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Endogenous Sex Hormones and Cognitive Function in Older Men*

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ABSTRACT

The objective of this study was to determine whether endogenous sex hormone levels predict cognitive function in older men. Our study design was an exploratory analysis in a population-based cohort in Rancho Bernardo, California. The study participants were 547 community-dwelling men 59–89 yr of age at baseline who were not using testosterone or estrogen therapy. Between 1984 and 1987, sera were collected for measurement of endogenous total and bioavailable testosterone and estradiol levels. Between 1988 and 1991, 12 standard neuropsychological instruments were administered, including two items from the Blessed Information-Memory-Concentration (BIMC) Test, three measures of retrieval from the Buschke-Fuld Selective Reminding Test, a category fluency test, immediate and delayed recall from the Visual Reproduction Test, the Mini-Mental State Examination with individual analysis of the Serial Sevens and the "World" Backwards components, and the Trail-Making Test Part B. In age- and education-adjusted analyses, men with higher levels of total and bioavailable estradiol had poorer scores on the BIMC Test and Mini-Mental State Examination. Men with higher levels of bioavailable testosterone had better scores on the BIMC Test and the Selective Reminding Test (long-term storage). Five associations were U-shaped: total testosterone and total and bioavailable estradiol with the BIMC Test; bioavailable testosterone with the "World" test; and total estradiol with the Trail-Making Test. All associations were relatively weak but independent of age, education, body mass index, alcohol use, cigarette smoking and depression. In these older men, low estradiol and high testosterone levels predicted better performance on several tests of cognitive function. Linear and nonlinear associations were also found, suggesting that an optimal level of sex hormones may exist for some cognitive functions. (*J Clin Endocrinol Metab* **84:** 3681–3685, 1999)

BIOLOGICALLY plausible mechanisms derived from animal studies (1–11) suggest that endogenous sex hormones affect cognition through an initial organizational role in the perinatal period (12, 13), during adult life (14, 15), and possibly extending to the prevention of dementia (16–21). Studies of men examining the relationship between endogenous estrogen (22–26) and testosterone (22–35) levels and cognition have yielded conflicting results. Six studies suggest a U-shaped (quadratic) relation between cognitive function and endogenous sex hormones (28, 30, 31, 35–37). Studies of androgen treatment effects have been largely limited to young men; the only clinical trial that studied testosterone supplementation and cognitive function in older men found that testosterone enhanced spatial cognition (37). We report here a population-based study of endogenous estrogen and testosterone levels and performance on 12 standardized neuropsychological tests in community-dwelling older men.

Subjects and Methods

From 1972 to 1974, 82% of older adult residents in Rancho Bernardo, a southern California community, participated in the Rancho Bernardo Study. All were ambulatory, middle to upper-middle class, and Caucasian (38). Vital status has been assessed by annual mail or telephone contacts to the present, with death certificates obtained for all decedents.

The baseline data for the present study was obtained between 1984 and 1987 when all surviving local residents who were members of the original cohort were invited to a clinic visit and 82% participated.

A standardized questionnaire, which asked about demographic data, cigarette smoking, alcohol consumption, and the use of selected medications, was completed. Medication use was validated by examination of prescriptions or pills brought to the clinic for that purpose. Height and weight were measured with subjects wearing light clothing and no shoes; body mass index (BMI) was calculated as $[kg/m^2] \times 100$. Blood was obtained by venipuncture from fasting subjects between 0700 and 1100 h; the plasma was frozen at −70 C for hormone assays. Information on depressed mood was obtained using 18 of the 21 items of the Beck Depression Index (BDI) (39). Three items (guilt, expectation of punishment, and self-hate) were excluded from the questionnaire because studies have suggested that as many as three fourths of the items from highly reliable measures can be dropped without much loss in sensitivity or specificity (40) and other studies have reported on the validity of a 13-item short-form BDI (41). Total scores on the BDI were computed by summing the responses to each question. Higher scores are indicative of depressed mood. These scores were then proportionally adjusted to correspond to scores and cutpoints previously established for the full 21-item scale. In this cohort, reliability as assessed by Cronbach's α was 0.75, which is comparable with the reliability obtained using samples of elderly community volunteers ($\alpha = 0.76$) and depressed outpatients ($\alpha = 0.73$) (42).

Between 1988 and 1991, 81% of surviving, community-dwelling local participants attended another clinic visit when they were individually evaluated using 12 standard tests of cognitive function as recommended by the Alzheimer's Disease Research Center at the University of California, San Diego. Informed consent was obtained from the subjects or their caregiver (10 subjects). All cognitive function tests were administered by one specifically trained nurse. Test items included two items from the Blessed Information-Memory-Concentration (BIMC) Test (43), Buschke-Fuld Selective Reminding Test (SRT) (44), a category fluency test (animals) (45), Visual Reproduction Test (VRT) (46), Mini-Mental

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State Examination (MMSE), with individual analysis of Serial Sevens, "World" Backwards (47), and Trail-Making Test Part B (Trails B) (48). For all tests except Trails B and SRT (short-term storage), a higher score denotes better cognitive function.

Two items from the BIMC were used to assess mental control and verbal memory. Naming the months of the year backward assesses mental control, and recalling a five-part name and address after a 10-min delay assesses verbal memory. The maximum possible score is 7.

The Buschke-Fuld SRT assesses storage, retention, and retrieval of spoken words with this verbal list learning task. Ten unrelated words are read to the subject at a rate of one word every 2 sec. Immediately following, the subject is asked to recall the entire list. Then, only those words not recalled on the first trial are read to the subject, and, immediately following, the subject is asked to recall the entire list. This procedure is followed for six trials. Items recalled immediately after prompting are retrieved from short-term storage, and items recalled on two consecutive trials without reminding come from long-term storage. High scores on short-term memory are a sign of memory deficiency; demented persons usually score less than 14 on long-term memory (49). Next, the subject is read two words at a time and asked to tell which of the words was from the original list; this is called the Buschke Word Recognition (BWR) test.

In Category Fluency (animals), the subject names as many animals as possible in 1 min to assess verbal fluency. The score is the number correctly named. Repetitions, variants (*e.g.*, dogs after producing dog), and intrusions (*e.g.*, apple) are not counted.

The VRT, Russell's adaptation of the VRT from the Wechsler Memory Scale, assesses memory for geometric forms. Three stimuli of increasing complexity are presented one at a time for 10 sec each. The subject is asked to reproduce the figures immediately to assess short-term memory and, after 30 min of unrelated testing, to assess long-term memory. After both memory trials have been administered, the subject is asked to copy the stimulus figures to assess visual-spatial impairment. Scores below 8 for immediate recall and below 3 for delayed recall are accepted cutoff scores for possible dementia.

The MMSE assesses orientation, registration, attention, calculation, language, and recall. Scores range from 0 to 30; subjects with dementia generally score below 24 (50). Two items from the MMSE were analyzed separately. To assess the ability to calculate, the subject is asked to count backward from 100 by sevens. To assess attention, the subject is asked to spell the word "world" backward. These two items provide information about mental control, and the maximum possible score is 5 for each test.

Trails B from the Halstead-Reitan Neuropsychological Test Battery tests visuomotor tracking and attention. The subject continuously scans a page to identify numbers and letters in a specified sequence while shifting from number to letter sets. A maximum of 300 sec is allowed; performance is rated by the time required to finish the test. Taking longer than 131 seconds suggests dementia.

Levels of total and bioavailable estradiol and testosterone from never previously thawed frozen plasma were measured in early 1992. Previous work in this laboratory demonstrated no hormone deterioration over 15 yr when samples were frozen and stored in tightly sealed containers (51). Sex hormone levels were measured by radioimmunoassay in an endocrinology research laboratory (52). Bioavailable testosterone and bioavailable estradiol were determined using a method modified from Tremblay and Dube (53), which measures free plus albumin-bound but not sex hormone-binding globulin-bound hormones. The sensitivity and intra-assay and interassay coefficients of variation were 37 pg/mL, 4%, and 6.8% for testosterone; 6 pg/mL, 5.9%, and 7.4% for estradiol; 37 pg/mL, 5.8%, and 7.6% for bioavailable testosterone; and 6 pg/mL, 3.7%, and 5.2% for bioavailable estradiol.

Data were analyzed using the Statistical Analysis System (SAS) (SAS User's Guide, Version 6, ed 1989–1996; SAS Institute, Inc., Cary, NC). Because hormone levels showed a slightly skewed distribution, analyses were performed using log transformed data. To aid in the interpretation of the results, mean values are presented for untransformed data; all P values are based on logged data. t tests were used for continuous variables, and χ^2 tests were used for discrete variables. All comparisons were adjusted using analysis of covariance for the covariates: age; age and education; age, education, and alcohol use; age, education, and BMI; and age, education, smoking, and BDI. The BDI score was used as a continuous measure of depressed mood and as a categorical variable measure of clinical depression, defined as a score greater than or equal to 13. Standard multiple regressions and partial Pearson correlations were calculated to assess possible associations between the 12 neuropsychological tests and the four sex hormones. Because the literature suggested nonlinear associations, quadratic terms were used to test for nonlinear or U-shaped associations as currently recommended (54), and associations were repeated examining cognitive function test scores by quartile of each sex hormone level. Because this was an exploratory analysis, no adjustment was made for multiple comparisons; instead, we show the number of comparisons made and report all nonsignificant results along with positive results. All tests are two-tailed.

Results

This study includes all 547 men who participated in both the 1984–1987 and the 1988–1991 visits. They were 55–89 yr of age at baseline and were not using exogenous estrogen or testosterone therapy. Mean age (70 yr), hormone levels, and cognitive function test scores are shown in Table 1, along with the distribution of major covariates. The mean endogenous sex hormone levels were similar to levels reported elsewhere for men of similar age (55). As reported elsewhere (56), bioavailable, but not total, estradiol and testosterone decreased with age ($r = -0.10$ and $r = -0.36$, respectively; $P < 0.01$). All cognitive function test scores worsened significantly with age ($P < 0.0001$) (data not shown).

Three tests of linear or stepwise associations were performed. Age and education-adjusted linear regression analyses for sex hormones and neuropsychological tests showed significantly poorer MMSE scores with increasing levels of total and bioavailable estradiol and significantly better BIMC Test scores with increasing levels of bioavailable testosterone (Table 2). Both age and education were highly significant in the linear model ($P < 0.0001$). No other significant hormone-cognitive function associations were seen with linear regression analyses. In a quartile analysis, age- and education-adjusted mean BIMC Test scores worsened with increasing levels of total estradiol (for linear trend, $P < 0.04$). This

TABLE 1. Baseline descriptive data for 547 Rancho Bernardo men: 1984–1987

	Mean (SD)	Interquartile range
Age (yr)	70.2 (8.3)	63.0–77
BMI (kg/m^2)	26.1 (3.1)	24.1–27.8
Daily alcohol (%)	53.0	
Completed 4 yr college (%)	51.0	
Current smoking (%)	10.0	
Hormones		
Total estradiol (pmol/L)	74.7 (24.9)	58.7–88.1
Bioavailable estradiol (pmol/L)	48.8 (16.4)	36.7–58.7
Total testosterone (nmol/L)	10.8 (3.6)	8.4–13.1
Bioavailable testosterone (nmol/L)	3.47 (1.06)	2.8–4.1
Cognitive function tests		
Blessed items	5.9 (1.5)	5–7
SRT, long-term recall	26.5 (12.7)	18–36
SRT, short-term recall	7.8 (4.5)	4–11
SRT, total recall	34.4 (9.6)	28–41
BWR	9.8 (0.7)	10–10
Category fluency	18.4 (5.4)	15–22
VRT, immediate recall	9.8 (3.9)	7–13
VRT, delayed recall	7.4 (4.6)	4–11
MMSE	26.7 (2.9)	26–28
World backward	4.7 (0.85)	5–5
Serial sevens	4.3 (1.1)	4–5
Trails B (sec)	131.8 (64.8)	85–156

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association was unchanged after adjusting for BMI, smoking, alcohol use, and depression ($P < 0.04$). Bioavailable estradiol and total and bioavailable testosterone were not associated with any neuropsychological test score in quartile analyses. Age and education-adjusted partial correlations were positive between bioavailable testosterone and BIMC Test (r = 0.10; $P = 0.03$) and negative between MMSE score and total and bioavailable estradiol [r = −0.10 ($P = 0.02$) and r = −0.09 ($P = 0.04$), respectively]. These results persisted after additional adjustment for alcohol use, BMI, smoking, and depression. No other significant associations were found.

To determine whether there was a threshold effect, age- and education-adjusted levels of endogenous sex hormones were analyzed for the six neuropsychological tests that could be dichotomized by screening criteria previously established by the University of California, San Diego, Alzheimer's Disease Research Center (49). As shown in Table 3, men who scored better (above the cutoff score) on the long-term memory component of the SRT had, on average, higher age- and education-adjusted levels of bioavailable testosterone than men who scored below the cutpoint. This result did not change after adjusting for alcohol use, BMI, smoking, or depression ($P < 0.05$). No significant differences were seen between age- and education-adjusted total testosterone, or total or bioavailable estradiol, and any cognitive function score above *vs.* below the cutpoint.

Finally, a multiple regression model was used to examine the independent contribution of the quadratic hormone level, linear hormone level, age, education, alcohol consumption, BMI, and smoking to the score on the neuropsychological tests (Table 4). In these analyses, both the linear and quadratic component for all hormones, except the bioavailable testosterone quadratic term, contributed significantly to the multiply-adjusted model for BIMC Test. In addition, both the linear and quadratic estradiol terms were significantly associated with Trails B. The quadratic terms for total testosterone and bioavailable testosterone were significantly associated with the "World" Backwards test and with VRT, respectively.

TABLE 2. Linear regression model (β) of hormone levels on cognitive function test scores adjusted for age and education

	Total estradiol	Bioavailable estradiol	Total testosterone	Bioavailable testosterone
Blessed items	−0.284	−0.072	0.095	0.286[a]
SRT, long-term	−0.985	−0.138	1.06	1.74
SRT, short-term	0.314	0.0034	−0.206	−0.421
SRT, total recall	−0.562	−0.121	0.995	1.35
BWR	−0.122	−0.122	−0.0197	−0.026
Category fluency	−0.356	−0.44	0.115	−0.042
VRT, immediate	−0.088	0.056	−0.094	0.107
VRT, delayed	0.3185	0.551	0.1734	0.584
MMSE	−0.6197[a]	−0.526[a]	−0.383	−0.304
World backward	−0.071	0.066	−0.063	0.0755
Serial sevens	−0.238	−0.057	−0.164	−0.012
Trails B	−3.67	−6.45	−4.47	−7.79

[a] $P < 0.05$.

Discussion

In this prospective study of older community-dwelling men, low estradiol levels were associated with better performance on two standard cognitive function tests, whereas high total or bioavailable testosterone levels predicted better performance on tests of verbal memory and mental control.

Some (23, 24, 28, 30, 32, 33, 35), but not all studies (22, 25, 27, 32), have found a significant positive association between endogenous testosterone levels and spatial abilities, including visuospatial orientation (34), spatial form comparison (33), composite visuospatial scores (24), and tactual-spatial measures (25). Administration of pharmacological doses of exogenous testosterone by patch or intravenous infusion has been shown to be associated with improved visuospatial ability in healthy older men (37) and higher scores on tests of serial subtraction in healthy young men (36).

Less work has been done on the association between cognitive function and estrogen in men. In contrast to the present study, three previous studies reported no association (22–25), one study reported a positive association between total estradiol level and performance on two measures of visual, but not verbal, memory (22), and one study reported a negative

TABLE 3. Age- and education-adjusted mean (SEM) hormone level by cognitive function cutpoint score

	Total testosterone	Bioavailable testosterone	Total estradiol	Bioavailable estradiol
SRT, long-term memory				
Normal (424)	10.95 (0.50)	3.65 (0.14)[a]	73.9 (3.36)	49.7 (2.2)
Failure (83)	10.97 (0.56)	3.43 (0.15)	72.8 (3.78)	47.5 (2.5)
Category fluency				
Normal (466)	10.98 (0.47)	3.56 (0.13)	73.20 (3.20)	48.56 (0.79)
Failure (74)	11.23 (0.60)	3.52 (0.16)	76.69 (4.10)	50.34 (2.13)
VRT,[b] immediate recall				
Normal (368)	10.96 (0.48)	3.59 (0.13)	73.99 (3.26)	49.41 (2.13)
Failure (164)	11.13 (0.52)	3.49 (0.14)	74.31 (3.54)	48.55 (2.31)
VRT, delayed recall				
Normal (409)	11.10 (0.59)	3.56 (0.02)	73.72 (4.07)	49.63 (2.63)
Failure (77)	11.99 (0.73)	3.35 (0.02)	74.02 (5.00)	46.06 (3.24)
MMSE				
Normal (497)	10.89 (0.47)	3.56 (0.13)	72.44 (3.22)	48.54 (2.11)
Failure (45)	11.59 (0.62)	3.49 (0.17)	80.23 (4.72)	50.79 (3.10)
Trails B				
Normal (326)	11.20 (0.61)	3.45 (0.17)	72.13 (4.18)	46.93 (2.73)
Failure (201)	11.23 (0.62)	3.43 (0.17)	74.04 (4.24)	47.55 (2.77)

[a] $P < 0.05$ for normal *vs.* failure.
[b] Visual Reproduction Test.

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TABLE 4. Multiply-adjusted[a] regression model (βs), including linear and quadratic hormone terms

	Total estradiol		Bioavailable estradiol		Total testosterone		Bioavailable testosterone	
	Linear	Quadratic	Linear	Quadratic	Linear	Quadratic	Linear	Quadratic
Blessed items	6.48[b]	−0.832[b]	2.095[b]	−0.316[b]	0.7705[b]	−0.215[b]	0.307[b]	0.0326
SRT long-term	3.63	−0.57	1.72	−0.259	3.056	−0.684	1.9	0.346
SRT short-term	0.472	−0.018	−0.66	0.09	−0.555	0.138	−0.504	−0.194
SRT total recall	2.12	−0.33	1.17	−0.18	2.22	−0.402	1.43	0.16
BWR	−0.131	−0.032	−0.036	−0.015	−0.146	0.0495	−0.017	0.029
Category fluency	12.96	−1.64	3.38	−0.56	0.248	−0.045	0.01	0.056
VRT[c] immediate	−0.6508	0.06	−3.48	0.511	−0.414	0.0995	0.253	0.399[b]
VRT delayed	5.23	−0.62	−1.66	0.31	0.866	−0.235	0.717	0.349[b]
MMSE	0.458	−0.132	−2.03	0.219	0.0959	−0.176	−0.308	0.053
World backward	1.882	−0.2402	0.32	−0.036	0.246	−0.107[b]	0.089	0.042
Serial sevens	0.6602	−0.107	−0.159	0.017	0.171	−0.104	−0.005	0.007
Trails B	−195.7[b]	23.7[b]	−46.8	5.9	−14.67	3.25	−8.98	−2.25

[a] Adjusted for age, education, alcohol use, BMI, and smoking.
[b] $P < 0.05$.
[c] Visual Reproduction Test.

association between spatial performance and estrone level in older men (26). To our knowledge, the effect of exogenous estrogen administration on cognitive function has not been examined in men.

Direct comparisons with other studies are problematic. Most previous studies have been conducted in young men (22–25, 27–36, 57–59), have not been population-based, and have used different neuropsychological tests to measure cognitive function (23, 27, 28, 30–32, 35, 57–59). Although most studies obtained blood samples during the morning to reduce diurnal variation (23, 24, 27–29, 32, 34), few required the subject to be in a fasting state (27). It is possible that a single hormone determination assay does not adequately describe the usual hormone status, but this would be more of a problem in young men who have more marked diurnal variation in testosterone. The 5-yr interval between obtaining blood samples and testing cognitive function could have reduced the magnitude of associations, but is unlikely to have created them. The 5–8 yr between obtaining blood samples and hormone assays could have weakened the strength of the associations (and the *P* values) if there was serious deterioration of hormones in frozen plasma; this seems unlikely because previous studies in this endocrinology research laboratory showed little deterioration in stored samples (unpublished data) and because the observed hormone levels were those expected in this age range (55).

The nonlinear hormone-cognition association in multiply-adjusted models is in agreement with several previous studies in men, which also found an inverted quadratic or "U-shaped" relation between testosterone and spatial ability (27, 29, 30, 34), serial subtraction (35), and mathematical ability (29). [Interestingly, these are all tests on which men score better than women (14).] Quadratic associations between sex hormones and some neuropsychological tests suggest an optimal hormone level for certain cognitive tasks.

Animal studies suggest that sex hormones play a role in the organization of the nervous system (60) and memory (61). Estrogen has been shown to maintain the production of neurotrophins, and the regulation of their receptors responsible for cognition (8) improve blood flow (18), modify the processing of amyloid precursor protein (which may reduce the deposition of β amyloid) (16), increase choline acetyltransferase levels that subsequently increase acetylcholine (1–3), and stimulate neuronal regeneration and neurotropic growth factors (4–7, 11). Testosterone may act directly on the brain or by conversion to estrogen.

In summary, this longitudinal, population-based study supports an association between endogenous sex hormone levels and cognition in older men. Low estradiol levels predicted better performance on two commonly used cognitive function tests, whereas moderately high testosterone levels predicted better mental control and long-term verbal memory. Clinical trials with dose-ranging protocols will be necessary to determine whether sex hormone therapy can prevent or delay loss of cognitive function in older men.

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