Serum Estrogen Levels, Cognitive Performance, and Risk of Cognitive Decline in Older Community Women

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OBJECTIVE: To determine the association between serum estrogen levels, cognitive performance, and risk of cognitive decline in older women.

DESIGN: Prospective cohort study with an average follow-up of 5 years.

SETTING: Clinical centers in Baltimore, MD, Minneapolis, MN, Portland, OR, and the Monongahela Valley in Pennsylvania.

PARTICIPANTS: 532 women aged 65 years or older who were the controls from two nested case-control studies in the ongoing Study of Osteoporotic Fractures.

OUTCOME MEASURES: Three cognitive tests — a modified Mini-Mental Status Exam, Digit Symbol, and Trails B — were administered at study initiation and were then repeated approximately 5 years later. Estrone and estradiol levels were determined by radioimmunoassay at two laboratories from baseline stored serum.

RESULTS: The characteristics of the women in the four serum estrogen quartiles did not differ except that body weight and change in weight since age 50 increased directly with higher quartile of serum estrogen ($P < .001$, for both estrone and estradiol). Initial cognitive performance on all three tests did not differ consistently by quartile of estradiol or by the estradiol to estrone ratio. Women in the higher estrone quartiles had 15% lower (worse) scores on Digit Symbol compared with the lower quartiles (P = .004) but there was no difference by quartile on the modified MMSE or on Trails B. Cognitive function test scores declined over the 5 years of follow-up. There was no difference in amount of change by quartile of estradiol, but women in the higher estrone quartiles had greater reduction of scores on Trails B compared with those in the lower quartiles (P = .012), even after adjusting for age, education, depression, stroke history, weight, and change in weight since age 50. The age-adjusted odds of cognitive decline (defined as tenth percentile of women with the largest decline in cognitive performance) did not vary across quartile of estrone or estradiol.

CONCLUSIONS: Endogenous estrogens are not associated consistently with cognitive performance or risk of cognitive decline on a selected battery of cognitive tests in older community-dwelling women. Worse performance on two cognitive tests among women with higher estrone levels was surprising and warrants further investigation. J Am Geriatr Soc 46:816–821, 1998.

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Recently, several studies have suggested that estrogen replacement therapy in postmenopausal women improves cognition,[1,2] prevents development of dementia,[3–5] and improves the severity of dementia.[6,7] There are plausible biological mechanisms to support a role for estrogen in cognitive function, including promotion of neuronal survival and dendritic sprouting, increases in acetylcholine activity, favorable lipoprotein alterations, and prevention of cerebral ischemia.[8–11]

See also p 918

Serum estrogens have been found to be lower in women with Alzheimer's disease compared with age-matched controls,[12] but few studies have examined the association of endogenous estrogens and cognitive function, and no study has explored the relationship between serum estrogen levels and cognitive decline over time. As part of an ongoing study of older women, we measured serum estrogens and cognitive function in 532 women to determine if serum estrogen is associated with poor cognitive performance or rapid decline in cognitive function.

METHODS

Subjects

The Study of Osteoporotic Fractures (SOF) is a prospective study of risk factors for fractures in older women. From September 1986 through October 1988, women who were at least 65 years of age were recruited for the study from population-based listings in four areas of the United States: Baltimore, Maryland, Minneapolis, Minnesota, Portland Oregon , and the Monongahela Valley near Pittsburgh, Pennsylvania.[13] Black women were excluded because of their low incidence of hip fracture, as were women who were unable to walk without assistance, women who had bilateral hip replacements, or women with dementia. All SOF participants

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were interviewed and examined during the baseline visit in 1986–1988. Participants then underwent three biennial clinic visits and completed annual questionnaires. Two nested case-control studies, in which subjects had serum hormones analyzed, were conducted as part of the SOF. One, a study of vertebral and hip fracture cases, included 320 controls, and the other, a study of breast cancer cases, included 212 controls. All controls were randomly selected women from the SOF (computer-generated random identification numbers) who were not taking exogenous hormones at baseline. The analyses presented here are based on these 532 controls, who had serum estrone measured, and a subset (n = 425), who had serum estradiol measured. Some of these subjects had subsequent fractures (n = 38) and breast cancer (n = 5). The institutional review board of each center approved the study; all participants signed an informed consent at study onset.

Measurement of Estrogens

During the initial clinic visit, 1986–1988, serum was collected from each participant between 10 a.m. and 2 p.m. All subjects were instructed to adhere to a fat-free diet overnight and the morning of the blood draw to minimize lipemia, which might interfere with hormonal assays. The serum was stored at −20°C for no more than a week, then transferred to long-term storage at −190°C until 1994, at which time levels of estrone and estradiol were determined by radioimmunoassay. Endocrine Sciences, Inc. (Calabasas Hills, CA) performed the estrogen measurements in 60% of the women, with estrone having a within-subject correlation (Lin's concordance coefficient) of 0.97 on a blind retest of 30 samples and estradiol having a within-subject correlation of 0.92 on a blind retest of 19 samples. The remaining subjects (n = 212) had estrone and estradiol measured at the Corning Nichols Institute (San Juan Capistrano, CA) and, based on 30 pairs, had a within-subject correlation (Lin's concordance coefficient) for estrone of 0.99 and for estradiol of 0.84. Results from 25 split serum specimens measured at the two reference laboratories showed similar results (Lin's concordance coefficient for estradiol, 0.85; for estrone, 0.95). The lowest detectable level for estradiol was <5 pg/mL.

Cognitive Function Assessment

Tests measuring cognitive functions were administered by a trained examiner during the initial clinic visit in 1986–88 or 2 years into the study and then repeated 6 years after enrollment (4–6 years after the initial tests). A modified version of the Mini-Mental Status Examination[14,15] with a maximum score of 26 was administered during the initial visit and then repeated at year 6. This is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory, with lower scores indicating poorer performance. Trails B, a test of speeded mental operations, attention, visual scanning, visual sequential abilities, and mental flexibility, was administered at year 2 and repeated at year 6.[16] Scores are measured in seconds, with higher scores indicating slower or poorer performance; an upper cut-off score of 421 seconds was used when time to complete exceeded 420 seconds. Digit Symbol, a subtest of the Wechsler Adult Intelligence Scale-Revised, which measures attention, psychomotor performance, and perceptual organization,[17] was administered at year 2 and repeated at year 6. Scores on Digit Symbol reflect the number correct within the timed trial; thus the lower scores indicate poorer performance.

We determined cognitive decline to be present in the tenth percentile of participants with the largest (worst) decline in cognitive function scores from the first to the repeat score.[18]

Other Variables

At the baseline clinic visit, participants completed a comprehensive questionnaire that included information on age, education, age at menopause, and whether they had a surgical or natural menopause. Participants were asked about current and past use of estrogen (by pill, patch, injection, or cream), and reports of current medications were checked by examining labels of drugs brought to the clinic. Medical histories were ascertained and subjects were asked specifically whether a physician had ever diagnosed them with dementia, a heart attack, or a stroke. During the interview, subjects were asked about alcohol consumption (drinks per week for the past 30 days) and cigarette smoking (lifetime pack-years). They were asked whether they thought they had more memory problems than most people and to rate self-perceived health status as excellent or good versus fair, bad, or very bad. Weight (in light clothes without shoes) was measured with a balance beam scale. Self-reported weight at age 50 years was used to calculated change in weight since age 50. At year 2, the 15-item Geriatric Depression Scale-Shortened (GDSS) was administered.[19] Scores for the GDDS range from 0 to 15, with higher scores indicating more depressive symptoms and a score of greater than 5 associated with clinically significant depression.[19] Deaths among the study population were recorded, and cause of death was determined by a study physician who reviewed the death certificates and medical records.

Statistical Analysis

Because the distribution of estradiol and estrone was skewed, we chose to analyze the hormones by quartile. For estradiol, 40% of participants had nondetectable levels and were placed in one group; the remainder were then divided into tertiles. For estrone, the 425 women were divided into quartiles. Descriptive characteristics were compared by ANOVA for continuous variables and chi-square for dichotomous variables across quartiles. For each of the three cognitive tests, a linear regression analysis was performed with hormone quartile as the predictor and either test score or change in test score as the outcome. We adjusted these models for variables that have previously been shown to affect cognitive function (age, education, depression, stroke history, and alcohol consumption) or varied statistically by quartile of estrogen. In our final multivariate model, we adjusted for age, education, depression score, history of stroke, alcohol use, weight, and change in weight since age 50. We performed multivariate logistic regression to determine the association of estrogen levels and cognitive decline. All significance levels reported are two-sided, and all analyses were performed using SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

The mean age of the participating women was 71.9 ± 5.1 years. Mean serum estrone was 22.8 ± 11.6 pg/mL, and mean serum estradiol was 6.4 ± 4.7 pg/mL. The characteristics of the women in the four estrone serum quartiles did not

Table 1. Characteristics of the 532 Women by Quartile of Serum Estrone

Characteristics	Quartiles of Estrone (Range in pg/mL) 0–15 (n = 142)	16–22 (n = 130)	22–28 (n = 122)	29–76 (n = 138)	P Value*
Age (years)	71.0 ± 4.9	72.4 ± 5.3	72.2 ± 5.1	72.0 ± 5.2	.101
Education (years)	12.4 ± 2.8	12.9 ± 3.1	12.3 ± 2.7	12.1 ± 2.6	.119
Weight (kgs)	63.7 ± 9.1	65.3 ± 11.2	69.1 ± 11.6	74.7 ± 13.7	<.001
Weight change since age 50 (kgs)	3.7 ± 0.7	3.9 ± 0.7	4.6 ± 0.7	8.0 ± 0.7	<.001
Cigarette use (pack-years)	10.2 ± 1.5	10.7 ± 1.6	8.3 ± 1.6	9.7 ± 1.6	.432
Alcohol consumption (drinks/week)	1.8 ± 3.8	1.6 ± 3.2	1.9 ± 5.2	1.5 ± 3.6	.837
Geriatric Depression Score	1.5 ± 2.1	1.7 ± 2.7	1.8 ± 2.4	2.1 ± 2.5	.350
Age at menopause (years)	47.7 ± 5.5	48.4 ± 4.6	47.8 ± 6.5	48.2 ± 5.7	.807
Natural menopause (%)	88	93	91	91	.724
No follow-up cognitive tests (%)	27	27	33	32	.304
Stroke history (%)	6	4	5	3	.810
Myocardial infarct history (%)	5	9	5	13	.064
Excellent/good self-reported health (%)	88	83	83	79	.246

*P value for overall ANOVA for continuous variables and overall 2 × 4 chi-square for dichotomous variables.

differ (Table 1), except that weight and weight gain since age 50 increased directly with higher quartile of serum estrogen ($P < .001$ for both estrone and estradiol). There were no differences in Geriatric Depression Score or the percentage of women with depression as defined by score > 5 on the Geriatric Depression Score. The percentage of subjects with natural menopause and mean age at menopause were also similar across quartiles. Similar trends were observed in the 425 women who had estradiol measured.

There were no differences in initial cognitive test scores by estradiol quartile (Table 2). Women in the higher estrone quartiles had approximately 15% lower (worse) scores on Digit Symbol compared with those in the lower quartiles ($P = .004$), but there was no difference by quartile on the modified MMSE or on Trails B (Table 3). Adjustment for depression score, age, education, stroke history, body weight, weight change since age 50, and alcohol use did not change the results. The percentage of women who reported "worse memory than other people" at study initiation did not differ by estrogen quartile (14%, 13%, 9%, and 17% for estradiol quartiles, $P = .97$; 14%, 9%, 13%, 16% for estrone quartiles, $P = .83$).

Cognitive testing was completed at follow-up in 73% of the women. Serum hormone levels did not differ in the 119 women who did not complete follow-up cognitive tests. (Table 1). Of the women who did not have repeat cognitive testing, 80% had died; only one subject died of dementia.

As expected, cognitive scores were lower at repeat testing 4 to 6 years later. The change in cognitive test score with repeat testing was similar across quartiles of estradiol (Table 2). Women in the higher estrone quartiles had greater reduction of scores on Trails B compared with those in the lower estrone quartiles ($P = .012$). Change in modified MMSE scores and in Digit Symbol did not differ by quartile of estrone. After adjusting for age, education, alcohol use, stroke history, depression score, weight, and weight change since age 50, Trails B change score remained greater in the higher estrone quartiles ($P = .037$). We calculated change in cognitive function as a percentage of the initial test score. Percent change did not differ by estradiol or estrone quartile

Table 2. Cognitive Function Test Score and Change in Score with Repeat Testing (4–6 Years Later) by Quartile of Estradiol

Cognitive Test	Quartiles of Estradiol (Range in pg/mL) <5	5–7	8–9	10–25	P Value*
Digit Symbol					
Initial score ± SD	46.1 ± 12.9	43.8 ± 11.4	43.3 ± 10.7	42.0 ± 11.9	.118
Change score ± SD	−4.0 ± 8.8	−4.4 ± 12.4	−2.4 ± 9.6	−4.4 ± 7.6	.666
Trails B					
Initial score (SD)	132 ± 89	132 ± 69	142 ± 69	141 ± 75	.655
Change score (SD)	13 ± 52	23 ± 72	31 ± 54	33 ± 54	.132
Modified MMSE†					
Initial score (SD)	24.7 ± 1.5	24.7 ± 1.6	24.6 ± 1.6	24.3 ± 2.3	.346
Change score (SD)	−0.8 ± 2.7	−0.4 ± 1.9	−0.4 ± 2.1	−0.3 ± 2.1	.553

*Overall ANOVA.
†MMSE = Mini-Mental State Exam.

Table 3. Cognitive Function Test Score and Change in Score with Repeat Testing (4–6 Years Later) by Quartile of Estrone

Cognitive Test	Quartiles of Estrone (Range in pg/mL) 0–15	16–22	22–28	29–76	*P* Value*
Digit Symbol					
Initial score ± SD	47.3 ± 12.3	44.8 ± 11.4	39.8 ± 10.0	41.2 ± 11.0	.004
Change score ± SD	−4.6 ± 7.6	−4.0 ± 8.1	−2.0 ± 7.2	−4.3 ± 9.2	.337
Trails B					
Initial score ± SD	127 ± 62	141 ± 74	145 ± 65	144 ± 70	.164
Change score ± SD	18 ± 60	14 ± 54	42 ± 68	29 ± 50	.012
Modified MMSE†					
Initial score ± SD	24.7 ± 1.7	24.5 ± 2.2	24.5 ± 2.0	24.5 ± 1.8	.751
Change score ± SD	−0.6 ± 2.5	−0.7 ± 2.4	−0.4 ± 2.2	−0.4 ± 1.8	.593

*Overall ANOVA.
†MMSE = Mini-Mental State Exam.

on any of the three tests (Figure 1). Seven women reported a history of physician-diagnosed Alzheimer's disease at the time of repeat cognitive testing; these women were evenly distributed by quartile of estradiol ($P = .43$) and estrone ($P = .65$).

To determine if a clinically significant change in cognitive function was associated with estrogen levels, we evaluated the women with the largest (worst) tenth percentile reduction in test scores from initial to repeat performance. For Trails B, the worst tenth percentile change was 69 seconds or more; for modified MMSE, −12.5 points or more, and for Digit Symbol, −30.7 points or more. The age-adjusted odds (95% confidence intervals) of cognitive decline using the lowest quartile of estradiol as reference ranged in the other quartiles from 0.9 (0.2–3.3) to 1.9 (0.6–6.0) for Trails B, from 0.5 (0.1–1.5) to 1.0 (0.4–2.7) for modified MMSE, and from 1.4 (0.4–4.2) to 2.2 (0.7–6.8) for Digit Symbol. For estrone, the results were similar, with the age-adjusted odds of cognitive decline ranging from 0.8 (0.3–2.1) to 1.2 (0.4–3.1) for Trails B, from 0.8 (0.2–2.0) to 1.2 (0.5–3.0) for modified MMSE, and 0.5 (0.1–1.6) to 1.3 (0.5–3.3) for Digit Symbol.

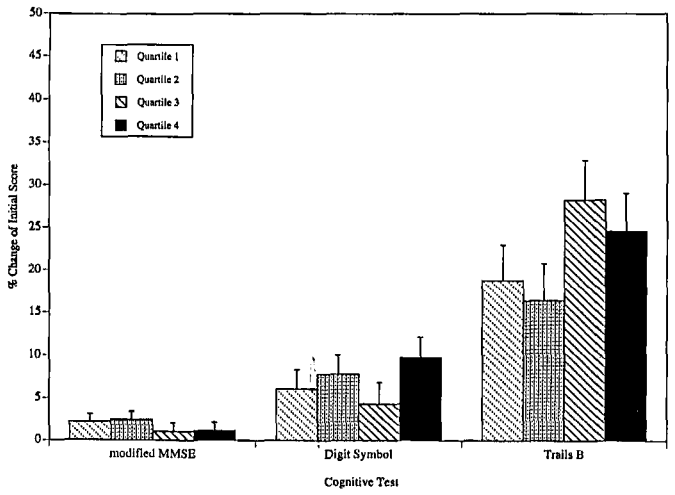

Figure 1. Percent change in cognitive test score (±SD) by quartile of estrone; *P* for overall ANOVA (modified MMSE $P = .679$; Digit Symbol $P = .415$; Trails B $P = .220$).

To determine if the ratio of estradiol to estrone was associated with cognitive performance, we performed a linear regression analysis with estradiol/estrone ratio as the predictor and each cognitive test score as the outcome. There was no association with estradiol/estrone ratio and initial or repeat modified MMSE ($P = .16$ and .36), Trails B ($P = .32$ and .44), and Digit Symbol ($P = .08$ and .19).

DISCUSSION

In this study of 532 older women, we found no consistent association of serum estrogen levels and cognitive function or change in cognitive performance 4 to 6 years later. This is the first study to analyze the relationship between endogenous estrogens and change in cognitive function over time. Our results are supported by a cross-sectional study of 19 women (mean age 48.2 years), in which serum estradiol was correlated with cognitive performance on only one of seven cognitive tests.[20]

Neurophysiological and biochemical studies have demonstrated several potential mechanisms whereby estrogen may enhance cognition and prevent cognitive decline. These mechanisms include promotion of cholinergic and serotonergic activity in specific areas of the brain,[9,21] enhanced neuronal survival,[8] favorable alterations in lipoproteins,[10] and prevention of cerebral ischemia.[11] Observational human studies comparing cognitive performance of postmenopausal women on estrogen replacement with those not on estrogen have had conflicting results.[1,2,20,22,23] These studies are susceptible to bias and confounding because there may be differences in the women who choose to take or are prescribed estrogen replacement, such as education, age, and health behaviors,[24] and these differences may also effect cognitive performance.[25] Trials of estrogen replacement in postmenopausal women have also had conflicting results.[26–32] Most of the studies that reported a positive effect of estrogen on cognition included women with perimenopausal symptoms whose resolution may have explained the improvement in cognitive performance.[27–29,31,32]

Our findings do not support the hypothesis that estrogen protects against cognitive decline. Studies that have found a protective effect have compared women on estrogen replacement therapy with women not taking estrogen. There may be a threshold effect of estrogen on cognition, such that premenopausal levels or those achieved on estrogen replacement

therapy, usually at least 10 times higher than postmenopausal levels,[33] are required to have a beneficial effect on cognitive performance. However, several studies suggest that even the low physiologic levels of estrogens present in postmenopausal women have a biologic effect on fracture risk and breast cancer risk.[34,35]

Poorer performance on initial Digit Symbol testing and the greater reduction in scores with repeat testing on Trails B among women with higher estrone quartiles was surprising. This paradoxical result may be a chance finding, although the association was found in the two of the three cognitive tests and was strongly statistically significant. Higher body weight associated with higher estrone levels may explain this association if these women are at risk for diseases that impair cognitive performance such as diabetes, hypertension, or myocardial infarction. However, after we adjusted our analyses for body weight and change in weight, the association between higher estrone and worse cognitive scores weakened but remained ($P = .01$ for Digit Symbol and $P = .037$ for change in Trails B score). There are two major forms of estrone. C-2 hydroxylated estrone may competitively inhibit the effects of estradiol, whereas C-16 hydroxylated estrone has estradiol agonist activity.[36,37] It is possible that poorer cognitive performance is associated with higher estrone if the ratio between estrogen antagonist to agonist activity is high. Inasmuch as we did not measure the two estrone subfractions, we cannot address this question.

Although we used three tests to measure cognitive function, we had no clinical assessment for dementia and, therefore, cannot determine the etiology and significance of the subjects' cognitive decline. We tried to assess clinical relevance by using a conservative criteria of cognitive decline, defined as those women with the greatest tenth percentile reduction in cognitive scores. This method has been reported to have high sensitivity and specificity for dementia.[18] The observed changes over time in cognitive tests in our subjects are consistent with those seen in other aging population studies[18,38] Had we performed a specific dementia evaluation, we do not expect that our results would be different. Our results are limited to the three cognitive tests administered; we did not test all aspects of cognitive function. In particular, some studies have suggested that estrogen may be associated with better verbal memory performance.[20,31] Approximately 25% of the subjects did not have repeat cognitive testing, and although their serum estrogens did not differ from those who did have follow-up, it is likely that they would have had worse cognitive function.

The estrogen measurements in this study were based on a single assay and may not be as precise as an average of several measures. We only measured estrone and estradiol at study initiation, but Hankinson has demonstrated that postmenopausal intra-individual changes in serum estradiol and estrone are minimal over at least a 3-year period.[39] Furthermore, serum estrogens tend not to vary with age in postmenopausal women.[40] We used two different labs for the determination of estrogen measurements, but there was good intercorrelation and reproducibility, and the mean serum estrogen levels were similar to other studies of community postmenopausal women not taking estrogen replacement.[41]

We conclude that endogenous estrone and estradiol in postmenopausal women do not correlate with cognitive function or predict cognitive decline on a selected battery of cognitive tests. Worse performance on two cognitive tests among women with higher estrone levels was surprising and warrants further investigation. Whether endogenous estrogens are predictive of cognitive function in older women, estrogen replacement therapy remains to be explored.

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