Endogenous sex hormone levels and cognitive function in aging men: Is there an optimal level?

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Is there an optimal level?

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Abstract—*Objective:* To determine whether endogenous sex hormone levels are associated with cognitive functioning in men. *Methods:* Cognitive performance was assessed in 400 independently living men between ages 40 and 80 in a population-based cross-sectional study. Compound scores were calculated for memory function, processing capacity/speed, and executive function. The Mini-Mental State Examination was used as a measure of global cognitive function. The adjusted association of testosterone (T) and estradiol (E_2) (total, bioavailable) with neuropsychological test scores in the total group and in subgroups was assessed by linear and logistic regression analysis. *Results:* Curvilinear associations were observed between T and memory performance and processing capacity/speed, suggesting optimal sex hormone levels. No association between E_2 and cognitive functioning was found. After the population was subdivided into four age decades, a linear association of T with cognitive functioning in the oldest age category remained. No association was found in the other age decades. Lower bioavailable T levels were associated with lower scores on processing capacity/speed and executive function; β (95% CI) values were 0.36 (0.07 to 0.66) and 0.17 (−0.01 to 0.35). Similar results were observed for total T. *Conclusions:* Higher testosterone (T) levels are associated with better cognitive performance in the oldest age category. Apparent curvilinear associations between T and certain cognitive functions in men suggest an optimal hormone level for particular cognitive tasks and are explained by linear associations in the oldest age category.

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Decline in cognitive function, typically memory, is a major symptom of dementia. The "preclinical phase" of detectable lowering of cognitive functioning precedes the appearance of dementia by many years.[1,2] Cognitive functions that decline with age include selective attention, processing capacity and speed, verbal fluency, complex visual and spatial skills, and language analysis.[3] There is evidence that a preclinical or subclinical phase of reduced cognitive function, including information-processing speed,[4,5] precedes the appearance of diagnosed dementia by at least 10 years. However, factors that contribute to cognitive function and decline have not been well characterized.

It has been hypothesized that the age-related decline in sex hormone levels in men[6] is associated with the decline in cognitive functioning and with mild cognitive impairment. Basic scientific studies and animal research support the biologic plausibility of a protective effect of testosterone (T) on cognitive function.[7,8] Experimental human studies in young men and clinical observations suggest that sex hormones may specifically modify verbal and spatial skills.[9] There has, however, been relatively little investigation of the possible relationships between hormone levels and changes in selective cognitive functions, such as memory and processing speed, which occur with aging in men. Several population-based studies dealing with the relationship between endogenous sex hormones and cognitive functions, such as memory, executive functions, and processing speed, in elderly men have been published.[10-14] However, these studies have yielded conflicting results. Some studies have suggested that an optimal level of sex hormones exists for certain cognitive tasks,[9,10] although no biologically plausible mechanism has been given.

We sought to assess the relation of circulating endogenous T and estradiol (E_2) with cognitive functioning and to examine the possibility of an optimal sex hormone level, assessed by testing a comprehensive range of cognitive domains, in a large population-based cohort of aging men. Furthermore, we examined the possible modifying effect of age on this association.

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Methods. *Subjects.* The study is a cross-sectional, single-center study in 400 independently living men ages 40 to 80 years. The subjects were recruited by asking women participating in other studies conducted by the department by letter whether they knew possibly interested men between ages 40 and 80. Invitation letters were sent to 770 participating women. Although it was not possible to assess the participation rate for this group, 240 men volunteered for participation.

Next, the names and addresses of randomly selected men ages 40 to 80 were drawn from the municipal register of Utrecht, a large-sized town in the middle part of the Netherlands. One thousand two hundred thirty invitation letters were sent to men living in Utrecht by means of a selection from the municipal register. From this group, 390 men volunteered for participation (participation rate of 31.7%). From the 630 volunteers, we excluded those who did not live independently and subjects who were not physically or mentally able to visit the study center independently (n = 16). No additional health-related eligibility criteria were used. Of the remaining 614 men, 400 men were randomly selected to participate. To yield equal numbers in each age decade from ages 40 to 80, we sampled 100 men in each decade of age. All participants gave written informed consent before enrollment in the study, and the institutional review board of the University Medical Center Utrecht approved the study. Data collection took place between March 2001 and April 2002.

Procedure. During the visit, medical histories were obtained. Participants were asked about current use of medications; these reports were checked by examining labels of drugs brought to the clinic. Furthermore, age, smoking history, alcohol consumption (using a validated food frequency questionnaire),[15] and highest level of education were assessed. As performance on cognitive tests can be influenced by depression, the relevant section of a Quality of Life Questionnaire (QUALLEFO) was used to assess mood.[16] Scores range from 5 to 45, with higher scores indicating less favorable mental health. During the examination, height and weight were measured in standing position without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Peripheral blood pressure (BP) was measured twice in the left and right brachial artery with a semiautomated device (Dynamap, Critikon, Tampa, FL). The average of the two measurements of systolic and diastolic BP was used for analysis and further calculation. A venipuncture was performed, and fasting blood samples were obtained. Platelet-free serum was obtained by centrifugation and immediately stored at −20 °C. An automatic enzymatic procedure was used to determine serum total cholesterol (Synchron LX Systems; Beckman Coulter, Fullerton, CA). Glucose levels were assessed using a GlucoTouch reflectometer (LifeScan, Benelux, the Netherlands), a reagent-strip glucose oxidase method. Venous whole blood was immediately applied to the test strip. Diabetes mellitus was defined as treatment with insulin or oral hypoglycemic agents and fasting plasma venous glucose level of >6.9 mmol/L.[17]

Hormone determinations. Levels of steroid were measured in serum. Total T was measured after diethylether extraction using an in-house competitive radioimmunoassay employing a polyclonal anti-T antibody (Dr. Pratt AZG 3290). [1α, 2α-^{3}H]T (DuPont, Nederland B.V.) was used as a tracer following chromatographic verification of its purity. The lower limit of detection was 0.24 nmol/L; interassay variation was 6.0, 5.4, and 8.6% at 2.1, 5.6, and 23 nmol/L (n = 85). Sex hormone binding globulin (SHBG) was measured using an immunometric technique (Diagnostic Products Corp., Los Angeles, CA). The lower limit of detection was 5 nmol/L; interassay variation was 6.1, 4.9, and 6.9% at 11.6, 36, and 93 nmol/L (n = 30). Bioavailable testosterone (FT) was calculated from SHBG and total T (TT) using the following formula: $([(SHBG - TT + 23)^2 + 92 \times TT]1/2 - [SHBG - TT + 23]) \times 21.7 = FT$.[18] Total E_2 was measured after diethylether extraction and Sephadex chromatography (Amersham Biosciences AB, Uppsala, Sweden) using an in-house competitive radioimmunoassay employing a polyclonal anti-E_2 antibody (Dr. F. de Jong, Erasmus MC, Rotterdam, the Netherlands). [2,4,6,7-^{3}H]E_2 (Amersham, Nederland B.V.) was used as a tracer following chromatographic verification of its purity. The lower limit of detection was 20 pmol/L (2-mL sample); interassay variation was 10.0 and 3.1% at 81 and 660 pmol/L (n = 24 and 17). Bioavailable E_2 was calculated using a previously described method.[19] This method is based on the knowledge of the total concentration of all steroids competing for the same binding site on SHBG, the concentration of albumin (using a fixed concentration of 40 g/L), the binding capacity of SHBG, and the association constant of E_2 to the binding proteins.

Cognitive tests. The subjects were tested during a morning visit in a silenced room. Specially trained personnel administered the tests. Cognitive tests were selected that have been documented to be sensitive to the effects of aging and that have been included in previous hormone studies.[10-12] Folstein's Mini-Mental State Examination (MMSE)[20] was used as measure of global cognitive function (maximum score = 30); "suboptimal cognition" was defined as a score below 26. The Rey Auditory Verbal Learning Test was used as a measure of verbal episodic memory.[21] In this test, the participants are asked to recall a 15-word list immediately (immediate recall) for five times consecutively (maximum score = 75) and after 25 to 30 minutes (delayed recall, maximum score = 15). Furthermore, the subjects are asked to recognize the words out of a list of 30 (recognition, maximum score = 30). The Doors Test was used to assess visual memory.[22] Subjects were shown two series of 12 photographs of doors, which they subsequently had to recognize from arrays of 4 pictures of doors. In the Digit Span Test, a subtest of the Wechsler Adult Intelligence Scale (WAIS),[23] subjects were asked to repeat a string of maximally eight digits in the original order (Digit Span Forward) and in the reversed order (Digit Span Backward), to give an impression of short-term memory and working memory. To test Verbal Fluency, the subject was asked to list as many nouns as possible beginning with the letter N and A and to name as many animals and occupations, each in 1 minute. The Digit Symbol Substitution Test, also from the WAIS,[23] measures cognitive and perceptual speed. The subject was given a code that pairs symbols with digits. The test consisted of pairing as many digits to their corresponding symbols as possible in 90 seconds. The Trail Making Tests are complex attention and mental flexibility tasks. In the Trail Making Test, pseudo-randomly placed circles with numbers (Trail Making A1), with letters (Trail Making A2), and with both letters and numbers (Trail Making B) have to be connected with a line as fast as possible in a fixed order.[24] More specifically, Trail Making B is a test of concept shifting. We also assessed the verbal IQ using the Dutch Adult Reading Test (DART), a Dutch version of the National Adult Reading Test,[25,26] in which the subjects have to read out loud a list of words with irregular pronunciation; the maximum score that can be achieved is 100. The DART reading score can provide an accurate estimate of premorbid intelligence levels.[27] For all tests except Trail Making, a higher score denotes better cognitive function. The completion of the entire test battery took 1 hour on average.

To assess cognitive domain scores and to increase precision, average or compound cognitive tests scores were made by transforming individual test scores into standardized *Z* scores (*Z* score = test score − mean test score/SD).[28] By pooling the *Z* scores, compound scores were estimated for 1) memory performance, 2) processing capacity and speed, and 3) executive function. Memory performance is tested by the Rey Auditory Verbal Learning Test and the Doors Test.[29,30] Processing capacity and speed are tested by the Digit Span Forward and Backward, the Digit Symbol Substitution Test, and Trail Making A.[29] Executive function is tested by Verbal Fluency and Trail Making B. For tests in which a higher score denotes worse performance (Trail Making), the sign was reversed before calculation of a pooled *Z* score.[30]

Data analysis. Data of cognitive function tests of five participants were excluded owing to visual handicap, refusal of participation, and insufficient motivation. Levels of sex hormones were categorized into quintiles. The association between cognitive function and endogenous sex hormones was evaluated using linear regression analysis, and the associations are presented with the linear regression coefficient (β) and its 95% CI. For the MMSE, we expected a skewed distribution, as this test is aimed at measuring gross cognitive dysfunction. Therefore, logistic regression analyses were used to estimate the odds ratios (ORs) and 95% CI for the data from the MMSE, with scores dichotomized into two groups, at a cut-off of 26. Regression models were adjusted for age, score on the DART, mood (QUALLEFO), smoking (pack-years), and alcohol consumption (g/day). Presence of curvilinear associations was tested with quadratic terms, which were added to the multivariate model. Analysis of covariance was used to obtain adjusted mean cognitive performance by quintiles of sex hormones. Be-

Table 1 *Characteristics of the study population (n = 395)*

	Mean ± SD or %	Range
Age, y	60.2 ± 11.3	40.0–80.0
BMI, kg/m^2	26.3 ± 3.5	17.3–43.3
Systolic blood pressure, mm Hg	138.6 ± 19.7	99.5–243.0
Diastolic blood pressure, mm Hg	77.2 ± 9.2	48.5–111.5
Glucose, mmol/L	5.9 ± 1.4	3.9–17.5
Cholesterol, mmol/L	5.8 ± 1.1	3.1–10.5
Smoking, pack-y	20.6 ± 16.6	0.0–131.3
Alcohol consumption, g/d	20.2 ± 21.6	0.0–79.0
Mood, score*	9.5 ± 2.7	5.0–21.1
Intelligence level, DART score	86.8 ± 14.1	12–100
Education, %		
Low grade	15.9	
Middle grade	28.8	
High grade	35.4	
University	19.9	
Diabetes, %	11.0	
Hormones		
Total testosterone, nmol/L	18.6 ± 5.3	7.2–39.6
Bioavailable testosterone, nmol/L	8.2 ± 2.2	2.7–16.3
Total estradiol, pmol/L	91.3 ± 22.9	20–205
Bioavailable estradiol, pmol/L	42.2 ± 11.5	8.1–110.6
SHBG, nmol/L	40.6 ± 14.5	12–91

* Mood score was assessed by the Quality of Life Questionnaire.

BMI = body mass index; DART = Dutch Adult Reading Test; SHBG = sex hormone binding globulin.

Table 2 *Median and range of cognitive test scores, n = 395*

	Median	Range
Memory performance		
Rey Immediate Recall, no. words	39	12–69
Rey Delayed Recall, no. words	8	0–15
Rey Recognition, no. words	29	18–30
Doors, no. doors	18	8–24
Processing capacity and speed		
Digit Span Forward, no. digits	6	3–11
Digit Span Reverse, no. digits	5	2–12
Digit Symbol Substitution, no. symbols	54	15–94
Trail A1, s	35	15–114
Trail A2, s	37	15–229
Executive function		
Trail B, s	80	29–439
Verbal Fluency: A, no. words	7	0–18
Verbal Fluency: N, no. words	5	0–18
Verbal Fluency: animal, no. words	21	8–44
Verbal Fluency: occupation, no. words	16	4–33
MMSE score	28	21–30
Memory performance, *Z* score	0	−6–4
Processing capacity and speed, *Z* score	0	−9–9
Executive function, *Z* score	−1	−6–4

MMSE = Mini-Mental State Examination.

cause of the large effect of age on cognitive function and on sex hormone levels, effect modification was studied by subgroup analyses on age (four age categories). The significance of possible effect modification was tested with interaction terms (age*hormone level), which were added to the multivariate model. To elucidate whether and to what extent the observed associations of sex hormone levels with cognitive performance might be explained by intermediates, further analysis also adjusted for cardiovascular risk factors (blood pressure, cholesterol, BMI, diabetes). Statistical analyses were performed using SPSS for Windows (version 11.0; Chicago, IL).

Results. The characteristics of the study population are presented in table 1. The median age of the total study group was 60 years (range 40 to 80 years). The mean endogenous sex hormone levels were higher than levels reported elsewhere.[10,12] However, participants in these studies were slightly older. Mean (SD) DART score (estimate of premorbid intelligence) was 86.8 (14.1), which is higher than scores reported elsewhere.[27] However, again, these subjects were older. Table 2 presents the medians and ranges of the cognitive functions studied. After these scores were standardized by transforming them into *Z* scores, all test scores were normally distributed.

Total and bioavailable T decreased with age, and SHBG showed an increase with age. No changes with age were found for E_2. BMI increased with decreased T (total and bioavailable), SHBG, and increased E_2. Current smoking, lower alcohol intake, low systolic BP, and low cholesterol levels were associated with higher T and SHBG levels. These results are described elsewhere.[31]

Memory performance. Memory performance is tested by the Rey Auditory Verbal Learning Test (immediate recall, delayed recall, recognition) and the Doors Test. These tests were significantly correlated with correlation coefficients between 0.3 and 0.8. Linear regression coefficients for the association of circulating sex hormones and memory performance were not significant (see table E-1 on the *Neurology* Web site at www.neurology.org). Multiply adjusted linear regression analyses showed a significant quadratic association between total T and memory performance (see table E-1). No association was found between E_2 and memory performance. After the cohort was subdivided in age categories, the previously observed curvilinear association disappeared and linear regression coefficients became nonsignificant (see table E-2). Age did not modify the effect between T and memory performance (*p* interaction for total T was 0.99 and for bioavailable T 0.79). Further adjustment for cardiovascular risk factors (BP, cholesterol, BMI, waist, diabetes) did not alter these associations.

Processing capacity and speed. Processing capacity and speed are tested by Digit Span Forward and Backward, Digit Symbol Substitution Test, and Trail Making A. These tests were significantly correlated with correlation coefficients between 0.3 and 0.7. Linear regression coefficients for the association of circulating sex hormones and processing and speed were not significant (see table E-1). Multiply adjusted linear regression analyses showed a sig-

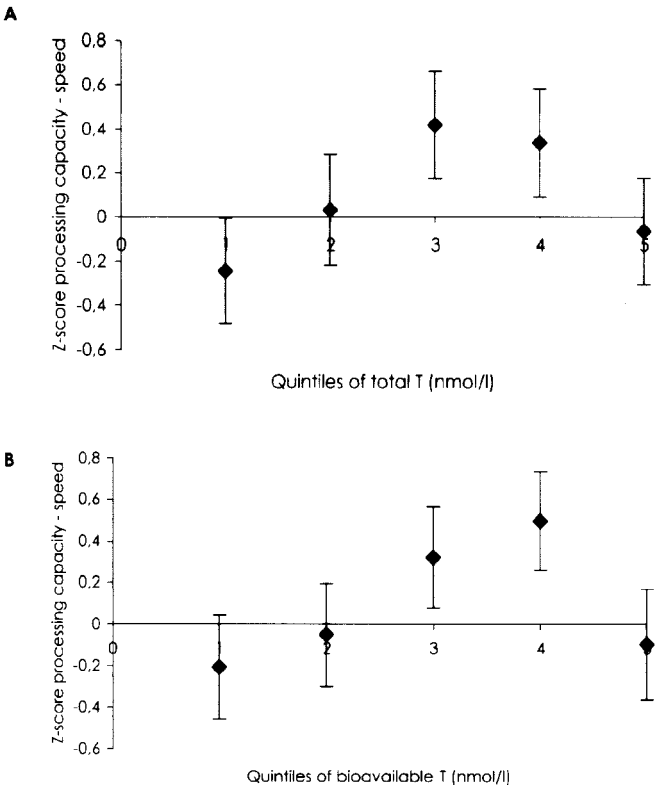

Figure. Relation between serum total testosterone (T) (A) and bioavailable T (B) in quintiles and cognitive function (expressed as mean Z score [± SEM]) in the total population (n = 395). Adjustments were made for age, intelligence level (Dutch Adult Reading Test score), mood (Quality of Life Questionnaire score), smoking (pack-years), and alcohol consumption (g/day). Limits in total T level for the different quintiles were as follows: first quintile 7.2 to 14.2 nmol/L, second quintile 14.2 to 16.8 nmol/L, third quintile 16.8 to 19.4 nmol/L, fourth quintile 19.4 to 22.8 nmol/L, fifth quintile 22.9 to 39.6 nmol/L. Limits in bioavailable T level for the different quintiles were as follows: first quintile 2.7 to 6.2 nmol/L, second quintile 6.2 to 7.4 nmol/L, third quintile 7.4 to 8.4 nmol/L, fourth quintile 8.4 to 9.9 nmol/L, fifth quintile 9.9 to 16.3 nmol/L.

nificant quadratic relation for total T and bioavailable T with processing capacity and speed (see table E-1). No association was found between E_2 and processing capacity and speed. The figure presents the mean (± SEM) *Z* scores for quintiles of sex hormones. After the group was subdivided in age categories, a higher total T and bioavailable T were associated with higher scores of processing capacity and speed in men ages 71 to 80: $\beta = 0.11$ (95% CI 0.01 to 0.21) and $\beta = 0.36$ (95% CI 0.07 to 0.66) (see table E-2). No association was found in the other age categories. However, age did not modify the effect between (total, bioavailable) T and processing capacity and speed (*p* values for interaction were 0.31 and 0.16). Table E-3 presents the results of multiply adjusted linear regression coefficients for the association between T and the individual cognitive tests within the oldest age category. Higher total and bioavailable T concentrations were associated with a lower score on the Trail Making A and a higher score on the Digit Span and the Digit Symbol Substitution Tests; however, the relations were not all significant. Figure E-1, A and C (on the *Neurology* Web site) presents mean (± SEM) *Z* scores for quintiles of total and bioavailable T for the oldest age category. The differences between extreme quintiles were approximately 1 SD of the *Z*-score distribution. The *p* values for linear trend for total and bioavailable T were 0.02 and 0.03. Further adjustment for cardiovascular risk factors (BP, cholesterol, BMI, waist, diabetes) did not alter the presented associations in the total group and in subgroups.

Executive function. Executive function is tested by Verbal Fluency and Trail Making B. These tests were significantly correlated with correlation coefficients between 0.4 and 0.7. Multiply adjusted linear regression analyses showed a weak significant linear association between total T and executive function (see table E-1). No relation was found for bioavailable T, total E_2, and bioavailable E_2 with executive function. However, a trend toward a quadratic association between bioavailable T and executive function was present (see table E-1). After the group was subdivided in age categories, higher total and bioavailable T levels were associated with higher scores of executive function in men ages 71 to 80 years: $\beta = 0.06$ (95% CI 0.00 to 0.12) and $\beta = 0.17$ (95% CI −0.01 to 0.35) (see table E-2). The *p* values for interaction for total T and for bioavailable T were 0.15 and 0.03. Table E-3 presents the results of multiply adjusted linear regression coefficients for the association between T and the individual cognitive tests within the oldest age category. Higher total and bioavailable T concentrations were associated with a higher score on the Verbal Fluency Tests and a lower score on the Trail Making B Test; however, no significant results were reached. Mean (± SEM) *Z* scores in the oldest age category for quintiles of sex hormones were calculated using analyses of covariance (see figure E-1, B and D). The differences between extreme quintiles were approximately 1 SD of the *Z*-score distribution. The *p* value for linear trend for both total and bioavailable T was 0.07.

Global cognitive function and MMSE. Fifty-two men had an MMSE score of ≤26. Multiple logistic regression analyses showed that there was no relationship for total T, bioavailable T, total E_2, or bioavailable E_2 with cognitive impairment after adjustment for age, intelligence level, mood, smoking, and alcohol consumption (data not shown). After the group was subdivided in age categories, an inverse association between bioavailable T and cognitive impairment (OR = 0.6; 95% CI 0.4 to 0.9) was found in the oldest age category, suggesting a risk of 0.6 for cognitive impairment with 1-nmol/L increase in bioavailable T. Test for interaction over age categories was $p = 0.23$. For total T, total E_2, and bioavailable E_2, no association with global cognitive function was found: OR = 1.0 (95% CI 0.8 to 1.1), OR = 1.0 (95% CI 0.7 to 1.3), OR = 0.4 (95% CI 0.1 to 1.9). Further adjustment for cardiovascular risk factors (BP, cholesterol, BMI, waist, diabetes) did not alter the associations.

Discussion. In this population-based cross-sectional study in men between ages 40 and 80, higher T levels are associated with better cognitive performance in the oldest age category. Men with T levels in the lowest quintile performed significantly worse (1 SD of the *Z*-score distribution) than men

with T levels in the highest quintile. The observed but artificial curvilinear associations between sex hormones and some cognitive functions suggested an optimal hormone level for certain cognitive tasks and were explained by effect modification by age. Notably, association of sex hormones with cognitive function was independent of cardiovascular risk factors, mood, and presence/absence of chronic disease.

To appreciate these findings, some issues concerning study design, assessment of cognitive status, and hormone levels need to be addressed. Strengths of the current study are the inclusion of a wide range of cognitive tests sensitive to aging, which reflect several cognitive domains. Owing to this wide range of tests, it was possible to assess compound scores. In addition, whereas previous studies included predominantly elderly or young samples, we also included middle-aged subjects. Actions to prevent cognitive decline can be taken in middle age, and therefore it is important to assess the association of sex hormones and cognition in age categories in which prevention is useful.[32] Another issue that needs to be addressed concerns adjusting for intelligence level. In this study, the DART was assessed, which is a more accurate way of measuring intelligence level than asking participants their highest level of education, especially in elderly men.[26] Finally, total T concentration was measured using a radioimmunoassay with extraction method, which is, compared with commercially available direct assays, more precise and reliable.[33]

The interpretability of the results may be limited by several factors inherent to the cross-sectional community-based design, which limits conclusions regarding within-person change or direction of causality. Because of self-selection, individuals who volunteer for research cannot be assumed to be representative of the populations from which they come, possibly affecting the generalizability of the data.[34] However, it is not likely that the presented associations between sex hormone levels and cognitive functioning were biased by this selection. Furthermore, the participants are ascertained from two separate groups. However, after adjustment for age, the two groups were comparable for all demographic factors and other important variables (data not shown). There are a number of systemic factors that increase SHBG levels that also affect cognition, including liver disease and hyperthyroidism.[35,36] We did not account for these possible confounders; however, it is unlikely that adjustment for these factors would have changed these results.

The crude nonlinear hormone–cognition association found in this study is in agreement with a previous population-based study in men, which reported an optimal T level for several cognitive functions, namely, memory performance and executive functions.[10] However, a curvilinear association between sex hormones and cognitive functions, which suggests an optimal sex hormone level for cognitive functioning, is difficult to explain. No biologically plausible mechanisms have been proposed that support the finding of an optimal sex hormone level. Moreover, supplementation of T in intervention trials, leading to a rise of T levels from around 20 to 40 nmol/L, still resulted in improved cognitive functioning.[37,38]

The positive linear associations between T and cognitive performance that were observed in the oldest age category could account for the observed curvilinear associations between T and cognitive functioning across the full age range. It could be hypothesized that because of increasing vulnerability in aging men, decreased T levels in elderly men lead to an imbalance of cognitive functioning, while in younger men, the balance is preserved by other factors. Exclusion of the subjects with an MMSE score of $\leq$26 did not change the current results in tables E1 through E3. We cannot exclude the possibility that this finding was due to chance, although it has been reported in the past that the relative importance of risk factors for a disease changes with age; for example, serum cholesterol level is a less important risk factor for coronary heart disease in very old men.[39]

These results showed that the association between bioavailable T and cognition is stronger than the association between total T and cognitive functioning, which is in line with other studies.[11,12] A possible explanation for this finding is that bioavailable T crosses the blood–brain barrier more readily than total T, which is largely bound by SHBG.[11]

For an association between E_2 and cognitive function in men, conflicting results have been found.[10,13,40-42] We could not establish an association between E_2 levels and cognitive functioning, which is in accordance with several other studies.[13,41,42]

Owing to the number of contrasts examined and the fact that from cross-sectional studies inherently no conclusions can be drawn about causality, the results require replication, preferably in prospective designs. Controlled trials will be necessary to determine definitely whether sex hormone therapy can prevent or delay loss of cognitive function in men.

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