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Lifetime estrogen exposure and cognition in late life: the Cache County Study

Joshua M. Matyi, MS,[1] Gail B. Rattinger, PharmD, PhD,[2] Sarah Schwartz, PhD,[1] Mona Buhusi, MD, PhD,[1] and JoAnn T. Tschanz, PhD[1]

Abstract

Objective: Prevalence of Alzheimer's disease (AD) is higher for women, possibly influenced by sex-dependent effects of the estrogen. We examined the association between estrogen and cognitive decline in over 2,000 older adult women in a 12-year population-based study in Cache County, Utah.

Methods: The baseline sample included 2,114 women (mean age = 74.94 y, SD = 6.71) who were dementia-free at baseline and completed a women's health questionnaire, asking questions regarding reproductive history and hormone therapy (HT). Endogenous estrogen exposure (EEE) was calculated taking the reproductive window (age at menarche to age at menopause), adjusted for pregnancy and breastfeeding. HT variables included duration of use, HT type (unopposed; opposed), and time of HT initiation. A modified version of the Mini-Mental State Examination (3MS) was administered at four triennial waves to assess cognitive status. Linear mixed-effects models examined the relationship between estrogen exposure and 3MS score over time.

Results: EEE was positively associated with cognitive status ($\beta = 0.03$, $P = 0.054$). In addition, longer duration of HT use was positively associated with cognitive status ($\beta = 0.02$, $P = 0.046$) and interacted with age; older women had greater benefit compared with younger women. The timing of HT initiation was significantly associated with 3MS ($\beta = 0.55$, $P = 0.048$), with higher scores for women who initiated HT within 5 years of menopause compared with those initiating HT 6-or-more years later.

Conclusions: Our results suggest that longer EEE and HT use, especially in older women, are associated with higher cognitive status in late life.

Key Words: Cognitive decline – Estrogen – Hormone therapy – Reproductive window.

Approximately two-thirds of the 5.5 million cases of Alzheimer's disease (AD) in the United States[1] are female, suggesting that sex-specific factors may contribute to greater risk of the disease.[2] Sex-dependent differences in gonadal hormone development and synthesis have been implicated as a potential factor underlying the higher prevalence of AD in females.[3]

Endogenous estrogen exposure

Estrogen has a significant role in overall brain health and cognitive function. A review of human and animal studies suggests a role for estrogen in promoting memory and learning and in dendritic spine growth in the hippocampus and medial prefrontal cortex.[4] A study of adult female rats found that as cycling estrogen levels increased, so did the density of dendritic spines in the CA1 region of the hippocampus.[5] Synaptic growth peaked during proestrus (the period during the estrous cycle that immediately precedes estrus) and decreased when estrogen levels dropped.

Estrogen levels in women vary throughout the lifespan in relation to a woman's reproductive history, including the length of the reproductive window (time between the onset of menarche to menopause), number of pregnancies, and postpartum breastfeeding. Several studies suggest that the duration of the reproductive window can affect later cognitive health and risk for neurodegenerative disease. One study found that a longer reproductive window was associated with higher scores on a verbal fluency task in a community-based sample of 996 older adult French women.[6] Age at first menses was, however, negatively associated with scores on tasks of visual memory and psychomotor speed, and length of the reproductive window was not significantly associated with cognitive *decline* measured at 4-year follow-up. Other cross-sectional research found no association between length of the reproductive window on cognitive functioning in 760 postmenopausal Australian women aged 60 to 64 years.[7] In the Epidemiologic Catchment

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From the [1]Department of Psychology, Utah State University, Logan, UT; and [2]School of Pharmacy and Pharmaceutical Sciences, Health Outcomes and Administrative Sciences, Binghamton University, Binghamton, NY.
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Address correspondence to: JoAnn T. Tschanz, PhD, Center for Epidemiologic Studies & Department of Psychology, Utah State University, 2810 Old Main Hill, Logan, UT 84322-2810.
E-mail: joann.tschanz@usu.edu

Area (ECA) study that included women aged 31 to 94 years, lower age at the onset of menopause (hence a shorter reproductive window) was associated with a 0.03-point per year decline in the Mini-Mental State Examination (MMSE) over a 12-year period.[8] In addition, women who experienced menopause between the ages of 16 to 40 years had the largest declines in MMSE scores from baseline to follow-up, with mean differences between 2.2 points in those aged 41 to 50 years and 1.6 points for those aged 51 to 63 years.

Pregnancy and breastfeeding affect estradiol levels [9] and research has suggested an association with cognitive decline. In a sample of 89 parous British women aged 70 to 98 years, women with a cumulative history greater than the median of 27 months pregnant (and presumably higher cumulative levels of circulating estrogen over the lifespan) had a 37% reduction in AD risk compared with those below the median.[10] In the ECA study, nulliparous women, however, had significantly higher MMSE scores (0.83 [95% CI = 0.11-1.54]) compared with parous women.[8] The latter is consistent with a study examining risk of AD and number of pregnancies in an Italian sample,[11] where women who had had three or more pregnancies had a 3.2-fold higher risk of AD than nulliparous women. With respect to duration of breastfeeding, women with longer duration of breastfeeding have showed a 23% *reduced* risk of AD compared with those with shorter duration.[12] Other research has, however, found a significant negative association ($r = -0.599$) between duration of breastfeeding and performance on a planning task in a sample of 50 older adult postmenopausal women.[13]

Hormone therapy

Use of hormone therapy (HT) further impacts lifetime estrogen exposure. Several observational studies report protective benefits of HT regarding AD[14,15] and cognitive decline,[16] with strongest effects in those above age 85 years in the latter study.[16] The randomized-controlled trial (RCT) of the Women's Health Initiative (WHI) Women's Health Initiative Memory Study (WHIMS), however, concluded that in a group of 4,532 postmenopausal women, HT not only failed to reduce the risk of mild-cognitive impairment (MCI), but doubled the risk of all-cause dementia.[17] Conversely, in the randomized-controlled Kronos Early Estrogen Prevention Study (KEEPS) authors found no change in cognitive outcomes over 4 years comparing HT with placebo for 662 healthy, postmenopausal women.[18]

Discrepancies between observational studies and the above RCTs have led to hypotheses related to the initiation of HT within a ''critical window'' promoting cognitive benefit.[19,20] A review of the critical window of HT suggests that women who begin HT shortly after the onset of menopause in the perimenopausal stage may experience benefits of reduced cognitive decline as compared with those who wait a substantial period of time before starting HT.[20] Furthermore, in a group of healthy postmenopausal women, a 17-beta estradiol patch initiated close to the onset of menopause was predictive of better executive functioning compared with placebo, although this interaction was at trend-level significance.[19] In the Cache County Study, a sample of 1,769 women (mean age = 75.3 y [SD = 6.6 y]) showed those who used HT within 5 years of menopause had a 30% reduced risk of AD.[15] In addition, those women who did not start HT until 5 or more years after menopause showed no reduction in risk and those who initiated *opposed* (ie estrogen that includes progesterone) HT within 3 years of study baseline showed a trend for an increase in AD risk (adjusted HR = 1.93 [95% CI, 0.94-3.96]).

One study of a British sample of older adult women examined both endogenous and exogenous estrogen exposure over the lifespan.[10] The authors calculated lifetime estrogen exposure by taking menopausal age, minus age at menarche, and subtracting the number of months spent breastfeeding after pregnancy to account for the lack of cycling estrogen during this time. The results suggested that for each additional month of endogenous estrogen exposure, there was a 0.5% decrease in AD risk. Also, for each additional month of extended HT exposure, there was an overall 0.56% decrease in AD risk. Limitations included the small sample size and inclusion of only parous women.

Our current study examined cumulative lifetime estrogen exposure and late-life cognitive decline in a population-based sample of over 2,000 older adult women in the Cache County (Utah, USA) Study. Lifetime estrogen exposure was based on endogenous exposure (time of menarche to menopause), number of pregnancies, duration of breastfeeding, and HT use. The role of potential confounding factors such as overall health predicting cognitive outcomes was also examined.

METHODS

Participants

This research used extant data from the Cache County Study on Memory in Aging (CCSMA; see Reference 21 for a detailed description), targeting women without dementia at the baseline (wave 1) visit. The majority (99%) of the participants were white. The Institutional Review Boards at Utah State University, Duke University, and Johns Hopkins University approved all study procedures.

Procedure

Briefly, beginning in 1995 in its first wave, this study surveyed 5,092 residents (2,928 women) of Cache County, Utah, 65 years of age or older.[21] Three triennial waves of dementia ascertainment were subsequently performed over the course of 12 years to identify risk factors for AD. Demographic information including age and education, genotype at the apolipoprotein E (APOE) locus, and history of medical conditions, self-report of height and weight, medication use, family history of dementia, depression, activities of daily living, diet, and lifestyle factors including physical activity, smoking, and drinking were obtained in wave 1 and updated in subsequent waves.

A multistaged dementia screening and assessment protocol was followed in each wave. Cognitive screening was conducted at each wave using an adaptation of the 100-point

modified Mini-Mental State Examination (3MS),[22] or if the participant was unable, dementia screening with a proxy using the Informant Questionnaire for Cognitive decline (IQCODE).[23] In waves 1 and 2, individuals who scored <87 on the 3MS or whose IQCODE was above 3.27 were sent to the next stage (Dementia Questionnaire [DQ]), which consisted of an interview with a knowledgeable informant to determine dementia symptomology. Participants whose interviews suggested either (1) the presence of significant cognitive impairment or (2) possible dementia as rated by a neuropsychologist or geropsychiatrist or (3) those who were members of a randomly selected panel to complete all stages of screening and assessment were selected to complete a clinical assessment. The clinical assessment included neuropsychological testing, medical and neurological evaluation, and a clinical interview with a knowledgeable informant. Results of the clinical assessment were reviewed by a study geropsychiatrist and neuropsychologist and preliminary diagnoses of a cognitive condition (if any) were assigned. Diagnoses of dementia followed the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria.[24] Differential diagnosis of AD followed criteria specified by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[25] Diagnoses of other dementias followed standard protocol.[21] Persons who were *not* identified with dementia at a given wave were followed at the subsequent wave(s) using similar procedures, except for the elimination of the DQ stage in waves 3 and 4.

Between waves 1 and 2, all surviving female participants without dementia in wave 1 were contacted by either telephone ($n = 2{,}099$) or through an in-person interview ($n = 48$) and administered a women's health questionnaire (WHQ) regarding their reproductive history. Survey items included age at menarche and menopause, number of pregnancies and live births, cumulative months spent breastfeeding, use of HT, and history of hysterectomy or oophorectomy. Data from these 2,147 women who completed the interview formed the basis of the present analyses.

Cognition

The 3MS[22] was used to measure cognitive status at each wave. The screening test assesses five factors including psychomotor skills, memory, identification and association, orientation, and concentration and calculation, implicating a broad measure of cognition.[26] The 3MS has shown high internal consistency ($\alpha = 0.87$) and validity in identifying dementia (area under curve [AUC] = 0.94 [SE = 0.01]; $Z = 5.38$, $P < 0.01$).[27] In the CCSMA, minor adaptations were made to the 3MS,[22] for example, substituting easily verifiable items (recall of prominent current and past political figures) for those related to personal demographics. As reported previously, 3MS scores were adjusted for sensory/motor deficits, by excluding items affected by these issues, with the adjusted score calculated from the remaining percentage of correct points out of the new total points (multiplied by 100), thus retaining the original scale of 0 to 100 points.[21]

Estrogen exposure

Lifetime endogenous estrogen exposure (EEE) was calculated after the methods of Fox, Berzuini, and Knapp[10] using the reproductive window (menopausal age minus age of menarche), minus total duration of breastfeeding. If no breastfeeding was reported for parous women, 1.5 months were subtracted per pregnancy to account for mean ovulatory regulation time.[28] Exogenous estrogen exposure was generated using duration of HT (independent of dosage) at each wave and treated as a time-varying variable. In addition, type of HT was coded (none; opposed [ie, estrogen compounds that include progesterone]; unopposed [estrogen alone]) as well as the timing of first use of HT expressed in years. HT timing relative to menopause was then transformed into a categorical variable a priori to include those who did not take HT (no HT; continuous or within 1 y of menopause; between 1 and 5 y of menopause; 6 y or more after menopause).

Additional covariates

Covariates tested in statistical models were guided by previous research on variables that potentially affect both estrogen (or its effects) and cognition in late-life. These included age, level of formal education, APOE genotype (number of E4 alleles), body mass index (BMI),[29] physical exercise,[30] overall health,[3] and depression status.[31] BMI at wave 1 was based on self-reported height and weight and calculated using the formula kg/m^2. Physical activity was categorized by the recommendations for older adults provided by American College of Sports Medicine and American Heart Association (ACSM; AHA) [32] using metabolic equivalent (MET) transformations of various physical activities.[33] Designations of ''sedentary'' (no physical activity reported), ''light'' (<450 MET-min/wk), ''moderate'' (450-750 MET-min/wk), and ''vigorous'' (>750 MET-min/wk) were assigned to the data depending on the frequency and duration of physical activity. Physical activity data were not collected in wave 2; therefore wave 1 data were carried forward to ensure that all available cases were included in analyses. Overall health was ascertained by asking participants to rate their health on the day of the interview as either ''excellent,'' ''good,'' ''fair,'' or ''poor.'' Depression status was assessed with the Diagnostic Interview Schedule (DIS) of the DSM-III-R[24] and was categorized as ''no current depressive episode/no current depression medication use,'' ''no depressive episode/with depression medication use,'' ''minor depression,'' and ''major depression.''[34]

Statistical analysis

In addition to providing descriptive statistics for the sample, comparisons for participants included versus excluded in the analyses were made using chi-square tests for categorical variables and independent samples *t* tests for continuous variables. A series of linear mixed effects models were used to investigate the proposed relationships between lifetime

TABLE 1. *Baseline participant characteristics comparing those included versus excluded in analyses*

	Included ($N = 2,114$)				Excluded ($N = 540$)						
Variables	Mean	SD	*N*	%	Mean	SD	*N*	%	*t*	χ^2	*P*
Age, y[a]	74.94	6.71			78.63	7.94			10.95		<0.001
Education, y [a]	12.89	2.27			12.19	2.38			−6.38		<0.001
BMI, kg/m^2[a]	26.75	4.98			25.61	5.05			−4.43		<0.001
3MS score[a]	92.01	5.79			85.97	10.16			−17.63		<0.001
APOE										0.04	<0.001
No E4			1,460	70			345	69			
1 or more E4			629	30			152	31			
Physical activity[a]										16.54	0.001
Sedentary			35	2			11	3			
Light			549	31			136	40			
Moderate			999	56			152	45			
Vigorous			187	11			38	12			
Depression[a]										9.12	0.028
No dep/no meds			1,321	63			359	67			
No dep/meds			29	1			13	2			
Minor			247	12			45	8			
Major			516	24			121	23			
Self-reported health[a]										60.22	<0.001
Excellent			577	28			86	17			
Good			1,217	58			281	56			
Fair			274	13			108	22			
Poor			29	1			24	5			

3MS, Modified Mini-Mental State examination; APOE, apolipoprotein E; BMI, body mass index; depression is coded as follows: No dep/no meds (no depression diagnosis and not on antidepressants); No dep/meds (no depression diagnosis but current taking antidepressants); Minor (diagnosis of minor depressive episode via DSM-III-TR); Major (diagnosis of major depressive episode via DSM-III-TR).
[a]Variables significant at $P < 0.05$ level for *t* test/χ^2 test of independence.

estrogen exposure and cognitive decline. The first model examined EEE; the second model examined EEE and duration of exogenous HT exposure (time varying); the third model examined EEE and type of HT (none, unopposed, opposed); and the fourth model examined EEE and timing of HT initiation relative to menopause. Finally, as a substantial number of participants discontinued HT use between waves 3 and 4 (coinciding with the FDA black box warning),[35] we examined in a subset of participants, any effects of stopping HT use on 3MS scores. For these analyses, a three-level categorical variable was calculated to capture (1) those who used HT continually through wave 3 but discontinued use at wave 4, (2) those who used HT continually through both wave 3 and wave 4, and (3) those who never used HT.

In addition to examining fixed effects, mixed effects models address within-participant correlation and random effects inherent in longitudinal data.[36] Furthermore, these models allow for missing data across time points and do not exclude cases on a list-wise basis. The inclusion of each variable/covariate was examined for improvement in model fit ($P < 0.05$) by comparing negative two log-likelihood values for nested models. All statistical models employed SPSS version 23.

RESULTS

Out of 2,654 eligible women to be administered the WHQ, 521 women did not complete the interview. Of the remaining 2,133 women, 19 had unknown cognitive status at baseline (screened positive on cognitive measures but failed to complete additional assessments) and were excluded from the present analyses. This resulted in a final sample of 2,114 women. Mean (SD) age of the sample was 74.94 (6.71) years and mean (SD) education was 12.89 (2.27) years. Women who were included in the analyses were among other factors, younger, had completed more years of education, were more physically active, had higher BMI, and had significantly higher 3MS scores at baseline compared with those who were excluded (see Table 1).

The mean years of endogenous estrogen exposure (EEE) for the sample was 32.99 (SD = 6.89) with a range of 2 to 61 years. Table 2 includes descriptive statistics for variables included in deriving EEE, including age at menarche and age at menopause. With respect to HT use, 833 of the 2,114 women included in the EEE analyses were never on HT. Compared with never HT users, women who ever used HT were significantly younger (mean age of 73.51 vs 77.14), had completed more education (mean 13.06 vs 12.63 y), had higher 3MS scores (mean 93.06 vs. 90.40), were significantly more physically active, and had higher frequency of major depression at baseline (data not shown).

Among HT users, Table 3 shows descriptive statistics for timing of HT initiation, HT duration, and HT type across all four waves. For women who were not using HT at baseline, the majority (>95%) did not initiate HT across the remaining waves. For women who took HT at baseline, the pattern of use across the remaining waves generally reflected either continued use with the same HT type (ie, women using unopposed HT at baseline continued to use unopposed HT if taking HT at subsequent waves; waves 1-2 = 94%; waves 2-3 = 94%; waves 3-4 = 91%) or a shift to discontinuing HT use (waves

TABLE 2. *Descriptive statistics for endogenous estrogen variables*

Variables	Mean	SD	Low value	High value
Endogenous estrogen exposure, y	32.99	6.89	2	61
Age at menarche, y	13.16	1.60	8	20
Age at menopause, y	47.59	6.82	16	78
Total pregnancies, *n*	4.70	2.63	0	20
Total live births, *n*	4.06	2.19	0	14
Total of children breastfed, *n*	2.41	2.36	0	14
Total months of breastfeeding, *n*	14.20	17.60	0	60

1-2 = 43%; waves 2-3 = 57%; waves 3-4 = 86%). The largest decrease in HT use was seen between waves 3 and 4, where 86% of women who were using HT at baseline stopped. This reduction in HT use chronologically coincided with the FDA ''black box'' warning placed on HT[35] after the WHI (FDA black box: 2002; wave 4 initiation: 2004).

Model 1—endogenous estrogen exposure and cognition

In the unadjusted model, EEE duration was significantly associated with 3MS such that for each additional year of EEE there was a 0.05-point higher score on the 3MS ($P = 0.008$). With the inclusion of covariates, EEE remained a predictor of overall 3MS score ($P = 0.054$) but was not predictive of rate of change in 3MS. Table 4 shows the results for the unadjusted and fully adjusted mixed models.

Model 2—hormone therapy and cognition

In an unadjusted model with EEE duration, time and time^2, HT duration (in years) was significantly associated ($P = 0.046$) with 3MS score. For each additional year of HT duration there was a 0.02-point higher score on the 3MS. HT duration was, however, modified by age (interaction: $P = 0.024$). To illustrate the nature of the interaction, a dichotomous age variable (median split of 65-74 vs 75 or older) was entered in place of the continuous age variable in the fully adjusted model. Results showed that in older women, higher total estrogen duration was associated with higher 3MS scores, but the opposite pattern was found in women in the younger age group. Figure 1 displays the interaction between HT duration and age group on the 3MS. Table 5 presents the unadjusted and fully adjusted models.

TABLE 3. *Descriptive statistics for hormone therapy (HT) variables*

			Type of HT use		
Variables	Mean	SD	None *N* (%)	Unopposed *N* (%)	Opposed *N* (%)
HT initiation from menopause, y	5.92	9.09			
HT duration, y					
Wave 1	13.18	11.77	833 (41)	777 (37)	450 (22)
Wave 2	2.48	1.25	1,160 (64)	459 (25)	208 (11)
Wave 3	2.44	2.04	909 (72)	271 (21)	88 (7)
Wave 4	2.41	1.08	733 (91)	68 (8)	10 (1)

TABLE 4. *Unadjusted and adjusted models for 3MS with endogenous estrogen exposure (EEE)*

	Model 1A		Model 1B		Model 1C	
Variable	β	Sig.	β	Sig.	β	Sig.
Intercept	91.17	0.001	102.92	0.001	101.86	0.001
Time	−0.01	0.889	0.24	0.001	0.25	0.001
Time^2	−0.07	0.001	−0.06	0.001	−0.07	0.001
EEE	0.05	0.008	0.02	0.088	0.03	0.054
Baseline age			−0.29	0.001	−0.29	0.001
Education			0.62	0.001	0.62	0.001
APOE						
1 or more E4 allele			−0.76	0.001	−0.64	0.002
No E4 (ref.)			—	—	—	—
Physical activity						
Light			1.64	0.001	1.60	0.001
Moderate			1.90	0.001	1.90	0.001
Vigorous			1.91	0.001	1.93	0.001
Sedentary (ref)			—	—	—	—
Self-reported health						
Excellent			1.46	0.005	1.82	0.001
Good			1.35	0.007	1.80	0.001
Fair			0.63	0.226	0.92	0.080
Poor (ref.)			—	—	—	—
Depression						
No dep/with meds			−0.57	0.148		
Minor			0.01	0.976		
Major			−0.35	0.088		
No dep/no meds (ref.)			—	—		
Baseline BMI			0.01	0.739		

3MS, Modified Mini-Mental State examination; APOE, apolipoprotein E; BMI, body mass index; EEE, endogenous estrogen exposure.

Model 3—hormone therapy type

Use of either type of HT (opposed or unopposed) was associated with higher 3MS scores ($P = 0.001$) when compared with no HT use in the unadjusted model. Women who used unopposed estrogen scored 0.57 points higher ($P = 0.002$) on the 3MS and women who used opposed estrogen scored 0.93 points higher ($P = 0.001$) on the 3MS than women not using HT. Type of HT was, however, no longer significant ($P = 0.365$) with the inclusion of significant covariates of age, EEE, education, APOE genotype, physical activity, and overall health (see Table 6).

Model 4—timing of hormone therapy

The timing of HT use relative to menopause was significantly associated with 3MS score ($P = 0.001$). Those who initiated HT regardless of time since menopause had higher 3MS scores than nonusers. In the fully adjusted model and compared with nonusers of HT, women who used estrogen continuously or within 5 years of menopause scored 1.02 and 1.23 points higher on the 3MS, respectively, whereas those who initiated HT 6 or more years after menopause scored 0.64 points higher on the 3MS (see Table 7).

Analyses of discontinuing HT use

Women who used estrogen through wave 3 or wave 4 were younger ($P < 0.001$), had higher education ($P < 0.001$), higher 3MS at baseline ($P < 0.001$), more physical activity ($P < 0.001$), and higher levels of depression ($P = 0.001$)

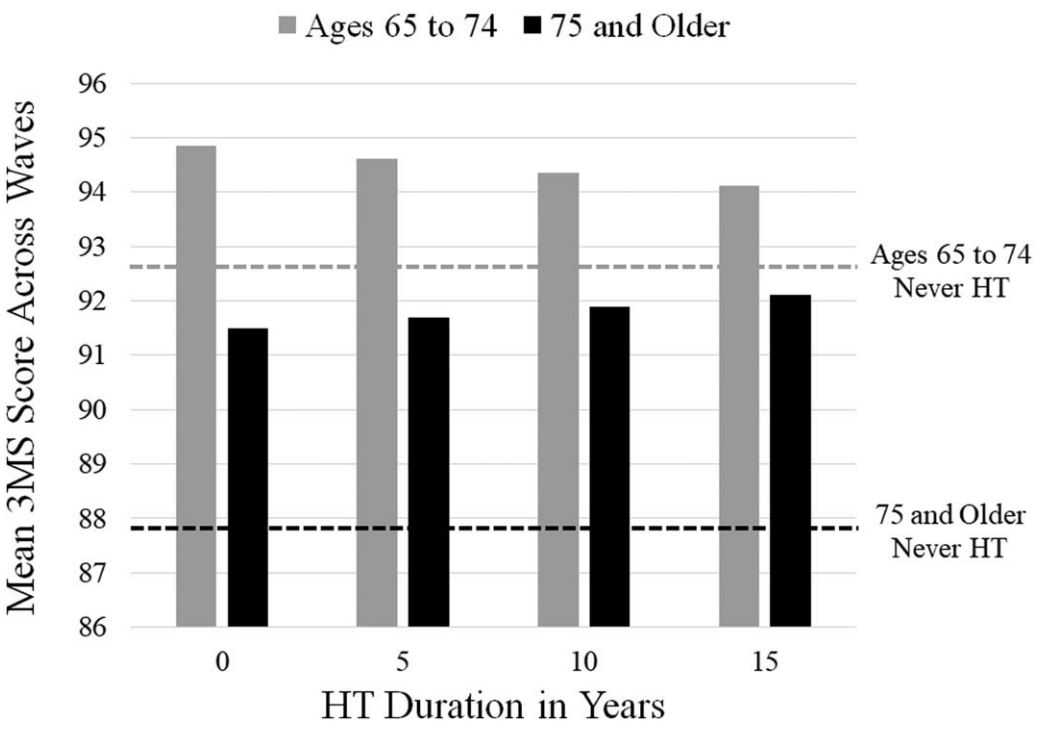

FIG. 1. Interaction between duration of hormone therapy (HT) use and age on Modified Mini-Mental State Examination (3MS) scores with greater benefit for longer duration of HT in women who were above the median of the sample (age 75 or older). Reference lines are added for comparison showing the estimated means of both age groups for women who never used HT.

compared with those who never used HT. Comparing those who used HT through wave 3 to those who used through wave 4, no significant differences were found in any variable (data not shown). In a mixed model including all relevant covariates from previous models, both HT groups (continuous use through wave 3 and continuous use through wave 4) had significantly higher 3MS scores through waves 3 and 4 (HT through wave 3: $\beta = 0.89$, $P = 0.037$; HT through wave 4: $\beta = 1.78$, $P = 0.004$) compared with never users. In a model restricted to HT users only, a comparison between HT users through wave 3 to HT users through wave 4 was not significant ($\beta = -0.78$, $P = 0.142$).

TABLE 5. *Unadjusted and adjusted models for 3MS with endogenous and exogenous estrogen duration*

	Model 2A		Model 2B		Model 2C		Model 2D	
Variable	β	Sig.	β	Sig.	β	Sig.	β	Sig.
Intercept	90.70	0.001	115.64	0.001	118.68	0.001	102.89	0.001
Time	0.04	0.554	−0.01	0.891	−0.04	0.573	0.24	0.001
Time^2	−0.07	0.001	−0.06	0.001	−0.07	0.001	−0.07	0.001
EEE duration	0.05	0.002	0.04	0.007	0.04	0.021	0.03	0.070
HT duration	0.02	0.046	0.01	0.321	−0.50	0.001	−0.26	0.028
Baseline age			−0.33	0.001	−0.37	0.001	−0.30	0.001
HT duration × baseline age					0.01	0.001	0.01	0.024
Education							0.63	0.001
APOE								
1 or more E4 allele							−0.54	0.011
No E4 allele (ref)							—	—
Physical activity								
Light							1.65	0.001
Moderate							1.91	0.001
Vigorous							1.96	0.001
Sedentary (ref.)							—	—
Self-reported health								
Excellent							1.78	0.001
Good							1.71	0.001
Fair							0.82	0.134
Poor (ref.)							—	—

3MS, Modified Mini-Mental State examination; APOE, apolipoprotein E; EEE, endogenous estrogen exposure; HT, hormone therapy.

TABLE 6. *Unadjusted and adjusted models for 3MS trajectory with hormone therapy (HT) type*

	Model 3A		Model 3B	
Variable	β	Sig.	β	Sig.
Intercept	92.20	0.001	101.57	0.001
Time	0.05	0.413	0.27	0.001
Time^2	−0.07	0.001	−0.07	0.001
HT type				
Unopposed	0.57	0.002	0.28	0.128
Opposed	0.93	0.001	−0.01	0.997
No HT (ref.)	—	—	—	—
EEE duration			0.03	0.027
Baseline age			−0.29	0.001
Education			0.62	0.001
APOE				
1 or more E4			−0.60	0.004
No E4 (ref.)			—	—
Physical activity				
Light			1.63	0.001
Moderate			1.89	0.001
Vigorous			1.93	0.001
Sedentary (ref.)			—	—
Self-reported health				
Excellent			1.88	0.001
Good			1.85	0.001
Fair			0.96	0.069
Poor (ref.)			—	—

3MS, Modified Mini-Mental State examination, APOE, apolipoprotein E, EEE, endogenous estrogen exposure, HT, hormone therapy.

TABLE 7. *Unadjusted and adjusted models for 3MS trajectory with hormone therapy (HT) timing*

	Model 4A		Model 4B	
Variables	β	Sig.	β	Sig.
Intercept	91.32	0.001	99.40	0.001
Time	−0.03	0.677	0.26	0.001
Time^2	−0.07	0.001	−0.07	0.001
HT initiation timing				
Within 1 y	2.22	0.001	1.02	0.001
Within 5 y	2.54	0.001	1.23	0.001
6 y or more	1.86	0.001	0.64	0.017
No HT (ref.)	—	—	—	—
EEE duration			0.03	0.035
Baseline age			−0.26	0.001
Education			0.61	0.001
APOE				
1 or more E4			−0.51	0.017
No E4 (ref.)			—	—
Physical activity				
Light			1.60	0.001
Moderate			1.87	0.001
Vigorous			1.93	0.001
Sedentary (ref.)			—	—
Self-reported health				
Excellent			1.76	0.002
Good			1.66	0.003
Fair			0.80	0.156
Poor (ref.)			—	—

3MS, Modified Mini-Mental State examination; APOE, apolipoprotein E; EEE, endogenous estrogen exposure; HT, hormone therapy.

DISCUSSION

In a sample of 2,114 women from a longitudinal, population-based study, longer duration of endogenous estrogen was associated with higher late-life cognitive status. The results with EEE were consistent with the results of other studies, demonstrating an association of a longer reproductive window with better cognitive health in late life.[6,8,10] Estrogen has been shown to be neuroprotective in cellular and animal models,[37] promoting brain-derived neurotrophic factor (BDNF) and increasing synaptic spine density in the hippocampus. It is possible that these effects help maintain neural health into late life. In addition, although the effect is small, it may have important implications for those who experience amenorrhea (no menstrual cycles) or early menopause (of surgical or nonsurgical origin).

When examining whether the beneficial effects of EEE were extended with HT, results varied by age. Older women (75 y and older) seemed to benefit from longer duration of HT compared with those who were younger (65-74 y). An earlier examination of this issue in the CCSMA data from wave 1 to 2 was similar, in that women older than 75 years had significant cognitive benefit from HT use, though duration was not directly measured.[16] We also found greatest benefit of HT when initiated within 5 years of menopause, consistent with a critical window of initiating HT.[20] Our results, however, also suggested that HT initiated more than 5 years postmenopause still resulted in beneficial effects compared with those who never used HT. Other factors may modify the effects of HT. As reviews discuss,[3,38] the differential effects of HT timing on cognition may depend on the health of the participant, such that healthy individuals (including less brain disease) will experience cognitive benefits of HT. As participants age and exhibit greater incidence of age-related health concerns, the initiation of HT, however, may be ineffective or even deleterious to cognitive health. Note, a recent paper of 84,739 women in Finland found a slight (9%-17%) increase in AD with long-term use of HT.[39] Although the authors included age of initiation, time from menopause was not examined. Other factors that may modify the effects of HT are dosage (higher doses posing greater risk of thrombosis), preparation (with or without progesterone), and APOE genotype with some suggestion that APOE E4 carriers show less cognitive benefit from HT.[40]

Notably, in the present study, HT use (or endogenous estrogen exposure) did not affect *rate* of change in cognition, suggesting that any beneficial effects of estrogen occur earlier in the lifespan. This is consistent with data collected, such that the majority of HT duration or use took place before the study. Alternatively, confounding factors (healthy user bias) in our sample may have played a role as women using HT had higher 3MS scores at baseline, were younger, had completed more years of formal education, and were more physically active compared with women not using HT. We did attempt to address these concerns by statistically controlling for relevant factors in all analyses. No significant interaction in endogenous estrogen exposure or HT and APOE genotype was observed. Furthermore, there was a significant reduction in HT use between waves 3 and 4 of the study. This reduction chronologically coincided with the FDA ''black box'' warning placed on HT [35] that followed the discontinuation of the

WHI HT trial [41] due to a greater incidence of coronary heart disease, stroke, and breast cancer in the treatment groups. This event may have resulted in earlier termination of HT by participants in our sample. In analyses comparing those who terminated HT use after wave 3 to those who continued use through wave 4, no significant difference in 3MS score was found. This suggests that any beneficial effects of HT on cognition occurred before the drop-out and that discontinuation of long-term HT use had little to no effect on cognition, at least within the 3-year period of observation in this study (wave 3 to wave 4).

Limitations of the present study included the exclusion of women who did not complete the WHQ, who at baseline were older, had completed fewer years of education, and had lower cognitive status than women included in the current analyses. Therefore, with our younger, highly educated sample, the use of the 3MS as a cognitive measure may introduce a ceiling effect and have reduced sensitivity to change.[22] In addition, although the 3MS allows for a general measure of cognitive ability, it is limited regarding assessment of specific cognitive domains. Another potential limitation is the reliance on retrospective recall of age at menarche and menopause to determine duration of the reproductive window, as well as other reproductive variables (eg, duration of breastfeeding). It is possible that those with worse cognitive status underestimated age at menopause, resulting in an erroneously shorter reproductive window. The reliability of retrospective report of estrogen variables (eg, age at menarche and menopause; HT initiation) has been shown to be moderate to strong, although the reports of older women ($\geq$66) are less reliable.[42] The strengths of the present study include a large, population-based sample collected longitudinally over a significant duration of 12 years of follow-up. The present study also included relevant covariates that have previously been associated with endogenous estrogen, HT, and cognition that have not been well investigated. Although the present study highlights the effects of the reproductive window and HT on late-life cognition, future research may focus on specific reproductive health-related variables associated with endogenous estrogen and HT efficacy (eg, cancers and cancer treatment).

CONCLUSIONS

In conclusion, longer duration of endogenous estrogen is associated with better cognitive status in older adult women. These effects are extended with HT use, particularly among the oldest women in our sample. In addition, women who initiated HT earlier showed higher cognitive test scores than those who initiated HT later, providing some support for the critical window hypothesis of HT. Future research might investigate factors known to disrupt endogenous estrogen (eg, cancer) or may target the initiation of HT in late-life, comparing health-related factors between participants to help elucidate the effects of HT on late-life cognition.

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