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Estrone, sex hormone binding globulin and lipid profiles in older women: an observational study

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Abstract

Objective: We investigated whether estrone and sex hormone binding globulin (SHBG) concentrations are associated with lipid concentrations in older postmenopausal women.

Methods: This was a cross-sectional study of 6358 Australian women, aged 70–95 years, recruited between 2010 and 2014. Associations between estrone and SHBG and lipid concentrations were examined in participants not using medications that influence estrogen concentrations or lipid-lowering therapy. Linear regression models included age, body mass index, smoking, alcohol consumption, renal function and diabetes, with the lowest quartile (Q1) as the reference for estrone and SHBG.

Results: The study included 3231 participants with median age of 74.0 (interquartile range 71.7–77.9) years. Estrone concentration Q3 and Q4 were positively associated with high-density lipoprotein cholesterol (HDL-C) ($p = 0.017$ and $p = 0.046$, respectively). Inverse associations were seen for estrone Q4 with total cholesterol ($p = 0.018$), Q2 and Q4 with non-HDL-C ($p = 0.045$ and $p = 0.002$, respectively) and Q3 and Q4 with triglycerides ($p = 0.030$ and $p = 0.001$, respectively). For SHBG, Q2, Q3 and Q4 were positively associated with HDL-C (all $p < 0.001$), and inversely with non-HDL-C (all $p = 0.001$) and triglycerides (all $p < 0.001$).

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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, Abbott Laboratories, Mayne Pharma, Gedon Richter and Roche Diagnostics; has been a consultant to Lawley Pharmaceuticals, Southern Star Research and Que Oncology; and has received institutional grant funding for Que Oncology and for Ovova Bio research. A.M.T. reports honoraria for Advisory Board participation from Amgen; Data Monitoring Committee membership from Merck, The Medicines Company and Novartis; and lectures from Pfizer.

Conclusions: Estrone and SHBG are associated with lipid concentrations in older women. SHBG, but not estrone, may provide additional clinical predictive utility for the assessment of cardiometabolic disease risk in older women.

Keywords

Menopause; estrone; sex hormone binding globulin; cholesterol; lipids

Introduction

Atherothrombotic cardiovascular disease (CVD) is the leading cause of morbidity and mortality in postmenopausal women [1,2]. Risk factors include smoking, diabetes, elevated blood pressure and dyslipidemia [3], with 47.1% of the population risk for myocardial infarction in women attributed to hypercholesterolemia [4].

Estrogens have been implicated as potentially protective against CVD in postmenopausal women [5]. The profound estrogen depletion seen in mouse models and in men with aromatase gene mutations is associated with hyperlipidemia and premature atherosclerosis [6,7]. Furthermore, exogenous estrogen therapy reduces blood low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol (HDL-C) blood concentrations in postmenopausal women with normal lipids, and with hypercholesterolemia [8,9]. Oral, but not transdermal, estrogen therapy may elevate triglycerides (TG) [3,10]. In both normolipemic and hypercholesterolemic postmenopausal women, estrogen therapy restores the adverse effects of menopause on endothelial function [5,11].

Few studies have examined the associations between endogenous estrogens and lipid concentrations in postmenopausal women. We previously reported no association between estradiol measured by immunoassay and lipid levels in 624 postmenopausal women with a mean age of approximately 54 years [12]. However, sex hormone binding globulin (SHBG) concentrations were inversely associated with non-HDL-C and TG, and positively with HDL-C concentrations [12]. The interpretation of the findings for estrogens in that study is limited by the use of an immunoassay, which lacked sensitivity and precision for the measurement of estradiol and estrone at the low concentrations seen after menopause [13].

With the exponential increase in CVD events with increasing age in women, the possible contribution of estrogen to CVD risk in older women merits exploration. We have measured estrogens and SHBG in the Sex Hormones in Older Women (SHOW) study, which was a sub-study of the ASPREE (ASPirin in Reducing Events in the Elderly) study [13]. We now report the associations between these variables and lipid concentrations in a large sample of community-dwelling women aged 70 years and older.

Methods

Study design and participants

The SHOW study was a sub-study of a longitudinal, multicenter, randomized, double-blinded, placebo-controlled trial of low-dose aspirin, the ASPREE study, which enrolled 19,114 participants, 16,703 in Australia, between 10 March 2010 and 31 December 2014.

The participants in Australia were aged at least 70 years, and 9180 (55%) were female. The details of the study design and the procedures for recruitment have been published previously [14,15]. In short, Australian recruitment was by collaboration with more than 2500 general practitioners and participants were from the southern Australian states of Victoria, South Australia, New South Wales, Tasmania and the Australian Capital Territory.

Exclusion criteria for the ASPREE study included known previous CVD events, atrial fibrillation, serious illness likely to cause death within 5 years, a high risk of major bleeding, anemia, an absolute contraindication or allergy to aspirin, current aspirin, antiplatelet drug or anticoagulant use, systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥105 mmHg, impaired cognition [16] or severe difficulty in performing any of the six Katz activities of daily living [17].

Ethical approval for the SHOW study was obtained from 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 each of the ethics committees of the participating centers. Written informed consent was given by all participants. The trial was registered with the International Standard Randomized Controlled Trial Number Register (ISRCTN83772183) and ClinicalTrials.gov (NCT01038583).

Clinical measurements/parameters

All demographic data were recorded at randomization. Clinical measurements included blood pressure, waist circumference, weight and height. Diabetes was defined as a fasting plasma glucose concentration of at least 126 mg/dl (≥7 mmol/l) or treatment of diabetes at baseline [18]. Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 ml/min per 1.73 m^2. Hypertension was defined as a blood pressure >140/90 mmHg or use of anti-hypertensive agents at study entry.

Biochemical measurements

At enrollment (or within 12 months), blood samples were taken and plasma kept under nitrogen vapor. Estrone and estradiol were measured in a single plasma sample using liquid chromatography–mass spectrometry in a single run without derivatization at the ANZAC Research Institute, University of Sydney, Australia [19]. The assay limits of detection, limits of quantification, and within-run and between-run coefficients of variation for estrone were 3.7 pmol/l, 11 pmol/l, 4.7% and 4.6–7.5%, and for estradiol were 11 pmol/l, 18 pmol/l, 6.6% and 4.8–8.6%, respectively [20]. An automated immunoassay (Roche Diagnostics Australia) was used to quantify SHBG in batches with a coefficient of variation ranging from 1.0% to 2.0% [21].

Measurement of total cholesterol, HDL-C and TG was undertaken by National Association of Testing Authorities (NATA) Australia-approved laboratories convenient to the participants and the results were provided to the ASPREE data team. Non-HDL-C, which measures the total number of atherogenic particles, was calculated as total cholesterol minus HDL-C.

Statistical analysis

Participants were excluded from this analysis if they were using any of the following at the time of recruitment: systemic or topical sex steroid therapy, tamoxifen, or other selective estrogen receptor modulator, aromatase inhibitors, anti-androgen therapy, glucocorticoid therapy or lipid-lowering medications. As more than 66% of the study participants had estradiol concentrations below the assay limit of detection, analysis of associations between estradiol and lipid concentrations was deemed inappropriate.

Descriptive statistics including the mean (± standard deviation), median (interquartile range), frequencies and percentages were used to describe the study population. The normality of the outcome data was checked using a histogram, and TG values were log-transformed as they were not normally distributed. For estrone and SHBG, medians and inter-decile ranges were reported as descriptive statistics, while quartiles were used to investigate the associations, and reported as the β-coefficient with 95% confidence interval (CI).

A simple linear regression was employed to determine the unadjusted associations between estrone, SHBG and each of the lipid concentrations. Multiple linear regression was performed to adjust for factors potentially influencing lipid concentrations including age, body mass index, smoking (current, former, never), alcohol consumption (current, former, never), impaired renal function and diabetes. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. The analysis was performed using Stata Version 17.0 (Stata Corporation, College Station, TX, USA). This manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies [22].

Results

Sufficient biobank samples for measurement of sex steroids and SHBG were available in 6358 study participants (Figure 1). Of these, 3231 participants, with a median age of 74.0 (interquartile range 71.7–77.9) years, were included in the analysis. Half (50.2%) were aged 70–74 years, and most (3207; 99.3%) were white/of European ancestry. The majority (2168; 67.3%) were overweight or obese, and 144 (4.5%) and 533 (17%) women had diabetes and impaired renal function, respectively (Table 1).

Associations between estrone, SHBG and lipids

Multiple linear regression was undertaken with quartile 1 (Q1) as the reference (Table 2). Higher estrone concentrations were statistically, significantly inversely associated with total cholesterol (Q4 vs. Q1, $\beta = -0.11$, 95% CI −0.19 to −0.02, $p = 0.018$), non-HDL-C (Q2 vs. Q1, $\beta = -0.09$, 95% CI −0.17 to −0.01, $p = 0.045$; and Q4 vs. Q1, $\beta = -0.14$, 95% CI −0.23 to −0.05, $p = 0.002$) and TG (Q3 vs. Q1, $\beta = -0.04$, 95% CI −0.08 to −0.01, $p = 0.030$; and Q4 vs. Q1, $\beta = -0.07$, 95% CI −0.11 to −0.03, $p = 0.001$). Statistically significant positive associations were seen for estrone and HDL-C (Q3 vs. Q1, $\beta = 0.05$, 95% CI 0.01–0.09, $p = 0.017$; and Q4 vs. Q1, $\beta = 0.04$, 95%, CI 0.01–0.09, $p = 0.046$). Only 1% of the variation in any lipid measured was explained by estrone.

In the multiple linear regression analysis, there were no associations between SHBG concentrations and total cholesterol. Statistically, significant inverse associations, compared with Q1, were seen for SHBG and non-HDL-C (SHBG concentrations Q2, $\beta = -0.16$, 95% CI −0.25 to −0.07, $p = 0.001$; Q3, $\beta = -0.15$, 95% CI −0.24 to −0.06, $p = 0.001$; and Q4, $\beta = 0.28$, 95% CI −0.37 to −0.18, $p < 0.001$). Similarly, statistically significant inverse associations were seen for SHBG concentrations and TG (SHBG Q2, $\beta = -0.14$, 95% CI −0.18 to −0.10, $p < 0.001$; Q3, $\beta = -0.21$, 95% CI −0.25 to −0.17, $p < 0.001$; and Q4, $\beta = -0.31$, 95% CI −0.34 to −0.27, $p < 0.001$).

SHBG concentrations were positively associated with HDLC (Q2, $\beta = 0.09$, 95% CI 0.05–0.14, $p < 0.001$; Q3, $\beta = 0.15$, 95% CI 0.11–0.19, $p < 0.001$; and Q4, $\beta = 0.21$, 95% CI 0.16 to 0.25, $p < 0.001$). The proportions of the variation in HDL-C, non-HDL-C and TG explained by SHBG were 6%, 2%, and 11%, respectively.

Discussion

This study shows that higher concentrations of each of estrone and SHBG are associated with more favorable lipid concentrations in older Australian women. SHBG alone explained as much as 6% of the variation in HDL-C and 11% of the variation in TG. Despite statistically significant associations, estrone alone accounted for no more than 1% of the variation in any of the measured lipids.

The production of estrone, together with estradiol, in postmenopausal women occurs in peripheral tissues and is dependent on adrenal C19 steroid precursors [23,24]. In contrast to the reproductive years, estrone is the main circulating estrogen in postmenopausal women, with estradiol being primarily an intracellular hormone with intracrine and paracrine effects [23]. Consequently, the majority of our study participants had estradiol concentrations below the limit of detection [13,23]. This most probably explains why no associations between serum estrogens measured by immunoassay and any lipid concentrations were found in a study of younger postmenopausal women [12]. Highly relevant to this study, we have shown circulating estrone to be a robust proxy for estradiol concentrations in older postmenopausal women, and hence a marker of the overall estrogen milieu [25]. While the highest estrone concentrations were statistically, significantly associated with more favorable lipid concentrations in our study, the findings for total cholesterol and HDL-C should be interpreted with caution in view of the multiple comparisons undertaken and it is noteworthy that less than 1% of the variation in any of these lipid concentrations was attributable to estrone. Consistent with this, we previously found no association between blood estrone levels and the risk of ischemic cardiovascular events in older postmenopausal women [26]. Together these findings suggest that although the estrogenic milieu of older postmenopausal women may influence lipid concentrations, and potentially also CVD risk, measurement of estrone is not clinically useful because tissue concentrations provide only a crude estimate of tissue effects [27]. However, the models that also included age, body mass index, smoking, alcohol consumption, estimated glomerular filtration rate and diabetes explained 11% and 12% of the variation in HDL-C and TG, respectively, which is consistent with what has been previously reported for younger postmenopausal women [12].

In our study SHBG exhibited more robust independent associations with the lipids measured, with the associations all in the same direction as estrone. Our findings are consistent with previous studies that have reported a positive association between SHBG and HDL-C and an inverse association between SHBG and TG [12,28]. There are no studies with which to compare our finding for the inverse association between SHBG and non-HDL-C. Non-HDL-C measures total atherogenic particles, including small dense low-density lipoprotein, very-low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol and lipoprotein A, as well as low-density lipoprotein cholesterol. In women with hypertriglyceridemia, non-HDL-C appears to be an important CVD risk marker [29]. It is noteworthy that SHBG explained as much as 6% of the variation in HDL-C and 11% of the variation in TG.

Therefore, overall our findings support the hypothesis that SHBG has physiological effects beyond being a carrier protein for sex hormones [30]. Low SHBG is an independent risk factor for an adverse lipid profile in young women, and women at midlife, even after accounting for other factors [12]. Low blood SHBG is an independent marker of insulin resistance and is a risk factor for type 2 diabetes [31], and has been independently associated with CVD risk [32–34]. Furthermore, a strong inverse association between SHBG and diastolic blood pressure has been reported in postmenopausal women [35].

Study strengths include the large sample size, precise measurement of estrone by liquid chromatography–mass spectrometry and exclusion of women taking medications that might influence their estrogen concentrations. Our analysis necessitated exclusion of women taking lipid-lowering therapy, which although a strength also limited the inclusion of women with more severe lipid disorders, such as familial hypercholesterolemia. Women with prior atherothrombotic cardiovascular events were excluded from the ASPREE study and therefore also from this study.

The study participants were predominantly of European ancestry, consistent with the composition of the Australian population of this age [36], limiting generalizability of our findings to other ethnicities. The cross-sectional design of our study allows us to report associations, but not causation.

Conclusions

Endogenous estrone and SHBG concentrations are significantly associated with lipid concentrations in older women. Measurement of SHBG, but not estrone, may provide additional clinical predictive utility for the assessment of cardiometabolic disease risk in older women. This possibility merits further investigation.

Source of funding

The ASPREE trial was supported by the National Institute on Aging and the National Cancer Institute at the National Institutes of Health [Grant U01AG029824]; the National Health and Medical Research Council (NHMRC) of Australia [Grant 34047], [Grant 1127060]; Monash University (Australia); and the Victorian Cancer Agency (Australia). The ASPREE Healthy Ageing Biobank was funded by the CSIRO (Flagship Grant); the National Cancer Institute [Grant U01 AG029824]; and Monash University. This analysis of sex hormones was funded by an NHMRC of Australia Project Grant [No. 1105305]. S.R.D. is an Australian NHMRC Senior Principal Research Fellow [Grant 1135843].

Data availability statement

After deidentification (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 study protocol is available on the ASPREE website. The ASPREE trial statistical analysis plan is published elsewhere [37]. 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, and details for applications provided through SHOW 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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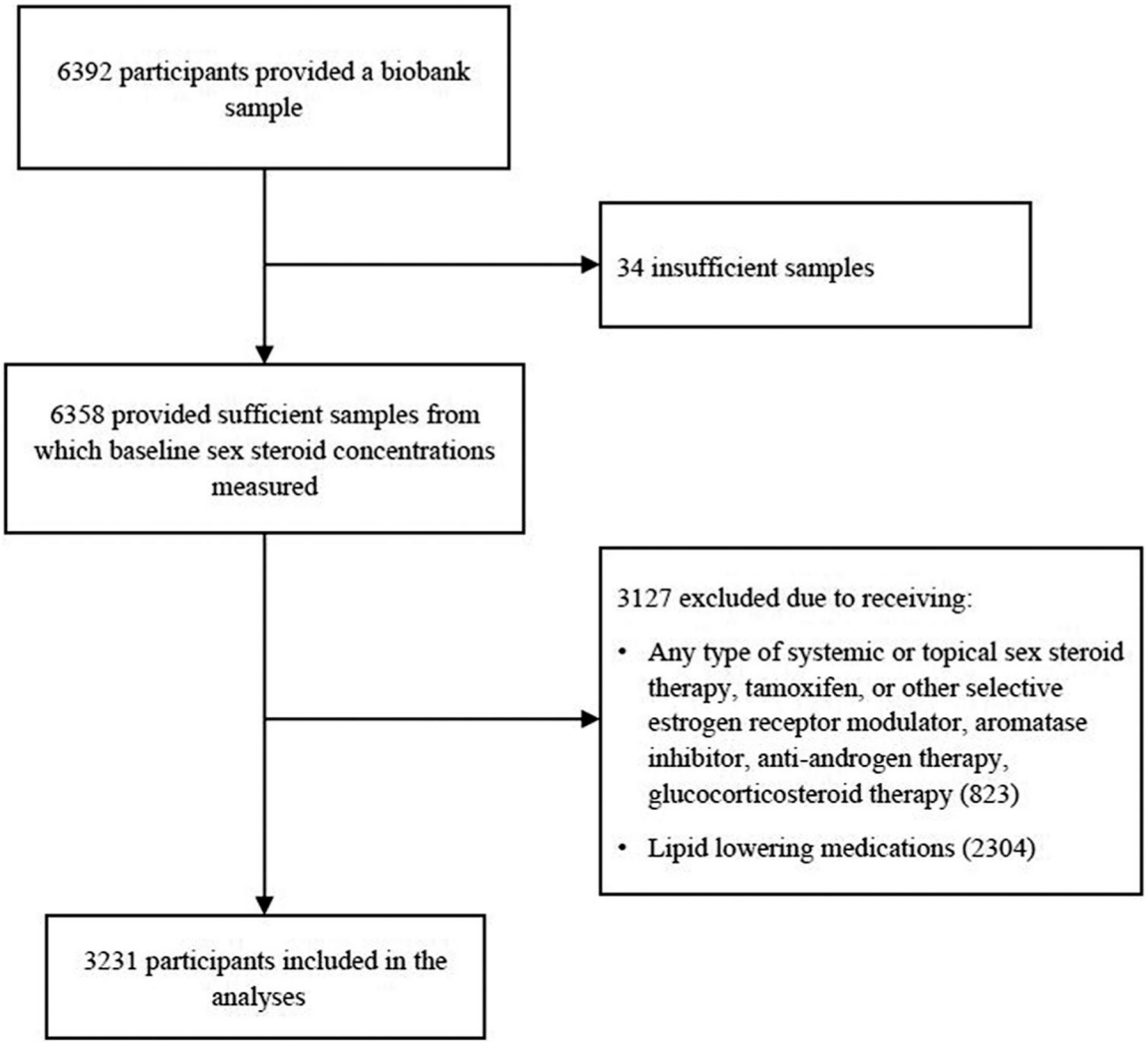

Figure 1.
Inclusion of participants in the analyses.

Table 1.

Baseline characteristics of the study participants.

Characteristic	Value
Overall, *n* (%)	3231 (100)
Age (years), median (IQR)	74.0 (71.7–77.9)
Age group, *n* (%)	
70–74	1621 (50.2)
75–79	991 (30.7)
80–84	462 (14.3)
≥85	157 (4.8)
Weight (kg), median (IQR)[a]	69 (60.8–78.4)
Height (cm), median (IQR)[b]	1.59 (1.55–1.64)
Body mass index (kg/m^2), *n* (%)[c]	
<18.5	37 (1.2)
18.5–24.9	1014 (31.5)
25.0–29.9	1231 (38.2)
≥30.0	937 (29.1)
Ethnicity, *n* (%)	
European ancestry	3207 (99.3)
Other[d]	24 (0.7)
Blood pressure (mmHg)	
Systolic, median (IQR)	140 (128–154)
Diastolic, median (IQR)	78 (71–85)
Smoking status, *n* (%)	
Current	90 (2.8)
Former	1,020 (31.6)
Never	2,121 (65.6)
Alcohol consumption, *n* (%)	
Current	2,431 (75.2)
Former	119 (3.7)

Characteristic	Value
Never	681 (21.1)
Diabetes, *n* (%)	
Yes	144 (4.5)
Impaired renal function, *n* (%)[e]	533 (17.0)
Estrone (pmol/l), median (10th-90th centile)	184.9 (88.8–347.7)
Sex hormone binding globulin (nmol/l), median (10th-90th centile)[f]	42.8 (25.0–70.2)

[a] Data available for 3223 participants.

[b] Data available for 3227 participants.

[c] Data available for 3219 participants.

[d] Includes Asian and Aboriginal or Torres Strait Islander participants.

[e] Data available for 3142 participants.

[f] Data available for 3228 participants.

IQR, interquartile range.

Table 2.

Associations between estrone, sex hormone binding globulin and blood lipid concentrations.

Characteristic	Total cholesterol		High-density lipoprotein cholesterol		Non-high-density lipoprotein cholesterol		Triglycerides	
	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, *N* (%), median (10–90th centile)								
Q1 (ref.): 767 (23.7), 96.2 pmol/l (48.1–122.1)	0	0	0	0	0	0	0	0
Q2: 828 (25.6), 155.3 pmol/l (133.1–177.5)	−0.05 (−0.13 to 0.34) 0.243	−0.06 (−0.15 to 0.02) 0.136	0.02 (−0.29 to 0.06) 0.501	0.02 (−0.02 to 0.07) 0.262	−0.06 (−0.15 to 0.02) 0.138	−0.09 (−0.17 to −0.01) 0.045	−0.02 (−0.06 to 0.21) 0.354	−0.02 (−0.06 to 0.01) 0.218
Q3: 846 (26.1), 218.2 pmol/l (188.6–258.9)	0.01 (−0.08 to 0.08) 0.978	0.01 (−0.08 to 0.09) 0.933	0.02 (−0.03 to 0.59) 0.489	0.05 (0.01 to 0.09) 0.017	−0.01 (−0.09 to 0.08) 0.849	−0.04 (−0.13 to 0.04) 0.337	−0.01 (−0.05 to 0.03) 0.504	−0.04 (−0.08 to −0.01) 0.030
Q4: 790 (24.4), 336.6 pmol/l (284.8–495.6)	−0.12 (−0.20 to −0.04) 0.005	−0.11 (−0.19 to −0.02) 0.018	−0.04 (−0.08 to 0.01) 0.107	0.04 (0.01 to 0.09) 0.046	−0.07 (−0.16 to 0.01) 0.090	−0.14 (−0.23 to −0.05) 0.002	0.01 (−0.03 to 0.05) 0.592	−0.07 (−0.11 to −0.03) 0.001
R^2	0.01	0.02	0.01	0.11	0.01	0.03	0.01	0.12
Sex hormone binding globulin, *N* (%), median (10–90th centile)								
Q1 (ref.): 691 (21.4), 25.3 nmol/l (18.2–29.9)	0	0	0	0	0	0	0	0
Q2: 823 (25.5), 36.3 nmol/l (32–40.6)	−0.04 (−0.12 to 0.05) 0.395	−0.07 (−0.15 to 0.02) 0.137	0.13 (0.09 to 0.18) <0.001	0.09 (0.05 to 0.14) <0.001	−0.17 (−0.25 to −0.08) <0.001	−0.16 (−0.25 to −0.07) 0.001	−0.17 (−0.21 to −0.13) <0.001	−0.14 (−0.18 to −0.10) <0.001
Q3: 862 (26.7), 47.4 nmol/l (42.8–53.4)	0.05 (−0.04 to 0.13) 0.269	0.01 (−0.08 to 0.09) 0.928	0.23 (0.19 to 0.27) <0.001	0.15 (0.11 to 0.19) <0.001	−0.18 (−0.27 to −0.09) <0.001	−0.15 (−0.24 to −0.06) 0.001	−0.27 (−0.31 to −0.23) <0.001	−0.21 (−0.25 to −0.17) <0.001
Q4: 852 (26.3), 66.2 nmol/l (56.8–92)	−0.02 (−0.11 to 0.06) 0.616	−0.07 (−0.16 to 0.02) 0.132	0.31 (0.26 to 0.35) <0.001	0.21 (0.16 to 0.25) <0.001	−0.33 (−0.41 to −0.24) <0.001	−0.28 (−0.37 to −0.18) <0.001	−0.38 (−0.41 to −0.34) <0.001	−0.31 (−0.34 to −0.27) <0.001
R^2	0.01	0.02	0.06	0.13	0.02	0.03	0.11	0.18

[a]Adjusted for age, body mass index, smoking, alcohol consumption, impaired renal function and diabetes.

CI, confidence interval; Q1–Q4, quartile 1–4.