Open access • Journal Article • DOI:10.1111/J.1365-2265.2005.02297.X

Endogenous oestrogens are related to cognition in healthy elderly women

Corinne E. I. Lebrun, Yvonne T. van der Schouw, Frank H. de Jong, Huibert A. P. Pols ...+2 more authors

Institutions: Erasmus University Medical Center, Utrecht University

Published on: 01 Jul 2005 - Clinical Endocrinology (Wiley-Blackwell)

Topics: Menopause, Cognitive decline and Sex hormone-binding globulin

Clinical Endocrinology (2005) **63**, 50–55 doi: 10.1111/j.1365-2265.2005.02297.x

ORIGINAL ARTICLE

Endogenous oestrogens are related to cognition in healthy elderly women

Corinne E. I. Lebrun*†, Yvonne T. van der Schouw†, Frank H. de Jong*, Huibert A. P. Pols*, Diederick E. Grobbee† and Steven W. J. Lamberts*

*Department of Internal Medicine, Erasmus University Medical Center Rotterdam, PO Box 1738, 3000 DR Rotterdam, the Netherlands, †Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Huispost STR 6.131, PO Box 85500, 3508 GA Utrecht, the Netherlands

Summary

Objective To investigate whether levels of endogenous hormones, in particular circulating oestrogens and SHBG, are associated with cognition in healthy postmenopausal women.

Design Cross-sectional study.

Patients Four hundred and two healthy postmenopausal women aged 50–74 years between 8 and 30 years after menopause, none taking oestrogen.

Measurements Serum concentration of oestradiol, oestrone, and sex hormone binding globulin (SHBG) determined by immunoassay. Cognition assessed using the mini-mental state examination questionnaire (MMSE).

Results In this group, 149 individuals had a MMSE score < 27, while only 89 individuals had a MMSE score < 26, indicating a relatively healthy population with regard to cognitive ability. Cognition decreased with age, time since menopause and blood pressure, and was better with higher age at menopause. Serum oestrogens and SHBG levels were not related to age, age at menopause, or time since menopause, and oestrogen levels were positively associated with blood pressure. After adjustment for mean arterial pressure and SHBG, the frequency of mild cognitive impairment decreased significantly with higher oestradiol and oestrone serum levels [ORs Q5 *vs.* Q1: 0·41 (95% CI 0·20–0·84) and 0·51 (95% CI 0·20–0·99) for oestradiol and oestrone, respectively].

Conclusions Postmenopausal women with higher remaining circulating oestradiol levels appear less likely to suffer from cognitive impairment. This effect is independent of age at menopause, time since menopause and BMI. These findings support the hypothesis that endogenous oestrogens may protect against cognitive decline with ageing.

Correspondence: Yvonne T van der Schouw, Associate Professor of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht PO Box 85500, Room D 01·335, 3508 GA Utrecht, the Netherlands. Tel.: + 31 30 2509360; Fax: + 31 30 2505485; E-mail: y.t.vanderschouw@umcutrecht.nl; (www. Juliuscentre.nl)

(Received 11 November 2004; returned for revision 25 November 2004; finally revised 21 February 2005; accepted 22 April 2005)

An increase of life expectancy is not necessarily accompanied by a similar increase in healthy life span, and understanding determinants of successful ageing and in particular the role played by endocrine factors has gained increased interest.[1] Women are likely to live one third of their lives in a state of relative oestrogen deficiency, which is held responsible for unfavourable long-term effects on bone metabolism, the cardiovascular system, and probably cognitive function culminating in dementia. There is growing evidence that oestrogens impact on memory, affect, and motor co-ordination in women, and they also appear to have a neuroprotective effect for Alzheimer's disease.[2,3] In contrast, results from studies with hormonal replacement therapy (HRT) have not supported a protective effect of exogenous oestrogens on cognitive functions.[4–6] A few studies have addressed the role of the remaining circulating postmenopausal oestrogens in cognition, but were hampered by small sample sizes or improper adjustment for potential confounders.[7–10] Two studies reported protective effect of higher oestradiol levels on cognitive decline,[3,11] while a recent study found that higher serum oestradiol levels were associated with a higher risk of Alzheimer's disease.[12]

The aim of this study was to determine the relationship between circulating oestrogen measured with new more sensitive methods and sex hormone binding globulin levels and cognition in healthy postmenopausal women.

Subject and methods

Study population

Participants were recruited from the PROSPECT study, one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC).[13] In PROSPECT a total of 17 395 healthy participants who came for breast cancer screening, aged 49–70 years, living in Utrecht and surroundings, were enrolled between 1993 and 1997. Using baseline data from PROSPECT, we selected women who had experienced a natural menopause between

8 and 30 years ago. In addition, inclusion criteria were an intact uterus and at least one intact ovary, and no use of sex steroids after the reported date of last menstruation. Out of 1803 eligible women, 902 women were invited and 553 (61%) answered positively. Four hundred and two participants were finally included in our study. Women were considered sufficiently healthy to participate when they were physically and mentally able to visit the study centre independently. Each participant underwent all tests and assessments during two visits to the study centre. The study was approved by the Institutional Review Board of the University Medical Centre, Utrecht, and written informed consent was obtained from all participants. Data collection took place between September 1999 and March 2000.

MMSE

Cognitive function was assessed by specially trained research assistants using the Dutch version of the 30-point mini-mental state examination questionnaire (MMSE).[14] This short general cognitive test has been used extensively in epidemiological studies and allows assessment of orientation to time and space, concentration, language, calculation, and immediate and delayed memory. Among older people a score below 24 indicates cognitive impairment. Because of our selection of a relatively young population, with exclusion of disabled women and those dependent on others for activities of daily living, we did not expect any woman participating in this study to qualify for the definition of clinical dementia. We used two different cut-off points: the widely used threshold of 26 below which moderate cognitive impairment is defined,[15] and a threshold of 27 below which mild cognitive impairment was considered to occur.

Biochemical assessments

Venous blood samples were collected in the morning between 8 and 11 a.m. after an overnight fast. Levels of oestradiol were estimated using an ultra-sensitive double-antibody radioimmunoassay (RIA) purchased from Diagnostic Systems Laboratories (Webster, TX, USA). Oestrone levels were measured using a double antibody RIA from the same supplier. SHBG was measured using a chemoluminescence-based immunometric assay on the Immulite 2000 system (Diagnostic Products Corporation, Los Angeles, CA, USA).

Other measurements

Information on health status was obtained by medical history, registration of current medication and physical examination. A standardized questionnaire on oestrogen use, alcohol consumption and smoking was obtained from all women as part of the medical history. Subjects were categorized into current smokers, former smokers and those who had never smoked. Height, weight, and waist and hip circumference were measured with the subject in standing position wearing indoor clothes and no shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres, and body fat distribution was assessed by the ratio of waist and hip circumferences. Blood pressure and heart rate were measured during the first visit by the an oscillometric automated device (DINAMAP 8100; Critikon, Johnson-Johnson, Tampa, FL, USA) according to the orthostatic hypotension protocol.[16] Measurements were conducted before 11 a.m., after an overnight fast.[17] After 5 min of rest, blood pressure was taken at the right brachial artery simultaneously with heart rate measure, twice with the participant lying down and three times with the participant in standing position, with a time laps of 1 min between each measurement. Systolic as well as diastolic blood pressure was defined as the average of the two supine measurements. Mean arterial blood pressure (MAP) was calculated by the following formula: diastolic blood pressure $+1/3 \times$ (systolic blood pressure – diastolic blood pressure).

Data analysis

Distributions of population characteristics are expressed according to the quintile distributions of oestradiol level. Associations between sex steroid levels and cognition were quantified using logistic regression models and odds ratios and their 95% confidence intervals are presented. Adjustments were made for age and other potential confounders. Statistical analyses were performed using SPSS for Windows (version 11·0).

Results

General characteristics of the entire study population and according to the quintile distribution of oestradiol serum levels are given in Table 1. Increasing oestradiol levels were associated with higher BMI and waist circumference, consistent with adipose tissue being an important source of postmenopausal oestrogen production. Oestrogens were also associated with increasing blood pressure, independently of BMI. Circulating oestradiol and oestrone levels were not associated with age, age at menopause, time since menopause or educational level of participants.

The distribution of MMSE scores is given in Fig. 1, and the educational level of participants is shown in Fig. 2. The frequency of cognitive impairment increased with age, with time since menopause, and with higher blood pressure, and both levels of cognitive impairment were decreased with higher age at menopause and higher educational level of participants (Table 2). The frequency of cognitive impairment was not related to BMI or fat mass, even after adjustment for blood pressure and/or age.

A slight decrease in the frequency of cognitive impairment was seen with increasing quintiles of oestradiol concentration (Table 1) and higher oestradiol and oestrone levels were significantly associated with lower frequency of mild cognitive impairment (MMSE < 27) (Table 3). These associations were stronger after adjustment for mean arterial blood pressure and/or SHBG, and remained unchanged after adjustment for BMI and educational level. Analyses with moderate cognitive impairment (MMSE < 26) showed essentially the same results, with variations explained by the smaller number of women in this category (Table 4).

Further adjustment for other possible confounders did not significantly change the associations. Sex hormone-binding globulin was not related to the level of cognitive decline. The same analyses performed after exclusion of early menopausal women (age at menopause ≤ 45 years) showed virtually the same results.

Table 1. Characteristics of the study population ($n = 402$) per quintiles oestradiol

Characteristic	Study population ($N = 402$)	Quintile 1 Oestradiol: 0–10 pmol/l ($N = 83$)	Quintile 2 10–15 pmol/l ($N = 87$)	Quintile 3 15–20 pmol/l ($N = 87$)	Quintile 4 20–29 pmol/l ($N = 74$)	Quintile 5 29–102 pmol/l ($N = 80$)
Age (years)	66·3 (3·8)	66·2 (3·8)	66·4 (3·9)	66·4 (3·7)	66·5 (4)	66 (3·9)
Time since menopause (years)	15·2 (5·4)	15·8 (5·8)	17·6 (6·5)	17·5 (6·5)	18 (6·5)	16·6 (6·8)
Age at menopause (years)	49·6 (4·5)	50·8 (3·4)	49·2 (4·4)	49·4 (4·7)	48·9 (4·6)	49·9 (5)
MMSE (points)	26·8 (1·9)	26·7 (2·1)	26·7 (2)	26·6 (1·9)	26·9 (2)	27·2 (1·7)
Moderate cognitive impairment (< 26) % (n)	22 (89)	24·1 (20)	24·4 (19)	21·8 (19)	23 (17)	17·5 (14)
Mild cognitive impairment (< 27) % (n)	37·1 (149)	38·6 (32)	44·9 (35)	41·4 (36)	33·8 (25)	26·3 (21)
Cardiovascular risk factors						
Body Mass Index (kg/m^2)	26·2 (4·4)	24·3 (3·1)	25·9 (4·3)	26 (4·1)	26·4 (4·6)	28·4 (4·9)
Waist (cm)	82·9 (10·8)	79·7 (9·4)	81·7 (10·2)	81·6 (9·8)	83·5 (11·6)	88·2 (11·3)
Mean arterial pressure (mmHg)	100 (14·8)	96·3 (14·5)	99·1 (15·9)	101·6 (15·6)	99·4 (12·7)	104 (14·6)
Educational level of participants % (n)						
Primary school completed	22·6 (91)	26·5 (22)	23·1 (18)	17·2 (15)	28·4 (21)	18·8 (15)
Technical/professional education	45·3 (182)	39·8 (33)	43·6 (34)	49·4 (43)	41·9 (31)	51·3 (41)
Secondary education	13·7 (55)	15·7 (13)	15·4 (12)	16·1 (14)	8·1 (6)	12·5 (10)
Academic education	18·2 (73)	18·1 (15)	16·7 (13)	17·2 (15)	21·6 (16)	17·5 (14)
Hormones						
Oestradiol (pmol/l)	20·2 (13·5)	5·3 (3·1)	12·6 (1·3)	18 (1·5)	24·9 (2·4)	41 (12·2)
Oestrone (pmol/l)	47 (35·9)	21·5 (16·25)	33·4 (18·7)	40·1 (21·3)	50 (25)	81·6 (53·8)
SHBG (nmol/l)	59·06 (26·7)	67·7 (24·7)	63·2 (26·7)	60·4 (23·5)	55·5 (28·1)	47·8 (26·9)

Values are expressed as mean (standard deviation) unless otherwise stated.

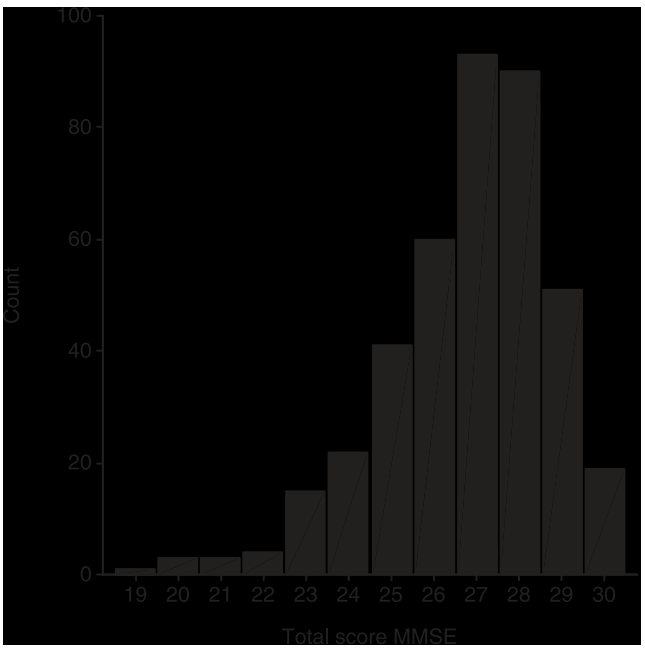

Fig. 1 Distribution of MMSE scores.

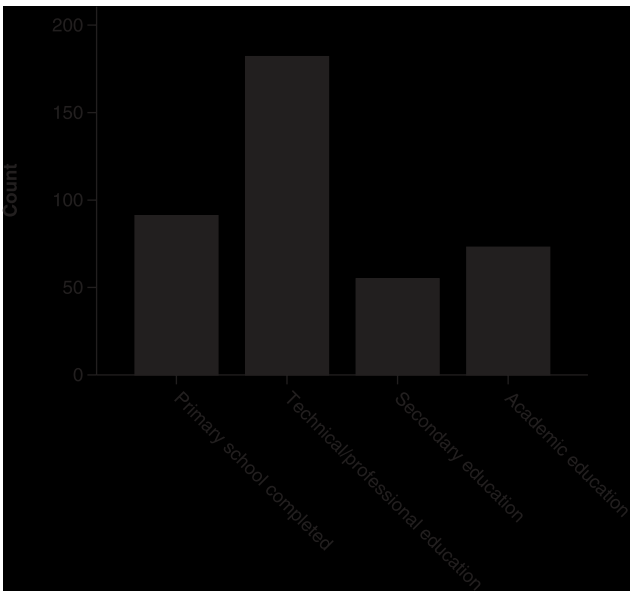

Fig. 2 Educational level of participants.

Table 2. Determinants of impaired cognition

Characteristics	MMSE score < 26 Odds ratio, 95% CI	MMSE score < 27 Odds ratio, 95% CI
Age (years)	1·064 (1·001–1·132)*	1·044 (0·991–1·1005)
Age at menopause (years)	0·911 (0·865–0·958)***	0·917 (0·875–0·96)***
Time since menopause (years)	1·073 (1·034–1·114)***	1·061 (1·028–1·096)***
Mean arterial pressure (mmHg)	1·017 (1·002–1·033)*	1·02 (1·006–1·034)**
Body mass index (kg/m^2)	1·011 (0·96–1·07)	1·018 (0·97–1·06)
Level of education	0·52 (0·391–0·69)***	0·452 (0·353–0·58)***

*$P \leq 0{\cdot}05$; **$P \leq 0{\cdot}01$; ***$P \leq 0{\cdot}001$.

Table 3. Odds ratios for the relations between quintiles of serum hormone levels and mild cognitive impairment (MMSE < 27)

Hormone OR (95%CI)	Quintile 1 Reference	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-value for trend
Oestradiol	1	1·30 (0·69–2·43)	1·13 (0·61–2·08)	0·81 (0·42–1·56)	0·57 (0·29–1·10)	0·039
Oestradiol*	1	1·28 (0·68–2·41)	1·11 (0·60–2·06)	0·80 (0·42–1·54)	0·57 (0·29–1·11)	0·040
Oestradiol* Edu	1	1·31 (0·66–2·57)	1·22 (0·63–2·36)	0·75 (0·37–1·52)	0·56 (0·28–1·13)	0·038
Oestradiol*†	1	1·22 (0·65–2·31)	0·99 (0·53–1·87)	0·75 (0·39–1·46)	0·48 (0·24–0·95)	0·013
Oestradiol*‡	1	1·24 (0·66–2·34)	1·06 (0·57–1·96)	0·73 (0·37–1·42)	0·48 (0·24–0·97)	0·015
Oestradiol*†‡	1	1·19 (0·63–2·26)	0·95 (0·51–1·79)	0·69 (0·35–1·35)	0·41 (0·20–0·84)	0·005
Oestradiol*†‡§	1	1·17 (0·61–2·23)	0·94 (0·50–1·77)	0·68 (0·34–1·34)	0·40 (0·19–0·83)	0·005
Oestradiol*†‡§ Edu	1	1·30 (0·65–2·60)	0·93 (0·58–2·23)	0·72 (0·35–1·49)	0·50 (0·23–1·08)	0·028
Oestrone*	1	0·85 (0·46–1·60)	0·52 (0·27–1·00)*	0·71 (0·37–1·34)	0·51 (0·27–0·99)	0·038

*Adjusted for age; †Adjusted for MAP; ‡Adjusted for SHBG. §Adjusted for BMI. Edu: Adjusted for educational level.

Table 4. Odds ratios for the relations between quintiles of serum hormone levels and moderate cognitive impairment (MMSE < 26)

Hormone OR (95%CI)	Quintile 1 Reference	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-value for trend
Oestradiol	1	1·01 (0·49–2·09)	0·88 (0·43–1·8)	0·94 (0·45–1·97)	0·67 (0·31–1·44)	0·32
Oestradiol*	1	1 (0·48–2·06)	0·86 (0·42–1·78)	0·92 (0·44–1·94)	0·67 (0·31–1·45)	0·32
Oestradiol Edu	1	1·05 (0·5–2·21)	0·94 (0·45–1·96)	0·91 (0·42–1·96)	0·68 (0·31–1·49)	0·32
Oestradiol†	1	0·95 (0·46–1·98)	0·78 (0·38–1·62)	0·88 (0·41–1·85)	0·58 (0·27–1·28)	0·198
Oestradiol‡	1	0·97 (0·47–2·01)	0·83 (0·4–1·71)	0·85 (0·4–1·81)	0·59 (0·26–1·3)	0·194
Oestradiol†‡	1	0·93 (0·45–1·94)	0·75 (0·36–1·57)	0·82 (0·38–1·74)	0·52 (0·23–1·17)	0·121
Oestradiol†‡§	1	0·94 (0·45–1·95)	0·76 (0·37–1·59)	0·83 (0·39–1·77)	0·51 (0·22–1·17)	0·124
Oestradiol†‡§ Edu	1	1·03 (0·48–2·21)	0·88 (0·41–1·87)	0·89 (0·4–1·94)	0·62 (0·27–1·45)	0·265
Estrone	1	0·95 (0·46–1·96)	0·85 (0·4–1·74)	0·7 (0·33–1·5)	0·75 (0·35–1·58)	0·299

*Adjusted for age; †adjusted for MAP; ‡adjusted for SHBG; §adjusted for BMI. Edu: adjusted for educational level.

Discussion

The results of this study among healthy women 8–30 years after menopause suggest that higher circulating oestrogen concentrations (predominantly oestradiol) are associated with a lower risk of cognitive decline. This effect was more pronounced after adjustment for blood pressure and SHBG, and was independent of BMI.

Before interpreting these data, some issues need to be addressed. We used the MMSE test to evaluate cognitive function because of its wide use and simplicity in performing on a large scale allowing subjective interpretation to be avoided. A cut-off value of 26 points was chosen to mark intact cognition because our objective was to determine cognitive function rather than to diagnose dementia.[18] Although detection of subtle cognitive change or specific cognitive function testing is not possible with the MMSE, its validity and usefulness as a test for overall cognitive screening has been well documented.[19,20] On an individual level the MMSE is probably not a very precise test to assess cognitive function, but on a population level it adequately reflects the distribution of cognition.[21] Because of a small number of women with MMSE < 26 in this relatively healthy group

of independently living women in which individuals with clearly impaired cognition were excluded at the start of the study, we used a threshold of 27 below which mild cognitive impairment was considered to occur. Both cognitive impairment analyses showed essentially the same results, with variations in significance explained by the smaller number of women in the category below 26.

There is a moderate increase of MMSE score with increasing quintiles of oestradiol concentration in this population. Although associations between higher oestrogen levels and lower frequency of mild cognitive impairment were significant, a risk of over interpretation cannot be totally excluded. It is once again stressed that this cross-sectional study was carried out in a group of menopausal women in relative health and of relatively good cognition.

Our findings are consistent with previously reported postmenopausal evolution of sex steroid serum concentrations, with intra-individual oestrone and oestradiol levels remaining relatively stable from 3 years after postmenopausal decline.[22–24] The principal source of oestrogens in postmenopausal women is peripheral aromatization of androstenedione to oestrone in adipose tissue and skin, which is subsequently reduced to oestradiol in peripheral tissues. Extragonadal oestrogen biosynthesis occurs in a number of sites, including adipose tissue, bone, various sites of the brain, and vascular endothelial and smooth muscle cells.[25] Postmenopausal oestrogen production is thus primarily influenced by body weight but not by age.

The protective effect of oestrogens on cognitive decline was more pronounced after adjustment for SHBG, suggesting that the bio-available oestrogen level is the principal determinant for an effect on the brain. This is consistent with the findings of Yaffe *et al.*[3] in 425 postmenopausal women aged 65 years and over, but not with the findings of Drake *et al.*[11] in a smaller group of 39 postmenopausal women aged 65–90 years; mean 78·8 ± 7·1 (SD). Apart from a lower power in the study of Drake *et al.*,[11] adjustment for SHBG probably better estimates oestrogen activity, apart from a possible additional intrinsic effect of SHBG. Recent evidence has shown that SHBG bound to specific SHBG receptors might promote steroid activity by activation of adenylate cyclase, thus without steroids entering the cell.[26] In both studies mentioned above[3,11] blood pressure was not measured. However, we found this to be a probable confounding factor in the relationship between circulating oestrogen levels and cognitive decline, which could have weakened the association between oestradiol and cognition.

Interestingly, in our population serum oestradiol levels increased with BMI, and frequency of impairment in cognitive functions decreased with higher serum oestradiol levels, but higher BMI did not protect against cognitive impairment. Fat mass or higher BMI was not related to cognition, which suggests the importance of other sources of oestradiol production than adipose tissue in postmenopausal women. Also, local oestrogen biosynthesis by aromatase activity in the brain may be important in the regulation of various cognitive and hypothalamic functions.[27] Simpson[28] and Labrie[29] have hypothesized that in postmenopausal women, and also in men, extragonadal oestradiol plays an important paracrine, autocrine and indeed, intracrine role.

Our findings do not agree with a recent study where higher oestradiol levels were, although not significantly, associated with higher risk of dementia.[12] Two other studies on Alzheimer's disease (AD) patients found the same trend, one with higher oestrone and androstenedione levels in the AD group,[10] and the other with not significantly increased levels of oestradiol in the AD group compared to healthy elderly subjects.[9] AD is associated with a disorder of the hypothalamic-pituitary-adrenal (HPA) axis and with increased levels of adrenocortical and gonadal hormones. The hypothesis that AD itself could be responsible for an abnormality of sex steroid production has been previously mentioned and deserves further investigation.[9,10]

In conclusion, postmenopausal women with higher 'remaining' oestradiol levels appear less likely to suffer from cognitive decline. This effect seems independent of age at menopause, time since menopause or body mass index, and stronger after adjustment for blood pressure. The findings of this study support the hypothesis that higher postmenopausal endogenous oestrogen levels may protect against cognitive impairment.

Acknowledgements

We would like to thank the participants of the study, and P. H. M. Peeters for giving access to the PROSPECT population. We are also grateful to A. A. A. Bak for all the work she has done in preparing the study. We acknowledge the skilful contribution of E. C. M. Verkerk, Esther van Lunteren, Gerry van Hemert, Hennie Pracht and Renate Wieman to the data collection and data management.

The Netherlands Organization for Health Research and Development (ZON) nr. 2100·0011 funded the study.

CEIL recruited the participants, collected and entered the data, performed the statistical analysis and wrote the first draft. All authors contributed to later drafts of the paper. YTvdS: supervised the recruitment of participants and data collection, analysis and interpretation of data, and participated in writing the paper. SWJL, FHdJ, HAPP and DEG originated and designed the study and obtained funding. FHdJ was responsible for laboratory assays. CEIL is the guarantor for the study.

References

1 Lamberts, S.W., van den Beld, A.W. & van der Lely, A.J. (1997) The endocrinology of aging. *Science*, **278**, 419–424.

2 Nappi, R.E., Sinforiani, E., Mauri, M., Bono, G., Polatti, F. & Nappi, G. (1999) Memory functioning at menopause: impact of age in ovariectomized women. *Gynecological Obstetrics and Investigations*, **47**, 29–36.

3 Yaffe, K., Lui, L.Y., Grady, D., Cauley, J., Kramer, J. & Cummings, S.R. (2000) Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. *Lancet*, **356**, 708–712.

4 Hays, J., Ockene, J.K., Brunner, R.L., Kotchen, J.M., Manson, J.E., Patterson, R.E., Aragaki, A.K., Shumaker, S.A., Brzyski, R.G., LaCroix, A.Z., Granek, I.A. & Valanis, B.G. (2003) Effects of estrogen plus progestin on health-related quality of life. *New England Journal of Medicine*, **348**, 1839–1854.

5 Yoon, B.K., Kim, D.K., Kang, Y., Kim, J.W., Shin, M.H. & Na, D.L. (2003) Hormone replacement therapy in postmenopausal women with Alzheimer's disease: a randomized, prospective study. *Fertility and Sterility*, **79**, 274–280.

6 Grady, D., Yaffe, K., Kristof, M., Lin, F., Richards, C. & Barrett-Connor, E. (2002) Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *American Journal of Medicine*, **113**, 543–548.

7 Wolf, O.T. & Kirschbaum, C. (2002) Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. *Hormones and Behavior*, **41**, 259–266.

8 Senanarong, V., Vannasaeng, S., Poungvarin, N., Ploybutr, S., Udompunthurak, S., Jamjumras, P., Fairbanks, L. & Cummings, J.L. (2002) Endogenous estradiol in elderly individuals: cognitive and noncognitive associations. *Archives of Neurology*, **59**, 385–389.

9 Rasmuson, S., Nasman, B., Carlstrom, K. & Olsson, T. (2002) Increased levels of adrenocortical and gonadal hormones in mild to moderate Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, **13**, 74–79.

10 Cunningham, C.J., Sinnott, M., Denihan, A., Rowan, M., Walsh, J.B., O'Moore, R., Coakley, D., Coen, R.F., Lawler, B.A. & O'Neill, D.D. (2001) Endogenous sex hormone levels in postmenopausal women with Alzheimer's disease. *Journal of Clinical Endocrinology and Metabolism*, **86**, 1099–1103.

11 Drake, E.B., Henderson, V.W., Stanczyk, F.Z., McCleary, C.A., Brown, W.S., Smith, C.A., Rizzo, A.A., Murdock, G.A. & Buckwalter, J.G. (2000) Associations between circulating sex steroid hormones and cognition in normal elderly women. *Neurology*, **54**, 599–603.

12 Geerlings, M.I., Launer, L.J., De Jong, F.H., Ruitenberg, A., Stijnen, T., van Swieten, J.C., Hofman, A., Witteman, J.C., Pols, H.A. & Breteler, M.M. (2003) Endogenous estradiol and risk of dementia in women and men: the Rotterdam Study. *Annals of Neurology*, **53**, 607–615.

13 Peeters, P.H., Beckers, C.G., Hogervorst, J.M. & Collette, H.J. (1994) Effect on breast cancer screening response in the Netherlands of inviting women for an additional scientific investigation. *Journal of Epidemiology and Community Health*, **48**, 175–177.

14 Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

15 Siu, A.L. (1991) Screening for dementia and investigating its causes. *Annals of International Medicine*, **115**, 122–132.

16 Lipsitz, L.A. (1989) Orthostatic hypotension in the elderly. *New England Journal of Medicine*, **321**, 952–957.

17 Jansen, R.W. & Lipsitz L.A. (1995) Postprandial hypotension: epidemiology, pathophysiology, and clinical management. *Annals of Internal Medicine*, **122**, 286–295.

18 Salas, M., In't Veld, B.A., van der Linden, P.D. *et al.* (2001) Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. *Clinical Pharmacological Therapy*, **70**, 561–566.

19 Breteler, M.M., Claus, J.J., Grobbee, D.E. & Hofman, A. (1994) Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *British Medical Journal*, **308**, 1604–1608.

20 Stolk, R.P., Breteler, M.M., Ott, A., Pols, H.A., Lamberts, S.W., Grobbee, D.E. & Hofman, A. (1997) Insulin and cognitive function in an elderly population. The Rotterdam Study. *Diabetes Care*, **20**, 792–795.

21 Tombaugh, T.N. & McIntyre, N.J. (1992) The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society*, **40**, 922–935.

22 Rannevik, G., Jeppsson, S., Johnell, O., Bjerre, B., Laurell-Borulf, Y. & Svanberg, L. (1995) A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. *Maturitas*, **21**, 103–113.

23 Cauley, J.A., Gutai, J.P., Kuller, L.H., LeDonne, D. & Powell, J.G. (1989) The epidemiology of serum sex hormones in postmenopausal women. *American Journal of Epidemiology*, **129**, 1120–1131.

24 Meldrum, D.R., Davidson, B.J., Tataryn, I.V. & Judd, H.L. (1981) Changes in circulating steroids with aging in postmenopausal women. *Obstetrics and Gynecology*, **57**, 624–628.

25 McEwen, B.S. (1999) Clinical review 108: the molecular and neuroanatomical basis for estrogen effects in the central nervous system. *Journal of Clinical Endocrinology and Metabolism*, **84**, 1790–1797.

26 Rosner, W., Hryb, D.J., Khan, M.S., Nakhla, A.M. & Romas, N.A. (1999) Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. *Journal of Steroid Biochemistry and Molecular Biology*, **69**, 481–485.

27 Bulun, S.E., Zeitoun, K., Sasano, H. & Simpson, E.R. (1999) Aromatase in aging women. *Seminars in Reproduction and Endocrinology*, **17**, 349–358.

28 Simpson, E., Rubin, G., Clyne, C., Robertson, K., O'Donnell, L., Davis, S. & Jones, M. (1999) Local estrogen biosynthesis in males and females. *Endocrine Related Cancer*, **6**, 131–137.

29 Labrie, F., Belanger, A., Cusan, L. & Candas B. (1997) Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. *Journal of Clinical Endocrinology and Metabolism*, **82**, 2403–2409.