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Association of Age at Menopause and Hormone Therapy Use With Tau and β-Amyloid Positron Emission Tomography

Gillian T. Coughlan, MS, PhD; Tobey J. Betthauser, PhD; Rory Boyle, PhD; Rebecca L. Koscik, PhD; Hannah M. Klinger, MS; Lori B. Chibnik, PhD, MPH; Erin M. Jonaitis, PhD, MS; Wai-Ying Wendy Yau, MD; Allen Wenzel, BS; Bradley T. Christian, PhD; Carey E. Gleason, PhD; Ursula G. Saelzler, PhD; Michael J. Properzi, BEng, BCompSci; Aaron P. Schultz, PhD; Bernard J. Hanseeuw, MD, PhD; JoAnn E. Manson, MD, DrPH, MACP; Dorene M. Rentz, PsyD; Keith A. Johnson, MD; Reisa Sperling, MD; Sterling C. Johnson, PhD; Rachel F. Buckley, PhD

IMPORTANCE Postmenopausal females represent around 70% of all individuals with Alzheimer disease. Previous literature shows elevated levels of tau in cognitively unimpaired postmenopausal females compared with age-matched males, particularly in the setting of high β-amyloid (Aβ). The biological mechanisms associated with higher tau deposition in female individuals remain elusive.

OBJECTIVE To examine the extent to which sex, age at menopause, and hormone therapy (HT) use are associated with regional tau at a given level of Aβ, both measured with positron emission tomography (PET).

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study included participants enrolled in the Wisconsin Registry for Alzheimer Prevention. Cognitively unimpaired males and females with at least 1 ^{18}F-MK-6240 and ^{11}C-Pittsburgh compound B PET scan were analyzed. Data were collected between November 2006 and May 2021.

EXPOSURES Premature menopause (menopause at younger than 40 years), early menopause (menopause at age 40-45 years), and regular menopause (menopause at older than 45 years) and HT user (current/past use) and HT nonuser (no current/past use). Exposures were self-reported.

MAIN OUTCOMES AND MEASURES Seven tau PET regions that show sex differences across temporal, parietal, and occipital lobes. Primary analyses examined the interaction of sex, age at menopause or HT, and Aβ PET on regional tau PET in a series of linear regressions. Secondary analyses investigated the influence of HT timing in association with age at menopause on regional tau PET.

RESULTS Of 292 cognitively unimpaired individuals, there were 193 females (66.1%) and 99 males (33.9%). The mean (range) age at tau scan was 67 (49-80) years, 52 (19%) had abnormal Aβ, and 106 (36.3%) were *APOE*ε4 carriers. There were 98 female HT users (52.2%) (past/current). Female sex (standardized β = −0.41; 95% CI, −0.97 to −0.32; $P < .001$), earlier age at menopause (standardized β = −0.38; 95% CI, −0.14 to −0.09; $P < .001$), and HT use (standardized β = 0.31; 95% CI, 0.40-1.20; $P = .008$) were associated with higher regional tau PET in individuals with elevated Aβ compared with male sex, later age at menopause, and HT nonuse. Affected regions included medial and lateral regions of the temporal and occipital lobes. Late initiation of HT (>5 years following age at menopause) was associated with higher tau PET compared with early initiation (β = 0.49; 95% CI, 0.27-0.43; $P = .001$).

CONCLUSIONS AND RELEVANCE In this study, females exhibited higher tau compared with age-matched males, particularly in the setting of elevated Aβ. In females, earlier age at menopause and late initiation of HT were associated with increased tau vulnerability especially when neocortical Aβ elevated. These observational findings suggest that subgroups of female individuals may be at higher risk of pathological burden.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Rachel F. Buckley, PhD, Department of Neurology, Massachusetts General Hospital, 149 13th St, Charlestown, MA 02129 (rfbuckley@mgh.harvard.edu).

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In the United States, approximately 6.2 million people live with a clinical diagnoses of Alzheimer disease (AD).[1] In the context of high β-amyloid (Aβ), substantial evidence suggests that female individuals exhibit greater AD-related neurofibrillary tau tangles than males.[2-6] What remains unclear are the biological mechanisms that might be exacerbating tau deposition in female individuals.

Premature or early menopause, occurring spontaneously or due to surgical intervention before the age of 40 or 45 years, respectively, is present in 1% to 10% of female individuals[7] and has been associated with deleterious clinical outcomes related to AD dementia.[8-10] Early trials and observational studies suggested that use of exogenous hormones, via hormone therapy (HT), may ameliorate cognitive impairment in menopausal or postmenopausal individuals.[11-13] Contrary to these findings, however, a seminal randomized clinical trial, the Women's Health Initiative (WHI), found that HT use, particularly estrogen plus progestin, was associated with approximately 2-fold higher incidence of probable dementia relative to placebo.[14-17] Follow-up randomized clinical trials and observational studies revealed that HT postmenopause was associated with increased risk of probable dementia relative to initiation of HT proximal to menopause onset.[18-23] Prior to the WHI findings, the prevalence of HT use in postmenopausal female individuals was approximately 46%, which subsequently dropped to 14.6% after publication.[24] HT treatment remains low in postmenopausal women and women with contraindications.[25-27]

In a cohort of male and female individuals, we sought to determine the extent to which self-reported female sex, younger age at menopause, and HT use (including late initiation of HT after menopause onset) are associated with regional tau deposition in adults without a diagnosis of mild cognitive impairment or dementia. Using positron emission tomography (PET) neuroimaging markers of tau deposition, we hypothesized that female sex and younger age at menopause would be associated with greater regional tau PET signal than male sex and older age at menopause, at a given level of neocortical Aβ. We further hypothesized that female individuals with a late initiation of HT would show a greater regional tau PET signal than those with early initiation. We focused on temporal, parietal, and occipital brain regions that have shown sex differences on tau PET in female individuals compared with males.[3,28]

Key Points

Question Are female sex, earlier age at menopause, and hormone therapy (HT) use associated with the deposition of tau pathology?

Findings In this cross-sectional study, female sex, earlier age at menopause, and HT use were significantly associated with higher regional tau in the context of high β-amyloid, as measured on the positron emission tomography signal. Late initiation of HT following menopause onset may underpin the association between HT use and the elevated tau positron emission tomography signal.

Meaning Earlier age at menopause and the late initiation of HT following menopause onset may be important sex-specific risk factors that underlie sex differences in tau deposition.

Methods

Participants

Male and female participants were from the Wisconsin Registry for Alzheimer Prevention, an ongoing longitudinal study that has enrolled over 1700 cognitively unimpaired, middle-aged individuals enriched with a parental history of AD.[29] Over 1400 participants underwent comprehensive cognitive, clinical evaluation, and apolipoprotein (*APOE*) genotyping, and subsets received neuroimaging, which are described elsewhere.[30] Participants eligible for this study also completed at least 1 ^{18}F-MK-6240 PET and ^{11}C-Pittsburgh compound B (PiB) scan[29] and were free of any major neurological or psychological disorders at enrollment or at the time of scanning. Data on race and ethnicity were collected by self-report. Written informed consent was obtained from all participants. Analyses of these data were approved by the institutional review board for the Massachusetts General Hospital. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed. Data were collected between November 2006 and May 2021.

Exposures

Age at final menses and HT use was surveyed by participant self-report on average 9 years before the Aβ PET scan and 12 years before the tau PET scan. Female individuals had a median of 17 years after final menses at the time of the tau PET scan. Age at menopause was calculated (ie, last period age plus 1 year[31]). For visualization and background characteristics, age at menopause was categorized into premature menopause (age at menopause, <40 years), early menopause (age at menopause, 40-45 years), and regular menopause (age at menopause, >45 years). For statistical analysis, age at menopause was treated as a continuous variable due to unbalanced sample size. Participants with missing data (n = 12) or an unlikely age at menopause (<20 years; n = 1) were excluded.[10] For all female individuals, their age at tau scan was at or beyond age at menopause, meaning the sample comprised all postmenopausal individuals. Type (problems sleeping, mood swings, depressive symptoms, and hot flashes) and severity of overall menopausal symptoms (range, 1-4) were reported. In the case of surgical menopausal cases, age at oophorectomy (part, 1, or 2 ovaries) and hysterectomy was collected, but it was not possible to differentiate between surgical and natural menopause. Responses for current HT use was cross-referenced against self-report current medications, which reached an agreement of 89.1%. Six female participants reported current HT use in 1, but not both, data sources and were included in the HT user group, bringing the final sample size to 98 (and 95 HT nonusers). Self-reported HT initiation age (n = 89) and formulation (n = 83) was provided in most cases. Female individuals were categorized into the following groups based on HT time of initiation: less than 5 years past age at menopause

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(n = 48) or HT initiation 5 or more years after age at menopause (n = 10). For exploratory comparisons, those who initiated HT 1 or more years before age at menopause (n = 27) were also examined in the same model (see eMethods in Supplement 1 for detailed information on reported HT use). Sample sizes and missing data are further documented in eFigure 1 in Supplement 1.

Aβ and Tau PET

The PiB Aβ PET scans were first acquired in 2010. The PET acquisition was initiated with injection of radiotracer and continued for 70 minutes and reconstructed using parameters that have been published previously.[32] Preprocessing steps are detailed in the eMethods in Supplement 1. PiB distribution volume ratio (DVR) was estimated from the dynamic acquisition using reference Logan graphical analysis to serve as an index of Aβ. A neocortical PiB composite included 8 regions of interest (ROIs) from the Automated Anatomical Labeling atlas,[33] including angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus.[34] The PiB DVR was treated as a continuous variable in the primary models and dichotomized into high and low for demographic comparisons. High PiB was defined as DVR above 1.16 based on Gaussian mixture modeling.[35] The first ^{18}F-MK-6240 PET tracer was acquired in 2017. Standard uptake value ratios were calculated from a 20-minute dynamic acquisition (4 × 5-minute frames) from 50 to 70 minutes postinjection using inferior cerebellar gray matter as the reference region.[36] Seven a priori sex-specific tau PET ROIs were selected and derived from the Harvard-Oxford atlas: entorhinal cortex, amygdala, inferior temporal gyrus, temporooccipital gyri, superior parietal lobule, temporal fusiform gyrus, and lateral occipital cortex.[2,3] There was a median (interquartile range) of 3 (0-7.1) years between the tau PET scan and Aβ PET used in this study. The median DVR from Aβ PET scans collected within the same year as the tau PET scan was not significantly different from the baseline DVR estimates used in our analysis (1.06 vs 1.07 PIB DVR).

Preclinical Alzheimer Cognitive Composite

Participants completed a neuropsychological battery at multiple visits.[29] A Preclinical Alzheimer Cognitive Composite (PACC) was computed by standardizing and calculating the mean of 3 summary scores that included test of memory and executive function, as detailed by Jonaitis and colleagues.[37,38] PACC scores derived from assessments administered nearest at the tau PET scan visit were included for clinicopathological inference.

Statistical Analysis

Analyses were run in R version 2021.09.0 (R Foundation). Demographic characteristics between the sexes and between HT users were compared using *t* tests or the nonparametric Kruskal-Wallis test, as appropriate, and categorical variables were compared using the Pearson χ^2 test. Linear regression models were fitted with an interaction term to estimate the extent to which sex moderated the association between the regional tau PET signal and neocortical Aβ PET in male and female individuals and age at menopause/HT use moderated the same association in females only. We also fit a linear regression model to test whether sex moderated the association between the regional tau PET signal and *APOE*ε4 carrier status (binarized to ε4 carrier vs non-ε4 carrier). Multiple comparison adjustment corrected for 7 comparisons based on the tau PET outcomes using the Benjamini-Hochberg false discovery rate control procedure $P < .05$ (FDRestimation package in R).[39] All analyses were also reexamined with nonparametric robust regression models (a Wald test for multiple coefficients) to reduce the association of outliers with outcomes. Sensitivity analysis involved adjusting all models (detailed below) for time between tau and Aβ scan. In models 2 and 3, lifestyle/medical factors that may produce spurious associations between age at menopause/HT use and the tau PET signal were adjusted for. These factors included years of education,[40] menopause symptom severity/indication, history of oophorectomy or hysterectomy,[10] *APOE*ε4 carrier status[41]and the office-based Framingham Heart Study cardiovascular disease risk score (FHS-CVD).[42] FHS-CVD is calculated from a sex-specific weighted sum of age, antihypertensive treatment (dichotomous), systolic blood pressure, body mass index, diabetes status (dichotomous), and cigarette smoking history (dichotomous).

The primary models were model 1A: tau ~ sex category + Aβ + age at tau scan; model 1B: tau ~ sex category × Aβ + age at tau scan; model 2A: tau ~ age at menopause continuous (females) + Aβ + age at tau scan; model 2B: tau ~ age at menopause continuous (females) × Aβ + age at tau scan; model 3A: tau ~ HT category (females) + Aβ + age at tau scan; and model 3B: tau ~ HT category (females) × Aβ + age at tau scan, in which ~ separates the dependent variable from the independent variables.

For the age at menopause analysis, floodlight analyses were performed to determine the threshold of Aβ beyond which age at menopause and tau are significantly associated (eMethods in Supplement 1).[43] Values were mapped to the Centiloid scale[44] using linear regression for reporting.[35] We also probed the influence of early vs late HT initiation in a linear regression model (with 3 timing groups) including Aβ PET interactions on regional tau PET. Models 1, 2, and 3 were repeated with the PACC as the outcome.

Results

Demographic Characteristics by Sex and HT Use

Of 292 individuals, the mean (range) age was 67.4 (49-80) years, 193 (66.1%) were female individuals (98 [53%] were HT users), 99 (33.9%) were males, and 106 (36.3%) were *APOEε4* carriers. *APOE*ε4 status and neocortical Aβ PET status did not differ as a function of age at menopause or HT use (**Table 1**). Female individuals with premature or early menopause self-reported a greater history of hysterectomy, and those with premature menopause also reported more menopause-related sleeping problems. Compared with HT nonusers, HT users had an older age at tau scan, were

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Table 1. Characteristics of the Study Cohort by Age at Menopause and HT Use[a]

Characteristic	No. (%)				No. (%)		
	Regular menopause (age >45 y)	Early menopause (age 40-45 y)	Premature menopause (age <40 y)	*P* value	HT user	HT nonuser	*P* value
No.	153	18	9	NA	98	95	NA
Age at tau PET, mean (SD), y	70.5 (5.7)	68.3 (6.6)	67.2 (6.2)	.30	64.9 (7.0)	69.8 (5.2)	<.001
Education, mean (SD), y	16.5 (2.9)	16.0 (2.6)	13.6 (2.8)	.02	16.1 (2.9)	16.3 (2.7)	.62
APOEε4 carrier	56 (36.8)	7 (38)	4 (50)	.77	34 (37)	36 (37)	.67
Race							
African American or Black	9 (5.9)	1 (5.6)	0	>.99	9 (9.5)	2 (2)	.04
White	141 (92)	17 (94.4)	8 (100)		83 (87.4)	96 (98)	
Other[b]	2 (1.4)	0	0		3 (3.2)	0	
Aβ positive[c]	25 (16.4)	3 (16.7)	3 (37.5)	.34	14 (16)	19 (20)	.51
Age at menopause, mean (SD), y	51.8 (3.17)	42.2 (1.26)	33.3 (4.95)	<.001	51.7 (4.2)	48.6 (6.4)	<.001
Oophorectomy	10 (6.6)	4 (22.2)	3 (37.5)	<.001	16 (8)	17 (8)	.25
Hysterectomy	10 (6.6)	8 (44.4)	5 (62.5)		6 (3)	12 (6)	
Mean (SD) age at oophorectomy, y	49.4 (12.6)	39.9 (7.7)	27.5 (9.7)	<.001	47 (14)	44 (12)	.27
Mean (SD) age at hysterectomy, y	49.6 (6.1)	45.3 (4.8)	39.1 (8.7)		50 (10)	45 (10)	.41
Severe menopausal symptoms	13 (8.6)	1 (5.6)	1 (12.5)	.59	4 (4.8)	10 (11)	.01
Problems sleeping	35 (23)	6 (33)	5 (63)	<.001	16 (16.3)	10 (10.5)	.01
Depressive symptoms	23 (15.1)	1 (5.6)	1 (12.5)	.49	45 (45.9)	44 (46.3)	.46
HT user	67 (44.4)	12 (66.7)	5 (55.6)	.02	98 (100)	0	NA
HT initiation age, mean (range), y	49.6 (6.10)	45.3 (4.81)	39.1 (8.76)	<.001	NA	47.08 (16-68)	NA
BMI, mean (SD)	28.4 (6.03)	29.4 (8.41)	30.9 (7.51)	.45	28.9 (6.74)	27.7 (5.00)	.51
Low PACC score	2 (1.3)	0	1 (12.5)	.05	2 (2.0)	1 (1.1)	.99
Cardiovascular risk, mean (SD)	9.79 (8.57)	15.0 (12.9)	10.8 (6.24)	.09	10.8 (8.16)	9.70 (9.69)	.42
Diabetes	10 (6.6)	3 (16.7)	2 (22.2)	.06	10 (10.2)	8 (8.4)	.94
Smoker	74.4 (49)	11 (61)	3 (33.3)	.24	47 (48.0)	46 (48.4)	.83
Blood pressure medication user	53 (35)	8 (44)	3 (33)	.41	36 (36.7)	31 (32.6)	.82
Total cholesterol, mean (SD), mg/dL	204 (32.7)	206 (35.5)	189 (22.5)	.42	201 (31.9)	201 (31.9)	.65
HDL cholesterol, mean (SD), mg/dL	64.3 (18.2)	69.4 (17.8)	63.7 (13.9)	.54	64.3 (16.9)	64.9 (18.6)	.82

Abbreviations: APOE, apolipoprotein gene; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density cholesterol; HT, hormone therapy; NA, not applicable; PACC, Preclinical Alzheimer Cognitive Composite; PET, positron emission tomography.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] *P* values–based *t* tests or the nonparametric Kruskal-Wallis test, as appropriate, and categorical variables were compared using the Pearson χ^2 test. The Framingham Heart Study cardiovascular disease risk score includes a sex-specific weighted sum of age, antihypertensive treatment, systolic blood pressure, body mass index, diabetes status, and cigarette smoking status.[42] Menopause symptoms included reports of mood swings, problems sleeping, sweats, hot flashes, sexual dysfunction, and depression.

[b] The other category included American Indian, Asian, and Hispanic/Spanish.

[c] Aβ positivity threshold was more than 1.16 distributed volume ratio.

younger at menopause, and had more severe menopausal symptoms. As summarized in eTable 1 in Supplement 1, male and female individuals did not differ by age at tau scan, race, *APOEε4* status, or neocortical Aβ PET status. However, female individuals reported 1 less year of education and had a 10% lower FHS-CVD score compared with males.

Interactive Associations Between Sex and Neocortical Aβ PET, and Sex and APOEε4, With Tau PET

Female individuals exhibited a high tau PET compared with age-matched males in the inferior-temporal gyrus (model 1A; β [female] = −0.11; 95% CI, −0.16 to −0.04; *P* = .02), superior parietal cortex (β = −0.08; 95% CI, −0.12 to −0.03; *P* = .02), temporal fusiform (β = −0.06; 95% CI, −0.11 to −0.01; *P* = .03), lateral occipital cortex (β = −0.12; 95% CI, −0.17 to −0.07; *P* = .002), and the temporo-occipital lobe (β = −0.11; 95% CI, −0.17 to −0.04; *P* = .02) (eFigure 2 in Supplement 1 and **Table 2**). As expected, we found an interaction between sex and neocortical Aβ on tau PET in the same ROIs such that female individuals exhibited higher tau PET than males in the setting of elevated Aβ PET burden (eFigure 3 in Supplement 1; Table 2; model 1B). All associations remained after adjusting for education, *APOE* carrier status, and FHS-CVD (eTables 2-4 in Supplement 1). Sex also interacted with *APOEε4* carrier status on temporo-occipital tau PET (female: β = −0.19; 95% CI, −0.33 to −0.05; *P* = .05) but was not statistically significant after multiple comparison correction (eTable 5 in Supplement 1). As sex and Aβ PET interactions with tau PET were distributed across all tau PET ROIs, we focused on interactive associations with Aβ PET in the subsequent analysis and retained *APOEε4* as a covariate in sensitivity analysis.

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Table 2. Regression Coefficients of Sex, Age at Menopause, and HT Use With Neocortical Aβ Interactions in Regional Tau PET[a]

	Sex + Aβ + age at tau scan (model 1A)				Age at menopause + Aβ + age at tau scan (model 2A)				HT use + Aβ + age at tau scan (model 3A)			
Tau PET	β (95% CI)	R^2	*P* value	Robust *P* value	β (95% CI)	R^2	*P* value	Robust *P* value	β (95% CI)	R^2	*P* value	Robust *P* value
Entorhinal tau	−0.04 (−0.09 to 0.01)	0.38	.11	.12	−0.01 (−0.01 to 0)	0.36	.46	.67	0.04 (−0.03 to 0.11)	0.41	.29	.27
Amygdala tau	0.01 (−0.05 to 0.05)	0.35	.98	.90	−0.01 (−0.01 to 0)	0.35	.92	.76	0.03 (−0.03 to 0.09)	0.41	.27	.37
Temporo-occipital tau	−0.11 (−0.17 to −0.04)	0.31	.02	<.001	−0.01 (−0.01 to −0)	0.33	.05	.83	0.03 (−0.06 to 0.12)	0.35	.48	.72
Interior temporal tau	−0.11 (−0.16 to −0.04)	0.31	.02	<.001	−0.02 (−0.01 to 0)	0.29	.12	.39	0.03 (−0.06 to 0.11)	0.36	.52	.91
Superior parietal tau	−0.08 (−0.12 to −0.03)	0.18	.02	<.001	−0.01 (−0.01 to 0)	0.29	.66	.75	−0.02 (−0.08 to 0.04)	0.22	.57	.63
Temporal fusiform tau	−0.06 (−0.11 to −0.01)	0.3	.03	.05	−0.01 (−0.01 to 0)	0.29	.23	.86	0.02 (−0.05 to 0.09)	0.36	.51	.39
Lateral occipital tau	−0.12 (−0.17 to −0.07)	0.28	<.01	<.001	−0.02 (−0.01 to 0)	0.27	.15	.69	0.01 (−0.09 to 0.06)	0.31	.73	.95
Tau PET	Sex × Aβ + age at tau scan (model 1B)				Age at menopause × Aβ + age at tau scan (model 2B)				HT use × Aβ + age at tau scan (model 3B)			
	β (95% CI)	R^2	*P* value	Robust *P* value	β (95% CI)	R^2	*P* value	Robust *P* value	β (95% CI)	R^2	*P* value	Robust *P* value
Entorhinal tau	−0.19 (−0.47 to 0.10)	0.38	.21	<.01	−0.05 (−0.07 to −0.02)	0.4	.001	<.001	0.34 (0.01 to 0.68)	0.42	.05	<.001
Amygdala tau	−0.12 (−0.37 to 0.14)	0.35	.37	<.001	−0.04 (−0.06 to −0.01)	0.38	.002	<.001	0.33 (0.05 to 0.62)	0.41	.03	.001
Temporo-occipital tau	−0.63 (0.94 to −0.31)	0.37	<.01	<.001	−0.11 (−0.14 to −0.08)	0.5	<.001	<.001	0.55 (0.14 to 0.96)	0.39	.02	<.001
Interior temporal tau	−0.65 (−0.97 to −0.32)	0.35	<.001	<.01	−0.11 (−0.14 to −0.09)	0.49	<.001	<.001	0.8 (0.40 to 1.20)	0.41	.008	<.001
Superior parietal tau	−0.5 (−0.73 to −0.27)	0.23	<.01	<.01	−0.04 (−0.07 to −0.02)	0.28	.001	<.001	−0.13 (−0.43 to 0.18)	0.23	.47	.45
Temporal fusiform tau	−0.47 (−0.74 to −0.20)	0.34	.01	.04	−0.08 (−0.10 to −0.05)	0.43	<.001	<.001	0.46 (0.13 to 0.80)	0.38	.02	<.001
Lateral occipital tau	−0.59 (−0.85 to −0.33)	0.33	<.01	<.01	−0.09 (−0.11 to −0.06)	0.42	<.01	<.001	−0.09 (−0.47 to 0.28)	0.31	.63	.02

Abbreviations: Aβ, β-amyloid; HT, hormone therapy; PET, positron emission tomography.

[a] Models 1A and 1B include male and female individuals (n = 292) and 2B (n = 189) and 3A and 3B (n = 193) include females only. Thirteen female individuals did not have age at menopause information or reported their age at menopause as at, or before, age 20 years. Sex and HT use are binarized (male vs female; HT user vs nonuser). In models 1A and 1B, female sex is the reference. In models 3A and 3B, HT nonuser is the reference. Neocortical Aβ, age at tau scan, and age at menopause are continuous. Age at menopause was visualized as categorical, according to clinical guidelines, but was included as a continuous variable in the statistical models. Robust represents the *P* value generated via a robust regression accounting for violations in ordinary least squares such as normality of the residuals or heteroscedasticity. β and 95% CIs are from the linear regression.

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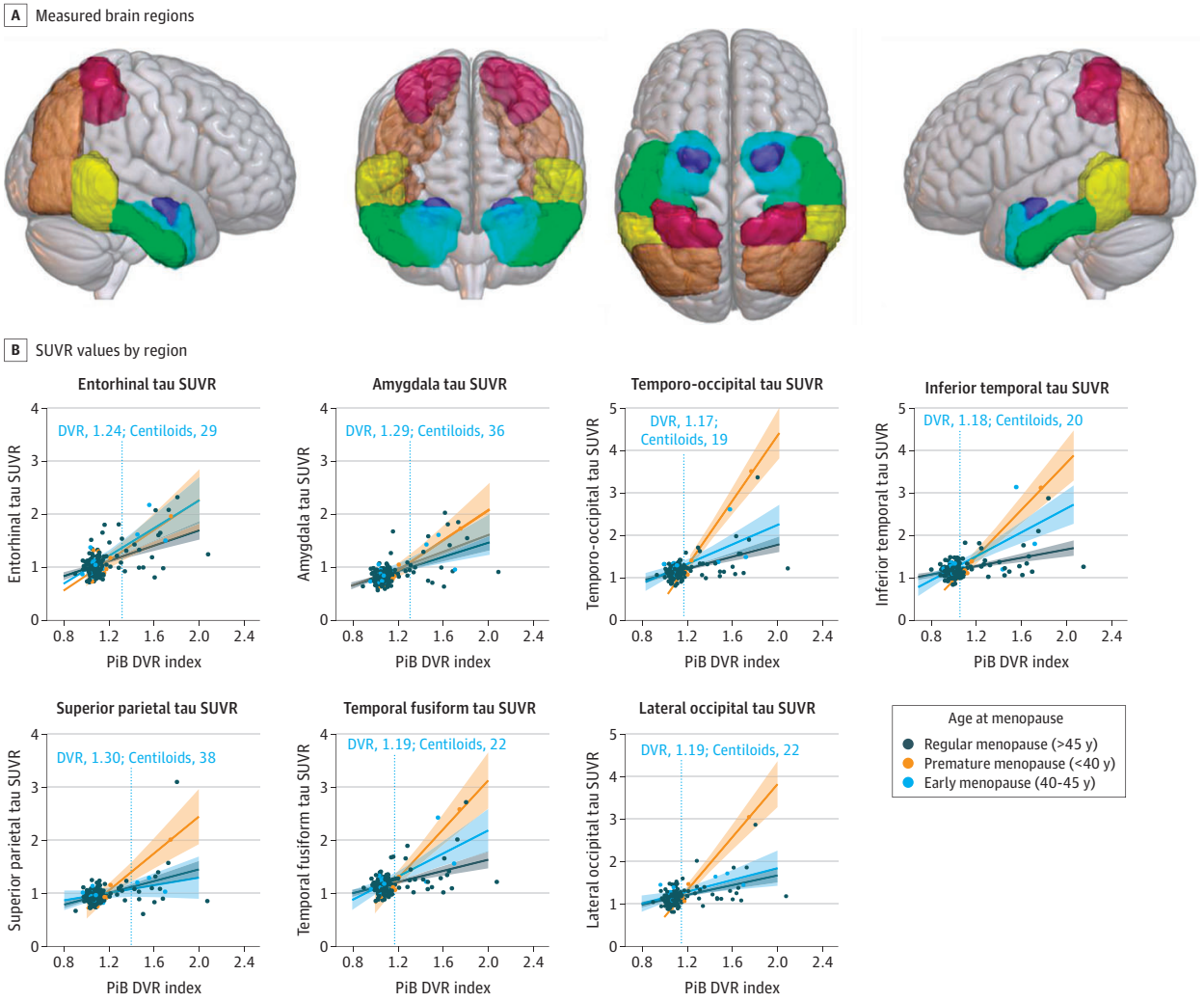
Figure 1. Association of Age at Menopause With Neocortical β-Amyloid Positron Emission Tomography Signal to Predict Regional Tau Positron Emission Tomography Signal in Cognitively Unimpaired Female Individuals



A, Regions are derived from the Harvard-Oxford atlas on a Montreal Neurological Institute brain template. Brown indicates lateral occipital lobe; dark blue, amygdala; green, inferior temporal gyrus; light blue, entorhinal cortex; light green, temporal fusiform gyrus; red, superior parietal lobe; yellow, temporo-occipital lobe. B, Standard uptake volume ratio (SUVR) values by region are shown. Neocortical ^{11}C-Pittsburgh compound B (PiB) distribution volume ratio (DVR) values to the right of the dashed line demonstrate when along the β-amyloid positron emission tomography spectrum age at menopause is associated with tau positron emission tomography $P < .05$. DVR values and equivalent Centiloid are reported. Age at menopause was specified as a continuous measure in the statistical models, with age bands specified above for visual purposes.

Interactive Associations Between Age at Menopause and Neocortical Aβ With Tau PET

Among female individuals, age at menopause yielded no main associations with regional tau PET (model 2A: Table 2). We did observe significant interactions between age at menopause and Aβ PET with tau PET, after adjusting for age at tau scan. Earlier age at menopause was associated with higher tau PET in those with higher levels of neocortical Aβ PET across the entorhinal cortex (model 2B; β = −0.05; 95% CI, −0.07 to −0.02; $P = .001$), amygdala (β = −0.04; 95% CI, −0.06 to −0.01; $P = .002$), inferior-temporal gyrus (β = −0.11; 95% CI, −0.14 to −0.09; $P < .001$), superior parietal cortex (β = −0.04; 95% CI, −0.07 to −0.02; $P = .001$), temporal fusiform (β = −0.08; 95% CI, −0.10 to −0.05; $P < .001$), lateral occipital cortex (β = −0.09; 95% CI, −0.11 to −0.06; $P = .004$), and the temporo-occipital lobe (β = −0.11; 95% CI, −0.14 to −0.08; $P < .001$; **Figure 1** and Table 2). These findings remained after adjusting for years of education, *APOEε4*, FHS-CVD, menopause symptom severity/indication, and menopause-related sleep problems (eTables 2-4, 6, and 7 in Supplement 1). Age at menopause and age at tau scan were not correlated ($r = −0.13$, $P = .09$). To test whether female individuals with surgical menopause were driving the interactions with Aβ, we conducted sensitivity analysis removing females with a history of oophorectomy (18 of 180 [10%]), given that oophorectomy typically induces menopause.[45] Age at menopause interactions with Aβ remained significant (eTable 8 in Supple-

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ment 1). Excluding female individuals with a tau standard uptake value ratios more than 2 or a PACC score less than 2, did not attenuate the findings (eTables 9 and 10 in Supplement 1). When female individuals with premature menopause were excluded (n = 9), age at menopause interactions with Aβ remained significant in the robust linear regression only (eTable 11 in Supplement 1). Finally, we used floodlight analysis to determine the threshold of neocortical Aβ PET burden required for a significant association between age at menopause and tau PET, which hovered above the abnormality threshold across ROIs (range, 1.17-1.30 neocortical PiB DVR or 19-38 Centiloids; see dashed lines in Figure 1). There was no age at tau scan by Aβ PET interaction on tau PET (eFigure 4 in Supplement 1), suggesting that age at menopause and not chronological age was moderating the Aβ PET and tau PET association.

Interaction Associations Between HT Use and Neocortical Aβ on Tau PET

We found no main association of HT use with the tau PET (model 3A: Table 2). When examining interactions with Aβ, HT users with higher Aβ PET burden exhibited higher tau PET than nonusers across most ROIs including the amygdala (model 3B: HT nonusers: β = −0.33; 95% CI, 0.05-0.62; *P* = .03), inferior-temporal gyrus (β = −0.80; 95% CI, 0.40-1.20; *P* = .008), temporal fusiform (β = 0.46; 95% CI, 0.13-0.80; *P* < .001), and the temporo-occipital lobe (β = −0.55; 95% CI, 0.14-0.96; *P* < .001; Table 2), after adjusting for age at tau scan. Findings remained using robust regression and after adjusting for years of education, *APOE*ε4, FHS-CVD (eTables 2-4 in Supplement 1) as well as menopause symptom severity (eTables 6 and 7 in Supplement 1), diabetes, smoking history (eTable 12 and 13 in Supplement 1), and reproductive surgery (eTable 14 in Supplement 1). When the HT user group was divided into self-reported past and current HT use, the HT interactions with Aβ were more widespread in past HT users (eTable 15 in Supplement 1). We post hoc tested whether the use of combined (estrogen plus progestin [n = 23]) vs unopposed (use of estrogen alone [n = 60]), influenced the tau PET or the association between *A*β and the tau PET. We found no main association of formulation (estrogen plus progestin vs estrogen alone) or interaction with Aβ on tau PET (eTable 16 in Supplement 1). A more fine-grained parcellation of estrogen types was not possible due to small sample sizes and potential type I error.

Exploratory Comparisons With Male Individuals

To post hoc probe the influence of HT on observed sex differences, we compared the association between regional tau PET and Aβ PET in HT users and nonusers with males (including males as a reference group), adjusting for age at tau scan. HT users exhibited higher tau PET compared with male individuals when Aβ PET was high in all ROIs, expect the amygdala (eFigure 5 in Supplement 1). HT nonusers also exhibited higher tau PET in the temporal and lateral occipital cortex compared with males when Aβ PET was high (eTable 17 in Supplement 1).

Associations Between HT Timing and Tau, Including Interactive Associations With Neocortical Aβ

We examined if late initiation of HT, more than 5 years following age at menopause, was associated with increased tau PET relative to early HT initiation, within 5 years after age at menopause (reference). Female individuals with late HT initiation exhibited higher tau PET in the entorhinal cortex (β = 0.23; 95% CI, 0.03-0.43; *P* = .02), inferior-temporal gyrus (β = 0.49; 95% CI, 0.27-0.43; *P* = .001), superior parietal (β = 0.19; 95% CI, 0.07-0.31; *P* = .002), temporal fusiform (β = 0.34; 95% CI, 0.16-0.52; *P* = .001), lateral occipital cortex (β = 0.13; 95% CI, 0.04-0.25; *P* = .001), and the temporo-occipital lobe (β = 0.46; 95% CI, 0.21-0.71; *P* = .001; **Table 3** and **Figure 2**). Interactions with neocortical Aβ PET were also found in the same ROIs, suggesting that in the context of high Aβ PET, late HT initiation was associated with a higher tau PET relative early initiation and results were consistent when using secondary robust regression (Table 3). We also observed that there were no significant differences in age at tau scan or neocortical *A*β between late and early HT initiation, suggesting that timing associations are not driven by older age or *A*β. Exploratory comparisons of very early HT initiation (>1 or more years before age at menopause) yielded no robust associations (Table 3). When HT timing was continuous, main associations remained in the superior parietal, temporo-occipital, and lateral occipital cortex; however, patterns of significance were attenuated to nonsignificant in analyses using robust regression (eTable 18 in Supplement 1).

Interactive Associations Between Sex, Age at Menopause, HT Use, and HT Timing, Including Neocortical Aβ With Cognition

Finally, we investigated a potential moderation association of sex, age at menopause, and HT with the association between Aβ PET and cognition. Female individuals had a higher PACC score compared with age-matched males (β = −0.42; 95% CI, −0.61 to −0.22; *P* < .001). Sex interactions with Aβ on PACC were not significant. Associations between earlier age at menopause and lower PACC performance were significant (β = −0.03; 95% CI, 0-0.05; *P* = .02). This association was strengthened in the setting of higher Aβ burden (interaction: β = −0.12; 95% CI, 0.02-0.23; *P* = .02). No main association of HT use or Aβ interactions with HT use were found on PACC performance, although there was a main association of HT timing (β = −0.83; 95% CI, −1.39 to −0.27; *P* = .004) and an interaction with Aβ (β = −3.32; 95% CI, −2.95 to −1.71; *P* = .006). Specifically, female individuals with late HT initiation performed subtly lower on the PACC compared with those with early HT initiation. This HT-PACC association was exacerbated in females who exhibited high Aβ (eFigure 6 in Supplement 1). Statistical values are summarized in eTable 19 in Supplement 1.

Discussion

Female individuals exhibited higher cortical tau than age-matched males, which was exacerbated in the setting of high neocortical Aβ. In the setting of high neocortical Aβ (approxi-

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Table 3. Regression Coefficients for HT Timing With Neocortical Aβ Interactions in Regional Tau PET[a]

Tau PET	HT within 5 y of menopause: HT >5 y after menopause + age at tau scan				HT >1 y before menopause + age at tau scan			
	β (95% CI)	R^2	*P* value	Robust *P* value	β (95% CI)	R^2	*P* value	Robust *P* value
Entorhinal tau	0.23 (0.03 to 0.43)	0.14	.022	.01	−0.06 (−0.19 to 0.06)	0.14	.31	.24
Amygdala tau	0.16 (−0.03 to 0.34)	0.11	.091	.01	−0.07 (−0.18 to 0.04)	0.11	.22	.23
Temporo-occipital tau	0.46 (0.21 to 0.71)	0.21	.001	<.001	−0.05 (−0.08 to 0.05)	0.60	.34	.07
Interior temporal tau	0.49 (0.27 to 0.43)	0.22	.001	.01	0.01 (−0.06 to 0.08)	0.83	.71	.07
Superior parietal tau	0.19 (0.07 to 0.31)	0.19	.002	.02	−0.03 (−0.09 to 0.03)	0.28	.22	.11
Temporal fusiform tau	0.34 (0.16 to 0.52)	0.21	.001	.01	0.02 (−0.10 to 0.14)	0.21	.75	.07
Lateral occipital tau	0.13 (0.04 to 0.25)	0.24	.001	.02	−0.04 (−0.09 to 0.05)	0.24	.60	.12
Tau PET	**HT within 5 y of menopause**							
	HT >5 y after menopause × Aβ + age at tau scan				**HT >1 y before menopause × Aβ + age at tau scan**			
Entorhinal tau	1.02 (0.37 to 1.67)	0.53	.002	.01	−0.62 (−1.38 to −0.04)	0.53	.04	.68
Amygdala tau	0.75 (0.15 to 1.34)	0.51	.014	.01	0.32 (−0.99 to 0.24)	0.51	.23	.68
Temporo-occipital tau	2.79 (2.27 to 3.31)	0.83	.001	<.001	0.92 (0.45 to 1.38)	0.83	.01	.55
Interior temporal tau	2.88 (3.29 to 2.03)	0.79	.001	.01	0.81 (0.34 to 1.28)	0.81	.01	<.001
Superior parietal tau	0.89 (0.51 to 1.27)	0.59	.001	.02	0.07 (−0.27 to 0.41)	0.59	.68	.68
Temporal fusiform tau	1.92 (1.47 to 2.38)	0.74	.001	.01	0.53 (0.12 to 0.94)	0.74	.01	.22
Lateral occipital tau	1.96 (1.48 to 2.45)	0.74	.001	.02	0.62 (0.19 to 1.05)	0.74	.02	.22

Abbreviations: HT, hormone therapy; PET, positron emission tomography.

[a] HT users (all female) were categorized into 3 groups depending on the time HT was initiated relative to age at menopause: more than 5 years after age at menopause (late; of interest group), within 5 years after age at menopause (early; reference group), and more than 1 year before age at menopause (very early; exploratory group). β and 95% CIs are from the linear regression.

mately ≥20 Centiloids), levels of tau were associated with a self-report younger age at menopause and a history of menopausal HT. Female individuals with late initiation of menopausal HT, more than 5 years after age at menopause, showed higher levels of tau, relative to those who initiated near their age at menopause. Cognitive performance at the tau scan was slightly lower in those with younger age at menopause and late HT use, compared with older age at menopause and early HT use.

Consistent with the notion that menopause is a critical time in which AD biomarkers diverge between the sexes, earlier age at menopause has been associated with an increased risk of cognitive decline.[8-10,28,46] This study extended these findings, showing that earlier age at menopause is associated with tau deposition in a range of temporo-occipital neocortical regions and that neocortical Aβ plays a synergistic role in this association. The association between age at menopause and tau pathology in the context of high Aβ suggested that female individuals with early or premature menopause may be vulnerable to tau deposition.[7] The low prevalence of premature menopause is reflected in the small number of individuals with premature menopause. Given that early and premature menopause can be induced via bilateral oophorectomy, we examined whether removing females with history of oophorectomy attenuated the association of age at menopause. These findings suggested that menopause at younger age, and not surgical removal of ovaries, may be an instigator of tau deposition in female patients. In this study, there exist a few prematurely menopausal individuals with high Aβ and tau who are of great interest to follow-up longitudinally. Importantly, those with premature and early menopause were more likely to self-report a history of hysterectomy and menopause-related sleep problems, suggesting that future research should investigate if such factors play a role in the link between age at menopause and tau PET. Robust statistics also showed higher regional tau in female individuals with early menopause, suggesting that those with early menopause women may also be a subgroup of interest.

Among postmenopausal individuals, HT use has been found to increase incidence rates for probable dementia.[15-17,21,47] Following randomized clinical trial findings published by the WHI in 2002 to 2003, HT use steeply declined by approximately 80% in the United States.[48] Our study extends these findings by showing that HT use in the setting of high Aβ is associated with elevated tau PET levels. Our secondary HT analysis suggested that female individuals with late HT initiation exhibited an elevated tau PET signal, compared with females who initiated HT proximal to menopause onset. This observation existed despite both these subgroups of cognitively unimpaired HT users being matched for age and Aβ burden. These findings are consistent with clinical guidelines that suggest HT is safe when used close to menopause onset and support the timing hypothesis, which posits that intervention increases risk for progression to AD dementia if initiated late.[18,20] To our knowledge, this is the first study to show that tau deposition may underlie the preestablished association between late HT intervention and AD dementia. The exclusion of female individuals with progestin use did not attenuate the unfavorable outcomes of HT, consistent with some other reports.[49]

Sex differences in incidence rates for AD dementia are somewhat controversial,[50] although some studies report

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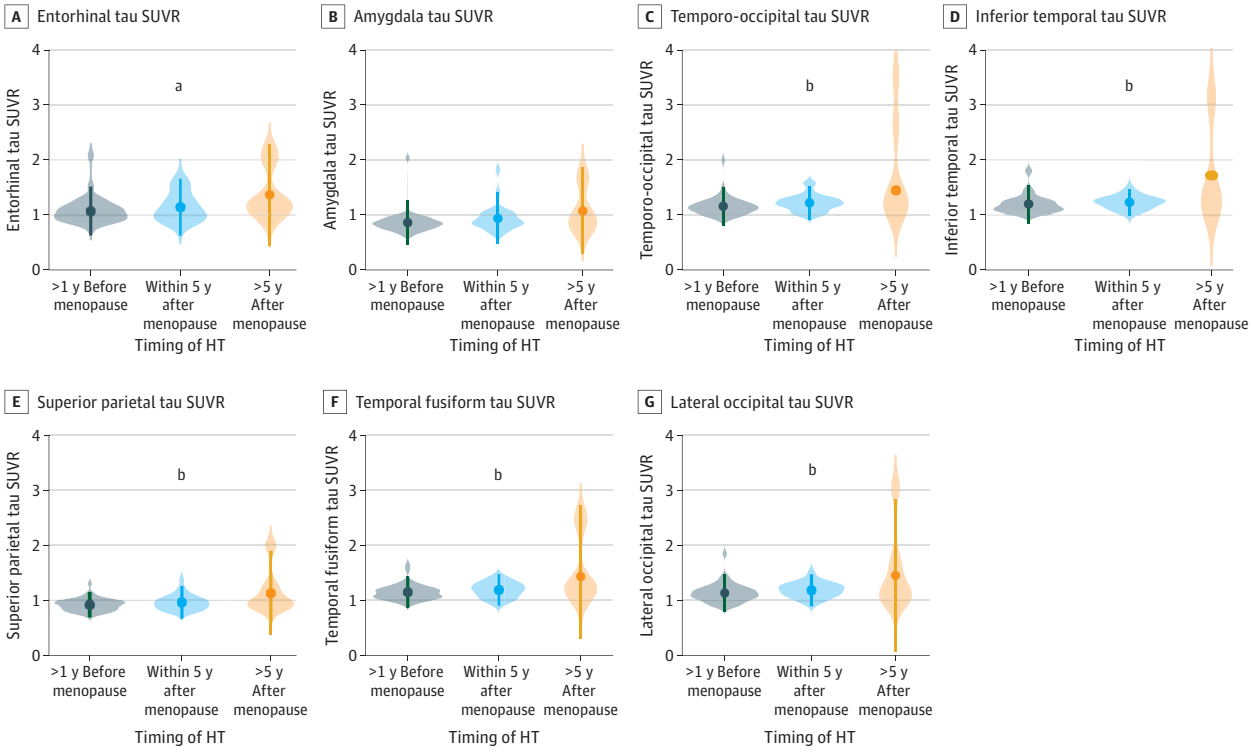
Figure 2. Association of Timing of Hormone Therapy (HT) With Regional Tau Positron Emission Tomography Signal in Cognitively Unimpaired Females, Collapsed Across Neocortical β-Amyloid



HT 1 or more years before age at menopause is indicated in gray. HT (n = 27) within 5 years after age at menopause is indicated in blue (n = 52). Five or more years after age at menopause is indicated in orange (n = 10). SUVR indicates standard uptake volume ratio.

[a] $P = .01$.

[b] $P = .001$.

greater risk for female individuals older than 80 years[51] and prevalence is undoubtably higher for females. Recent simulations acknowledge the partial contribution of female longevity and survival bias to risk for progression to dementia[52] but could not negate the possibility of sex biological influences.[53] In this study, we observed that higher tau in female individuals persisted following adjustment for other factors associated with AD pathology including APOEε4 status and years of education. Similarly, cross-sectional work has suggested better cognitive performance in female individuals relative to males for a given level of tau burden.[54,55] Longitudinally, however, faster rates of cognitive decline are observed in females and males with equally high levels of tau.[56] A loss of compensatory mechanism in male individuals over time may provide an explanation for sex differences in cross-sectional and longitudinal cognitive trajectories. Indeed, postmortem evidence suggests that for a given level of AD pathology, global cognitive performance gathered just prior to death is far lower in female individuals than males.[4] Thus, females appear to lose a cognitive advantage over the course of disease, potentially due to a loss of reserve that is present in the preclinical stage of disease.

It is important to note that the association between a younger age at menopause and tau deposition occurred at or above the amyloid positivity threshold of 20 Centiloids.[44] For context, current preclinical AD trials enroll individuals with Aβ burden above 20 Centiloids, suggesting that sex dimorphic tau pathways are exacerbated by relatively mild Aβ load. Analysis of the Kronos Early Estrogen Prevention Study (KEEPS) Continuation Study will provide critical evidence for whether the risks and benefits of HT vary within a specific threshold of Aβ.[41]

Approximately a quarter of postmenopausal female individuals (70 years and older) have a history of HT use and have now entered a critical age of AD risk.[56,57] These findings may help inform AD diagnostic treatment plans for postmenopausal individuals with a history of postmenopausal HT use. Our observations will also impact future generations as the demand for HT rises in some Western countries.[58] Clinical guidelines do not recommend HT in individuals up to 10 years after age at menopause.[25] Whether alternative age thresholds closer to age at menopause should be considered is a topic of further investigation. It is also important to consider how to address menopausal symptoms like hot flashes and disrupted sleep in menopausal individuals using alternatives to HT, for example selective serotonin reuptake inhibitors or gabapentin (an anticonvulsant). These findings may also have implications for understanding and mitigating the risk of tau pathology associated with age at menopause. The best predictor of natural early menopause is smoking.[59] Understanding whether premature menopause acts to moderate associations between risk factors such as smoking

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and AD incidences in female individuals will have future implications for clinical practice.[60] Prospective randomized data with early menopausal individuals are needed to assess the extent to which tau vulnerability exists in female individuals and when along the chronological age span faster rates of tau accumulation may appear. In other cohorts, earlier age at menopause has been associated with higher cardiovascular risk,[61] suggesting that menopause could serve as a catalyst for cardiovascular-related AD insult in female individuals and warrant investigation in larger cohorts with more diverse cardiovascular risks.

Strengths and Limitations

The strengths of this study include a large sample of cognitively unimpaired adults with both Aβ and tau PET imaging and carefully phenotyped self-report information on menopause status, HT use, and potential confounding factors. This study also possessed limitations. Although we accounted for potential influences of medical and menopause-related psychiatric factors, information on what precipitated premature/early menopause and the reason behind why female individuals chose to initiate HT was absent in this study. Such information may play an unexamined confounding role in the findings and should be addressed in future research. Future studies should also investigate potential differential effects of past and current HT use in a larger sample. Age at menopause varies by racial and ethnic background, with Asian Indian individuals typically entering menopause at age 46 years,[54] and Hispanic individuals at age 48.5 years, which is years earlier than non-Hispanic White individuals at age 51 years.[55] As this sample consisted of predominantly non-Hispanic White individuals and a small group of Black individuals, additional studies including racially diverse samples are required to test the generalizability of these findings. In addition, these data were self-reported, and we cannot rule of the possibility that incorrect recall of age at menopause or unreliable self-report data about age at menopause could play a role in our findings, despite this being a cognitively unimpaired sample. Finally, the secular trend in HT use (based on the WHI findings) is reflected by the significantly different age profiles of the HT user and nonuser groups. That said, early and late HT users did not differ by age, providing support to our interpretation of HT timing.

Conclusions

Our data show that female sex, earlier age at menopause, and HT use moderates the association between Aβ and tau PET. The findings of the present study may inform AD risk discussions relating to female reproductive health and treatment. Female individuals who experience younger age at menopause may represent a subgroup for priority inclusion in AD prevention trials. Clinical trials to assess the potential implications of HT timing on tau deposition are also warranted.

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Author Affiliations: Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston (Coughlan, Boyle, Klinger, Chibnik, Yau, Properzi, Schultz, Hanseeuw, Rentz, Sperling, Buckley); Wisconsin Alzheimer's Disease Research Center, University of Wisconsin, School of Medicine and Public Health, Madison (Betthauser, Koscik, Jonaitis, Christian, Gleason, S. C. Johnson); Department of Medicine, University of Wisconsin–Madison, Madison (Betthauser, Koscik, Jonaitis, Wenzel, S. C. Johnson); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and the Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Chibnik, Manson); Department of Psychiatry, University of California, San Diego, San Diego (Saelzler); Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Boston, Massachusetts (Schultz, Hanseeuw, Rentz, K. A. Johnson, Sperling, Buckley); Department of Neurology, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium (Hanseeuw); Gordon Center for Medical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston (Hanseeuw, K. A. Johnson); Institute of Neuroscience, Université Catholique de Louvain, Brussels, Belgium (Hanseeuw); Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia (Buckley).

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Concept and design: Coughlan, Betthauser, Koscik, Manson, K. Johnson, Buckley.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Coughlan, Yau.
Critical revision of the manuscript for important intellectual content: Coughlan, Betthauser, Boyle, Koscik, Gleason, Klinger, Chibnik, Jonaitis, Saelzler, Properzi, Wenzel, Christian, Hanseeuw, Schultz, Manson, Rentz, K. Johnson, Sperling, S. Johnson, Buckley.
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