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Association of bilateral oophorectomy with cognitive function in healthy, postmenopausal women

Keiko Kurita, Ph.D.[a], **Victor W. Henderson, M.D., M.S.**[b], **Margaret Gatz, Ph.D.**[c,d], **Jan St. John, M.P.H.**[d,e], **Howard N. Hodis, M.D.**[d,e,f,g], **Roksana Karim, M.B.B.S., M.S., Ph.D.**[d,e], and **Wendy J. Mack, Ph.D.**[d,e]

[a]Department of Population Health, School of Medicine, New York University, New York, New York

[b]Department of Health Research and Policy (Epidemiology) and Department of Neurology and Neurological Sciences, School of Medicine, Stanford University, Stanford, California

[c]Department of Psychology, University of Southern California

[d]Department of Preventive Medicine, Keck School of Medicine, University of Southern California

[e]Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California

[f]Department of Medicine, Keck School of Medicine, University of Southern California

[g]Department of Molecular Pharmacology and Toxicology, School of Pharmacy, University of Southern California, Los Angeles, California

Abstract

Objective—To investigate the association between bilateral oophorectomy and cognitive performance in healthy, older women.

Design—Retrospective analysis of clinical trial data.

Setting—Academic research institution.

Patient(s)—Healthy postmenopausal women without signs or symptoms of cardiovascular disease or diabetes (n = 926).

Intervention(s)—Randomized interventions (not the focus of this analysis) in analyzed trials included B-vitamins, soy isoflavones, oral estradiol, and matching placebos.

Main Outcome Measure(s)—Measures in five cognitive domains (executive functions, semantic memory, logical memory, visual memory, and verbal learning) and global cognitive function.

Result(s)—Using data from three clinical trials conducted under uniform conditions, bilateral oophorectomy and its timing were analyzed cross-sectionally and longitudinally in relation to cognitive function in linear regression models. Covariates included age, education, race/ethnicity, body mass index, trial, and randomized treatment (in longitudinal models). Duration of

Reprint requests: Wendy J. Mack, Ph.D., 2001 N. Soto St., SSB 202Y, Los Angeles, California 90033 (wmack@usc.edu).

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menopausal hormone use was considered as a possible mediator and effect modifier. Median age of oophorectomy was 45 years. When evaluating baseline cognition, we found that surgical menopause after 45 years of age was associated with lower performance in verbal learning compared with natural menopause. Evaluating the change in cognition over approximately 2.7 years, surgical menopause was associated with performance declines in visual memory for those who had an oophorectomy after 45 years of age and in semantic memory for those who had oophorectomy before 45 years of age compared with natural menopause. Oophorectomy after natural menopause was not associated with cognitive performance. Adjustment for duration of hormone use did not alter these associations.

Conclusion(s)—Cognitive associations with ovarian removal vary by timing of surgery relative to both menopause and age.

Keywords

Cognitive function; oophorectomy; surgical menopause

Bilateral ovarian removal, or oophorectomy, results in a sudden and dramatic reduction of levels of ovarian hormones including estrogen (1). Oophorectomy has been associated with various health consequences including declines in cognitive domains such as verbal memory, logical memory, visual memory, and semantic memory (2–5). However, these associations are not consistently found, perhaps due to differences in timing of oophorectomy relative to natural menopause and hormone use (6–10). In addition, age at surgical menopause may be associated with differences in cognitive performance, with younger age at oophorectomy carrying an increased risk (4, 11). Thus, in examining the oophorectomy-cognition association, it may be important to consider timing of oophorectomy relative to natural menopause, age of surgical menopause, and hormone therapy use.

Another factor that has not been fully explored is comorbid conditions such as cardiovascular disease and diabetes, both of which are common in older adults and associated with decreased cognitive function (12–15). Cardiovascular disease may be especially relevant as bilateral oophorectomy has been reported to increase the risk of cardiovascular disease (16). In addition, local estrogen biosynthesis in adipose tissue is a primary source for estrogen in postmenopausal women, and body mass index (BMI) has been associated with cognitive function in late life (17–20).

Using data from three randomized, double-blinded, placebo-controlled trials–the B-Vitamin Atherosclerosis Intervention Trial (BVAIT), the Women's Isoflavone Soy Health Trial (WISH), and the Early versus Late Intervention Trial with Estradiol (ELITE)–we tested the association of bilateral oophorectomy with cognitive performance in healthy post-menopausal women, evaluating baseline and longitudinal measures of cognition. We predicted that [1] women who had ovarian removal would show reduced cognitive performance, particularly in verbal learning as this domain has been generally found to be associated with oophorectomy, compared with women with intact ovaries; [2] the association of oophorectomy with reduced cognition would be stronger among women who had had their oophorectomy before natural menopause, especially at younger ages; and [3]

estrogen-based hormone therapy would ameliorate the association between oophorectomy and reduced cognition.

Material and Methods

Participants

As BVAIT, WISH, and ELITE (21–23) were conducted by the same research group using similar study inclusion criteria and had uniform data collection, data were combined for this study's cross-sectional and longitudinal analysis of bilateral oophorectomy and its timing with cognitive function. For each trial, the primary trial objective was to test the effects of interventions (folic acid, vitamin B_{12}, and vitamin B_6; soy isoflavones; and oral estradiol, respectively) on the progression of subclinical atherosclerosis in healthy postmenopausal women. Trial inclusion criteria required [1] absence of diabetes mellitus; [2] no clinical signs or symptoms of cardiovascular disease; [3] absence of untreated thyroid disease; [4] absence of uncontrolled hypertension; and [5] life expectancy of at least 5 years. The BVAIT participants had elevated levels of serum homocysteine. There were no exclusion criteria related to cognitive or psychiatric conditions. The study was conducted under the approval of the institutional review board at the University of Southern California, and the participants signed a written informed consent.

The current analysis included participants in all three trials who [1] were postmenopausal women; [2] had completed the baseline and follow-up visits that included questionnaires and cognitive testing; [3] had a documented history of bilateral oophorectomy or no history of ovarian removal at the beginning of the trial. Women with only one intact ovary were excluded from this analysis as unilateral oophorectomy has also been associated with cognitive dysfunction (24, 25). Of 1,190 postmenopausal women in the three trials, 926 women (123 with bilateral oophorectomy, 803 with intact ovaries) met our inclusion criteria (see Supplemental Fig. 1, available online).

Table 1 lists demographic and clinical characteristics by trial. The participants were generally well-educated, with 35% holding graduate degrees; were racial/ethnically heterogeneous, with 32% self-identifying a race/ethnicity other than non-Hispanic White; and were generally overweight (34% overweight and 26% obese).

Procedures

All trials were conducted at the Atherosclerosis Research Unit at the University of Southern California. Participants were primarily drawn from the general population of Los Angeles County. At baseline for each trial, the participants completed structured questionnaires and were administered a cognitive battery. The same cognitive battery was administered to participants an average of 2.7 years later (standard deviation [SD] ± 0.6) by trial design. Change in cognitive scores comprised secondary trial outcomes for the three trials.

Measures

Cognitive function—The cognitive battery included 14 tests, which were administered by one trained psychometrist (Supplemental Table 1, available online). The test scores were

used to calculate composite performance scores of global cognitive function and five previously identified cognitive domains of executive function, semantic memory, logical memory, visual memory, and verbal learning. Cognitive domain composite scores were based on the factor loadings generated from principal components analysis performed on the cognitive tests, using consecutive uncorrelated factors extracted for the trials (26, 27). The baseline mean and SD for each test were used to calculate standardized test scores (Z-scores) for each administration using all participants in the trials (all available scores were used to calculate means and standard deviations). A composite score for each cognitive domain was calculated as the sum of Z-scores of each test identified as a factor in the domain (the sign was reversed for the timed Trail Making Test, part B).

Global cognitive function was calculated as the sum of the Z-scores of all 14 tests (the sign was again reversed for the Trail Making Test, part B). Higher composite scores indicated better cognitive performance. To examine each participant's performance over time, change in Z-scores for global cognitive function and domain composite scores were calculated by subtracting the baseline composite scores from the follow-up scores. If a participant had a missing test score for a cognitive domain, the composite score was considered missing. If a participant was missing any one of the cognitive domain scores, the global cognitive function score was considered missing. Therefore, only participants with complete cognitive domain component scores were considered in the analyses.

Oophorectomy—At baseline, participants completed a reproductive history questionnaire that included history of oophorectomy and hysterectomy and date of last menstrual period. If oophorectomy was reported, participants were asked whether one or both ovaries were removed, and the information was verified with medical records or blood tests which confirmed levels of follicle-stimulating hormone. Women who reported that only one ovary was removed (n = 25) were excluded from the present analysis. No participant underwent oophorectomy during the trials.

The age at surgery was calculated as the difference between birth date and the reported date of surgery. Age at menopause was calculated as the difference between birth date and the self-reported date of the last menstrual period. Age at menopause could not be calculated for the women who initiated hormone therapy before menopause.

A set of dichotomous variables was created to indicate timing of bilateral oophorectomy with respect to menopause: [1] with unknown dates; [2] after last menstrual period; [3] that led to menopause at age >45 (approximately the median age of surgical menopause); and [4] that led to menopause at age ≤ 45. The combined group of bilateral oophorectomy leading to menopause at any age (n = 69) was also examined.

Hysterectomy without oophorectomy has also been found to be associated with cognitive impairment (24). In this study, only 8% (n = 67) of the participants who had ovaries intact had undergone hysterectomy; they were too few for separate analysis by each oophorectomy status subgroup.

Hormone therapy—Prior systemic and vaginal menopausal hormone use was reported by participants at the trial baseline. Current use of hormone therapy was an exclusionary criterion for the WISH and ELITE trials; women currently using hormones required a 1-month washout before trial enrollment.

Demographic, medical, trial, and other covariate information—Demographic variables were derived from a structured questionnaire completed at baseline, including age, race/ethnicity, and years of education. Weight and height measured at baseline were used to calculate BMI (in kg/m^2). The BMI was then categorized using standard BMI categories of underweight (< 18.5), normal (18.5–24.9), overweight (25–29.9), and obese (≥ 30). Depressive symptoms at baseline was with the 20-item Center for Epidemiologic Studies Depression (CES-D) scale (28).

Variables were created to indicate the trial from which each participant was recruited (e.g., BVAIT, WISH, ELITE) so that inclusion and exclusion criteria and unique trial population characteristics could be statistically adjusted. A dichotomous variable indicated whether women were on the placebo arm or the active treatment arm of either BVAIT (B-vitamin intervention), WISH (soy isoflavone protein intervention), or ELITE (oral estradiol alone or, for women with a uterus, oral estradiol plus vaginal progesterone gel).

Missing data—Comparisons were made between the women who were excluded from the study due to missing at least one cognitive composite score or other information with women included in the study. Respectively, the proportions of the women who had bilateral oophorectomy were 13.0% versus 13.3%, hysterectomy were 17.2% versus 20.4%, ever been on hormone therapy were 66.1% versus 63.2%. Respectively, the mean (±SD) ages were 60.4 (7.3) versus 60.7 (7.2) and the mean (SD) Z-scores for global cognitive function were −2.3 (8.6) versus 0.9 (8.2).

Statistical Analysis

Linear regression was used for all analyses. Each of the cognitive domain and global cognitive function composite scores were first regressed on covariates, followed by blocks of oophorectomy variables of interest. All composite scores were statistically significantly associated (as tested by either Pearson or Spearman correlation) with age (except for logical memory), education level, non-Hispanic White versus other race/ethnicity (except for visual memory), and BMI (except for logical memory). These variables as well as trial indicators were included in all models as covariates. Oophorectomy variables added to the base covariate model were [1] dichotomous oophorectomy indicator, regardless of timing; [2] three indicator variables specifying timing of oophorectomy relative to natural menopause (i.e., before last menstrual period, after last menstrual period, and unknown timing); [3] four indicator variables specifying age and timing of oophorectomy (i.e., bilateral oophorectomy that led to menopause at age ≤ 45, bilateral oophorectomy that led to menopause at age >45, bilateral oophorectomy after last menstrual period, and bilateral oophorectomy with unknown dates).

To examine oophorectomy status in relation to cognitive performance over 2.7 years, the models were repeated with change in composite scores of the cognitive domains or the

global composite as the dependent variable. The baseline score of the dependent cognitive change variable and an indicator for treatment arm (active vs. placebo) were included as additional covariates.

To examine the possible moderating effect of hormone use on the oophorectomy associations with cognition, an interaction variable, the product of oophorectomy status and duration of hormone treatment, was tested (29). The data analysis used SAS versions 9.2 and 9.3 (SAS Institute). Two-tailed $P<.05$ was considered statistically significant, unadjusted for multiple comparisons.

Results

Table 2 compares the characteristics of the women who had bilateral oophorectomy and had intact ovaries. Of the women who had bilateral oophorectomy, 26 (21%) had surgery after their last menstrual period, 33 (27%) had surgery resulting in menopause after 45 years of age, and 36 (29%) had surgery resulting in menopause at or before 45 years of age. Timing of surgery was unknown for 28 (23%) women. Compared with the women who had intact ovaries, women who had bilateral oophorectomy were statistically significantly older at initial testing, had a younger age at menopause, and were more likely to have used hormone therapy and for a longer duration.

Baseline cross-sectional analyses are shown in Table 3, where Model I examined the effect of oophorectomy regardless of timing. Model II examined oophorectomy before the last menstrual period regardless of age, and Model III examined the timing of oophorectomy with age. Model IV built on Model III with the addition of duration of hormone use. All models were adjusted for trial, age, education, race/ethnicity, and BMI. Oophorectomy regardless of timing (Model 1) and bilateral oophorectomy at any age leading to surgical menopause (Model II) were not associated with a decline in cognitive domains or global cognition. Oophorectomy after age 45 but before a final menstrual period resulting in surgical menopause was associated with lower performance in verbal learning (Model III; $P=.03$); the regression coefficient for this variable was altered less than 15% with adjustment for duration of hormone use (Model IV; $P=.04$). The other oophorectomy timing variables, including history of oophorectomy after last menstrual period, were not statistically significantly associated with global cognitive function or any cognitive domain composite scores. Duration of prior hormone use was not statistically significantly associated with any cognitive domain composite scores.

Table 4 summarizes associations with cognitive performance changes over an average of 2.7 years. In all cognitive domains, subtracting the baseline scores from the follow-up evaluation resulted in negative values, suggesting that the standardized domain performance in this sample decreased relative to baseline performance of all of the participants in the clinical trials. The changes in domain performance were largest in executive function with a mean decline of 0.2 and smallest in visual memory with a mean decline of 0.03. Model V examined the effect of oophorectomy regardless of timing. Model VI examined oophorectomy before last menstrual period regardless of age, and Model VII examined

timing of oophorectomy with age. Model VIII built on Model VII adjusting for duration of hormone use.

Oophorectomy before 45 years of age resulting in surgical menopause was statistically significantly associated with declines in semantic memory performance (Model VII; P=.01). Oophorectomy after age 45 resulting in surgical menopause was associated with declines in visual memory performance (Model VII; P=.004). In both cognitive domains, there was < 15% change in the regression coefficient estimate when duration of hormone use was included in the models (Model VII; P=.006 and P=.003, respectively). When adjusted for duration of hormone use, bilateral oophorectomy leading to surgical menopause before 45 years of age was also associated with decline in global cognitive function (Model VIII; P=.04). Bilateral oophorectomy at any age leading to surgical menopause was also associated with a decline in semantic memory when compared to natural menopause (Model VI; P=.04) but not in other cognitive domains or global cognitive function.

The other oophorectomy timing variables, including oophorectomy after last menstrual period, were not statistically significantly associated with global cognitive function or any cognitive domain composite scores. Hormone use tended to be positively associated only with change in global cognitive function (P=.05). Furthermore, age at menopause in the regression models did not change the statistical significance of oophorectomy variables, and age at menopause itself was not associated with cognitive functions (all P>.4). Taken together, these results suggest that oophorectomy before natural menopause, both at younger and later ages, is associated with decreased cognitive performance and that the age of oophorectomy leading to menopause may have associations with different cognitive domains.

Analysis of interactions provided no evidence for modification of the oophorectomy association with cognition by duration of hormone use in cross-sectional analyses (all P values for interaction P>.1, adding the interaction term and duration of hormone use to Model I; results not shown). Similarly, duration of prior hormone therapy did not modify the association of oophorectomy with change in cognitive performance (all P values for interaction P>.3, adding the interaction term and duration of hormone use to Model VII; results not shown).

Discussion

We examined associations of bilateral oophorectomy, its timing relative to natural menopause, and hormone therapy with cognitive function in healthy postmenopausal women who were free of signs or symptoms of cardiovascular disease and diabetes. Our hypotheses were partially supported. Compared with women with intact ovaries, ovarian removal resulting in surgical menopause was inversely associated with cognitive performance in verbal learning, visual memory, and semantic memory. The oophorectomy-cognition relationships were specific to the age at which surgery occurred and to cognitive domain. Oophorectomy after age 45 resulting in surgical menopause was associated with lower performance in verbal learning at baseline and in decline in visual memory over an average 2.7 years. Oophorectomy before age 45 resulting in surgical menopause was associated with

decline in performance on semantic memory over the same period of time. Adjustment for duration of hormone use did not alter these findings.

Other studies have generally reported an association between oophorectomy and declines in verbal memory and visual memory within a few years of surgery (2, 3). Our study tested these associations farther from the time of surgery (on average, 15 years after surgery) and also found associations with these domains.

Our findings of changes in cognitive performance over time in relation to prior oophorectomy are consistent with a recent longitudinal study of older women observed up to 18 years, finding that surgical menopause was associated with larger declines in semantic memory and global cognitive function compared with natural menopause (4). Our results, taken together with those of other investigators, suggest that surgical menopause may be deleterious for aspects of cognitive function (10). The oophorectomy association is not simply explained by an association of earlier age at menopause, regardless of type of menopause, with worse cognitive function (30). Age at menopause did not change the significance of oophorectomy variables, and age at menopause itself was not associated with cognitive functions. Several possible explanations, including the possible effects of genetic variants and nongenetic factors, and the fact that there may be different cognitive vulnerabilities at different ages, may explain our findings (11).

In the cross-sectional analyses, the hypothesis of hormone use as a moderator of the association between oophorectomy and cognition was not supported. This is consistent with existing literature, which has not found a statistically significant buffering association between hormone use and performance in visual recall, paragraph recall, attention, or language (31, 32). However, because there were differences in both history of ever using hormones and duration of hormone use in women with oophorectomy compared with intact ovaries (Table 2), more investigation may be warranted.

Strengths and Limitations

The relatively small number of women in the oophorectomy subgroups limited the ability to detect smaller effects of oophorectomy on cognition. Nonetheless, effects were found, encouraging additional research that examines ages at oophorectomy and cognitive testing as considerations in the association between oophorectomy and cognitive function. By design, the participants were likely healthier than the general population of midlife and older women and are therefore not fully representative. Although participant selection bias may be a concern in this context, it is unlikely that participation of women by oophorectomy status in the trials was related to cognitive status. Furthermore, any selection bias of participants into the trials would not be evident in the analyses of cognitive change. Missing information on the timing of oophorectomy and incomplete cognitive performance tests may have biased results. Although the women were healthy, more detailed health information of the women (such as indications for oophorectomy) may have been relevant. More corroborating data regarding history of hormone therapy and detailed information on hormone use specific to the time immediate after oophorectomy may have been helpful in limiting potential reporting bias or better understanding the possible effect of hormone use immediately after oophorectomy.

The strengths of this study are that detailed cognitive function and history of bilateral oophorectomy in an ethnically diverse sample of older women were closely examined while considering relevant demographic and medical variables such as BMI and duration of hormone use. Use of a sample largely free of signs or symptoms of potentially confounding or mediating factors such as cardiovascular history and diabetes is an additional strength. We were able to examine cognitive effects of oophorectomy in women who had already experienced natural menopause as well as in surgically menopausal women.

Conclusions

The results from this study support prior findings of negative associations between ovarian removal and aspects of cognitive function. Thus, providers should consider the timing of oophorectomy when feasible. According to the American College of Obstetricians and Gynecologists, strong consideration should be given for retaining normal ovaries in premenopausal women who are not at increased genetic risk of ovarian cancer (33).

Future research should continue to explore the relation between cognitive function and ovarian removal at different ages over a longer period of time in a healthy population. In addition, research should include more detailed information about hormone regimen, such as use of estrogen alone or combination estrogen with a progestogen, continuous versus sequential use, dose, and timing, as some studies suggest that different compounds may be associated with varying cognitive domain changes (34–36). These studies will hopefully provide a better understanding of the modifiable factors that are protective in cognitive function in older women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Sample characteristics of healthy postmenopausal women participants

Characteristic	BVAIT (n = 145)	WISH (n = 271)	ELITE (n = 510)	Combined (n = 926)
Oophorectomy status				
Bilateral	30 (20.1)	29 (10.7)	64 (12.6)	123 (13.3)
Intact	115 (79.9)	242 (89.3)	446 (87.5)	803 (86.7)
Education				
8th grade or less	0 (0)	1 (0.4)	1 (0.2)	2 (0.2)
Some high school	1 (0.7)	2 (0.7)	1 (0.2)	4 (0.4)
High school graduate	11 (7.6)	10 (3.7)	17 (3.3)	38 (4.1)
Trade/business school	7 (4.8)	14 (5.2)	13 (2.6)	34 (3.7)
Some college	53 (36.6)	79 (29.2)	137 (26.9)	269 (29.1)
Bachelor's degree	40 (27.6)	69 (25.5)	145 (28.4)	254 (27.4)
Graduate/professional	33 (22.8)	96 (35.4)	196 (38.4)	325 (35.1)
Race/ethnicity[a]				
White, non-Hispanic	96 (66.2)	173 (63.8)	362 (71.0)	631 (68.1)
Black, non-Hispanic	26 (17.9)	14 (5.2)	40 (7.8)	80 (8.6)
Hispanic	15 (10.3)	41 (15.1)	67 (13.1)	123 (13.3)
Asian or Pacific Islander	7 (4.8)	32 (11.8)	40 (7.8)	79 (8.5)
Native American	1 (0.7)			1 (0.1)
Other		11 (4.1)	1 (0.2)	12 (1.3)
BMI (kg/m^2)				
Underweight (<18.5)	2 (1.4)	5 (1.9)	8 (1.6)	15 (1.6)
Ideal (≥ 18.5, <25)	39 (26.9)	122 (45.0)	191 (37.5)	352 (38.0)
Overweight (≥ 25, <30)	51 (35.2)	85 (31.4)	181 (35.5)	317 (34.2)
Obese (≥ 30)	53 (36.6)	59 (21.8)	130 (25.5)	242 (26.1)
Hysterectomy status				
Hysterectomy	51 (35.2)	52 (19.2)	86 (16.9)	189 (20.4)
Intact uterus	94 (65.3)	219 (80.8)	424 (83.1)	737 (79.6)
Hormone use				
Current hormone use at baseline	62 (42.8)	1 (0.4)[b]	3 (0.6)[b]	66 (7.1)
History of hormone use but no current use	42 (29.0)	193 (71.2)	359 (70.4)	594 (64.1)
No history of ever using hormones	35 (24.1)	66 (24.4)	148 (29.0)	249 (26.9)
Unknown	6 (4.1)	11 (4.1)		17 (1.8)
Treatment				
Active	72 (49.7)	138 (50.9)	256 (50.2)	466 (50.3)
Placebo	73 (50.3)	133 (49.1)	254 (49.8)	460 (49.7)
Age (y) at testing, mean (±SD)				
Baseline	62.7 (±7.6)	60.8 (±7.0)	60.1 (±7.1)	60.7 (±7.2)
Follow-up	65.4 (±7.6)	63.5 (±7.0)	62.8 (±7.0)	63.4 (±7.2)
Depressive symptoms (CES-D score), mean (±SD)[c]	7.7 (±7.9)	7.0 (±6.6)	8.3 (±9.0)	7.8 (±8.2)

Characteristic	BVAIT (n = 145)	WISH (n = 271)	ELITE (n = 510)	Combined (n = 926)
Years on hormones, for those on therapy, mean (±SD)[d]	8.4 (±7.6)	6.5 (±6.6)	7.4 (±7.0)	7.3 (±7.0)
Age (y) at menopause, mean (±SD)[e]	44.7 (±9.9)	49.1 (±5.7)	49.3 (±5.5)	49.1 (±5.8)

Note: Data presented as frequency (%) or mean (±SD). BMI = body mass index; BVAIT = B-Vitamin Atherosclerosis Intervention Trial; CES-D = Center for Epidemiologic Studies Depression; ELITE = Early versus Late Intervention Trial with Estradiol; WISH = Women's Isoflavone Soy Health Trial; SD = standard deviation.

[a] In the analyses, race/ethnicity was a dichotomous variable White, non-Hispanic versus all other.

[b] Current hormone use was an exclusion criterion for the WISH and ELITE trials. Participants taking hormones at screening did not take hormones during the 1-month washout period before randomization.

[c] Sample sizes: BVAIT = 144; WISH = 271; ELITE = 510; total = 925.

[d] Sample sizes: BVAIT = 105; WISH = 196; ELITE = 362; total = 663.

[e] Sample sizes: BVAIT = 26; WISH = 271; ELITE = 510; total = 807.

Table 2
Sample characteristics of participants by oophorectomy status

Characteristic	Bilateral oophorectomy (n = 123)	Intact ovaries (n = 803)
Age (y) at testing		
Baseline[a]	61.9 (±7.1)	60.5 (±7.2)
Follow-up[a]	64.7 (±7.0)	63.2 (±7.2)
Education		
8th grade or less		2 (0.3)
Some high school	1 (0.8)	3 (0.4)
High school graduate	6 (4.9)	32 (4.0)
Trade/business school	6 (4.9)	28 (3.5)
Some college	44 (35.8)	225 (28.0)
Bachelor's degree	28 (22.8)	226 (28.1)
Graduate/professional	38 (30.9)	287 (35.7)
BMI category		
Underweight (<18.5)		15 (1.9)
Ideal (≥ 18.5, <25)	44 (35.8)	308 (38.4)
Overweight (≥ 25, <30)	41 (33.3)	276 (34.4)
Obese (≥ 30)	38 (30.9)	204 (25.4)
CES-D score at Test Administration 1[b]	9.0 (±8.2)	7.7 (±8.2)
Timing of bilateral oophorectomy surgery		
With unknown dates[c]	28 (22.8)	
After last menstrual period	26 (21.1)	
That led to menopause at age >45	33 (26.8)	
That led to menopause at age ≤45	36 (29.3)	
Time since surgery (y)[d]	15.2 (±8.9)	
Age at menopause (y)[e]	45.1 (±5.4)	49.6 (±5.7)
Years on hormones, for those on therapy[e,f]	11.1 (±8.8)	6.5 (±6.2)
Hormone use[e]		
Current hormone use at baseline	19 (15.5)	47 (5.9)
History of hormone use but no current use	96 (78.1)	498 (62.0)
No history of ever using hormones	8 (6.5)	241 (30.0)
Unknown		17 (2.1)

Note: Data presented as frequency (%) or mean (±SD). BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression; SD = standard deviation. Tests performed include independent t test, Wilcoxon, Kruskal-Wallis for ordinal variables.

[a] Significant difference in group, $P < .05$.

[b] Sample sizes: bilateral oophorectomy = 122; intact ovaries = 803.

[c] Of these women, 82.1% had a history of hormone therapy.

[d] n = 95, based on birthdate, date of surgery, and age at testing.

[e] Significant difference in group, $P < .0001$.

[f] Sample sizes: those with oophorectomy =115; those without oophorectomy = 548.

Table 3

Oophorectomy and cognitive performance: cross-sectional associations

	Unstandardized regression coefficient (SE) *P* value					
Model	**Global cognitive function**	**Executive function**	**Semantic memory**	**Logical memory**	**Visual memory**	**Verbal learning**
I: Not considering timing						
Oophorectomy	−0.2 (0.7) 0.79	−0.2 (0.4) 0.67	−0.1 (0.1) 0.54	−0.0 (0.2) 0.94	0.1 (0.2) 0.65	−0.0 (0.2) 0.95
II: Timing of last MP						
Unknown timing[b]	1.8 (1.5) 0.22	0.5 (0.8) 0.55	0.3 (0.3) 0.37	0.6 (0.4) 0.11	0.0 (0.4) 0.94	0.5 (0.4) 0.16
After last MP	0.9 (1.4) 0.54	0.4 (0.7) 0.58	0.0 (0.3) 0.88	0.1 (0.4) 0.72	0.0 (0.4) 0.89	0.2 (0.4) 0.52
Any age, before last MP	−1.3 (0.9) 0.14	−0.6 (0.5) 0.21	−0.3 (0.2) 0.15	−0.3 (0.2) 0.20	0.1 (0.2) 0.57	−0.3 (0.2) 0.19
III: Age (y) of last MP						
Unknown timing[b]	1.8 (1.5) 0.22	0.5 (0.8) 0.55	0.3 (0.3) 0.37	0.6 (0.4) 0.11	0.0 (0.4) 0.94	0.5 (0.4) 0.16
After last MP	0.9 (1.4) 0.54	0.4 (0.7) 0.58	0.0 (0.3) 0.88	0.1 (0.4) 0.72	0.1 (0.4) 0.89	0.2 (0.3) 0.51
Age >45, before last MP	−2.4 (1.3) 0.06	−0.9 (0.7) 0.17	−0.4 (0.3) 0.16	−0.1 (0.4) 0.29	−0.1 (0.3) 0.76	−0.7 (0.3) 0.03[a]
Age ≤ 45, before last MP	−0.3 (1.2) 0.80	−0.3 (0.6) 0.65	−0.2 (0.3) 0.47	−0.2 (0.3) 0.42	0.3 (0.3) 0.27	0.1 (0.3) 0.81
IV: Age (y) of last MP						
Hormone use, y	−0.0 (0.0) 0.48	−0.0 (0.0) 0.88	−0.0 (0.0) 0.44	−0.0 (0.0) 0.34	0.0 (0.0) 0.59	−0.0 (0.0) 0.15
Unknown timing[b]	2.0 (1.5) 0.19	0.5 (0.8) 0.54	0.3 (0.3) 0.32	0.6 (0.4) 0.09	−0.1 (0.4) 0.89	0.6 (0.4) 0.11
After last MP	1.0 (1.4) 0.47	0.4 (0.7) 0.56	0.1 (0.3) 0.78	0.2 (0.4) 0.60	0.0 (0.4) 0.96	0.3 (0.4) 0.37
Age >45, before last MP	−2.3 (1.3) 0.06	−0.9 (0.7) 0.17	−0.4 (0.3) 0.18	−0.3 (0.3) 0.32	−0.1 (0.3) 0.73	−0.7 (0.3) 0.04[a]
Age ≤ 45, before last MP	−0.1 (1.3) 0.97	−0.3 (0.7) 0.70	−0.1 (0.3) 0.64	−0.2 (0.3) 0.62	0.3 (0.3) 0.37	0.2 (0.3) 0.52

Note: Model I included the effect of oophorectomy regardless of timing. Model III included the timing of oophorectomy relative to natural menopause. Model IV built on Model III by including the addition of duration of hormone use. All models were adjusted for trial, age, education, race/ethnicity, and body mass index. Oophorectomy timing in order presented in Models III and IV: bilateral oophorectomy with unknown dates or timing; bilateral oophorectomy after last menstrual period; bilateral oophorectomy that led to menopause at age >45; bilateral oophorectomy that led to menopause at age ≤45. All oophorectomy variables are relative to women with intact ovaries. MP = menstrual period; SE = standard error of the mean.

[a] $P<.05$.

[b] Of these women, 82.1% had a history of hormone therapy.

Table 4

Oophorectomy and cognitive performance: associations over time

	Unstandardized regression coefficient (SE) *P* value					
Model	**Global cognitive function**	**Executive function**	**Semantic memory**	**Logical memory**	**Visual memory**	**Verbal learning**
V: Not considering timing						
Oophorectomy	−0.7 (0.4) 0.06	−0.3 (0.2) 0.12	−0.1 (0.1) 0.16	0.0 (0.2) 0.81	−0.2 (0.1) 0.17	−0.2 (0.1) 0.17
VI: Timing of last MP						
Unknown timing[b]	−0.6 (0.8) 0.49	0.1 (0.4) 0.64	−0.2 (0.2) 0.32	0.3 (0.4) 0.43	−0.1 (0.2) 0.78	−0.3 (0.3) 0.25
After last MP	−0.7 (0.8) 0.34	−0.4 (0.3) 0.21	0.2 (0.2) 0.24	−0.3 (0.3) 0.34	0.1 (0.2) 0.74	−0.2 (0.3) 0.55
Any age, before last MP	−0.7 (0.5) 0.12	−0.4 (0.2) 0.10	−0.2 (0.1) 0.04[a]	0.1 (0.2) 0.69	−0.3 (0.2) 0.06	−0.1 (0.2) 0.43
VII: Age (y) of last MP						
Unknown timing[b]	−0.5 (0.8) 0.49	0.2 (0.4) 0.64	−0.2 (0.2) 0.32	0.3 (0.4) 0.43	−0.1 (0.2) 0.78	−0.3 (0.3) 0.24
After last MP	−0.7 (0.7) 0.33	−0.4 (0.3) 0.21	0.2 (0.2) 0.24	−0.3 (0.3) 0.34	0.1 (0.2) 0.74	−0.2 (0.3) 0.54
Age >45, before last MP	−0.4 (0.7) 0.50	−0.4 (0.3) 0.21	−0.0 (0.2) 0.77	0.2 (0.3) 0.45	−0.6 (0.2) 0.004[a]	0.0 (0.2) 0.90
Age <45, before last MP	−1.0 (0.6) 0.12	−0.3 (0.2) 0.25	−0.4 (0.2) 0.01[a]	−0.0 (0.3) 0.88	0.0 (0.2) 0.97	−0.3 (0.2) 0.22
VIII: Age (y) of last MP						
Hormone use, y	0.0 (0.0) 0.05	0.0 (0.0) 0.22	0.0 (0.0) 0.34	0.0 (0.0) 0.38	0.0 (0.0) 0.31	0.0 (0.0) 0.81
Unknown timing[b]	−0.7 (0.8) 0.35	0.1 (0.4) 0.77	−0.2 (0.2) 0.27	0.2 (0.4) 0.50	−0.1 (0.3) 0.69	−0.3 (0.3) 0.24
After last MP	−1.0 (0.8) 0.20	−0.5 (0.3) 0.15	0.2 (0.2) 0.33	−0.4 (0.3) 0.26	0.0 (0.2) 0.88	−0.2 (0.3) 0.53
Age >45, before last MP	−0.5 (0.7) 0.42	−0.4 (0.3) 0.19	−0.1 (0.2) 0.71	0.2 (0.3) 0.50	−0.6 (0.2) 0.003[a]	0.0 (0.2) 0.91
Age <45, before last MP	−1.4 (0.7), 0.04[a]	−0.4 (0.3) 0.16	−0.5 (0.2) 0.006[a]	−0.1 (0.3) 0.66	−0.1 (0.2) 0.80	−0.3 (0.2) 0.22

Note: Model V included the effect of oophorectomy regardless of timing. Model VII included the timing of oophorectomy relative to natural menopause. Model VIII built on Model VII by including the addition of duration of hormone use. All models were adjusted for trial, age, education, race/ethnicity, body mass index, treatment indicator, and the baseline cognitive domain score. Oophorectomy timing in order presented in Models VII and VIII: bilateral oophorectomy with unknown dates or timing; bilateral oophorectomy after last menstrual period; bilateral oophorectomy that led to menopause at age >45; bilateral oophorectomy that led to menopause at age ≤ 45 years. All oophorectomy variables are relative to women with intact ovaries. Mean change in cognitive composite Z-scores = Z-scores from Test Administration 2 – Z-scoresfrom Test Administration 1. MP = menstrual period; SE = standard error of the mean.

[a] $P<.05$.

[b] Of these women, 82.1% had a history of hormone therapy.