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Sex hormones, SHBG and cognitive performance among older Australian women: an observational study

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Abstract

Objective: This study aims to explore the associations between sex hormones and cognitive performance in older women.

Methods: Associations between sex hormones, sex hormone binding globulin (SHBG) and cognitive performance were examined in women aged at least 70 years, without dementia and not using medications that influence sex hormones. Linear and generalized linear regression models included age, body mass index, education, smoking, alcohol, living circumstances, diabetes, hypertension, depression and impaired renal function.

Results: The included 5511 women had a median (interquartile range) age of 73.9 (71.6–77.6) years. No associations were found for estrone, estradiol, testosterone or dehydroepiandrosterone and cognitive performance. SHBG concentrations above quartile 1 (Q1) were significantly inversely associated with processing speed (Q2, $\beta = -0.94$, 95% confidence interval [CI] −1.64 to

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Potential conflict of interest S.R.D. has been paid for developing and delivering educational presentations for Besins Healthcare, Abbott, Mayne Pharma, BioFemme and Lawley Pharmaceuticals; has been on Advisory Boards for Theramex, Abott Laboratories, Mayne Pharma, Gedon Richter and Roche Diagnostics; is a consultant to Lawley Pharmaceuticals, Southern Star Research and Que Oncology; and has received institutional grant funding for Que Oncology and Ovova Bio research. R.M.I. has received support from Lawley Pharmaceuticals for conference attendance. F.S. holds a Monash University Graduate Research and International Tuition Scholarship.

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There are no other relevant potential conflicts to declare.

−0.24, $p = 0.009$; Q3, $\beta = -0.82$, 95% CI −1.53 to −0.10, $p = 0.025$; and Q4, $\beta = -0.95$, 95% CI −1.70 to −0.20, $p = 0.013$).

Conclusions: Sex hormones were not associated with cognitive performance. The finding that low SHBG is associated with better processing speed warrants further investigation. The null findings for the sex hormones establish a firm baseline to confidently explore the association between sex hormones and longitudinal cognitive performance in this population.

Trial Registration: International Standard Randomized Controlled Trial Number Register (ISRCTN83772183) and ClinicalTrials.gov (NCT01038583).

Keywords

Postmenopause; estrogen; sex hormone binding globulin; dementia; cognitive function; cognitive performance

Introduction

Cognitive decline and dementia are amongst the most important contributors to the loss of quality-adjusted life years, dependency and death worldwide [1-3]. Sex hormones have been implicated as protective against Alzheimer's disease and vascular dementia by reducing amyloid toxicity, oxidative stress and apoptosis [4-6] and by exerting favorable cardiometabolic effects [7].

Estrogen receptors and androgen receptors are widespread throughout the brain. Dehydroepiandrosterone (DHEA), which is synthesized de novo in the brain, is an important precursor for local tissue estrogen and testosterone production [8]. In a rodent model, brain testosterone concentrations declined following castration, while brain estradiol concentrations were preserved, suggesting that sufficient DHEA and testosterone were available after castration for estradiol production to be maintained within the brain [9].

The extent to which circulating sex hormones influence brain function is uncertain. In women, both low and high circulating estradiol have been associated with an increased dementia risk [10,11]. Most studies of estrogen and cognitive performance have only measured estradiol, with some studies reporting it being below the limit of detection (LOD) of the assay used in as many as half of the included women [12-14]. Furthermore, as the main circulating estrogen after menopause is estrone, it should be measured along with estradiol [15].

Higher endogenous testosterone concentrations have been associated with better verbal fluency, but not memory, in small studies of postmenopausal women [16,17]. However, our recent systematic reviews indicated that most studies reporting associations between sex hormones and cognitive performance used conventional immunoassays which lack precision for the measurement of testosterone in women [18,19].

This article reports the findings from a cross-sectional study of the associations between sex hormones measured by liquid chromatography–tandem mass spectrometry (LCMS), and sex hormone binding globulin (SHBG), and cognitive performance in a large sample

of community-dwelling Australian women aged 70 years and older, without clinically significant cognitive impairment [20].

Methods

Study design and participants

The Sex Hormones in Older Women (SHOW) study is a cohort sub-study of the longitudinal randomized ASPREE (ASPirin in Reducing Events in the Elderly) trial [21,22]. Between 10 March 2010 and 31 December 2014, the ASPREE trial recruited 16,703 Australian men and women aged 70 years and older via primary care across the southern Australian states of Victoria, South Australia, New South Wales, Tasmania and the Australian Capital Territory. The SHOW study comprised 6392 of the 9180 Australian female participants who provided biobank specimens at enrollment and consented to measurement of an array of biomarkers.

Participants were required to be free of cardiovascular disease events and dementia (excluded for a score <78 on the Modified Mini-Mental State Examination [3MS] or prior medical history of dementia) [23]. Participants with less than 5 years of life expectancy or having significant disability were excluded from the ASPREE trial, as were regular users of aspirin and people with a high risk of bleeding, other contraindications to aspirin, clinically significant anemia or uncontrolled hypertension.

The SHOW study was approved by the Monash Human Research Ethics Committee (CF16/10-2016000001) and the Alfred Hospital Human Research Ethics Committee (616/15). The ASPREE trial was also approved by the ethics committee at each participating center. In Australia, primary ethics approval was granted by Monash University Human Research Ethics Committee (CF07/3730-2006/745MC). All participants provided written informed consent to contribute biological specimens to the ASPREE Healthy Ageing Biobank. The findings are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies [24]

Assessment of sex hormones

Non-fasting blood samples were obtained after the screening visit and plasma aliquots were stored under nitrogen vapor. Sex hormones were measured by LCMS in a single plasma sample without derivatization at the ANZAC Research Institute (Sydney, NSW, Australia) [25]. All hormone standards and internal standards have been previously described in detail [26]. The assay LODs, limits of quantification and within-run and between-run coefficients of variations were 3.7 pmol/l, 11 pmol/l, 4.7% and 4.6–7.5% for estrone, 11 pmol/l, 18 pmol/l, 6.6% and 4.8–8.6% for estradiol, 35 pmol/l, 0.09 nmol/l, 2.0% and 3.9–6.5% for testosterone and 0.07 nmol/l, 0.17 nmol/l, <10% and <10% for DHEA [15]. SHBG was measured by automated immunoassay (Roche Diagnostics, North Ryde, NSW, Australia) in batches with a coefficient of variation of 1.0–2.0%.

Assessment of cognitive performance

Cognitive performance was evaluated using a comprehensive battery of neuropsychological tests at study baseline. Tests were administered by the staff fully trained and accredited in conducting the assessments. This article presents data from the baseline assessment.

The Hopkins Verbal Learning Test – Revised

The Hopkins Verbal Learning Test – Revised (HVLT-R) is a brief and multicomponent test of verbal learning and episodic memory [27]. This test involves presentation and subsequent free recall of a list of 12 nouns (four words from three semantic categories, e.g. fish, parts of building, weather phenomena) after a 20–25 min delay. It yields an immediate recall (0–36) and a delayed recall (0–12) score. A higher score indicates better episodic memory for both immediate and delayed recall. The HVLT-R has good test–retest reliability [27] and construct validity [28].

The Controlled Oral Word Association Test (single-letter version)

The Controlled Oral Word Association Test (COWAT) (letter ‘F’ version) is a word association rest that evaluates executive function and verbal fluency by requiring participants to produce words starting with a designated letter [29]. There is high internal consistency between the individual letters [30]. The minimum score is 0 with no upper limit, and a higher score indicates better executive functioning. The COWAT has significant test-retest reliability [31].

The Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) assesses psychomotor speed (processing speed plus motor speed). The test is a paper-pencil measure that requires a participant to match or substitute digits with abstract symbols using a reference key, each paired with a numeral [32]. The number of correct substitutions or responses within a 90 s time period is recorded as the score (possible score 0–110). The SDMT psychometric properties exhibit high reliability [33] and validity [34].

Potential confounders

Baseline information included demographics (age, education and living circumstances), lifestyle factors (smoking and alcohol), physical measures (body mass index) and ever diagnosis of diabetes, hypertension, depression and impaired renal function. According to the ASPREE trial statistical analysis plan, diabetes was defined as self-reported diabetes by the participant, having a fasting plasma glucose concentration of at least 126 mg/dl (≥7 mmol/l) or receiving treatment for diabetes at baseline [35]. Hypertension was defined as blood pressure above 140/90mmHg or receiving treatment for high blood pressure at study entry. Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 ml/min per 1.73 m [36].

Statistical analysis

Categorical data are reported as percentages, and continuous data as the median (interquartile range) based on the shape of the distribution. Participants using sex hormone

therapy, anti-estrogens, anti-androgens or systemic glucocorticosteroids were excluded from the analysis. For hormone concentrations, the median and inter-decile range were reported as descriptive statistics and quartiles (lowest quartile [Q1] as the reference) were used to investigate the associations.

To explore the associations between serum concentrations of sex hormones, SHBG and cognitive performance, both univariable and multivariable linear regression analyses were used and reported with the β-coefficient and 95% confidence interval (CI). The distribution of baseline scores for delayed recall was not normally distributed even after log transformation and evaluation of normality of residuals. Therefore, the generalized linear model with robust variance was used for the outcome of delayed recall. An exploratory analysis was also employed to examine the association between women who had detected estradiol and who had estradiol below the LOD (detected vs. not detected) and cognitive performance.

Potential risk factors for cognitive performance included in the multivariable regression models were age, body mass index, education, smoking status, alcohol consumption, living circumstances, diabetes, hypertension, depression and impaired renal function. The multicollinearity between independent variables was checked before entering them into the model. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed by Stata 17.0 (Stata Corporation, College Station, TX, USA).

Results

A total of 6392 women provided a biobank sample. Following the exclusion of the 823 participants using medications that might influence sex hormone concentrations and 24 women with Parkinson's disease, the analyses included 5511 participants (Figure 1). These women had a median (interquartile range) age of 73.9 (71.6–77.6) years. The majority were overweight or obese (70.8%) and hypertensive (73.2%), and 41.1% were living alone (Table 1).

Association between sex hormones, SHBG and cognitive performance

In the unadjusted analyses, DHEA concentrations were significantly positively associated with immediate recall (Q3 vs. Q1, $\beta = 0.57$, 95% CI −0.16 to 0.97, $p = 0.006$; and Q4 vs. Q1, $\beta = 0.51$, 95% CI 0.10 to 0.92, $p = 0.013$), delayed recall (Q3 vs. Q1, $\beta = 0.03$, 95% CI 0.01 to 0.06, $p = 0.013$) and processing speed (Q2 vs. Q1, $\beta = 0.88$, 95% CI 0.14 to 1.62, $p = 0.020$; Q3 vs. Q1, $\beta = 0.99$, 95% CI 0.24 to 1.73, $p = 0.009$; and Q4 vs. Q1, $\beta = 1.12$, 95% CI 0.38 to 1.88, $p = .003$) (Table 2). These associations did not persist after adjustment for confounders.

There were no associations between estrone or testosterone and cognitive outcomes (Table 2). As more than 66% of the included women had an estradiol concentration below the assay LOD, we compared women with measurable versus unmeasurable concentrations of estradiol. In this exploratory analysis, cognitive performance was not different in women

who had estradiol below the LOD compared with women with measurable estradiol (Table 3).

After adjusting for confounders, significant inverse associations were seen for SHBG and immediate recall (Q2 vs. Q1, $\beta = -0.62$, 95% CI −1.01 to −0.23, $p = 0.002$) and processing speed (Q2 vs. Q1, $\beta = -0.94$, 95% CI −1.64 to −0.24, $p = 0.009$; Q3 vs. Q1, $\beta = -0.82$, 95% CI −1.53 to −0.10, $p = 0.025$; and Q4 vs. Q1, $\beta = -0.95$, 95% CI −1.70 to −0.20, $p = 0.013$).

Discussion

To our knowledge, this is the first cross-sectional study to examine the associations between endogenous estrone, estradiol, testosterone or DHEA, measured by LCMS, and cognitive performance in a large sample of older Australian women. In women aged 70 years and older without significant cognitive impairment, blood sex hormone concentrations were not associated with cognitive performance. A significant inverse association was seen for SHBG with better processing speed.

Critical to the interpretation of this analysis was the exclusion of people with substantial cognitive impairment or dementia on screening using the 3MS. Hence, unlike most prior cross-sectional studies of sex hormones and cognition that have included women with moderate cognitive impairment or dementia [13,37-40], the focus of this study was to examine sex hormone concentrations in older women without substantial cognitive impairment or dementia.

Of the two previous cross-sectional studies that excluded cognitively impaired older women, one reported a positive association between total testosterone and global cognition [41]. The other study found inverse associations between total testosterone and both memory and psychomotor speed, but positive associations between DHEA and verbal and visual memory [42]. Both studies measured testosterone by immunoassays that lack precision at low blood concentrations. Importantly, Hogervorst et al. reported that 52% of the included women had total testosterone concentrations below the assay LOD [41]. This highlights the inadequacy of immunoassays for studies of this nature [18]. The study by Bojar et al. reported the inclusion of 21% of carriers of the apoe4 allele which is a known risk factor for dementia [42]. Our recent systematic review of endogenous testosterone, and another systematic review by de Menezes et al. of DHEA and DHEA sulfate, similarly demonstrated inconclusive cross-sectional associations between these hormones and cognitive performance [19,43]. Consequently, our findings for testosterone and DHEA cannot be seen as in conflict with prior studies.

Boss et al. published a systematic review of estrogens and cognitive performance that included studies of women with and without cognitive impairment [44]. Interpretation of the inconclusive associations between estradiol, estrone, testosterone and cognitive performance irrespective of study designs was limited again by the use of conventional immunoassays by 25 of the 26 included studies, small to moderate sample sizes, methodological differences between studies and the use of single global tests of cognition [44]. Additionally, most of the included studies did not report findings for estrone, the main circulating estrogen

in postmenopausal women. We have previously shown that estrone is a robust proxy for estradiol concentrations in older postmenopausal women and is thus a marker of the overall estrogen milieu [15]. Consistent with our finding of no association between estrone and cognitive function, in our exploratory analysis women with estradiol concentrations below the LOD did not perform differently on cognitive testing from those with measurable estradiol.

With multiple analyses in this study, the inverse association between high SHBG and immediate recall involving Q2 only is most likely a chance finding. However, the inverse association between low SHBG and better processing speed is more robust. This was an unexpected finding as low SHBG concentrations are seen in conditions associated with greater dementia risk including diabetes, hyperinsulinemia, hypertension, dyslipidemia and obesity [45-48]. Conversely, higher concentrations of SHBG are seen in women with low body mass index, liver disease and thyroid disease [49,50]. The free hormone hypothesis proposes that low SHBG results in sex hormones being more available to tissues because of less high-affinity binding to SHBG. However, this assumes SHBG and albumin-bound sex hormones are not freely available to tissues, which remains to be determined [51]. Thus, SHBG might be a proxy marker for other conditions adversely influencing cognitive function or may act as an ‘umbrella variable’, compared with an individual factor in predicting dementia [50,52].

Study strengths are the large community-based sample size of relatively healthy women aged 70 years and older, formal testing of executive function, verbal, visual and semantic memory and processing speed, measurement of sex hormones by LCMS and exclusion of women with medications potentially influencing sex hormones. A limitation to the generalizability of our findings is that our sample comprised predominantly women of European ancestry, and the screening and exclusion of ASPREE participants with substantial cognitive impairment did not allow us to assess associations between sex hormones and major impairments in cognitive performance.

Conclusions

In summary, endogenous sex hormones were not associated with cognitive performance in Australian women aged 70 years and older without substantial cognitive impairment, while low SHBG was positively associated with more favorable psychomotor processing speed. The lack of any association between sex hormones and cognitive performance provides an important baseline for the longitudinal analysis between sex hormones and cognitive decline in this population.

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Data availability statement

After de-identification (i.e. text, tables, figures and supplementary material), individual participant data will be made available. On application, meta-data and a data dictionary will be made available to others. The ASPREE (ASPirin in Reducing Events in the Elderly) study protocol is available on the ASPREE website. The ASPREE trial statistical analysis plan is published elsewhere [53]. On request, a copy of the clinical trial consent form can be made available. Requests for data access will be via the ASPREE Principal Investigators with details for applications provided through the Sex Hormones in Older Women (SHOW) Principal Investigator. Sub-study data on sex hormones can be requested through this system with approval by the corresponding author. Data will be made available to investigators whose proposed use of the data, registered as a project through the ASPREE Access Management Site, has been approved by a review committee. Access will be through a secure web-based data portal (the ASPREE Safe Haven system), based at Monash University (Monash, VIC, Australia).

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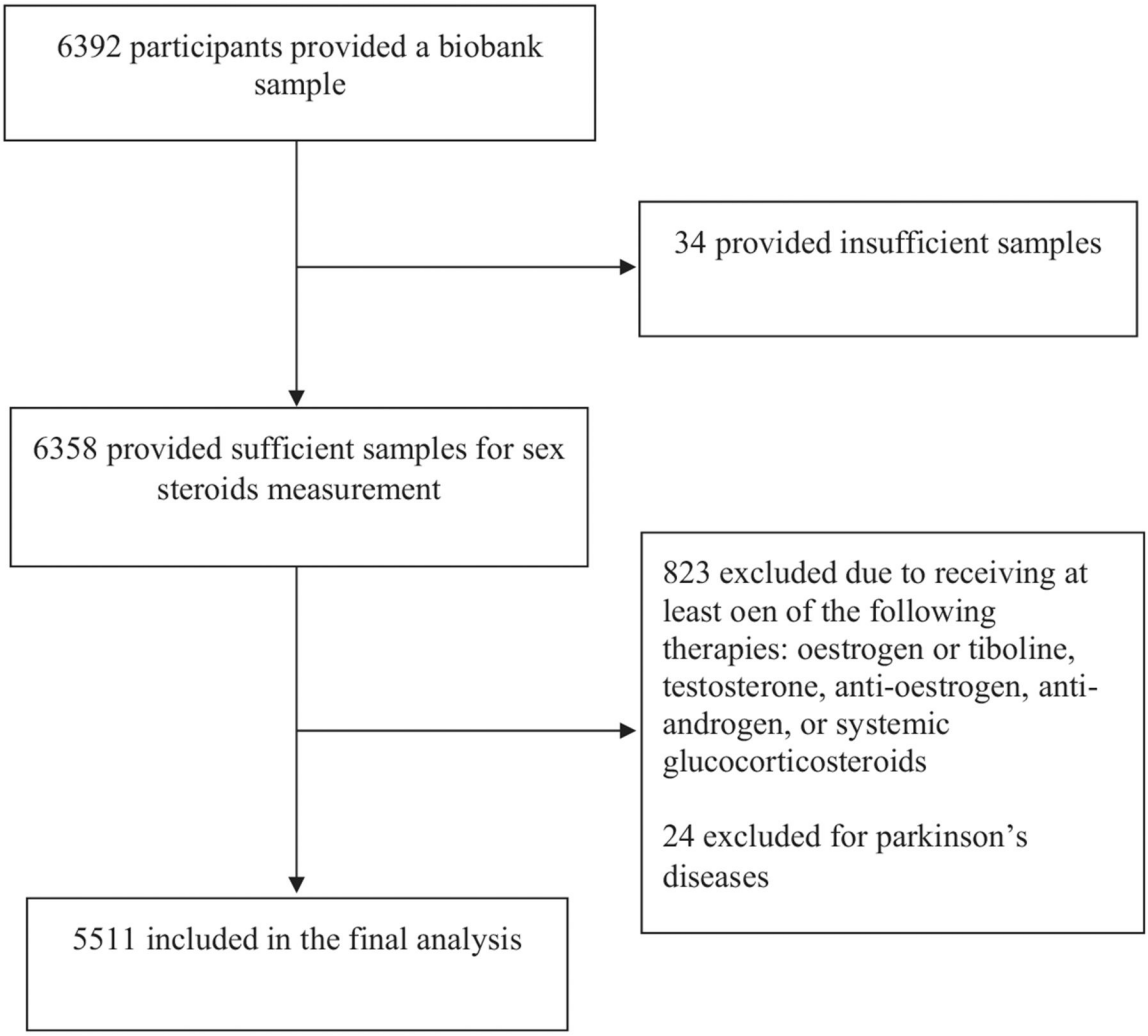

Figure 1.
Study profile: inclusion of participants in the analyses.

Table 1.

Baseline characteristics of the study participants.

Characteristic	Value
Number of participants, *n*	5511
Age (years), median (IQR)	73.9 (71.6–77.6)
Age group (years), *n* (%)	
70–74	2766 (50.2)
75–79	1739 (31.6)
80–84	758 (13.7)
≥85	248 (4.5)
Weight (kg),[a] median (IQR)	69.8 (61.8–79.2)
Height (m),[b] median (IQR)	1.59 (1.55–1.63)
Body mass index (kg/m^2)[c], *n* (%)	
<18.5	44 (0.8)
18.5–24.9	1557 (28.4)
25.0–29.9	2173 (39.6)
≥30.0	1708 (31.2)
Years of education, *n* (%)	
<12 years	2867 (52.0)
12 years and above	2644 (48.0)
Depression, *n* (%)	315 (5.7)
Diabetes, *n* (%)	436 (7.9)
Hypertension, *n* (%)	4037 (73.2)
Living alone, *n* (%)	2267 (41.1)
Smoking status, *n* (%)	
Current	156 (2.8)
Former	1735 (31.5)
Never	3620 (65.7)
Alcohol consumption, *n* (%)	
Current	4114 (74.6)
Former	215 (4.0)
Never	1182 (21.4)
Impaired renal function[d], *n* (%)	1004 (18.7)
Sex hormone and SHBG (median, 10th–90th centile)	
Estrone (pmol/l)	181.2 (85.0–343.9)
Estradiol (pmol/l)[e]	22.0 (11.0–58.7)
Testosterone (nmol/l)	0.38 (0.17–0.85)
DHEA (nmol/l)	2.60 (1.04–6.10)
SHBG (nmol/l)[f]	41.4 (24.0–68.6)
Cognitive performance, median (IQR)	

Characteristic	Value
Immediate recall (HVLT-R)	24 (20–28)
Delayed recall (HVLT-R)	9 (6–10)
Executive function and verbal fluency (COWAT)	12 (9–16)
Processing speed (SDMT)	39 (32–46)

[a]Data available, $n = 5493$.

[b]Data available, $n = 5497$.

[c]Data available, $n = 5482$.

[d]Data available, $n = 5358$.

[e]Reported only detectable, $n = 1862$ (33.8%).

[f]Data available, $n = 5500$.

COWAT, Controlled Oral Word Association Test; DHEA, dehydroepiandrosterone; HVLT-R, Hopkins Verbal Learning Test – Revised; IQR, interquartile range; SDMT, Symbol Digit Modalities Test; SHBG, sex hormone binding globulin.

Table 2.

Association between sex hormones, SHBG and cognitive performance.

Sex hormone/SHBG, N (%), *median (10th–90th centile)*	*Immediate recall (HVLT-R)*		*Delayed recall (HVLT-R)*		*Executive function and verbal fluency (COWAT)*		*Processing speed (SDMT)*	
	Unadjusted β*-coefficient (95% CI),* p*-value*	*Adjusted*[a] β*-coefficient (95% CI),* p*-value*	*Unadjusted* β*-coefficient (95% CI),* p*-value*	*Adjusted*[a] β*-coefficient (95% CI),* p*-value*	*Unadjusted* β*-coefficient (95% CI),* p*-value*	*Adjusted*[a] β*-coefficient (95% CI),* p*-value*	*Unadjusted* β*-coefficient (95% CI),* p*-value*	*Adjusted*[a] β*-coefficient (95% CI),* p*-value*
Estrone								
Q1 (ref.): 1399 (25.4), 96.2 pmol/l (48.1–122.0)	0	0	0	0	0	0	0	0
Q2: 1419 (25.7), 155.3 pmol/l (133.1–177.5)	−0.11 (−0.51 to 0.28) 0.577	−0.17 (−0.56 to 0.21) 0.379	0.01 (−0.01 to 0.03) 0.488	0.01 (−0.02 to 0.03) 0.722	−0.17 (−0.51 to 0.16) 0.315	−0.19 (−0.53 to 0.14) 0.262	0.04 (−0.67 to 0.77) 0.906	−0.05 (−0.75 to 0.64) 0.876
Q3: 1422 (25.8), 220.1 pmol/l (188.6–258.9)	−0.13 (−0.52 to 0.27) 0.525	−0.02 (−0.41 to 0.37) 0.909	−0.01 (−0.02 to 0.02) 0.961	0.01 (−0.02 to 0.02) 0.958	−0.24 (−0.58 to 0.10) 0.173	−0.20 (−0.55 to 0.13) 0.233	0.19 (−0.54 to 0.92) 0.612	0.32 (−0.38 to 1.01) 0.372
Q4: 1271 (23.1), 336.6 pmol/l (284.8–484.5)	−0.24 (−0.65 to 0.17) 0.246	−0.07 (−0.48 to 0.33) 0.728	−0.01 (−0.03 to 0.02) 0.659	0.01 (−0.02 to 0.02) 0.973	−0.24 (−0.59 to 0.11) 0.179	−0.05 (−0.41 to 0.30) 0.769	−0.72 (−1.48 to 0.02) 0.058	−0.08 (−0.81 to 0.64) 0.817
Testosterone								
Q1 (ref.): 1634 (29.6), 0.17 pmol/l (0.10–0.24)	0	0	0	0	0	0	0	0
Q2: 1101 (20.0), 0.31 pmol/l (0.28–0.35)	−0.01 (−0.42 to 0.40) 0.974	0.03 (−0.37 to 0.43) 0.878	0.01 (−0.01 to 0.04) 0.309	0.01 (−0.01 to 0.04) 0.293	0.35 (−0.01 to 0.69) 0.054	0.35 (−0.01 to 0.69) 0.051	0.11 (−0.64 to 0.87) 0.773	0.22 (−0.49 to 0.94) 0.539
Q3: 1489 (27.0), 0.45 pmol/l (0.38–0.55)	0.15 (−0.22 to 0.53 0.418	0.08 (−0.29 to 0.44) 0.682	0.01 (−0.01 to 0.03) 0.360	0.01 (−0.02 to 0.03) 0.595	0.13 (−0.19 to 0.45) 0.429	0.04 (−0.28 to 0.36) 0.799	0.48 (−0.21 to 1.18) 0.174	0.29 (−0.37 to 0.95) 0.387
Q4: 1287 (23.4), 0.79 pmol/l (0.59–1.9)	0.18 (−0.21 to 0.57) 0.369	0.29 (−0.08 to 0.68) 0.125	0.01 (−0.02 to 0.03) 0.539	0.01 (−0.01 to 0.04) 0.246	0.12 (−0.22 to 0.45) 0.490	0.09 (−0.24 to 0.43) 0.563	−0.01 (−0.73 to 0.71) 0.979	0.27 (−0.41 to 0.96) 0.434
DHEA								
Q1 (ref.): 1304 (23.7), 1.11 pmol/l (0.52–1.52)	0	0	0	0	0	0	0	0
Q2: 1413 (25.6), 2.08 pmol/l (1.69–2.46)	0.37 (−0.03 to 0.77) 0.074	0.10 (−0.29 to 0.49) 0.618	0.02 (−0.01 to 0.04) 0.119	0.01 (−0.02 to 0.03) 0.563	0.02 (−0.32 to 0.37) 0.898	−0.01 (−0.35 to 0.34) 0.973	0.88 (0.14 to 1.62) 0.020	0.34 (−0.36 to 1.04) 0.346

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	Immediate recall		*Delayed recall*		*Executive function and verbal fluency*		*Processing speed*	
	(HVLT-R)		*(HVLT-R)*		*(COWAT)*		*(SDMT)*	
Sex hormone/SHBG*, N (%), *median (10th–90th centile)	***Unadjusted β-coefficient (95% CI), p-value***	***Adjusted[a] β-coefficient (95% CI), p-value***	***Unadjusted β-coefficient (95% CI), p-value***	***Adjusted[a] β-coefficient (95% CI), p-value***	***Unadjusted β-coefficient (95% CI), p-value***	***Adjusted[a] β-coefficient (95% CI), p-value***	***Unadjusted β-coefficient (95% CI), p-value***	***Adjusted[a] β-coefficient (95% CI), p-value***
Q3: 1419 (25.7), 3.19 pmol/l (2.70–3.81)	0.57 (−0.16 to 0.97) 0.006	0.18 (−0.21 to 0.58) 0.364	0.03 (0.01 to 0.06) 0.013	0.01 (−0.01 to 0.03) 0.380	−0.05 (−0.40 to 0.29) 0.757	−0.12 (−0.47 to 0.22) 0.494	0.99 (0.24 to 1.73) 0.009	0.11 (−0.60 to 0.81) 0.769
Q4: 1375 (25.0), 5.58 pmol/l (4.19–8.63)	0.51 (0.10 to 0.92) 0.013	0.11 (−0.29 to 0.51) 0.589	0.02 (−0.01 to 0.04) 0.136	−0.01 (−0.03 to 0.02) 0.871	0.02 (−0.33 to 0.37) 0.898	0.05 (−0.29 to 0.40) 0.763	1.12 (0.38 to 1.88) 0.003	0.20 (−0.51 to 0.91) 0.580
SHBG								
Q1 (ref.): 1374 (25), 25.1 pmol/l (17.7–29.8)	0	0	0	0	0	0	0	0
Q2: 1417 (25.8), 36.2 pmol/l (32.0–40.6)	−0.77 (−1.17 to −0.37) 0.000	−0.62 (−1.01 to −0.23) 0.002	−0.03 (−0.06 to −0.01) 0.006	−0.02 (−0.05 to −0.01) 0.044	0.07 (−0.26 to 0.42) 0.663	−0.03 (−0.37 to 0.31) 0.861	−1.18 (−1.91 to −0.45) 0.002	−0.94 (−1.64 to −0.24) 0.009
Q3: 1408 (25.6), 47.4 pmol/l (42.6–53.2)	−0.54 (−0.94 to −0.15) 0.007	−0.29 (−0.69 to 0.11) 0.156	−0.02 (−0.05 to −0.01) 0.042	−0.01 (−0.03 to 0.02) 0.591	0.23 (−0.11 to 0.58) 0.180	0.03 (−0.32 to 0.38) 0.864	−1.38 (−2.11 to −0.64) 0.000	−0.82 (−1.53 to −0.10) 0.025
Q4: 1301 (23.6), 65.8 pmol/l (56.8–91.2)	−0.46 (−0.86 to −0.05) 0.027	−0.02 (−0.44 to 0.40) 0.928	−0.02 −0.05 to −0.01) 0.087	0.01 (−0.02 to 0.03) 0.488	0.37 (0.02 to 0.72) 0.037	0.03 (−0.33 to 0.40) 0.848	−1.87 (−2.62 to −1.12) 0.000	−0.95 (−1.70 to −0.20) 0.013

[a] Adjusted for age, body mass index, education, depression, diabetes, hypertension, living alone, smoking status, alcohol consumption and impaired renal function.

CI, confidence interval; COWAT, Controlled Oral Word Association Test; DHEA, dehydroepiandrosterone; HVLT-R, Hopkins Verbal Learning Test – Revised; Q1–Q4, quartile 1–4; SDMT, Symbol Digit Modalities Test; SHBG, sex hormone binding globulin.

Table 3.

Association between estradiol (detected vs. not detected) and cognitive performance.

	Immediate/total recall (HVLT-R)		*Delayed recall (HVLT-R)*			*Executive function and verbal fluency (COWAT)*	*Processing speed (SDMT)*	
Estradiol*, N (%), *median (10th–90th centile)	***Unadjusted* β-*coefficient* (95% CI), p-*value***	***Adjusted*[a] β-*coefficient* (95% CI), p-*value***	***Unadjusted* β-*coefficient* (95% CI), p-*value***	***Adjusted*[a] β-*coefficient* (95% CI), p-*value***	***Unadjusted* β-*coefficient* (95% CI), p-*value***	***Adjusted*[a] β-*coefficient* (95% CI), p-*value***	***Unadjusted* β-*coefficient* (95% CI), p-*value***	***Adjusted*[a] β-*coefficient* (95% CI), p-*value***
Detected (ref.): 1862 (33.8), 22.0 pmol/l (11.0–58.7)	0	0	0	0	0	0	0	0
Not detected: 3649 (66.2)	0.01 (−0.31 to 0.29) 0.934	0.11 (−0.19 to 0.40) 0.470	−0.01 (−0.02 to 0.01) 0.582	0.01 (−0.01 to 0.02) 0.724	0.15 (−0.10 to 0.41) 0.242	0.05 (−0.20 to 0.31) 0.688	−0.13 (−0.69 to 0. 42) 0.635	0.01 (−0.52 to 0.54) 0.972

[a]Adjusted for age, alcohol, body mass index, depression, diabetes, education, hypertension, impaired renal function, living alone and smoking.

CI, confidence interval; COWAT, Controlled Oral Word Association Test; HVLT-R, Hopkins Verbal Learning Test – Revised; SDMT, Symbol Digit Modalities Test.