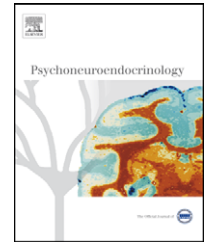




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# Sex hormones and cognitive decline in elderly men

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**Summary** Decline of cognitive function with age may be due, in part, to hormonal changes and it has been hypothesized that higher levels of endogenous sex hormones preserve brain function. The aim of this prospective cohort study was to determine the relative contribution of endogenous sex hormones to cognitive decline in a population-based sample of 242 elderly men aged 73–91 at baseline. Endogenous sex hormone levels were measured at baseline and participants underwent a cognitive assessment at baseline and at follow-up after 4 years. Higher estradiol (total and bioavailable) and estrone levels were associated with an increased risk of cognitive decline in elderly men independent of age, cardiovascular risk factors, atherosclerosis, and APOE genotype. These findings do not support the hypotheses that higher levels of endogenous sex hormones preserve brain function.

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## 1. Introduction

Decline in cognitive function is one of the major symptoms of dementia. The “preclinical phase” of detectable lowering of cognitive functioning precedes the appearance of dementia by many years (Park et al., 2003). Recently, sex hormones have been identified as factors that modulate risk for cognitive decline. The actions of testosterone and estradiol in the brain of older people are not well understood, but in vivo and in vitro experimental studies suggest these hormones

may have multiple neuroprotective effects (Veiga et al., 2004).

In addition to the experimental data, the results of observational studies are contradictory (Muller et al., 2003). Several studies suggest that higher levels of endogenous estradiol or testosterone may preserve brain function (Barrett-Connor et al., 1999; Yaffe et al., 2000; Muller et al., 2005). More recently, however, adverse effects of estrogen on brain function in women have been demonstrated (Geerlings et al., 2003; Shumaker et al., 2003). And in recent prospective studies in men and women, higher levels of total and bioavailable estradiol were associated with an increased risk of cerebral small vessel disease, cognitive decline and Alzheimer’s disease (Geerlings et al., 2006; Irie et al., 2006; Ravaglia et al., 2007). Here, we examine the association of endogenous levels of sex hormones with cognitive decline in very old Caucasian men.

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## 2. Methods

### 2.1. Subjects

In 1996, names and addresses of all male inhabitants >70 years of age were drawn from the municipal register of Zoetermeer, a medium-sized town in the Midwestern part of the Netherlands, and 1567 men were invited as described previously (Muller et al., 2004). A total of 886 men did not respond to the mailed invitation in which it was already mentioned that subjects who did not live independently or with severe mobility problems would not be allowed to participate. After exclusion of subjects who did not live independently and those who were not physically or mentally able to visit the study center independently, 403 men 73–94 years of age (25.7%) participated. All participants provided written informed consent, and the Medical Ethics Committee of the University Hospital Rotterdam approved the study. No additional health-related eligibility criteria were used. The baseline examination in 1996 comprised a structured interview, physical examination, blood sampling, and measurements of cognition at the research center. We reinvited the 328 participants who were still living for a second examination in 2000, of whom 242 (61%) participated.

### 2.2. Procedure

At baseline, participants were asked about medical history, current use of medications, and smoking history. Height and weight were measured at baseline and body mass index (BMI) was calculated ( $\text{kg}/\text{m}^2$ ). Blood pressure was measured twice with a semi-automated device (Dynamap). The average of the two measurements was used for analysis and further calculation. Hypertension was defined as systolic blood pressure  $\geq 160$  mmHg and/or diastolic blood pressure  $\geq 95$  mmHg or use of anti-hypertensive medication. Diabetes mellitus was defined as treatment with insulin or oral hypoglycemic agents or fasting plasma venous glucose  $> 6.9$  mmol/L. Serum cholesterol concentrations were measured by use of commercially available radioimmunoassay kits. Carotid intima media thickness (IMT) was assessed as a quantitative measure of atherosclerosis as described previously (Muller et al., 2004). Genotyping for *APOE* was performed on coded DNA specimens without knowledge of the diagnosis. We classified persons as homozygous or heterozygous for the *APOE*- $\epsilon 4$  allele or not having any  $\epsilon 4$  allele.

### 2.3. Cognitive decline

Folstein's Mini Mental State Examination (MMSE) was used as a measure of global cognitive function (max score = 30) (Folstein and Folstein, 1975; Tombaugh and McIntyre, 1992). Because of a highly skewed distribution, cognitive decline was defined as a decline in MMSE-score of 4 points or more after 4 years of follow-up (Kalmijn et al., 1999; Volpato et al., 2002).

### 2.4. Hormone measurements

At baseline, blood samples were collected in the morning after an overnight fast. Serum concentrations of total testosterone (nmol/L), sex hormone-binding globulin (nmol/L),

estrone (nmol/L), and estradiol (nmol/L) were measured by radioimmunoassay with commercial kits (Diagnostic Systems Laboratories, Inc.). The intra-assay coefficients of variation (CV) for these assays were 8.1%, 3.0%, 5.6%, and 5.3%, respectively. The interassay CV were 10.5%, 4.4%, 10.2%, and 8.1%. The detection limits for total testosterone, sex hormone-binding globulin, estrone, and estradiol were 0.28 nmol/L, 5.0 nmol/L, 4.4 pmol/L, and 8.1 pmol/L, respectively. The percentages of undetectable levels were 0.7%, 0.2%, 0.0%, and 0.5%, respectively. As a measure of biologically active testosterone and estradiol, free testosterone (nmol/L) and free estradiol (pmol/L) was calculated according to the method described by Sodergard et al. (1982). Albumin (g/L) was measured by photometry with a commercial kit (ALB, Boehringer).

### 2.5. Data analyses

Distributions of anthropometric and lifestyle characteristics, sex hormone concentrations, and cardiovascular risk factors according to tertiles of estradiol were expressed as mean and S.D., and were quantified by ANOVA, Kruskal–Wallis, and  $\chi^2$ -analyses. The association between baseline hormones levels and baseline MMSE were assessed with the Kruskal–Wallis test, a nonparametric test.

In multivariate logistic regression models, baseline testosterone, estrogen, and estradiol levels were investigated in relation to cognitive decline. In these models, hormone levels were examined in two ways: as a continuous variable expressed as increase per standard deviation and as tertiles. In the first model, we adjusted for age; in the second model we added BMI ( $\text{kg}/\text{m}^2$ ), cholesterol levels (nmol/L), IMT (mm), diabetes (yes/no), hypertension (yes/no), smoking status (current/former/never), and *APOE* allele (one or two  $\epsilon 4$  alleles/no  $\epsilon 4$  allele). To assess whether *APOE* genotype interacts with endogenous sex hormone levels in association with cognitive decline, analyses were repeated within strata of *APOE* genotype and an interaction term was added to the multivariate regression models. To account for cognitive impairment at baseline, secondary analyses were done after excluding subjects with a baseline MMSE of 24 or lower ( $n = 24$ ). Additional exclusion of possible outliers did not change the results substantially. Data analyses were performed with SPSS statistical software (version 12.0).

## 3. Results

Mean age of the population at baseline was 77.4 years (range, 73–91 years). Subjects in the study ( $N = 242$ ) were significantly younger and had a higher MMSE at baseline than the subjects who dropped out ( $N = 161$ ). No differences were found in baseline hormone levels, life style factors, and cardiovascular risk factors.

Descriptive values of the sex hormone levels and general characteristics at baseline according to total estradiol tertiles are presented in Table 1. Mean (S.D.) total estradiol level was 95.8 (48.0) pmol/L. Mean (S.D.) total testosterone levels was 9.0 (2.8) nmol/L and 77% of the population had hypogonadal levels ( $< 11$  nmol/L). High estradiol levels seemed to be associated with lower prevalence of hypertension and lower frequency of *APOE*  $\epsilon 4$  (Table 1). Median

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