

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

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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 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. (Fertil Steril® 2016; ■:■-■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Cognitive function, oophorectomy, surgical menopause

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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 postmenopausal 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 B₁₂, and vitamin B₆; 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

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