Prospective study of reproductive span and menopausal hormone therapy and cognitive decline over 8 years in the Nurses' Health Study

Namuunaa Juramt, MPH,[1] Jae H. Kang, ScD,[1] Dong D. Wang, MD, ScD,[1,2] Chirag M. Vyas, MBBS, MPH,[3] Cheng Peng, ScD,[1] Sharon Curhan, MD,[1] Erica T. Warner, ScD, MPH,[4] Oana A. Zeleznik, PhD,[1] Bernard A. Rosner, PhD,[1,5] Molin Wang, PhD,[1,5,6] Meir J. Stampfer, MD, PhD,[1,2,6] Francine Grodstein, ScD,[7] Olivia I. Okereke, MD,[1,3,6] and Audrey Heather Eliassen, ScD[1,2,6]

Abstract

Objectives: Higher endogenous estrogen may be associated with better cognition, but associations with menopausal hormone therapy (MHT) have been inconsistent, possibly due to differences in the timing of use. This prospective cohort study aimed to evaluate the associations between reproductive span, as a proxy for endogenous estrogen history, MHT use, and cognitive function.

Methods: We assessed cognitive change (1995-2008) with four telephone interviews (primary outcome: global composite score average of six test *z*-scores) in 14,217 Nurses' Health Study participants (mean age 74.3 y) and examined associations with reproductive span ([age at menopause]−[age at menarche]), and MHT use duration, separately by 0-10 years, and 11+ years after menopause.

Results: A longer reproductive span was associated with better cognitive trajectories (mean annual rate of change difference [95% CI]$_{41\text{-}46 \text{ vs. } \leq 33 \text{ y}} = 0.008$ [0.00005, 0.015]; *P*-trend = 0.02). MHT use 0-10 years postmenopause was associated with faster decline (mean difference$_{8\text{-}10 \text{ vs. } 0 \text{ y}} = -0.007$ [−0.016, 0.002]; *P*-trend = 0.02); use during 11+ years postmenopause was not associated.

Conclusions: Although MHT use was not inversely associated, a longer reproductive span was associated with better cognitive trajectories.

Key Words: Cognitive decline, Endogenous estrogen history, Menopausal hormone therapy, Nurses' Health Study, Reproductive factors, Reproductive span.

(*Menopause* 2026;33:000–000)

Cognitive decline can be considered a preclinical marker of dementia. Women experience faster cognitive decline than men, and it is hypothesized that sex hormones may contribute to this disparity.[1] Estrogen plays an important role in the regulation of cognition and neurogenesis in females,[2] with potential beneficial effects of estrogen on the central nervous system.[3-6] Estrogen is

Received for publication August 1, 2025; accepted February 6, 2026.

From the [1]Department of Medicine, Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA; [3]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA; [4]Clinical Translational Epidemiology Unit, Department of Medicine, Mongan Institute, Massachusetts General Hospital, Boston, MA; [5]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA; [6]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; and [7]Department of Internal Medicine, Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL.

Funding/Support: This work was supported by the National Institutes of Health [UM1 CA186107, AG 13482, AG 15424].

Financial disclosure/Conflicts of interest: C.M.V. has past financial relationships with Haleon and Harvard Medical School, has an ongoing institutional financial relationship with Alzheimer's Association, and receives research salary support from the Mars Edge, Nestle Purina PetCare Company, and American Foundation for Suicide Prevention. S.C. has current institutional financial relationships with the National Institute of Health and GlaxoSmithKline. E. T.W.'s institution has a Pfizer research grant. O.A.Z. has ongoing institutional financial relationships with the National Institute of Health and the Department of Defense, and Dr Zeleznik's spouse is employed by Novartis. F.G. has an ongoing financial relationship with Up-to-Date. In the prior 36 months, O.I.O. has been a member of the Board of Directors of the American Association for Geriatric Psychiatry and has received grant support from the Alzheimer's Association. The other authors have nothing to disclose.

N.J. J.H.K., O.I.O., and A.H.E. contributed equally.

This study was previously presented at the Alzheimer's Association International Conference, Philadelphia, PA, July 2024.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.menopause.org.

Address correspondence to: Namuunaa Juramt, MPH, Department of Medicine, Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115. E-mail: nhnju@channing.harvard.edu.

eISSN: 1530-0374
DOI: 10.1097/GME.0000000000002782

associated with enhanced cholinergic activity, the protection of dopaminergic neurons, and the maintenance of mitochondrial function, all of which are vital pathways for brain health and are believed to play key roles in the aging process of cognition.[2]

Reproductive span, defined as the time between age at menarche and age at menopause, represents an important aspect of endogenous estrogen history.[7] Observational studies found inconsistent results between reproductive span and cognition. Some found beneficial associations,[8-15] while other studies found adverse associations or null results.[16-20] In addition, many of the studies were limited by sample sizes, study design, number of cognitive tests and domains, short follow-up, or a focus on early-onset dementia.

Studies of the effects of exogenous hormones, particularly menopausal hormone therapy (MHT), on cognition have also yielded conflicting results. The Women's Health Initiative Memory Study, a large randomized clinical trial, showed a deleterious effect of MHT in relation to cognition.[21] Some studies suggested that the adverse association may be due to the timing of the MHT.[22] According to the "critical period" hypothesis, MHT started within 10 years of menopause may be neuroprotective[23,24]; however, relatively few studies have addressed the issue of timing, and research findings are mixed.[25-28] It remains unclear whether the duration of MHT use and its relation with cognition may depend on the timing of use with respect to the menopause transition.

Given the major inconsistencies in prior research regarding reproductive span, timing of MHT, and their associations with cognitive decline and the critical need to better understand the etiology of cognitive decline in women, who experience clinically significant faster cognitive decline than men,[1] more research is urgently needed for better understanding and mitigating the risk of cognitive decline in older women undergoing menopause transition. Therefore, we used over 30 years of prospectively collected data from 14,217 participants of the Nurses' Health Study (NHS), a large cohort with detailed and regularly updated information on menarche, menopause, and MHT, particularly from before, during, and after the menopause transition. We evaluated reproductive span, age at menarche, age at menopause, and surgical menopause, and their associations with cognition. We hypothesized that a longer reproductive span, as a proxy for the endogenous estrogen history, is associated with better cognitive maintenance. We posit that a more prolonged estrogen history confers neuroprotection and thus better cognitive performance. In addition, we hypothesized that the timing of MHT influences cognition. Consistent with the critical period hypothesis, we expect that women who started MHT within 10 years of menopause will show more favorable cognitive maintenance.

METHODS

Study population

The NHS began in 1976 with 121,700 female registered nurses aged 30-55 years enrolled. Questionnaires were mailed every 2 years, with more than 85% follow-up maintained.[29] Between 1995 and 2001 (which is referred to as "baseline" henceforth), 23,565 participants, aged 70 years or older, and free of stroke, were selected for the cognitive function substudy. Among them, 19,395 participants completed the baseline cognitive assessment interview. We further excluded women who did not report natural menopause or surgical menopause due to bilateral oophorectomy (we excluded those who reported unilateral oophorectomy or menopause due to radiation or chemotherapy because their age of menopause could not be determined accurately), missing information on age at menopause, age at menarche, or MHT use status. After these exclusions, 14,217 participants were included in the analysis (Fig. 1). The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Ascertainment of reproductive span and MHT

Reproductive span was defined as the time between age at menarche and age at menopause. For those who had surgical menopause due to bilateral oophorectomy, their age at menopause was defined as the age at surgery. Age at menarche was ascertained on the 1976 questionnaire, where participants were asked: "At what age did your menstrual periods begin?" and was recorded as a continuous variable. Information on age and type of menopause was collected biennially from 1976. Information on reproductive factors was found to be highly accurate in a validation study that compared participants' self-reports with their medical records. Among women who reported surgical menopause on the 1976 questionnaire, 95% accurately reported their age at menopause to within 1 year. Similarly, among women reporting natural menopause, 82% provided accurate age information to within a 1-year range.[30] Although self-reported reproductive variables were subject to recall error, both age at menarche and age at menopause were recorded over 15 years before the outcome cognitive assessment. Consequently, this misclassification is expected to be nondifferential with respect to the outcome. Nondifferential misclassification likely biased the effect estimate toward the null, implying that our observed results are likely conservative.[31] In addition, reproductive variables in the NHS have previously demonstrated robust associations with other health outcomes such as breast cancer risk, consistent with findings from a broad range of epidemiologic studies.[32]

We collected detailed information on MHT since 1976. On each biennial questionnaire, participants were asked whether they had ever used MHT and, if so, the type of hormone used most recently during the previous 2 years. Women were asked about the use of specific preparations, including oral and nonoral preparations. This information was used to categorize participants by duration of use and the type of hormone used. Because studies focusing on the critical period hypothesis found significant differences in various outcomes between those

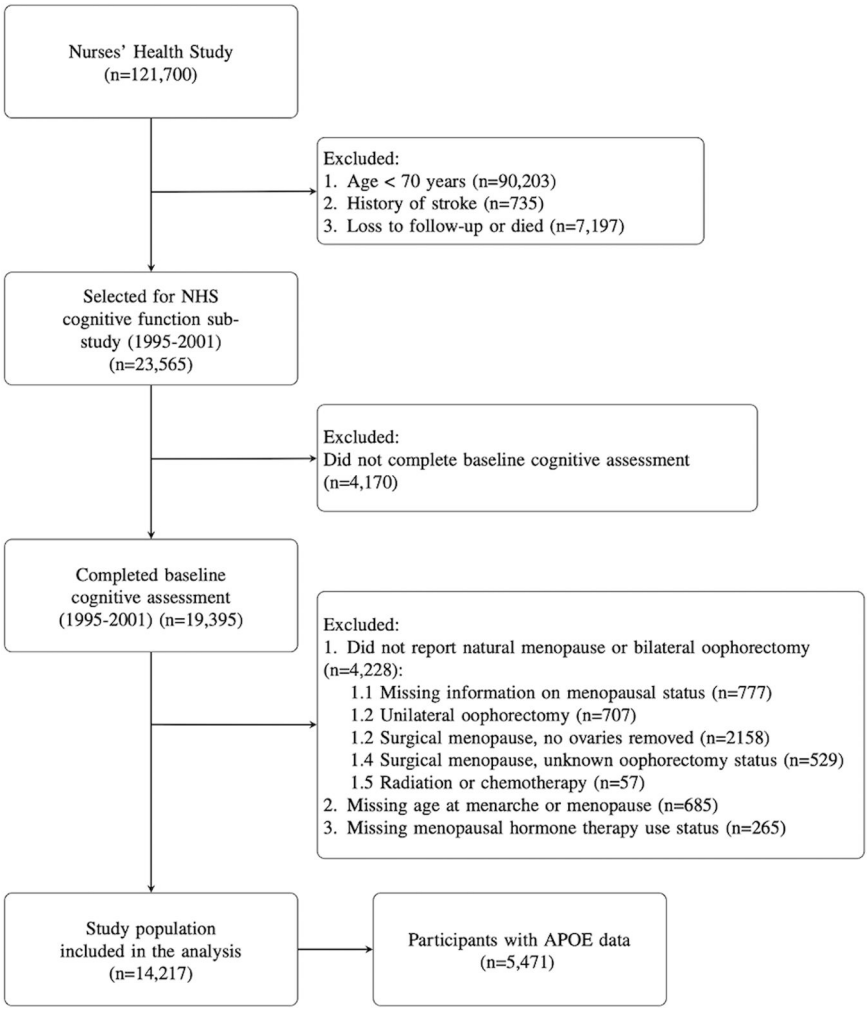

FIG. 1. Flow chart of the study population attrition. APOE, apolipoprotein E; NHS, Nurses Health Study.

who used MHT in the 0-10 years after menopause (referred to henceforth as "MHT use within the 10-y window of menopause") versus in the period 11 or more years postmenopause (referred to henceforth as "MHT use outside the 10-y window of menopause"),[22] our primary analysis of MHT focused on duration of MHT use, separately in those two periods. In a secondary analysis, we examined the associations of estrogen-only hormone therapy and estrogen and progestin combined hormone therapy separately. Participants who reported that menopause occurred before the 1976 questionnaire (53%) and for whom we were unable to obtain their accurate date of initiation of MHT, we assumed that their start dates of MHT were within the 2 years of their reported age of menopause, given that in our study population, the majority of women initiated MHT during this period. As a supplemental analysis, we examined the association between duration of MHT use and cognitive performance among participants who reported menopause after the 1976 questionnaire (n = 5,088), for whom we were able to accurately determine the initiation date of MHT. The duration of MHT use was categorized as 0 years, 1-5 years, 6-10 years, and 10 or more years. A timeline demonstrating the collection of major exposure and outcome variables is presented in Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/MENO/B502.

Genetic data for apolipoprotein E (APOE) were obtained through blood samples (1989-1990), or buccal cell samples (2002-2004) as previously described.[33] APOE genotype was imputed from multiple genome-wide association studies on various genome-wide association study chips.[34] We had APOE information for 5,471 participants in this analysis.

Cognitive function assessment and its validity

The NHS cognitive assessment included six tests: (1) the Telephone Interview for Cognitive Status (TICS),[35] which is a telephone adaptation of the Mini-Mental State Examination; (2) immediate and (3) delayed recall of the

East Boston Memory Test[36]; (4) animal naming in 60 seconds[37]; (5) delayed recall of the TICS 10-word list; and (6) digit span backwards. The primary outcome of our study was a global composite score. The composite scores were created by first standardizing each cognitive test score into a *z*-score (with a mean of 0 and an SD of 1). Next, all six *z*-scores were averaged to form the composite score. Secondary outcomes included four cognitive domains[28]: (1) general cognition: TICS score; (2) verbal memory: composite score averaging the *z*-scores of immediate and delayed recalls of the TICS 10-word list, and immediate and delayed recalls of East Boston Memory Test; (3) category fluency: animal naming; and (4) attention: digit span backwards.

The NHS cognitive assessment has been extensively validated. We found a correlation of 0.81 comparing the global scores of the in-person neuropsychological testing versus the telephone interview. Poor cognition based on the NHS cognitive assessment predicted a higher dementia risk.[38] As an indirect validation, APOE-e4 carriers scored 0.55 units lower compared with noncarriers.[39]

Covariates

We included a priori determined risk factors for cognitive decline as covariates based on established findings. All included covariates were self-reported through a questionnaire and updated biennially as of the questionnaire before the baseline cognitive assessment. Demographic factors included age (years), education (registered nurse diploma, bachelor's degree, graduate degree), and husbands' education (high school graduate or less, college graduate, graduate education), which was included as an indicator for socioeconomic status. Lifestyle factors included body mass index (BMI) (<22, 22-24.9, 25-29.9, 30+ kg/m^2), alcohol consumption (nondrinker, 1-14 g/wk, 15 g/wk), smoking status (current, past, never), multivitamin use (yes, no), and physical activity (total energy expenditure in metabolic equivalents/wk). Mental health status was assessed by antidepressant use (yes, no), and the Mental Health Inventory-5 (MHI-5) subscale of the Medical Outcomes Short Form-36, dichotomized using a validated cutoff of 52 (≤ 52 vs. >52).[40] Comorbidities included high blood pressure (yes, no), elevated cholesterol (yes, no), myocardial infarction (yes, no), and diabetes (yes, no); reproductive factors included menopause type (natural, surgical), parity (no. pregnancies $\geq$ 6 mo), age at first birth (years), and oral contraceptive use (≥ 2 y).

Statistical analysis

Linear mixed-effects models were used to model mean differences in the annual rate of change in cognitive performance over time; in these models, the exposure, time, and a term for the interaction of exposure and time are included. The primary estimates of interest were differences in slopes of change over time associated with each risk factor, represented as the beta coefficient in the exposure × time variable (eg, interaction term of reproductive span in years × time). Time was modeled as a continuous variable representing years between the first cognitive assessment and subsequent cognitive assessments. All models included random effects for intercept and time, were multivariable-adjusted models, and incorporated the correlation between cognitive assessments within the same subject over time using unstructured covariance structures. Linear mixed-effects models handle missing data by utilizing all available cognitive assessments for each participant, under the assumption that data are missing at random.[41] Therefore, participants were not required to complete all follow-up assessments to be included in the analysis. The effect estimates reflect the mean difference in annual rate of change in cognitive performance over time based on all available data points. Tests of trend were performed by evaluating the significance of a variable representing the median value for each quintile of the relevant exposure as a continuous variable in the models. Proc MIXED in SAS (SAS 9.4, SAS Institute Inc.) was used for analyses.

Subgroup analyses

For reproductive span, we tested effect modifications by MHT duration, APOE-e4 status (carrier vs. noncarrier), BMI, and surgical menopausal (yes vs. no). For MHT, we tested effect modification by APOE-e4 status. The interaction terms were modeled as three-way interactions between reproductive span/MHT duration, the factor of interest, and time to examine the effect modifications. In addition, to assess whether the observed associations differed based on the type of menopause, subgroup analyses were also conducted in participants with natural menopause only or with surgical menopause (bilateral oophorectomy) only.

Secondary analyses

We performed three secondary analyses. First, due to the relatively small cognitive decline observed over time and to reduce measurement error, we performed secondary analyses using linear regression models by modeling the outcome data as the average of cognitive scores from the available assessments. Second, telephone interviews are dependent on hearing ability[42]; therefore, we further conducted sensitivity analyses excluding participants who reported having hearing difficulty. Third, we excluded participants who scored in the bottom 10% global scores (n = 1,231) at the first cognitive assessment for sensitivity analyses, to evaluate whether associations would be similar when including those with and without likely cognitive impairment.

RESULTS

Reproductive span in 14,217 participants was categorized into approximate quintiles, with the lowest reproductive span quintile (Q1) being ≤ 33 years, and the highest quintile (Q5) having a span of 41-46 years (Table 1). The overall mean age was 74.3 years at the first cognitive assessment. Age at menopause differed substantially based on reproductive span quintiles, with 42.3 years for Q1 and 53.6 years for Q5. Participants in

TABLE 1. Characteristics of participants at first cognitive assessment (1995-2001) by reproductive span quintiles (N = 14,217)

	Overall	Reproductive span[a]				
	(N = 14,217)	Q1: ≤ 33 y (n = 2,820)	Q2: 34-36 y (n = 3,152)	Q3: 37-38 y (n = 3,127)	Q4: 39-40 y (n = 2,877)	Q5: 41-46 y (n = 2,241)
Age, y	74.3 (2.3)	74.3 (2.3)	74.1 (2.3)	74.3 (2.3)	74.5 (2.3)	74.5 (2.3)
White, %	95	94	95	95	95	94
Married, %	81	81	80	81	81	82
Age at menopause, y	49.1 (4.5)	42.3 (4.7)	48.3 (1.6)	50.3 (1.3)	51.8 (1.2)	53.6 (1.1)
Age at menarche, y	12.7 (1.4)	13.2 (1.6)	13.1 (1.5)	12.8 (1.3)	12.4 (1.2)	11.8 (1.1)
Surgical menopause, %	20	50	21	13	9	7
Any use of MHT, %	51	68	53	47	41	39
Duration of MHT within the 10-y window, y	1.9 (2.9)	3.0 (3.4)	2.0 (3.0)	1.6 (2.7)	1.4 (2.4)	1.4 (2.6)
Duration of MHT outside the 10-y window, y	3.7 (5.8)	6.7 (8.6)	3.6 (5.4)	3.1 (4.8)	2.5 (4.1)	2.3 (3.7)
Parity, no. pregnancies ≥ 6 mo	3.2 (1.8)	2.9 (1.8)	3.1 (1.8)	3.2 (1.8)	3.3 (1.9)	3.3 (1.8)
Age at first birth, y	26.2 (3.7)	26.1 (3.7)	26.2 (3.8)	26.2 (3.6)	26.3 (3.8)	26.2 (3.6)
Oral contraceptive use ≥ 2 y, %	14	9	14	15	16	15
Body mass index ≥ 30, %	17	15	16	17	16	20
Masters/Doctorate degree, %	6	6	5	5	6	7
Husband with graduate degree, %	16	14	15	17	18	17
Alcohol consumption ≥ 15 g/wk, %	8	8	9	9	8	7
Current smoker, %	9	10	11	9	8	6
Multivitamin use, %	58	57	56	60	58	60
Physical activity, MET-hours/wk	15.4 (18.8)	15.0 (18.4)	15.0 (18.3)	15.5 (18.0)	15.8 (20.4)	16.1 (19.3)
Population density, number/square kilometer[b]	1,302 (2,660)	1,244 (2,271)	1,357 (3,054)	1,293 (2,612)	1,299 (2,603)	1,313 (2,693)
Living with spouse or partner, %	82	81	81	82	82	82
Antidepressants use, %	5	5	5	6	5	5
High blood pressure, %	55	58	54	54	54	57
High cholesterol, %	64	65	65	64	63	65
Myocardial infarction, %	6	7	6	6	6	5
Diabetes, %	10	10	10	9	10	11
Global score[c]	−0.004 (0.605)	−0.032 (0.613)	−0.011 (0.606)	0.008 (0.595)	0.003 (0.613)	0.019 (0.589)
Verbal memory[c]	−0.0086 (0.699)	−0.022 (0.696)	−0.008 (0.705)	−0.003 (0.673)	−0.011 (0.704)	0.005 (0.667)
Attention (digit span backwards)	6.721 (2.427)	6.671 (2.421)	6.711 (2.407)	6.772 (2.437)	6.748 (2.434)	6.693 (2.435)
Category fluency	16.81 (4.63)	16.58 (4.56)	16.64 (4.53)	16.87 (4.68)	16.91 (4.76)	17.17 (4.59)
TICS	33.72 (2.73)	33.61 (2.85)	33.67 (2.71)	33.80 (2.67)	33.74 (2.73)	33.80 (2.7)
APOE-e4 carrier,[d] %	26	27	26	25	25	26

APOE, apolipoprotein E; MET, metabolic equivalent of task; MHT, menopausal hormone therapy; TICS, telephone interview for cognitive status.

Values are means (SD) for continuous variables; percentages for categorical variables. All covariates were defined as of the questionnaire immediately before the baseline telephone interview.

[a]Reproductive span was calculated as age at menopause minus age at menarche.

[b]Population density based on participant address in 1994 linked to 1990 US Census tract data.

[c]Global score and verbal memory were the average *z*-scores of component tests.

[d]E4 carrier status among participants with APOE data (n = 5,471).

Q1 were more likely to have a late age at menarche (Q1: 13.2 y vs. Q5: 11.8 y). Half of the participants in Q1 had surgical menopause, and more than half had used MHT. In general, Q1 and Q5 participants were similar across demographic, reproductive, lifestyle, and health variables. Q5 had higher mean baseline cognitive scores compared with Q1. APOE-e4 frequency was similar across quintiles.

As the 14,217 women were a subset of the larger NHS study, we compared the study population with the overall NHS population in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/MENO/B502. While women in the study population had similar characteristics (eg, reproductive span, age at menopause, age at menarche) compared with the overall population, our study population was older, and we observed a higher prevalence of surgical menopause and MHT use.

Associations of reproductive span and cognitive performance

A longer reproductive span was significantly associated with more favorable cognitive change (Fig. 2). Compared with women with the shortest reproductive span (Q1: ≤ 33 y), women with the longest reproductive span (Q5: 41-46 y), demonstrated better global cognition (dif-

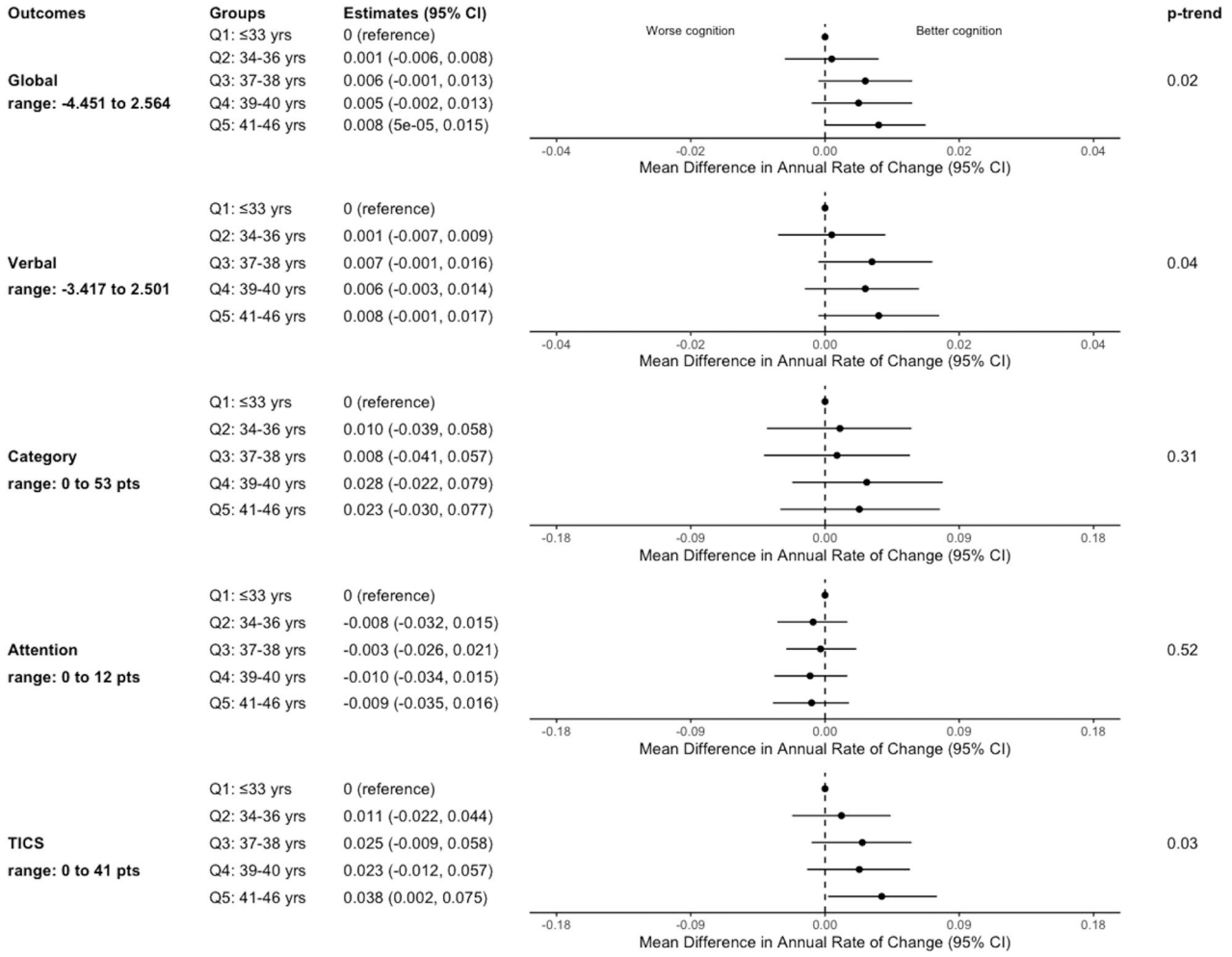

FIG. 2. Mean difference (95% CI) in annual rate of change in cognitive performance with reproductive span (n = 14,217). Models adjusted for age, education, high blood pressure, diabetes, antidepressant use, myocardial infarction, high cholesterol, husband's education, physical activity, body mass index, smoking status, alcohol intake, multivitamin use, Mental Health Inventory-5 score, duration of menopausal hormone therapy use (within the 10-y window and outside the 10-y window), and surgical menopause. Global score is a composite score averaging *z*-scores of the TICS, verbal memory, category fluency, and attention scores. The difference in the annual rate of change in global score for women in Q5 was equivalent to that observed in women 1.4 years apart in age. Verbal memory is a composite score averaging the *z*-scores of the immediate and delayed recalls of the TICS 10-word list and East Boston Memory Test. TICS, telephone interview for cognitive status.

ference in annual rate of change$_{Q.5\ vs.\ Q1}$: 0.008; 95% CI: 0.00005 to 0.015; *P*-trend = 0.02). The observed difference was equivalent to women who were 1.4 years apart in age, which was calculated based on the estimated coefficient for the age × time interaction term in the model. We observed similar trends with TICS (difference in annual rate of change$_{Q.5\ vs.\ Q1}$: 0.038; 95% CI: 0.002-0.075; *P*-trend = 0.03; equivalent to women 1.4 years apart in age), and verbal memory (difference in annual rate of change$_{Q.5\ vs.\ Q1}$: 0.008; 95% CI: −0.001 to 0.017; *P*-trend = 0.04; equivalent to women 1.4 years apart in age). However, associations with category fluency (*P*-trend = 0.31) and attention (*P*-trend = 0.52) were less clear.

Associations of MHT and cognitive performance

Compared with never use, longer duration of MHT use within the 10-year window of menopause was significantly associated with a worse global cognitive trajectory (*P*-trend = 0.02; difference in annual slope for MHT$_{8\text{-}10\ ys\ vs.\ 0\ y}$ [95% CI] = −0.007 [−0.016 to 0.002]), and suggestive associations with verbal memory and attention (*P*-trend = 0.09) (Fig. 3). The associations were significant for the duration of MHT between 5 and 7 years of use within the 10-year window of menopause for global score (difference in annual rate of change: −0.012; 95% CI: −0.020 to −0.004), and verbal memory (difference in annual rate of change: −0.012; 95% CI: −0.022 to −0.003).

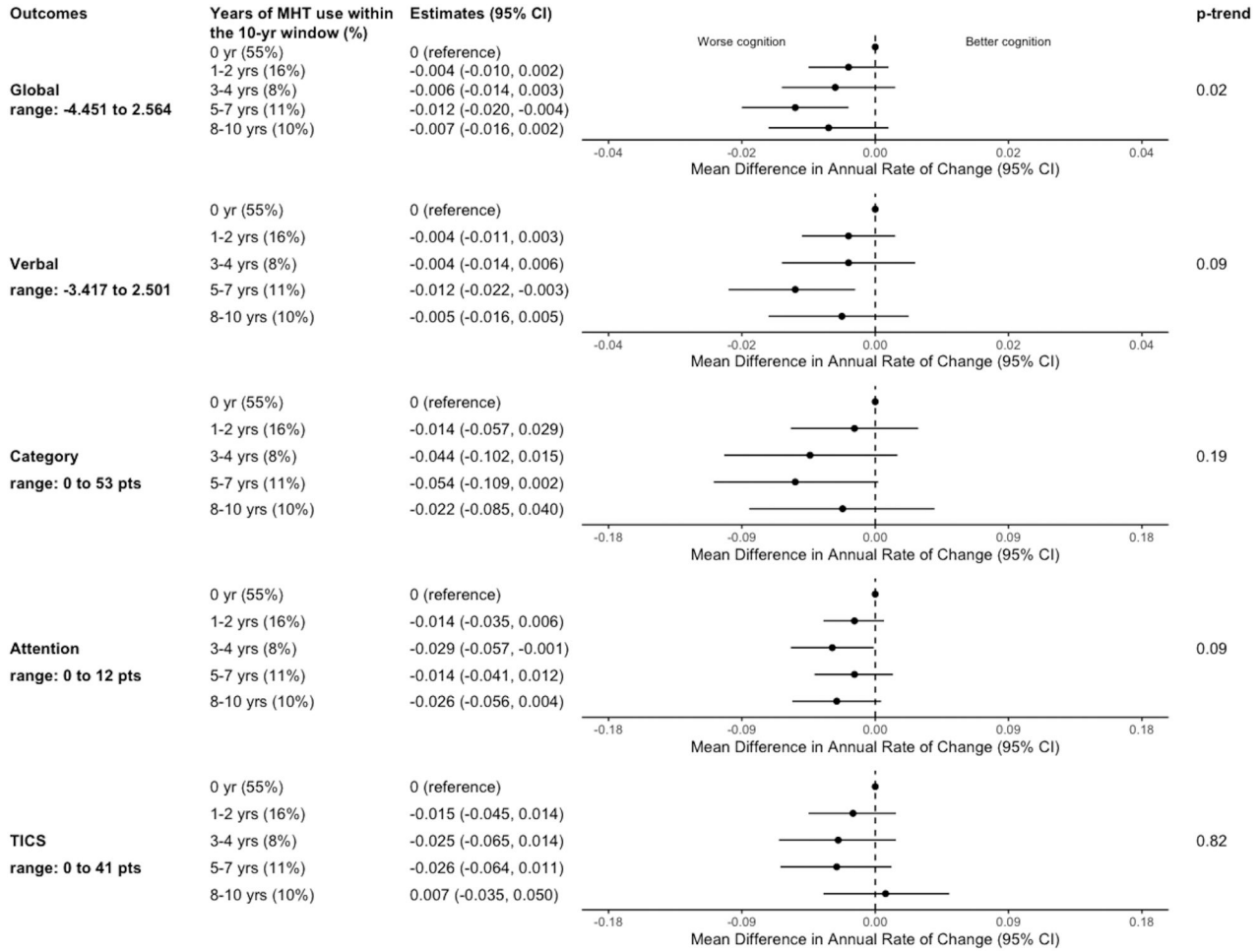

FIG. 3. Mean difference (95% CI) in annual rate of change in cognitive performance with years of MHT use within the 10-year window of menopause (n = 14,217). Models adjusted for age, education, high blood pressure, diabetes, antidepressant use, myocardial infarction, high cholesterol, husband's education, physical activity, body mass index, smoking status, alcohol intake, multivitamin use, Mental Health Inventory-5 score, reproductive span, surgical menopause, and MHT use in years outside of the 10-year window. Global score is a composite score averaging *z*-scores of the TICS, verbal memory, category fluency, and attention scores. Verbal memory is a composite score averaging the *z*-scores of the immediate and delayed recalls of the TICS 10-word list and East Boston Memory Test. MHT, menopausal hormone therapy; TICS, telephone interview for cognitive status.

We found no significant associations for MHT use outside the 10-year window of menopause and cognitive scores (Fig. 4). For global cognition, the difference in annual rate of change for > 7 years outside the window versus 0 years outside the window was 0.004 (95% CI: −0.009 to 0.017; *P*-trend = 0.07).

We further analyzed the associations between different types of MHT with cognition, for both within and outside the 10-year window of menopause (Supplemental Figure 2, Supplemental Digital Content 1, http://links.lww.com/MENO/B502). Within 10 years of menopause, compared with never users, those who used estrogen+progestin for more than 5 years showed a significant worse cognitive change in performance (mean difference in annual rate of change $_{\text{6-10 y of estrogen-progestin vs. 0 y}}$ = −0.019; 95% CI: −0.037 to −0.001); those who used estrogen only showed nonsignificant adverse associations (mean difference in annual rate of change $_{\text{6-10 y of estrogen vs. 0 y}}$ = −0.011; 95% CI: −0.033 to 0.010). Outside of the 10-year window, no significant associations were found with either type.

Associations of reproductive factors and cognitive performance

We examined the associations of factors that determined reproductive span and cognitive decline (Fig. 5). A younger age at menopause was significantly associated with worse rate of change in global cognition (difference in annual rate of change for 20-46 years vs. 53-55 years: −0.008; 95% CI: −0.016 to −0.001; *P*-trend = 0.02), meaning that those with older age at menopause had better trajectories in global cognition. A similar trend

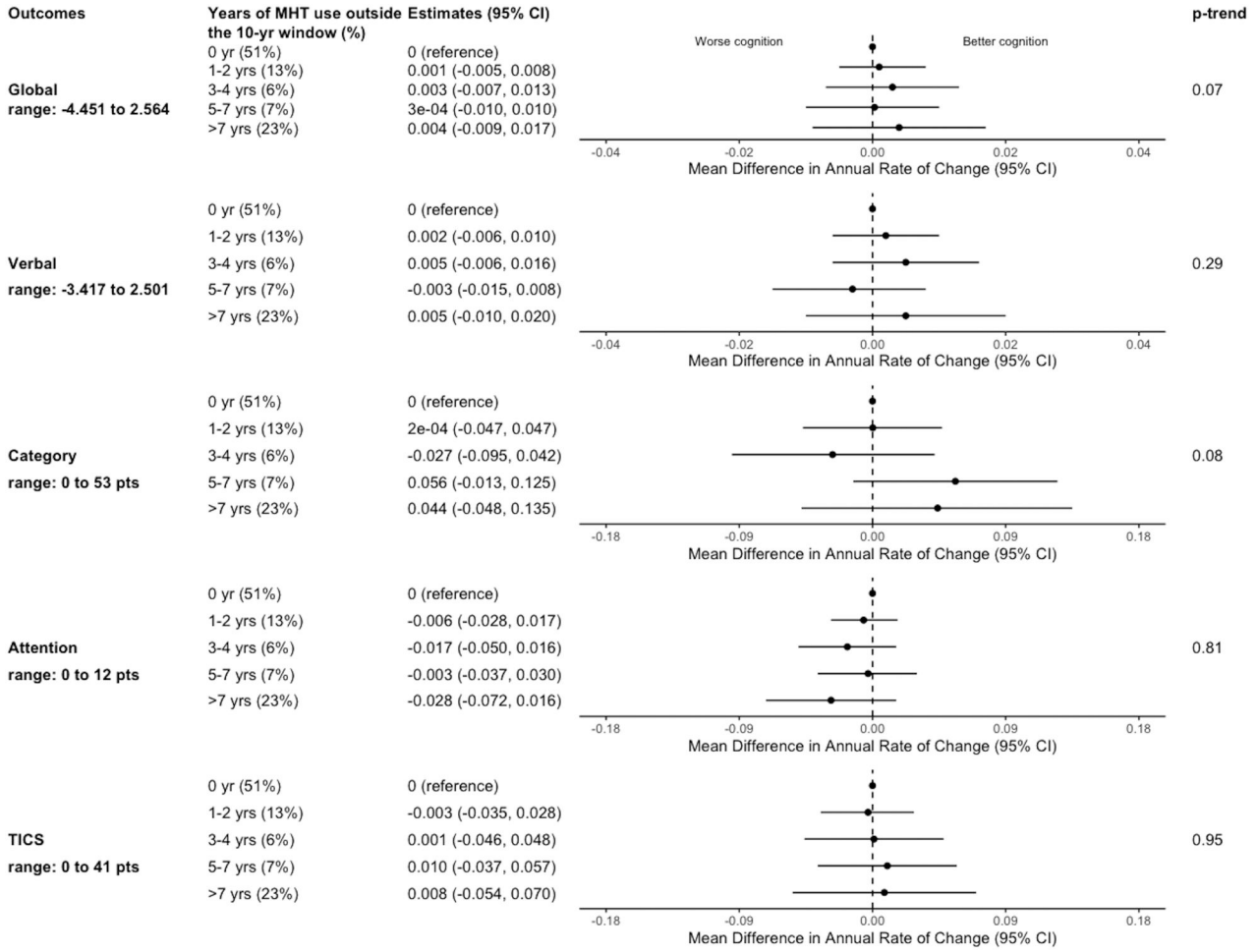

FIG. 4. Mean difference (95% CI) in annual rate of change in cognitive performance with years of MHT use outside the 10-year window of menopause (n = 14,217). Models adjusted for age, education, high blood pressure, diabetes, antidepressant use, myocardial infarction, high cholesterol, husband's education, physical activity, body mass index, smoking status, alcohol intake, multivitamin use, Mental Health Inventory-5 score, reproductive span, surgical menopause, and MHT use in years within the 10-year window. Global score is a composite score averaging *z*-scores of the TICS, verbal memory, category fluency, and attention scores. Verbal memory is a composite score averaging the *z*-scores of the immediate and delayed recalls of the TICS 10-word list and East Boston Memory Test. MHT, menopausal hormone therapy; TICS, telephone interview for cognitive status.

was also found for the TICS (*P*-trend = 0.04). A younger age at menarche was significantly associated with better category fluency scores ($P = 0.04$) but showed no significant association with global cognitive scores or other cognitive domains (*P*-trend ≥ 0.10). We found no significant associations between surgical menopause and cognitive decline.

Parity (difference in annual rate of change$_{\geq 5 \text{ births vs. } 0\text{-}1 \text{ birth}}$: −0.002, 95% CI: –0.012 to 0.008; *P*-trend = 0.49), age at first birth (difference in annual rate of change$_{28\text{-}46 \text{ y vs. } 15\text{-}23 \text{ y}}$: –0.003, 95% CI: –0.009 to 0.004; *P*-trend = 0.13), and oral contraceptive use (difference in annual rate of change$_{\geq 2 \text{ vs. } < 2 \text{ y of use}}$: 0.002, 95% CI: –0.004 to 0.008, *P*-trend = 0.57) were not significantly associated with global cognition (Supplemental Figure 3, Supplemental Digital Content 1, http://links.lww.com/MENO/B502).

Subgroup analyses

For reproductive span, across all cognitive outcomes, we did not observe significant interactions with surgical menopause (*P*-interactions ≥ 0.31), BMI (*P*-interaction ≥ 0.18), baseline scores (*P*-interaction ≥ 0.26), and APOE-e4 (*P*-interactions ≥ 0.08). Also, no significant interactions (*P*-interaction ≥ 0.05) were found for reproductive span and MHT use, with one exception: a significant interaction for reproductive span and duration of MHT use within the 10-year window of menopause for category fluency (P-interaction = 0.02), with longer reproductive span associated with better category fluency in those who had longer MHT use when used within the 10-year menopause window. We observed a significant interaction between duration of MHT use within the 10-year window and APOE-e4 carrier status (P-interaction = 0.03) for global

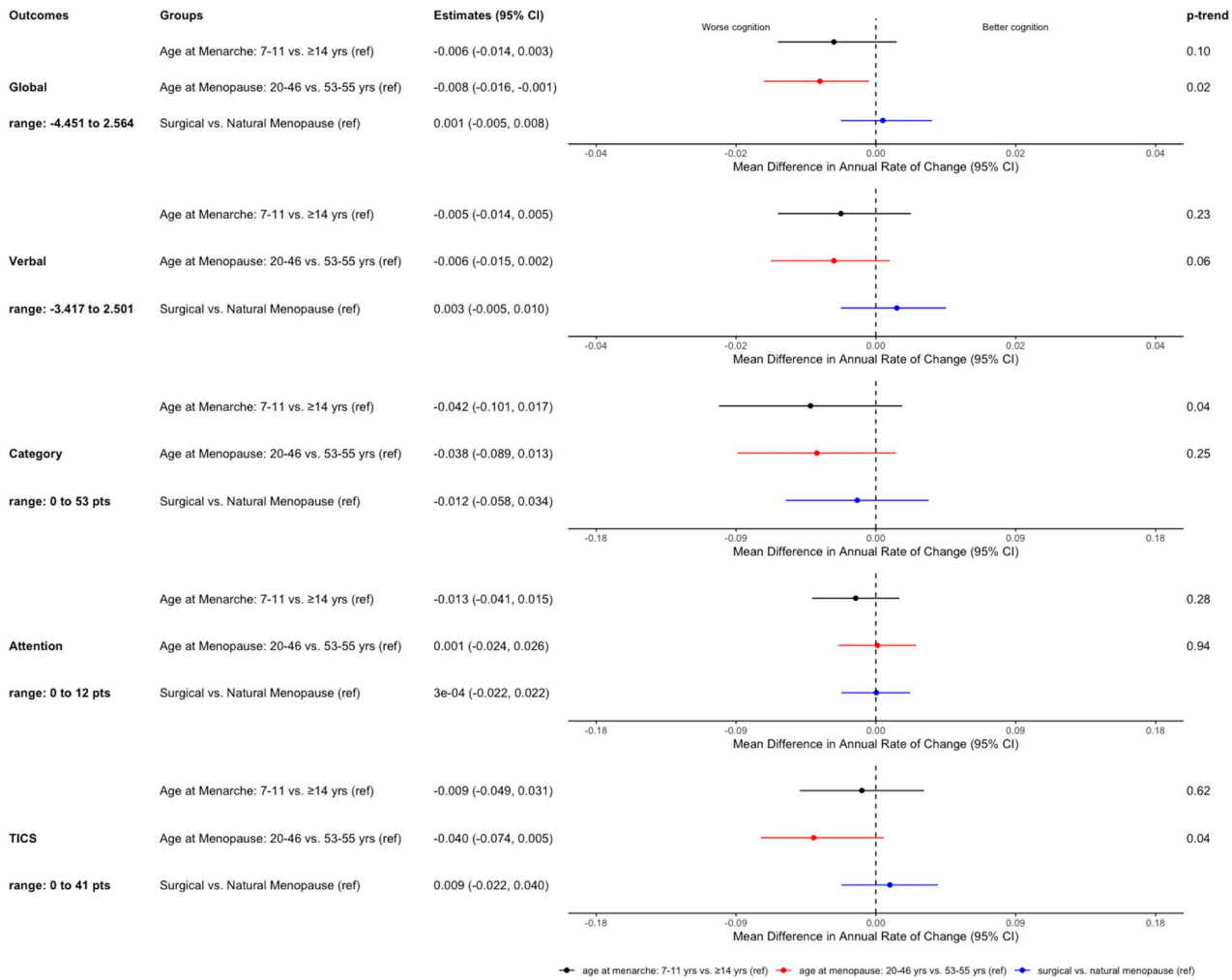

FIG. 5. Mean difference (95% CI) in annual rate of change in cognitive performance with reproductive variables (n = 14,217). Models adjusted for age, education, high blood pressure, diabetes, antidepressant use, myocardial infarction, high cholesterol, husband's education, physical activity, body mass index, smoking status, alcohol intake, multivitamin use, Mental Health Inventory-5 score, oral contraceptive use, parity, age at first birth, and MHT use in years (within 10 y window and outside 10 y window). Age at menarche, age at menopause, and surgical menopause were mutually adjusted for in the same model. *P*-trends were calculated for age at menarche and age at menopause. Global score is a composite score averaging *z*-scores of the TICS, verbal memory, category fluency, and attention scores. Verbal memory is a composite score averaging the *z*-scores of the immediate and delayed recalls of the TICS 10-word list and East Boston Memory Test. MHT, menopausal hormone therapy; TICS, telephone interview for cognitive status.

cognition. In stratified analyses, longer duration of MHT use was significantly associated with a worse global cognitive performance among noncarriers (*P*-trend = 0.002; difference in annual slope for $MHT_{8\text{-}10\ \text{vs.}\ 0\ \text{y}}$ [95% CI] = –0.019 [–0.033 to –0.005]). Among carriers, no significant associations were observed (*P*-trend = 0.42; difference in annual slope for $MHT_{8\text{-}10\ \text{vs.}\ 0\ \text{y}}$ [95% CI] = –0.009 [–0.036 to 0.019]). We conducted subgroup analyses in participants with natural and surgical menopause separately (*P*-interaction by type of menopause ≥ 0.31). Both subgroups showed similar associations of longer reproductive span with better cognitive trajectories. However, likely due to the limited sample sizes, neither was statistically significant (Supplemental Figures 4 and 5, Supplemental Digital Content 1, http://links.lww.com/MENO/B502). In addition, in the natural menopause–only group, younger age at menopause also showed similar trends of adverse associations with cognitive change (difference in annual rate of change $_{20\text{-}46\ \text{vs.}\ 53\text{-}55\ \text{y}}$: –0.007; 95% CI: –0.015 to 0.001; *P*-trend = 0.11).

Among women who reported menopause after 1976 (ie, in 1978 and 1980; n = 5,088), for whom we had more accurate information on the timing of MHT initiation, we examined the associations between duration of MHT use

—combining years within 10 years of menopause and years beyond 10 years—and cognitive outcomes (Supplemental Figure 6, Supplemental Digital Content 1, http://links.lww.com/MENO/B502). For category fluency, we observed a significant trend of improved performance with longer duration of MHT use (P-trend = 0.03; difference in annual slope for $MHT_{10+\ vs.\ 0\ y}$ [95% CI] = 0.065 [–0.004 to 0.134]). However, no significant association was found for global cognitive performance (P-trend = 0.61; difference in annual slope for $MHT_{10+\ vs.\ 0\ y}$ [95% CI] = 0.003 [–0.006 to 0.013]).

Secondary analysis

In a secondary analysis using averaged scores from available assessments as outcomes, similar associations for reproductive span and cognitive performance were found, but were not statistically significant. After excluding participants who reported hearing problems at any of the four cognitive assessments, similar significant trends were observed for reproductive span (difference in annual rate of $change_{Q.5\ vs.\ Q1}$ = 0.014; 95% CI: 0.002-0.026; P-trend = 0.004) and MHT use within the 10-year window of menopause (difference in annual rate of $change_{8\text{-}10\ vs.0\ y}$ = –0.013; 95% CI: –0.028 to 0.001; P-trend = 0.04). After excluding participants who scored in the bottom 10% in global score at the first cognitive assessment, we found similar associations of global cognitive scores with reproductive span (difference in annual rate of $change_{Q.5\ vs.\ Q1}$: 0.011; 95% CI: 0.002-0.019; P-trend = 0.005) and MHT (difference in annual rate of $change_{8\text{-}10\ vs.0\ y}$: −0.010; 95% CI: –0.020 to 0.00007; P-trend = 0.01).

DISCUSSION

In this prospective cohort study of 14,217 women, reproductive span, a marker of endogenous estrogen exposure history, was significantly associated with better cognitive trajectories in older women. The difference observed was equivalent to that observed between women 1.4 years apart in age. Older age at menopause showed the strongest association with better cognitive trajectories among reproductive factors. However, longer duration of MHT, either within or outside 10 years of menopause, was not associated with better global cognitive performance over time.

Our results showing slower rates of decline with greater reproductive span aligned with biological evidence for the neuroprotective effects of estrogen. Estradiol, the most common form of estrogen during reproductive years in females, declines precipitously during menopause. Estradiol is neuroprotective and neurotrophic and can pass through the blood-brain barrier to regulate neural activity.[43] Estradiol decline can lead to cognitive decline in animal models,[44–46] including in nonhuman primates.[47,48] One hypothesized mechanism has been mitochondrial aging;[49] in rodents, estrogen loss caused decreases in glycolytic gene expression and upregulation of genes related to mitochondrial function, and fatty acid uptake was observed.[50] This metabolic adaptation from glucose to ketones as the primary energy source has been correlated with reduced synaptic plasticity, a key marker of cognitive performance.[2] A human study also showed differences in energy metabolism and cognitive aging across menopause transition stages.[51] Alterations in the brain cholinergic system have been hypothesized to contribute to cognitive dysfunction. Estradiol signaling interacts with the cholinergic system to preserve cholinergic neurons, which are crucial for cognitive maintenance. In addition, estradiol may play a key role in protecting dopaminergic neurons, which are known to decline with age. These findings collectively suggest that estradiol may have a myriad of neuroprotective effects, important for maintaining cognitive function during the aging process.[2] Alternatively, a shorter reproductive span may serve as a marker for accelerated biological aging.[52] Early menopause may represent a sign of systemic aging and reduced longevity, rather than acting exclusively as a hormonal risk factor.[53] Future studies incorporating biomarkers of aging and longevity data are warranted to disentangle these potential nonestrogenic pathways.

Several prospective studies have reported that a longer reproductive span was associated with lower risks of dementia[8,54] and better cognitive trajectories.[11] Several cross-sectional studies also found similar beneficial results for cognition with a longer reproductive span.[9,12,55,56] However, other studies reported null results: for example, the 10/66 study and a Taiwan Biobank study found null associations between reproductive span and dementia and cognitive performance.[17,57] It is possible that other studies had different results than ours because they had smaller sample sizes or different demographic characteristics (women were from the Caribbean, Latin America, and China). Other studies conducted among Hispanic/Latina women also found no overall associations with reproductive span[15,58]; however, among a subset of women over 60 years old, longer reproductive span was associated with better memory performance, which aligned with our study results. The null overall results in their study may be attributed to the younger baseline age of their participants (59.5 vs. ≥ 70 y for our study). In addition, our study had up to four cognitive assessments, which made our results more statistically powerful for evaluating change. Interestingly, there were studies reporting adverse associations with longer reproductive span and dementia risk. The Rotterdam Study[59] and a Swedish Gothenburg cohort[16] found that a longer reproductive span was associated with increased risks of dementia. The Gothenburg study had a smaller sample size (n = 1,364), younger participants (mean age < 60 y), different demographics (Swedish population), and reproductive characteristics (eg, lower proportion of MHT, oral contraceptives users) compared with our study. Similarly, the Rotterdam Study was smaller in sample size (N = 3,601) and included younger participants (mean age = 55 y). In addition, their definition of surgical menopause (defined as menopause due to gynecologic surgery, drug induction, or radiation therapy) differed from that used in our study; however, given that our results were not different between natural and surgical

menopause, this discrepancy is less likely to explain the differences in the results. Thus, given the inconsistent results, future studies should include prospective studies with large sample sizes, long follow-up, and inclusion of older women at the highest risk of cognitive impairment.

Similar to the findings from the Women's Health Initiative (WHI),[60,61] our results also suggest that MHT does not confer cognitive benefits. A key distinction between our study and the WHI lies in the timing of initiation of MHT. Participants in our NHS cohort were younger at the initiation of MHT (< 55 y old and within 2-3 years of menopause onset) compared with the WHI cohort, where participants were on average 63 years old at screening, with 64%-82% having initiated MHT more than 10 years after menopause onset.[62] Our population offered a major advantage in understanding the potential cognitive effects of MHT during the early stages of menopause, specifically among women who began MHT within 2-3 years of menopause onset. Overall, our study results did not support the "critical period" hypothesis. We did not observe significant cognitive benefits for MHT users either within or outside the 10-year window, although many participants who used MHT outside the 10-year window of menopause also used MHT in the earlier years of menopause. In addition, our supplemental analyses—limited to participants for whom we had the most accurate information on the timing of MHT initiation—also did not support the "critical period" hypothesis. Specifically, while a modest positive trend was observed for category fluency with longer MHT use, for the global score, we did not find significant associations, suggesting that MHT use within 10 years of menopause may be protective and use beyond 10 years may be detrimental for global cognitive performance. These findings contrast somewhat with earlier studies that have reported more favorable cognitive outcomes with earlier MHT initiation. The Cache County study found that prior MHT use (more likely started during the menopausal period) was associated with reduced risk of AD,[25] and an Australian cohort found that MHT initiated during early menopause had better cognitive performance.[23] However, compared with our study, both the Cache study (N = 1,889) and the Australian study (N = 428) had much smaller populations. We found significant adverse associations for estrogen+progestin combined therapy within the 10-year window and global cognition, which was consistent with a recent meta-analysis that found adverse associations with dementia.[63] This association may result from the antagonistic effect of progestin on estrogen receptors, potentially counteracting the neuroprotective properties of estrogen[64] and the potential adverse cardiovascular mechanisms increasing the risk of stroke.[65] In addition, our finding of null or adverse relations may be associated with the reasons for MHT initiation. Women who use MHT may experience more severe vasomotor symptoms (eg, hot flashes, night sweats), which may constitute the primary indication for treatment. Some evidence suggests that vasomotor symptoms may be independently associated with adverse brain structural changes, including greater white matter hyperintensity burden, a marker of brain aging and future cognitive risk.[66] In the current study, we conducted a sensitivity analysis adjusting for symptom severity. We found that adjusting for symptom severity did not alter the associations with MHT duration, suggesting that the results may not be driven by confounding by indication. However, for reproductive span, the association was attenuated (difference in annual rate of change $_{Q5\ vs.\ Q1}$: −0.001; 95% CI: −0.008 to 0.006; *P*-trend = 0.27), likely due to shorter reproductive span being more strongly collinear with worse symptoms, given that those with shorter spans include those with surgical menopause, which induces worse symptoms as a consequence of abrupt hormonal transition.

Other reproductive factors may also influence endogenous estrogen exposure; however, we did not find significant associations with greater parity, higher age at first birth, or longer oral contraceptive use. One study found that nulliparity was associated with cognitive decline,[67] and the Women's Health Initiative Memory Study found that higher parity was associated with lower risk of dementia.[68] However, these studies had smaller sample sizes compared with our study. The UK Biobank found that younger age at first birth was associated with a greater dementia risk,[8] and older age at first birth was associated with better cognitive functioning.[9] However, the results were likely confounded by socioeconomic status. Our study population consisted primarily of highly educated White women; thus, this homogeneity in socioeconomic status was a strength in reducing potential confounding. A recent systematic review reported no associations with oral contraceptive use and cognitive decline,[69] which aligned with our study results.

Surgical menopause was not associated with any cognitive domains, which was consistent with a recent meta-analysis.[70] However, other studies[14,16] found that younger age at surgical menopause, before the age of 45, was associated with a greater risk of dementia, which aligned with the results in our study showing that earlier age of menopause overall was associated with worse cognitive trajectories. Although a recent meta-analysis on age at menopause and cognitive outcomes found no significant associations,[71] their findings suggested that such associations may still exist, as the lack of significance could be due to heterogeneity among the studies in the meta-analysis. Younger ages at menarche did not show strong associations with cognitive benefits in the current study. The UK Biobank found a U-shaped association of age at menarche and dementia,[8] while a Taiwanese study found that late menarche was associated with poor cognition.[57] Compared with our study, a major difference was that these studies included younger women, indicating that their findings may only be applicable to the early onset of poor cognition or dementia.

The strengths of our study included a large sample size (14,217 NHS participants), a large prospective cohort design with up to 4 cognitive assessments over 8 years, providing statistical power to evaluate differences in rates

of change over time. Information on age at menopause and MHT use was collected biennially from 1976, reducing the potential for misclassification bias. We had a high response rate with more than 80% follow-up rate maintained. We had information on a rich set of covariates that were biennially updated, reducing the possibility of residual confounding.

Nevertheless, our study had some limitations. The NHS cohort primarily consisted of highly educated White females, which may limit the generalizability of our study findings. In addition, MHT dosages evolved over time, with current guidelines recommending the lowest effective dose. Our findings primarily reflect menopause management practices common from the late 1970s to the 1990s. The MHT usage patterns in our cohort were highly homogenous (eg, $<2\%$ of participants used transdermal patches), and nonstandard doses were infrequently prescribed in that era. Due to the limited statistical power, we were unable to separately evaluate alternative preparation doses and the route of administration. Furthermore, rates of hysterectomy were higher during this period. This historical context may influence the generalizability of our findings regarding surgical menopause, as the indications for and frequency of these procedures have evolved. Reproductive health variables were self-reported, but they were updated biennially, and validation studies have shown these self-reports to be highly accurate within the NHS cohort. We likely had differential loss to follow-up, where those with cognitive impairment were less likely to participate or may have died during the study period. Therefore, our results may be subject to attrition and survival biases. However, we tried to minimize such biases by ensuring a high participation rate overall (80%). In addition, given the high education attainment of our study population, the component tests of our cognitive assessments may be susceptible to ceiling effects, potentially limiting the ability to detect differences in cognitive trajectories. While we captured data on MHT use, we were unable to evaluate the impact of over-the-counter medications, supplements, or herbal remedies for menopausal symptoms. The prevalence of such supplement use in this study population was too low to permit meaningful statistical analysis.

CONCLUSIONS

In conclusion, longer reproductive span, a marker of endogenous estrogen exposure, was significantly associated with better cognitive trajectories in this cohort of educated older women, while MHT use within 10 years of menopause showed adverse associations with cognition. Future studies should explore the potential mechanisms linking longer reproductive span and cognitive change.

ACKNOWLEDGMENT

This work used data provided by participants in the Nurses' Health Study.

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