of postmenopausal hormone therapy on glucose and insulin concentrations. *PEPI Investigators Postmenopausal estrogen/progestin interventions Diabetes Care* 1998;21:1589-1595. doi:10.2337/diacare.21.10.1589
16. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003;138:1-9. doi:10.7326/0003-4819-138-1-200301070-00005
17. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2959-2968. doi:10.1001/jama.291.24.2959
18. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947-2958. doi:10.1001/jama.291.24.2947
19. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2663-2672. doi:10.1001/jama.289.20.2663
20. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2651-2662. doi:10.1001/jama.289.20.2651
21. Miller VM, Naftolin F, Asthana S, et al. The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned. *Menopause* 2019;26:1071-1084. doi:10.1097/gme.0000000000001326
22. Krotkiewski M, Björntorp P, Sjöström L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest* 1983;72:1150-1162. doi:10.1172/jci111040
23. Hartz AJ, Rupley DC Jr, Kalkhoff RD, Rimm AA. Relationship of obesity to diabetes: influence of obesity level and body fat distribution. *Prev Med* 1983;12:351-357. doi:10.1016/0091-7435(83) 90244-x
24. Ohlson LO, Larsson B, Svärdsudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985;34:1055-1058. doi:10.2337/diab.34.10.1055
25. Cornier M-A, Després J-P, Davis N, et al. Assessing adiposity. *Circulation* 2011;124:1996-2019. doi:10.1161/CIR.0b013e318233bc6a
26. Divoux A, Sandor K, Bojcsuk D, et al. Fat distribution in women is associated with depot-specific transcriptomic signatures and chromatin structure. *J Endocr Soc* 2020;4:bvaa042. doi:10.1210/jendso/bvaa042
27. Bouges S, Fischer BL, Norton DL, et al. Effect of metabolic syndrome risk factors on processing speed and executive function in three racialized groups. *J Alzheimers Dis* 2023;92:285-294. doi:10.3233/jad-220920
28. Farruggia MC, Small DM. Effects of adiposity and metabolic dysfunction on cognition: a review. *Physiol Behav* 2019;208:112578. doi:https://doi.org/10.1016/j.physbeh.2019.112578
29. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. *Lancet Diabetes Endocrinol* 2014;2:246-255. doi:10.1016/s2213-8587(13)70088-3
30. McEwen BS. Invited review: Estrogens effects on the brain: multiple sites and molecular mechanisms. *J Appl Physiol (1985)* 2001;91:2785-2801. doi:10.1152/jappl.2001.91.6.2785
31. Morgan KN, Derby CA, Gleason CE. Cognitive changes with reproductive aging, perimenopause, and menopause. *Obstet Gynecol Clin North Am* 2018;45:751-763. doi:10.1016/j.ogc.2018.07.011
32. Maki PM, Sundermann E. Hormone therapy and cognitive function. *Hum Reprod Update* 2009;15:667-681. doi:10.1093/humupd/dmp022
33. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med* 2014;161:249-260. doi:10.7326/m14-0353
34. Harman SM, Brinton EA, Cedars M, et al. KEEPS: the Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3-12. doi:10.1080/13697130500042417
35. Bollen KA *Structural Equations With Latent Variables*. Wiley; 1989.
36. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Stat Method* 2018;57:289-300. doi:10.1111/j.2517-6161.1995.tb02031.x
37. Rosseel Y. lavaan: An R package for structural equation modeling. *J Stat Softw* 2012;48:1-36. doi:10.18637/jss.v048.i02
38. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-419. doi:10.1007/bf00280883
39. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 2018;20:12. doi:10.1007/s11906-018-0812-z
40. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord* 2013;13:47. doi:10.1186/1472-6823-13-47
41. Kerwin DR, Zhang Y, Kotchen JM, et al. The cross-sectional relationship between body mass index, waist-hip ratio, and cognitive performance in postmenopausal women enrolled in the Women's Health Initiative. *J Am Geriatr Soc* 2010;58:1427-1432. doi:10.1111/j.1532-5415.2010.02969.x

42. Brinton RD. Estrogen regulation of glucose metabolism and mitochondrial function: therapeutic implications for prevention of Alzheimer's disease. *Adv Drug Deliv Rev* 2008;60:1504-1511. doi:10.1016/j.addr.2008.06.003
43. Espeland MA, Shumaker SA, Leng I, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med* 2013;173:1429-1436. doi:10.1001/jamainternmed.2013.7727
44. Karlamangla AS, Lachman ME, Han W, Huang M, Greendale GA. Evidence for cognitive aging in midlife women: study of women's health across the nation. *PLoS One* 2017;12:e0169008. doi:10.1371/journal.pone.0169008
45. Kumar R, Rizvi MR, Saraswat S. Obesity and stress: a contingent paralysis. *Int J Prev Med* 2022;13:95. doi:10.4103/ijpvm.IJPVM_427_20
46. Chao AM, Jastreboff AM, White MA, Grilo CM. Sinha R. Stress, cortisol, and other appetite-related hormones: prospective prediction of 6-month changes in food cravings and weight. *Obesity (Silver Spring)* 2017;25:713-720. doi:10.1002/oby.21790
47. Gleason CE, Dowling NM, Kara F, et al. Long-term cognitive effects of menopausal hormone therapy: findings from the KEEPS Continuation Study. *PLoS Med* 2024;21:e1004435. doi:10.1371/journal.pmed.1004435