WOMEN'S HEALTH

Associations between hormone therapy use and tau accumulation in brain regions vulnerable to Alzheimer's disease

Gillian T. Coughlan[1], Zoe Rubinstein[1], Hannah Klinger[1], Kelly A. Lopez[1], Stephaine Hsieh[1], Rory Boyle[2], Mabel Seto[1], Diana Townsend[1], Danielle Mayblyum[3], Emma Thibault[3], Heidi I. L. Jacobs[4], Michelle Farrell[1], Jennifer S. Rabin[5,6,7], Kate Papp[1], Rebecca Amariglio[1], Suzanne Baker[8], Cristina Lois[3], Dorene Rentz[1], Julie Price[3], Aaron Schultz[1], Michael Properzi[1], Keith Johnson[3,9], Reisa Sperling[1,9,10], Rachel F. Buckley[1,9,11]*

Elucidating the downstream impact of exogenous hormones on the aging brain will have far-reaching consequences for understanding why Alzheimer's disease (AD) predominates in women almost twofold over men. We tested the extent to which menopausal hormone therapy (HT) use is associated with later-life amyloid-β (Aβ) and tau accumulation using PET on *N* = 146 baseline clinically normal women, aged 51 to 89 years. Women were scanned over a 4.5-year (SD, 2.1; range, 1.3 to 10.4) and 3.5-year (SD, 1.5; range, 1.2 to 8.1) period for Aβ and tau, respectively, ~14 years after the initiation of HT. In older women (aged >70 years), HT users exhibited faster regional tau accumulation relative to non-users, localized to the entorhinal cortex and the inferior temporal and fusiform gyri, with an indirect effect of HT on cognitive decline through regional tau accumulation. In younger women (aged <70 years), HT associations with tau accumulation were negligible. Findings are relevant for optimizing menopausal treatment guidelines.

INTRODUCTION

If current trends continue, Alzheimer's disease (AD) dementia will affect 13.8 million Americans by 2060, almost two-thirds of whom will be women. Growing evidence shows that this disproportionate rate of AD dementia in women may be due to the earlier deposition (*1*–*5*) and progression (*6*–*8*) of tauopathy relative to age-matched men. What remains unclear are the biological mechanisms influencing the pathological progression of tauopathy in women.

One-third of women in the United States are currently peri- or postmenopausal (*9*). Menopausal hormone therapy (HT) offers 90% treatment efficacy for symptoms (*10*), particularly those of a vasomotor nature. Over the past two decades, there has been a lack of clarity on how HT affects the brain. In the early 2000s, the world's largest randomized controlled trial of HT from the Women's Health Initiative showed that HT, particularly the combined estradiol and progestin formulation, doubled the incidence rate of probable all-cause dementia (*11*). Further ancillary studies from the trial demonstrated long-standing adverse effects on cognition, when HT was prescribed at 65 years and above (*12*). Observational studies and clinical trials later replicated increased rates of cognitive decline, higher rates of AD dementia (*13*–*15*), and faster neurodegeneration (*16*, *17*) in women prescribed HT at older ages. In younger women close to menopause, however, some studies reported minimal to lower risk for cognitive decline (*14*, *18*). The divergent levels of risk dependent on advancing age led to the emergence of the HT timing hypothesis, which suggests that HT use in women should be initiated within 10 years following their age at menopause to avoid adverse effects (*19*–*21*). Today, the timing hypothesis informs clinical guidance offered by board-certified organizations across the United States and Europe (*22*–*25*).

On the basis of existing smaller cross-sectional AD biomarker studies, HT may influence the pathophysiology of AD. For example, HT use (particularly estradiol therapy) in younger women close to menopause is associated with lower amyloid-β (Aβ) (*26*, *27*) and tau (*28*, *29*) levels, supporting the timing hypothesis. Conversely, in a sample of clinical normal women, regional tau burden is elevated in older women who had long delay between their age at menopause and their initiation of HT (*30*), consistent with findings from the Women's Health Initiative clinical trial on HT (*11*). Whether HT predicts AB and tau trajectories, with potential implications for cognitive decline remains unknown.

Until now, very few observational studies had the statistical power to examine the extent to which HT influences Aβ and tau accumulation as measured with positron emission tomography (PET) neuroimaging, despite the critical need to substantiate cross-sectional HT findings in longitudinal studies. In a cohort of baseline clinically normal age-matched HT users ($N = 73$) and non-users ($N = 73$), we tested the extent to which self-report HT use is associated with Aβ and tau accumulation as a function of advancing age. Women were scanned over a mean 4.5-year period for Aβ (SD, 2.1; range, 1.3 to 10.4) and a mean 3.5-year period for tau (SD, 1.5; range, 1.2 to 8.1).

[1]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA. [2]Penn Frontotemporal Degeneration Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. [3]Gordon Center for Medical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA. [4]The Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02129, USA. [5]Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada. [6]Harquail Centre for Neuromodulation, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Ontario, Canada. [7]Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada. [8]Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA. [9]Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Boston, MA 02115, USA. [10]Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA. [11]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia.
*Corresponding author. Email: rfbuckley@mgh.harvard.edu

We hypothesized that rates of accumulation would differ in HT users versus non-users in an age-dependent manner.

RESULTS

Baseline characteristics by HT

HT use was surveyed by participant self-report at the time of the first Pittsburgh Compound-B Aβ-PET scan, approximately 4.4 years (SD, 2.5) before the first Flortaucipir tau-PET scan. From a total of 89 non-HT users, we obtained 73 who were age-matched to the 73 HT users [using the MatchIt package in R (*31*)], resulting in a total of 146 women (73 HT non-users and 73 HT users). The mean baseline age of the age-matched women at the first Aβ-PET and tau-PET scan was 70.8 years (SD, 7.6) and 74.2 years (SD, 8.2), respectively. As summarized in Table 1, HT users had a lower baseline body mass index (BMI) relative to non-users ($P = 0.03$). As such, a baseline BMI × time interaction was included as a covariate in all following analyses. There were no other significant differences between HT users and non-users. A subset of well-phenotyped HT users ($N = 58$) self-reported 7.45 years of exposure, with an average initiation age of 55.2 years. The temporal lag between the initiation of HT and the first Aβ-PET scan was 18.7 years on average (based on $N = 58/73$ women who reported HT initiation age).

Minimal effect of HT on neocortical Aβ accumulation as a function of advancing age

There was no main effect of HT on global Aβ-PET accumulation (Table 2) as measured with change in a composite of regions including the frontal, lateral, temporal, and retrosplenial cortices (*32*). We found a marginally significant interaction between HT and baseline age such that older HT users exhibited marginally faster rates of neocortical Aβ accumulation relative to older non-users [Aβ = −0.07; 95% confidence interval (CI), −0.01 to 0.15; $P = 0.051$; Fig. 1 and Table 2], adjusting for baseline BMI × time. There was minimal neocortical Aβ

Table 1. Characteristics of the female age-matched sample. WM, white matter; PET, positron emission tomography; DVR, distribution volume ratio; EC, entorhinal cortex; ITG, inferior temporal gyrus; Aβ, amyloid-β.

Characteristics	HT non-users	HT users	Total	*P*
Total no. (%)	73	73	146	–
Baseline age years (SD)	70.3 (8.1)	71.4 (7.1)	70.8 (7.6)	0.3
Total no. baseline age < 70 years (%; range)	41 (54; 51–69)	42 (57; 52–69)	83 (56; 51–69)	0.9
Total no. baseline age > 70 years (%; range)	32 (44; 70–89)	31 (43; 71–89)	63 (44; 70–89)	0.9
Baseline tau-PET age (SD)	73.5 (8.8)	74.9 (8.1)	74.2 (8.5)	0.3
Baseline Aβ-PET DVR (SD)	1.16 (0.2)	1.17 (0.2)	1.17 (0.2)	0.8
Baseline EC tau-PET DVR (SD)	1.12 (0.1)	1.12 (0.1)	1.12 (0.1)	0.7
Baseline ITG tau-PET DVR (SD)	1.21 (0.1)	1.21 (0.1)	1.21 (0.1)	0.4
Baseline WM hyperintensity log* (SD)	−1.78 (1.27)	−1.76 (1.36)	−1.77 (1.31)	0.9
Baseline PACC score	0.23 (0.71)	0.31 (0.61)	0.27 (0.66)	0.2
Ethnicity Hispanic (%)	6 (8.2)	4 (5.5)	10 (6.8)	0.7
*APOEε*4 carrier (%)	18 (25)	21 (29)	39 (27)	0.7
Education years (SD)	15.8 (2.8)	16.1 (3.1)	16.0 (3.0)	0.3
BMI (SD)	27.9 (5.33)	25.9 (4.61)	26.9 (5.05)	0.03
Cardiovascular risk score (SD)†	19.6 (12.0)	19.6 (12.0)	19.8 (11.9)	0.9
Aβ-PET follow-up time (SD)	4.32 (2.0)	4.56 (2.1)	4.45 (2.1)	0.5
Tau-PET follow-up time (SD)	3.59 (1.59)	3.40 (1.42)	3.50 (1.5)	0.5
Mean years of HT use (range), $N = 58$	–	7.45 (1–25)	7.45 (1–25)	–
Mean HT start age (range), $N = 58$	–	55.2 (30–80)	55.2 (30–80)	–

*The total WM hyperintensity measure was log-transformed similar to existing studies (*69*). †Office-based Framingham Heart Study cardiovascular disease risk score (FHS-CVD) is calculated from a sex-specific weighted sum of age, antihypertensive treatment (dichotomous), systolic blood pressure, BMI, diabetes status (dichotomous), and cigarette smoking status (dichotomous).

Table 2. HT associations with longitudinal Aβ-PET. Time reflects the number of years between the first and last PET scan. Age reflects individual participant's study enrollment age. HT non-users are the reference.

Model 1	HT × Time + Age × Time + BMI × Time			HT × Age × Time + BMI × Time		
Longitudinal Aβ-PET	**β**	**(95% CI)**	***P***	**β**	**(95% CI)**	***P***
Global PiB-DVR	0.04	−0.04 to 0.10	0.436	0.07	0.01–0.15	0.051

accumulation in younger women, irrespective of HT (Fig. 1). The interaction between HT and baseline age became attenuated when adjusting for an *APOE*ε4 status × time interaction ($P = 0.162$).

Significant effect of HT on regional tau accumulation as a function of advancing age

There was no main effect of HT on regional tau accumulation (Table 3), as measured with change in Flortaucipir PET. When examining interactions with baseline age over time, older HT users exhibited significantly faster regional tau accumulation relative to older non-users (Table 3 and Fig. 2A), adjusting for BMI × time. Affected regions included the entorhinal cortex (β = 0.20; 95% CI, 0.04 to 0.35; $P = 0.014$), the inferior temporal gyrus (β = 0.19; 95% CI, 0.04 to 0.34; $P = 0.011$), and the temporal fusiform gyrus (β = 0.19; 95% CI, 0.02 to 0.30; $P = 0.023$; Fig. 2B). In younger women, HT users appeared to be protected from entorhinal tau accumulation relative to non-HT users (Fig. 2), suggesting that HT use may have the opposite influence on entorhinal tau accumulation depending on a woman's age. All findings survived multiple correction (further details reported in Materials and Methods) and were consistent after adjusting for time interactions with *APOE*ε4 (table S2), baseline Framingham cardiovascular risk score (table S3), baseline white matter (WM) hyperintensities (table S4), and years of education (table S5) and excluding baseline BMI as a covariate (table S6). The findings also remained after adjusting for baseline neocortical Aβ-PET over time (table S7) and using balanced weights for each individual's baseline Aβ burden (table S8). When including all covariates in one model (i.e., time interactions with *APOE*ε4, cardiovascular risk, baseline WM hyperintensities, years of education, and baseline Aβ burden), HT interactions with baseline age over time remained significant on tau accumulation (table S9). The effects of HT on regional tau accumulation were also similar in the original non–age-matched sample of women (table S10).

As HT start age and duration of use were available in a subgroup of HT users ($N = 58$), we post hoc tested whether these characteristics of use were driving the association between HT and the longitudinal tau-PET signal. There was no association between HT start age or duration of use with tau over time, including or excluding the baseline age interaction. It should be noted that the small sample size may increase the likelihood of type II error. Finally, we repeated our analysis of interest (i.e., examining interactions between HT and baseline age on regional tau accumulation) in a constrained sample of participants with detailed HT information, along with 58 age-matched HT non-users. Characteristics of this constrained sample are presented in table S11. The results again show a significant interaction between HT and baseline age on tau accumulation in the entorhinal cortex, the inferior temporal gyrus, and the temporal fusiform gyrus (table S12).

Partial mediation effect of regional tau accumulation on the association between HT and cognitive decline in older women

As epidemiological studies show that exposure to HT is significantly associated with cognitive change (*13, 33*), we tested whether the

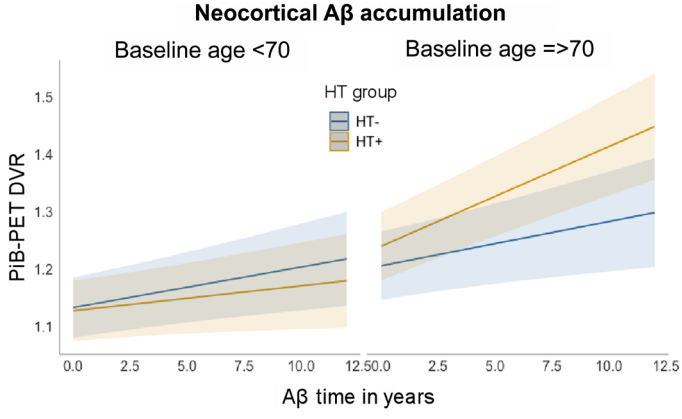

Fig. 1. HT interaction with age to predict the neocortical Aβ accumulation in cognitively unimpaired females. Neocortical PiB DVRs are shown. Baseline age was entered as a continuous variable and categorized for visualization.

Table 3. HT associations with longitudinal tau-PET. Time reflects the number of years between the first and last tau-PET scan. Age reflects individual participant's study enrollment age. HT non-users are the reference. Bold reflects *P* value, with significance α below 0.025.

Model 2	**HT × Time + Age × Time + BMI × Time**			**HT × Age × Time + BMI × Time**		
Longitudinal tau-PET	**β**	**(95% CI)**	***P***	**β**	**(95% CI)**	***P***
Entorhinal cortex	−0.07	−0.22 to 0.08	0.365	0.2	0.04–0.35	**0.014**
Inferior temporal	0.13	−0.01 to 0.27	0.063	0.19	0.04–0.34	**0.011**
Inferior parietal	0.02	−0.16 to 0.19	0.863	0.1	−0.07 to 0.27	0.249
Superior parietal	0.04	−0.14 to 0.22	0.665	−0.02	−0.22 to 0.17	0.81
Temporal fusiform	0.12	−0.03 to 0.28	0.121	0.19	0.02–0.30	**0.023**
Lateral occipital	0.07	−0.07 to 0.21	0.399	0.14	−0.02 to 0.31	0.094

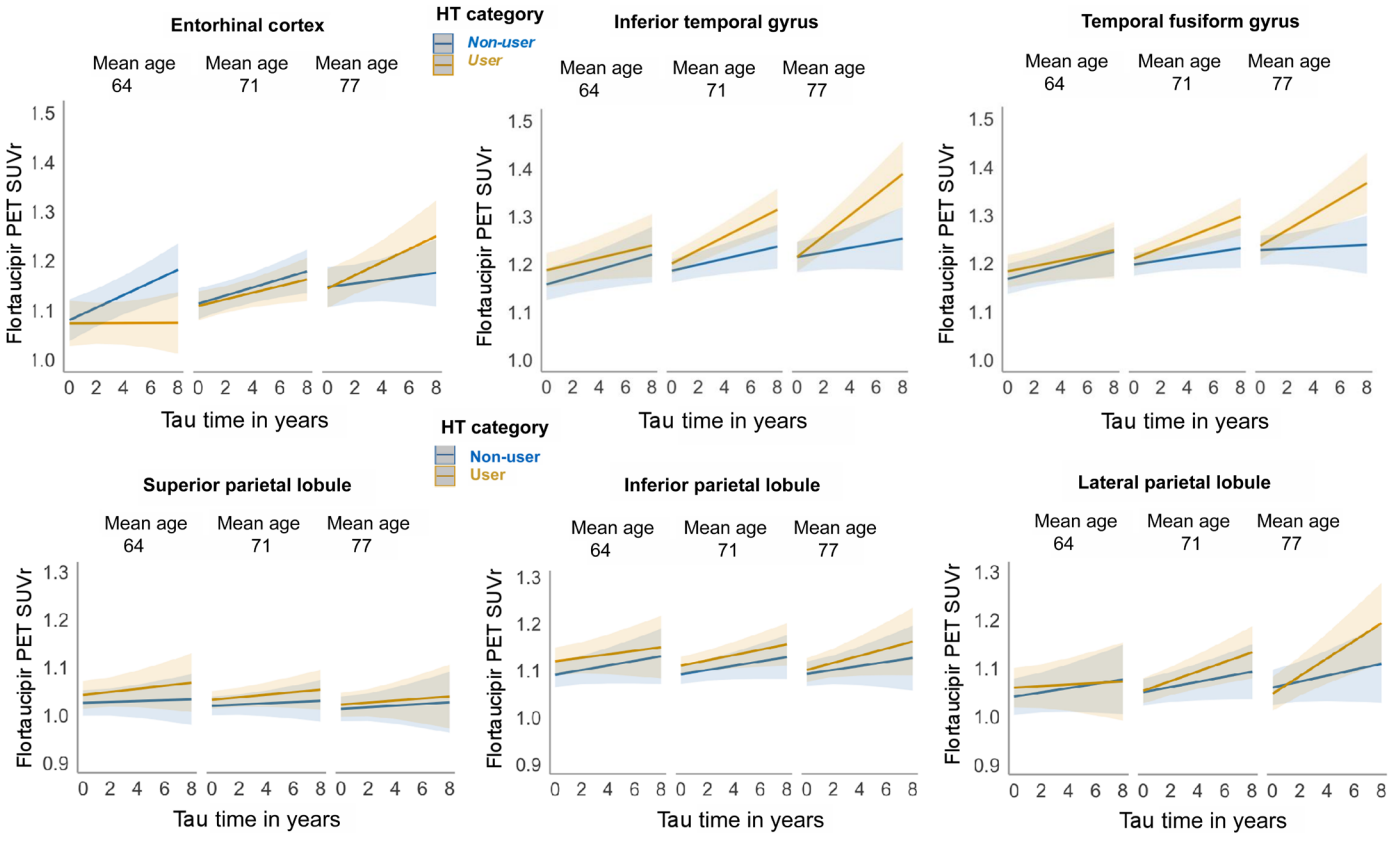

Fig. 2. HT interaction with age to predict regional tau accumulation in cognitively unimpaired females. SUVR values by region are shown. Baseline age was entered as a continuous variable and categorized for visualization.

relationship between HT and cognitive change was mediated by regional tau accumulation in older women [>70 years, $N = 63$ (32 non-users and 31 users)]. We focused on tau accumulation in the inferior temporal gyrus because HT associations were strongest in this region. To run the mediation analysis, participant-specific inferior temporal tau standard uptake value ratio (SUVR) slopes (as a measure of the rate of regional tau change) and PACC (Preclinical Alzheimer's Cognitive Composite) performance slopes (as a measure of cognitive decline) were extracted from a mixed effects model (separately), with a random intercept and random slope term. The total effect of HT on PACC performance change was not statistically significant ($P = 0.39$; model 3); however, the effect of HT was significantly associated with the mediating variable: rate of inferior temporal tau change ($t = 2.99$, $P = 0.004$; model 3). The indirect effect of HT on change in PACC performance via inferior temporal tau change was also statistically significant ($\beta = -0.01$; 95% CI, −0.01 to −0.001; $P = 0.012$; model 3), covarying for baseline age, years of education, and BMI. The proportion partially mediated was −0.18. See figs. S1 and S2 for visual representation of the significant correlation between the rate of inferior temporal tau change and cognitive decline in HT users and the nonsignificant correlation in non-users.

DISCUSSION

Among a cohort of clinically unimpaired women, faster regional tau accumulation was associated with self-reported history of menopausal HT use in older women, with minimal to no associations present in younger women. HT associations with tau accumulation were observed in the entorhinal cortex, the inferior temporal gyri, and the temporal fusiform gyri, areas of known vulnerability in preclinical AD. In sensitivity analyses, the observed longitudinal differences between HT users and non-users remained after adjusting for potentially confounding factors such as the influence of baseline BMI, educational attainment, *APOE*ε4, and vascular health/lesions over time. A significant association between inferior temporal tau accumulation and cognitive decline was observed in HT users but not in non-users. HT associations with global Aβ accumulation were notably weak and did not survive confounder adjustment in sensitivity analyses. Together, these observational findings suggest that in older women, HT use predicts pathological progression of tau with implications for cognitive decline, even when HT use was reported more than a decade after the first PET scan.

It is important to note that the association between HT use and regional tau accumulation was observed only in older women (approximately >70 years of age). Before the publication of the seminal randomized controlled trial from the Women's Health Initiative, HT was widely assumed to ameliorate cognitive impairment in postmenopausal women based on early data from observational studies (*34*–*36*). Thus, women who entered menopause before the Women's Health Initiative trial were typically prescribed HT at older ages. After the trial was prematurely halted, the recommendations surrounding HT prescriptions markedly shifted in terms of dosage and

mode of administration (*37*). As a result, HT use in the older women from the current study may not meet the current standards of care, which may in turn help explain the negative impact of HT use on tauopathy among our older population of women. Conversely, the association between HT and tauopathy in younger women was negligible: supporting the use of HT in younger women, particularly as it remains the most effective therapy for menopausal vasomotor symptoms and urogenital atrophy (*10*, *38*, *39*).

In terms of clinical implications, approximately a quarter of currently postmenopausal women (70 years and older) have a history of HT use and have now entered a critical age of AD risk. Therefore, the findings from this study underscore the importance of gathering information on reproductive history to inform AD diagnostic treatment plans for older women with a history of postmenopausal HT use. The demand for HT is rising in many countries (*40*) due to growing awareness of debilitating menopausal symptoms that can last approximately 7.4 years (*41*). As such, HT remains a critical and timely topic for optimizing brain health over the life span (*10*). Current guidelines recommend HT in individuals up to 10 years after age at menopause (*39*, *42*). It should also be noted that given the observational nature of the data, we are unable to definitively state a causal association between HT to drive AD biomarker accumulation; however, the Women's Health Initiative (WHI) demonstrated clear evidence of an association between delayed HT initiation and greater dementia incidence rates. Our findings lend weight to the evidence suggesting that delayed initiation of HT, particularly in older women, is associated with poor AD-related outcomes.

In the context of a plethora of evidence for female vulnerability to tauopathy (*1*, *5*, *28*, *43*), these findings highlight a potential biological pathway for future investigation. Rodent and human studies show a strong link between menopause-related hormonal fluctuations and AD risk (*30*, *44*–*47*). In a mouse study, fluctuations in estrogen levels were found to drive hippocampal tau hyperphosphorylation (*46*). Similarly, in human studies, menopause (particularly premature or early menopause) is associated with higher levels of tau (*30*, *43*) and cognitive decline (*48*), even after accounting for advancing age. Whether endogenous and exogenous hormones have a synergistic or independent effect on tauopathy remains to be tested. Although few mechanisms beyond the hormonal milieu have so far been proposed to explain sex dimorphic rates of tau accumulation, pathways that are currently being explored include X-linked genes (including IL2RG, RAB9A, and EMD) (*49*), X-linked escapee genes (USP11) (*50*), and female microglial activation (*51*). To what extent genetic and inflammatory pathways moderate the relationship between hormones and tauopathy in women remains a fruitful avenue of investigation (*52*).

The strengths of this study include a relatively large female population with longitudinal PET neuroimaging, as well as self-report information on HT use and clinical information. This study also has limitations. As expected, HT was associated with tau accumulation in an age-dependent manner. However, we cannot definitively conclude whether the influence of chronological age is due to secular trends in HT use (as discussed earlier) or simply due to a higher tau-PET signal typically observed at more advanced ages. While we were unable to establish the temporal association between HT initiation and women's age-at-menopause, this timing measure may address our first limitation and potentially hold greater implications for downstream tauopathy (*30*) compared to chronological age. Future studies that offer a rigorous reporting of age at menopause, age of HT initiation, duration of use, and formulation are warranted. It is also important to note that there were approximately 14 years between the initiation of HT use and PET neuroimaging, and therefore, many intervening events may have occurred (*53*). To mitigate potential confounders, we controlled for various clinical factors including cardiovascular risk and WM lesions. Generalizability is also limited as our sample largely consisted of non-Hispanic white and highly educated adults, so these findings will need to be replicated in more racially, ethnically, and socioeconomically diverse samples (*54*). Finally, an important caveat of our observational study design precludes the ability to draw causal links between menopausal HT and AD pathological progression. In addition, effects of cutting-edge non–hormonal-based menopause treatments, such as elinzanetant, on the outcomes of interest (*55*) are an important next step.

In conclusion, our data show that HT use predicts tau accumulation as a function of age, with implications for cognitive decline. Secular trends in the prescribing patterns of HT may explain the age-dependent effect of HT on tau progression. The findings may inform AD risk discussions relating to women's reproductive health and treatment.

MATERIALS AND METHODS

Participants

Female data were obtained from the Harvard Aging Brain Study (HABS). Inclusion criteria included a score of 0 on the Clinical Dementia Rating Scale, a score of greater than 25 on the Mini-Mental State Examination, scores above age and education-adjusted cutoffs on the 30-Minute Delayed Recall of the Logical Memory Story A [(*56*), ADNI-based cutoffs; http://www.adni-info.org/], and a score of less than 11 on the Geriatric Depression Scale. Exclusion criteria included history of alcoholism, drug abuse, head trauma, or current serious medical/psychiatric illness. At enrollment, participants were considered clinically normal based on neuropsychological testing and a clinical consensus panel that included behavioral neurologists, clinical neuropsychologists, and geriatric psychiatrists (*57*). Women underwent at least two time points of ^{11}C-Pittsburgh Compound-B (PiB) PET and Flortaucipir PET and had corresponding neuropsychological evaluations. Study procedures for HABS were approved by the Partners Human Research Committee, the Institutional Review Board for Massachusetts General Brigham hospitals (2023P002045). Written informed consent was obtained from all study participants.

Aβ and tau-PET

All PET images were acquired using a Siemens HR+ scanner. PET data underwent reconstruction and attenuation correction and were evaluated for head motion. T1 magnetic resonance imaging was performed for all participants. Aβ-PET imaging was performed using the radiotracer PiB, and acquisition parameters followed previously published protocols (*57*). In brief, Aβ-PET images were acquired with a 315- to 555-MBq bolus injection and a subsequent 1-hour dynamic acquisition over 69 volumes (12 × 15 s, 57 × 60 s). PET images were co-registered to a subject-specific T1 average (using the longitudinal Freesurfer v6 pipeline) computed from all T1 scans available across time for each individual using a six–degree of freedom rigid body registration. Distribution volume ratios (DVRs) were calculated using the Logan graphical method (40 to 60 min). Aβ-PET was analyzed as a neocortical aggregate of the frontal, lateral temporal, and retrosplenial cortices, which were defined by

FreeSurfer (version 6.0) using the Desikan-Killiany atlas (*58*). The mean Aβ-PET follow-up time was 4.45 (interquartile range, 1.3 to 10.4 years).

Tau-PET imaging was acquired approximately 80 to 110 min post-injection with ^{18}F-Flortaucipir and co-registered to each participant's T1 image (segmented with Freesurfer). The acquisition parameters followed previously published protocols (*59*). The tau-PET signal was computed using SUVRs and referenced to cerebellar gray. On the basis of existing findings for an elevated regional tau-PET signal in HT users in a fully independent sample, seven a priori tau-PET regions of interest were selected and derived from the Desikan-Killiany atlas: entorhinal cortex (Braak II), temporal fusiform gyrus (Braak III), inferior temporal gyrus (Braak IV), inferior parietal lobule, superior parietal lobule, and lateral occipital cortex (Braak V) (*30*, *60*). The mean tau-PET follow-up time was 3.5 years (interquartile range, 1.2 to 8.1 years). Partial volume correction was not applied as it is typically not recommended for longitudinal PET studies due to higher variance (*61*).

Preclinical Alzheimer's cognitive composite

Cognition was assessed using PACC-5, which is the average of *z* scores on five neuropsychological tests: the Mini Mental State Examination, Logical Memory Delayed Recall, Digit-Symbol Substitution Test, Free and Cued Selective Reminding Test (both cued and free recall), and Category Fluency (*62*, *63*). We chose this composite given its initial development to represent Aβ-related cognitive decline (*62*). We used PACC scores that corresponded to the tau-PET visits.

HT exposure

History of postmenopausal HT use was surveyed by participant self-report at study enrolment: "Have you ever been on post-menopause estrogen replacement medication?" For statistical analysis, HT use was considered as a categorical variable (user/non-user). A subset of women ($N = 58$) retrospectively self-reported year at HT initiation (continuous) and year at HT end (continuous) was collected. HT initiation age and duration of use were computed.

Statistical analyses

All analyses were conducted using RStudio version 2021.09.0 (R Foundation). Eighty-nine HT non-users were age-matched to 73 HT users using the MatchIt package in R (*31*), resulting in a total of 146 women (73 HT non-users age-matched to 73 users). Basic characteristics of the original non–age-matched sample can be found in table S1. Demographic and baseline PET differences between the age-matched sample are presented in Table 1 and tested using *t* tests or the nonparametric Kruskal-Wallis test, as appropriate, and categorical variables were compared using the Pearson χ^2 test. HT users had significantly lower body mass (BMI) index relative to non-users, potentially because an elevated BMI (>30) can be considered an HT contraindication (*22*–*24*). For the downstream analysis, we adjusted for a BMI × time interaction. A series of linear mixed effects models were fitted with a three-way interaction term to estimate the extent to which HT moderated the association between the baseline age (i.e., age at study enrollment/first Aβ-PET scan and continuous variable) and longitudinal neocortical Aβ-PET (model 1), and the extent to which HT moderated the association between the baseline age and longitudinal regional tau-PET (model 2). For multiple comparison adjustment, we used principal components analysis (PCA) to determine the overlapping variance across the tau-PET regions. The PCA produced two factors. Thus, correction for multiple comparisons was performed using the Bonferroni procedure considering the two tau outcomes (corrected $\alpha = 0.025$). Nominal *P* values are reported. Clinical factors that may produce spurious associations between HT and the PET signal were covaried. These factors included years of education (also considered a proxy measure of socioeconomic status) (*64*), *APOE*ε4 carrier status (*26*), baseline WM lesions, and the baseline office-based Framingham Heart Study Cardiovascular disease risk score (*65*). This risk score is calculated from a sex-specific weighted sum of age, antihypertensive treatment (dichotomous), systolic blood pressure, BMI, diabetes status (dichotomous), and cigarette smoking status (dichotomous). All covariates were interacted with time.

Primary models

The primary models were as follows:

Model 1A: Aβ-PET DVR ~ HT category × Time + Baseline Age × Time + BMI × Time, random = ~ time|ID.

Model 1B: Aβ-PET DVR ~ HT category × Baseline Age × Time + BMI × Time, random = ~ time|ID.

Model 2A: Regional Tau-PET SUVr ~ HT category × Time + Baseline Age × Time + BMI × Time, random = ~ time|ID.

Model 2B: Regional Tau-PET SUVr ~ HT category × Baseline Age × Time + BMI × Time, random = ~ time|ID.

For the longitudinal tau-PET analysis, we repeated our analysis including balanced weights in the mixed effects model for each individual's baseline Aβ burden, using the WeightIt package in R (*66*). Although baseline Aβ burden was not significantly different between HT users and non-users, we downweighted HT users with elevated baseline Aβ to help mitigate nonsignificant differences in baseline Aβ burden that may spuriously drive HT effects on tau accumulation.

As epidemiological studies show that exposure to HT is significantly associated with cognitive decline (*13, 33*), we tested whether the relationship between HT and PACC performance was mediated by regional tau accumulation in older women, including years of education and BMI as covariates (model 3). Our a priori mediator selection was guided by evidence that inferior temporal tau-PET rate of change is more proximal to cognitive decline than the Aβ-PET rate of change (*1*, *67*, *68*). To run the mediation analysis, participant-specific slopes were extracted from a mixed effects model for PACC and for inferior temporal tau (separately), with a random effect of participant ID and time.

Supplementary Materials

This PDF file includes:

Figs. S1 and S2

Tables S1 to S12

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